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Original Article

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

Atefeh Zandifar[1], Rahim Badrfam[2], Ahmad Shamabadi[2], Shakiba Jalilevand[2], Shayan Pourmirbabaei[2], Farbod Torkamand[2], Erfan Sahebolzamani[2], Shahin Akhondzadeh[2*]

Abstract

Objective: Major depressive disorder (MDD) is predicted to be one of the biggest disease burden in the future. The antidepressant activity of gemfibrozil has been recently considered. In this study, we assessed the effectiveness of gemfibrozil as a sertraline adjunct in treating patients with MDD.
Method: In this study, 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 divided into two groups. One group was treated with 300 mg of gemfibrozil daily and the other group treated with placebo. Each group was treated simultaneously with 100 mg of sertraline daily for 8 weeks. The trial was randomized and double-blind. To assess the response to treatment, patients were evaluated at baseline and then at weeks 2, 4 and 8 using the HAM-D score.
Results: The study was completed by 45 patients up to the final stages and 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 notable difference was seen in time [p–value < 0.001]. The test of between-subject effects also represented a remarkable consequence 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 notable different between the 2 trial groups [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*

1. Imam Ali Hospital, Alborz University of Medical Sciences, Karaj, Iran.
2. Psychiatry and Psychology Research Center, Roozbeh Hospital, Tehran University of Medical Sciences, Tehran, Iran.

***Corresponding Author:**
Address: Psychiatry and Psychology Research Center, Roozbeh Hospital, Tehran University of Medical Sciences, South Kargar Street, Tehran, Iran, Postal Code: 1333795914.
Tel: 98-21 55413540, Fax: 98-21 55421959, Email: s.akhond@neda.net

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Major depressive disorder (MDD) is defined as one or more episodes of major depression while there have been no manic episodes in lifetime (1). MDD occurs almost two fold 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). It is predicted that by 2030, it will be the main cause of disease burden in the world. (4).

Available and commonly used treatments for MDD comprise psychotherapy, pharmacotherapy, and electroconvulsive therapy. Pharmacotherapy plays the first role in the treatment of MDD. (5). for the past recent decades, the monoaminergic systems as the underlying neurobiology of MDD, have received considerable attention. (6).

In the 1950s, tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) were presented as the first antidepressant medicines. Selective serotonin reuptake inhibitors (SSRIs) or selective serotonin and norepinephrine reuptake inhibitors (SNRIs) were the next generations of antidepressant drugs, and now they are the most common treatments and medicines for MDD, which are considered as the best treatments in this field in scientific circles. (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). Based on our review, no evaluation so far surveyed this effect on humans. However, improvements in depressive symptoms were noted after treatment of severe hypertriglyceridemia in one study (15). Based on the evaluation, we hypothesize that the use of gemfibrozil with sertraline is associated with greater clinical improvement than sertraline alone in the treatment of 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

Setting

This two-centric study was performed for 8 weeks to evaluate the effect of gemfibrozil in combination with sertraline on the improvement of MDD at Roozbeh psychiatric hospital and Imam Hossein psychiatric hospital from April 2019 to February 2020. Trial registry number is IRCT20090117001556N119.

Ethics

The study was conducted in full agreement with the provisions of the Helsinki Declaration and its subsequent revisions. The study protocol was approved with the ethics code IR.TUMS.VCR.REC.1397.880. Participants could leave the study at any situation and this would never lead to any negative consequences on their therapy. If they wished to participate in the study, they would complete an informed consent form.

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, having 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

Patients who were eligible to participate in the study in terms of inclusion and exclusion criteria were distinct into two 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. Meanwhile, the control group received sertraline 100 mg daily and placebo. Treatment of both groups continued for 8 weeks. They did not receive any other treatment during the study, such as ECT and behavioral therapy.

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 aim of it was not to measure the most effective dose of gemfibrozil for the improvement of MDD. Thus, further studies on the optimum dosage of gemfibrozil in MDD patients can improve our knowledge in this subject.

Outcome

Patients were evaluated at the beginning of the study and then at 2, 4 and 8 weeks after the intervention. 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 aim of it was to assess the effect 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 (≥20% reduction in HAM-D score within the first two weeks), response rates (≥ 50% reduction in the HAM-D score), remission rates (HAM-D score ≤7)(17) and time to response or remission were also evaluated between the 2 groups. Also, during the postintervention evaluation, adverse events were checked using a side-effect checklist (18).

Sample Size

In this study, 40 patients were considered (20 in each group) 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% .

