

Efficacy of Gemfibrozil as an Adjunct to Sertraline in Major Depressive Disorder, A Double-Blind, Randomized, and Placebo-Controlled Clinical Trial

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Abstract

Objective: Major depressive disorder (MDD) is predicted to be the first cause of burden of disease. The antidepressant activity of gemfibrozil has been recently considered. This study was designed to evaluate the effectiveness of gemfibrozil as a sertraline adjunct in treating patients with MDD.

Method: A total of 46 patients with MDD based on the DSM-V criteria with a minimum score of 22 on the 17-item Hamilton Rating Scale for Depression (HAM-D) were randomized to receive either 300 mg daily gemfibrozil or placebo in addition to 100 mg sertraline for 8 weeks in a randomized, double-blind placebo-controlled trial. Patients were evaluated for response to treatment using the HAM-D score at baseline and weeks 2, 4, and 8.

Results: Forty-five patients completed the study and took part in all follow-up visits. Repeated measure ANOVA with a Greenhouse-Geisser correction showed a significant difference for time×treatment interaction on within-subjects HAM-D scores [p-value= 0.026]. A significant difference was seen in time [p-value < 0.001]. The test of between-subject effects also showed a significant effect of treatment on HAM-D scores at weeks 2, 4, and 8 [p-value = 0.07]. Using Kaplan-Meier estimate curves, time to remission periods were significantly different between the 2 trial arms [Log-Rank p-value = 0.003].

Conclusion: Gemfibrozil is an effective adjunctive treatment in MDD and can be used to reduce depression symptoms.

Key words: *Adjunctive Treatment; Depression; Gemfibrozil; Major Depressive Disorder; Randomized Controlled Trial*

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Major depressive disorder (MDD), commonly known as depression, is a mental disorder defined as one or more episodes of major depression in the absence of lifelong mania(1). MDD occurs almost twice as often in women as in men and affects 1 in 6 people during their lifetime (2). About 2%–9% of depressed adults die due to suicide, and about half who die by suicide have MDD or other mood disorders (2, 3). By 2030, it is predicted to be the world's leading cause of the burden of disease (4). Available and commonly used treatments for MDD comprise psychotherapy, pharmacotherapy, and electroconvulsive therapy. Pharmacotherapy is the first-line treatment in MDD (5). For the past recent decades, the monoaminergic systems have received the most attention in the neurobiology of MDD (6).

In the 1950s, tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) were introduced as the first antidepressant medicines. Selective serotonin reuptake inhibitors (SSRIs) or selective serotonin and norepinephrine reuptake inhibitors (SNRIs) were the second generations of antidepressant drugs, and now they are the most common treatments and medicines for MDD, recommended by most guidelines as the first line of treatment (5, 7). Despite the progress of these treatments and drugs, the effectiveness of treatment initiates with a delay, or there is an incomplete response to treatment in one-third of patients (8, 9). One of the ways to overcome the resistance that has been considered by researchers is the use of complementary and alternative medicines (10).

Sertraline is metabolized by cytochrome P450 (CYP) while gemfibrozil inhibits the CYP; hence, gemfibrozil is expected to prolong the half-life of sertraline and its duration of action. Nevertheless, no interaction has been identified and detected by the prescription of these 2 drugs together (11). For these reasons and because sertraline is a typical antidepressant commonly used clinically in first-line pharmacotherapy, this drug is intended for coadministration with gemfibrozil in this study (5, 11). Gemfibrozil is a fibric acid derivate and a lipid-lowering agent, which is mainly used in the treatment of hypertriglyceridemia (12). This antihypertriglyceridemic effect could be partly due to its effect on the activation of PPAR- α receptors (13). Recent studies have shown other effects of gemfibrozil (13). It has an anti-inflammatory effect on chronic inflammatory diseases by different mechanisms. It can have an immunomodulatory effect by switching autoimmune T helper 1 to T helper 2 cells, which may be useful in relieving symptoms of multiple sclerosis. Gemfibrozil showed antioxidant activity by reducing reactive oxygen species and free radicals (13).

