



# Adjunctive simvastatin treatment in schizophrenia patients; a double blind randomized and placebo controlled trial

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## Abstract

**Introduction:** Statins such as simvastatin are recently introduced as agents that may have beneficial effects in schizophrenia regarding their prominent anti-inflammatory properties.

**Objectives:** This study was designed to evaluate the effects of simvastatin on schizophrenia symptoms.

**Patients and Methods:** In a double-blinded randomized clinical trial, 40 hospitalized schizophrenia patients (according to the DSM-IV-TR criteria) were studied for 6 weeks. One group of the patients ( $n=20$ ) received simvastatin (with the dose of 40 mg/d) and the other group received ( $n=20$ ) placebo. The patients were evaluated by the Positive and Negative Syndrome Scale (PANSS) for schizophrenia symptoms. Data were analyzed with mixed model repeated measure ANOVA, t test, and  $\chi^2$  test or Fischer's exact test by SPSS software. The significant cutoff was considered at  $P<0.05$ .

**Results:** The mean age of the patients was  $34.05 \pm 9.74$  years and 50% of them were men. There was not a significant difference between the two groups regarding negative symptoms reduction.

**Conclusion:** Our study demonstrated that adding simvastatin on atypical antipsychotic treatment had no significant beneficial effects on the negative and positive symptoms in patients with schizophrenia disorder.

**Trial Registration:** The trial protocol was approved by the Iranian Registry of Clinical Trials (identifier: IRCT2017052034046N1; <https://en.irct.ir/trial/26134>, ethical code; ETH-457).

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## Introduction

Schizophrenia disorder is a clinical syndrome including alternating psychological vulnerability, and is so destructive that involves cognition, excitement, perception, and other spiritual aspects. Occurrence of these manifestations changes in different people during the time, but the disease effects are always severe and lasts long (1). The prevalence of schizophrenia disorder is about 0.5% in different societies according to the definition of the disease and various geographical situations (2).

Currently, the main treatment for schizophrenia patients is anti-psychotic drugs (first and second generation). Although these agents have a remarkable effect on positive symptoms in patients with schizophrenia, their impact on negative symptoms (as the best predictors for disease prognosis and social function) is limited. These deficiencies in our current knowledge have urged a need for extensive researches to discover new agents to help fight against

## Key point

The current clinical trial study showed that adding a 6-weeks administration of simvastatin on atypical antipsychotic treatment had no significant beneficial effects on the negative and positive symptoms in patients with schizophrenia disorder.

negative symptoms (3).

Several studies have recently shown that some cytokines including interleukin 1 beta (IL-1 $\beta$ ), interleukin 6 (IL-6), transforming growth factor - $\beta$ , tumor necrosis factor alpha (TNF- $\alpha$ ), Interferon- $\gamma$ , and nuclear factor kappa-light-chain-enhancer of B cell play an important role in the pathogenesis of schizophrenia disorder (4-8). For example, some pro-inflammatory cytokines such as IL-1 $\beta$  led to the induction of some negative symptoms like lethargy, anhedonia, and social withdrawal by affecting dopaminergic and glutamatergic receptors (9). Our current knowledge about inflammatory mechanisms has strengthened this hypothesis that inhibiting the inflammatory mechanisms

could diminish the symptoms of schizophrenia, especially negative symptoms (10). Based on this hypothesis some clinical trials showed that the addition of celecoxib and aspirin to standard treatment of schizophrenic patients had a positive effect in the treatment of negative symptoms (11).

