

The effects of combined sertraline and aspirin therapy on depression severity among patients with major depressive disorder: A randomized clinical trialZahra Sepehrmanesh¹, Hosein Fahimi², Goudarz Akasheh³, Mohamadreza Davoudi⁴, Hamidreza Gilasi⁵, Amir Ghaderi⁶

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Abstract

Background: Different studies have been conducted to find the best adjuvant therapies for depression management. There are controversies over the effects of aspirin as an adjuvant therapy for depression.

Objective: To determine the effects of combined sertraline and aspirin therapy on depression severity among patients with major depressive disorder.

Methods: This randomized clinical trial was conducted at Kargarnejad Psychiatric Hospital in Kashan, Isfahan, Iran, from September 1, 2016 to November 1, 2016. The study participants included 100 patients with major depressive disorder who were assigned to aspirin and placebo groups by the use of computer-generated random numbers. Patients in these groups respectively received sertraline-aspirin and sertraline-placebo for eight consecutive weeks. Patients were prescribed 80 milligrams of aspirin twice a day. Also, sertraline was administered at a dose of 50-200 milligrams daily. Beck Depression Inventory was employed for depression severity assessment at four time points, namely before, two, four, and eight weeks after the beginning of the intervention. Medication side effects were also assessed eight weeks after the beginning of the intervention. Data were analyzed by SPSS version 12.0, using Chi-square and the Independent-samples t-test ($\alpha=0.05$).

Results: Both groups were matched in terms of age ($p=0.46$), gender ($p=0.539$), and depression severity ($p=0.509$, with mean score 33.5 ± 4.1 vs. 32.8 ± 5.9) at baseline. However, depression scores were reduced significantly four and eight weeks after initiation of therapy just in the sertraline-aspirin group ($p<0.05$).

Conclusion: As an adjuvant therapy, aspirin can reduce depression severity among patients with major depressive disorder. Yet, further studies are needed to prove the effectiveness of aspirin and other anti-inflammatory agents in reducing depression severity.

Trial registration: The trial was registered at the Iranian Registry of Clinical Trials (<http://www.irct.ir>) with the IRCT ID: IRCT2016082829556N1.

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1. Introduction

Major depressive disorder (MDD) is one of the leading causes of disability (1). It accounts for 2%–4% of global disability-adjusted life years (1, 2). Around the world, four per 100 persons suffer from MDD (3, 4). In fact, with a prevalence of 17% depressive disorder, it is the most prevalent psychiatric disorder in the world, hence it is called the “common cold” of psychiatric conditions (5, 6). Depression leads to different consequences such as disability, low quality of life, sleep disorders, academic failure, marital conflicts, and suicide (6). Moreover, due to disability, depressed individuals become a burden to their societies. Thereby, given the high prevalence of MDD and MDD-induced disability, MDD annually causes billions of dollars of economic damage worldwide (7). It also aggravates illnesses such as asthma, diabetes mellitus, and arthritis (8). More seriously, MDD is associated with a high prevalence of suicidal and even homicidal thoughts (6, 9). Therefore, prompt treatment is needed to promote depressed people’s functional status, and reduce the risk of suicide and homicide. There are two main approaches to MDD management, namely medication therapy and psychotherapy (10, 11). The most important psychotherapies are cognitive behavioral therapy (12, 13) and mindfulness-based therapies (such as Acceptance and commitment therapy and Dialectical behavior therapy) both of which have been known to have significant effects on MDD (14, 15). On the other hand, the most important medications for MDD management are tricyclic antidepressants, monoamine oxidase inhibitors, and serotonin reuptake inhibitors (16, 17). As one of the inhibitors of serotonin reuptake, sertraline is the best treatment option for the improvement of MDD symptoms (8). Recently, depression symptoms were found to have a reciprocal relationship with inflammation (18). Moreover, autoimmune disorders (such as rheumatoid arthritis) and infectious diseases (such as hepatitis) have been found to dramatically heighten the risk for developing depression (19, 20). The prevalence of depression among hospitalized patients with autoimmune disorders and infectious diseases was reported to be 45% and 62%, respectively (21). In addition, more than one fourth of patients who receive interferon (a medication for hepatitis C which causes serious inflammation) develop depression (22). Moreover, high levels of peripheral inflammatory markers (such as C-reactive protein, tumor necrosis factor alpha, and interleukin) were observed among depressed patients who suffered from no comorbid physical problems, denoting the probable effects of inflammation on depression (23). However, despite the known effectiveness of antidepressant medications and psychotherapy in alleviating the symptoms and the severity of MDD, these modalities have no significant effects on inflammation and cannot alleviate inflammatory symptoms which can affect depression (23). Aspirin is a non-steroidal anti-inflammatory drug (NSAID) which inhibits cyclooxygenase (24). As one of the most important structural enzymes, cyclooxygenase has a significant role in the production of inflammatory mediators such as prostaglandin, prostacyclin, and thromboxane (25). Thus, pharmacological inhibition of cyclooxygenase can alleviate inflammatory symptoms (26). Besides its contribution to pain and inflammation, cyclooxygenase is assumed to be involved in neural degenerative disorders associated with depression (27). Antidepressants and anxiolytic agents have slight, if any, effects on inflammation (28), and hence, the treatment of choice for the management of depression-related inflammatory symptoms would be anti-inflammatory agents (29). Previous studies into the effects of anti-inflammatory drugs on depression symptoms, reported contradictory results. The main reasons behind these contradictions have been the selection of patients from certain age groups (30, 31), the administration of aspirin in association with inappropriate antidepressants (such as citalopram instead of sertraline) (32) and the use of NSAIDs instead of aspirin (33). The present study was done to remove the effects of such confounders and investigate the effects of combined sertraline and aspirin therapy on depression severity among patients with MDD.

