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# Effect of fenofibrate on the acquisition and reinstatement of ethanol-induced conditioned place preference in mice

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## ABSTRACT

**Introduction:** Fenofibrate is a ligand for peroxisome proliferator-activated receptors (PPARs) and increases catalase activity in the liver. Hence, it could be a potential candidate to mitigate alcohol dependence. Here, we tested whether fenofibrate attenuates alcohol dependency in a mouse model.

**Methods:** Conditioned place preference (CPP) was induced in male mice. Three groups were used: 1. Saline-Ethanol / Saline-Saline; 2. Saline-Ethanol / Fenofibrate -Ethanol ; 3. Saline-Saline/ Fenofibrate -Saline. CPP was defined as significantly more time spent on the drug-paired floor (grid) versus the saline-paired floor (hole). After extinction, reinstatement was triggered by a priming dose of ethanol, with or without fenofibrate pretreatment.

**Results:** Ethanol (2 g/kg) significantly increased time spent on the grid floor compared to the hole floor ($P < 0.01$), indicating successful CPP. Fenofibrate alone did not induce CPP ($P > 0.05$). In the fenofibrate + ethanol group, no significant difference was observed between grid and hole times ($P > 0.05$), indicating inhibition of CPP acquisition. During extinction, place conditioning was absent in all groups. Pretreatment with fenofibrate significantly reduced reinstatement of ethanol-induced CPP ($P < 0.05$).

**Conclusion:** Fenofibrate reversed the establishment of ethanol-induced CPP and attenuated its reinstatement in mice. These findings suggest that fenofibrate may be a potential candidate for further research on alcohol dependence, though additional investigations are needed.

**Keywords:** Addiction, Alcohol, Fenofibrate, Conditioned place preference.



## Introduction

Alcohol use disorder (AUDs) is a persistent and recurring condition with several treatment cycles and a severe recurrence even after long periods of abstinence (1). Excessive alcohol consumption imposes tremendous health, social, and economic burdens throughout the world (2, 3). While different therapeutic agents exist to treat ethanol dependence, alcohol use disorders are still a leading health problem within the world, and alcohol reinstating consumption and heavy drinking are unsuccessfully managed with available treatments (4, 5).

Although ethanol modulates various neural pathways, including neurotransmitter systems, ion channels, and neurocircuitry in several brain areas, the detailed incentive-rewarding mechanisms responsible for excessive consumption are unknown (4, 6). Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors that play an essential role in controlling and regulating genes responsible for lipid, energy metabolism, and inflammation (7, 8). The PPAR subfamily consists of three subtypes involving PPAR α, PPAR β (also known as PPAR δ), and

PPAR γ, each showing a different distribution and ligand preference (9). The distribution of PPARs in the CNS and their possible effect on dopamine neurotransmission, as the essential system corresponding to the rewarding effect of ethanol, has led to increased attention to targeting PPAR receptors as a feasible treatment option for alcoholism (10, 11). A recent study showed that activation of PPARs agonists suppressed ethanol consumption and stress-induced relapse to alcohol-seeking behavior and excluded withdrawal symptoms in rodent models of alcoholism (12, 13).

Fenofibrate (a pro-drug for fibrinic acid) is a synthetic PPAR agonist conventionally used to treat dyslipidemia. Recent studies have shown that fenofibrate reduced voluntary ethanol intake in lab animals due to producing a marked increase (2.5-fold) of catalase levels in the liver. As fenofibrate attenuated alcohol self-administration in chronically drinking rodents, it was hypothesized that it might also affect the development of Conditioned place preference (CPP) (14, 15) .The CPP is a widely used and validated animal model to investigate conditioned rewarding and incentive motivational effects of many abused drugs and relapse of drug-seeking behavior after a period of drug withdrawal or abstinence. This study investigated whether fenofibrate would interfere with the development and reinstatement of ethanol-induced CPP in mice.

