Research Paper
Comparing the Effects of Adjunct Aspirin and Simvastatin on Psychopathology Among Inpatients With Schizophrenia

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ABSTRACT

Objectives: As a severe mental health condition, schizophrenia presents a chronic and complex clinical manifestation and neuropathology. A large body of literature exists on the pharmacological treatment of schizophrenia. However, evidence on some dimensions of such interventions (e.g., eligible candidates, potential predicting factors of the therapeutic outcomes, safe implementation of these interventions, etc.) are notably scarce. Studies revealed superior influences of adjunct statin therapy over placebo among patients with schizophrenia. The study aimed to investigate the effects of aspirin and simvastatin as adjunctive therapy, compared to placebo on positive and negative symptoms and general psychopathology of patients with schizophrenia.

Methods: This is a double-blind, randomized clinical trial. The sample size was estimated to be 15 individuals for each one of the three research groups (n=45). The Positive And Negative Syndrome Scale (PANSS) and the Hamilton Rating Scale For Depression (HAM-D) were employed to collect the study data in the present study. The study patients were recruited from patients admitted to the psychiatric wards of Razi Hospital were identified. The study subjects were randomly divided into two test groups and one control group. All groups were initially treated with risperidone 4 mg daily for 3 weeks. Then, group A received aspirin (325 mg twice daily), whereas group B was prescribed 40 mg/d of simvastatin. However, the control group received a placebo. Psychiatric symptoms were recorded according to the PANSS at the beginning of the study and then at weeks 4 and 8. The results were analyzed using inferential statistics (repeated-measures analysis of covariance) and descriptive statistics in SPSS software v. 20.

Results: Of 45 patients, 35(77.78%) were men (Mean±SD age: 45.8±10.5 years), and 10(22.23%) were women (Mean±SD age: 42.3±7.8 years). The mean scores of the positive symptoms of PANSS significantly decreased in the groups treated with aspirin and simvastatin (P=0.006 and P=0.005, respectively). However, no such difference was seen in the controls (P=0.447). Furthermore, the mean scores of the negative symptoms of PANSS significantly decreased in the intervention groups (P<0.001); in addition, no significant differences were seen in the controls after the end of the research program (P=0.18). In addition, the mean scores of the general symptoms of PANSS significantly decreased in the aspirin and simvastatin groups (P<0.001). There was an increase in the same value in the controls, but the increase was not significant (P=0.31). Finally, while the total mean scores of the PANSS increased in the control group (P=0.25), the corresponding scores significantly decreased in the test groups receiving aspirin and simvastatin (P<0.001).

Discussion: The present study results indicate that either aspirin or simvastatin can reduce the symptoms of schizophrenia, including general psychopathology, negative symptoms, and positive symptoms in the explored patients. Also, the effectiveness of both drugs was similar, and no significant difference was detected between these medications in reducing the symptoms mentioned above.

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Highlights

● Aspirin and simvastatin can both reduce the symptoms of schizophrenia, including negative symptoms, positive symptoms, and general psychopathology in patients with schizophrenia.

● The effectiveness of combined aspirin and simvastatin was similar in reducing the symptoms of patients with schizophrenia.

● Using aspirin and simvastatin is recommended as adjunctive therapy and should not be considered a substitute for the main treatment.

Plain Language Summary

Schizophrenia is a chronic and complex disease. Studies support better effects of adjunct statin therapy compared to placebo in patients with schizophrenia. We explored the impacts of aspirin and simvastatin as adjunctive therapy, compared to placebo on positive and negative symptoms and general psychopathology in patients with schizophrenia. The results indicate that aspirin and simvastatin reduce the symptoms of schizophrenia, including negative symptoms, positive symptoms, and general psychopathology. The effectiveness of both drugs was similar, and no significant difference was observed between these drugs in reducing these symptoms.

1. Introduction

Schizophrenia is a complicated psychiatric disorder influencing almost 1% of the population during their lifetime worldwide [1]. As a severe mental health condition, schizophrenia presents a chronic and complex clinical manifestation and neuropathology [2]. The global number of schizophrenia spectrum disorders is above 21 million [3]. Estimations suggest that approximately 7 out of 1000 individuals will develop this disorder during their lifetime [4]. This disease could be developed in any society and geographical area, and its incidence and prevalence rates follow almost the same trend worldwide [4]. Schizophrenia is associated with 3 different symptoms: positive, negative, and cognitive, with significant public health implications [5]. Positive symptoms are the most straightforward manifestations to be detected and are considered "psychotic behaviors not seen in healthy people" [6]. On the other hand, the most difficult symptoms to be identified are negative ones: such symptoms could be primarily linked with the diagnosis of this illness or be secondary to another psychotic condition, adverse effects of pharmacotherapy, or simply raised by the effects of the surrounding environment of the patient [6].