The antidepressant activity of gemfibrozil has been recently considered. In a study on mice, improvement of depression was suggested by effecting the BDNF signaling pathways (14). To the best of our knowledge, no study surveyed this effect on humans. However,

improvements in depressive symptoms were noted after treatment of severe hypertriglyceridemia in one study (15). Based on available data, we hypothesized that a combination of sertraline and gemfibrozil would be more effective than sertraline alone in treating patients with major depressive disorder. Therefore, we designed this randomized, double-blind, placebo-controlled trial to investigate the effects and tolerability of gemfibrozil as an adjunct to sertraline in patients with MDD.

Materials and Methods

Trial Design and Setting

An 8-week, 2-center, randomized, double-blind, placebo-controlled, parallel-group study was performed on the efficacy of gemfibrozil compared to placebo in improving symptoms of major depressive disorder at Roozbeh psychiatric hospital and Imam Hossein psychiatric hospital from April 2019 to February 2020. The trial was registered at the Iranian registry of clinical trials (www.irct.ir; registration no. IRCT20090117001556N119).

Ethics

The protocol was conducted in agreement with the Declaration of Helsinki and its subsequent revisions. The institutional review board of Tehran University of Medical Sciences also has approved the protocol with approval number IR.TUMS.VCR.REC.1397.880. All participants were informed they were free to leave the study at any time and this would never lead to any negative consequences on their therapy. Written informed consent was obtained from all participants who took part in the trial.

Participants

Eligible patients were all men and women aged 18-60 years with already diagnosed MDD, according to the Diagnostic and Statistical Manual of Mental Disorders (Structured Clinical Interview), Fifth Edition, (DSM-5), with a minimum score of 22 on the 17-item Hamilton Rating Scale for Depression (HAM-D) without any psychotic impressions. The exclusion criteria were as follow: No history of using any psychological drugs in 6 months before the trial, no alcohol and substance abuse in 6 months - they might have used alcohol and substance beforehand as reported in Table 1 - before the trial (except for caffeine and nicotine, IQ<70, current use of warfarin, insulin, statins or niacin, presence of any other mental disorder, presence of comorbidities, such as chronic kidney disease (CKD), liver disease, cardiovascular diseases, prior history of gallstones or any specific neurological disorders and suicidal ideation (score > 2 on the suicide item of the HAM-D).

Intervention

Those patients who were eligible due to the inclusion and exclusion criteria were randomly assigned into 2 groups. One group received 100 mg sertraline daily (beginning with 50mg daily and increased to 100 mg daily) in combination with 300 mg gemfibrozil daily. On the other hand, the control group received sertraline 100

mg daily and placebo. Treatment of both groups continued for 8 weeks. They were not allowed to undergo ECT or any other behavioral intervention therapy while they were taking part in the trial. Patients were evaluated in weeks 2, 4, and 8 postintervention, and in each of these evaluation meetings, they were also asked if they used their medication correctly.

In this study the daily dose of gemfibrozil given to each patient in the treatment group was 300 mg and was equal for all patients without any weight consideration. We were looking for any positive effect of gemfibrozil on MDD and the primary purpose of this study was not to measure the most effective dose of gemfibrozil for the treatment of MDD. Thus, further studies on the optimum dosage of gemfibrozil in MDD patients can improve our knowledge in this subject.

Outcome

The patient evaluations were conducted at baseline and in weeks 2, 4, and 8 postintervention. The evaluations of the 17-item rating scale HAM-D were done (16). Two senior psychiatrists performed the evaluations with an inter-reliability of >90% on both HAM-D ratings. The primary goal of this study was to evaluate the efficacy of gemfibrozil + sertraline in the improvement of depressive symptoms compared with placebo + sertraline based on improvement in HAM-D score changes during the trial using linear repeated measure models. Reduction in HAM-D scores from baseline at each time point, early improvement ($\geq 20\%$ reduction in HAM-D score within the first two weeks), response rates ($\geq 50\%$ reduction in the HAM-D score), remission rates (HAM-D score ≤ 7) (17) and time to response or remission were also compared between the 2 groups. Also, during the postintervention evaluation, adverse events were checked using a side-effect checklist (18).

