Original Article

Comparison of Efficacy and Tolerability Between Sertraline and Fluoxetine in Patients With Major

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ABSTRACT

Objective: Aim of this study was to compare the efficacy and tolerability between Sertraline and Fluoxetine to determine suitable treatment of major depression in Pakistani population.

Place and Duration: This study was conducted in the outpatients department of psychiatry, Jinnah Postgraduate Medical Centre, Karachi. The duration of the study was 24 weeks conducted from January – December 2008.

Materials and Methods: 100 male and female patients between 18 to 65 years of age with a diagnosis of major depressive disorder were selected. Two groups A1 and A2 were made of 50 patients each. Group A1 received Tab Sertraline while Group A2 received Cap Fluoxetine daily for 24 weeks after going through screening tests and diagnostic evaluation. Efficacy was evaluated by using 21 item Hamilton Depression Rating Scale (HDRS) and 20 item Self Reporting Questionnaire (SRQ). The patients were asked to attend the OPD every 15 days. Side effects and compliance of the patients was noted at each visit.

Results: The results showed that both groups showed significant improvement in depression from week 0 to week 24 with minimal adverse effects. Compliance of the patients in both groups was good. Although HDRS and SRQ scores were significantly reduced in both groups, it was noted that Tab Sertraline improved the symptoms earlier than Cap Fluoxetine.

Conclusion: It can be concluded that both sertraline and fluoxetine are efficacious in major depression causing few adverse effects but because sertraline improves symptoms earlier and it is cost effective it may be preferred to fluoxetine.

Key Words: Major depression, Hamilton Depression Rating Scale, Self Reporting Questionnaire, Bradford Somatic Inventory.

INTRODUCTION

Depression is common is all regions of the world. It constitutes substantial proportion of the global burden of disease and is projected to form the second most common cause of disability by 2020[1,2].

In Pakistan the magnitude of mental illness is serious. The prevalence of depressive disorder is the highest. Besides other social evils, these mental morbidities are responsible for the high suicide rate as noted recently[1,3].

Social adversity and relationship problems are major risk factor for depressive disorder in Pakistan. The prevalence of depression in Pakistan is 33% that is every third Pakistani is expected to be suffering from depression. Rates for depressive disorder are reported to be higher in women than men that is consistent with the estimates from western countries[1,4].

Depression is the eighth leading cause of death in the United States. Fortunately, about 80% to 90% of depressed patients can be treated successfully. About 65% of patients ultimately respond to antidepressant drug therapy and completely recover[5].

Although very common, depression is often ignored, misdiagnosed and left untreated. Such inattention can be life-threatening: major depression in particular has a high suicide rate[6].

Fortunately, there are a number of efficacious medications to choose from when treating a depressed patient. The most significant class of antidepressants marketed in recent years is the selective serotonin reuptake inhibitors (SSRIs). Primary use for the SSRIs is unipolar major depression. Among the SSRIs, there are more similarities than differences. Nevertheless, there are differences between SSRIs that could be clinically significant [7].

The objective of this study is to describe the significant differences in efficacy and tolerability between two most commonly used SSRIs that are fluoxetine (Prozac) and sertraline (Zoloft) and to identify their role in treatment of major depression. SSRIs are potent inhibitors of serotonin reuptake. Three neurotransmitter deficiency syndromes are associated with depressed mood. These include a serotonin, a norepinephrine, and a dopamine deficiency syndrome. Fluoxetine has effects on serotonin and norepinephrine while sertraline has effects on serotonin and dopamine[7].

Fluoxetine & Sertraline

These drugs work by preventing the reuptake of neurotransmitter, serotonin, by nerve cells after it has been released. Since uptake is an important mechanism for removing released neurotransmitters and terminating their actions on adjacent nerves, the reduced uptake causes increased free serotonin that stimulates nerve cells in the brain. In USA alone fluoxetine is the third most prescribed antidepressant. Sertraline in 2007, was the most prescribed antidepressant in US[8].

Onset of Activity: the mood-elevating effect of antidepressant medication usually begins about 1 to 2 weeks after initiation of treatment. The clinical rule of thumb is that a patient must be treated with an adequate dosage for at least 6 weeks before the clinician considers changing the treatment[5].

MATERIALS AND METHODS

This study was conducted in the outpatients departments at the Department of Psychiatry, Jinnah Post Graduate Medical Centre, Karachi and Department of Psychiatry, PNS Shifa Hospital, Karachi in patients diagnosed with major depressive disorder.

