A Review of the Efficacy of Selective Serotonin Reuptake Inhibitors in Obsessive-Compulsive Disorder

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Background: Obsessive-compulsive disorder (OCD) is a chronic illness associated with substantial morbidity; it often requires long-term medication. The best-studied therapeutic agent in the treatment of this disorder is the tricyclic antidepressant clomipramine. Since other tricyclic antidepressants appear to lack efficacy in OCD, that of clomipramine has been linked to its potent effects on serotonin. Consequently, agents that selectively inhibit serotonin reuptake have been the focus of several large-scale, placebo-controlled studies of OCD. Their efficacy in OCD is the focus of our review.

Data sources: MEDLINE search (1966 to present) of OCD treatment with clomipramine or SSRI antidepressant medication using the key words *obsessive-compulsive disorder, serotonin reuptake inhibitors, clomipramine,* and *pharmacology*.

Study findings: The selective serotonin reuptake inhibitors fluoxetine, sertraline, fluvoxamine, and paroxetine have, in separate multicenter trials, demonstrated efficacy and tolerability in the treatment of OCD. In contrast, clomipramine, though efficacious, is often associated with substantial adverse events, particularly anticholinergic side effects. While 2 recent meta-analyses support the superior efficacy of clomipramine over selective serotonin reuptake inhibitors in the treatment of OCD, 5 of 6 head-to-head comparisons of either fluoxetine or fluvoxamine versus clomipramine have found similar efficacy but a lower incidence of side effects with the selective serotonin reuptake inhibitor. A recently completed multicenter, 12-week, double-blind trial of paroxetine versus clomipramine versus placebo showed paroxetine to be as effective as clomipramine. With significantly fewer dropouts due to adverse effects than clomipramine, paroxetine was also associated with superior tolerability.

Conclusion: The suggestion that selective serotonin reuptake inhibitors possess efficacy similar to that of clomipramine, but have a superior side effect profile, may have important implications for patients with OCD who require long-term treatment.

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Obsessive-compulsive disorder (OCD) is a chronic and crippling illness that can have a profound impact on the lives of sufferers and their families. In comparison with the general population, individuals with OCD are more likely to remain single, have an elevated risk for divorce and marital separation, and display social withdrawal tendencies.[1–3] Patients with OCD also perceive a greater number of distressing life events.[4] Perhaps most indicative of the pervasive impact of the illness is the fact that families of patients with OCD also manifest substantial dysfunction in such areas as family routine, leisure activities, personal relationships, and finances.[5] Individuals with OCD often experience persistent symptoms throughout their lives and, without treatment, the natural course of the disease is chronic and unremitting.[1] Most patients require long-term treatment with medication[2] and/or behavior therapy.[2,3]

Although early studies reported that OCD was relatively rare, recent general population-based studies have verified that this disorder is both common and geographically widespread, confirming earlier suspicions that OCD may well represent a hidden epidemic.[6–8] The currently accepted lifetime prevalence rate for OCD is 2% to 3%[6,7]; however, interview assessments used to determine prevalence rates (such as the National Institute of Mental Health [NIMH] Diagnostic Interview Schedule) have been shown to have poor validity.[9] Thus, the true prevalence of OCD is probably still unknown.

Preclinical studies demonstrated that clomipramine and other tricyclic antidepressants (TCAs) act by inhibiting the presynaptic reuptake of both norepinephrine and serotonin (5-HT).[10] Clomipramine, however, has more potent effects on 5-HT reuptake when compared with other TCAs.[11] During clinical trials conducted in the 1960s, patients with comorbid depressive and OCD symptoms were noted to respond better to clomipramine

than to other TCAs. The "serotonin hypothesis of OCD" evolved from the speculation that the unique efficacy of clomipramine in OCD was due to its effects in facilitating 5-HT neurotransmission.[12–17]

