Research Article

Improvement of Deficit Syndrome by Escitalopram: A Local Pilot Study

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1. Abstract

1.1. Objective: The negative symptoms of schizophrenia remain a major clinical trouble against available therapeutic treatments. Escitalopram is known as the most selective SSRI with minimal effects on nor epinephrine and dopamine neuronal uptake. The purpose of present trial is to assess the influence of escitalopram on negative symptoms of schizophrenia.

1.2. Method: This assessment was an 8-week, randomized, placebo-controlled trial of escitalopram set against placebo, as an add-on medication, in treatment of 50 patients with diagnosis of schizophrenia. While the 'Scale for Assessment of Negative Symptoms' was used as the primary outcome measure, the 'Scale for Assessment of Positive Symptoms', the 'Simpson-Angus Scale' and the 'Hamilton Depression Scale', as well, were used as secondary measure for evaluation of positive, extrapyramidal and depressive symptoms, respectively.

1.3. Results: The primary outcome of the present assessment was a significant reduction in the mean total score of the 'Scale for Assessment of Negative Symptoms (SANS)' in the target group, compared to placebo, at the end of trial. Ultimately, most of the subscales of SANS, as well, demonstrated significant improvements by escitalopram.

1.4. Conclusions: According to the findings, escitalopram can be helpful, as add-on medication, in amelioration of negative symptoms of schizophrenia.

2. Keywords: schizophrenia; negative symptoms; deficit syndrome; escitalopram; adjunctive treatment, add-on medication.

3. Introduction

Negative symptoms in schizophrenia signify the lack or attenuation of normal behaviors and functions and constitute a significant dimension of psychopathology. They include decrease in verbal output or expressiveness, flattened or blunted affect, subjective reduction in interests, desires and goals, and a behavioral reduction in purposeful acts, including a lack of self-initiated social interactions [1, 2]. Insistent negative symptoms are held to account for much of the chronic morbidity and poor functional outcome of patients with schizophrenia [3-6]. An imperative clinical partition is between primary negative symptoms, which encompass an enduring deficit state, and secondary negative symptoms, which are subsequent to positive psychotic symptoms, depression or demoralization, or drug induced parkinsonism [5,7]. Secondary negative symptoms may be best improved by management of the relevant underlying reason [8]. In individuals with recognized schizophrenia, negative symptoms are seen to a variable degree in up to three-quarters [9, 10]. The writings concerning to pharmacological management of negative symptoms mostly involves analyses of acute effectiveness studies [11]. Though the proof advocates short-term effectiveness for a few mediations, there is no tough confirmation for an operative treatment for insistent primary negative symptoms. Antidepressants, as like as other psychotropic drugs, have a long and mixed history as potential therapeutic agents in negative symptoms of schizophrenia [12, 13], with rather unpredictable results [14-24]. Escitalopram, an S (+) enantiomer of citalopram, is the utmost selective serotonin reuptake

blocker with negligible effects on dopamine and norepinephrine neuronal uptake. It has no or very low affinity for serotonergic (5HT1-7) or other receptors including dopamine (D1-5), histamine (H1-3), alpha- and beta-adrenergic, muscarinic (M1-5), and benzodiazepine receptors [1]. So, Purpose of this study included evaluation of the effectiveness of escitalopram, as add-on medication, on negative symptoms of schizophrenia.

4. Method

While the human studies in this work were carried out in accord with the 'Declaration of Helsinki and Ethical Principles for Medical Research Involving Human Subjects' [25], the participants were informed regarding the procedure, and a printed permission was received from those who were attentive to participate in the assessment. Also, samples were allowed to take away from the study at any point without prejudice. Fifty patients were randomly allocated to either the placebo group (n=25) or escitalopram group (n=25). The participants and the investigators, also, were blind regarding which group was taking placebo or escitalopram. The age of the samples ranged amid 29 to 53 years old (41. 63±5.97 y/o), and all of them were man. The inclusion criteria consisted of the diagnosis of schizophrenia, according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text- Revised (DSM-IV-TR) [26], the existence of negative symptoms, and the period of schizophrenia for at least two years.