A large body of literature exists on the pharmacological treatment of schizophrenia. However, evidence on some dimensions of such interventions (e.g., eligible candidates, potential predicting factors of the therapeutic outcomes, safe implementation of these interventions, etc.) are notably scarce; scholars have proposed no intervention of choice with persistent and robust effects. However, adjunct therapy of antipsychotics or other treatment methods has gained substantial attention due to the restricted effects of antipsychotics [7]. The primary purpose of treating schizophrenia is the control of symptoms, the prevention of relapse, and the increased adaptive functions to integrate the patient into society eventually [8]. While numerous second-generation antipsychotic medications present advantages in treating schizophrenia over the first-generation ones, there exist serious knowledge gaps concerning the relevant pharmacological properties of antipsychotics' new generation as well as their adverse effects on patients' wellbeing and quality of life [9].

As mentioned earlier, the main antipsychotic pharmacotherapy is focused on blocking dopamine and serotonin receptors [10]. The pleomorphic pathophysiology of schizophrenia is associated with immunological and inflammatory impairments; thus, scholars suggested using anti-inflammatory agents as additive medications in this respect [11]. Acetylsalicylic acid (Aspirin), a nonsteroidal anti-inflammatory medication, irreversibly inhibits cyclooxygenase COX-1 and COX-2 and generates potential positive impacts in improving the symptoms of schizophrenia [12]. Furthermore, statins (3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] reductase inhibitors) have not only extensive therapeutic indications in the prevention of cardiac and cerebrovascular

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conditions but also present anti-inflammatory effects, e.g., declining C-reactive protein (CRP) concentrations [13]. Studies revealed superior efficacy of adjunct statin therapy versus placebo in patients with schizophrenia with respect to improving negative symptoms concerning poverty of speech, emotional withdrawal, blunted affect, and apathetic social withdrawal [14].

Numerous clinical trials provided supportive data concerning the therapeutic potential of anti-inflammatory methods to improve the symptoms of schizophrenia as well as other complicated conditions [15]. Another study highlighted the final therapeutic effect of combining aspirin with antipsychotic drugs on negative and positive symptoms and general psychopathology. This finding was achieved 4 weeks after the completion of the intervention [16].

Because of the high mortality risk, treatment costs, and the burden of schizophrenia disorder on the affected individuals and society, it is necessary to develop complementary therapies to reduce these risks. The etiology of schizophrenia has remained unclear. Besides, the use of drugs that can not only reduce the symptoms of the disease but also increase the life expectancy of patients and reduce the incidence of other diseases in this population is of particular importance. Therefore, the present study intends to examine the effects of aspirin and simvastatin as adjunctive therapy versus placebo on general psychopathology and negative and positive symptoms in patients with schizophrenia.

2. Materials and Methods

This research is a randomized, double-blind clinical trial study. The obtained RCT code is IRCT20210110049994N1. The study subjects were randomly divided into one control and two intervention groups through randomized block design. In total, three intervention groups were considered. This study was performed from May to December 2019 in Razi Psychiatric Hospital, Tehran Province, Iran.

The study's inclusion criteria were as follows: the age range of 19-60 years; diagnosed by schizophrenia based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5); the duration of the disease to be at least 3 years; presenting healthy physical examination results according to the assistant in charge of project implementation; consuming only one type of antipsychotic drug (risperidone); the lack of alcohol and drug dependence (except for nicotine); obtaining a maximum score of 4 from the depression subscale of

the positive and negative syndrome scale (PANSS) or a maximum of 14 from the Hamilton Rating Scale For Depression (HAM-D); the lack of suicidal ideation based on interview and clinical diagnostic evaluation; achieving an Intelligence Quotient (IQ) score of more than 70 based on interview and clinical diagnostic evaluation; no history of serious biological or neurological diseases; presenting no extrapyramidal symptoms; no breastfeeding; not using anti-inflammatory drugs, systemic antibiotics, or P450 inhibitors; no contraindications for aspirin use (e.g., asthma, gastritis, renal disease, active bleeding, etc.); no history of chronic NSAID (non-steroidal anti-inflammatory drugs) use; no concurrent use of corticosteroids, and the provision of informed consent forms for participating in the study by a companion or guardian.