One of the potential agents that can be used in treating schizophrenia due to inflammatory properties is the statin family. Statins are the inhibitors of HMG-CoA ((3-hydroxy-3-methylglutaryl-coenzyme A)) that commonly used as cholesterol-lowering drugs (10,12,13). It has recently been indicated that statins like simvastatin may reduce IL-1 $\beta$  and TNF- $\alpha$  which are among important factors in schizophrenia pathogenesis (14). In addition to inflammatory mechanisms, statins could theoretically be useful in schizophrenia treatment through the following mechanisms; positive effect of simvastatin on regulating the disorders through N-methyl-D-aspartate receptor (NMDA) receptors and preventing neuronal degeneration by influencing cell membrane phospholipids metabolism (15-16). Glutamate is another transmitter that plays an important role in the pathogenesis of schizophrenia disorder. Malregulation of this transmitter exists in schizophrenia (17). Simvastatin has an important role in regulating psycho-degenerative disorders through NMDA receptors (16). One of the other pathways involved in the pathology of schizophrenia is the metabolic abnormalities of cell membrane phospholipids. Reduction in polyunsaturated fatty acids (PUFAs) content of the cell membrane has been observed in brain tissue and peripheral tissues such as red blood cells and dermal fibroblasts in patients affected by schizophrenia disorder (18-20). Statins such as PUFA prevent neuronal degeneration and cause improved cognitive and learning functions (15). Additionally, simvastatin is widely being administered in affected patients especially with atypical anti-psychotic drugs and improves lipid profile and reduces cardiovascular diseases risk in these patients. On the other hand, it is well tolerated and has no significant interaction with anti-psychotic drugs (10,12,13). Recently, few clinical trials have examined the effect of simvastatin on schizophrenia symptoms that *their results were controversial* (13). Therefore, conducting more studies, especially clinical trials seem absolutely necessary.

## Objectives

The current study was designed and carried out with the aim of bridging this gap in our current knowledge regarding the impact of simvastatin on negative symptoms of schizophrenia patients.

## Patients and Methods

### Study design

This trial was a double-blinded, parallel-group, placebo- and active-controlled study that was conducted from June until December in 2012.

## Participants

This study was performed in the psychiatry ward of Golestan hospital, Ahvaz, southwest of Iran as the biggest referral center for psychiatry in the southwest of the country. The participants included 40 patients with schizophrenia aged 18-58 years who had recently been hospitalized in psychiatry ward and had received one of the atypical antipsychotic agents (in therapeutic dose range). Schizophrenia was diagnosed according to criteria of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) (21) by an expert psychologist. Inclusion criteria included patients with schizophrenia diagnosis based on DSM-IV-TR criteria, the general score of 50 or higher in the Positive and Negative Syndrome Scale (PANSS) scale, the negative score of 15 or higher in PANSS scale and duration of at least one year from disease beginning. Exclusion criteria included patients with history of allergy to statins, active hepatic disease, renal failure and concomitant other serious medical or psychological disorders, drug abuse or dependency during the last month, pregnancy, lactation and the use of statins or anti-inflammatory agents and drug-resistant schizophrenia.

## Interventions

Based on the clinical guidelines recommendations, all the patients received a standard therapeutic regimen that had a second generation of antipsychotic agents. Individuals were randomly (based on block randomization method) divided into two groups (20 in each group) for receiving simvastatin or placebo, along with their usual treatment of schizophrenia for six weeks.

All patients were treated with oral atypical antipsychotics (equivalent to 200-1000 mg/d of chlorpromazine) and if needed, bipyridine (2-6 mg/d) and/or clonazepam (0.5-2 mg/d).

Whenever parenteral haloperidol and bipyridine were required, later they were considered in calculations. In the case group, patients received simvastatin with the dose of 40 mg/d for 6 weeks. In the control group, the placebo tablet which was completely like simvastatin regarding appearance and physical properties and had been produced by Pharmacy Faculty of Ahvaz Jundishapur University of Medical Sciences was administered at a similar manner for the patients. It should be noted that researchers did not make any intervention in the standard treatment of patients and simvastatin or placebo were just added to their treatment regimens based on their groups.

Regarding the double-blinded nature of the study, the researcher who had divided the patients into two groups did not have any role in the therapeutic program or completing the questionnaires. Moreover, those psychiatrists who were responsible for the treatment and filling the questionnaires were not aware of the patients' treatment group. Patients follow up was conducted by their codes.

## Outcomes

The primary endpoint of this trial was the effectiveness of simvastatin on schizophrenia symptoms. In order to investigate the primary outcome, we employed the PANSS (22) at the beginning of the study and also weeks three and six after the beginning of treatment.

