

Clomipramine versus Sertraline in the Treatment of Obsessive Compulsive Disorder*

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SUMMARY:

CLOMIPRAMINE VERSUS SERTRALINE IN THE TREATMENT OF OBSESSIVE COMPULSIVE DISORDER

Objective: The aim of this study was to compare the efficacy, safety, and tolerability of sertraline and clomipramine in the treatment of obsessive-compulsive disorder (OCD). **Method:** Outpatients met the DSM-IV criteria for OCD for 1 year or longer and scores of ≥ 20 on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) and ≥ 4 on the Clinical Global Impression Severity Scale (CGI-S) were included in the study. Patients who had significant concomitant physical disease, suicidal tendency, a history of seizure or organic brain disorder, substance abuse within the previous six months, DSM-IV axis I diagnoses other than OCD and who had had medication for 1 month were not included in the study. Patients were randomized to receive 8-week of single-blind treatment with either fixed dose of sertraline (n=20) 50 mg/day or clomipramine (n=22) initially 50 mg/day and 150 mg/day after 1 week. No additional medication was given to patients. Clinical evaluations were conducted before the treatment and on two-week schedule throughout the 8-week trial using the Y-BOCS and the CGI-S. **Results:** Four of clomipramine (18.2%) and 2 of sertraline (10.0%) patients dropped out because of adverse events or lack of effectiveness. Thirty six patients completed the trial (sertraline n=18; clomipramine n=18). The mean baseline Y-BOCS and CGI-S scores were 24.95 and 4.75 respectively for sertraline and 23.54 and 4.85 for clomipramine ($p>0.05$). A significant reduction in OCD symptoms from baseline to the end of 8th week of the trial was found in both sertraline and clomipramine treated groups ($p<0.05$). Mean baseline to final visit changes were -69.06% (Y-BOCS) and -65.75% (CGI-S) for sertraline and -69.26% (Y-BOCS) and -53.78% (CGI-S) for clomipramine ($p>0.05$). The number of patients withdrawn because of adverse events was substantially greater for clomipramine (22.2%) than sertraline (11.1%). The incidence of side effects was significantly higher in clomipramine-treated patients versus sertraline-treated patients. The most frequent adverse events with sertraline were headache (38.8%), nausea (33.3%), irritability (11.1%) and tremor (11.1%), while clomipramine was most commonly associated with dry mouth (50%), weight gain (50%), constipation (27.7%), yawning (27.7%), sedation (22.2%) and dizziness (11.1%). **Conclusions:** At fixed doses, both clomipramine and sertraline showed a similar therapeutic efficacy in the treatment of OCD. Clomipramine produced more side effects and dropout rate. The results indicate that sertraline is as effective as clomipramine in the treatment of OCD and is better tolerated.

Key words: obsessive-compulsive disorder, sertraline, clomipramine, treatment.

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ÖZET:

OBSESSİF KOMPULSİF BOZUKLUK TEDAVİSİNDE KLOMİPRAMİN VE SERTRALİN KARŞILAŞTIRILMASI

Amaç: Bu çalışmada obsesif-kompulsif bozukluk (OKB) tedavisinde klomipramin ve sertralinin etkinlik, güvenlik ve kullanılabilirliğinin karşılaştırılması amaçlandı. **Yöntem:** DSM-IV tanı kriterlerine göre 1 yıl veya daha uzun süredir OKB tanısı alan, Yale-Brown Obsesif-Kompulsif Skalası'ndan (Y-BOCS) 20 ve üstünde ve Klinik Global İyileşme Skalası'ndan 4 ve üstünde puan alan poliklinik hastalar çalışmaya alındı. Belirgin fiziksel hastalığı, intihar eğilimi, epilepsi veya organik beyin hastalığı hikayesi olan, önceki 6 ay süresince madde kullanan, OKB dışında DSM-IV Eksen I tanısı alan hastalar ve önceki 1 ay süresince ilaç tedavisi alan hastalar çalışmaya alınmadı. Hastalara rastgele olarak, tek kör yöntemle sertraline (n=20) 50 mg/gün veya klomipramin (n=22) başlangıçta 50 mg/gün, 1 hafta sonra 150 mg/gün sabit dozda ilaç tedavisi verildi. Ek olarak başka bir ilaç verilmedi. Tedaviden önce ve 2 haftalık aralarla Y-BOCS ve CGI-S skalaları kullanılarak klinik değerlendirmeler yapıldı. Dört klomipramin (18.2%) ve 2 sertraline (10.0%) hastası yan etkiler nedeniyle tedaviyi bıraktı. Tedaviyi 36 hasta tamamladı (sertraline n=18; klomipramin n=18). Veriler Mann-Whitney U, Freidman two-way ANOVA x2 ve Wilcoxon testleri ile istatistiksel olarak değerlendirildi. **Bulgular:** Tedavi öncesi ortalama Y-BOCS ve CGI-S skorları sertraline için sırasıyla 24.95 ve 4.75 ve klomipramin için 23.54 ve 4.85 bulundu ($p>0.05$). Sertraline ve klomipramin gruplarının her ikisinde 8 haftalık tedavi sonrası OKB belirtilerinde tedavi öncesine göre belirgin bir düşme bulundu ($p<0.001$). Tedavi öncesi ve son görüşme arasındaki Y-BOCS ve CGI-S yüzde değişiklikleri sertraline grubunda -69.06%; -65.75% ve klomipramin grubunda -69.26%; -53.78% idi ($p>0.05$). Yan etkiler nedeniyle tedaviye devam edemeyen hastalar klomipramin grubunda (%22.2) sertraline grubuna (%10.0) göre daha fazla bulundu. Klomipramin tedavisi alan hastalarda sertraline hastalarına göre anlamlı derecede daha sık yan etki gözlemlendi (%72.2 %38.8, $p<0.05$). Sertraline en sık baş ağrısı (%38.8), bulantı (33.3), irritabilite (%11.1) ve tremor (%11.1) görülürken, klomipramin en sık olarak ağız kuruluğu (%50), kilo alma (%50), kabızlık (%27.7), esneme (%27.7), sedasyon (%22.2) ve baş dönmesine (%11.1) yol açtı. **Tartışma:** OKB tedavisinde sabit dozlarda klomipramin ve sertraline benzer etkinlik gösterdiler. Klomipramin daha sık yan etki ve tedaviyi bırakmaya yol açtı. Sertralinin OKB tedavisinde klomipramin kadar etkili olduğu ve daha iyi tolere edildiği görüldü.

Anahtar sözcükler: obsesif kompulsif bozukluk, sertraline, klomipramin, tedavi.

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INTRODUCTION

Several lines of investigation support a serotonergic hypothesis for the pathophysiology and treatment of OCD. Clomipramine, a tricyclic antidepressant that is a potent serotonin uptake inhibitor, was

the first pharmacologic treatment for OCD to be studied in large multicenter trials. The successful outcome of these studies resulted in marketing approval by the United States Food and Drug Administration in 1989.

While the efficacy of clomipramine has been suppor-

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ted in numerous studies, its unfavorable side-effect profile, which includes a higher risk of seizure than other tricyclic antidepressants (TCAs), led to evaluation of the newer selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, fluvoxamine and sertralines in OCD.

Subsequently, similar multicenter trials have been undertaken with the selective serotonin uptake inhibitors, fluvoxamine, sertraline, and fluoxetine. Sertraline is a potent and highly selective serotonin reuptake inhibitor with established efficacy in the treatment of depression. Unlike the TCAs, sertraline shows negligible activity on other neurotransmitter systems and is, therefore, devoid of the anticholinergic, antihistaminergic and antidopaminergic side effects associated with these drugs (5,12).

Sertraline may be particularly useful for patients who have been unable to tolerate the restlessness that has often been associated with other SSRIs. Even newer SSRIs may be distinguished by an increasing degree of specificity for certain parts of the nervous system.

