

Amelioration of Negative Symptoms in Schizophrenia by Escitalopram: A Double-Blind, Placebo-Controlled Clinical Trial

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Abstract

Objective: The negative symptoms of schizophrenia remain a major clinical challenge. Escitalopram is the most selective SSRI with minimal effects on norepinephrine and dopamine neuronal uptake. The aim of this study is to evaluate the effect of escitalopram on the negative symptoms of schizophrenia. **Method:** This study was an eight-week, randomized, placebo-controlled trial of escitalopram versus placebo as an adjunctive to haloperidol (5 mg) in the treatment of 50 patients using the *Diagnostic and Statistical Manual of Mental Disorders--4th Edition--Text Revision (DSM-IV-TR)* criteria for schizophrenia. **Results:** The primary finding of the trial was a significant diminution in the Scale for Assessment of Negative Symptoms (SANS) in the escitalopram group compared to placebo at the end of eight weeks. In this regard, most of the subscales of SANS demonstrated significant improvements. **Conclusions:** This study suggests a potential role for escitalopram in the amelioration of the negative symptoms of schizophrenia.

Key Words: Schizophrenia, Negative Symptoms, Escitalopram

Introduction

Antidepressants have a long and mixed history as potential therapeutic agents in the negative symptoms of schizophrenia (1, 2). Although negative symptoms (affective blunting, alogia, avolition, apathy, anhedonia, asociality and attention deficit) are not uncommon in schizophrenia, their

treatment is still challenging (3). Much of the available data is inconsistent, partly due to methodological and diagnostic difficulties. For example, the use of antidepressants in the presence of concomitant depression in schizophrenia raises the question of whether treatment has primarily an antidepressant effect or a direct effect on negative symptoms. Nevertheless, the efficacy of imipramine on negative symptoms in stable schizophrenic patients with depressive symptoms has been reported (3).

Most of the trials of antidepressants in schizophrenia are add-on studies. Placebo-controlled trials of antidepressants in non-depressed schizophrenic patients have not shown consistent results (1-3). Fluvoxamine, 100 mg daily, has shown efficacy over placebo in a five-week trial (4). Two fluoxetine trials at 20 mg doses have suggested efficacy in

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schizophrenia as demonstrated by greater improvement in total scores (5) and improvement in Brief Psychiatric Rating Scale (BPRS) negative scores (6). However, there are trials of citalopram and fluoxetine with negative results, making definitive conclusions difficult (7, 8).

Other antidepressants have been studied in placebo-controlled designs. While trials of amitriptyline augmentation of perphenazine were reported to have some efficacy (9), no significant effect of maprotiline was noted (10).

Escitalopram, an S(+) enantiomer of racemic citalopram, is the most selective serotonin reuptake inhibitor with minimal effects on norepinephrine and dopamine neuronal uptake. It has no or very low affinity for serotonergic (5HT1-7) or other receptors including alpha- and beta-adrenergic, dopamine (D1-5), histamine (H1-3), muscarinic (M1-5), and benzodiazepine receptors. Therefore, the aim of this study was to assess the efficacy of escitalopram as an adjunctive drug on negative symptoms of schizophrenia.

Method

The study was approved by the University Medical Ethics Committee. The patients were informed about the procedure, and a written consent was received from those who were interested in participating in the study. Patients were free to withdraw from the study at any stage without prejudice. There was no drop-out in both the placebo and escitalopram groups. Fifty patients were randomly allocated to either the escitalopram (25 patients) group or the placebo (25 patients) group. The patients and the researchers were blind about which group was taking escitalopram or placebo. The age of these fifty patients ranged between 29 to 53 years (mean 41 ± 5 years), and all of them were male. The patients were hospitalized with a chronic course (not less than two years). The demographic variables of the two groups are presented in Table 1.

The inclusion criteria consisted of the diagnosis of schizophrenia according to the *DSM-IV* (11), the presence of negative symptoms of schizophrenia, and the duration of schizophrenia for more than two years. Almost 16% of the patients in the escitalopram group, and 21% of the patients in the control group, met Carpenter's Criteria for the Deficit Syndrome. The Scale for Assessment of Negative Symptoms (SANS) was used as the primary outcome for evaluating affective blunting (restricted emotional expression), avolition (reduced spontaneous speaking), anhedonia (lack of sense of pleasure) and attention deficit (12).

The Scale for Assessment of Positive Symptoms (SAPS), the Simpson-Angus Scale (SAS) and the Hamilton Depression Scale (HDS) were also used for comparison of the intervening parameters in this study. High negative symptom

scores (more than 20% of total SANS), low positive symptom scores (less than 20% of total SAPS), low extrapyramidal symptom scores (less than 25% of total SAS), and, finally, low depressive symptom scores (HDS less than 10) were the foundation of our inclusion criteria.

Table 1 Demographic Profile of Patients Participating in the Placebo and the Escitalopram Groups

	Placebo (N=25)	Escitalopram (N=25)
Gender (male)	25	25
Age (years); mean (SD)	41(±4)	39(±4)
Duration of illness (years); mean (SD)	7(±2)	8.3(±2)
Mini Mental State Examination (MMSE) score; mean (SD)	24.4(±1)	25.1(±1.1)
Hamilton Depression Scale (HDS) score; mean (SD)	4.2(±4)	5.1(±4)

The exclusion criteria are presented in Table 2. To exclude depression and cognitive disturbances, which can be confused with the negative symptoms of schizophrenia, the Hamilton Depression Scale (HDS) and Mini Mental Status Examination (MMSE) were used. An HDS greater than 10 and an MMSE less than 25 were diagnosed as depression and cognitive disturbance, and led to patient exclusion. All patients, after a waiting period of two weeks subsequent to the tapering off of their previous typical antipsychotics (neither group had received any form of depot injection during the last six months before entering the study), were receiving daily haloperidol (5 mg/day). They were randomized to placebo or escitalopram (10 mg daily) groups. The placebo and escitalopram tablets had the same shape and color, making it difficult for the patients and the physician to differentiate them. The study duration was eight weeks, and the patients were assessed at both the start and at the end of the trial.