The exclusion criteria of the study included the dissatisfaction of the patients or their guardian to continue study participation; the generation of any drug-induced adverse effects; the necessity of following a specific pharmacotherapy regimen for the patient during the study that interferes with aspirin or simvastatin or when their concomitant use is contraindicated. The relevant, informed consent form was obtained from all study participants before the study.

The sample size was calculated according to this Equation 1:

$$1.\ 3n=[(Z\alpha/3+Z\beta)3\times\{3(\acute{o})3\}]/(\mu1-\mu)$$

Given the confidence interval of 85% and the power of 96%, and the difference calculated between the groups based on a prior study, the sample size was estimated to be 15 individuals per group (n=45). The following tools were employed to collect the necessary data in the present study.

Positive and negative syndrome scale

Positive And Negative Syndrome Scale (PANSS) inventory is among the optimal tools, i.e., validated to explore general psychopathology and positive and negative syndromes in schizophrenia. This standardized clinical interview rates the existence and severity of the positive and negative symptoms, and general psychopathology of schizophrenia within the past week. The PANSS includes 30 items; of them, 7, 7, and 16 items address positive symptoms, negative symptoms, and general psychopathology symptoms, respectively. The severity of symptom per item is rated by a 7-point scale (1=absent; 7=extreme) to precisely describe symptom presentation [17]. This scale demonstrated desirable validity

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and reliability both in international and domestic studies. The aspects under the receiver operating characteristic (ROC) curves of the CDSS, HAM-D, PANSS-D, and BDI were 0.94, 0.89, 0.90, and 0.81, respectively [18].

Using the random-cluster sampling method, 527 students from Azad University in Tehran were selected to complete the PANSS to assess the psychometric properties of this tool. Exploratory factor analysis and principal component analysis were conducted in varimax rotation. The scale's factor structure presented two dimensions and predicted 43.631% of total variances. Moreover, the internal consistency of the scale was measured to be 0.777. Based on the collected findings, PANSS can be implemented in Iranians (Sharifi, H. P., Bashardoust, S., & Emami, P. S. 2012).

Hamilton rating scale for depression (HAM-D)

HAM-D is one of the most frequently applied clinician-rated inventories to assess the severity of depression in individuals diagnosed with a depressive disorder. This scale contains 12 items that examine mood, feeling of guilt, suicidal ideation, insomnia, agitation, anxiety, weight loss, physical symptoms, and insight. Based on the total scores obtained, the severity of depression is determined. The reliability of this test was reported to be 21% using the test-retest method [19].

To conduct the study, patients admitted to the psychiatric wards of Razi Hospital who met the study's inclusion criteria were identified. Then, the study data, including demographic characteristics (age, gender), were collected. Initially, all recruited patients were tested by the HAM-D, and those with depression were excluded from the research. Next, the study subjects were randomly assigned to the test and control groups using the randomized block design. Groups A and B were classified as the intervention groups and group C as the control group.

All three groups were initially treated with risperidone 4 mg daily for 3 weeks. Then, group A received aspirin (325 mg twice daily), whereas group B received simvastatin (40 mg/d). However, the controls received a placebo. The packaging and form of the presented medications and placebo were similar to observe the blindness of the study. Moreover, to prevent gastrointestinal complications, all patients were given one 40 mg pantoprazole tablet daily. These patients were followed up for 8 weeks. In case of sleep disturbances, dystonia, or akathisia during treatment, lorazepam 1 mg, biperiden 6 mg, and propranolol 20 mg were used. Furthermore, aspirin and simvastatin were evaluated concerning regular

adverse effects during regular psychiatry resident visits. Psychiatric symptoms were recorded according to the PANSS at the beginning of the study and on weeks 4 and 8. The data were analyzed using descriptive statistics (Mean±SD) and inferential statistics (repeated-measures analysis of covariance) in SPSS software v. 20.

3. Results

The present study investigated 45 patients with schizophrenia. Three patients (1 female, 2 males) were excluded from the study due to not completing the PANSS and were substituted with 3 other patients. Of these 45 patients, 35(77.78%) were men (Mean±SD age: 45.8±10.5 years), and 10(22.23%) were women (Mean±SD age: 42.3±7.8 years).