2. Material and Methods

2.1. Trial design

This study was a randomized clinical trial that was conducted from September 1, 2016 to November 1, 2016.

2.2. Participants

This clinical trial was conducted in an Iranian governmental educational hospital (Kargarnejad Psychiatric Hospital). Kargarnejad Psychiatric Hospital is the largest psychiatric center in Kashan, Isfahan, Iran, and it is affiliated with Kashan University of Medical Sciences. The research population was comprised of patients with major depression disorder diagnosis who referred to Kargarnejad Psychiatric Hospital.

2.3. Selection criteria

Eligibility criteria were an age of more than forty, a definite diagnosis of MDD based on the criteria reported in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), no history of NSAID use or mania, no history of alcohol or drug abuse during the past six months preceding the study, no contraindication for aspirin therapy (such as gastric ulcer), and no affliction by the risk factors of cardiovascular and neurologic diseases. Patients who became

pregnant (Examined by home pregnancy tests (HPTs) during the study, who were unwilling to stay in the study and use other NSAID during the study, were excluded.

2.4. Interventions

Patients in the aspirin group received sertraline and aspirin while their counterparts in the placebo group received sertraline and placebo. In both groups, sertraline (Sobhan Pharmaceutical Co. Iran) was administered at a dose of 50 to 200 milligrams daily at the discretion of a psychiatry resident (i.e. the first author). Aspirin (Pars Darou Pharmaceutical Co. Iran) was also administered to patients in the aspirin group at a dose of 80 milligrams twice a day. Patients in the placebo group received placebo tablets (Pars Darou Pharmaceutical Co. Iran) which were in the shape and size similar to aspirin tablets.

2.5. Outcomes

Depression symptom severity, psychiatric condition, and sertraline side effects were respectively assessed using Beck Depression Inventory, Structured Clinical Interview for DSM-IV disorders, and a sertraline side effect checklist.

2.5.1. Beck Depression Inventory (BDI):

BDI is a 21-item inventory for assessing depression symptoms. The total BDI score is 0-63 and is interpreted as follows: 0-9: minimal depression; 10-18: mild depression; 19-29: moderate depression; and 30-63: severe depression. The one-week test-retest correlation coefficient of BDI is 0.93. Moreover, BDI score significantly correlates with the scores of the Hamilton Depression Rating Scale, the Minnesota Multiphasic Personality Inventory, and the Symptom Checklist-90 ($r > 0.60$). BDI was also used in our country, Iran, and was reported to have a Cronbach's alpha of 0.70-0.90 (34).