Table 2 Exclusion Criteria

Major depressive disorder	Using antidepressants or lithium
Schizoaffective disorder	Medical complications
Mental retardation	Unstable, irritable, aggressive patients
Bipolar disorder	Duration less than one year
Neurological disorders	Parkinsonism
Using atypical antipsychotic	Medical deafness or muteness

Statistical Analysis

The statistical tests that were applied were Student's *t* test, Chi-square test, and Fisher's exact test. Comparisons between the escitalopram and placebo groups at baseline were performed using the Chi-square test for demographic data. For comparison between the scores of SANS, SAPS, SAS and HDS at the baseline and at the end of the study, we used Student's *t* test. Finally, Fisher's exact test was used to assess differences in subtests of SANS among these groups at the end of the trial. A *P* value <0.05 was considered statistically significant.

Results

The primary outcome measure was SANS, and at the baseline visit, day 0, there were no significant differences in the scores for the SANS total and negative subscales of the two groups. The same outcome was obvious regarding the SAPS, SAS and HDS evaluations at both the initiation and the closing stages of the study as well. However, at the conclusion of the study, escitalopram showed a significant, improved effect on the negative symptoms. (See Table 3.)

anhedonia-asociality subtest showed the most improvement, and alogia revealed the least alleviation. Although there were not any comparable significant shifts in the positive, extrapyramidal and depressive symptoms in both groups during the study, it should be noted that 38% of the patients in the placebo group, and 35% of the patients in the target group, needed an anticholinergic drug (trihexyphenidyl, 4-6 mg per day) for remission of tremors or parkinsonism during the study.

Discussion

The results of this study show the robust effects of escitalopram in reducing the negative symptoms of schizophrenia. Escitalopram is a new SSRI antidepressant approved by the FDA for the treatment of major depressive disorder (13). It does not have any remarkable blocking effect on muscarinic acetylcholine and histaminic receptors. The ameliorating effect of citalopram on the negative symptoms of schizophrenia in an earlier study (14), and the relatively safe profile of escitalopram in regard to side effects and pharmacokinetic interactions, created the motivation for this study.

Table 3 Patients with Significant Improvement* in Total and Subtest Scale for Assessment of Negative Symptoms (SANS) Scores in the Escitalopram Group as Compared to the Placebo Group

Negative Symptoms	Placebo (%)	Escitalopram (%)	P value
AB	1 (4%)	7 (28%)	0.025
ALOGIA	4 (16%)	10 (40%)	0.1
AA	4 (16%)	7 (28%)	0.04
An As	1 (4%)	8 (32%)	0.01
AD	2 (8%)	8 (32%)	0.05
Total	9 (36%)	20 (80%)	0.005

*Significant improvement defined as a reduction of 20% or more in the severity of SANS scores.
AB=Affecting Blunting; AA=Avolition-Apathy; An As=Anhedonia-Asociality; AD=Attention Deficit

At the end of the trial, the SANS negative scale scores were improved in 80% of the patients in the escitalopram group compared to 36% of the patients in the placebo group. In this regard, the SANS mean total score in the target group decreased from 84 ± 4.6 to 73 ± 3.7 ($df=1$, $p<0.05$) at the end of the study, while such a result was not evident in the placebo group (82 ± 5.3 to 79 ± 6.1 , $df=1$, $p>0.05$).

Most of the subtests of SANS demonstrated a significant improvement in the escitalopram group as compared with the placebo group. Improvement was defined as a reduction of 20% or more in the severity of each item. Among them, the

The results of our study further support the role of antidepressants as adjunctive in reducing the negative symptoms of schizophrenia. An association between negative symptoms and dysregulation of the serotonin system is suggested by an abnormal prolactin response to fenfluramine in schizophrenia and schizoaffective disorder (15). The current view is that blockade of serotonin receptors may be key to the reduction of negative symptoms and extrapyramidal side effects (16). Moller, based on MEDLINE searches from 1995 to September 2002, identified that selective serotonin reuptake inhibitors seem to have a certain place in the treatment

of negative symptoms (17). Our findings with escitalopram as a serotonin reuptake inhibitor are consistent with these studies.

There are certain limitations to this study, with the small sample size and the short duration being primary examples. Larger studies with similar aims are needed. It may be possible that the addition of escitalopram to atypical neuroleptics could have the same effect as was evidenced with haloperidol. It is known that negative symptoms continue to decline for some months after initiation of treatment. Thus, the eight-week duration of this trial, in addition to the lower dosage of the drug used in this study, may have underestimated the full efficacy of escitalopram on negative symptoms. On the other hand, perhaps the selection of samples according to Carpenter's Criteria for the Deficit Syndrome, with its accentuation on primary enduring negative symptoms, would be a better strategy for such types of evaluations. This is a point that cannot be overlooked in future studies. Nevertheless, these results are encouraging since they demonstrate a robust decrease in the negative symptoms of schizophrenia in the escitalopram group compared to placebo at endpoint, a symptom profile that has remained refractory to many previous attempts at treatment.

Conclusions

This study suggests a potential role for escitalopram as adjunctive with haloperidol in alleviating the negative symptoms of schizophrenia.

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