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The Effectiveness of Gemfibrozil on Nicotine Dependence, Smoking Cessation, and its Symptom Among Smokers: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

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Abstract

Background: Based on animal models, the antagonists of alpha-peroxisome proliferator-activated receptors (PPAR-α) such as fibrates decrease reinforcement, brain rewards, and nicotine-related effects.
Objectives: The present study aimed at investigating the effect of Gemfibrozil on smoking cessation.
Methods: This is a double-blind, randomized clinical trial that performed on 75 adult cigarette smokers from 200 smokers. Hence, 75 adult cigarette smokers were divided into two groups after matching. The experimental group (37 peoples) and the placebo group (38 peoples). The participants received 300 mg Gemfibrozil or placebo at the same amount twice a day for 7 weeks. This study was conducted in a university affiliated hospital, Kashan, Iran. To investigate nicotine dependency, signs of deprivation syndrome and smoking cessation, the Fagerstrom test, Minnesota Scale (MNWS), and exhalation carbon monoxide markers were used.
Results: There was no significant difference in demographic characteristics between the two groups. At the seventh week, Fagerstrom mean score was 3.1 ± 3.1 and 5.1 ± 3.4 ($P = 0.023$) for the treatment and placebo groups respectively. According to the Minnesota criteria, the treatment group showed more increased weight gain and appetite, as well as more decreased desire to smoke ($P < 0.001$). The success rate of smoking cessation at the end of the intervention and follow-up periods indicated that there was no significant difference between the two groups in this factor ($P > 0.05$).
Conclusions: Gemfibrozil only reduced the symptoms of nicotine deprivation syndrome but did not show significant potential for smoking cessation.

Keywords: Dependency, Deprivation, Gemfibrozil, Nicotine, Smoking Cessation

1. Background

Despite global warnings about the great dangers of nicotine, smoking is increasing every day (1). In fact, more than 1.2 billion people are direct smokers worldwide (2, 3) who are at higher risk of developing more than 25 types of life-threatening illnesses, including chronic obstructive pulmonary disease, lung cancer, Alzheimer's, and diabetes (1, 2, 4-6). In recent decades, to reduce the risk of such diseases and treat cigarette dependency, a wide range of drug treatments, including nicotine replacement products, bupropion, and varenicline therapy has been proposed (7). However, only about 5% to 70% of the smokers may succeed following cessation therapy (2). However, 70% - 90% of them, smoke again less than 12 months later (8-10). These results suggest the need to pay attention to new dimensions of smoking cessation in order to increase the rates of withdrawal and recovery in individuals.

For years, the role of nicotine has been emphasized in creating reward effects and craving for smoking to achieve enjoyable stimulation through the influence on the mesolimbic transmission pathways of dopamine (11). In addition, the regulation of central dopaminergic neurons by nicotine-acetylcholine receptors (nAchRs) play an important role in behavior, cognition, stimulation, and reward (12). In fact, the nAchRs-complex itself also includes 5 subunits, found both in central and peripheral nervous systems (13). The a4b2 subunit plays a prominent role in the human brain, and it is believed that it is the main mediator receptor in nicotine dependence (14).

Peroxisome proliferator-activated receptors (PPARs) are a group of nucleic protein receptors primarily used to

regulate gene expression (15). They consist of three isoforms of the PPARs, alpha, delta, and gamma, each of which has been translated from various genes (16). Alpha-type PPAR reduces ionic transport by increasing the phosphorylation of nicotine receptors placed on the dopaminergic neurons in the ventral tegmental area and modifying them. As a result, the response of dopamine neurons to nicotine is reduced. Through such a mechanism, both endogenous PPAR agonists, such as oleoylethanolamide and palmitoylethanolamide (OEA and PEA), as well as synthetic agonists such as fibrates, can inhibit nicotine ability to stimulate mesolimbic dopaminergic neurons and consequently, the effects of nicotine reward is blocked (8). Previous researches have shown that PPAR agonists and fatty acids amid hydrolase (FAAH) inhibitors suppress the effects of nicotine rewards in animals and act similar to cannabinoid reverse antagonists/agonists. Another promising issue is the lack of psychological side effects caused by cannabinoid CB1 receptors in PPAR agonists (17-20).

