

Original Research Article

Escitalopram add-on in stable Schizophrenia with subsyndromal depression

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Received: 21 December 2019

Accepted: 26 December 2019

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ABSTRACT

Background: Significant proportion of the patients of schizophrenia suffer from subsyndromal symptomatic depressive symptoms (SSD) which not only add to the burden of disease but also to the already pre-existing challenges of living with this serious mental illness. Many psychiatrists prescribe antidepressants to patients with schizophrenia who have subsyndromal symptomatic depressive symptoms but data regarding SSD in schizophrenia is meagre. Aim was to study the effect of addition of Escitalopram on psychopathology, cognition and functioning in patients with stable schizophrenia having subsyndromal depressive symptoms and to compare these parameters with patients treated with antipsychotics alone.

Methods: The study was a prospective, 8-week randomized double-blind placebo-controlled trial. Seventy four patients who fulfilled the diagnostic criteria of Schizophrenia on the basis of the ICD10-DCR, adjudged to be stable clinically and not requiring any increase in dose of antipsychotic medication over the last eight weeks were recruited into the study. The patients randomly received either Antipsychotics with add-on Escitalopram (10 mg/day) or Antipsychotics with placebo for 8 weeks. The patients were assessed using the HAM-D, CDRS, PANSS, SCoRS, SOFAS and CGI scores at the end of 8 weeks. Patients were also assessed for adverse events at baseline, week 4 and week 8.

Results: A total of sixty-six patients who completed the study were analyzed. The HAM-D, CDRS and PANSS score showed significantly better cognition and functioning in the patients of add-on Escitalopram group when compared with the placebo group. There was no significant difference between the two groups in terms of observed side effects.

Conclusions: Escitalopram addition to the standard anti-psychotic treatment of schizophrenia, in patients having subsyndromal depressive symptoms, results in better cognition and improved functioning.

Keywords: Escitalopram, Schizophrenia, Subsyndromal depression

INTRODUCTION

Symptoms of Schizophrenia are categorized into domains of positive symptoms, negative symptoms, cognitive symptoms, affective symptoms and aggressive/hostile symptoms.¹ Among different domains of Schizophrenia, affective symptoms are the least defined. Significant proportion of the patients of schizophrenia suffer from

affective symptoms (depressive) during their illness either in the initial or later part.^{2,3} The expression of these symptoms varies across patients and over time, and its effects are usually severe and long lasting.⁴ This not only adds to the burden of disease but also to the already pre-existing challenges of living with this serious mental illness resulting in greater disability, demoralization, poor motivation, utilization of various health services, suicidal

attempts, decreased work productivity, major depression, psychiatric comorbidity, impaired functionality, poor overall outcome of primary illness and increased risk of relapse.⁵⁻⁷

Frequently patients present with depressive symptoms that result in significant impairment in social functioning but are insufficient in number or duration to satisfy the DSM criteria of major depressive episode. This constellation of symptoms, termed as “subsyndromal depressive symptoms” are defined as two or more symptoms of depression of the same quality as in major depression excluding depressed mood and anhedonia.⁸

A prospective study assessing depression during the longitudinal course of schizophrenia found that only 24% of the subjects remained free of depressive symptoms, 36% met the criteria for major depressive episode and 40% experienced 2-4 symptoms of depression.⁹ The one month point prevalence of SSD in the general population is 3.9% as compared to 1.5% for minor depression and 2.3% for major depression.¹⁰ Considering the high prevalence of depressive symptoms in schizophrenia, some investigators have argued that depression is a core component of schizophrenia in addition to positive, negative and disorganized symptom clusters.¹¹ Many authors have stressed the need to focus on this less touched domain of schizophrenia, as it has a great impact on the functional outcomes of the sufferer.⁸

Whether these depressive symptoms are a core feature of schizophrenia, a reaction to this debilitating chronic disorder, a prodromal or residual symptom of psychosis, drug effect, a part of akinetic syndrome or of negative syndrome complex, or perhaps all of the above is still undetermined. However, regardless of the etiology such symptoms should be given attention and treated. Approximately one in three patients with schizophrenia in out-patient settings are treated with anti-depressants, but data regarding SSD in schizophrenia is meagre.¹

Keeping in view these facts, author planned to evaluate the effect of adding Escitalopram, to usual antipsychotic treatment, on psychopathology, cognition and functioning in patients with stable schizophrenia having subsyndromal depressive symptoms.