## Materials and methods

### *Animals*

Adult male NMRI mice (weighing 25–30 g) were obtained from the Razi Vaccine and Serum Research Institute (n=84). Animals were group-housed in cages (50*40*30) (n=6) at 20 ± 4 °C, with the humidity of 10% and 12-h light/dark cycle with free access to pellet diet ad libitum and water. The study was approved by the Animal Research Ethics Committee of the Mashhad University of Medical Science (number: 87123).

### *Dose selection*

The selected doses are justified by previous studies that used similar doses in ethanol self-administration models, as well as by our own pilot study (data not shown) which tested doses of 50, 100, and 150 mg/kg and showed that 100 and 150 mg/kg produced the greatest inhibitory effect on CPP without motor side effects (10).

### *Conditioned place preference (16)*

*Apparatus*

The CPP apparatus consisted of a stainless steel box divided into three compartments: a black compartment with a grid floor (15 cm×15 cm ×15 cm height), a black compartment with a hole (15 cm×15 cm× 15 cm height), and the red compartment (middle section) (7cm length × 15 cm width × 15cm height) separated by guillotines from the other parts. The tangible cues consist of two different replaceable floor halves that served as conditioned stimuli (CSs). One floor was made of stainless steel rods with a diameter of 2.3 mm mounted 6.4 mm apart in acrylic rails ("grid" floor). The second floor was 16-gauge stainless-steel drilled with 6.4-mm round holes on 9.5-mm staggered centers ("hole" floor). This combination of tangible cues was chosen based on previous investigations indicating that the control-treated group had almost the same preference for each cue, i.e., the method was unbiased (17).

### *Experimental Design (Table 1)*

*Conditioned place preference I*

The CPPI step consisted of three phases: habituation (one 5-min session), conditioning (eight 5-min sessions), and preference testing (one 30- min session). Habituation: This phase was designed to reduce any effect of experimental novelty by adapting mice to the procedure. Animals were received saline intraperitoneal (ip) and 10 minutes later put in the center compartment and had free access to the whole apparatus for 5 min.

Conditioning: Twenty-four hours after habituation, the conditioning phase started. The mice were haphazardly divided into 3 groups as follows: 1. Saline-Ethanol / Saline-Saline (Sal-Eth/Sal –Sal) (n=36); 2. Saline-Ethanol / Fenofibrate -Ethanol (Sal-Eth/Feno-Eth) (n=24); 3. Saline-Saline/ Fenofibrate -Saline (Sal-Sal/Feno-Sal) (n=24). Each group was further subdivided into 2 subsets: grid+ conditioning subgroups and grid- conditioning subgroups. For animals in the grid+ conditioning subgroups, ethanol was administered ip just before placement on the grid floor (drug-paired floor) (CS +), and saline was administered just before placement on the hole floor (saline-paired floor) (CS-). These

floor-drug contingencies were inverted for mice in the grid- conditioning subgroups. These experiments happen on alternating days over 10 days (including a 2-day weekend break between conditioning experiments 4 and 5). Preference testing: Twenty-four hours after the final conditioning day, mice were put in the central compartment and had free access to all parts of the device for 30 min in a drug-free condition.

*The extinction of ethanol-induced CPP (CPPII)*

The saline-ethanol /saline-saline group entered the extinction started the day after the test in six 5-minute sessions. At this stage, 10 minutes after treating animals with saline, they were placed in CS+ for 5 minutes. The following day, animals received saline and were placed in another chamber CS, for 10 minutes. Twenty-four hours after the last day of the test, the CPP II test was performed for 30 minutes to determine if the ethanol-induced CPP had been extinguished.

*The reinstatement of ethanol-induced CPP (CPPIII)*

The animals went through the ethanol reinstatement test the day after the extinction test. The mice received fenofibrate (100 mg/kg) or saline 60 min before a single-dose ethanol injection (2 g/kg, ip) or saline. Ten minutes after the ethanol administration, the animals were subjected to a reinstatement experiment in which the mice were freely allowed to seek both compartments for 30 min. The time spent on each part was measured.

***Statistical analysis***

Data are presented as mean ± standard error of the mean (SEM). Normality of distribution was verified using the Shapiro–Wilk test. Between-group comparisons were performed using one-way analysis of variance (ANOVA), followed by Tukey's post hoc test for multiple comparisons. A p value of less than 0.05 was considered statistically significant. All analyses were conducted using GraphPad Prism software (version 8.0).

