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FLUVOXAMINE VERSUS CLOMIPRAMINE FOR OBSESSIVE COMPULSIVE DISORDER: A COMPARATIVE STUDY TO DETERMINE SAFETY AND EFFICACY OF THE DRUGS

Psychiatry

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ABSTRACT

Objective: The aim of this 12-week, blind randomized control comparative study was to determine the safety and efficacy of fluvoxamine and clomipramine in adult outpatients with obsessive-compulsive disorder (OCD). **Method:** 156 adult outpatients with DSM-IV OCD were randomly assigned into two groups to receive 100 to 300 mg of fluvoxamine CR (N=78) or Clomipramine (N = 78) once daily at bedtime for 12 weeks. Intent-to-treat, analysis of efficacy assessments with the Yale- Brown Obsessive Compulsive Scale (YBOCS), Clinical Global Impressions-Severity of Illness scale (CGI-S) was done. **Results:** 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) by LOCF analysis. Fluvoxamine CR and Clomipramine showed a significant (>35%) decrease in YBOCS total score beginning at week 2. This early response was sustained at all subsequent visits. At endpoint, there was a mean decrease of 11.65 ± 0.7 (44.89%) in the YBOCS total score compared with baseline in the fluvoxamine CR treatment group versus a mean decrease of 12.3 ± 0.7 (46.32%) in the clomipramine treatment group (p = .001). It was observed that FLV was better tolerated than CMI among subjects; patients treated with CMI had more anticholinergic side effects (dry mouth, constipation, and tremor) and premature withdrawals due to adverse events. CGI-S scores also showed a statistically significant improvement of 59.25% in FLV group and 55.14% in CMI group. **Conclusion:** The study show that both fluvoxamine and clomipramine has equivalent efficacy, wherein both the drugs start showing significant reduction in primary efficacy parameters: YBOCS and CSI-S scores since the end of second week. Treatment dropout rate was higher in the Clomipramine (24%) group than the fluvoxamine (17%) group. We concluded that with long-term or even life- long treatment appearing necessary for people with OCD, Fluvoxamine would appear to be the treatment of choice in view of their tolerability and safety advantages compared with clomipramine.

KEYWORDS

Obsessive-Compulsive Disorder, Fluvoxamine, Clomipramine, Efficacy, Tolerability, Side-effects.

INTRODUCTION

Obsessive-Compulsive Disorder (OCD) known as a chronic and debilitating mental health condition affecting millions of individuals worldwide. It is characterized by anxiety-provoking, intrusive obsessions that are followed by a repetitive compulsive actions to elevate the anxiety, causing a marked distress or significant functional impairment.[1,2].

Over the last two decades constant efforts have been made to improve the treatment for OCD, and the treatment has substantially due to the introduction of the selective serotonin (5- hydroxytryptamine [5-HT]) reuptake inhibitors (SSRIs), such as Fluoxetine, Fluvoxamine, Paroxetine, Sertraline, and Citalopram, which resulted in the symptom reduction in about 40% to 60% of OCD patients.[3]

Extensive research has demonstrated that OCD responds selectively to serotonergic agents and that desipramine a non-serotonergic antidepressants has little to no effects on OCD symptoms.[4,5] 5-HT system which is mainly involved in the pathophysiology of the disease is the main target receptor of these SSRI's. The selective response of OCD patients to these SSRIs has focused attention on the role of the 5-HT system.

For more than 2 decades, the 5-HT hypothesis has provided a frame of reference[6] for understanding the pathophysiology of OCD. Clomipramine, a tricyclic antidepressant that preferentially blocks 5-HT reuptake, compared to other tricyclics or placebo came out as a first evidence of effectiveness.[7-9] This evidence was subsequently confirmed by the superiority of SSRIs over other agents.[8–12]

OCD has a chronic course, a few patients achieve a complete symptom remission.[10] Most of the patients with OCD are kept on long term treatment regimens; So to achieve a high drug compliance it is very important to achieve substantial symptom relief, better drug tolerability, and a more convenient dosing regimen. 80% of patients have shown recurrence in symptom profile after the discontinuation of treatment results, even after when treatment course was administered for more than 2 years.[11] In one study, the risk of relapse was 2.7 times greater in patients who discontinued therapy compared with patients who remained on medication.[12]

Among the medications commonly prescribed for OCD, fluvoxamine and clomipramine have been established as effective options. Through this article we aim to study the long-term effectiveness of these two medications in the treatment of OCD, with a comparative analysis of their efficacy, side effects, and overall tolerability by exploring the latest research findings and clinical insights.