Sample Size

In this study a sample size of 40 patients (20 in each group) was calculated because of the equality of means and variances between the 2 groups and by assuming a clinically significant difference of 3 for the HAM-D score, standard deviation (SD) of 3, a 2-sided significance level of 5%, power of 90%, with an effect size of 1, and a dropout rate of 20% .

Randomization, Allocation Concealment, and Blinding

A computerized random number generator was used to separate the participants into 2 random groups. The mentioned system uses blocks of 4 and an allocation ratio of 1:1. The generation of randomization codes was conducted by an independent party who was not involved elsewhere in the study. Concealment of allocation was performed using sequentially numbered, sealed, opaque, and stapled envelopes. Separate individuals were responsible for randomization and treatment allocation and the rating. All patients, the research team, raters, and statisticians were blinded to the treatment allocation. Both gemfibrozil and placebo had identical shapes, color, size, odor, and texture.

Statistical Analysis

All statistical analyses were performed using IBM SPSS statistics 25 (IBM corporation, Armonk, NY, USA). For statistical analysis, the categorical variables were presented as number and percentage of patients while continuous variables were reported as mean \pm standard deviation (SD). An independent sample t test was applied to compare continuous variables for the 2 groups at baseline. The HAM-D score for the 2 groups at weeks 2, 4, and 8 was compared using a mixed repeated-measures analysis of variance (ANOVA). In this test, the between-subject factor was considered as 2 treatment groups, and the HAM-D score at weeks 2, 4, and 8 was set as the within-subjects factor. The results of Greenhouse-Geisser were reported whenever Mauchly's test of sphericity was significant. The χ^2 test or Fisher's exact test was used to compare categorical variables. A comparison of the time needed to respond to treatment between the 2 groups was conducted using Kaplan-Meier estimation with the log-rank test. In all analyses, a p value of less than 0.05 was considered significant in all the mentioned analyses.

Results

Participants

From 60 patients who were screened for the eligibility criteria, 46 fulfilled all criteria and were included in this study. These 46 patients were randomized into 2 groups: one that received sertraline in combination with gemfibrozil (n = 23), and the other group received sertraline and placebo (n = 23).

One of the patients in the placebo group withdrew from the study before the first postbaseline visit, and 45 patients completed the study and took part in all follow-up visits (Figure 1) .

Outcomes

Baseline HAM-D scores showed no significant difference between gemfibrozil and placebo [33.17 ± 3.77 vs. 32.81 ± 3.83 ; respectively, df = 43, t = 0.31, p value = 0.69] (Table 1). The results of repeated measure ANOVA with a Greenhouse-Geisser correction showed a significant difference for time \times treatment interaction on within-subjects HAM-D scores [F (2.600, 111.790) = 3.403, p value = 0.026] (Figure 2). In addition, a significant difference was seen in time [F (2.600, 111.790) = 635.356, p value < 0.001]. The test of between-subject effects also showed a significant effect of treatment on HAM-D scores at weeks 2, 4, and 8 [F(1,43)=8.115, p value = 0.07] (HAM-D score changes in each time set can be seen in Table 2). The observed difference in early improvement (≥ 20 reductions in HAM-D score in the first 2 weeks) in the gemfibrozil group compared to the placebo group (80.0% and 20.0% of members of each group; respectively) was statistically significant [p value = 0.001]. No significantly different response rate was observed in the gemfibrozil group compared to the placebo group at weeks 4 and 8, while the remission rate

shows to be significantly higher in the gemfibrozil group at week 8 (Table 3). Using Kaplan-Meier estimate curves, time to response periods between the 2 groups showed no significant difference [Log-Rank P-value = 0.088] although time to remission was significantly different between the 2 trial arms [Log-Rank p value = 0.003].