The potential role of 5-HT in the pathogenesis of OCD led to the investigation of other agents, in particular the selective serotonin reuptake inhibitors (SSRIs) that potently or selectively inhibit 5-HT reuptake. In addition to the scientific merit of such inquiries, the side effect profile of clomipramine provided impetus for the identification and development of alternative therapeutic agents for the treatment of OCD. Because clomipramine possesses significant affinity for muscarinic and histaminergic receptors,[18] it is frequently associated with troublesome side effects such as dry mouth, sedation, orthostasis, sexual dysfunction, and weight gain. Considerable toxicity in overdosage and a relatively elevated risk for seizures at dosages greater than 250 mg/day may further limit the use of clomipramine in OCD patients.[10,19–23] Recent investigations have focused primarily on newer agents in the hope that these agents may possess similar or enhanced antiobsessional efficacy and/or a more favorable side effect or toxicity profile. With these issues in mind, this article presents an overview of the comparative antiobsessional efficacy and tolerability of SSRIs and clomipramine as determined by meta-analyses and direct comparison studies.

DATA SOURCES

A MEDLINE database (National Library of Medicine electronic database) search was conducted for relevant published literature (1966 to the present) concerning the pharmacologic treatment of OCD with clomipramine and SSRI antidepressants by cross-referencing the following key words: *obsessive-compulsive disorder, serotonin reuptake inhibitors, clomipramine,* and *pharmacology*. Additionally, references from the articles retrieved from the MEDLINE search were reviewed for potential inclusion of other relevant literature not identified in the MEDLINE search. The objective was to comprehensively review the medical literature concerning the treatment of OCD with clomipramine or SSRI antidepressant medication, including acute and long-term efficacy and tolerability.

CLOMIPRAMINE IN OCD

Since its introduction, the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)[24] has become the most widely used and accepted instrument for measuring change in OCD symptoms. The Y-BOCS is a 10-item, observer-rated scale that was developed to assess obsessive thoughts and compulsive behaviors in patients with OCD. The range of total scores on the Y-BOCS is between 0 (none) and 40 (most severe). A mean reduction from baseline of 25% to 35% on the Y-BOCS is generally considered a clinically meaningful change in OCD symptom severity.

Clomipramine has been the most extensively studied medication in the treatment of OCD. In a study by the Clomipramine Collaborative Study Group,[19] more than 500 patients meeting DSM-III criteria for OCD participated in a multicenter, double-blind investigation of clomipramine versus placebo. Clomipramine was associated with significantly greater reductions in OCD symptoms (mean Y-BOCS reduction, 40%) in comparison to placebo administration (mean Y-BOCS reduction, ≤ 10%). Earlier observations that nondepressed OCD patients were as likely as depressed OCD patients to respond favorably to clomipramine were also confirmed.[19,25] The most common side effects experienced during clomipramine treatment were dry mouth, dizziness, tremor, fatigue, somnolence, constipation, nausea, increased sweating, headache, ejaculation failure, abnormal vision, anorexia, dyspepsia, insomnia, and change in libido.[19,20]

In contrast to the placebo response rates often associated with depression (30% to 40%) or panic disorder (40% to 50%), the relatively small placebo response rate (3% to 5%, Y-BOCS and NIMH global scale) is consistent with the chronic and refractory nature of OCD. On the basis of these studies, however, clomipramine was the first medication to be approved by the Food and Drug Administration (FDA) for the treatment of OCD in the United States and has remained the "gold standard" against which any new pharmacologic treatment for this disorder is compared.[26]

SSRIs IN OCD

In addition to the potent effect of SSRIs on 5-HT neurotransmission, extensive worldwide experience with depressed patients suggests that SSRIs are associated with an improved side effect profile and minimal toxicity in overdosage as compared with clomipramine and other TCAs.[27,28] Separate controlled trials of the SSRI antidepressants fluoxetine,[29] sertraline,[30] fluvoxamine,[31] and paroxetine[32] have since been conducted in OCD patients. Each of these studies is characterized by (1) a multicenter, placebo-controlled design; (2) inclusion of patients meeting DSM-III-R criteria for OCD; (3) at least 10 weeks of double-blind SSRI versus placebo administration; and (4) use of the Y-BOCS in intent-to-treat populations as either the primary efficacy variable or 1 of the 3 main efficacy variables.