Fluvoxamine belonging to the class of drug Selective serotonin reuptake inhibitor which blocks the reabsorption of serotonin by presynaptic neurons, increasing the serotonin 5-HT in synaptic clefts. It has proven to be effective in a number of double-blind, controlled treatment studies in OCD,[13,14,15,16] social anxiety disorder,[17] panic disorder,[18,19] chronic posttraumatic stress disorder,[20] and major depressive disorders.[21]

Clomipramine is a tricyclic antidepressant with potent serotonin reuptake inhibition[22]; 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. In addition, various meta-analytic studies.

METHOD:

Study Design

This is hospital based, randomized controlled study comparing the efficacy and safety of fluvoxamine CR (100–300 mg/day) with clomipramine (100-300 mg/day) for a 12-week treatment period in subjects with OCD. The study was approved by the institutional ethics committee. Initially a 1-week placebo administration was given to patients who were eligible under the criteria of selection, then through blinded selection subjects were randomly assigned to receive either fluvoxamine CR or clomipramine. Subjects who were assigned to receive fluvoxamine CR, began at a bedtime dose of 100 mg and were increased weekly as tolerated in doses of 50-mg increments to a bedtime dose between 100 and 300 mg/day over the first 6 weeks of treatment; Similarly for the subjects who were assigned to receive dose of clomipramine, began at a bedtime dose of 100 mg and were increased weekly as tolerated in doses of 50-mg increments to a bedtime dose between 100 and 300 mg/day over the first 6 weeks of treatment there- after, the dose was to remain constant for the duration of the randomized control trial period. Subjects unable to tolerate the doses of 100 mg in both subject groups of fluvoxamine and clomipramine during the first week of treatment were discontinued from the study. After the completion of 1 week and until the end of 6 weeks, the dose could be decreased in case of an intolerable adverse event, where in the usual prescription on 2 capsules can be decreased to 1 capsule at bedtime in both subject groups. In case of an intolerable adverse event which required a dose decrease after week 6, the subject was discontinued from the study. It should be noted that No increase in dose was allowed if it was reduced once. Efficacy and adherence to study regimen was assessed by counting the number of pills, patients

who took less than 80% or more than 120% of a prescribed dosage during the interval in between the two visits, and if such was repeated on 2 or more occasions then they were considered no adherent and were discontinued from the study. During the randomized control treatment phase, efficacy of the patients and treatment regimen was assessed using the Yale-Brown Obsessive Compulsive Scale (YBOCS)[23] and the Clinical Global Impressions-Severity of Illness (CGI-S).

YBOCS and CGI-S assessments were performed at the time of screening of the patients, on day 1 (baseline), and subsequently at the end of weeks 2, 4, 6, 8, 10, and 12; Routine investigations done at every visit included vital signs, weight, adverse events, and concomitant medications. An electrocardiogram (ECG) and physical examination were performed on the day 1 of screening and on week 12 visits.

Subject Selection

Male and female patients presented to the outpatient department aged 18 years or older were eligible, if they met the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV) criteria for OCD and the diagnosis was confirmed through the Structured Clinical Interview for DSM-IV.[24] A Total of 180 patients were selected out of which 156 were taken under study after the final evaluation.All patients YBOCS 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 1. Patients' Selection Data

Characteristics	Fluvoxamine	Clomipramine
No. of patients	78	78
Male: Female ratio	10 : 9	4: 3
Mean of AgeSD (years)	24.15 ± 7.76	25.95 ± 2.3
(range)	(21-54)	(20-56)

Subjects having any other current primary DSM-IV diagnosis were excluded from the study. Also subjects who were considered to be at significant risk of suicide; subjects with serious medical conditions, clinically significant ECG abnormalities, or clinically significant laboratory abnormalities; Pregnant and lactating women were excluded. Subjects who received electroconvulsive therapy within 90 days prior to or during the study were excluded. After a complete disclosure of the study pattern was provided to the subjects, a written informed consent was obtained from all patients and their first informant.

