Pharmacologic Treatment of Obsessive-Compulsive Disorder: Comparative Studies

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The predominant hypothesis about obsessive-compulsive disorder (OCD) pathophysiology implicates abnormal serotonergic function regulation. Pharmacologic agents with potent serotonin reuptake-inhibiting properties have demonstrated effectiveness in treating OCD. In short-term clinical trials compared by meta-analysis, clomipramine and serotonin selective reuptake inhibitors (SSRIs) were found superior to placebo in improving symptoms of OCD. In one-to-one comparative studies, clomipramine has been found as efficacious as fluoxetine and fluvoxamine, and in a comparative trial of clomipramine with sertraline, there was a statistically superior response to sertraline after 16 weeks of treatment; moreover, discontinuation rate in patients taking clomipramine was more than twice that in patients taking sertraline (26% vs. 11%). In contrast to patients receiving clomipramine who showed poor tolerance in long-term use, patients maintained on fluoxetine for 24 weeks after an acute phase well tolerated the medication. In another study, patients responding to 12 weeks of sertraline treatment also showed improved tolerance during an additional 40-week period, with 75% completing the continuation phase. With long-term or even lifelong treatment appearing necessary for people with OCD, those agents that result in better tolerance will prove preferable.

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Pharmacologic challenge studies and neuroimaging studies have resulted in compelling evidence supporting neurobiological abnormalities in patients suffering from obsessive-compulsive disorder (OCD). The predominant hypothesis about OCD pathophysiology, originating from treatment studies and pharmacologic manipulation of the serotonin system, implicates an abnormal regulation of brain serotonergic function.[1] The efficacy of antidepressants such as clomipramine or fluvoxamine, which have potent serotonin transport-inhibiting properties, is in sharp contrast to the lack of efficacy of antidepressants such as desipramine, phenelzine, and clorgiline, which have no blocking effect on serotonin transport.[2–4] Potent serotonin transport inhibition appears to be one prerequisite for effective treatment.[5–9] Clomipramine was the first compound found to have a sizable effect on obsessive-compulsive (OC) symptoms. Although the first reports were made more than 20 years ago,[10,11] unequivocal demonstration of its efficacy in large double-blind placebo-controlled studies has only recently been made.[12]

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In recent years, new antidepressants with potent serotonin transport-inhibiting properties have been shown conclusively to have both short-term and long-term efficacy in reducing OC symptomatology.[13–18] Five antidepressants currently are available for frontline pharmacologic treatment: clomipramine, fluvoxamine, fluoxetine, sertraline, and paroxetine. In this paper, we review available data on the differences between these agents.

COMPARATIVE EFFICACY AND TOLERANCE IN SHORT-TERM TREATMENT

Meta-Analysis

The first comparative approach relies on meta-analysis. Several studies have been published in the last 2 years suggesting the superior efficacy of clomipramine over specific serotonin selective reuptake inhibitors (SSRIs) in the treatment of OC symptoms.[14,19,20] In a multicenter meta-analysis by Greist et al.,[14] placebo-controlled trials found clomipramine, fluoxetine, fluvoxamine, and sertraline superior to placebo. However, a significantly greater percentage of patients receiving clomipramine (60%) were rated as "much improved" or "very much improved" on the Clinical Global Impression (CGI) improvement scale compared with those receiving fluoxetine (38%), fluvoxamine (43%), or sertraline (39%). Surprisingly, the rate of premature discontinuation of treatment (due to adverse effects, lack of efficacy, or other causes) was also significantly lower in the clomipramine trials compared with the rate of

Table 1. Subject Characteristics and Mean Y-BOCS Changes in Pivotal Placebo-Controlled Studies*

Agent (Study)	N	Average Age (y)	Duration of Illness (y)	Baseline Y-BOCS	Y-BOCS Change Active Drug	Y-BOCS Change Placebo
Clomipramine (CCSG, 1991[12])						
Study 1	238	35.4	15.1	26.1	–8.5	–0.83
Study 2	263	35.6	16.3	26.7	–9.8	–0.94
Fluoxetine (Tollefson et al, 1994[18])	355	36.9	NR	24.0	–5.9[a]	–0.7
Sertraline (Greist et al, 1995[13])	320	38.6	5.0	23.8	–5.6	–3.4
Fluvoxamine (Greist et al, 1995[16])	159	35.6	14	23.1	–4.9	–1.7

*Abbreviations: CCSG = Clomipramine Collaborative Study Group; NR = not reported; Y-BOCS = Yale-Brown Obsessive Compulsive Scale.
[a]Calculated by authors.

premature discontinuation associated with the other three agents. However, the observed discrepancies among studies may not be accounted for by differences in drug effect. The clomipramine studies included in the meta-analysis all used a flexible dose titration, while the fluoxetine, sertraline, and paroxetine studies were fixed-dose studies, which may have produced a higher incidence of adverse events, particularly in the higher dosage groups.