## Results

***The effect of fenofibrate on the ethanol-induced CPP (CPP I)***

Twenty-four hours after conditioning, the mouse was placed at the center of the device, and the elapsed time in CS + and CS - was calculated at 30 minutes. As shown in Fig. 1, ethanol injection (2 g/kg) significantly increased the time elapsed in CS + compared to the saline group ($P<0.01$). High-dose injections of fenofibrate (150 mg/kg) alone did not induce CPP ($P>0.05$). Pretreatment of fenofibrate (100, 150 mg/kg) 30 minutes before ethanol injection inhibited the CPP induced by ethanol. There was no difference between the two fenofibrate doses in eliminating the ethanol-induced CPP.

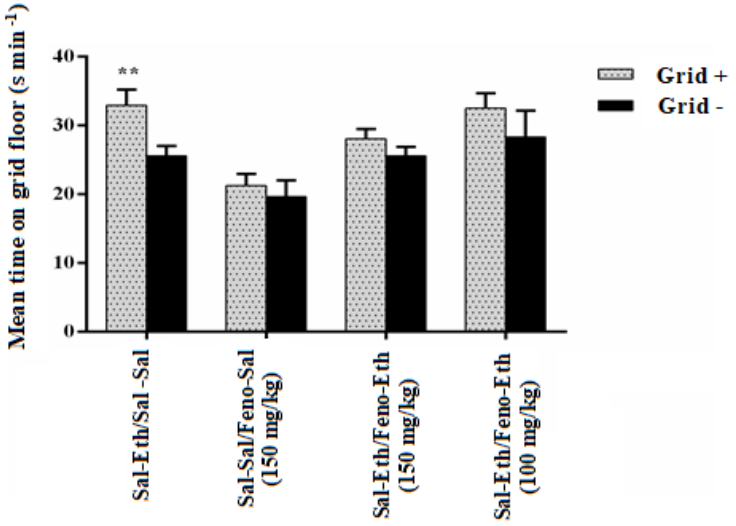


**Fig 1. Effect of fenofibrate on acquisition of ethanol-induced CPP (CPP I). Ethanol (2 g/kg, i.p.) was paired with the grid floor (CS+) and saline with the hole floor (CS−) in grid+ subgroups; contingencies were reversed in grid− subgroups. CPP was defined as significantly more time spent on CS+ vs. CS−. Data are mean ± SEM; one-way ANOVA followed by Tukey's post hoc test. **P < 0.01 for time on grid floor between grid+ and grid− subgroups (n = 12–18 per subgroup, depending on group). Ethanol (Et); Fenofibrate (Feno); Saline (Sal)**

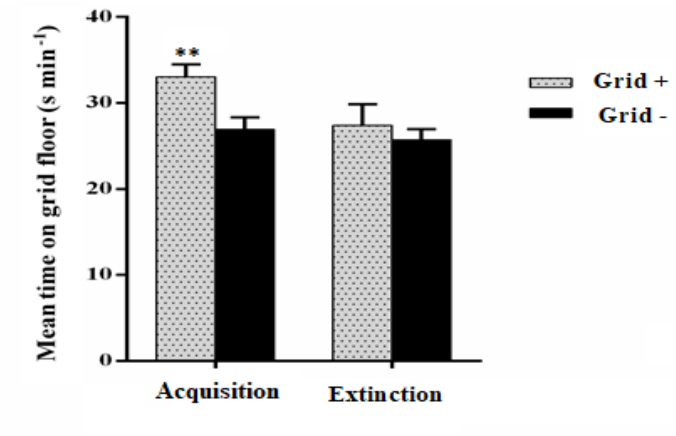


**Fig 2. Extinction of ethanol-induced CPP (CPP II). After CPP acquisition with ethanol (2 g/kg), extinction was performed using saline injections. No significant place conditioning remained. Data are mean ± SEM; one-way ANOVA with Tukey's post hoc test. **P < 0.01 for time on grid floor between grid+ and grid− subgroups (n = 18 per subgroup).**

