Original article

Sertraline as an add-on treatment for depressive symptoms in stable schizophrenia: A double-blind randomized controlled trial

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BACKGROUND: There have been few studies to specifically examine the efficacy of selective serotonin reuptake inhibitors (SSRIs) for the symptoms of depression in schizophrenia. This study aimed to determine the efficacy of sertraline as a treatment for depressive symptoms in patients with stable schizophrenia. **METHODS:** A 12-week randomized, double-blind, placebo-controlled clinical trial was designed in 2010 with an active medication (sertraline) and a matching placebo. Sertraline was administrated 50-200 mg/daily. A total number of 60 patients were randomized into two groups in a 1:1 fashion. Calgary Depression Scale for Schizophrenia (CDSS) was used as the primary measure and Global Assessment of Functioning (GAF) scale was used as the secondary measure. The data was analyzed by repeated measures analysis of variance (ANOVA) model to determine the effectiveness of sertraline. **RSULTS:** After 12 weeks, sertraline was significantly more effective than placebo in improving depressive symptoms in stable schizophrenia ($p = 0.003$). The mean score of GAF did not differ significantly in the sample population as a whole ($p = 0.093$). The difference between the two groups was not significant, either ($p = 0.453$). In addition, the rate of side effects was little but it was significantly more in the sertraline group ($p < 0.001$). **CONCLUSIONS:** The results of this study suggested sertraline to be useful as a treatment for depressive symptoms in patients with stable schizophrenia.

KEYWORDS: Sertraline, Schizophrenia, Post-Psychotic Depressive Disorder of Schizophrenia, Subsyndromal Depressive Symptoms, Negative Symptoms

BACKGROUND

While schizophrenia and depression have historically been regarded as separate disorders, it is now well recognized that depressive symptoms are common in schizophrenia.[1] It has been noted that most depressive symptoms occur concurrently with the acute psychotic symptoms, and resolve once antipsychotic treatment is implemented and the psychosis remits.[2] However, there are patients with schizophrenia who experience persistent depressive symptoms that are not responsive to antipsychotic treatment alone.

A clinical entity, defined as post-psychotic depressive disorder of schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders-fourth edition-text revision (DSM-IV-TR) criteria, is quite important in terms of follow up procedures, prognosis, and determination of the treatment strategy in schizophrenic patients. On the other hand, clinically significant subsyndromal depressive symptoms have been reported to be more prevalent than full depressive episodes in this patient population.[3] Indeed, they are so prevalent that some investigators have argued that depression is a core component of schizophrenia, similar to positive, negative, and disorganized symptom clusters.[4]

These persistent (or emergent) depressive symptoms may be particularly important in the post-psychotic period, as they have been found to be associated with an increased risk of relapse,[5] suicidality,[6] and impaired social and vocational functioning.[7] Therefore, in the chronic course of schizophrenia, depressive symptoms appear to be negative prognostic indicators,[7] in such a way that changes in the quality of life of schizophrenic patients is inversely related to changes in the concurrent mood disruption. Early therapeutic interventions directed at a broader constellation of schizophrenic symptomatology, including mood, may thus be helpful in improving an individual patient's quality of life.[8]

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We believe that the early recognition and proper treatment of this relatively common depressive state which arise during the treatment of schizophrenic patients, especially during maintenance therapy, are essential. Otherwise, the prognosis and the quality of life achieved through treatment will be quite poor.

A meta-analysis evaluated the results of trials about the clinical efficacy of antidepressant medications [either tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) or others] in the treatment of depression in schizophrenic patients. In this study, in a subset of 5 trials (209 patients), the improvement rate in the antidepressant group was higher than in the placebo group and there was no evidence that antidepressant treatment induced a deterioration of psychotic symptoms.[9] The use of newer antidepressants in combination with antipsychotics to treat the depressive symptoms of schizophrenia is encouraged because of significantly more side effects in other antidepressants such as TCAs[10,11] and the positive results of such treatments compared to placebo in the studies of augmentation of antipsychotics.