Another striking difference between the studies included in meta-analyses is the variation in the placebo response. Studies of clomipramine showing a large treatment effect and a low placebo effect are compared with later studies of sertraline and fluoxetine showing a smaller treatment effect and a larger placebo effect (Table 1).[12,13,18] These differences, observed over time, suggest that discrepant populations of patients with OCD were being studied. For example, patients included in later studies have a shorter duration of illness and/or a lower baseline score on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) than patients included in earlier studies. Important differences between treatment studies suggest that comparisons using meta-analysis are likely to be misleading. One-to-one comparative studies avoid this problem.

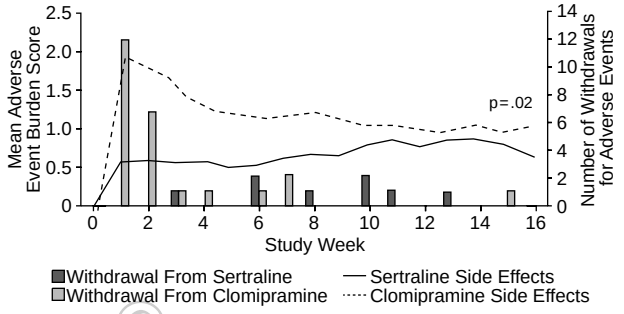
Comparative Trials

Clomipramine has been compared with other potent serotonin transport inhibitors such as fluvoxamine, fluoxetine, and sertraline, and with antidepressants lacking potent serotonin transport-inhibiting properties. A small comparative study[21] did not find any efficacy or tolerance difference between clomipramine and fluoxetine. A parallel group trial in 55 patients[22] found fluoxetine and clomipramine to be equally effective on the primary outcome parameter (Y-BOCS total mean score); however, clomipramine was significantly more effective than fluoxetine on one secondary outcome measure (CGI severity scale). In an unblinded comparison of 22 patients, clomipramine was superior to fluoxetine in reducing Y-BOCS total mean scores after 12 weeks of treatment.[23] All clomipramine recipients had decreases in Y-BOCS total mean scores, whereas in the fluoxetine treatment group only 6 patients improved and 5 patients experienced deterioration of their condition.

Clomipramine and fluvoxamine have been compared in three studies and have been found equally efficacious.[24–26] In a 10-week multicenter study of 66 patients, Freeman et al.[25] compared the effects of 100 to 250 mg of fluvoxamine with the effects of the same dose range of clomipramine. Both treatments resulted in more than a 30% reduction in Y-BOCS scores. No statistically significant differences were found between the two treatments; however, fluvoxamine was found to be more effective in patients with a disorder duration greater than 1 year. There was no difference in dropout rate for side effects in both treatment groups. However, one patient experienced seizures with 200 mg of clomipramine. As expected, the side effect profile differed in the two treatment groups. Clomipramine-treated patients experienced more anticholinergic-type side effects. The most common side effect in both treatment groups was nausea, observed in more than 30% of patients. In a multicenter double-blind study of 79 outpatients by Koran et al.,[26] fluvoxamine and clomipramine were also found to be equally efficacious, with 7 patients (17%) withdrawing because of treatment-related adverse events in the clomipramine group and 5 (14%) withdrawing in the fluvoxamine group. As in the previous study, a decrease of 30% in Y-BOCS scores was observed in both treatment groups after 12 weeks of treatment. Both drugs were considered well tolerated, but side effects differed. Fluvoxamine produced a higher incidence of insomnia (35.1%), nervousness (32.4%), and nausea (37.8%), while dry mouth (73.2%), postural hypotension (22%), and dizziness (39%) were more often observed with clomipramine. Although these two comparative studies demonstrate the equivalent efficacy of clomipramine and fluvoxamine, the existence of a sizable difference between the two cannot be excluded, given the relatively small sample size of both studies.

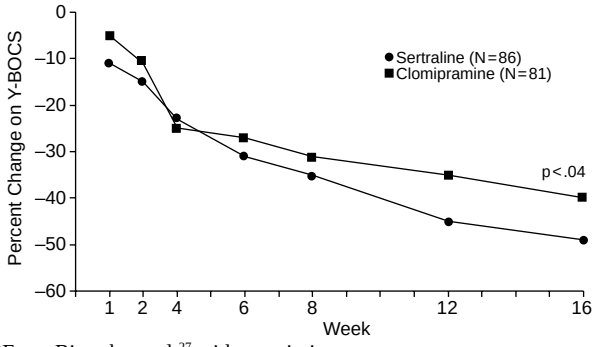
Sertraline and clomipramine have been compared in a large multicenter study involving 168 nondepressed OCD outpatients.[27] Patients included in this 16-week study were moderately to severely ill, with a mean Y-BOCS score of about 27 and a 7-year mean duration of illness. After a 1- to 2-week placebo washout, patients received either clomipramine or sertraline at a starting dose of 50 mg for a period of 4 weeks. The dose was then adjusted according to

Figure 1. A Double-Blind Comparison of Sertraline and Clomipramine in Outpatients With OCD: Relationship Between Adverse Events and Withdrawals*



*From Bisserbe et al,[27] with permission.