According to Table 1, there was no significant gender-wise difference between the study groups (P=0.576). Table 2 indicates that the mean scores of the positive symptoms of PANSS significantly decreased in the groups treated with aspirin and simvastatin (P=0.006 & P=0.005, respectively); however, there was no such difference in the controls (P=0.447). Furthermore, the mean scores of the negative symptoms of PANSS significantly decreased in the intervention groups (P<0.001). In addition, no significant differences were seen in the controls after the end of the research program (P=0.18).

In addition, the mean scores of the general symptoms of PANSS significantly decreased in the aspirin and simvastatin groups (P<0.001). There was an increase in the same value in the controls; however, such an increase was not statistically significant (P=0.31). Finally, while the total mean scores of the PANSS increased in the control group (P=0.25), the same scores significantly decreased in the intervention groups receiving aspirin and simvastatin (P<0.001) (Table 2).

The repeated-measured analysis of covariance (ANCOVA) data indicated no significant decrease in the positive symptoms of the PANSS between the groups receiving aspirin and simvastatin (Figure 1). As per Figure 1, repeated-measures ANCOVA revealed no significant difference concerning the positive symptoms of the PANSS between the groups under aspirin and simvastatin (P=0.006, P=0.005, respectively).

According to Figure 2, the repeated-measures ANCOVA result demonstrated no significant difference concerning the negative symptoms of the PANSS between the groups receiving aspirin and simvastatin (P<0.001).
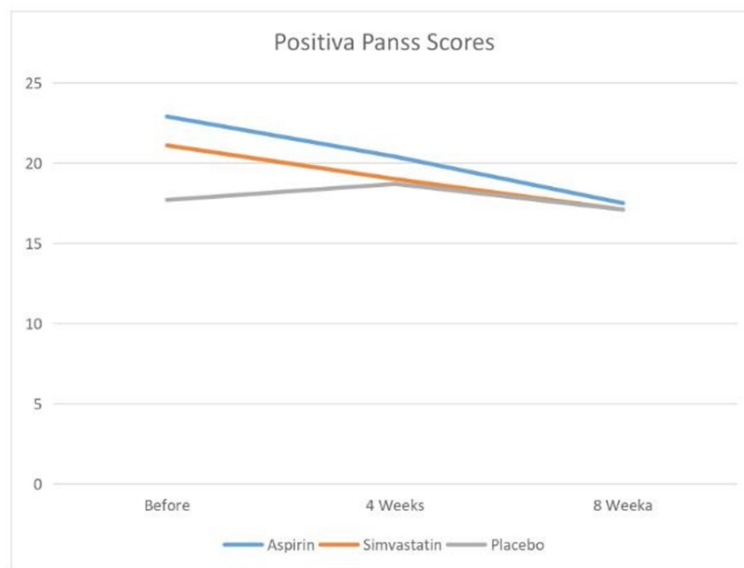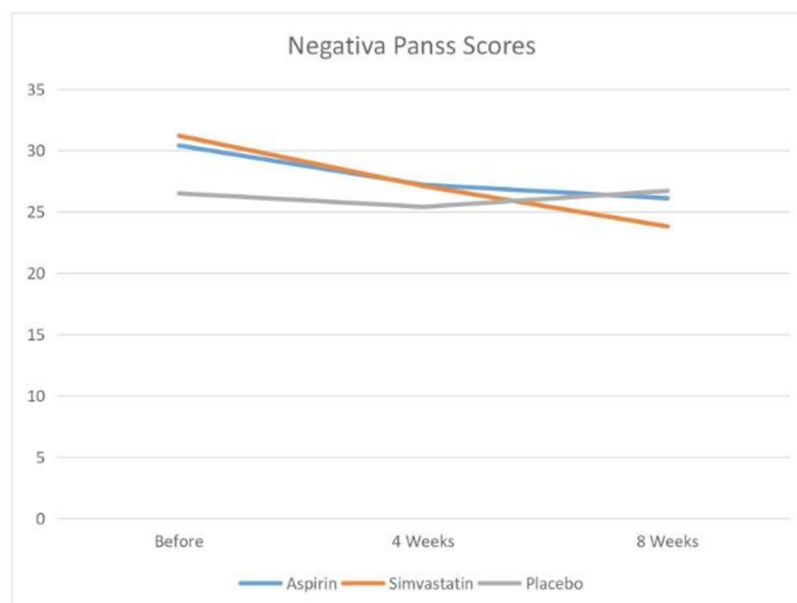
Figure 1. The Mean Score of the Positive and Negative Syndrome Scale (PANSS) Positive Symptoms at Different Study Phases in the Study Groups

Repeated-measures ANCOVA data respecting the scores of the general psychopathology of the PANSS suggested no significant difference between the experimental groups (P<0.001) (Figure 3).