Fibrates are a class of PPAR-alpha-activating drugs that are widely used to improve lipid profile and prevent cardiovascular diseases (15). Following the studies carried out on cannabinoids, the interest in PPAR-α as a target for drug treatment of addiction has been increased (21). In fact, according to the results of previous researches, this system is involved in details of drug addiction and similar deficits (22-24). Thereby to detect the effect of PPAR-α agonist on individuals, the animal models have been used that led to promising results. For example, a study by Melis and Pistis demonstrated the effects of PPAR-α-stimulating drugs on nicotine addiction. They showed that these drugs reduced the absorption of nicotine and reversed the nicotine-induced behaviors in mice and monkeys (12).

Gemfibrozil, belonging to the fibrate group, activates PPAR-α and involves in the metabolism of carbohydrates and fats (25, 26). In addition, it has considerably low side effects.

When this study was conducted in 2015 - 2016, there were no published RCT studies on the use of PPAR-α agonists as aids for smokers. However, the result was contradictory in one study that evaluated Fenofibrate (another fibrate medication) Efficacy in aiding smoking abstinence (27). In addition, the study did not have two distinct groups of control and intervention that may lead to bias in the results.

2. Objectives

Thus regarding these limitations in previous studies, this study aimed at investigating the effectiveness of Gemfibrozil on nicotine dependence, smoking cessation, and its symptom among smokers.

3. Methods

3.1. Design

This double-blind clinical trial included all people referred to the smoking cessation clinic of Kargarnejad Hospital (teaching hospital of Kashan University of Medical Sciences and the only psychiatric hospital in Kashan) to stop their smoking.

Inclusion criteria were age of 19 to 65; daily use of 10 or more cigarettes over a year or more; no history of admission due to psychiatric illness; no history of drug abuse; and no use of any interfering or contraindicating medication with Gemfibrozil, including anticoagulants, statins, other fibrates, other lipid-lowering drugs such as niacin, herbal remedies, and any oral or injectable drug for diabetics. Exclusion criteria also included drug abuse during the intervention and follow-up periods, pregnancy during the study, and reluctance to continue treatment.

Recruited patients were randomly divided into Gemfibrozil and placebo groups using block randomization technique with five-patient blocks. Random assignment was done by the 2nd author researchers in the team, while study intervention was implemented by another researcher in the team. In other words, Mohammad Reza Davoudi was aware while others were blind to group assignment and intervention. Moreover, all participants were blind, whether they were in the Gemfibrozil or the placebo groups.

3.2. Sample Size

Considering that there is not such a study with similar aim yet and also there are similar mechanisms for varenicline and fibrate effects on smoking cessation, such as nicotinic acetylcholine a4b2 receptors and their other subtypes, the sample size was estimated. We referred to a study comparing the effect of varenicline and placebo on smoking cessation continuity. That study reported 44% and 16% success in treatment and placebo groups, respectively. Considering 95% confidence interval and 80% power of test, a minimum of 75 persons was calculated for two groups (16). Thus experimental group sample size included 37 smokers and placebo group included 38 smokers.

$$n = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 \left(P_1\left(1-P_1\right) + P_2\left(1-P_2\right)\right)}{\left(P_1 - P_2\right)^2} \quad (1)$$

3.3. Interventions

After entering the study, each person was assigned a number then the participants were divided into two groups via the method of Permuted Blocked Randomization by the computer software of random numbers. In other words, the participants were randomly divided into experimental and control groups using block randomization method, using units of 5 blocks. Patients in the treatment and control groups received Gemfibrozil at a dose of 300 mg twice a day, taken orally 30 minutes before the morning and evening meals and placebo (manufactured by Sobhan Darou) at the same amount of Gemfibrozil and times, respectively.