The 'Scale for Assessment of Negative Symptoms (SANS)' was used as the main outcome measure for assessing alogia (reduced spontaneous speaking), affective blunting (limited emotional manifestation), anhedonia (absence of sense of pleasure), avolition (deficiency of drives), and attention deficit [27]. The 'Scale for Assessment of Positive Symptoms (SAPS)' [28], the 'Simpson-Angus Scale (SAS)' [29] and the 'Hamilton Depression Scale (HDS)' [30] were also used as secondary measures for evaluation of positive, extra pyramidal and depressive symptoms, respectively. High negative symptom scores (higher than twenty percent of overall SANS), low positive symptom scores (lesser than twenty percent of overall SAPS), low extra pyramidal symptom scores (lesser than twenty-five percent of overall SAS), and, lastly, low depressive symptom scores (HDS lesser than ten) were the basis of our inclusion criteria. The exclusion criteria, as well, are shown in **(Table 1)**. To exclude cognitive disturbance and depression, which could be confused with the negative symptoms of schizophrenia, the 'Mini Mental Status Examination (MMSE)' [31] and 'Hamilton Depression Scale (HDS)', respectively, were used. MMSE lesser than 25, and HDS more than 10, were identified as cognitive disturbance and depression, respectively, and could lead to patient exclusion. All participants, after a washout period of 2-weeks, subsequent to tapering off of their former typical antipsychotics (neither group had received any form of depot injection during the last 6 months before entering the study), had been prescribed daily haloperidol (five milligram per day). They were randomized to placebo or escitalopram (10 milligram per day) groups. The escitalopram and placebo tablets had the same color and shape, making it difficult for the physician and patients to distinguish them. The assessment duration was 8 weeks, and the participants were evaluated at both the initiation and at the conclusion of the trial.

5. Statistical Analysis

Patients were compared on baseline characteristics by 'chi-square tests' for categorical variables and 't tests' for continues variables. Moreover, comparison between the scores of SANS, SAPS, SAS and HDS at baseline and assessing differences in subtests of SANS, between these groups, at the end of the trial, had been accomplished by means of 't test 'or 'compression of proportions'. Statistical significance was defined as a 2-sided p value < or = to 0.05. MedCalc, version 9.4.1.0, was used as statistical software tool for analysis.

6. Results

Since there was no drop-out in both groups, analysis for efficacy was based on data from an equal number of patients in both groups, which were initially comparable, with analogous demographic and diagnostic variables **(Table 2)**. Though progress was demarcated as a lessening of twenty percent or further in the severity of each subtest, at the final stage of assessment, the SANS' scores were enhanced in eighty percent of the patients in the target group compared to thirty-six percent of the participants in the placebo group (Table 3). In this regard, the SANS' mean total score in the target group reduced from 84. 10±4.68 to 73.95±3.74 ($t=8.47$, $p<0.00$, CI: 7.74, 12.56) at the end of the evaluation, whereas such an outcome was not evident in the other group (82. 39±5.30 to 79.37±6.11 ($t = 1.84$, $p>0.06$, CI: -0.23, 6.27). Likewise, most of the sub-tests of SANS confirmed a significant upgrading in the target group as compared with the placebo group. Among them, the anhedonia-asociality sub-test revealed the furthermost progress, and a logia exposed the minimum mitigation. Granting there were not any similar significant alterations in the positive, extra pyramidal and depressive symptoms in both groups throughout the evaluation, it should be pointed that thirty-eight percent of the participants in the placebo group, and thirty-five percent of the samples in the target group, needed an anti cholinergic drug (trihexyphenidyl, 4-6 mg per day) for improvement of parkinsonism or tremors in the course of assessment.

Table 1 – 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 antipsychotics	Medical deafness or muteness

Table 2- Demographic profile of participants.

Variables	Placebo (n=25)	Escitalopram (n=25)	T	P	CI
Gender (male)	25	25	0	1	-0.19,0.19
Age (years); mean (SD)	41.63(±4.72)	39.12(±4.93)	1.83	0.072	-0.23, 5.25
Duration of illness (years); mean (SD)	7.35(±2.74)	8.36(±2.87)	-1.27	0.209	-2.61, 0.59
Mini Mental State Examination score; mean (SD)	24.41(±1.68)	25.16(±1.10)	-1.86	0.068	-1.56, 0.06
Hamilton Depression Scale (HDS) score; mean (SD)	4.29(±4.18)	5.17(±4.41)	-0.72	0.472	-3.32, 1.56

Table 3 – Responders by at least 20% decrease in SANS' subscales.