2.5.2. Structured Clinical Interview (SCI) for DSM-IV disorders:

As a semi-structured interview, SCI for DSM-IV disorders is used to diagnose psychiatric disorders based on the criteria of DSM-IV (35). It was translated into Persian and cross-culturally adapted for the Iranian context. The Persian SCI was found to have a high agreement with the results of clinical psychiatric evaluators' judgments about psychiatric diagnoses (Kappa's agreement coefficient greater than 0.60) (35).

2.5.3. Sertraline side effect checklist:

This checklist was produced by the first author based on the side effects of sertraline reported in pharmacology textbooks. The checklist contained side effects such as fatigue, sleep disorders (mainly insomnia), mild nausea, diarrhea, gastric discomfort, dry mouth, common cold symptoms (such as nasal congestion and sneezing), increased perspiration or urination, weight changes, and sexual problems (such as decreased libido). This checklist was completed for each patient eight weeks after the beginning of the study intervention. The presence of each side effect was documented by placing a checkmark in front of it in the checklist (8). The data on depression severity and response to treatment were collected at four time points, namely before, two, four, and eight weeks after the beginning of the intervention.

2.6. Sample size

Based on the results of an earlier study (36), a type I error of 5%, and a power of 80%, 47 patients were determined to be needed for each study group. However, given the likelihood of dropouts, fifty patients were recruited to each group. Sampling was done consecutively because only a limited number of patients referred to the study setting each day.

2.7. Randomization and blinding

Recruited patients were randomly assigned to aspirin ($n=50$) and placebo groups (50) using block randomization technique with four-patient blocks. Random assignment was done by the one of the researchers in the team, while study intervention was implemented by another researcher in the team. In other words, Hossein Fahimi was aware while Mohammad Reza Davoudi was blind to group assignment and intervention. Moreover, all participants were blind, whether they were in the aspirin or the placebo group.

2.8. Statistical methods

Collected data were analyzed via the SPSS software (v. 12.0) (SPSS Inc., Chicago, Illinois, USA) and through performing the Chi-square and the Independent-samples t-test. Results were reported using descriptive statistics such as mean, standard deviation, and absolute and relative frequencies. Significance level was set at less than 0.05.

2.9. Research ethics

The proposal for this thesis research was presented to the Ethics Committee of Kashan University of Medical Sciences after its scientific approval by the psychiatric department. The Ethics Committee approved the study with the number IR.KAUMS.REC.1394.37 on June 11, 2015, and the enrollment of patients began on September 1, 2016, and the study continued until November 1, 2016. This study was also registered in the Iranian Registry of Clinical Trials (irct.ir) with the ID: IRCT2016082829556N1. It should also be noted that we registered the study in irct.ir as a retrospective registration because we were allowed to conduct the thesis after the approval of the Ethics Committee, which is affiliated with the Office of the Vice Chancellor for Research at Kashan University of Medical Sciences. Also, all the authors confirm that all ongoing and related trials for this drug are registered. Indeed, in this study, for research ethical considerations, the participants were informed about the objective and nature of the study, and each participant provided her written consent prior to the study. Also, we were committed to keeping all the participants' information and date confidential.

3. Results

Initially, fifty patients were recruited to each study group, 100 in total. None of them left the study and thus, data analysis was done on the data collected from all 100 patients (Figure 1). On average, patients in the aspirin and the placebo groups were aged 48.9 ± 7.5 and 47.8 ± 7.3 , respectively. No significance between-group difference was observed regarding patients' age, gender, marital and educational status, monthly income, and depression-anxiety comorbidity ($p < 0.05$; Table 1). Table 2 shows depression severity at the four assessment time points. Before the intervention, depression severity scores in the aspirin and the placebo groups were 33.55 ± 4.1 and 32.8 ± 5.9 , respectively. Between-group difference at baseline was not statistically significant ($p = 0.509$). The same finding was observed at two weeks after the beginning of the intervention ($p = 0.509$). However, at four and eight weeks after the beginning of the intervention, depression in the placebo group was more severe than the aspirin group ($p < 0.05$; Table 2). Data on the frequency of sertraline side effects are presented in Table 3. Most side effects on the aspirin group include 8% for Nausea, 8% for Dyspepsia and also 8% for Diarrhea. Although in placebo groups, headache has the highest rate of side effects at 12%. In total, study groups did not significantly differ from each other regarding sertraline side effects ($p > 0.05$). In other words, the side effects of sertraline among patients who received aspirin were as similar as patients who received placebo. Also, Table 4 compares clinically significant response between groups at the four assessment time points. Study groups did not significantly differ from each other at two and four weeks after the intervention ($p = 0.109$ for 2nd week after beginning of the intervention). But Study groups significantly differed from each other at the eight weeks after the beginning of the intervention ($p = 0.008$).