3.4. Instruments

3.4.1. Demographic Information Questionnaire

This was a self-made questionnaire (by the first author) to evaluate the variables such as age, sex, marital status, the number of cigarette smoking per day, and educational and job status.

3.4.2. Minnesota Deprivation Measurement Scale

This scale consisted of 8 sections that examined the cessation symptoms and categorized them between 0 and 4 points. This questionnaire was translated during cigarette cessation clinic programs, and its validity and reliability were examined in 2008 (28, 29).

3.4.3. Fagerstrom Scale

This test included questions about the first smoking time after sleep, the number and frequency of cigarette smoking daily, the best cigarette smoking, cigarette smoking tendency in the illness, and having a problem in prohibited areas. This test is accepted as a standard method by the World Health Organization and the World Anti-Tuberculosis and Pulmonary Diseases Association, as well as many reference books of internal and lung medicine (30).

3.4.4. Smoking Cessation

To assess nicotine use, the levels of carbon monoxide (CO) were monitored with the Micro-smokerlyzer CO monitor. If the amount of carbon monoxide was equal to 5 ppm or higher in the exhalation, the person would be considered a smoker (31).

3.5. Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, N.Y., USA). Descriptive statistics and Chi-square and *t* test were used for this purpose. Results were reported as mean and standard deviation (mean $\pm$ SD). The P value ≤ 0.05 was considered statistically significant.

3.6. Ethical Considerations

The proposal for this thesis 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.1394.29 on May 30, 2015, and the enrollment of the patients was initiated on August 23, 2015, and the study continued until December 15, 2015. This study was also registered in the Iranian Registry of Clinical Trials (irct.ir) with the ID: IRCT2017101732057N3.

Prior to the study, the patients were informed about the research and ethical issues. Subsequently, written informed consent was obtained from all participants. They were ensured that their information would remain secure.

4. Results

This double-blind clinical trial was conducted on the smokers aged 19 - 65 who tended to quit smoking in Kashan in 2015. Hence, 37 and 38 people were assigned to Gemfibrozil group and placebo group, respectively and the intervention was conducted from 2015-08-23 to 2015-12-15, (One of the participants did not refer to the study setting because of an unknown reason). Figure 1 shows clinical trial flowchart of this study.

According to the results, there were 3 (8.1%) females and 34 (91.9%) males in Gemfibrozil group, and 1 (0.7%) female and 37 (99.3%) males in the placebo group. The mean age was 34 $\pm$ 10 years in the Gemfibrozil group and 33.6 $\pm$ 10.6 years in the placebo group. In fact, there was no statistically significant difference between the two groups in terms of sex and age ($P > 0.05$). Table 1 compares demographic variables between the two groups.

In addition, the mean of the smoking period was 13.1 $\pm$ 9.3 years in the Gemfibrozil group and 13.1 $\pm$ 9.3 years in the placebo group. No significant difference was observed between the two groups ($P = 0.904$).

On the other hand, the Fagerstrom score in the Gemfibrozil and placebo group was 8.4 $\pm$ 1. 1 and 1.8 $\pm$ 1, respectively ($P = 0.196$) at the beginning of the study (Table 2), which they changed to 3.3 $\pm$ 3 and 5.1 $\pm$ 3.4, respectively in the seventh week. There was a significant difference between the two groups ($P = 0.023$). The mean of changes was 5.2 $\pm$ 5 in the Gemfibrozil group and 2.9 $\pm$ 2.8 in the placebo group. The difference between the two groups was significant ($P = 0.001$).