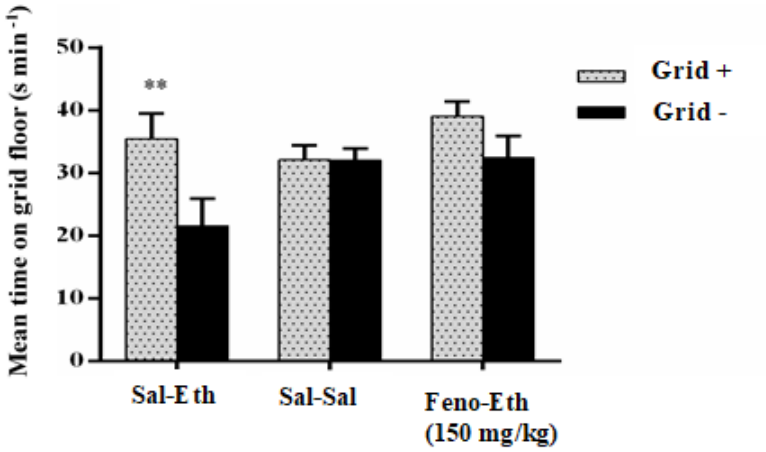


**Fig 4. Effect of fenofibrate (150 mg/kg) on reinstatement of ethanol-induced CPP. Reinstatement was triggered by a priming injection of ethanol (2 g/kg) after extinction. Fenofibrate (150 mg/kg) or saline was given 60 min before ethanol. Data are mean ± SEM; one-way ANOVA with Tukey's post hoc test. **P < 0.01 for time on grid floor between grid+ and grid− subgroups (n = 6 per subgroup). Ethanol (Et); Fenofibrate (Feno); Saline (Sal)**

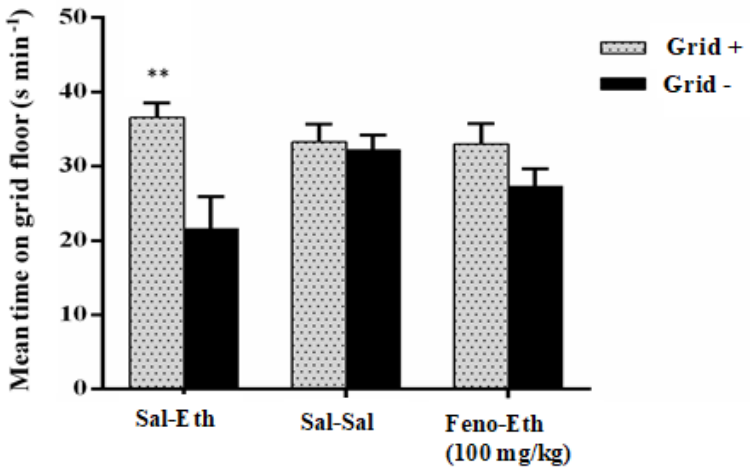


**Fig 3. Effect of fenofibrate (100 mg/kg) on reinstatement of ethanol-induced CPP. Reinstatement was triggered by a priming injection of ethanol (2 g/kg) after extinction. Fenofibrate (100 mg/kg) or saline was given 60 min before ethanol. CPP was measured as time on CS+ vs. CS−. Data are mean ± SEM; one-way ANOVA with Tukey's post hoc test. **P < 0.01 for time on grid floor between grid+ and grid− subgroups (n = 6 per subgroup). Ethanol (Et); Fenofibrate (Feno); Saline (Sal)**

***The extinction of ethanol-induced CPP (CPPII)***

As shown in Fig. 2, although ethanol injection in the acquisition stage significantly increases the time elapsed in the grid (+), in the extinction step, ethanol-induced CPP disappeared ($p>0.05$).

***The effect of fenofibrate on the reinstatement of ethanol-induced CPP (CPPIII)***

Ethanol injection alone increased the CPP ($P <0.01$) in the reinstatement stage, but in the case of pretreatment with fenofibrate (100 and 150 mg/kg) attenuated the reinstatement of ethanol ($P <0.05$). There was no difference between the two doses of fenofibrate (Fig 3 and 4).