The secondary outcome of this study was side effects caused by simvastatin compared to placebo. Drug side effects were checked weekly. Furthermore, the symptoms and clinical condition of the patients were also assessed weekly. All the evaluations for measuring the primary and secondary outcomes were conducted by an expert psychiatrist specialist.

## Data analysis

Data were reported as mean  $\pm$  SD using descriptive statistics parameters. The mixed model repeated measure ANOVA was applied for evaluating the main results that included the effect of time, group and interaction between the effects of time and group. Besides, in order to analyze the continuous quantitative data, *t* test was utilized and  $\chi^2$  test (chi-square test) or Fisher's exact test was utilized for the qualitative data.  $P < 0.05$  was considered significant. All the data were analyzed by SPSS version 18 software.

## Results

At the beginning of the study, 65 schizophrenic patients were examined for eligibility criteria. Twenty-five patients did not have needed criteria for enrolling in the study. The 40 remaining patients were divided into two groups of case and control by block randomization method (Figure 1). The mean age of patients was  $34.05 \pm 9.74$  years. Twenty people (50%) were women. Other demographic characteristics of the patients have been shown in Table 1. Thirty-five (88%) patients completed the 6-week treatment period. Two samples (5%) of the intervention group just had two evaluations because were discharged

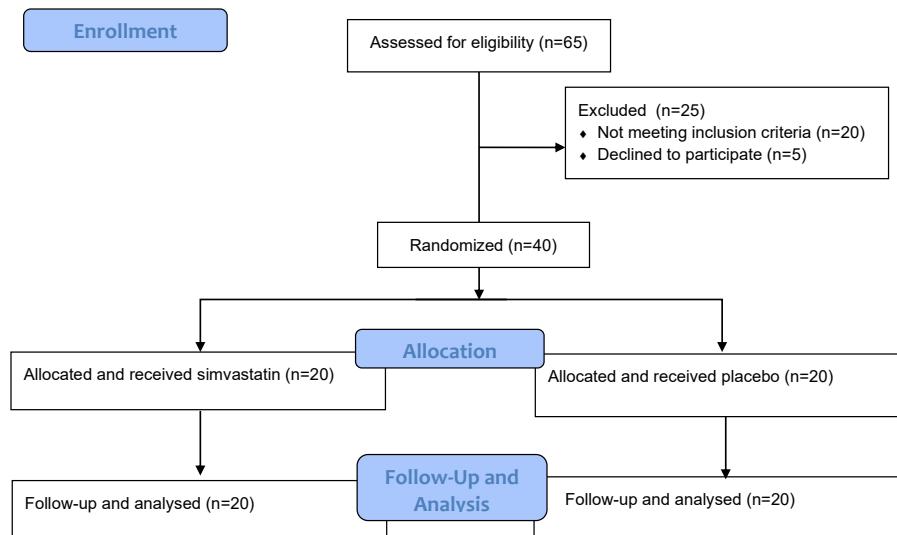
**Table 1.** Baseline data

Variables	Simvastatin group (n=20)	Placebo group (n=20)	P value
Age (Mean $\pm$ SD)	36.25 $\pm$ 10.41	31.85 $\pm$ 8.73	NS*
Gender (male/female)	10/10	10/10	NS
Smoking status	9	7	NS
Education Level			NS
Under diploma	9	10	
Diploma	8	8	
Higher diploma	3	2	
Marital status			NS
Single	6	7	
Married	5	8	
Divorced	9	5	
PANSS scores			NS
Negative	36.25 $\pm$ 19.06	43.40 $\pm$ 27.40	
Positive	56.55 $\pm$ 16.34	54.80 $\pm$ 18.17	

\* Not significant.

against medical advice. One person (2%) of the placebo group also left the hospital against medical advice before week 5. Two other people (5%) of the placebo group also left the study on week 4 due to electroconvulsive therapy (ECT) treatment beginning. The rate of exiting the study did not have a significant difference between the two groups ( $P > 0.05$ ).

