

# Treatment-Responsiveness of Negative Symptoms in Schizophrenia: A double-blind placebo-control clinical trial

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## Abstract

**Background:** The negative symptoms of schizophrenia remain a major clinical challenge. Nortriptyline is a serotonin and noradrenalin reuptake inhibitor and belongs to secondary amine tricycles. The aim of this study is to evaluate the effect of nortriptyline on the negative symptoms of schizophrenia.

**Methods:** This study is a six-week randomized placebo-control trial of nortriptyline or placebo as an adjunctive to haloperidol (5 mg) in the treatment of 50 patients with Diagnostic and statistical manual for Mental Disorders (DSM-IV) criteria for chronic schizophrenia.

**Result:** The primary finding of the trial was a significant reduction in Scale for Assessment of Negative Symptoms (SANS) in the nortriptyline group compared to placebo at the end of 6 week. All the subscales of SANS demonstrate significant improvement.

**Conclusion:** This study suggests a potential role for nortriptyline in the treatment of negative symptoms of schizophrenia.  
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**Keywords** • Schizophrenia • negative symptom • nortriptyline

## Introduction

Antidepressants have a long and mixed history as potential therapeutic agents in negative symptoms of schizophrenia.<sup>1,2</sup> Although negative symptoms such as avolition, anhedonia, restricted emotional expression, lack of drive and attention deficit, are not common in schizophrenia, their treatment is challenging. Much of the available data, due to methodological and diagnostic difficulties, is inconsistent. For example, the use of antidepressants in the presence of concomitant depression in schizophrenia patients raises the question whether the treatment is primarily an antidepressant effect or a direct effect on negative symptoms. Nevertheless, the efficacy of imipramine in negative symptoms in stable schizophrenic patients with depressive symptoms has been reported.<sup>3</sup>

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.<sup>1-3</sup> Fluvoxamine, 100 mg daily, has shown to be efficacious over placebo in a five-week trial.<sup>4</sup> Two fluoxetine trials at 20 mg doses have suggested efficacy in schizophrenia as greater improvement in total scores,<sup>5</sup> and improvement in Brief

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Psychiatric Rating Scale (BPRS) negative scores.<sup>6</sup> There are however, trials of citalopram and fluoxetine with negative results, making definitive conclusions difficult.<sup>7,8</sup>

Other antidepressants have been studied in placebo-controlled designs. While trials of amitriptyline augmentation of perphenazine were reported to have some efficacy.<sup>9</sup> However, no improvement was noted with maprotiline.<sup>10</sup> Nortriptyline is a serotonin and norepinephrine reuptake inhibitor with anticholinergic effects. Therefore, this study was to assess the efficacy of nortriptyline as an adjunctive drug on negative symptoms of schizophrenia.

### Patients and Methods

The study was approved by University Medical Ethics Comity. The patients were informed about the procedure and a written consent was received from those who were interested to participate in the study. Patients were free to withdraw from the study at any stage without prejudice. There was one drop out in the placebo group due to myocardial infarction.

Fifty patients were randomly allocated to either nortriptyline (25 patients) or placebo (25 patients) groups. The patients and the researchers were blind about which group was taking nortriptyline or placebo. The age of these patients was between 38-48 year (mean 43±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.

**Table 1:** Demographic presentation of patients participated in the placebo and nortriptyline groups.

	placebo	Nortriptyline
Gender (male)	25	25
Age (yr)	44±4	42±4
Education (yr)	9.0±2.0	10.1±2.0
MMSE	23.5±1.0	24.2±1.1
HDS	5.3±4.0	6.1±4.0

The inclusion criteria consisted of diagnosis of Schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV),<sup>11</sup> the presence of negative symptoms of schizophrenia, and duration of schizophrenia of more than two years. The exclusion criteria are presented in Table 2. To exclude depression and cognitive disturbances that can be confused with negative symptoms of schizophrenia Hamilton Depression Scale (HDS) and Mini-Mental Status Examination (MMSE) were used respectively. A HDS more than 10 and MMSE less 20 were diagnosed as depression and cognitive disturbance and led to patient exclusion.