METHODS

It is a prospective, randomized, double blind, placebo-controlled trial conducted at Department of Psychiatry of a tertiary care center in Lucknow, India over a 1-year period (2015-2016). The study was approved by the Institutional Ethics Committee of King George’s Medical University, Lucknow, U.P.

Sample selection

All adult patients suffering from schizophrenia, attending Psychiatry Outpatient department, who were adjudged to

be stable clinically and not requiring any increase in dose of antipsychotic medication over the last eight weeks were screened and selected if they fulfilled the selection criteria.

The selection criteria were stable patients with Schizophrenia aged between 18 to 50 years, willing to give written informed consent and having subsyndromal depression (SSDs) as defined for the purpose of this study. Patients were excluded if they had a clinically significant medical disorder / disability or were taking treatment for same, if they had any comorbid psychiatric disorder other than nicotine dependence, already receiving antidepressants or mood stabilizers during last 8 weeks, patients who have received electroconvulsive therapy, other somatic treatments or any form of Psychotherapy during the last six months, having any significant abnormality in routine investigations at baseline (Hb, TLC, DLC, RBS, S.Urea, S.Creatinine, LFT), pregnant and lactating females. Patients were dropped out from study if they were non adherent to treatment (i.e. missing >20% of the prescribed dose), missed any appointments beyond window period (± 3 days), had intolerable side effects, had worsening of symptoms, developed any emergent safety condition or withdrew consent. A total number of 112 patients were screened. Of these, 74 patients who fulfilled selection criteria were enrolled in the study.

Following enrolment, the socio-demographic and clinical details of the patients were recorded in the semi-structured proforma. The Mini International Neuropsychiatric Interview (MINI) v 6.0.0 was applied and clinical evaluation conducted, to rule out any psychiatric co-morbidity. A thorough clinical evaluation with emphasis on cardiovascular system, and Gastrointestinal System, was conducted, along with the routine investigations i.e. Hb, TLC, DLC, RBS, Serum Urea, Serum Creatinine and Liver function test. Baseline clinical variables were measured using Calgary depression rating scale (CDRS) for depressive symptoms, Schizophrenia Cognition Rating Scale (SCoRS) for cognitive functioning, Social and Occupational Functioning Assessment Scale (SOFAS) for occupational and social functioning, Clinical Global Impression scale for severity (CGI-S). The patients were then randomized into two treatment groups, A and B, using a computer-generated randomization table. Identical capsules of Escitalopram and Placebo were prepared and pre-labelled as: Group A /Group B by one of the co-supervisors and both the patients and clinical investigator were blind to this random allocation. The drugs were made available in pre labelled containers. The study drugs were procured from reputed production firms from a single production batch. One of the treatment group (study group) received Escitalopram 10mg as add-on for the duration of the study starting from day 1, while the other group received placebo in addition to the usual antipsychotic treatment (control group).

Each subject received identical capsules containing either escitalopram or placebo, for 8 weeks. Rescue medications allowed in the study were Clonazepam up to 1mg/day for Anxiety and Zolpidem up to 10mg/day for insomnia. All patients were followed up for treatment adherence and clinical assessment at week 4 and week 8, with a window period of three days. The appropriate scales were applied by the investigator on each visit for assessment and monitoring, i.e. Positive and Negative Symptom Scale (PANSS), Hamilton Depression rating Scale (HAM-D), CDRS, SCoRS, SOFAS, CGI-S/I/E, UKU side effects scale. Physical examination was done at each visit and routine investigation was done at week 8 for safety monitoring. Adherence was assessed by verbal report of patient and caregiver and by pill count on each visit.

Statistical analysis

The results are presented in mean±SD and percentages. The continuous score variables were tested for normalcy by using Kolmogorov-Smirnov Z test and found to be non-normal. The Mann-Whitney U test was used to compare the scores between Group A and Group B at different time periods. The Chi-square/Fisher exact test was used to compare the categorical variables/dichotomous variables. The p-value <0.05 was

considered significant. All the analysis was carried out using SPSS 16.0 version.