As per Figure 4, repeated-measures ANCOVA findings revealed no significant difference in the total scores of the PANSS between the groups under aspirin and simvastatin (P<0.001). The study groups were separately compared with their baseline scores.

4. Discussion

The current study investigated the effects of adding aspirin and simvastatin adjunct therapy to the standard treatment of schizophrenia concerning negative and positive symptoms and general psychopathology in patients with schizophrenia admitted to Razi Psychiatric Hospital. Three study groups were subjects receiving aspirin, simvastatin, or a placebo. The obtained data suggested significant decreases in the scores of the posi-

Figure 2. Mean Score of the Positive and Negative Syndrome Scale (PANSS) Negative Symptoms at Different Study Phases in the Study Groups

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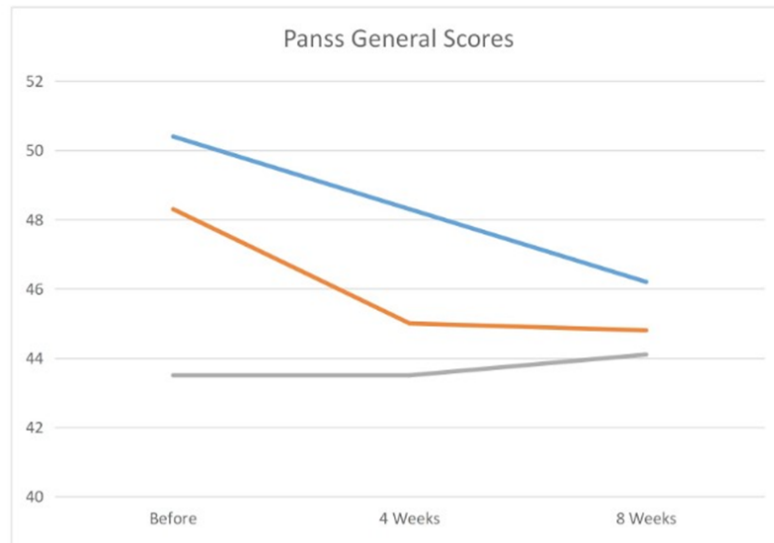
Figure 3. Mean Score of the General Psychopathology at Different Study Phases in the Study Groups

tive symptoms of the PANSS in the group under aspirin adjunct therapy compared to the controls. This finding was in line with prior research exploring the effects of add-on aspirin on treating schizophrenia [20]. Accordingly, they concluded that aspirin provided better therapeutic outcomes compared to placebo in the studied individuals [20].

The present study findings also revealed that using simvastatin as an adjunct therapy for managing schizophrenia could significantly reduce the negative symptoms of the study participants over 8 weeks; however, no such decline was observed in the scores of the negative symptoms of the PANSS after the intervention period in the group receiving placebo. This result was con-

sistent with those of Tajik-Esmaeeli et al. (2017) who detected a significantly more decline in the scores of the negative symptoms of the PANSS, compared with the placebo group, after 8 weeks; the same trend was observed in terms of the relevant total scores [14]. Therefore, as mentioned earlier, due to the influence of inflammatory factors on the symptoms of schizophrenia, anti-inflammatory medications can effectively reduce these symptoms.