The proposed study was spread over a period of 24 weeks. All the patients fulfilling the following inclusion and exclusion criteria were included in the study:

Inclusion Criteria

1) Male and female outpatients, 18 to 65 years of age.
2) The patients had to meet the DSM-IV criteria for major depressive disorder, single episode or recurrent.

Exclusion Criteria

1) Failure to respond to more than one adequate trial of an approved antidepressant medication for the current episode of depression.
2) Presence of a primary psychiatric illness other than major depression.
3) Pregnant and breast-feeding women.
4) Previous head injury.

Subject Recruitment:

Despite extensive research to find a diagnostic test, the diagnosis of depression remains clinical. The criteria for the diagnosis of major depression are the core signs and symptoms. A clinician's index of suspicion about the diagnosis of depression should be raised if a patient presents with a chief complaint of fatigue, pain, sleep disturbances, anxiety, irritability, or gastrointestinal problems[5].

100 patients were enrolled in this study, 50 patients received tablet sertraline 50 -200 mg daily (group A1), while 50 patients received capsule fluoxetine 20 -80 mg daily (group A2). Both these groups were compared for efficacy, compliance and tolerability after going through screening tests and diagnostic evaluation by Psychiatrists.

All subjects gave written consent before induction in the study[9].

All subjects were at least 18 years of age, conversant in Urdu, and willing to be available for participation in the 24-week study[10].

On enrolment, each patient received complete physical examination, and laboratory tests were also performed.

All registered patients were advised to attend the respective OPDs every 2 weeks until the end of this study.

Psychiatric diagnoses based on DSM-IV criteria were determined by a consensus of at least two psychiatrists using the Structured Clinical Interview for DSM IV [9,10,11].

Evaluation of Subjects:

Psychiatrists have developed a variety of ways to rate how a person is feeling more objectively using psychiatric "RATING SCALES".

Measures used for the initial evaluation of subjects included;

a. Self-Reporting Health Questionnaire (SRQ) [12,13].
b. Bradford Somatic Inventory (BSI)[14,15].
c. Hamilton Depression Rating Scale (16),(17),(18).

Efficacy was evaluated by using the 21 item version of the Hamilton depression scale (HDRS) and 20 item Self Reporting Questionnaire (SRQ).

Hamilton Depression Rating Scale (HDRS) has been the gold standard for the assessment of depression for more than 40 years.

Unlike other depression measures, the HDRS was developed in a medical setting and, for more than 30 years, used concurrently with antidepressant medication to evaluate treatment response. The HDRS has retained this function and is now the most commonly used measure of depression[16,18].

The total HDRS score provides an indication of the level of a patient's depression and over time, provides a valuable guide to our patient's progress.

In general, the higher the total score, the more severe is the depression.

HDRS Score: Level of depression:

10 - 13 Mild

13 – 17 Mild to Moderate

> 17 Moderate to severe

The patients should be assessed at 2 weekly intervals following the initial assessment.

SRQ & BSI

Both SRQ and BSI are effective screening instruments in detection of probable psychiatric cases particularly in case of women. Both the instruments use a simple Yes/No format, which has been found to be easier to comprehend by our population as compared to more complicated response scales.

We have used SRQ scale for efficacy at the beginning and at the end of therapy. SRQ is a 20 item scale with optimal threshold score Males - ≤ 4, Females - ≤ 8.
Bradford Somatic Inventory (BSI) is a 44 item scale with threshold score 25/26 and was used at the beginning of the study.
Subjects had to have normal physical examination and laboratory results, including a complete blood count with Hb%, ESR, Blood sugar (R), AST, ALT. All laboratory tests were repeated at the end of the study period.
Medication compliance was documented at each visit by a count of returned blister packs.
Safety was assessed by physical examination, clinical laboratory tests at screening and at endpoint. At each visit, patients' vital signs were recorded. Subjects were asked about adverse events at each visit and a Utvalg for Kliniske Undersogelser (UKU) side effect scale was used. Adverse effects were divided into psychic adverse effects, neurological adverse effects, autonomic adverse effects and other adverse effects[19].

RESULTS

Statistical comparison was performed by using chi-square for qualitative variables and student t-test, or analysis of variance (ANOVA) for quantitative variables according to treatment within Sertraline and Fluoxetine. In all statistical analysis only p-value <0.05 was considered significant.