In the first such SSRI trial reported, 355 OCD patients participated in a 13-week, fixed-dose trial of fluoxetine (20, 40, or 60 mg/day) versus placebo.[29] Fluoxetine at 20 mg/day (mean Y-BOCS reduction, 20%), 40 mg/day

(mean Y-BOCS reduction, 22%), or 60 mg/day (mean Y-BOCS reduction, 27%) was significantly more effective than placebo (mean Y-BOCS reduction, 3%) in reducing OCD symptoms. The trend suggested greater efficacy with increasing dosage. The side effects of nausea, dry mouth, or tremor were experienced significantly more often by the fluoxetine group than by the placebo group.[29] Fluoxetine is now FDA-approved for the treatment of OCD in the United States.

Greist et al.[30] reported the results of a 12-week, fixed-dose study of sertraline (50, 100, or 200 mg/day) and placebo in 324 patients with OCD. Sertraline doses of 50 mg/day (mean Y-BOCS reduction, 24%) and 200 mg/day (mean Y-BOCS reduction, 28%) were significantly more effective than placebo (mean Y-BOCS reduction, 15%) in reducing OCD symptoms. Interestingly, a sertraline dose of 100 mg/day (mean Y-BOCS reduction, 19%) was not significantly different from placebo in reducing OCD symptoms during the study. The most likely reason for this result was the high (33%) dropout rate in this group. Side effects experienced at a significantly higher rate in the sertraline-treated group versus the placebo-treated group were diarrhea, insomnia, decreased libido, nausea, anorexia, ejaculation failure, tremor, increased sweating, and weight gain.[30]

Over 300 patients participated in a 10-week, flexible-dose study of fluvoxamine (100–300 mg/day) versus placebo for the treatment of OCD.[31] Fluvoxamine (mean Y-BOCS reduction, 20%) was significantly more effective than placebo (mean Y-BOCS reduction, 5%) in reducing OCD symptoms. The mean dose of fluvoxamine was 249 mg/day during the study. The most common side effects experienced at a significantly higher rate in the fluvoxamine versus the placebo-treated groups were insomnia, nausea, asthenia, somnolence, abnormal ejaculation, nervousness, and dry mouth.[31]

Results from a 12-week, fixed-dose study of paroxetine (20, 40, or 60 mg/day) versus placebo in 263 patients with OCD have also been reported.[32] Doses of paroxetine at 40 mg/day (mean Y-BOCS reduction, 25%) and at 60 mg/day (mean Y-BOCS reduction, 29%) were significantly more effective than placebo (mean Y-BOCS reduction, 13%) in reducing OCD symptoms. However, there was no significant difference in symptom reduction between 20 mg/day of paroxetine (mean Y-BOCS reduction, 17%) and placebo. Paroxetine was apparently well tolerated during the study, and the adverse event profile in the OCD patients was similar to that observed in depressed patients.[32]

Despite the superior efficacy of these SSRIs over placebo and their safety and tolerability in patients with OCD,[33] key questions remain unanswered. Are SSRIs as effective as clomipramine in the treatment of patients with OCD? Are there significant differences between the specific SSRIs in terms of antiobsessive efficacy?

DIRECT COMPARISONS OF CLOMIPRAMINE VERSUS SSRIs

Our group[34] reported the first direct comparison of SSRI and clomipramine treatment in patients with OCD. Clomipramine and fluoxetine were associated with similar and significant reductions from baseline in OCD symptoms as measured by the Y-BOCS during the 26-week, randomized, double-blind crossover study (N = 11). However, clomipramine was associated with a significantly higher incidence of adverse effects in comparison to fluoxetine treatment.