Siris suggested SSRIs as the most frequently prescribed antidepressants whose combination with an atypical antipsychotic was preferred.[12] Several published trials, including double-blind, placebo-controlled trials, have examined SSRIs in the treatment of depressive symptoms in patients with schizophrenia and have provided contradictory results. In the trial with fluvoxamine, the difference in mean scores of Hamilton Depression Rating Scale (HDRS) between the two groups at the end of the study period was not significant.[13]

With fluoxetine, two of three studies demonstrated no benefit over placebo in the treatment of depressive symptoms in patients with schizophrenia.[14,15] However, the third study compared fluoxetine with placebo and found it to lead to a slight improvement in depressive symptoms.[16] In two studies with citalopram, no scales to assess depression were used.[17,18] Nevertheless, in a recent study, citalopram was more effective than placebo in relieving depression, negative symptoms, mental functioning, and quality of life of older patients with schizophrenia.[19] While in one study, using sertraline in treatment of patients with remitted schizophrenia and major depression showed no benefit,[20] in another research, sertraline-treated patients showed a significant improvement on the anxiety/depression subscale of the Brief Psychiatric Rating Scale (BPRS).[21]

Sertraline is an antidepressant drug that has been proved to be effective in the treatment of depression, with fewer side-effects than TCAs.[22] It protecting against the recurrence and relapse of depression and carries a very low risk of exacerbating psychotic symptoms.[23] Considering lack of studies and conflicting results of treating depressive symptoms with this drug, we aimed to compare the efficacy of sertraline with placebo in the treatment of depressive symptoms in schizophrenic patients who were not in the active phase. We used a specific scale named Calgary Depression Scale for Schizophrenia (CDSS) which has been seldom used in previous studies.[9] CDSS was the first scale specifically designed and validated for the evaluation of depressive symptoms in patients with schizophrenia.[24] It has been shown not to overlap with negative symptoms and extrapyramidal symptoms.[24,25]

METHODS

Subjects

With a confidence interval of 95%, power of 80%, and estimation of clinical standard deviation of schizophrenia in both control and intervention groups, which was 1.6 of the range of CDSS score changes, study subjects were determined as 30 patients in each group. Patients were chosen from both admitted or outpatients in the psychiatric ward or clinic of Noor Hospital (Isfahan, Iran), respectively. All of them had a diagnosis of schizophrenia. All subjects aged 16-65 years, were receiving a stable dose of an atypical antipsychotic medication, were clinically stable and diagnosed with post-psychotic depressive disorder of schizophrenia according to DSM-IV-TR or clinically significant subsyndromal depressive symptoms. Stability was defined as a period of at least one month when the patient maintained a score of at least four or less on all positive symptoms of the Positive and Negative Symptoms Scale (PANSS). This definition is based on that used by Schooler et al. who used the BPRS among patients that were stabilized on antipsychotic medication.[26] The translation and back-translation method was used to make the Persian translation of PANSS valid. PANSS was translated to Persian by two psychiatrists and then two other bilingual psychiatrists translated the same text to the first language. The translated texts were evaluated by the translation team for final decision. On the other hand, subjects met none of the following exclusion criteria: 1) any serious medical condition that would interfere with safe study participation; 2) any substance abuse or dependency except nicotine; 3) pregnancy or nursing in women; 4) using any psychotropic drugs except atypical antipsychotics.

Design and Procedures

The study used a randomized, double-blind, placebo-controlled clinical trial design with an active medication condition and a matching placebo. The study followed the Declaration of Helsinki on Biomedical Research Involving Human Subjects and was approved by the Ethics Committee at Isfahan University of Medical Sciences (Isfahan, Iran). All participants provided written informed consents. At the screening visit, after providing demographic data, eligible subjects were randomly assigned to sertraline or placebo groups (1:1). Patients in the first group started sertraline at 50 mg/day and the dose was raised to 100 mg/day after four weeks, and 200 mg/day after eight weeks if partial response was not seen.

Efficacy and Safety Assessments

The subjects were assessed at the screening visit and weeks 8 and 12 by the CDSS and Global Assessment of Functioning (GAF) scale. In each visit, subjects were assessed for urine pregnancy test in women and drug side effects. The translation and back-translation method was used to make the Persian translation of CDSS valid. CDSS was translated by two psychiatrists to Persian and then two other bilingual psychiatrists translated the same text to first language. Translated texts were evaluated by the translation team for final decision.

Statistical Methods:

The data was analyzed using the $SPSS_{18.0}$ (SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to determine the demographic characteristics of the studied population. The difference between the two groups and the follow-up time (time effect) were determined using repeated measures analysis of variance (ANOVA). P-values less than 0.05 showed statistical significance.