The objective of this study was to compare the efficacy and tolerability of sertraline with clomipramine in the treatment of patients with OCD.

METHODS

Subjects

Forty-two outpatients between 18 and 65 years old (mean±SD: 25.14±10.15) and met the DSM-IV criteria for OCD for 1 year or longer were included in the study (table 1).

Table 1. Patients screening data.

Characteristics	Sertraline	Clomipramine
N	18	18
M : F	9 : 9	7 : 11
Age mean±SD (years) (range)	23.10 ± 7.76 (10-43)	27.00 ± 11.78 (10-54)

Patients who had significant concomitant physical disease, suicidal tendency, a history of seizure or organic brain disorder, substance abuse within the previous sixth months, DSM-IV axis I diagnoses other than OCD and who had had medication for 1 month were not included in the study. All patients Y-BOCS scores were more than or equal to 20 and CGI-S scores were ≥ 4 . Baseline obsession, compulsion

items and total score of Y-BOCS and CGI-S scores were not significantly different (table 2).

Procedure

Eligible patients were randomized to receive 8 week of single-blind treatment with either fixed dose of sertraline (n=20) 50 mg/day or clomipramine (n=22) initially 50 mg/day and 150 mg/day after 1 week. No additional medication was given to the patients.

Patients were assessed at the baseline and after 2, 4, 6 and 8 weeks of treatment. Assessments were made by three specialists. The assessments of different investigators at baseline and at the end of the trial were not significantly different. The primary efficacy variables were the Y-BOCS and the CGI-S. Tolerability was assessed by recording spontaneous reports of adverse events at each visit. No additional laboratory tests and electrocardiogram were required.

Statistical analysis

Mean percentage changes between baseline and final visit in Y-BOCS total, obsession and compulsion items and CGI-S were analyzed using Mann-Whitney U test.

Changes from baseline in Y-BOCS and CGI-S at each visit were analyzed using Friedman two-way ANOVA. A Fisher's exact test was used to compare the incidence of adverse events between the two groups. Treatment group comparisons of patient's demographic characteristics and baseline severity measurements were done using χ^2 test and Wilcoxon test, respectively.

Group differences were analyzed using Wilcoxon test at baseline and each visit.

RESULTS

Thirty-six patients completed the trial. Four of the clomipramine and 2 of the sertraline patients dropped out because of severe side effects. There were no significant age, sex, Y-BOCS and CGI-S scores differences between sertraline (n=18; M:F, 9:9; mean age±SD = 23.10±7.76) and clomipramine group (n=18; M:F, 7:11; mean age±SD= 27.00±11.78) (Table 1).

Table II. Mean baseline and mean percentage change from baseline to final visit scores in efficacy outcome variable.

Efficacy Variable	n	Sertraline			n	Clomipramine			Between treatment p. value
		Baseline Score	Final visit score	Mean % change		Baseline Score	Final visit score	Mean % change	
Y-BOCS Total*	18	24.95	7.55	-69.06	18	23.55	7.14	-69.26	0.614
Obsession Items 1-5	17	13.10	4.45	-66.00	18	13.09	4.23	-66.66	0.410
Compulsion Items 6-10	18	11.85	3.10	-74.24	18	10.45	2.91	-71.06	0.869
CGI-Severity Of illness*	18	4.75	1.65	-65.75	18	4.86	2.18	-53.78	0.173

Efficacy

Table II presents the mean baseline percentage change from baseline to final visit scores for all patients with postbaseline efficacy data in the two treatments groups for each of the efficacy outcome measures.

Both of sertraline and clomipramine produced statistically significant differences in Y-BOCS and CGI-S scores at 2, 4, 6 and 8 weeks ($p < 0.001$). The mean percentage improvements in the total Y-BOCS score between sertraline and clomipramine group at the final visit were 69.06% vs. 69.26% ($p = 0.614$) and CGI-S ratings were 65.75% vs. 53.78% ($p = 0.173$) (fig 1).

