Original Article

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Impact of Combined Forced Exercise with Escitalopram on Stress-Induced Depressive-Like Behavior in Male Rats

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ABSTRACT

Background & Objective: The efficacy of escitalopram, a pharmaceutical antidepressant, and exercise, a lifestyle intervention, in mitigating depressive symptoms has been established. This study investigated the impact of varying doses of escitalopram and the combination of forced exercise with escitalopram on stress-induced depressive-like behavior in male rats.

Materials & Methods: Sixty-four male rats were allocated into eight groups: control (Co), sham (Sh), depression without treatment (Dep-WT), depression with exercise (Dep-Exe), depression with escitalopram at 10 mg/kg (Dep-Esc10), depression with escitalopram at 20 mg/kg (Dep-Esc20), depression with escitalopram at 10 mg/kg combined with exercise (Dep-Esc10-Exe), and depression with escitalopram at 20 mg/kg combined with exercise (Dep-Esc20-Exe). To induce depression, chronic restraint stress was administered for 6 hours per day over a period of 14 days. Following the stress induction period, rats were administered escitalopram (at doses of 10 or 20 mg/kg, i.p), subjected to treadmill running (20-21 m/min for 1 h/day), or subjected to a combination of both interventions. Depressive-like behaviour induced by stress and locomotor activity were assessed using the forced swimming test (FST) and the open field test (OFT), respectively.

Results: In the FST, the immobility time significantly increased in the Dep-WT, Dep-Exe, and Dep-Esc10 groups, while it significantly decreased in the Dep-Esc20, Dep-Esc10-Exe, and Dep-Esc20-Exe groups compared to the Dep-WT group. In the OFT, the central time and total travelled distance significantly decreased in the Dep-WT group. Conversely, central time significantly increased in the Dep-Esc10-Exe and Dep-Esc20-Exe groups, and all treatment groups exhibited a significant increase in central time compared to the Dep-WT group.

Conclusion: The findings suggest that combining exercise with escitalopram yields additive effects, representing a promising treatment protocol for anxiety, depression, and locomotor activity.

Keywords: **Restraint stress, Exercise, Escitalopram, Depression, locomotor activity, Rats**

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1. Introduction

Stressful life events have been identified as triggers for anxiety- and depressive-like behaviours, primarily by modulating stress biomarkers and biochemical substances within the brain (1). Pharmacological interventions and exercise have been indicated for their potential effects to modulate these factors, thus presenting as viable approaches for mood disorder management (2, 3). Notably, serotonin stands out as a pivotal neurotransmitter implicated in mood regulation and emotional behaviours (4). Among pharmacotherapeutic options, Selective Serotonin Reuptake Inhibitors (SSRIs) play a central role in anxiety and depression management (5). These agents exert their effects by blocking presynaptic serotonin reuptake sites, consequently augmenting serotonergic neurotransmission (6). Escitalopram is the newest

SSRI with fewer side effects and studies suggest it is more effective and tolerable for anxiety and depression than other SSRIs (7). Nonetheless, a notable proportion of patients, approximately 30–40%, exhibit resistance to citalopram-like SSRIs, often experiencing delayed therapeutic responses However, about 30–40% of patients do not respond to citalopram-like SSRIs, and these medications can have a delayed onset of action (8). Hence, there is a pressing need for enhanced and innovative therapeutic modalities. Concurrently, exercise has garnered attention as a dependable and efficacious strategy for managing anxiety and depression (9). Consequently, exercise not only emerges as a potential alternative to SSRIs but also holds promise as an adjunctive therapy alongside SSRIs for addressing stress-related disorders.

2. Materials and Methods

2.1 Animals

Sixty-four male Wistar rats (200-250g) were procured from the animal facility of the Pharmacy department at Isfahan University of Medical Sciences, Iran.

The rats were housed under a 12-hour light/dark cycle (with lights on 07:00-19:00) and maintained at a constant temperature of 23±2°C with a humidity level of 55±5 %. They had *ad libitum* access to food and water throughout the study period. Prior to experimentation, the animals underwent a seven-day acclimatization period to adapt to the laboratory conditions. All experimental procedures were conducted in compliance with the Ethics Committee of Animal Use and received approval (IR.MUI.MED.REC.1398.607).

The study spanned a duration of 28 days for each group, with eight distinct groups (n=8 each) as follows:

-Control (Co) group: Rats relocated to the laboratory without any interventions.

-Sham (Sh) group: Rats subjected to an inactive treadmill (1 hour/day) for the next 14 days.

-Depression-Without treatment (Dep-WT) group: Rats were exposed to restraint stress for 14 days, followed by 14 days without interventions.

-Depression-Exercise (Dep-Exe) group: Rats were exposed to restraint stress for 14 days, followed by 14 days of regular exercise (1hour/day).

-Depression-Escitalopram10 (Dep-Esc10) group: Rats were exposed to restraint stress for 14 days, followed by 14 days of escitalopram treatment (10mg/kg/day).