This study was conducted in 2010 and registered in the Iranian Registry of Clinical Trials (project number: IRCT201110187839N1).

RESULTS

Among a total of 101 individuals who were screened, 60 met all inclusion and no exclusion criteria and were randomized into two groups of 30 to receive either sertraline or placebo. However, 3 patients were eliminated from the placebo group since one did not answer the phone, one's family refused to continue the treatment, and one had poor compliance. Similarly, 3 patients were eliminated from the sertraline group due to taking a trip (1 patient) and drug side effects including sedation and gastrointestinal disturbances (2 patients) (Figure 1). The age range of the subjects was 20-56 years with the mean ± standard deviation (SD) of 34.1 ± 8.5. The demographic and clinical features of the participants are reported in table 1. There were no statistically significant imbalances on demographics or symptom severity between treatment groups at baseline. The only significant difference was that subjects assigned to the placebo group were more likely to have a more prolonged illness ($p = 0.004$) (Table 1).

The differences between mean scores of CDSS at baseline and after eight and twelve weeks of intervention were significant in the sample as a whole (both placebo and sertraline groups) ($p < 0.001$) (Table 2). However, the subjects assigned to active medication demonstrated a significantly greater percentage decline compared to the placebo group ($p = 0.003$) (Figure 2, Table 2). Although the randomization was generally effective, an analysis of covariance was conducted for disease duration.

The differences between mean scores of GAF at baseline and after eight and twelve weeks of intervention were not significant in the sample as a whole (both placebo and sertraline groups) ($p = 0.093$) (Table 2). In addition, there were no significant differences between the treatment groups ($p = 0.453$) (Figure 3, Table 2).

Rates of side effects were significantly different between the groups with no side effects in the placebo group and 20.7% in the sertraline group ($p < 0.001$). The most common side effects were gastrointestinal disturbances ($n = 3$) and sedation ($n = 2$).

DISCUSSION

Studies of depressive symptoms in schizophrenia have used a variety of measures, and non specific scales (such as HDRS or Beck Depression Inventory) are the most commonly used in spite of the fact that these scales do not allow the distinction of depressive from negative symptoms in schizophrenic patients.[9] Studies on fluvoxamine,[13] fluoxetine,[14,15] and sertraline,[21] which used these non specific scales, had contradictory results. We used CDSS which was the first scale specifically designed and validated for the evaluation of depressive symptoms in patients with schizophrenia.[24] This scale has been shown not to overlap with negative symptoms and extrapyramidal symptoms of schizophrenia.[25,27]

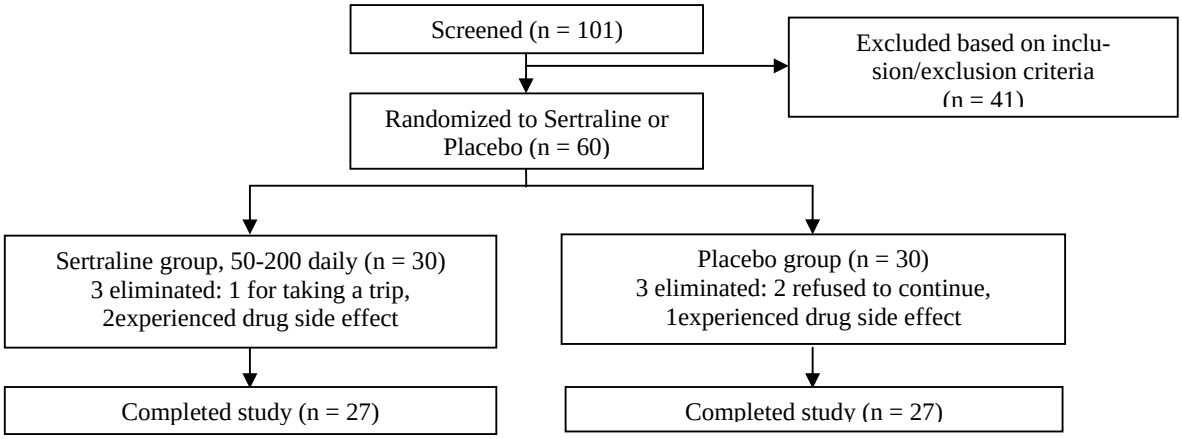

Figure 1. Study design flowchart

Table 1. Demographics and clinical characteristics of the subjects (n = 54)