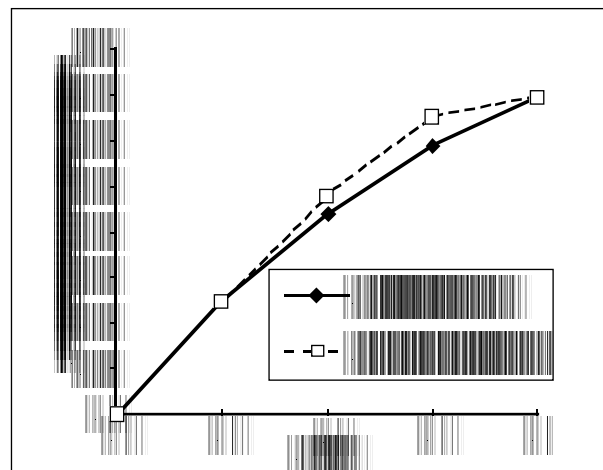
Six (33.3%) subjects markedly and 10 (55.6%) subjects moderately improved according to CGI-S, and there was no difference at 2 (11.1%) subjects on clomipramine group.

Six (33.3%) subjects markedly and 12 (66.7%) subjects moderately improved on sertraline group.

There were no differences on Y-BOCS and CGI-S scores between two groups at the end of the trial ($p > 0.05$).

Y-BOCS obsession and compulsion items also produced statistically significant decreases with sertraline and clomipramine treatment at 2, 4, 6 and 8

weeks ($p < 0.001$). At final visit there were no significant differences on obsession and compulsion items between sertraline and clomipramine groups. The mean percentage changes in the Y-BOCS obsession items (66.0% vs. 66.6%, $p = 0.410$) and compulsion items (74.2% vs. 71.1%, $p = 0.865$) were similar.

Figure 1. Mean Percentage change from baseline to the end of the trial in Y-BOCS total score by visit week.

Safety

Groups showed different side-effect profiles. The

Table III. Adverse events reported by 10% or more of patients in either treatment group during therapy.

	Sertraline (n=18)		Clomipramine (n=18)	
	n (%)		n (%)	
Headache	7 (38.8%)		Dry mouth	9 (50%)
Nausea	6 (33.3%)		Weight gain	9 (50%)
Irritability	2 (11.1%)		Constipation	5 (27.7%)
Tremor	2 (11.1%)		Yawning	5 (27.7%)
			Sedation	4 (22.2%)
			Dizziness	2 (11.1%)

overall proportion of patients spontaneously reporting adverse events was higher in the clomipramine group (72.2%) than in the sertraline group (38.8%) ($p < 0.05$).

Two of the sertraline and 4 of the clomipramine patients were dropped out. One of patients in both groups were dropped out because of the lack of efficacy and another one of sertraline and three of clomipramine patients were dropped out because severe side effects.

The most common adverse events reported by sertraline treated patients were headache 38.8%, nausea 33.3%, irritability 11.1% and tremor 11.1%, and in the clomipramine-treated patients, dry mouth 50%, weight gain 50%, constipation 27.7%, yawning 27.7, sedation 22.2% and dizziness 11.1 (table III).

DISCUSSION

OCD is now known as a chronic debilitating disorder that requires long-term, sometimes even life-long treatment (11).

The advantage of 5-HT selectivity in the treatment of OCD has been demonstrated in comparative trials. SSRIs have also been shown to be effective in the treatment of OCD independent of a patient's comorbid mood status.

The SSRIs appear to be associated with similar levels of efficacy to clomipramine in short-term treatment, but to have significant tolerability advantages.

In a double-blind study of clomipramine versus sertraline 10 % of the sertraline patients and 26% of the clomipramine patients were dropped out. Both groups had a significant improvement in symptoms, and the drugs had equivalent efficacy. A 1-year continuation study showed that the side effects of sertraline decreased over time. Thus, authors concluded that the tolerability of a drug is a key determinant of clinical utility in the treatment of OCD (8).