Additionally, Laan et al. explored the effects of adding aspirin to the pharmacotherapy regimen of patients with schizophrenia on positive, negative, and cognitive symptoms and immunological parameters. In line with the current research results, they observed improvements in
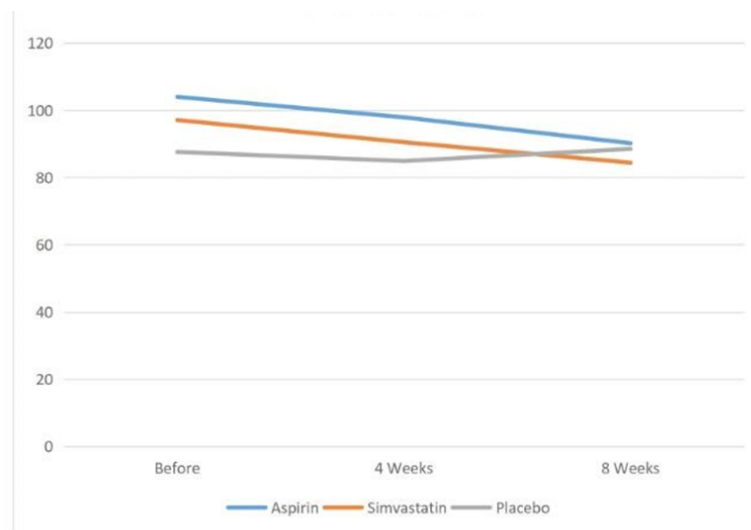
Figure 4. Mean Total Scores of the Positive and Negative Syndrome Scale (PANSS) at Different Study Phases in the Study Groups

Table 1. Gender-Wise distribution of the study groups

Gender \ Group	No. (%)			P
	Aspirin	Simvastatin	Placebo	
Male	11(73.34)	12(80)	12(80)	
Female	4(26.66)	3(20)	3(20)	0.576*
Total	15(100)	15(100)	15(100)	

*The Chi-squared test.

the investigated symptoms [10]. However, no long-term follow-up study has been performed on patients after the discontinuation of adjuvant medications to determine the consequent effects concerning the severity of the symptoms of this disorder.

Furthermore, the collected results demonstrated that the mean scores of PANSS positive symptoms decreased in patients receiving simvastatin, i.e., a statistically significant difference, compared to the placebo group. Another similar study investigated the effects of pravastatin as an adjunct approach among the schizophrenia population. Accordingly, inconsistent with the present study data, they reported no positive impact of this drug on improving the symptoms of the explored patients [21]. Such data discrepancy could be due to differences in the

Table 2. The Mean±SD Positive and Negative Syndrome Scale (PANSS) scores at different assessment stages in the study groups

Phase \ Group	Variables	Mean±SD		
		Aspirin	Simvastatin	Placebo
Before the intervention	The positive symptoms scores of PANSS	22.9±10.8	21.1±9.4	17.7±5.6
Four weeks after the intervention		20.42±10.65	19.05±8.6	18.7±7.8
Eight weeks after the intervention		17.5±8.6	17.1±5.1	17.1±6.6
P		0.006	0.005	0.447
Before the intervention	The negative symptoms scores of PANSS	30.45±7.29	31.25±6.9	26.51±6.24
Four weeks after the intervention		27.17±7.40	27.12±6.25	25.38±6.59
Eight weeks after the intervention		26.17±7.64	23.8±8.37	26.74±6.14
P		<0.001	<0.001	0.18
Before the intervention	The general symptoms scores of PANSS	50.47±13.99	48.32±11.21	43.46±10.57
Four weeks after the intervention		48.35±14.51	45.07±10.48	43.51±10.57
Eight weeks after the intervention		46.25±15.77	44.82±16.18	44.10±10.53
P		<0.001	<0.001	0.31
Before the intervention	The total scores of PANSS	104.05±26.97	97.10±28.20	87.66±17.45
Four weeks after the intervention		97.95±27.61	90.50±26.20	84.97±21.15
Eight weeks after the intervention		90.22±29.07	84.48±16.17	88.56±16.94
P		<0.001	<0.001	0.25

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drug dose used. Thus, it can be hypothesized that statins, in higher doses, can be effective on the symptoms of schizophrenia.

Besides, the achieved results outlined a significant difference in reducing the scores of negative symptoms, positive symptoms, and general psychopathological symptoms of the PANSS between the groups of patients receiving aspirin and simvastatin. Aspirin and simvastatin alone reduced the symptoms of schizophrenia in the explored patients, and the effectiveness of both drugs was similar and did not significantly differ. In general, the use of drugs with anti-inflammatory properties, such as aspirin and simvastatin, as adjunctive therapy in patients with schizophrenia provides positive effects, which support the effect of inflammatory factors in the etiology of schizophrenia. Using these medications may also be effective in preventing cardiac and metabolic adverse effects of antipsychotics in the long run; thus, this issue is suggested to be considered in future studies.