Characteristics	Sertraline n = 27	Placebo n = 27	P-value
Sex			
Male	13 (48.1)	14 (51.9)	0.785
Female	14 (51.9)	13 (48.1)	
Age (mean ± SD)	33.4 ± 6.9	34.7 ± 10.2	0.593
Marital status			
Single	14 (51.9)	10 (37.0)	0.413
Married	7 (25.9)	13 (48.1)	
Widowed	3 (11.1)	2 (7.4)	
Divorced	3 (11.1)	2 (7.4)	
Education			
Illiterate	5 (18.5)	4 (14.8)	0.839
Primary school	12 (44.4)	12 (44.4)	
High school	8 (29.6)	7 (25.9)	
College	2 (7.4)	4 (14.8)	
Habitation			
Alone	2 (7.4)	3 (11.1)	0.593
With parents	15 (55.6)	10 (37.0)	
With family	10 (37)	14 (51.8)	
Occupation			
Employee	1 (3.7)	3 (11.1)	0.412
Self-employed	14 (51.9)	15 (55.6)	
Unemployed	12 (44.4)	9 (33.3)	
Number of family members			
≤ 2	25 (92.6)	23 (85.4)	0.604
≥ 3	2 (7.4)	4 (14.8)	
Duration of disease			
< 1 year	18 (66.7)	6 (22.2)	0.004
1-5 years	5 (18.5)	9 (33.3)	
> 5 years	4 (14.8)	12 (44.4)	
Number of admissions			
None	5 (18.5)	8 (29.6)	0.649
1 time	9 (33.3)	8 (29.6)	
≥ 2 times	13 (48.2)	11 (40.8)	
Antipsychotic			
Clozapine	7 (25.9)	9 (33.3)	0.551
Risperidone	10 (37.0)	8 (29.6)	0.564
Aripiprazole	2 (7.4)	4 (14.8)	0.669
Olanzapine	5 (18.5)	4 (14.8)	0.851
Quetiapine	3 (11.1)	2 (7.4)	0.865
CDSS score (mean ± SD)			
Before intervention	12.2 ± 3.4	11.2 ± 2.4	0.216
GAF score (mean ± SD)			
Before intervention	5.6 ± 1.7	6.2 ± 1.6	0.164

All variables are number (%) unless otherwise indicated.
CDSS: Calgary Depression Scale for Schizophrenia; GAF: Global Assessment of Functioning

Table 2. Scores of Calgary Depression Scale for Schizophrenia (CDSS) and Global Assessment of Functioning (GAF) in the patients during the eighth and twelfth weeks of follow-up controlling for duration of illness using repeated measures analysis of variance

Main Effects	F-test	df	P-value
CDSS:			
Follow-up (time effect)	12.40	2.48	< 0.001
Intervention (group effect)	9.90	1.49	0.003
Follow-up Intervention (interaction effect)	22.90	2.48	< 0.001
GAF:			
Follow-up (time effect)	2.50	2.51	0.093
Intervention (group effect)	0.57	1.52	0.453
Follow-up Intervention (interaction effect)	2.70	2.51	0.072

CDSS: Calgary Depression Scale for Schizophrenia; GAF: Global Assessment of Functioning

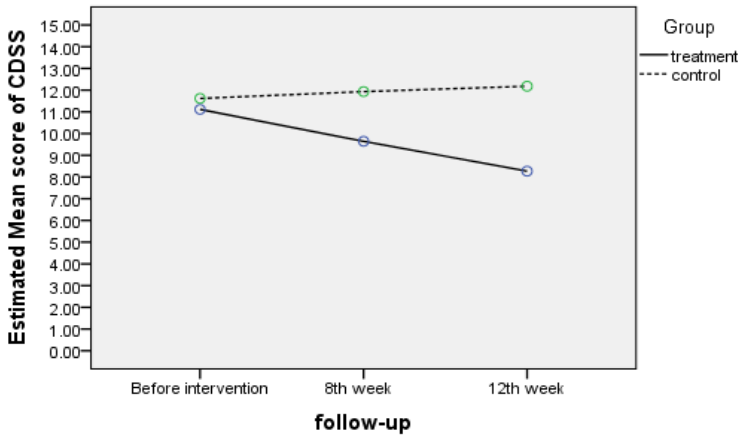

Figure 2. Changes in the Calgary Depression Scale for Schizophrenia (CDSS)