RESULTS

A total number of 112 patients were screened to enroll 74 patients to the study. The enrolled patients (74) were randomized into study group (37) and control group (37) using computer generated randomized table. Total 66 patients completed the study (Figure 1).

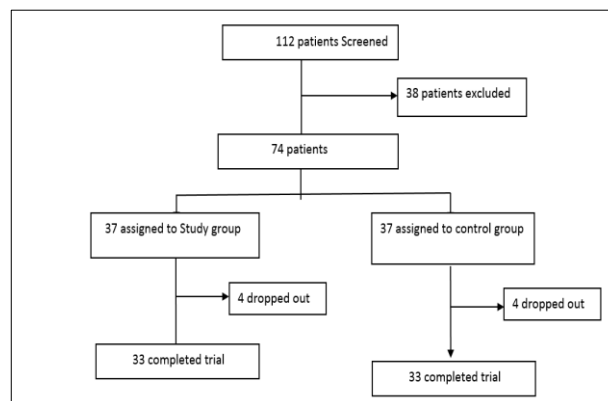


Figure 1: Flow diagram of the trial.

Table 1: Sociodemographic profile of patients.

		Escitalopram+ Antipsychotics (n=33)	Placebo+ Antipsychotics (n=33)	p-value
Age (in years)	18-30	11 (33.3)	16 (48.5)	0.31
	31-40	17 (51.5)	15 (45.4)	
	41-50	5 (15.2)	2 (6.1)	
Sex	Males	25 (75.8)	24 (72.7)	0.77
	Females	8 (24.2)	9 (27.3)	
Religion	Hindu	24 (87.9)	28 (84.8)	0.72
	Muslim	9 (12.1)	5 (15.2)	
Education	Primary School	13 (39.4)	15 (45.4)	0.93
	High School	10 (30.3)	9 (27.3)	
	Intermediate	4 (12.1)	3 (9.1)	
	Graduate and above	6 (18.2)	6 (18.2)	
Occupation	Housewife	6 (18.2)	7 (21.2)	0.11
	Unemployed	11 (33.3)	14 (42.4)	
	Unskilled/ Semi-skilled worker	13 (39.4)	9 (27.3)	
	Skilled worker	2 (6.1)	2 (6.1)	
	Service/ Self Employed	1 (3.0)	1 (3.0)	
Family income (Rs/month)	<5000	9 (27.3)	7 (21.2)	0.61
	5000-10000	11 (33.3)	9 (27.3)	
	>10000	13 (39.4)	17 (51.5)	
Marital status	Married	24 (72.7)	17 (51.5)	0.19
	Unmarried	8 (24.3)	15 (45.5)	
	Separated	1 (3.0)	1 (3.0)	
Domicile	Rural	26 (78.8)	21 (63.6)	0.17
	Urban	7 (21.2)	12 (36.4)	
Type of family	Joint	22 (66.7)	18 (54.5)	0.31
	Nuclear	11 (33.3)	15 (45.5)	

Both the groups were comparable at baseline on all the socio-demographic parameters (Table 1).

The mean age of the study group was 33.48 ± 5.76 years and the control group was 31.48 ± 6.34 years. The groups were also compared on all the clinical variables at baseline, using Mann Whitney U Test. Both the groups were comparable at baseline on all the clinical variables including duration of illness in years, subtypes of

Schizophrenia, HAM-D, PANSS total score as well as positive, negative and general psychopathology score, Schizophrenia Cognitive Rating Scale (SCoRS), Social and Occupational Functioning Assessment Scale (SOFAS), and Clinical Global Impression scale (Severity). However, the mean score for depressive symptoms on CDRS shows significant difference and the severity of the depressive symptoms was higher in the control group on CDRS (Table 2).

Table 2: Baseline clinical characteristics of patients.