-Depression-Escitalopram20 (Dep-Esc20) group: Rats were exposed to restraint stress for 14 days, followed by 14 days of escitalopram treatment (20mg/kg/day).

-Depression-Escitalopram10-exercise (Dep-Esc10-Exe) group: Rats were exposed to restraint stress for 14 days, followed by 14 days of escitalopram treatment (10mg/kg/day) along with regular exercise (1 hour/day).

-Depression-Escitalopram20-exercise (Dep-Esc20-Exe) group: Rats were exposed to restraint stress for 14 days, followed by 14 days of escitalopram treatment (20mg/kg/day) along with regular exercise (1 hour/day).

The design of this study protocol was demonstrated in Figure 1.

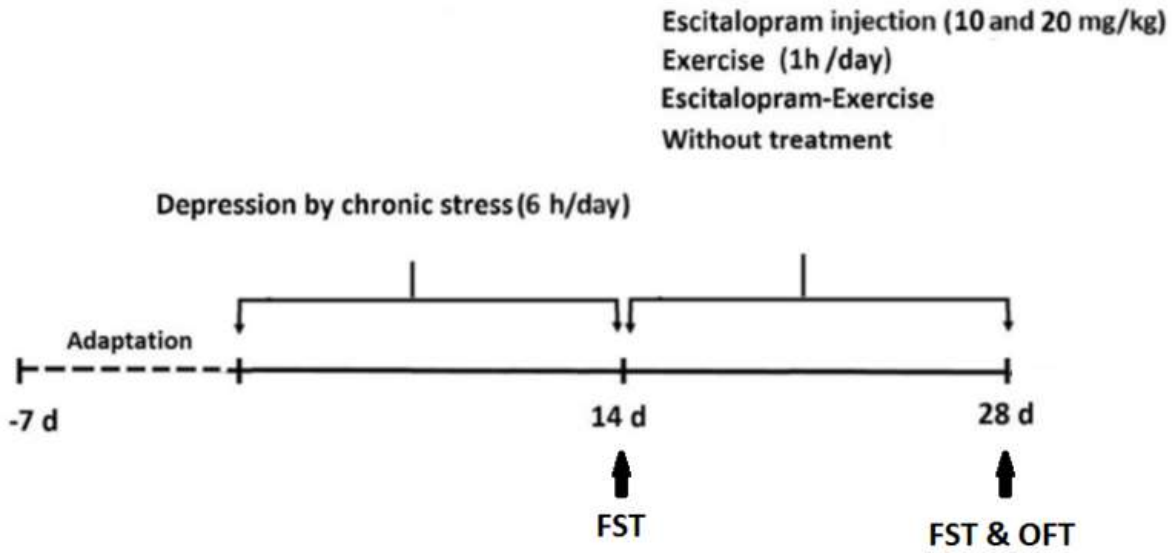


Figure 1. Experimental design for all experimental groups. Forced Swimming and Open Field tests (FST and OFT, respectively) were used in the present study.

2.2 Drug treatment

The rats received intraperitoneal (i.p.) injections of escitalopram oxalate powder (10 and 20mg/kg; Sobhan-Daru Co., Rasht, Iran) dissolved in sterile normal saline (0.9%) for 14 consecutive days (10).
Exercise treatment the rats engaged in a daily 1-hour treadmill exercise protocol for 14 consecutive days (20–21 m/min, slope of 0º) (Maze Router Co., Tabriz, Iran). Prior to the commencement of the study, the rats underwent a three-day acclimatization period to familiarize themselves with the exercise regimen **(11).**

2.3 Induction of depression

Chronic restraint stress is a standard animal model for inducing anxiety and depression. Each rat was confined in a transparent plastic cylinder for 6 hours per day over a period of 14 consecutive days, from 8:00 to 14:00 (11).

2.4 Behavioral tests

2.4.1 Forced swimming test

The forced swimming test (FST) is a well-established method for assessing behavioral despair and depressive-like behavior in rodents. It is predicated on the observation that when placed in a water-filled cylinder, animals initially attempt to escape but eventually adopt a state of immobility. Rats were placed individually into a transparent cylinder measuring 80 cm in height and 45 cm in diameter (Tajhiz Gostar Iranian Co., Tehran, Iran), filled with water to a depth sufficient to prevent floor contact or wall jumping. Video recording equipment was positioned adjacent to the cylinder to capture the rats' behavior. The water temperature was maintained at approximately 25 ºC. Each rat underwent a 300-second testing session, during which increased immobility was interpreted as indicative of depressive-like behavior (12). The FST was conducted on days 14 and 28 of the study. Initiation of additional treatments occurred subsequent to depression confirmation on day 14. Notably, restraint stress exposure (6 hours/day for 14 days) yielded an 80% success rate in inducing depression.