Our findings also show that efficacy of sertraline and clomipramine is equivalent and drop out rates of clomipramine are higher than sertraline.

According to Bissler, SSRIs appear preferable to clomipramine as the first-line treatment in most cases. While all SSRIs are effective in OCD, he questioned early studies that found that higher doses were needed than those used for depression. However, more recent studies have found that clomipramine is

often effective at 75-150 mg daily, a dose that reduces side effects(8). Other recent studies have found no difference in efficacy between low and high doses for sertraline and fluoxetine, although paroxetine does require slightly higher dosing. These new data are important for clinicians treating patients with OCD, since dropout rates increase for each drug as the doses increase(8,12).

In our study the doses of sertraline (50 mg/d) and clomipramine (initially 50 mg/day, 150 mg/day) were used. Clomipramine was started at smaller doses and reached 150 mg daily in one week in this study.

In a review of the efficacy of antidepressant drug treatment in patients with obsessive-compulsive disorder (OCD), using a meta-analytic approach, Piccinelli and colleagues showed that antidepressant drugs are effective in the short-term treatment of patients suffering from OCD (17). Although the increase in improvement rate over placebo was greater for clomipramine than for SSRIs, direct comparison between these drugs showed that they had similar therapeutic efficacy on obsessive-compulsive symptoms. Clomipramine and fluvoxamine had greater therapeutic efficacy than antidepressant drugs with no selective serotonergic properties; concomitant high levels of depression at the outset did not seem necessary for clomipramine and for SSRIs to improve obsessive-compulsive symptoms.

Two large meta-analyses comparing clomipramine and SSRIs showed that both were superior to placebo with a slight trend for greater effectiveness of clomipramine over SSRIs (5, 17). However, it was noted that studies followed patients in different differing time periods and placebo effects changed with time; patients' expectations may have increased over time as more information about OCD was disseminated. Also, studies varied in the level of severity of patients' symptomatology. In head-to-head studies of clomipramine and SSRIs, no difference in efficacy was found (12,13).

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 (11). In one-to-one comparative studies, clomipramine was 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, disconti-

uation rate in patients taking clomipramine was more than twice that in patients taking sertraline (26% vs. 11%) (8,10, 11,12).

Greist et al (5) compared the results from four large multicenter placebo-controlled trials of the serotonin transport inhibitors clomipramine hydrochloride (n= 520), fluoxetine hydrochloride (n= 355), fluvoxamine maleate (n= 320), and sertraline hydrochloride (n= 325) in the treatment of obsessive-compulsive disorder. All four agents were significantly more effective than placebo, with clomipramine significantly more effective than the other three treatments, which did not differ in effect size. A significantly greater percentage of patients treated with clomipramine were rated more or much more improved than patients treated with fluoxetine, fluvoxamine, or sertraline. And they concluded: while the results of this meta-analysis support the superiority of clomipramine, head-to-head, double-blind comparisons of these compounds would be the best test of comparative efficacy and tolerability.

Results from these multicenter trials indicate that all these drugs are more effective than placebo in tre-

ating OCD. However, meta-analytic techniques applied to the data from controlled trials of these drugs suggest that the effect size for clomipramine is somewhat larger than that of the selective serotonin uptake inhibitors.

Most of the studies find sertraline has equivalent efficacy with clomipramine, where as some other studies find that clomipramine (17) or sertraline (8) has better efficacy. Sertraline was found better-tolerated than clomipramine in several studies (6,8,12). In long-term treatment this tolerability and safety of clomipramine becomes more important.

Our results indicate that, at fixed doses, both clomipramine and sertraline showed a similar therapeutic efficacy in the 8 week treatment of OCD. While the drugs have different side effect profiles, clomipramine produced more side effects and dropout rate.

We concluded that with long-term or even life-long treatment appearing necessary for people with OCD, SSRIs would appear to be the treatment of choice in view of their tolerability and safety advantages compared with clomipramine.

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