Subjects
Out of 100 patients 18% were male (10% in A1 and 8% in A2) while 82% were female (40% in A1 and 42% in A2). Mean age in group A1 was 42.2 years while in group A2 it was 40.2 years. Laboratory tests like BMI, Hemoglobin, ESR, RBS, AST and ALT were performed at the initial induction and then at the end of the 24 week study period. It was seen that between wk 0 and wk 24 no statistically significant difference was noted in these tests except for AST and ALT that were increased significantly from wk-0 to wk-24 ($p<0.05$) (Table No. I).
Mean scoring level of depression according to HDRS was 24 with 22.2 in A1 group (Sertraline group) and 25.8 in A2 group (Fluoxetine group). According to SRQ and BSI the mean levels are 9.4 (9.2 for A1 and 9.7 for A2) and 21.7 (21.4 in A1 and 22.1 in A2) respectively (Table No.2).
At wk 0 the number of patients was 50 in each group that was reduced to 46 in group A1 and 47 in group A2. The relative change from baseline on the HDRS - 21 score was calculated. The responder rate was defined as a reduction of at least 50% on the HDRS - 21 score. Remission was defined as a reduction in HDRS - 21 to 9 or less. After treatment at wk 24 group A1 showed highly significant improvement in HDRS scores, so was the case with group A2 that also showed highly significant improvement at the end of the study period with mean values reducing from 22.2 in Group A1 to 10.7 and in Group A2 from 25.8 to 14.1 with p-value of 0.001 (Table No.3 & 5).
The tolerability and adverse effects were recorded and divided into psychic adverse effects, neurological adverse effects, autonomic adverse effects and other/misc adverse effects. All adverse effects were noted starting from wk 2 and then subsequently every 2 weeks until the end of the study period at 24th week (Table No.6).

Table No. I: Baseline parameters of unipolar depression according to treatment groups (Sertraline A1 vs Fluoxetine A2)

Parameters		SSRIs (n=100)			P-Value
		Overall all (n=100)	Group A1 (n=50)	Group A2 (n=50)	Group A1 vs. A2
Gender	Male	18	10 (20%)	8 (16%)	0.603
	Female	82	40 (80%)	42 (84%)	
Age in years	Mean ± S.D	41.2 ± 9.0	42.2 ± 9.7	40.2 ± 8.4	0.278
BMI	Mean ± S.D	26.9 ± 3.6	27.2 ± 2.9	26.4 ± 2.7	0.165
Hemoglobin	Mean ± S.D	11.4 ± 1.5	11.9 ± 1.6	10.8 ± 1.3	0.001
ESR	Mean ± S.D	17.1 ± 4.9	14.2 ± 4.3	20.0 ± 3.5	0.001
Random Blood Sugar	Mean ± S.D	120.7 ± 17.8	123.5 ± 21.9	117.8 ± 11.9	0.105
AST	Mean ± S.D	22.4 ± 8.8	19.5 ± 6.7	25.3 ± 9.7	0.001
ALT	Mean ± S.D	19.9 ± 4.9	20.6 ± 5.2	19.3 ± 4.5	0.166

Group A1 = Sertaline, Group A2= Fluoxetine

Table No.2: Laboratory findings at Wk-0 and Wks-24 in both groups

Parameters	SSRIs (n=100)							
	Group A1 (n=50)				Group A2 (n=50)			
	Wk - 0		Wks - 24		Wk - 0		Wks - 24	
	No	Mean ± S.D	No.	Mean ± S.D	No.	Mean ± S.D	No.	Mean ± S.D
BMI	50	27.2 ± 2.78	46	27.4 ± 2.91	50	26.3 ± 2.73	47	26.4 ± 2.64
Hemoglobin	50	11.9 ± 1.61	46	12.3 ± 1.52	50	10.9 ± 1.27	47	11.4 ± 1.09
ESR	50	14.2 ± 4.34	46	18.3 ± 4.88	50	20.0 ± 3.53	47	21.8 ± 4.45
RBS	50	124 ± 21.8	46	122 ± 6.7	50	118 ± 11.9	47	122 ± 6.7
AST	50	19.5 ± 6.7	46	25.8 ± 5.6	50	25.3 ± 9.7	47	25.9 ± 5.6
ALT	50	20.6 ± 5.2	46	35.5 ± 10.1	50	19.3 ± 4.5	47	40.9 ± 11.3

Group A1 = Sertraline, Group A2= Fluoxetine

Only AST and ALT were statistically significant from Wk-0 to Wk-24 $p<0.05$ in group A1 while only ALT was significantly changed ($p<0.05$) from Wk-0 to Wk-24 in group A2.