**Table 2:** Exclusion criteria

1	Major depressive disorder
2	Schizoaffective disorder
3	Mental retardation
4	Bipolar disorder
5	Neurological disorders
6	Using atypical antipsychotic
7	Using antidepressants or lithium
8	Medical complications
9	Unstable, irritable, aggressive patients
10	Duration less than one year
11	Parkinsonism
12	Medical deafness or muteness

All patients were receiving daily haloperidol (5 mg/day). They were randomized to placebo or nortriptyline (started with 25 mg daily and during a period of three weeks increased to 50 mg/day) groups. The placebo and nortriptyline tablets had the same shape and color to make it difficult for the patients and the physician to differentiate them. The study duration was six weeks, and the patients were assessed at the start and at the end of the trial. Scale for Assessment of Negative Symptoms (SANS) was used as the primary outcome of evaluating Affective blunting (restrictive emotional expression), Alogia (reduced spontaneous speaking), Avolition (lack of drives), Anhedonia (lack of sense of pleasure) and Attention deficit.<sup>12</sup>

### Statistical analyses

Comparisons between the nortriptyline and placebo groups at baseline were performed using the Chi-square test for demographic data, and Fisher's exact test was used to assess differences in SANS score between the two groups at the end of the trial.

### Results

The primary outcome measure was SANS and at the baseline visit (day 0) and there was no significant difference in the scores for the SANS total and negative subscales of the two groups.

Nortriptyline had a significant effect on the negative symptoms, which was evident as early as week three, and continued for six weeks, the remaining period of the study (Table 3).

**Table 3:** Patients with significant improvement in total and subtests of Scale for Assessment of Negative Symptoms (SANS) in nortriptyline group compared to placebo group

	Placebo # (%)	Nortriptyline # (%)	P value
AB	2(8)	6(24)	0.029
Alogia	6(25)	11(46)	0.031
AA	1(4)	8(32)	0.002
An As	4(17)	11(46)	
Total	9(37)	8(32)	

AB= Affecting Blunting; AA= Avolition Apathy;  
An As= Anhedonia Asociality, AD= Attention Deficit

At the end of the trial, the SANS negative scale scores was improved in 80% of patients in nortriptyline group comparing to 37.5% of patients in placebo group. All subtests of SANS also demonstrated significant improvement in nortriptyline group compared with placebo group ( $P < 0.05$ ). Among them avolition-apathy subtest showed the most alleviation ( $P < 0.012$ ) and alogia revealed the least alleviation but still significant ( $p < 0.031$ ).

## Discussion

The result of this study shows a robust effect for nortriptyline in reducing the negative symptoms of schizophrenia. Nortriptyline is a secondary tricyclic antidepressant drug with actions on norepinephrine, serotonin (5-HT) and to a lesser extent dopamine.<sup>14</sup> It has also a blocking effect on muscarinic acetylcholine and histaminic receptors, however, its potential therapeutic effects in schizophrenia remain speculative.<sup>13</sup>

In a Meta analysis survey it was demonstrated that the efficacy and safety of antipsychotic and antidepressant combination in the treatment of the negative symptoms of schizophrenia is superior to either antipsychotic or antidepressant alone, but this finding needs to be corroborated by further large trials.<sup>14</sup> The results of our study further supported 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.<sup>15</sup> The current view is that blockade of serotonin receptors may be key to reduction of negative symptoms and extra pyramidal side-effects.<sup>16</sup> Moller HJ based on MEDLINE searches in the databases from 1995 to September 2002 identified that specific serotonin reuptake inhibitor seem to have a certain place in the treatment of negative symptoms.<sup>17</sup> Our finding with nortriptyline as a serotonin and noradrenalin reuptake inhibitor is consistent with the above studies.

Noradrenalin appears to have a function in drive,<sup>18</sup> and noradrenergic reuptake inhibitors such as reboxetine may have a greater beneficial effect on social functioning.<sup>19</sup> It is thus possible that the effect of nortriptyline on negative symptoms relates to increase in noradrenergic function. The negative symptoms of schizophrenia may be associated with impaired dopaminergic function in the prefrontal cortex,<sup>17,20</sup> suggesting a possible mechanism of action of nortriptyline via receptors on cortical dopamine in this disorder.

There are certain limitations to this study, with the small sample size being a primary example. Larger studies with similar aims are necessary. It may be possible that addition of nortriptyline to atypical neuroleptics will not have the same effect as was evident with haloperidol. Further dose ranging data are also necessary. It is known that negative symptoms continue to decline for some months after initiation of treatment. The 6-week duration of this trial may thus have underestimated the full efficacy of nortriptyline on negative symptoms. Nevertheless, these results are encouraging since they demonstrate a robust decrease in negative symptoms of schizophrenia in the nortriptyline group at the endpoint, a symptom profile that has remained refractory to many attempts at treatments before.

## Conclusion

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

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