Smeraldi and colleagues[35] failed to detect significant differences between clomipramine and fluvoxamine treatment in a small study of OCD patients. However, it must be stressed that the sample size in each group (N = 5) was too small for results to be considered statistically viable. In a larger, multicenter, flexible dose, double-blind trial conducted in the United Kingdom, similar and significant reductions in OCD symptoms occurred during 10 weeks of fluvoxamine (mean Y-BOCS reduction, 33%) and clomipramine (mean Y-BOCS reduction, 31%) administration in 66 patients with OCD.[36] The frequency of adverse events was also similar for the fluvoxamine- and clomipramine-treated groups, with nausea the most commonly reported adverse event for both groups. Fluvoxamine (100–300 mg/day) and clomipramine (100–250 mg/day) had comparable efficacy in reducing OCD symptoms in nondepressed OCD patients (N = 79) in a subsequent study conducted in the United States.[37] Similarly, in an 8-week, double-blind, controlled study of patients with OCD (N = 55), the efficacy of fluoxetine (40 mg/day) and that of clomipramine (150 mg/day) were comparable in terms of the decrease in total Y-BOCS.[38]

A 16-week, double-blind comparison of sertraline (N = 86) versus clomipramine in patients with OCD was also recently reported.[39] This study had greater than an 80% probability of detecting a 2.3 point difference between the treatment groups in the mean change from baseline in total Y-BOCS. The sertraline-treated group had a statistically greater ($p < .05$) reduction in OCD symptoms than the clomipramine-treated group (mean Y-BOCS reduction, 51% versus 43%). However, a fair comparison may have been precluded because of the greater number of clomipramine subjects who withdrew early in the study (18 clomipramine-treated subjects versus 3 sertraline-treated subjects within 28 days). The large number of withdrawals was possibly due to the higher-than-recommended starting dose of clomipramine (50 mg/day versus 25 mg/day). In addition, the mean final daily dose of clomipramine (90 mg/day) used during the study (intent-to-treat population) was well below the usual dosage (150–250 mg/day) associated with antiobsessional efficacy, whereas the corresponding dose of sertraline (129 mg/day) was well within the normal therapeutic range for

Table 1. Percentage of Patients With Adverse Experiences Starting During Paroxetine Treatment[a]

Type of Adverse Experience	Paroxetine (N = 201)	Clomipramine (N = 99)	Placebo (N = 99)
Any adverse experience	81.1%	85.9%	78.8%
Anticholinergic type	28.4%[b,c]	52.5%[b]	12.1%
Severe grade	30.8%	38.4%[d]	23.2%
Drug-related	15.9%[e]	28.3%[b]	8.1%
Withdrawals due to adverse events	9.0%[f]	17.2%[d]	6.1%

[a]Data from reference 40.
[b]$p \leq .001$ vs. placebo; [c]$p < .001$ vs. clomipramine; [d]$p < .05$ vs. placebo; [e]$p < .01$ vs. clomipramine; [f]$p < .05$ vs. clomipramine.

this disorder.[19,30,39] The dosage discrepancy was possibly due to the poor tolerability of clomipramine.[39] The trial protocol stipulated that dosage could be escalated after a minimum of 4 weeks; in those patients receiving at least 4 weeks' double-blind treatment, the mean final doses of clomipramine and sertraline were 101 mg and 132 mg, respectively, reaching 110 mg and 136 mg in completers.[39] Efficacy of treatment in these groups was equivalent.

The preceding studies represent the only direct comparisons of antiobsessive agents. Five of the 6 studies reviewed failed to detect clinically significant differences between the antiobsessive agents compared, although the sample sizes may have been insufficient to detect significant differences. Furthermore, none of these studies included a placebo cell.[34–39]

Recently, the first multicenter, placebo-controlled comparative trial of an SSRI versus clomipramine was reported in patients with OCD. Zohar and Judge[40] completed a double-blind comparison of paroxetine, clomipramine, and placebo in 399 patients. Patients enrolled in the study had met DSM-III-R criteria for OCD for at least 6 months.