No significant differences were found between the two groups in any of the subscales of Minnesota criteria at the

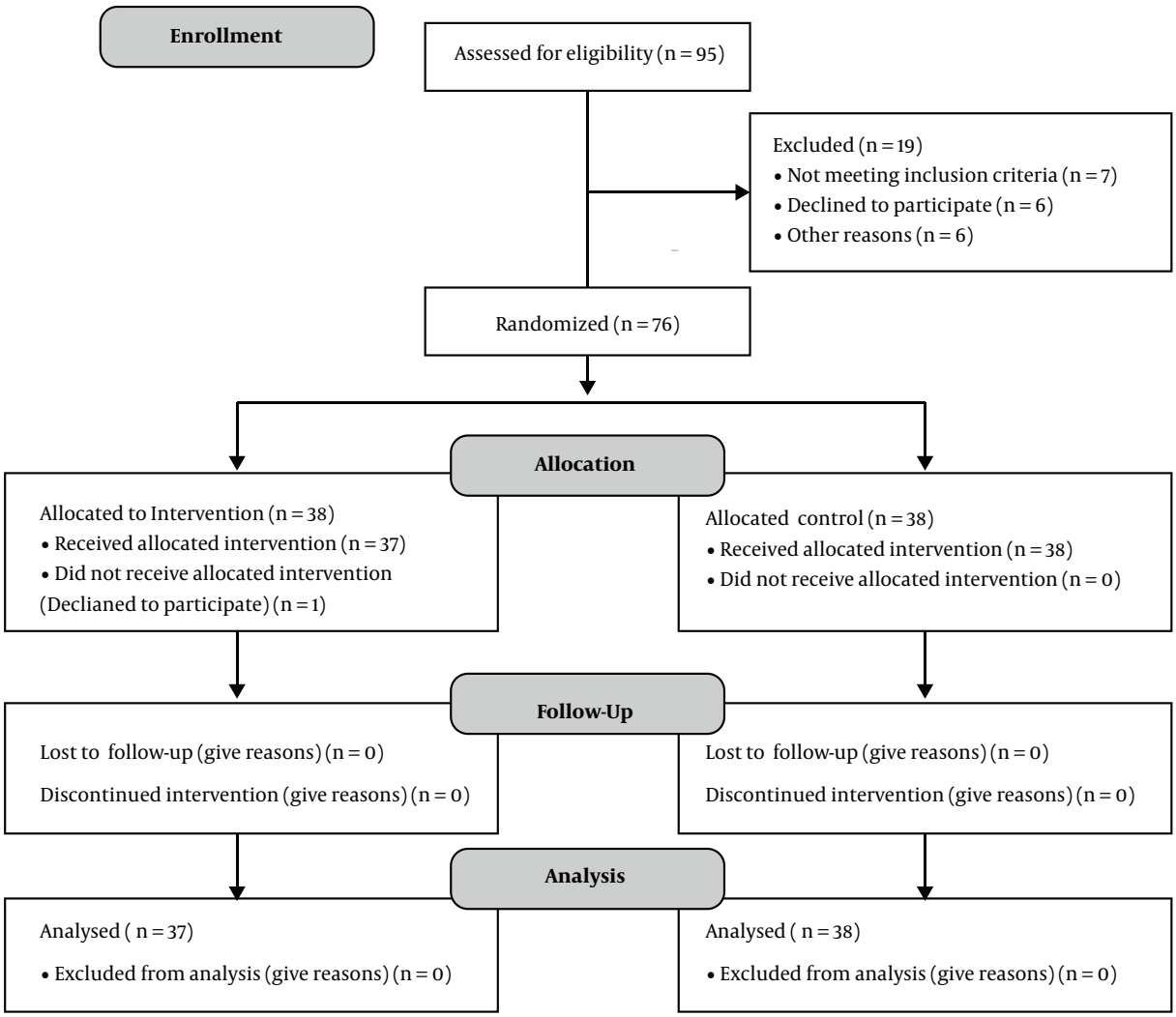

Figure 1. Clinical trial flowchart of the study

beginning of the study. Also, only the subscales of smoking craving, weight gain, and appetite showed a significant difference between the two groups at the end of the seventh week (Tables 3 and 4).