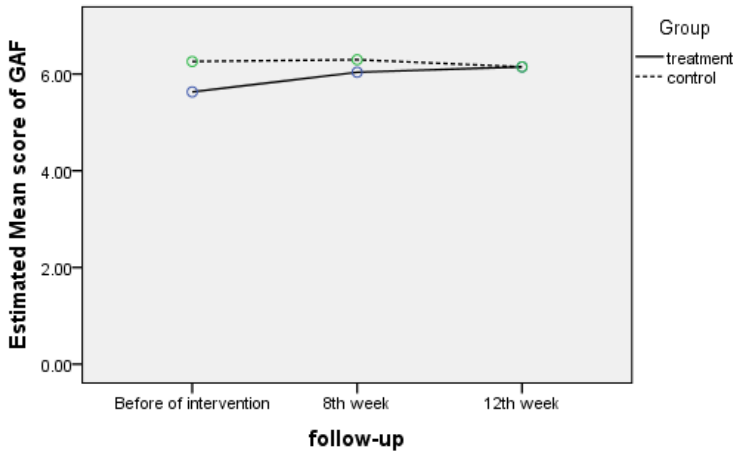

Figure 3. Changes in the Global Assessment of Functioning (GAF)

Table 3. Scores of Calgary Depression Scale for Schizophrenia (CDSS) and Global Assessment of Functioning (GAF) in weeks zero, eight, and twelve

SCALE	Sertraline Mean ± SD	Placebo Mean ± SD	P-value
CDSS			
Before intervention	12.2 ± 3.4	11.2 ± 2.4	0.216
After 8 weeks	10.6 ± 2.7	11.6 ± 2.5	0.163
After 12 weeks	9.2 ± 2.7	11.8 ± 2.6	0.001
GAF			
Before intervention	5.6 ± 1.7	6.2 ± 1.6	0.164
After 8 weeks	6.0 ± 1.5	6.3 ± 1.5	0.520
After 12 weeks	6.1 ± 1.4	6.1 ± 1.4	1

The results of the current 12-week, double-blind study suggested that sertraline is more effective than placebo in improving depressive symptoms. Moreover, the difference between mean scores of CDSS at baseline and after 8 and 12 weeks of intervention was significant in both placebo and sertraline groups but repeated measures ANOVA revealed a significant main effect for group, time, and interaction of group and time, i.e. subjects assigned to active medication had a significantly greater percentage decline compared to the placebo group. This is not consistent with another double-blind study with sertraline which similarly used CDSS as the rating scale.[20] The difference could be due to of the lower dose (maximum 100 mg) and shorter duration (6 weeks) of treatment in that study.[20] However, according to references on using SSRIs for treating depression,[22] we used sertraline up to 200 mg and for 12 weeks. Although the two groups of our study did not differ significantly before the twelfth week, after that, sertraline was significantly more effective than placebo. Zisook et al. used CDSS and concluded that augmentation with citalopram was significantly more effective than placebo in improving depressive symptoms in older patients with schizophrenia.[19] The results of our study using this specific scale, which does not overlap with negative symptoms and extrapyramidal symptoms of schizophrenia, suggest the efficacy of sertraline for treatment of depressive symptoms in stable schizophrenia.

In this study, although the randomization was generally effective, subjects assigned to the placebo group were more likely to have more prolonged illness ($p = 0.004$). Therefore, an analysis of covariance was conducted for duration of illness.

Moreover, the difference between mean scores of GAF was not significant between the two groups of the study. However, after 8 weeks, the improvement was better in the sertraline group and this was clinically obvious. This improvement in patients with chronic schizophrenia is a matter of concern and is consistent with improvement in depressive symptoms. In a double-blind study, Kasckow et al. showed citalopram to result in higher mental functioning and quality of life scale (QOLS) scores compared to placebo.[28] These results suggest that improvement in depressive symptoms in patients with stable schizophrenia may cause improvement in their general function and quality of life which is very important in prognosis of chronic cases.

Finally, the rate of side effects was little but it was significantly more in the sertraline group. In fact, 2 patients discontinued treatment due to drug side effects. This is noteworthy, because poor compliance is a matter of concern in patients with chronic diseases like schizophrenia.

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