Design

Using a computerized random number generator, patients were divided into two random groups. The mentioned system uses blocks of 4 and an allocation ratio of 1:1. An independent party managed creation of random codes. Concealment of allocation was carried out using sequentially numbered, sealed, amorphous, and clipped envelopes. Other 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

SPSS software version 25 was used for statistical analysis of data. (IBM Corporation, Armonk, NY, USA). For statistical analysis, the categorical variables were presented as number and percentage of participants while continuous variables were reported as mean ± 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. Whenever Mauchly's sphericity test was notable, Greenhouse-Geisser results were reported the χ ^ 2 test or Fisher's exact test was used to evaluate categorical variables. A comparison of the time needed to respond to treatment between the 2 groups was managed using Kaplan-Meier estimation with the log-rank test. If the p value was less than 0.05, it was considered significant.

Results

Participants

According to the inclusion and exclusion criteria, out of 60 patients screened, 46 fulfilled all criteria and were considered for study. These 46 patients were randomized into 2 groups: one that received sertraline in combination with gemfibrozil (n = 23), and the other one received sertraline and placebo (n = 23).

One of the participants in the placebo group did not continue the survey before the first postbaseline visit, and 45 other participants continued the study to the end. (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×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. In terms of side effects, the two groups were not significantly differen and no serious adverse event was detected (Table 4).

Table 1. Status of Participants in Terms of Demographic and Basic Characteristics 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%)	
Married	14 (60.9%)	10 (45.5%)	0.36
Divorced	2 (8.7%)	3 (13.6%)	
Widow	3 (13.0%)	1 (4.5%)	
Educational status, n (%)			
Illiterate	1 (4.3%)	2 (9.1)	
Primary	5 (21.7%)	9 (40.9)	0.43
High school	11 (47.8%)	7 (31.8%)	
Higher education	6 (26.0%)	4 (18.2%)	
Occupational status, n (%)			
Unemployed	1 (4.3%)	4 (18.2%)	
worker	2 (8.7%)	1 (4.5%)	
Housewife	11 (47.6%)	7 (31.6%)	0.58
Employee	2 (8.7%)	4 (18.2%)	
tradesman	6 (26.1%)	5 (22.7%)	
retired	1 (4.3%)	1 (4.5%)	
Smoking, Yes (%)	11 (47.8%)	9 (40.9%)	0.64
Substance use, Yes (%)	7 (30.4%)	10 (45.5%)	0.29
Suicide attempts, Yes (%)	10 (43.5%)	7 (31.8%)	0.42
Baseline HAM-D score, mean ± SD	33.17 ± 3.77	32.81 ± 3.83	0.69
Baseline MMSE score, mean ± SD	25.04 ± 2.38	25.04 ± 2.59	0.66

Table 2. Status 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. Status of Response to Treatment and Remission Rates at Different Study Period between the Two Groups

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 Different Groups under Evaluation (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