In addition, the frequency of success in quitting smoking at the end of the follow-up period was 16 (43.2%) and 11 (28.9%) subjects in treatment and placebo groups, respectively without any significant difference between the two groups (P = 234) (Table 5).

5. Discussion

The aim of this study was to determine the effects of Gemfibrozil on nicotine dependence, smoking cessation, and its symptom among the smokers: A randomized, double-blind, and placebo-controlled clinical trial. The results indicated that the use of Gemfibrozil only reduced the symptoms of nicotine deprivation syndrome but did not show significant potential for quitting smoking. Since this issue is novel, there are few studies in this regard. For example, in a study by Mascia and colleagues, it was shown that PPAR-α, found in the body of dopaminergic neurons in the Ventral Tegmental Area, modulates nicotine receptors and reduces ion transfer by increasing the phosphorylation of them. Through such mechanism both endogenous PPAR agonists, such as oleoylethanolamide and palmitoylethanolamide (OEA and PEA), as well as synthetic agonists such as fibrates, can inhibit nicotine ability to stimulate mesolimbic dopaminergic neurons and consequently, the effects of nicotine reward is blocked. In

Table 1. Frequency of the Distribution of Demographic Characteristics Within the Study Groups[a]

Variable	Gemfibrozil Group (N = 37)	Placebo Group (N = 38)	P Value
Age			0.902[b]
< 30	17 (45.9)	18 (47.3)	
≥ 30	20 (54.1)	20 (52.7)	
Age (mean ± SD)	34 ± 10.6	33.6 ± 10.6	0.856[c]
Gender			0.358[b]
Male	34 (91.9)	37 (99.3)	
Female	3 (8.1)	1 (0.7)	
Marital status			0.805[b]
Single	11 (29.7)	13 (34.2)	
Married	26 (70.3)	25 (65.8)	
Education			0.718[b]
Secondary school	4 (10.8)	4 (10.5)	
Diploma	14 (37.8)	18 (47.4)	
Academic	19 (51.4)	19 (42.1)	
Occupation			0.652[b]
Unemployed	4 (10.8)	7 (18.4)	
Self employed	11 (29.7)	8 (21.1)	
Employed	16 (43.2)	18 (47.4)	
House wife	3 (8.1)	1 (2.6)	
Others	3 (8.1)	4 (10.5)	

[a] Values are expressed as No. (%) unless otherwise indicated.
[b] Chi-square test.
[c] *T* test.

Table 2. Fagerstrom Mean Score in Study Groups at the Start of Study, Week Seven

Time	Gemfibrozil Group (N = 37)	Placebo Group (N = 38)	P Value[a]
Start of study	8.4 ± 1.1	8.1 ± 1	0.196
Week seven	3.3 ± 3.1	5.1 ± 3.4	0.023
Changes	5 ± 2.3	2.9 ± 2.8	0.001
P value[b]	< 0.001	< 0.001	

[a] *T* test independent.
[b] *T* test dependent.

line with our findings, a study that has evaluated the effects of PPAR-α-stimulating drugs on nicotine addiction showed that these drugs reduced the absorption of nicotine and reversed the nicotine-induced behaviors in mice and apes (15). Also, in another study by Michalik et al. the effect of fibrate class drugs on reward-related behavior, electrophysiological, and neurochemical effects of nicotine in rats and monkeys was investigated and it was revealed that such drugs prevent nicotine-dependent behaviors in simple animals; however, they definitely reduce nicotine use in experienced- and skilled animals and cope with recurrence effects of nicotine use after smoking quit period, which is also consistent with the present study (15).

Perkins et al. concluded that the use of phenophyllinate, during a short period, was not effective on smokers who tended to quit smoking, which is in line with our results (27).