Adverse Effects

Recorded adverse effects during the trial are reported in Table 4. There was no significant difference due to adverse effects between treatment groups, and no serious adverse event was detected (Table 4).

Table 1. Comparison of Participants' Baseline Characteristics between Two Groups Using Independent T-Test

Item	Gemfibrozil+Sertraline group (n=23)	Placebo+Sertraline group (n=22)	p-value
Age, mean ± SD	35.60 ± 10.36	34.31 ± 10.88	0.64
Sex, Female (%)	12 (52.1%)	12 (54.5%)	0.87
Duration of illness, mean ± SD years	6.08 ± 3.35	5.90 ± 2.22	0.23
Marital status, n (%)			
Single	4 (17.4%)	8 (36.4%)	0.36
Married	14 (60.9%)	10 (45.5%)	
Divorced	2 (8.7%)	3 (13.6%)	
widow	3 (13.0%)	1 (4.5%)	
Educational status, n (%)			
Illiterate	1 (4.3%)	2 (9.1)	0.43
Primary	5 (21.7%)	9 (40.9)	
High school	11 (47.8%)	7 (31.8%)	
Higher education	6 (26.0%)	4 (18.2%)	
Occupational status, n (%)			
Unemployed worker	1 (4.3%)	4 (18.2%)	0.58
Housewife	2 (8.7%)	1 (4.5%)	
Employee	11 (47.6%)	7 (31.6%)	
tradesman	2 (8.7%)	4 (18.2%)	
retired	6 (26.1%)	5 (22.7%)	
Smoking, Yes (%)	1 (4.3%)	1 (4.5%)	0.64
Substance use, Yes (%)	11 (47.8%)	9 (40.9%)	0.29
Suicide attempts, Yes (%)	7 (30.4%)	10 (45.5%)	0.42
Baseline HAM-D score, mean ± SD	10 (43.5%)	7 (31.8%)	0.69
Baseline MMSE score, mean ± SD	33.17 ± 3.77	32.81 ± 3.83	0.66
	25.04 ± 2.38	25.04 ± 2.59	

Table 2. Comparison of HAM-D Score Changes between Two Groups Using Independent T-Test

HAM-D score	Gemfibrozil+Sertraline group	Placebo+Sertraline group	Mean difference (95% CI)	t(50)	p-value
Change from baseline to week 2, mean ± SD	7.82 ± 3.95	5.40 ± 2.75	-2.41 (-4.47 to -0.37)	-2.37	0.022
Change from baseline to week 4, mean ± SD	12.08 ± 4.90	9.50 ± 3.51	-2.58 (-5.16 to -0.1)	-2.02	0.049
Change from baseline to week 8, mean ± SD	25.95 ± 4.15	22.45 ± 4.1	-3.50 (-5.99 to -1.01)	-2.83	0.007

HAM-D: Hamilton Depression

Table 3. Comparison of Response to Treatment and Remission Rates at Different Study Points between the Two Groups. Response Rate Means $\geq 50\%$ Reduction in the HAM-D Score, and Remission Rate Means HAM-D Score ≤ 7

Outcome	Gemfibrozil + Sertraline group	Placebo + Sertraline group	p-value	Odds Ratio (95%CI)
Number (%) of responders, at week 2	0 (0 %)	0 (0 %)	1.00	
Number (%) of responders, at week 4	2 (8.7 %)	0 (0 %)	0.48	0.91 (0.80-1.03)
Number (%) of responders, at week 8	23 (100 %)	21 (95.5%)	0.48	1.04 (0.95-1.14)
Number (%) of remissions, at week 8	13 (56.5%)	3 (13.6%)	0.005	0.12 (0.02-0.52)

Table 4. Frequency of Side Effects in each of the Study Groups (Gemfibrozil and placebo)