Figure 2. A Double-Blind Comparison of Sertraline and Clomipramine in Outpatients With OCD: Change in Baseline Y-BOCS Score by Visit Week/Intent-to-Treat Population, Last Observation Carried Forward*



*From Bisserbe et al,[27] with permission.
Abbreviation: Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

tolerance and clinical efficacy. The most salient finding of this study was the striking difference in tolerance between the two treatments (Figure 1). Discontinuation caused by adverse events occurred in 26% of the patients in the clomipramine group compared with 11% in the sertraline group ($p = .02$). Most dropouts discontinued treatment within the first 28 days of double-blind therapy, and a greater proportion of clomipramine patients (82%) compared with sertraline patients (30%) withdrew while receiving the lowest daily dose of the study drug (50 mg). Consistent with this observation, the mean daily dose of double-blind medication at the final visit was 90 mg in the clomipramine group compared with 129 mg in the sertraline group. Final daily doses of medication were higher in patients evaluated for drug efficacy, i.e., those who received at least 28 days of double-blind therapy (clomipramine 101 mg, sertraline 132 mg), and in patients completing the study (clomipramine 110 mg, sertraline 136 mg).

OCD symptoms responded to both treatments. Analysis of the mean changes in the primary efficacy variables from the first to the final visit (intent-to-treat sample with last observation carried forward) indicated a statistically significant difference favoring sertraline ($p < .04$) (Figure 2).[27] Specifically, the mean percentages of improvement at the final visit in the total Y-BOCS score (–51% versus –43%, $p = .036$), National Institute of Mental Health Obsessive Compulsive (NIMH-OC) score (–42% versus –34%, $p = .023$), and CGI-severity of illness rating (–38% versus –30%, $p = .008$) were significantly greater in patients in the sertraline group than in those in the clomipramine group. Seventy-two percent of sertraline-treated patients had a $\geq 35\%$ decrease in total Y-BOCS score from baseline to final visit, compared with 65% of clomipramine-treated patients. To compensate for the greater number of clomipramine patients who withdrew early, since in many cases these patients probably withdrew before they were able to respond adequately to treatment, similar efficacy analyses were repeated using data from patients who received at least 4 weeks of medication. Results of these analyses showed no statistically significant differences in efficacy between the treatments.

As expected, adverse event profiles were different for both treatments. The overall proportion of patients spontaneously reporting adverse events was higher in the clomipramine group (57 of 82, or 70%) than in the sertraline group (56 of 86, or 65%). Of the 155 adverse events reported in the sertraline group, 16 were evaluated by the investigator as severe, while of 185 adverse events reported in the clomipramine group, 53 were evaluated as severe. Adverse events reported with an incidence of 10% or more in sertraline-treated patients were nausea (12%) and diarrhea/loose stools (12%). Adverse events in the clomipramine-treated patients were dry mouth (20%), anxiety (17%), constipation (16%), nausea (15%), tremor (11%), and somnolence (11%). The incidence of anxiety tended to be higher ($p = .056$) for patients treated with clomipramine (17%) than for patients treated with sertraline (7%). Consistent with this finding was the difference in sedative use between treatment groups. Despite the higher incidence of somnolence reported in the clomipramine group, 33% of clomipramine-treated patients, compared with 26% of sertraline-treated patients, required night sedation during the study.[27]

These tolerance results are in contrast with the findings of earlier clomipramine studies, which reported a high incidence of adverse experiences together with a low treatment discontinuation rate. This difference may reflect change over time in patient population. Change in drug availability and increased public knowledge of OCD have clearly had an impact on patient expectations. While in earlier studies clomipramine was the sole effective drug, in later studies patients were aware of the availability of an array of antiobsessional medications and, in some cases, had experienced previous treatment with clomipramine as the first truly effective treatment they had

Table 2. Pharmacologic Treatment of OCD: Clomipramine Effect Size in Recent Studies*