Clinical variables	Escitalopram+Antipsychotics (n=33)	Placebo+ Antipsychotics (n=33)	p- value
Duration of illness (mean±SD) (years)	4.09±1.42	4.21±1.47	0.74
Subtypes of Schizophrenia			
Paranoid	22 (66.7)	20 (60.6)	0.86
Undifferentiated	9 (27.2)	11 (33.3)	
Catatonic	2 (6.1)	2 (6.1)	
Total PANSS score (Mean±SD)	49.36±6.73	48.09±7.37	0.39
HAM-D score (Mean±SD)	9.00±0.86	9.36±1.00	0.18
CDRS score (Mean±SD)	9.00±0.86	5.18±0.88	0.01*
SCoRS (Mean±SD)	43.80±7.71	42.37±6.70	0.64
SOFAS (Mean±SD)	60.03±8.12	60.96±9.16	0.64
CGI-S (Mean±SD)	3.51±0.61	3.67±0.54	0.21

The Escitalopram group, when compared to the control group had a significant reduction in the HAM-D score at week 4 ($p=0.0001$) and week 8 ($p=0.0001$) (Table 3) and mean change in the HAM-D score was significantly higher in the Escitalopram group from 0 week to 4 weeks ($p=0.0001$) and from 0 week to 8 weeks ($p=0.0001$) (Table 4).

The mean score at baseline for depressive symptoms on CDRS shows significant difference and the severity of the depressive symptoms was higher in the control group.

At week 4 and week 8 the mean change in the CDRS score was significantly higher in the Escitalopram group from 0 week to 4 weeks ($p=0.0001$) and from 0 week to 8 weeks ($p=0.0001$) (Table 4).

On comparing the groups on the total PANSS score, at week 8 ($p=0.005$) the Escitalopram group had significantly lower scores than control group (Table 3). The comparison of mean change demonstrated a significantly larger fall in the score of total PANSS in the Escitalopram group from week 0 to week 4 ($p=0.0001$) as well as from week 0 to week 8 ($p=0.0001$) (Table 4).

On comparing the groups on the positive scores of PANSS, at week 8 ($p=0.0001$) the Escitalopram group had significantly lower scores than control group but on

the negative score and general psychopathology scores of PANSS there was no clinically significant difference between both the groups (Table 3). However, the comparison of mean change demonstrated a significantly larger fall in the score of positive symptoms scale in the Escitalopram group from week 0 to week 4 ($p=0.0001$) as well as from week 0 to week 8 ($p=0.0001$) and there was significantly larger fall in the negative symptoms scale from week 0 to week 4 ($p=0.01$) as well as from week 0 to week 8 ($p=0.0001$) whereas in general psychopathology scale there was no clinically significant difference observed (Table 4).

The comparison on SCoRS revealed significantly lower scores at week 8 hence a better outcome in the study group ($p=0.0001$) (Table 3) and the mean change in adjusted scores on SCoRS were significantly more in the study group from 0 week to 4 week ($p=0.002$) and from week 0 to week 8 ($p=0.0001$) (Table 4).

The comparison on SOFAS revealed significantly higher scores at week 8 hence a better outcome in the study group ($p=0.0001$) (Table 3) and the mean change in SOFAS were significantly more in the study group from 0 week to 4 week ($p=0.002$) and from week 0 to week 8 ($p=0.0001$) (Table 4). On the Clinical Global Impression, the outcomes were significantly better in the study group (Table 4).

Table 3: Comparison of HAM-D, CDRS and total PANSS score, SOFAS, SCoRS and CGI-S at 4 weeks and 8 weeks from baseline between the Escitalopram group and the placebo group.

Time periods	Escitalopram+Antipsychotics (n=33)		Placebo+Antipsychotics (n=33)		Z-value	p-value
	Mean±SD	95%CI	Mean±SD	95%CI		
HAM-D						
At 4 week	6.39±0.86	6.09-6.70	8.12±1.08	7.74-8.51	5.46	0.0001*
At 8 week	3.81±0.72	3.56-4.08	6.96±1.21	6.54-7.40	6.80	0.0001*
CDRS						
At 4 week	3.18±0.68	2.94-3.42	4.54±0.97	4.20-4.89	5.16	0.0001*
At 8 week	1.66±0.64	1.44-1.90	3.90±0.97	3.56-4.26	6.58	0.0001*
Total PANSS						
At 4 week	43.12±5.84	41.05-45.19	44.97±7.05	42.47-47.47	0.77	0.44
At 8 week	37.42±4.28	35.91-38.94	42.09±6.66	39.73-44.46	2.77	0.005*
SCoRS						
At 4 week	39.56±6.85	37.14-42.00	40.25±6.22	38.04-42.46	0.20	0.45
At 8 week	31.91±5.19	30.07-33.76	38.33±6.07	36.17-40.48	3.70	0.0001*
SOFAS						
At 4 week	66.78±7.80	64.02-69.56	65.45±7.42	62.82-68.09	0.74	0.45
At 8 week	75.63±4.19	74.15-77.12	68.93±6.59	66.60-71.28	4.56	0.0001*
CGI-S						
At 4 week	2.87±0.64	2.65-3.11	3.03±0.46	2.86-3.20	1.12	0.26
At 8 week	1.70±0.58	1.49-1.90	2.79±0.48	2.62-2.96	5.91	0.0001*