Side effects	Gemfibrozil group (n=23)	Placebo group (n=22)	p-value
Abdominal pain, n (%)	0 (0%)	1 (4.5 %)	0.48
Heartburn, n (%)	1 (4.3 %)	0 (0 %)	1.00
Nausea, n (%)	1 (4.3 %)	1 (4.5 %)	1.00
Dry mouth, n (%)	1 (4.3 %)	0 (0 %)	1.00

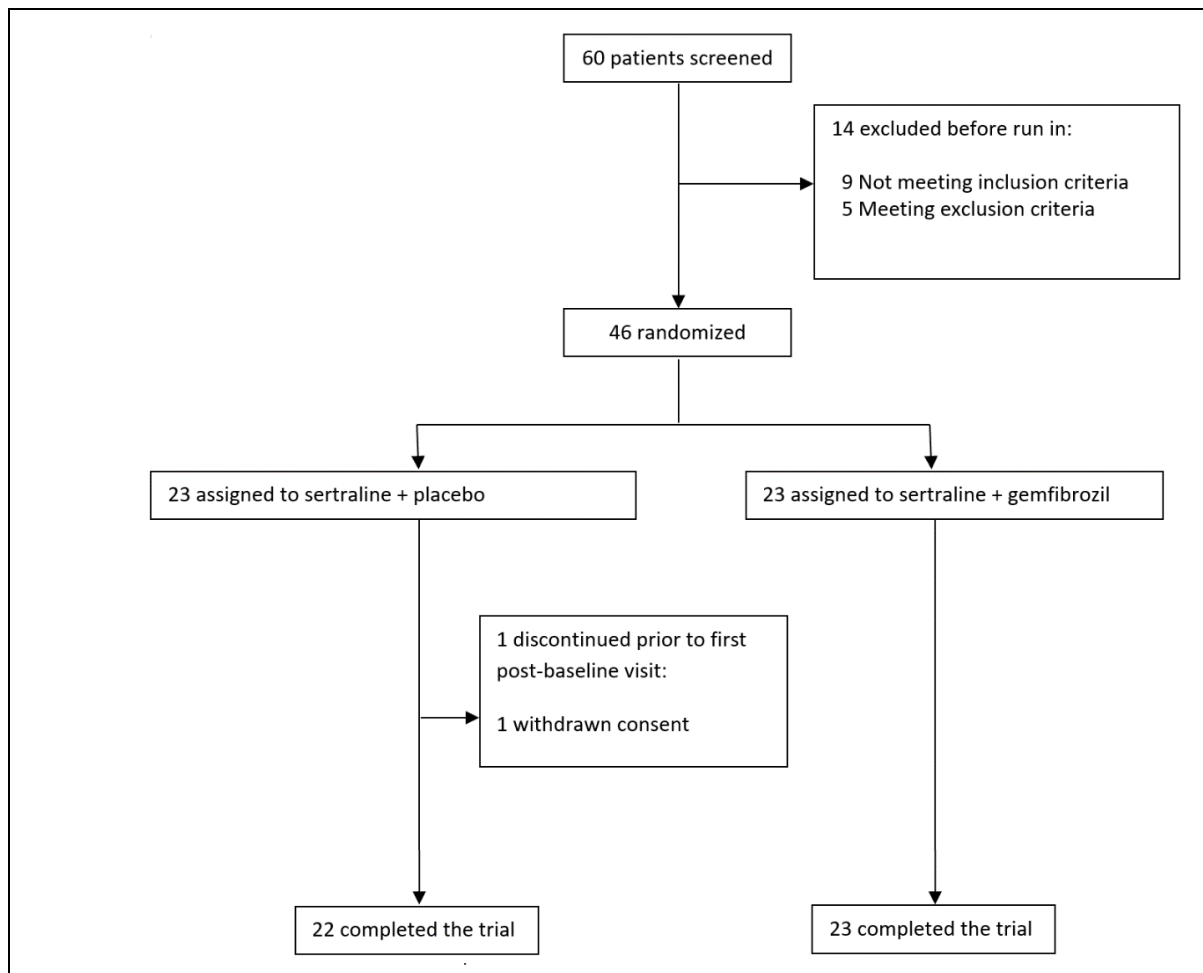


Figure 1. Flow Diagram Representing Case selection for the Trial Program

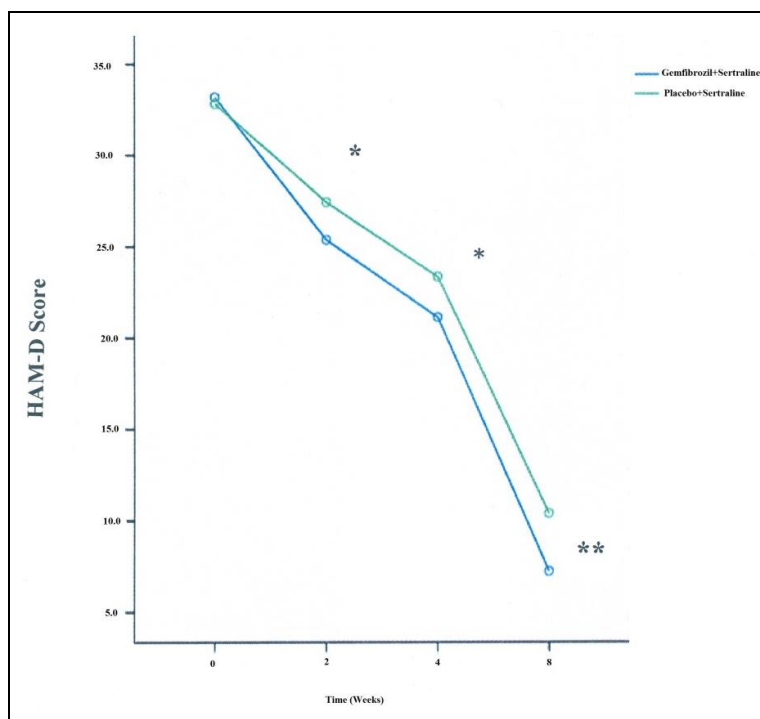


Figure 2. Repeated Measure ANOVA for Comparison of the Effects of Two Treatments on Hamilton Depression Rating Scale (HAM-D) at baseline and weeks 2, 4 and 8. Using the Greenhouse-Geisser Correction in between-Subject Effect for Treatment Shows a P-Value of less than 0.05

Discussion

This randomized, double-blind, placebo-controlled study was designed to evaluate the effectiveness of gemfibrozil as a sertraline adjuvant in the treatment of the major depressive disorder (MDD). We followed-up 45 MDD patients over 8 weeks of therapy via HAM-D scores. In this study, improvement of depressive disorder with combination therapy of sertraline and gemfibrozil was achieved in the follow-up of patients in the second, fourth, and eighth weeks of the trial. Also, in these patients, gemfibrozil was well tolerated and had no serious adverse effects. Overall, in this trial, gemfibrozil had satisfactory outcomes as treatment.

In major depressive disorder, multiple regions and networks of the brain are altered structurally, functionally, and molecularly (19). There are several theories in the pathogenesis of the disorder, with dysfunction of the monoaminergic system followed by the glutamatergic system malfunction receiving the most attention (20, 21). Role of inflammatory processes, oxidative stress, neuroendocrine and neurotrophic cascades, and vascular comorbidities in the pathophysiology of this disorder have also been studied (19, 22). Brain-derived neurotrophic factor (BDNF) is a neurotrophic agent and has a significant role in protecting neurons and their growth (23). Also, it has an essential role in emotion and cognition (22). BDNF exerts its function by binding to cellular receptors such as tyrosine kinase B (TrkB) receptor and pan75 neurotrophin receptor (p75NTR). It activates several