**Discussion**

Alcohol addiction is one of the most significant risk factors for population health globally. Epidemiological studies have shown that prolonged and excessive alcohol consumption leads to liver diseases, chronic pancreatitis, cancers, malnutrition, and depression (18). Chronic intake of alcohol can alter the critical pathways of the brain neurotransmitter, including the dopaminergic, serotonergic, glutaminergic, GABA, and opioid pathways (19, 20). Despite the drug and psychotherapy for ethanol dependence, the risk of relapse is high because of the rewarding effect of alcohol. So the research continues to find more effective therapies for recurrence prevention in alcohol abuse and dependence (21, 22).

The current study showed that pretreatment with fenofibrate at doses of 100 and 150 mg/kg inhibited the ethanol-induced conditioned preferences and prevented alcohol reinstatement in mice. Administration of ethanol (2 g/kg of 20% v/v ethanol) alone resulted in a significant increase in elapsed time in CS + in the CPPI phase and the reinstatement stage. Administration of fenofibrate alone did not have a considerable effect on conditioned preferences**.** This is consistent with previous investigations, which indicated that PPARα receptor agonists attenuated the acquisition, extinction, and reinstatement of drug-induced CPP**.** Rivera-Mezastudy et al. (2017) reported that fenofibrate could alter the motivational effects of ethanol. Fenofibrate (50 mg/kg/day, orally) in chronically ethanol-drinking rats could generate a prolonged (30 days) decrease in ethanol consumption, suggesting that fenofibrate could act more effectively than acetaldehyde in generating aversion. It is known that fenofibrate can enhance catalase activity three times and consequently increase acetaldehyde by 10%. This effect of fenofibrate is similar to that of disulfiram, which increases the level of acetaldehyde with an unpleasant impact on the consumer, reducing the voluntary consumption of alcohol by 60-70% (14, 15, 23).

Blednov et al. (2015) used two different behavioral tests (24-hour 2-bottle choice and limited access (3-hour) 2-bottle choice, drinking in the dark) to measure the consumption of 15% ethanol in mice. They measured the effects of pioglitazone, fenofibrate, GW0742, tesaglitazar, and bezafibrate on ethanol consumption and preference. They reported that activating two isoforms of PPARs, α and γ, decreased ethanol intake and preference in the tested mice. However, a selective PPARδ agonist or a pan agonist for all 3 PPAR isoforms could not significantly change the ethanol consumption (24).

In another study, Mascia et al. found that the administration of PPARα agonists (WY14643 and methOEA) inhibited the self-administration of nicotine in mice and monkeys. When the treatment was discontinued, animals returned to their highest level of consumption. The administration of these drugs also inhibited the reinstatement of nicotine in animals exposed to nicotine. Mechanistic studies showed that PPARα agonists decreased the dopamine level in the ventral tegmental area and increased it in the nucleus accumbens. Since these effects were suppressed in the co-administration of the PPARα antagonist (MK886), these effects are related to the PPARα receptor activation (25).

Based on previous studies, PPARα agonists have been identified as anti-inflammatory agents due to their ability to inhibit transcription factors such as NF-κB, which has been associated with reduced alcohol consumption and preference in mice. Therefore, it may be hypothesized that the effect of fenofibrate in reducing ethanol consumption and preference could be related to its anti-inflammatory effects; however, this mechanism was not directly investigated in the present study and requires further experimental validation (26, 27).

Based on previous studies, fenofibrate can modulate the expression of various genes in the

prefrontal cortex and amygdala, regions known to be involved in ethanol dependence. Another hypothesis is the possible involvement of GABA, a primary inhibitory neurotransmitter in the brain, which plays a pivotal role in many of ethanol's pharmacological and behavioral effects. Previous research has shown that chronic alcohol consumption results in significant down-regulation of GABAergic signaling, which is associated with increased alcohol intake. It has been suggested that fenofibrate may reverse this attenuation of GABAergic neurotransmission in the amygdala, potentially leading to reduced ethanol drinking. Nevertheless, these GABAergic mechanisms were not directly examined in the current study, and future research should investigate them specifically (28-30).