Table 4: Comparison of mean changes in the HAM-D, CDRS and total PANSS score, SOFAS, adjusted SCoRS and CGI-S from baseline between the Escitalopram group and the placebo group.

Time periods	Escitalopram+Antipsychotics (n=33)		Placebo+Antipsychotics (n=33)		Z-value	p-value
	Mean±SD	95%CI	Mean±SD	95%CI		
HAM-D						
Week 0 to Week 4	2.60±0.86	2.29-2.91	1.24±0.66	1.01-1.47	5.45	0.0001*
Week 0 to Week 8	5.18±0.98	4.83-5.53	2.39±1.11	1.99-2.78	6.54	0.0001*
CDRS						
Week 0 to Week 4	1.51±0.61	1.11-2.42	0.63±0.48	0.20-0.89	5.11	0.0001*
Week 0 to Week 8	3.03±0.72	1.22-4.56	1.27±0.71	1.11-3.25	6.39	0.0001*
Total PANSS						
Week 0 to week 4	6.24±1.82	5.59-6.88	3.06±1.65	2.47-3.64	5.96	0.0001*
Week 0 to week 8	11.93±3.39	10.73-13.14	5.93±1.76	5.31-6.56	6.12	0.0001*
Adjusted SCoRS						
Week 0 to Week 4	4.24±4.01	2.81-5.66	2.12±2.57	1.20-3.03	4.63	0.002*
Week 0 to Week 8	11.88±4.21	10.39-13.38	4.03±2.58	3.12-4.95	6.13	0.0001*
SOFAS						
Week 0 to Week 4	6.75±4.38	5.20-8.31	4.48±3.64	3.19-5.77	3.15	0.002*
Week 0 to Week 8	15.60±5.91	13.51-17.70	7.96±5.35	6.07-9.86	4.82	0.0001*

DISCUSSION

There are guidelines for treating depressive symptoms in schizophrenia in different countries of the world with similar principles. If the depressive symptoms are intrinsic to acute psychotic episode, an appropriate antipsychotic medication (may be atypical antipsychotics) that resolves the symptoms of psychosis could facilitate the depression by itself, with no need for antidepressants. In stable chronic psychotic phase, when

antipsychotic agents do not have any beneficial mood effect, persistent depressive symptoms may respond to antidepressant in addition to antipsychotics. There was significant improvement in the depressive symptoms in the Escitalopram group as evidenced by statistically significant reduction in the HAM-D and CDRS score and mean change in the HAM-D and CDRS. Previously only in a small number of studies have showed that antidepressant augmentation was effective in the treatment of depressive symptoms in the patients of

schizophrenia, like Imipramine was found effective in a study, so was Fluoxetine, as was Sertraline and Citalopram.¹²⁻¹⁵ Studies also found Reboxetine to be effective, Duloxetine was also found effective as was Mirtazapine.¹⁶⁻¹⁸ The result of study also shows a better improvement in the depressive symptoms in the Escitalopram group and it seems that these effects start even before the fourth week.