Statistical Methodology

The study was carried forward and efficacy parameters were kept in records with the intention to treat the patient and achieve highest efficacy with respective drugs. Subjects were selected for the randomized control trial, and were divided randomly into two study groups and subjects from both the groups were started with the desired drug and desired dosage as a study medication. Baseline values of efficacy parameters were recorded to understand the severity of the parameters under evaluation, also post evaluation efficacy parameters were recorded to under the difference in the values at the end of the study. Statistical analyses were performed using data from visit wise and the last-observation-carried-forward (LOCF) algorithms. Statistical tests that were taken were 2-sided and were considered statistically significant if $p < .05$. The changes from baseline to endpoint in YBOCS and CGI-S scores using LOCF, were analyzed using an analysis of variance model with terms for treatment and pooled center. Responder and remitter analyses were implemented by Fisher exact test and were considered as significant if $p < .05$.

RESULTS

For the purpose of the study total of 156 patients were selected and through a blinded randomized selection they were assigned into two groups: 78 subjects in the fluvoxamine CR treatment group and 78 subjects in the clomipramine group. Precautions were taken specifically so that there were no statistically significant differences between the 2 groups in order of demographics or disorder characteristics at baseline; (n=78; M:F, 10:9; mean age±SD = 24.15±7.76; Baseline YBOCS=25.95±0.3;CSI-S=4.5±0.3) and Clomipramine group (n=78; M:F, 4:3; mean age±SD= 26.55±9.78; Baseline YBOCS=26.55±0.3; CSI-S=4.8±0.3) (Table 1).

From the subjects that were randomly assigned in two groups, finally 65 in the fluvoxamine CR group and 60 in the clomipramine group completed the study at the end of the 12th week. Thirty-one subjects were excluded from the study analyses because either no study medication was taken or faced severe side effects within the drug profile. The mean daily dose of fluvoxamine CR over the duration of the study was 200 mg and at the endpoint was 300 mg, with comparatively equivalent doses clomipramine of 150 mg and 250 mg, respectively.

Total of 125 subjects had completed the trial. 13 of the Fluvoxamine CR group and 18 of the Clomipramine group subjects faced severe side effects within the drug profile and had to discontinue the treatment. Table 2 represents the mean baseline scores of the subjects for efficacy variables such as YBOCS scores; Obsession component scores; Compulsion component scores; CSI-S ratings.

Table 2. Mean baseline and mean percentage change from baseline to final visit scores in efficacy outcome variable.

Efficacy Variable	n	Fluvoxamine Baseline Final Score visit score	Mean % n change	Clomipramine Baseline Final Score visit score	Between Mean % treatment change p. value
Total*	78	25.95 14.30	44.89 78	26.55 14.25	-46.32 0.614
Obsessi on					
Items 1-5	78	14.65 7.40	-49.48 78	14.95 7.35	-50.83 0.510
Compul sion					
Items 6-10	78	11.30 6.9	-38.17 78	11.60 6.9	-40.12 0.669
CGI-Severity					
Of illness*	78	4.86 1.98	-59.01 78	4.86 2.18	-55.14 0.173

It also represents the mean percentage change from baseline to final visit scores in the above mentioned efficacy parameters. It also compares the post baseline efficacy data in the two treatments groups for each of the efficacy parameters. Both of Fluvoxamine CR and Clomipramine treatment groups recorded statistically significant reduction in Y-BOCS and CGI-S scores at 2, 4, 6 and 8 weeks ($p<0.001$). 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) by LOCF analysis; YBOCS decreased from 25.95 to 14.3 with FLV vs 26.55 to 14.25 with CMI). It was observed that FLV was better tolerated than CMI among subjects; patients treated with CMI had more anticholinergic side effects (dry mouth, constipation, and tremor) and premature withdrawals due to adverse events. CGI-S scores also showed a statistically significant improvement of 59.25% in FLV group and 55.14% in CMI group.