The McBride et al. study stated that P substance is a mediator for the caudal nucleus basalismagnocellularis system, and serotonin secreted from a dorsal and median raphe nucleus, an important anatomical component of the brain, constitutes the brain reward system. In general, Intracranial Self-Administration (ICSA) and intracranial site conditioning (ICPC) studies indicated that there were several receptors, neural pathways, and brain regions that constituted brain reward pathways (32). A study by Quezada-Berumen et al. suggested that fibrates can facilitate smoking cessation. In fact, studies and clinical trials have shown that fibrates are effective drugs for tobacco-dependent people, especially smokers with an impaired fat profile, their results are similar to those of our study (33).

Hurt et al. studied 650 people and showed that the slow-release bupropion formulation is effective in quitting smoking, which reduces weight gain and the side effects of smoking cessation, nevertheless, it has no effect on depression criteria. Consistent with their result, Gemfibrozil also reduced craving to smoke in our study (34).

Despite these results, in Cinciripini et al. study on 294 volunteers, a three-month-follow-up after smoking cessation discloses that both varenicline and bupropion were effective in reducing the symptoms of smoking cessation compared with placebo, however, in the six-month-follow-up, the symptoms of smoking cessation decreased only among those who used varenicline. In addition, varenicline generally reduces depression and desire for cigarettes compared with other treatments; however, both varenicline and bupropion compared with placebo, improved concentration, reduced craving for cigarette smoking, and reduced negative effects and upset (35). In fact, these results were in contrast to the results of the present study, probably due to the fact that higher doses or other peroxisome proliferator-activated receptors (PPARs) were not evaluated in this study and such dose is not a suitable dose for smoking cessation (27).

5.1. Conclusions

According to the results of this research, it can be concluded that Gemfibrozil may play a key role in reducing nicotine deprivation syndrome by its PPAR-α agonistic

Table 3. Frequency of Distribution in Minnesota Scale in Week One[a]

Symptoms	Gemfibrozil Group					Placebo Group					P Value[b]
	Without Symptom	Very Low	Low	Moderate	High	Without Symptom	Very Low	Low	Moderate	High	
Depression	3 (8.0)	10 (27)	18 (48.6)	5 (13.5)	1 (2.7)	3 (7.9)	14 (36.8)	13 (34.2)	8 (21.1)	0 (0)	0.567
Insomnia	3 (8.1)	12 (32.4)	13 (35.1)	7 (18.9)	2 (5.4)	3 (7.9)	13 (34.2)	13 (34.2)	8 (21.1)	1 (2.6)	1
Irritability	2 (5.4)	11 (29.7)	14 (37.8)	9 (24.3)	1 (2.7)	0 (0)	8 (21.1)	16 (42.1)	12 (31.6)	2 (5.3)	0.596
Anxiety	2 (5.4)	6 (16.2)	14 (37.8)	13 (35.1)	2 (5.4)	0 (0)	8 (21.1)	18 (47.4)	11 (28.9)	1 (2.6)	0.612
Concentration problems	2 (5.4)	2 (5.4)	14 (37.8)	12 (32.4)	7 (18.9)	2 (5.3)	6 (15.8)	13 (34.2)	13 (34.2)	4 (10.5)	0.590
Restlessness	3 (8.1)	12 (32.4)	13 (35.1)	7 (18.9)	2 (5.4)	3 (7.9)	13 (34.2)	13 (34.2)	8 (21.1)	1 (2.6)	1
Increased weight gain & appetite	15 (40.5)	22 (59.5)	0 (0)	0 (0)	0 (0)	16 (42.1)	22 (57.9)	0 (0)	0 (0)	0 (0)	1
Smoking craving	2 (5.4)	4 (10.8)	23 (62.2)	7 (18.9)	1 (2.7)	4 (10.5)	2 (5.3)	21 (55.3)	10 (26.3)	1 (2.6)	0.787

[a] Values are expressed as No. (%).
[b] Fisher's exact test.