Table No.3: Level of depression according to HRSD, SRQ and BSI with SSRIs in both groups

Level of depression		SSRIs (n=100)			P-Value
		Overall all (n=100)	Group A1 (n=50)	Group A2 (n=50)	Group A1 vs. A2
HRSD	Mild to Moderate (13-17)	7	6 (12%)	1 (2%)	0.050
	Severe (>17)	93	44 (88%)	49 (98%)	
	Mean ± S.D	24.0 ± 4.6	22.2 ± 4.1	25.8 ± 4.4	0.001
SRQ	Normal (M<=4 or F <=8)	27	15 (30%)	12 (24%)	0.499
	Abnormal (M>.4 or F>8)	73	35 (70%)	38 (76%)	
	Mean ± S.D	9.4 ± 1.8	9.2 ±1.7	9.7 ± 1.9	0.213
BSI	Mean ± S.D	21.7 ± 2.6	21.4 ± 2.3	22.1 ± 2.7	0.150

Table No.4: Level of depression according to HRSD from Wk - 0 to Wks -24 in Group A1 and A2), values in Mean, S.D

HRSD	SSRIs					
	Group A1			Group A2		
	No.	Mean	S.D	No.	Mean	S.D
0	50	22.2	4.1	50	25.8	4.4
2	50	21.6	4.2	50	24.9	4.3
4	50	18.9	3.6	50	22.7	4.4
6	49	16.4	3.9	50	21.1	4.3
8	49	15.2	3.9	50	18.7	3.8
10	48	14.3	4.0	49	17.3	3.9
12	48	13.5	3.7	49	16.0	3.7
14	47	12.9	3.5	49	15.5	3.7
16	47	12.5	3.4	48	15.1	3.4
18	47	12.0	3.2	48	14.8	3.5
20	47	11.6	3.2	47	14.6	3.6
22	46	11.0	3.0	47	14.4	3.8
24	46	10.7	3.0	47	14.1	4.1

Group A1 = Sertraline, Group A2= Fluoxetine. HDRS (Hamilton Rating Scale for depression)

Sertraline vs. Fluoxetine

Improvement in depression during the 24 wk study, measured by Hamilton depression scale and Self Reporting Health Questionnaire did not differ significantly between the two groups. Gradual improvement was seen from 2nd week onwards with highly significant improvement in both scores at the end of treatment in both drug groups.

Compliance in both groups was more than 90% and no difference was noted between the 2 groups.

When adverse effects were compared it was seen that in psychic adverse effect, decreased duration of sleep was most commonly seen with Fluoxetine group while in Sertraline group sleepiness and increased duration of sleep were most common. In neurological adverse effects tremors were most often seen with Sertraline group while with Fluoxetine paresthesias were most commonly observed. In autonomic nervous system, nausea was the most commonly observed adverse effects seen maximally with both drug groups. Weight loss was seen more with Sertraline group while headache was seen with both groups (Table No.6).

Table No.5: Comparison of Hamilton Rating Scale for Depression (HDRS) and Self Reporting Questionnaire (SRQ) in both groups at Wk 0 to Wks-24 in SSRIs

Parameters		Overall all (n=100) Mean ± S.D	Group A1 (n=50) Mean ± S.D	Group A2 (n=50) Mean ± S.D
HRSD	Wks – 0	24.0 ± 4.6	22.2 ± 4.1	25.8 ± 4.4
	Wks – 24	12.4 ± 3.9	10.6 ± 3.0	14.1 ± 4.1
	P-Value	0.001	0.001	0.001
SRQ	Wks – 0	9.4 ± 1.8	9.2 ± 1.8	9.7 ± 1.9
	Wks – 24	7.2 ± 1.6	6.7 ± 1.2	7.6 ± 1.8
	P-Value	0.001	0.001	0.001

Group A1 = Sertraline, Group A2= Fluoxetine

Table No.6 : Most Common Treatment Emergent Adverse Effects: Incidence in Clinical Trial between group A1 and A2