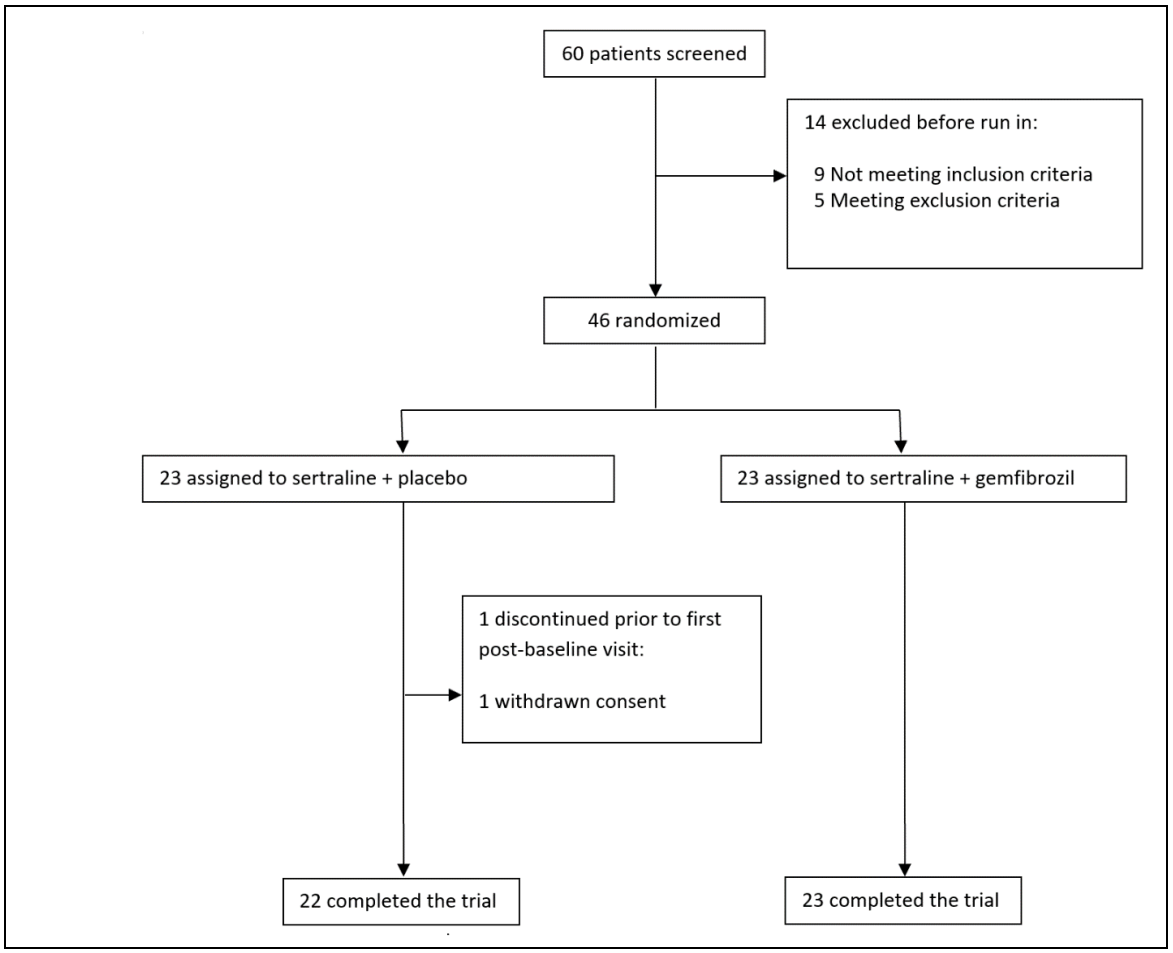

Figure 1. Flow Diagram on How to Select Cases for the Trial Program

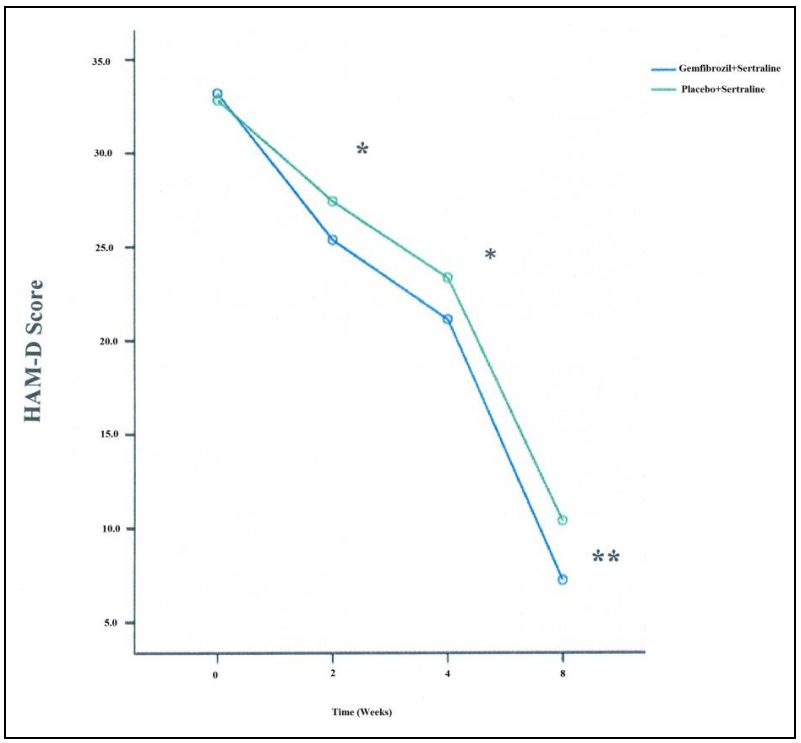

Figure 2. Repeated Measure ANOVA for Comparison of the Effects of Two Treatments on Hamilton Depression Rating Scale (HAM-D) at Baseline and Weeks 2, 4 and 8. Using the Greenhouse-Geisser Correction in between-Subject Effect for Treatment Shows a P-Value of less than 0.05

Discussion

This study was designed to assessment the efficacy of gemfibrozil as a sertraline adjuvant on improving the symptoms 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 survey. 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 our 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), there were a number of limitations. First, in order to comply with ethical principles, the placebo-only group was not used, 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 study period. It is recommended that future studies be performed to maintain the advantages and eliminate the mentioned limitations.

Conclusion

This study, which was a double-blind clinical trial for 8 weeks, showed the effectiveness of gemfibrozil as adjunctive therapy in patients with major depressive disorder. 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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