Study	N (Intent-to-Treat Sample) Clomipramine	Mean Y-BOCS Total Score				
		Baseline	Week 8	Week 10	Week 12	Week 16
CCSG, 1991[12]						
Study 1	118	26.3	17.1 (–34.8%)	16.21 (–38.3%)	…	…
Study 2	134	26.2	16.2 (–38.2%)	14.7 (–43.9%)		
Freeman et al, 1994[25]	30	25.5	…	17.7 (–30.5%)	…	…
Koran et al, 1996[26]	39	24.3	…	17.0 (–30.0%)		
Bisserbe et al, 1997[27]	82	27.4	17.9 (–34.7%)	…	16.3 (–40.5%)	15.7 (–42.7%)

*Abbreviations: CCSG = Clomipramine Collaborative Study Group; OCD = Obsessive-compulsive disorder; Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

encountered. That prior experience may have encouraged patients in subsequent studies to be less stoic when encountering side effects. Of patients included in the sertraline-clomipramine comparative study, only one fourth had not received previous drug treatment for their OCD symptoms.

Poor tolerance of clomipramine limited dose increases. Although both drugs could be escalated after 4 weeks in increments of 50 mg every 2 weeks to a maximum daily dose of 200 mg/day, the mean final daily doses in the intent-to-treat patient group were 129 mg for sertraline and only 90 mg for clomipramine. For those patients who did not withdraw from the study, the mean doses were 136 mg for sertraline and 110 mg for clomipramine. However, in this study, the response to clomipramine and sertraline is comparable with the response observed in the large studies of the Clomipramine Collaborative Study Group and in recent comparative studies, in which higher doses of clomipramine were used (Table 2). It should be pointed out that in the absence of clomipramine fixed-dose studies in patients with OCD, there is no definitive answer regarding the optimal dose of clomipramine. Furthermore, in placebo-controlled studies, doses of 75 mg/day[28] and 150 mg/day[29] have been found highly efficacious in reducing OCD symptoms. Other small, double-blind, placebo-controlled studies have demonstrated the short-term efficacy of clomipramine in doses ranging from 120 mg to 180 mg.[30,31] High doses of clomipramine may not be necessary to elicit a response in patients with OCD and, in addition, may be associated with an increased incidence of serious toxicity, including seizures.[12]

LONG-TERM EFFICACY AND TOLERANCE

There are few data to answer the question of optimal duration of pharmacologic OCD treatment. Clinical experience suggests the necessity of long-term, and in some cases lifelong, treatment. Only one study has specifically addressed this question in adult OCD patients, finding that in 18 patients treated with clomipramine from 5 to 27 months, relapse occurred in 16 patients 3 weeks after treatment discontinuation.[32] Long-term treatment is likely for a large percentage of, if not all, people with OCD. Thus, drug tolerance is expected to play a key role in treatment compliance, affecting long-term efficacy. Efficacy lasting from 6 months to 2 years has been demonstrated in long-term studies for most antiobsessional drugs. During the continuation phase of most studies, the drug was tolerated better than it was in the initial treatment phase.

In a long-term study by Tollefson et al.,[33] 76 patients who responded to fluoxetine and were included in a 24-week double-blind continuation phase not only maintained their acute treatment gains but continued to improve, according to Y-BOCS endpoint scores. Fluoxetine was better tolerated in the continuation phase, during which only 5.3% of the patients discontinued for adverse events, whereas 12% had discontinued in the acute phase of the study.[18] In a longer study by Greist et al.,[15] the safety and tolerability of sertraline treatment also improved in a 40-week continuation phase. The rate of patient withdrawal for adverse effects in this study dropped from 10% during the initial 12 weeks (versus 6% for placebo) to 4% during the 40-week continuation period (versus 5% for placebo). Of the 96 patients who responded to the initial 12 weeks of sertraline treatment and entered the 40-week continuation phase, 72 patients (75%) completed the study.

These findings are similar to the favorable tolerance profiles of sertraline and fluoxetine (unlike clomipramine) in long-term treatment studies of depression.[34,35] In a study by Katz et al.,[36] the effects of clomipramine versus placebo in the treatment of OCD patients were assessed in a 10-week double-blind trial followed by a 42-week double-blind extension study. Of the 110 clomipramine-treated patients who entered the extension phase, 15% subsequently discontinued the study because of adverse events. Overall, only 28 patients (25%) completed the study.

CONCLUSION

We reviewed available studies comparing clomipramine and SSRIs for the treatment of patients with OCD. While meta-analyses suggest a slightly superior efficacy for clomipramine, one-to-one comparative studies indicate that fluoxetine, fluvoxamine, and sertraline are as efficacious as clomipramine. The better tolerance of SSRIs—particularly sertraline—found in short-term treatment results in better global effectiveness. Long-term comparative studies have also found that SSRIs are tolerated better than clomipramine. In conclusion, SSRIs appear preferable as the frontline pharmacologic treatment of most cases of OCD.

Drug names: clomipramine (Anafranil), desipramine (Norpramin and others), fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), phenelzine (Nardil), sertraline (Zoloft).

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