The scores of all the patients from both groups in negative subgroup have been demonstrated in Table 2. These results showed that although there has been a reduction in the negative and positive symptoms in the simvastatin group, there was not a statistically significant difference ( $P > 0.05$ ). The mean scores of positive and negative symptoms of PANSS have been indicated in Table 2 and Figures 2A and 2B. In patients of both groups, no side effect related to simvastatin or placebo was seen. In the intervention group, three cases showed tremor which



**Figure 1.** CONSORT flow diagram of the study.

**Table 2.** Comparison of the mean PANNS scores in the group treated with simvastatin and placebo at weeks 0, 3 and 6

Variables		Simvastatin group (n=20) Mean ± SD	Placebo group (n=20) Mean ± SD	P value
PANSS scores	Negative symptoms	Week 0	36.25±19.06	43.40±27.40
		Week 3	26.95±18.85	30.45±18.73
		Week 6	21.70±14.79	21.80±14.10
	Positive symptoms	Week 0	56.55±16.34	54.80±18.17
		Week 3	38.45±16.43	37.65±15.14
		Week 6	28.50±16.22	25.90±14.48

did not have any significant difference between the two groups ( $P>0.05$ ).

## Discussion

This study was a double-blinded randomized clinical trial that examined the effect of simvastatin (with a dose of 40 mg/d) on the reduction of negative symptoms. We found out that including simvastatin in treatment of schizophrenic patients during six weeks did not have a significant effect on reducing the negative symptoms of the patients.

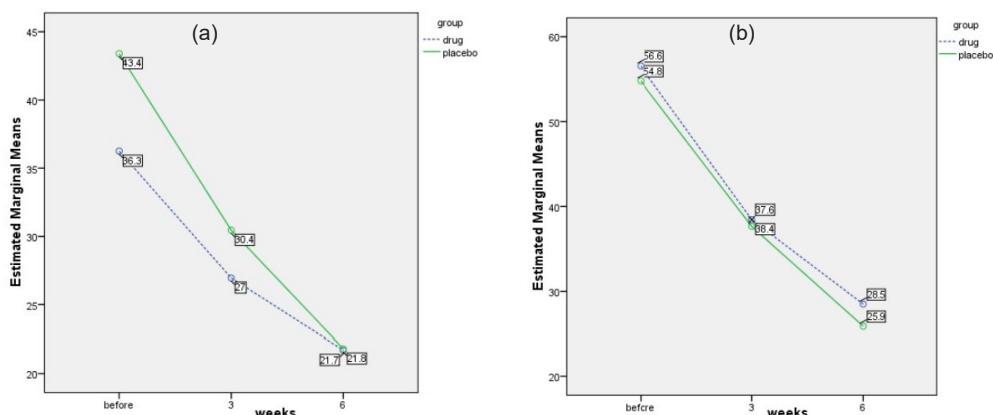
The dopamine pathway is still considered as the most accepted theory for the explaining of schizophrenia; however, this theory has not fully explained the various aspects of schizophrenia, especially in the context of negative symptoms, the increasing attention to other pathways; especially the inflammatory process is spreading (23).

Several studies have been conducted regarding the role of anti-inflammatory agents in improving negative symptoms of schizophrenia; however, the statin agents have been tested in just a few trials despite their clear anti-inflammatory effects. Currently, statins are widely being administered in schizophrenia patients especially along with the second generation of anti-psychotic agents for treating hypercholesterolemia. Some studies suggested that statins have clear anti-inflammatory properties and act completely like cyclooxygenase 2 inhibitors for some characteristics. The idea of using statins in schizophrenia

treatment relies on anti-inflammatory properties of these agents, their high tolerability, few side effects, wide usage in the current treatment of patients as a preventive factor for lipid profile disturbances and lack of remarkable interaction with other anti-psychotic drugs. All these benefits besides considering the insufficiency of existing evidence are all rational reasons for additional studying of simvastatin on negative symptoms of schizophrenia (1,2,4-8,10,12,13).