Randomly assigned patients received paroxetine (N = 201; 10–60 mg/day), clomipramine (N = 99; 25–250 mg/day), or placebo (N = 99) in a flexible-dose fashion over 12 weeks. Response was defined a priori as a 25% or higher reduction in total Y-BOCS from baseline. Both paroxetine and clomipramine had similar efficacy at weeks 6, 8, and 12 with significantly ($p < .05$) more patients meeting response criteria in comparison to placebo at weeks 6 and 12. At week 12, 55% of patients receiving paroxetine and 55% of patients receiving clomipramine met response criteria as compared with 35% of the placebo group. Forty-seven percent of patients receiving paroxetine also met the response criterion compared with placebo (33%, $p < .05$) at week 8. Significantly more patients receiving paroxetine (76%) compared with clomipramine (66%) or placebo (61%) completed the full 12-week study. The mean daily doses across the study period were 37.5 mg for paroxetine and 113.1 mg for clomipramine. Clomipramine, but not paroxetine, was associated with significantly more adverse effects (drug-related, severe in grade, or the reason for study withdrawal) compared with placebo (Table 1). Moreover, patients receiving paroxetine had significantly fewer adverse events (drug-related or the reason for withdrawal) than the clomipramine-treated patients did.[40] In summary, these results support the similar efficacy of paroxetine and clomipramine in OCD, but suggest that paroxetine may be associated with fewer adverse events than clomipramine.

META-ANALYSES OF CLOMIPRAMINE VERSUS SSRIs

Piccinelli and colleagues[41] reported a meta-analysis of data collected from studies with clomipramine, fluoxetine, fluvoxamine, or sertraline versus placebo, several of which have been reported here[19,30,31,34,35] or used in the meta-analysis of Greist et al.[33] As compared with placebo, all medications resulted in a significantly greater improvement in Y-BOCS-rated OCD symptoms. Moreover, clomipramine treatment was associated with significantly greater OCD symptom reduction (mean Y-BOCS reduction, 61%) compared with the SSRIs (mean Y-BOCS reduction, fluoxetine, 28.5%; fluvoxamine, 28%; and sertraline, 22%). There was no significant difference between the OCD symptom relief associated with fluoxetine, fluvoxamine, or sertraline treatment.[41]

Greist and colleagues[33] conducted a meta-analysis of data on OCD treatment collected from 4 multicenter, placebo-controlled trials of clomipramine, fluoxetine, fluvoxamine, and sertraline. Clomipramine was significantly more effective than fluoxetine, fluvoxamine, or sertraline in reducing OCD symptoms as measured by reduction in the Y-BOCS. Furthermore, a significantly greater percentage of patients treated with clomipramine were rated "much" or "very much" improved than were patients treated with fluoxetine, fluvoxamine, or sertraline. Interestingly, the total dropout rate (due to side effects, lack of efficacy, and other causes) associated with clomipramine was significantly less than the dropout rate associated with the SSRI antidepressants. Dropouts attributed solely to side effects were similar for the different agents (clomipramine, 8%; fluoxetine, 12%; fluvoxamine, 15%; and sertraline, 10%).[33]

Meta-analysis provides a means of combining multiple data sets into a large group of data with less likelihood of errors generated from factors such as inadequate sample size and the random occurrence of unlikely adverse events, as can occur with single medication trials. However, variables such as study design, time period, chronology, and site-specific factors, which may have a critical impact on the results, cannot be considered or accounted for by meta-analyses. For example, patients in the clomipramine trial included in the Greist meta-analysis[33] may have been more likely to tolerate substantial side effects in the hopes of eventually attaining improvement in their

OCD symptoms because alternatives such as SSRIs were not available at the time. In contrast, alternative medications (clomipramine, fluoxetine, etc.) were available when the SSRI trials were conducted and therefore patients may have been less willing to tolerate adverse events or a sustained lack of efficacy. It is estimated that as many as 20% of the patients enrolled in the sertraline and fluvoxamine trials had previously not responded in the clomipramine or SSRI trials,[33] suggesting that these patients were relatively treatment refractory. These factors must be considered when comparing the efficacy and tolerability data collected from the clomipramine versus the subsequent SSRI trials in patients with OCD.