Twenty-three (33%) subjects markedly and forty four (63.2%) subjects moderately improved according to CGI-S, and there was no difference at 8 (11.1%) subjects on clomipramine group. Twenty-five (33.7%) subjects markedly and forty nine (66.7%) subjects moderately improved on Fluvoxamine group. There were no extreme 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 recorded at 2, 4, 6 and 8 weeks showed statically significant reduction in symptoms with the augmentation of fluvoxamine and clomipramine treatment in both groups ($p<0.001$). The records of obsession and compulsion items at the final visit showed a significant reduction in mean percentage change which was similar in both treatment groups. The mean percentage changes in the Y-BOCS score (FLV vs CMI):YBOCS Total (44.89 vs.46.32, $p=0.614$) obsession items (49.48% vs. 50.83, $p=0.510$) and compulsion items (38.17% vs. 40.12%, $p=0.669$) were similar.

The number of patients reporting adverse effects was much higher in the clomipramine group (62.4%) as compared to fluvoxamine study group (36.8%) ($p<0.05$).

Table 3. Adverse events reported by 10% or more of patients in either treatment group during therapy.

	Fluvoxamine (n=78) n (%)		Clomipramine (n=78) n (%)	
Headache		30(38.8%)	Dry mouth	56(62%)
Nausea		29(37.3%)	Weight gain	39(50%)
Irritability		8(11.1%)	Constipation	22(29.4%)
Tremor		8 (11.1%)	Yawning	21 (27.7%)
Insomnia		23(30.1%)	Sedation	25(32.2%)
Nervo usness		5(32.5%)	Dizziness	24(31.1%)

Total of 31 patients dropped out from the study population, 13 (17%) patients from the Fluvoxamine group and 18 (24%) from the Clomipramine group. Three patient from each group were dropped because of irregularity in the treatment course. 10 patients from fluvoxamine group and 15 patients from clomipramine left the treatment in between because of severe adverse effects. The most common adverse events reported by Fluvoxamine treated patients were insomnia (30.1%); headache (38.8%), nausea (37.3%); irritability (11.1%); nervousness (32.5%) and tremor (11.1%); and in the clomipramine-treated patients, dry mouth (72%); weight gain (50%); constipation (29.4%); sedation (32.2%) and dizziness (39.1%) (Table 3)

DISCUSSION:

Obsessive compulsive disorder is a chronic debilitating disorder, often known for its long-term, sometimes even life-long treatment in some patients[25]. Many multi-centre comparative trails have shown the 5-HT selectivity in the treatment of OCD to be advantageous over the non-selective ones[6,7-9]. SSRIs have proven to be effective in the treatment of OCD independent of a patient's comorbid mood status[8-12]. In the short term treatment regimen SSRIs proved to have similar efficacy levels in comparison with clomipramine, but had much significant tolerability than clomipramine.

Number of double-blind comparative studies have shown fluvoxamine maleate to be better effective in the treatment of number of disorders such as OCD,[13,14,15,16] social anxiety disorder,[17] panic disorder,[18,19] chronic posttraumatic stress disorder,[20] and major depressive disorders.[26–30] Fluvoxamine maleate is advised to be taken in a twice daily schedule. A new, controlled-release (CR) formulation of fluvoxamine maleate, fluvoxamine CR, with different pharmacokinetic properties, has already been developed. With the administration of fluvoxamine CR once daily there could be an increase in patient compliance in the long-term therapy, and reduced fluctuations in plasma concentration may be associated with fewer side effects and greater symptom improvement.

U.S.Food and drug administration have approved and proved the efficacy and safety of Fluvoxamine and other SSRI's in the treatment of OCD .[13,14,31-35.] With fewer severe side effects and efficacy similar to that of clomipramine, SSRIs may improve the treatment compliance.[32,15.]

Clomipramine and fluvoxamine were compared in three studies and have been found equally efficacious in the treatment of OCD.[15,16,36] In a 10-week multicenter study, Freeman et al.[15] compared the effects of fluvoxamine a with the effects of the same dose range of clomipramine. A more than 30% reduction in Y-BOCS scores was recorded in both treatment regimen. Two treatments groups statistically showed no difference in efficacy profile; however, fluvox- amine was found to be more effective in patients with a disorder of duration greater than 1 year. There was difference in the side effect profile of 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 by Koran et al., [16] similar results were found like the previous study, where in fluvoxamine and clomipramine were also found to be equally efficacious. During the study 17% subjects in Clomipramine group and 14% in Fluvoxamine group dropped out of the trail because of treatment-related adverse events. As observed 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 had different side effects within the respective drug profile. Fluvoxamine produced a higher incidence of insomnia, nervousness, and nausea, while dry mouth, postural hypotension, and dizziness were more often observed with clomipramine.