Unfortunately, in spite of the strong theoretical support for statins' impact on schizophrenia treatment, just a few studies have been conducted on this subject. Accordingly, Deakin et al carried out a study to evaluate the effect of ondansetron and simvastatin (dose of 40 mg/d) with 2×2 design and six months follow up on 302 patients with schizophrenia-related diagnosis. They concluded that simvastatin had limited effects on schizophrenia patients (24).

These results are consistent with our findings. In line with our study, Ghanizadeh et al evaluated the effect of lovastatin in adjunctive treatment of schizophrenia patients during eight weeks in a clinical trial. Their study did not succeed to show any significant effect of statins in comparison with placebo in schizophrenia symptoms. One of the defects of this study was a significant difference in risperidone dosage between the patients of two groups, which could affect the conclusion. (10). Tajik-Esmaeeli et al in an 8-week randomized clinical trial investigated the effects of adjunctive treatment with simvastatin (dose

**Figure 2.** Comparison of the mean (a) negative and (b) positive symptoms of PANNS scores between the simvastatin and placebo group at weeks 0, 3 and 6.

of 40 mg/d) on negative symptoms of 33 schizophrenia patients who had received a fixed dose of risperidone in the last previous month. Contrary to our findings, their study demonstrated that simvastatin significantly reduced negative symptoms in patients at the end of the 8<sup>th</sup> week relative to the baseline in comparison with the placebo group (13). In another 12-week clinical trial, the addition of simvastatin to treatment diminished symptoms, although this difference was not significant (25).

One of the reasons that can be considered as a rational explanation for the statin failure in our trials and other trials with similar results is the more complexity of the anti-inflammatory hypothesis than TH1/TH2 hypothesis. It seems that the dysregulation of cytokines has a more important role in the schizophrenia pathogenesis than just increase in the interleukins levels. The evidence for this issue is the existing inconsistency in studies about cytokines role especially IL-6. For example, in contrast to other studies, Singh et al, indicated that IL-6 level was lower in schizophrenia patients (26). Additionally, our theoretical knowledge about statins' role in the regulation of inflammatory cytokines is more based on animal models of inflammation. Usually in animal models, synthetic inflammation factors are used to simulate the inflammatory processes and it seems that these processes do not have enough time for irreversible changes, while schizophrenia mechanisms usually occur chronically and mostly led to irreversible neurodegenerative injuries in affected people, therefore the removal of inflammatory factors can only prevent the progression of the disease.

### Conclusion

Our study showed that although simvastatin was well tolerated in schizophrenia patients, it could not significantly reduce the symptoms of these patients. Although the final result is negative for any effect, this study is worth considering that its data can be included in potential future meta-analyses in the field.

Finally, we suggest that this study be conducted in outpatients and also in recent diagnosed schizophrenia patients, with larger sample size, higher doses and prolonged follow up.

### Study limitations

It seems that the duration of six weeks is insufficient to induce anti-inflammatory effects, especially for the central nervous system (10). Furthermore, all our patients were hospitalized ones who usually are poor prognosis and this factor could also be considered as a limitation of our study. Moreover, as the effects of simvastatin treatment are expected to be modest (especially at 40 mg dosage), the treatment duration of only six weeks seems insufficient to study its potential beneficial effects. The small samples in each group (n=20) suggest that the study was underpowered.

### Authors' contribution

SA, SMG and HB designed the protocol of study. SR, NE, ZA and PN participated in the implementation study. All authors worked for data analysis and manuscript writing.

### Conflicts of interest

The authors have declared no conflict of interest.

### Ethical issues

The study was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences. The trial was registered by the Iranian Registry of Clinical Trials with ETH-457 ethical code. The informed consent was obtained from all the participants before beginning the study according to the Declaration of Helsinki. This study was part of psychiatry residential thesis of Ahvaz Jundishapur University of Medical Sciences. The trial protocol was approved by the Iranian registry of clinical trial (IRCT2017052034046N1; <https://en.irct.ir/trial/26134>). Additionally, ethical issues including plagiarism, double publication, and redundancy were completely observed by the authors.

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