Although the results of Piccinelli et al.[41] and Greist et al.[33] support the superiority of clomipramine over the SSRIs in the treatment of OCD, both groups concluded that head-to-head, double-blind comparisons of clomipramine and the SSRIs or of the SSRIs are the best test of comparative efficacy and tolerability.

Two other analyses indicate a superior tolerability of SSRIs over clomipramine. A lower incidence of side effects in fluoxetine-treated patients compared with clomipramine-treated patients was reported in a retrospective comparison of tolerability in OCD patients.[42] Overall, significantly more of the fluoxetine-treated (43%) compared with the clomipramine-treated (3%) patients with OCD had no side effects. A meta-analysis conducted by Anderson and Tomenson[43] in 6029 depressed patients concluded that SSRIs (fluoxetine, fluvoxamine, paroxetine, sertraline, or citalopram) were associated with significantly fewer dropouts due to adverse events than were the TCAs.

LONG-TERM EFFICACY OF SSRIs IN OCD

Despite the chronicity of OCD and the recommendation that pharmacotherapy should exceed 9 to 12 months' duration, there are comparatively few published data on the efficacy of SSRIs or clomipramine for periods longer than 20 weeks.[12,21] Long-term efficacy and tolerability of anti-OCD treatment therefore represent key issues.

The Clomipramine Collaborative Study included a 1-year, double-blind extension study[19] involving completers of the 10-week core phase of clomipramine versus placebo who were judged to have been at least minimally responsive. In the extension phase, significantly more of the clomipramine-treated (75%) group were rated as "very much improved" or "much improved" compared with the placebo-treated (17%) group.[19] These results are consistent with earlier smaller studies reporting that OCD patients maintain their level of improvement as long as they remain on clomipramine therapy.[44–46]

Patients with OCD who both completed and responded during the acute phase of a multicenter fluoxetine study[47] (N = 76) maintained the OCD symptom improvement during a 24-week continuation phase. Moreover, two thirds of the patients who did not respond during the core phase of the study (N = 198) achieved a clinical response when switched to their maximum-tolerated dose (up to 80 mg) of open-label fluoxetine during the 24-week extension phase.[47]

Sertraline was reported to be safe and efficacious during a 1-year controlled trial in the treatment of patients with OCD.[48] Several studies of long-term paroxetine treatment have been completed. The results suggest that OCD symptoms continue to improve for up to 6 months of paroxetine therapy and that significantly more patients relapsed after switching to placebo than patients who were maintained on paroxetine therapy in a double-blind extension study. Furthermore, the placebo group relapsed almost 3 times faster than the paroxetine group during the paroxetine extension study.[49]

In a 2-year, open-label follow-up of OCD patients (N = 130) who were responders to clomipramine, fluoxetine, or fluvoxamine, maintenance treatments were found to be significantly superior to discontinuation in preventing relapses.[50]

CONCLUSION

While the efficacy of clomipramine in the treatment of OCD is well established, there remains a need for new agents, particularly for treating those patients who are unresponsive to, or intolerant of, clomipramine. Although meta-analyses have indicated the superior efficacy of clomipramine over the SSRIs in the treatment of OCD, these results need to be treated with a degree of caution, since critical variations, such as those in study design and drug availability, for instance, could not be addressed. More recent results of comparative, controlled clinical trials suggest that, when compared with clomipramine, the SSRIs have equivalent efficacy and superior tolerability. Of particular benefit is their lack of anticholinergic side effects.

OCD patients for whom clomipramine provides an effective and well-tolerated treatment should not have their treatment changed to an SSRI. Indeed, an SSRI may prove ineffective in such patients. However, because long-term maintenance treatment with medication is frequently necessary in OCD, data supporting the superior tolerability of SSRIs over clomipramine have important implications for future therapeutic options.

Drug names: citalopram (Celexa), clomipramine (Anafranil), fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), sertraline (Zoloft).

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