Table 4. Frequency Distribution of Minnesota Scale in Week Seven[a]

Week	Gemfibrozil					Placebo Group					P Value[b]
	Without Symptom	Very Low	Low	Moderate	High	Without Symptom	Very Low	Low	Moderate	High	
Depression	4 (10.8)	10 (27)	19 (51.4)	4 (10.8)	0 (0)	5 (13.2)	13 (34.2)	16 (42.1)	4 (10.5)	0 (0)	0.557
Insomnia	3 (8.1)	14 (37.8)	15 (40.5)	4 (10.8)	1 (2.7)	6 (15.8)	13 (34.2)	11 (28.9)	7 (18.4)	1 (2.6)	0.676
Irritability	3 (8.1)	12 (32.4)	17 (45.9)	5 (13.5)	0 (0)	1 (2.6)	7 (18.4)	24 (63.2)	6 (15.8)	0 (0)	0.342
Anxiety	2 (5.4)	9 (24.3)	20 (54.1)	5 (13.5)	1 (2.7)	1 (2.6)	9 (23.7)	24 (63.2)	4 (10.5)	0 (0)	0.792
Concentration problems	2 (5.4)	2 (5.4)	22 (59.5)	11 (29.7)	0 (0)	2 (5.3)	6 (15.8)	18 (47.4)	12 (31.6)	0 (0)	0.486
Restlessness	3 (8.1)	15 (40.5)	17 (45.9)	2 (5.4)	0 (0)	3 (7.9)	16 (42.1)	16 (42.1)	3 (7.9)	0 (0)	1
Weight gain and appetite increase	0 (0)	8 (21.6)	17 (45.9)	12 (32.4)	0 (0)	10 (26.3)	26 (68.4)	2 (5.3)	0 (0)	0 (0)	< 0.001
Smoking craving	2 (5.4)	26 (70.3)	9 (24.3)	0 (0)	0 (0)	0 (54.1)	1 (2.6)	12 (31.6)	23 (60.5)	2 (5.3)	< 0.001

[a] Values are expressed as No. (%).
[b] Fisher's exact test.

Table 5. Frequency of Success in Cigarette Cessation in Two Groups

Success In Cigarette Cessation	Gemfibrozil Group	Placebo Group	P Value
Yes	16 (43.2)	11 (28.9)	0.234[a]
No	21 (56.8)	27 (71.9)	
Total	37 (100)	38 (100)	-

[a] Chi-square test.

properties and nicotine receptors-modulating. However, there was no significant difference between Gemfibrozil and placebo groups in the response rate to the treatment, and more studies should be done with different doses and different receptors for more illustration.

5.2. Limitations, Recommendations, and Strong Points

The strong points include 1. This study was one of the first studies exploring the role of Gemfibrozil in smoking cessation. 2. We used a randomized clinical trial. 3. A number of 75 smokers participated and helped us to explore the

pure effect of the dependent variable. 4. To assess nicotine use, the levels of carbon monoxide (CO) was used. This instrument is more reliable than self-reporting about cessation or cigarettes smoking.

This study was limited in the duration of treatment with Gemfibrozil which was lower than other similar studies as well as the matching of lipid profile between the groups due to the limited sample available in Kashan. Therefore, a similar study with a longer duration of Gemfibrozil treatment, larger and varied sample size, and comparison different doses of Gemfibrozil is recommended.

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Footnotes

Clinical Trial Registration: This study also was registered in the Iranian Registry of Clinical Trials (irct.ir) with the ID: IRCT2017101732057N3. https://www.irct.ir/trial/25072.

Conflict of Interests: The authors declare that they have no conflict of interests.

Ethical Considerations: The Ethics Committee approved the study with the number IR.KAUMS.REC.1394.29 on May 30, 2015, and the enrollment of patients was initiated on August 23, 2015, and the study continued until December 15, 2015.

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