Negative symptoms	Placebo (%)	Escitalopram (%)	Z	P	CI
Affective Blunting	1(4%)	7(28%)	-2.31	0.02	-0.44,-0.03
Alogia	4(16%)	10(40%)	-1.88	0.05	-0.48,0.008
Avolition-Apathy	4(16%)	7(28%)	-1.02	0.3	-0.34,0.10
Anhedonia-Asociality	1(4%)	8(32%)	-2.57	0.01	-0.49,-0.06
Attention Deficit	2(8%)	8(32%)	-2.12	0.03	-0.46,-0.01
Total	9(36%)	20(80%)	-3.15	0.001	-0.71,-0.16

7. Discussion

In first-episode psychosis, the existence of negative symptoms has been associated to poor outcome in terms of level of social functioning and recovery [32]. Also, there is proof to propose that the earlier a psychotic disorder is successfully treated, the less probable is the progress of negative symptoms over time [33]. Nevertheless, when deducing such facts, it should be noticed that an early clinical picture characterized by negative symptoms, may contribute to interruption in presentation to clinical facilities and so be connected with a longer period of untreated psychosis [34]. On the other hand, while with regard to antidepressant management of negative symptoms, a Cochrane review had determined that this may be an operative approach for decreasing alogia, avolition and affective flattening [35], analysis of outcomes have found only unpredictable confirmation for minimal effectiveness [36, 37, 38]. Nevertheless, psychotic disorder should be recognized and treated as early as possible because this may cause some safety against the progress of negative symptoms [37]. For any patient, the antipsychotic drug that offers the best balance between general effectiveness and adversative effects should be used, at the lowermost dosage that preserves control of positive symptoms [35]. Also, where negative symptoms continue further than an acute episode of psychosis, the clinician should ensure that depression and extra pyramidal symptoms have been identified and treated if existing [36]. Currently, there is not enough proof to support a sanction for any specific pharmacological management for negative symptoms. Nonetheless, a trial of add-on drug for which there is some strong evidence for effectiveness, such as an antidepressant, may be worth bearing in mind in some cases, ensuring that the choice of the add-on medication is grounded on minimizing the potential for compounding adversative effects through pharmaco-kinetic or pharmaco-dynamic drug interactions [38]. On the other hand, a link between negative symptoms and deregulation of the serotonin system has been proposed by an abnormal prolactin response to fenfluramine in schizophrenia [39]. The present view is that barricade of serotonin receptors may be key to the lessening of negative symptoms and extra pyramidal adverse effects [40]. In this regard, Moller has indicated that selective serotonin reuptake inhibitors seem to have a certain place in the treatment of negative symptoms [41]. So, while the outcomes of our evaluation further support the role of antidepressants as adjunctive or add-on medications in improvement of negative symptoms of schizophrenia, our results with escitalopram, are consistent with the abovementioned studies. Also, it may be probable that adding escitalopram to atypical antipsychotics could have the same outcome as was proven with haloperidol. Also, it is well-known that negative symptoms continue to lessen for some months after beginning of treatment. Therefore, the 8-week length of this assessment, in addition to minor dose of the drug used in this appraisal, may have underrated the full usefulness of escitalopram on negative symptoms. Alternatively, maybe the assortment of patients in line with Carpenter's Standards for the Deficit Syndrome, with its accentuation on primary lasting negative symptoms, would be a better policy for such types of estimations. This is a point that cannot be disregarded in forthcoming studies. Nevertheless, these consequences are inspiring since they reveal a tough decline in negative symptoms of schizophrenia in the target group compared to placebo group at endpoint, a symptom profile that has stayed refractory to many previous psychotherapeutic endeavors. while the small sample size and short duration of assessment were among the weaknesses of the present estimation, for sure, larger methodical studies, in future, with comparable objectives, are required for finding better

answers with respect to successful management of negative symptoms.

8. Conclusions

According to the findings, escitalopram can be helpful, as add-on medication, in amelioration of negative symptoms of schizophrenia.

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