It has been well established that mesolimbic dopamine system dysregulation plays a critical role in ethanol dependence. Based on previous studies, activation of the PPARα receptor by fenofibrate may regulate the activity of dopaminergic neurons through negative regulation of β2-nAChRs, which in turn reduces dopamine neuron activity (31, 32). Accordingly, it may be hypothesized that the mitigation of alcohol preference in fenofibrate-treated mice could result from the PPARα signaling pathway, anti-inflammatory effects, and modulation of mesolimbic dopamine transmission. However, because the present study did not directly measure dopamine levels, GABAergic activity, or inflammatory markers, these mechanistic interpretations remain speculative. Future studies should directly assess these pathways using techniques such as microdialysis, immunohistochemistry, or selective receptor antagonists

## Conclusion

The results demonstrate that fenofibrate affects the development and reinstatement of ethanol-induced CPP in mice. According to the current investigation findings and previous studies of its therapeutic effect, tolerability, and safety, it seems that fenofibrate may be a potential candidate for future translational studies in the treatment of ethanol dependence.

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## Conflicts of interest

All authors declared that there are no conflicts.

## Authors' contributions

Kobra Shirani contributed to this research in investigation, methodology, validation, writing, and editing. Faezeh Vahdati Hassani contributed to this research in investigation, methodology, writing, and editing. Maliheh Ezati contributed to this research in investigation. Ali Roohbakhsh contributed to this research through methodology, software, supervision, and validation. Gholamreza Karimi contributed to this research in supervision and editing.

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## Data availability

Data available on request from the authors

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**Table 1. Experimental design for the conditioned place preference.**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Conditioned Place Preference: CPP | | | | | | | | |
| Free access to the whole apparatus (5 min) | | | 10 min | | saline | One 5-min session | | Habituation |
| 24 h | | | | | | | | |
| Eight 5-min sessions | | | | | | | | Conditioning |
| Odd days | Grid | | Eth | | Sal | Subgroup grid + (n=18) | | Group Sal-Eth/Sal -Sal |
| Even days | Hole | | Sal | | Sal | | | |
| Odd days | Hole | 10 min | Eth | 30 min | Sal | Subgroup grid - (n=18) | | |
| Even days | Grid | | Sal | | Sal | | | |
| Odd days | Grid | | Eth | | Sal | Subgroup grid + (n=12) | | Group Sal-Eth/Feno-Eth |
| Even days | Hole | | Eth | | Feno | | | |
| Odd days | Hole | 10 min | Eth | 30 min | Sal | Subgroup grid - (n=12) | | |
| Even days | Grid | | Eth | | Feno | | | |
| Odd days | Grid | | Sal | | Sal | Subgroup grid + (n=12) | | Group Sal-Sal/Feno-Sal |
| Even days | Hole | | Sal | | Feno | | | |
| Odd days | Hole | | Sal | | Sal | Subgroup grid - (n=12) | | |
| Even days | Grid | | Sal | | Feno | | | |
| 24 h | | | | | | | | |
| Free access to the whole apparatus (30 min) | | | | | | Preference testing (CPP I) | | |
| 24 h (group Sal-Eth/Sal -Sa) | | | | | | | | |
| 5 min** - CS | 10 min | Sal | 24 h | 5 min*CS (+) | 10 min | Sal | Six 5-min sessions | Extinction |
| 24 h | | | | | | | | |
| Free access to the whole apparatus (30 min) | | | | | | Preference testing (CPPII) | | |
| Sale | | | 30 min | | Sal | | | Reinstatement |
| Eth | | | 30 min | | Sal | | | |
| Eth | | | 30 min | | Feno | | | |
| 10 min | | | | | | | | |
| Free access to the whole apparatus (30 min) | | | | | | Preference testing (CPPIII) | | |

Normal saline (Sal) dose: 10 mL/kg
Ethanol (Eth) dose: 2 g/kg; 20% v/v
Fenofibrate (Feno) dose: 100 and 150 mg/kg
*CS (+): grid + or hole (+)
**CS - : grid - or hole (-)a