	A1 (Sertraline)						A2 (Fluoxetine)					
Body system/Adverse event	**(n = 50)**						**(n = 50)**					
	Wk 4	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**
Psychic Disorders												
↓ed duration of sleep	5	5	5	5	4	4	7	6	7	4	4	4
Asthenia	5	5	3	4	4	4	2	2	2	2	2	2
↑ed duration of sleep	6	5	2	3	3	3	3	3	3	2	2	2
Sleepiness	4	6	4	5	4	5	3	3	3	1	1	1
Tension	2	2	3	2	1	1	2	1	1	1	1	1
Neurologic Disorders												
Dystonia	2	2	1	0	0	0	1	1	1	1	1	1
Paresthesias	5	5	2	1	1	1	7	7	6	6	6	6
Tremors	4	4	4	1	1	1	1	0	0	0	0	0
Autonomic Nervous System Disorders												
↑ed salivation	2	2	3	3	3	3	2	1	1	1	1	1
Nausea	10	9	2	0	0	0	8	11	4	3	2	2
Orthostatic dizziness	2	2	5	3	3	3	2	2	3	3	3	3
↑ed sweating	2	4	4	6	5	5	3	2	3	6	6	6
Constipation	0	2	2	2	2	3	4	7	1	1	1	1
↓ed salivation	0	0	0	1	1	1	3	3	6	5	5	5
Palpitations	1	1	1	2	3	3	0	4	1	2	3	3
Other Disorders												
Weight loss	0	1	2	4	6	5	0	0	1	1	2	3
Headache	3	0	0	1	1	0	4	3	1	1	0	0
Weight gain	0	0	0	1	1	2	0	0	1	1	1	1

DISCUSSION

The use of antidepressant medications and the resulting costs have increased dramatically in recent years, partly because of the introduction of selective serotonin reuptake inhibitors (SSRIs).

This is the first reported independent study comparing selective serotonin receptor blockers like Sertraline and Fluoxetine in Pakistani population suffering from major depression.

This study shows that females suffer from depression much more than males and the average age lies between 40 yrs and 45 years that is coinciding with the study of Naqvi in 2007 (20).

The clinical response with both drugs was excellent with minimal adverse effects.

Although HDRS scores were highly significantly reduced from week 0 – week 24 in both groups with p value <0.001 but it was seen that improvement with group A1 occurred earlier than group A2. In both groups there is a gradual improvement throughout the 24 week study period.

With SRQ scores it was noted that both groups were again highly efficacious at the end of the study period with p value <0.001.

4 patients in group A1 did not complete the study period because of adverse effects or for the reason that there was no improvement in their symptoms. 3 patients in group A2 did not complete the study for the same reasons. Nausea was the most common adverse effect leading to discontinuation of treatment.

Patient compliance was not a significant problem in any of the groups.

When efficacy of Sertraline was compared with Fluoxetine, it was seen that Sertraline was numerically better than Fluoxetine but this was not statistically significant. Both drugs caused a highly significant improvement in HDRS scores with remission in the disease.

Both Sertraline and Fluoxetine are highly and almost equally efficacious as seen by the HDRS and SRQ scales.

This study is in accordance with the study of Fava and Rosenbaum et. al. (21). who compared these drugs and found that patients demonstrated similar baseline to endpoint improvement in HAMD-17 scores. Each treatment was similarly effective in improving depression. Overall, both treatments were well tolerated.

Our study is in accordance with the combined analysis published in 2003 showing treatment response similar with sertraline and fluoxetine, although sertraline may be slightly more advantageous in severe depression (22).

In another study comparing efficacy and safety of Sertraline and Fluoxetine conducted in 1993, (23) the results were very similar to our study. Although there was a numerical advantage for Sertraline on several efficacy measures, there was no statistically significant difference found between the treatment groups. The incidence of adverse events was similar for both treatments; 40.4% for Sertraline and 39.3% for Fluoxetine. However, adverse events were generally rated by patients as of lower severity in the Sertraline group. In addition, for the Fluoxetine group, there was a higher incidence of agitation, anxiety and insomnia than for Sertraline. Sertraline was considered to be better tolerated than Fluoxetine overall, since only 9.6% of Sertraline-treated patients discontinued treatment due to therapy failure whereas in the Fluoxetine-treated group this figure was 19.6%. By contrast, 13.5% of Sertraline-treated patients discontinued prematurely because of clinical improvement, compared with 10.7% of Fluoxetine-treated patients.

In contrast to our study, Geddes and Cipriani (24) show that SSRIs do not work much better than placebo. This may be because they have considered short term randomized trials of SSRIs in children and adolescents while we conducted our study only in adults.

In our study both Sertraline and Fluoxetine treated patients demonstrated robust antidepressant responses as reflected by large decreases in ratings on the HDRS and SRQ. None of the patients in both groups demonstrated any suicidal thoughts. Both drugs were well tolerated. The levels of AST and ALT were raised at the end of the study from the baseline, and trials of these drugs for longer duration should be done to know its significance. Although, further studies with larger groups of patients and comparisons with placebo are required to establish the superiority of one drug over the other but we suggest that Sertraline which showed earlier improvement in scores and is cost effective as well may be a better choice to treat major depression.

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