The existing evidence provided by prior trials is inconclusive, preventing scholars from drawing precise conclusions on the therapeutic impact of aspirin on schizophrenia [20]. A comprehensive meta-analysis was performed on an adjunct statin for treating schizophrenia. The collected data revealed that statin provided no significant difference after the discontinuation or adverse outcomes compared to placebo. The authors concluded that statins might present considerable potential as an adjunct drug for schizophrenia [22]. Furthermore, a meta-analysis study compared using or not statins adjunctive therapy among schizophrenia patients regarding psychiatric symptoms. Six RCTs were included in the analysis, consisting of 339 subjects (169 cases and 170 controls). The overall effect examination suggested that the PANSS positive and negative scales significantly declined in those under therapy with statins. Accordingly, adjunctive therapy with statins was concluded to promote positive and negative symptoms [23].

The present study had some limitations. The study's sample size was relatively small; therefore, conducting a study with a larger sample size could provide more reliable results. The course of study, as well as the follow-up phase, were short; thus, longer study periods along with a longer-term follow-up are recommended for future research. The present study population included patients with schizophrenia hospitalized for a long-term in Razi Psychiatric Hospital, and a long time was passed since the onset of their disorder. Accordingly, they have received antipsychotics for a long time. As a result, the obtained results should be generalized with caution. It is suggested that future studies be performed on patients with schizophrenia whom a short time passed from their disease. Furthermore, future studies are recommended to compare the PANSS scores of the three research groups from the study's onset.

5. Conclusion

The current study results indicated that aspirin and simvastatin could alone reduce the symptoms of schizophrenia, including negative symptoms, general psychopathology, and positive symptoms, in the explored patients. However, the effectiveness of both drugs was similar, and no significant difference was observed between the considered medicines in reducing the symptoms mentioned above. Using these medications is recommended as adjunctive therapy and should not be considered a substitute for the main treatment.

Ethical Considerations

Compliance with ethical guidelines

Funding

Authors' contributions

Conflict of interest

Acknowledgments

References

[1] Lam M, Chen CY, Li Z, Martin AR, Bryois J, Ma X, et al. Comparative genetic architectures of schizophrenia in East Asian and European populations. Nature Genetics. 2019; 51(12):1670-8. [DOI:10.1038/s41588-019-0512-x] [PMID] [PMCID]

[2] Stępnicki P, Kondej M, Kaczor AA. Current concepts and treatments of schizophrenia. Molecules. 2018; 23(8):2087. [DOI:10.3390/molecules23082087] [PMID] [PMCID]

[3] World Health Organization (WHO). Schizophrenia. Geneva: World Health Organization; 2022. https://www.who.int/news-roo Schoonover m/fact-sheets/detail/schizophrenia

[4] McGrath J, Saha S, Chant D, Welham J. Schizophrenia: A concise overview of incidence, prevalence, and mortality. Epidemiologic Reviews. 2008; 30:67-76. [DOI:10.1093/epirev/mxn001] [PMID]

[5] Schoonover KE, Roberts RC. Markers of copper transport in the cingulum bundle in schizophrenia. Schizophrenia Research. 2021; 228:124-33. [DOI:10.1016/j.schres.2020.11.053] [PMID] [PMCID]

[6] Berg GD, Donnelly S, Warnick K, Medina W, Miller M. Dose-response effects for depression and Schizophrenia management on hospital utilization in Illinois Medicaid: A multivariate regression analysis. BMC Health Services Research. 2014; 14:288. [DOI:10.1186/1472-6963-14-288] [PMID] [PMCID]

[7] Remington G, Addington D, Honer W, Ismail Z, Raedler T, Teehan M. Guidelines for the Pharmacotherapy of Schizophrenia in Adults. Canadian Journal of Psychiarty. 2017; 62(9):604-16. [DOI:10.1177/0706743717720448] [PMID] [PMCID]

[8] Dipiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM. Pharmacotherapy: A pathophysiologic approach. New York:McGraw-Hill Education; 2017. https://www.googl-com/books/edition/Pharmacotherapy_A_=en

[9] Andrade C. Anti-inflammatory strategies in the treatment of schizophrenia. Expert Review of Clinical Pharmacology. 2016; 9(2):161-3. [DOI:10.1586/17512433.2016.1095086] [PMID]