Table 1. Participants' demographic characteristics

Variables		Aspirin; n (%)	Placebo; n (%)	p-value*
Age (year)	40-50	28 (56)	30 (60)	0.469
	51-65	22 (44)	20 (40)	
Gender	Male	21 (42)	18 (36)	0.539
	Female	29 (58)	32 (64)	
Marital Status	Single	13 (26)	12 (24)	0.996
	Married	28 (56)	29 (58)	
	widowed	5 (10)	5 (10)	
	Divorced	4 (8%)	4 (8)	
Educational status	Primary school	11 (22)	4 (8)	0.838
	Guidance school	18(36)	19 (38)	
	High school diploma	16 (32)	18 (36)	
	Higher	5 (10)	19 (38)	
Monthly income (U.S. dollar)	< 250	33 (66)	38 (76)	0.425
	250–750	14 (28)	11 (22)	
	> 750	3 (6)	1 (2)	
Comorbid anxiety	Yes	29 (58)	19 (38)	0.638
	no	21 (42)	31 (62)	

* Chi-square test

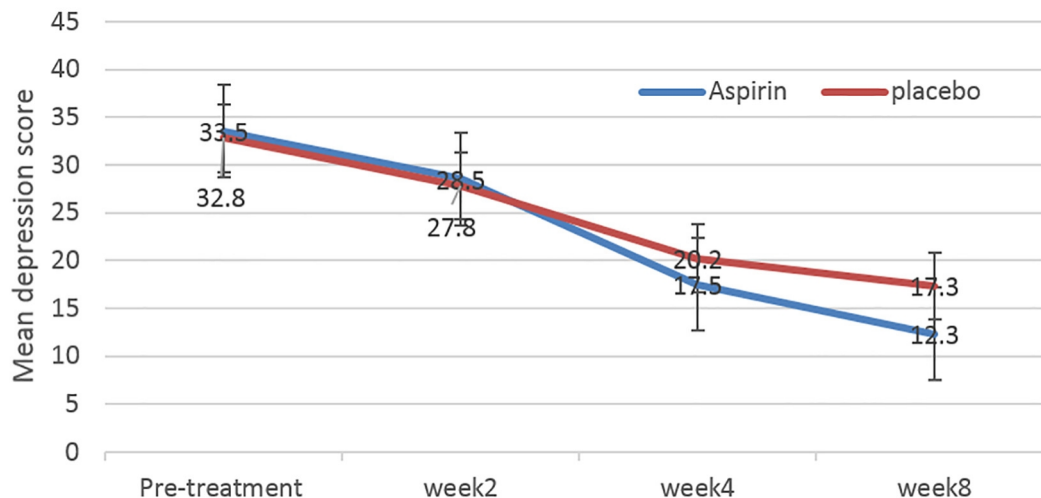


Figure 1. The variations of depression severity mean score across the four measurement time points

Table 2. Between-group comparison regarding the mean score of depression severity

Times	Aspirin	Placebo	p-value*
Pretest	33.5±4.1	32.8±5.9	0.509
Two weeks after	28.5±4.1	27.8±5.9	0.509
Four weeks after	17.5±3.7	20.2±5.8	0.006 ^a
Eight weeks after	12.3±3.4	17.3±4.7	0.001 ^a
The difference between pretest and the third posttest	21.2±3.2	15.6±3.9	0.001 ^a