Although the two studies showed comparatively similar efficacy profile for both fluvoxamine and Clomipramine, the study had a sizable difference in patient profile and also the study sample selected for the trail was comparatively small.

Abramowitz's meta-analysis[37] study showed that clomipramine had moderately superior efficacy rates than all the SSRI's but it should be noted that this was possible after the side effect profiles were adjusted with drug dosage.

In the Eddy KT et al. study,[38] even here again, clomipramine had greater effective results than the other SSRIs with the notice that the studies considered are earlier reports and there was a high dropout rate. Greist JH, Jefferson JW, et al.(1995)[39] According to the first meta-analytic study conducted on the anti-obsessional medications compared the results from four large multicenter placebo-controlled trials of the serotonin transport inhibitors.

At that time it was found that clomipramine was significantly more effective than other SSRI selective for 5HT reuptake inhibition, when compared with the placebo. 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, he- ad-to-head, double-blind comparisons of these com- pounds would be the best test of comparative efficacy and tolerability.

Piccinelli M, Pini S[17.] and colleagues through their meta analytic approach reviewed the efficacy of antidepressant drug used in the treatment of patients with obsessive-compulsive disorder (OCD), It was observed that in the short-term treatment antidepressant drugs are effective. Interestingly clomipramine showed an increased in improvement rate than other SSRI's in comparison to placebo. In the direct comparison between these drugs all showed the similar therapeutic efficacy on the obsessive-compulsive symptoms. Clomipramine and fluvoxamine had greater therapeutic efficacy than antidepressant drugs with no selective 5HT reuptake inhibition properties.

Along with it's SNRI properties, clomipramine has anti- cholinergic, antihistaminergic, and anti–adrenergic effects. Clomipramine mainly acts by blocking the receptors in the cholinergic, histaminergic, and adrenergic system which proves it's clinical side effect profile in patients. M_1 receptor inhibition results in constipation, blurred vision, dry mouth, and drowsiness; H_1 receptor inhibition results in weight gain and drowsiness; α_1-adrenergic receptor inhibition results in dizziness and decreased blood pressure. Over the time some patients may become habituated to these side effects, while others cannot tolerate this side effect profile, resulting in reduced compliance.

CONCLUSION:

Our study analysis of safety data showed that fluvoxamine CR was safe and well tolerated in the dosage range of 100 to 300 mg/day over the 12-week treatment period as compared to the Clomipramine treatment in the dose range of 100 to 300 mg/day. These findings are similar to the study done in the past to compare the efficacy and tolerability of these two drugs.[15,16,39,40]

High medication compliance range in fluvoxamine group (83%) proves that fluvoxamine is better tolerated than clomipramine group(76%) in long term treatment course. Also treatment dropout rate was higher in the Clomipramine group than the fluvoxamine group. Even this finding is similar to the finding done in the previous studies[10,15,16].

Most of the studies show that both fluvoxamine and clomipramine has equivalent efficacy, wherein both the drugs start showing significant reduction in primary efficacy parameters, YBOCS and CSI-S scores since the end of second week. The same efficacy for the other SSRI's was comparatively achieved at later intervals in previous studies when they were compared with placebo trails[14,34,35].

Subjects taking fluvoxamine reported symptoms such as headache, insomnia, nausea; irritability; nervousness and tremor; and in the

clomipramine-treated patients anticholinergic side effects were reported more such as dry mouth; weight gain; constipation; sedation and dizziness(table 3) in the long term treatment course.

We concluded that with long-term or even life- long treatment appearing necessary for people with OCD, Fluvoxamine would appear to be the treatment of choice in view of their tolerability and safety advantages compared with clomipramine, keeping in mind that both have same efficacy profiles and choice should be made taking into account patient preference and safety.

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