[10] Miyamoto S, Duncan GE, Marx CE, Lieberman JA. Treatments for schizophrenia: A critical review of pharmacology and mechanisms of action of antipsychotic drugs. Molecular Psychiatry. 2005; 10(1):79-104. [DOI:10.1038/sj.mp.4001556] [PMID]

[11] Laan W, Grobbee DE, Selten JP, Heijnen CJ, Kahn RS, Burger H. Adjuvant aspirin therapy reduces symptoms of schizophrenia spectrum disorders: Results from a randomized, double-blind, placebo-controlled trial. Journal of Clinical Psychiatry. 2010; 71(5):520-7. [DOI:10.4088/JCP.09m05117yel] [PMID]

[12] Berk M, Dean O, Drexhage H, McNeil JJ, Moylan S, O'Neil A, et al. Aspirin: A review of its neurobiological properties and therapeutic potential for mental illness. BMC Medicine. 2013; 11:74. [DOI:10.1186/1741-7015-11-74] [PMID] [PMCID]

[13] Kim YK. Frontiers in psychiatry: Artificial intelligence, precision medicine, and other paradigm shifts. London: Springer Nature Singapore; 2019. https://www.google.com/books/edition/Frontiers_in_Psychiatry/FEe9DwAAQBAJ?hl=en&gbpv=0

[14] Tajik-Esmaeeli S, Moazen-Zadeh E, Abbasi N, Shariat SV, Rezaei F, Salehi B, et al. Simvastatin adjunct therapy for negative symptoms of schizophrenia: A randomized double-blind placebo-controlled trial. International Clinical Psychopharmacology. 2017; 32(2):87-94. [DOI:10.1097/YIC.0000000000000159] [PMID]

[15] Hong J, Bang M. Anti-inflammatory strategies for schizophrenia: A review of evidence for therapeutic applications and drug repurposing. Clinical Psychopharmacology and Neuroscienc. 2020; 18(1):10-24. [DOI:10.9758/cpn.2020.18.1.10] [PMID] [PMCID]

[16] Attari A, Mojdeh A, Soltani FA, Najarzadegan MR. Aspirin inclusion in antipsychotic treatment on severity of symptoms in schizophrenia: a randimized clinical trial. Iranian Journal of Psychiatry and Behavioral Sciences. 2017; 11(1):e5848. [DOI:10.5812/ijpbs.5848]

[17] Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophrenia Bulletin. 1987; 13(2):261-76. [DOI:10.1093/schbul/13.2.261] [PMID]

[18] Kim SW, Kim SJ, Yoon BH, Kim JM, Shin IS, Hwang MY, Yoon JS. Diagnostic validity of assessment scales for depression in patients with schizophrenia. Psychiatry Research. 2006; 144(1):57-63. [PMID]

[19] Carrozzino D, Patierno C, Fava GA, Guidi J. The Hamilton Rating Scales for Depression: A Critical Review of Clinimetric Properties of Different Versions. Psychotherapy and Psychosomatics. 2020; 89(3):133-50. [DOI:10.1159/000506879] [PMID]

[20] Schmidt L, Phelps E, Friedel J, Shokraneh F. Acetylsalicylic acid (aspirin) for schizophrenia. Cochrane Database of Systematic Reviews. 2019; 8(8):CD012116. [DOI:10. /14651858.CD012116.pub2] [PMID] [PMCID]

[21] Vincenzi B, Stock S, Borba CP, Cleary SM, Oppenheim CE, Petruzzi LJ, et al. A randomized placebo-controlled pilot study of pravastatin as an adjunctive therapy in schizophrenia patients: Effect on inflammation, psychopathology, cognition and lipid metabolism. Schizophrenia Research. 2014;159(2-3):395-403 [DOI:10.1016/j.schres.2014.08.021] [PMID] [PMCID]

[22] Nomura I, Kishi T, Ikuta T, Iwata N. Statin add-on therapy in the antipsychotic treatment of schizophrenia: A meta-analysis. Psychiatry Research. 2018; 260:41-7. [DOI:10.1016/j.psychres.2017.11.033] [PMID]

[23] Shen H, Li R, Yan R, Zhou X, Feng X, Zhao M, et al. Adjunctive therapy with statins in schizophrenia patients: A meta-analysis and implications. Psychiatry Research. 2018; 262:84-93. [DOI:10.1016/j.psychres.2018.02.018] [PMID]

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