An age range of 18-50 years was chosen as child and adolescent schizophrenia may have different characteristics in domains of symptomatology and etiopathogenesis than adult schizophrenia. Patients with total PANSS score less than 70 were included and score <4 in delusions (P1), conceptual disorganization (P2), hallucination (P3), grandiosity (P5), suspiciousness/persecution (P6), hostility (P7), unusual thought content (G9) items of PANSS as these patients usually have a stable course and low level of symptomatology while patients above 70 usually require interventions such as hospitalization, injectables and have a higher risk and safety concerns and are generally difficult to manage. The period of eight week off medications was set keeping that 5 half-lives is required to completely washout the drugs from the body. Patients having any other psychiatric illness except nicotine dependence were excluded as the current work is on subsyndromal symptomatic depression in stable patients with schizophrenia only. Patients having history of ischemic heart disease, hypertension, liver disease, cardiac failure, cerebrovascular disease, immunological disorders, obesity, diabetes were ruled out to reduce the confounding factors. The patients having any co-morbid physical illness or on any concomitant drugs including alternative medicine and nutritional supplements were ruled out as these drugs may interfere the drugs used in this study. Pregnant females were excluded as Escitalopram is a category C drug (i.e. the risk of adverse effects cannot be ruled out) as per FDA pregnancy classification. Lactating females were excluded as Escitalopram is L2 category (i.e. limited studies about safety) as per FDA classification

Escitalopram group showed significant reduction in positive symptom scale, negative symptom scale as well as total PANSS score. Antidepressants seem to have no desirable effect on positive symptoms of schizophrenia, as almost all RCTs were disappointing in this respect. The only exception was a study in which mirtazapine (but not placebo) added to on-going therapy with various first-generation antipsychotics improved positive symptoms.¹⁸ There is increasing evidence that serotonergic dysfunction is also associated with Schizophrenia. Interestingly, serotonergic agonists as well as serotonergic antagonists have been used to treat negative symptoms in some schizophrenic patients. In particular, selective serotonin reuptake inhibitors (SSRIs) have been used successfully in the treatment of negative and positive symptoms of some schizophrenic patients. However, the exact mechanisms whereby SSRIs exert their therapeutic action is not clear. Improvement of the

negative symptom was found in most of the other studies. The findings are very important as the schizophrenic negative symptoms are often treated insufficiently by the currently available antipsychotics. The sum total of the three subscales (positive, negative and general psychopathology), indicative in some sense of the total psychopathology was found to show a significantly better outcome in the Escitalopram group. This is an important finding as not only the total improvement in psychopathology is better in the Escitalopram group, the rate of improvement is significantly better, and thus the time taken for the results to differ significantly is as low as 4 weeks.

Diminished cognitive abilities are one of the more debilitating features of schizophrenia. It is also the one that is found to linger long after the core psychopathological features of the illness have been treated by the antipsychotics. Cognition was measured by Schizophrenia Cognition Rating Scale (SCoRS) in this study. At the 8th week the scores in the study group were significantly lower than the control group showing a better outcome in the domain of cognition when patients were given Escitalopram. The mean change in the study group was also significantly better than the control group, becoming significant as early as the fourth week of treatment and maintains significantly better improvements at week 8. The functioning status in schizophrenia understandably is related to the cognition, functional capacity and the symptom severity in all the domains. This has been demonstrated in other studies as well. At the week 8 the study group had a higher SOFAS score and thus better functioning as compared to the control group. This is expected given the improvement in the psychopathology and the cognition as noted earlier. The mean change in the SOFAS was significantly better in the Escitalopram group denoting a good functional recovery and overall a better functional outcome in these patients. Improvement in the functioning was also observed in previously done studies. The beneficial effects of antidepressants in reducing subsyndromal symptomatic depression and in turn improving psychopathology need to be investigated further as they propose a pharmacological intervention with a promise of better and quicker functional recovery.

On the Clinical Global Impression, the outcomes were significantly better in the study group. These findings are similar to those made by Salokangas et al, and Leucht S, et al, and also in accordance to the improvement in the PANSS, HAM-D, CDRS, SCoRS and SOFAS ratings seen in the Escitalopram group in the current study.^{19,20} The fact that a significant effect was observed not only in HAM-D and CDRS score but also in CGI, points to a convincing effect.

CONCLUSION

Escitalopram in addition to the standard anti-psychotic treatment for schizophrenia patients with subsyndromal

depressive symptoms results in better cognition and improved functioning.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee of King George's Medical University, Lucknow, Uttar Pradesh, India

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Cite this article as: Nischal A, Singh P, Agarwal M, Nischal A, Gupta B, Tripathi A. Escitalopram Add-on in stable Schizophrenia with subsyndromal depression. *Int J Adv Med* 2020;7:211-7.