* Independent-samples t-test

Table 3. The frequency distribution of drug side effects

Side effects	Aspirin n (n %)	Placebo n (n %)	p-value*
Nausea	(8) 4	(8) 4	p>0.99
Agitation	2 (4)	2 (4)	p>0.99
Headache	3 (6)	6 (12)	0.486
Dyspepsia	4 (8)	3 (6)	p>0.99
Diarrhea	4 (8)	5 (10)	p>0.99
Decreased libido	1 (2)	2 (4)	p>0.99
No side effects	32 (64)	28 (56)	0.537

* Independent-samples t-test

Table 4. The results of clinically significance of depression

Time	Clinically response	Experimental group; n (%)	Control group; n (%)	p-value
Two weeks after	Have	0 (0)	0 (0)	Not assigned
	Not have	50 (100)	50 (100)	
Four weeks after	Have	28 (56)	20 (40)	0.109
	Not have	22 (44)	30 (60)	
Eight weeks after	Have	42 (84)	30 (60)	0.008
	Not have	8 (16)	20 (40)	

* Chi-square test

4. Discussion

The aim of this study was to determine the effects of combined sertraline and aspirin therapy on depression severity among patients with MDD. Findings revealed that compared with sertraline-placebo therapy, combined use of aspirin and sertraline was associated with more significant improvement in depression symptoms. Moreover, the prevalence of the side effects of sertraline-placebo therapy was not greater than that of sertraline-aspirin therapy. These findings are in line with the findings of several earlier studies. For example, Berk et al. (2016) made a

retrospective study on 19,114 elderly people, and found regular aspirin use (for five years) effective in significantly preventing the occurrence of depression (37). Rahola (2012) also reported that aspirin adjacent to antidepressants significantly improved depression symptoms (38). Another study also reported the effectiveness of fluoxetine-aspirin in alleviating depression symptoms (39). Savitz et al. (2012) also conducted a study on 120 patients with bipolar disorder who were in depressive phase, and found that aspirin significantly reduced the side effects of antidepressants and significantly improved depression symptoms (36). Similarly, Almeida et al. (2012) reported that aspirin use significantly reduced the risk of developing depression among 3,687 older men with high plasma level of homocysteine (40). The first phase of a longitudinal study also illustrated aspirin use effective in alleviating both inflammatory and depression symptoms among young adults with MDD (41). Contrary to our findings, a study showed that combined use of aspirin (160 mg daily) and citalopram (20 mg daily) caused severe anxiety, akathisia, and suicidal behaviors among elderly people (30). The treatment of choice for depression management among elderly people is sertraline; thus, these conflicting findings can be attributed to the side effects of citalopram (30, 31). In addition, a retrospective study on 811 patients with MDD showed that combining nortriptyline and citalopram with NSAIDs did not significantly increase their antidepressant effects (32). These contradictory results can be attributed to the differences in the effects of different NSAIDs (33). Patients with MDD have high blood levels of C-reactive protein, tumor necrosis factor alpha, and interleukin (23). These factors adjust local and systemic inflammatory responses to microbial pathogens (42). Moreover, they affect the brain to prepare the body to fight infection and thereby, bring about behavioral symptoms of sickness (24, 42) such as fever, irritability, fatigue, and depressed mood (42). Therefore, symptoms such as irritability, fatigue, and depressed mood among patients with MDD may be due to chronic increased levels of these inflammatory markers. As an NSAID, aspirin lowers the levels of inflammatory mediators (such as prostacyclin and thromboxane) through inhibiting cyclooxygenase and thereby, reduces inflammation and alleviates behavioral symptoms of sickness (37). The present study had several limitations such as short follow-up period, limited age range of participants, and failure to assess the effects of other antidepressants.

5. Conclusions

Based on our results, we can conclude that Aspirin may have significant roles in preventing the progression or alleviating the symptoms of MDD through its anti-inflammatory and anti-oxidative effects. So, therapists can prescribe aspirin for reducing or alleviating the symptoms of MDD. Future studies are recommended to compare the effects of different doses of aspirin as well as the effects of different antidepressants in combination with aspirin on depression symptoms.

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Conflict of Interest:

There is no conflict of interest to be declared.

Authors' contributions:

All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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