downstream pathways, which finally lead to the activation of cAMP-response element-binding protein (CREB) (14, 24). Studies show that the level of BDNF is altered in different parts of the brain in depressive disorders. Its level is decreased in the hippocampus and prefrontal cortex during depression and stress, but it is increased in area-nucleus accumbens and amygdala. Use of antidepressants changes the BDNF levels back to normal in mentioned areas (25). Also, a decrease in serum and plasma levels of BDNF is noted in persons with depression, suicidal thoughts, and stress. These levels also tend to normalize after treatment (22). Peroxisome proliferator-activated receptor- α (PPAR- α) is a subtype of the PPAR nuclear receptor family. In previous studies, selective agonists of PPAR- α showed antidepressant activities by enhancing the BDNF pathway and increasing the BDNF level in the hippocampus. It also directly activates CREB, which is a downstream signaling pathway of BDNF, and these mechanisms play an essential role in combating depression (14). PPAR- α agonists, which were previously studied in animals and showed promising antidepressant activity include fenofibrate, WY14643, and gemfibrozil (14).

In this study, gemfibrozil potentiated the antidepressant effect of sertraline. CYP metabolizes sertraline; also, CYP is inhibited by gemfibrozil; therefore, gemfibrozil can prolong the half-life and effect of sertraline and has an indirect antidepressant effect (26, 27). This was consistent with animal studies on other PPAR- α

agonists, fenofibrate, and WY14643, showing antidepressant activity (28, 29). The most accepted pathway of action of PPAR- α agonists is through the BDNF-CREB pathway. Downregulation of this pathway in the prefrontal and hippocampal regions were seen in depressive patients, and PPAR- α agonists activate this pathway, which leads to activation of the BDNF-CREB pathway opposing depression. The first study showing this antidepressant activity was by Jiang et al who reported WY14643, a PPAR- α agonists have more antidepressant activity on mice compared to placebo-treated controls (28). In another study on mice, the same result was seen with fenofibrate (29). Ni et al later studied gemfibrozil in mice whose antidepressant activity was strongly suggested and explained by the BDNF pathway mentioned above (14). According to the similar drug effecting site in gemfibrozil and previous drugs, we expect that these drugs act by the same pathway that leads to suppressing depression.

In the present study, the adverse effects of both gemfibrozil and sertraline were mild and rare, and there was almost no difference in side effects between the 2 groups. From previous studies, we know that gemfibrozil has many side effects in humans, which mostly include gastrointestinal side effects, nausea, and skin rash (30). This drug is contraindicated in renal or hepatic failure, and its usage in pregnancy should be under great caution. Some studies suggest that gemfibrozil may affect malignancies, gallbladder disease, myopathies, and noncoronary mortalities (13, 31). The most significant disadvantage of using gemfibrozil could be gastrointestinal disturbances (13). Gastrointestinal side effects are common side effects of different antidepressant drugs. Constipation via tricyclic antidepressant use, nausea, appetite change, and diarrhea by selective serotonin receptor inhibitors are the most common side effects (32). The additive effect of drug combinations or interactions could be a significant problem for treated patients (13, 33).

Limitation

Despite the advantages of this study (a double-blind, randomized placebo-controlled design and with careful adjustment of baseline clinical variables), some limitations need to be mentioned. First, due to ethical considerations, there was no placebo-only group in this study; therefore, it was not possible to evaluate the antidepressant effect of gemfibrozil exclusively. The second and third limitations are the small sample size and the short duration of follow-up. It is recommended that future studies be performed to maintain the advantages and eliminate the mentioned limitations.

Conclusion

In this 8-week double-blind clinical trial, it was found that gemfibrozil is an effective adjunctive treatment in major depressive disorder patients and can be safely used to reduce symptoms of depression. Gemfibrozil, at

a dose of 300 mg daily demonstrated no severe side effects. However, the safety and efficacy of more extended treatment periods with gemfibrozil were not evaluated in this study.

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Conflict of Interest

None.

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