2.4.2 Open field test

The open field test (OFT) is a widely used method for assessing stress levels, anxiety-like behavior, and locomotor activity in rodents (13). It involves placing an animal in an unfamiliar, enclosed environment and observing its behavior. The OFT apparatus consists of an open box (90×90×60 cm) (Tajhiz Gostar Iranian Co., Tehran, Iran). On day 28 of the study, each rat was positioned in the center of the OFT for a duration of 300 seconds. Video recording equipment positioned above the apparatus captured the rats' behavior. NeuroVision software (Tajhiz Gostar Iranian Co., Tehran, Iran) was utilized to quantify the time spent and total distance travelled in the OFT. Prior to testing each rat, the open field was thoroughly cleaned with 70% ethanol to eliminate any potential olfactory cues.

2.5 Statistical analyses

The data were presented as means ±SEM and analyzed using one-way ANOVA, followed by Tukey's post-hoc test for multiple groups. The paired sample t-test was used to compare immobility levels within groups on days 14 and 28. A P-value<0.05 was considered statistically significant. All statistical analyses were conducted using SPSS 26.

3. Results

The Co and Sh groups exhibited no significant differences in any of the behavioral assessments. Consequently, the Co group was designated as the standard reference group for all comparative analyses conducted in this study.

3.1 Assessment of forced swimming test

On day 14, all experimental groups exhibited significantly increased immobility time in the FST compared to the Co group (p<0.001 for all groups). Following the induction of depression, additional treatments were administered to the subjects. On day 28, the Dep-WT, Dep-Exe, and Dep-Esc*10 groups demonstrated significantly increased immobility time compared to the Co group (*p<0.001, p<0.01, and p<0.01, respectively) (Figure 2). These findings suggested that the absence of treatment, exercise alone, and the administration of escitalopram at a dose of 10 mg/kg following depression induction did not prevent the onset of depressive-like behaviour.
Figure 2 showed that the Dep-Esc20, Dep-Esc10-Exe, and Dep-Esc20-Exe groups had significantly reduced immobility time compared to the Dep-WT group on day 28 (p<0.05, p<0.05, and p<0.01, respectively). This indicated that escitalopram 20mg/kg and the combination of exercise with both doses of escitalopram were effective in reversing depressive-like behavior on day 28.
A paired sample t-test was employed to assess changes in immobility time within groups on days 14 and 28. Statistically significant differences were observed between days 14 and 28 in all treatment groups (p<0.01 in the Dep-Exe, Dep-Esc10, Dep-Esc20, and Dep-Esc10-Exe groups; p<0.001 in the Dep-Esc20-Exe group) (fig.3).

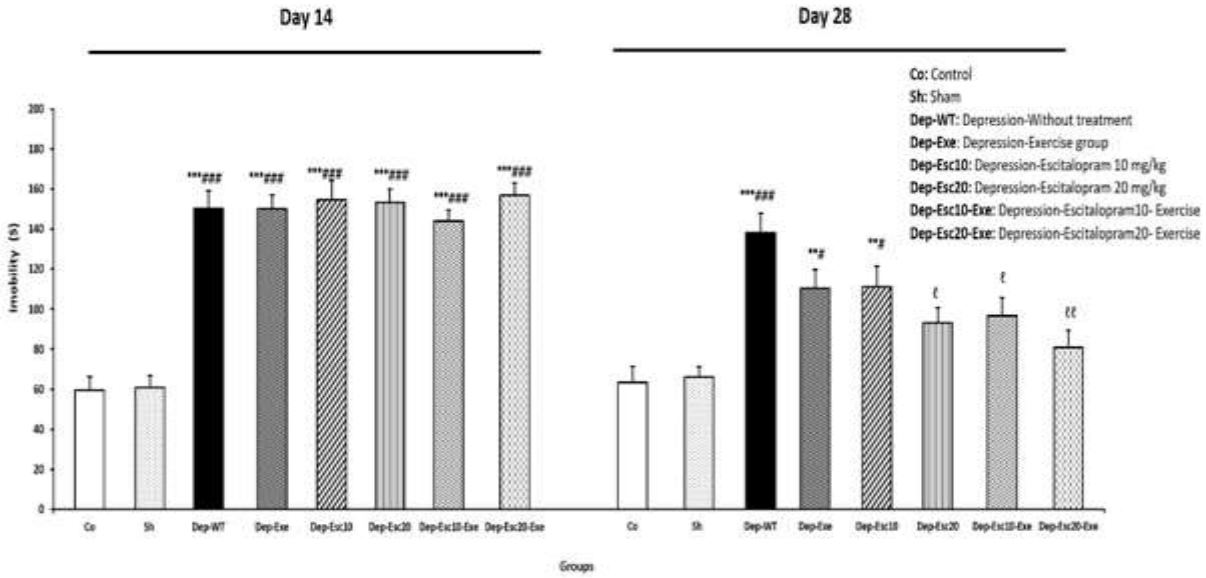


Figure 2. The immobility time in the FST on days 14 and 28. Data represent mean± SEM (One-way Analysis of variance (ANOVA) followed by Tukey's post hoc test). $^{**}p<0.01$ and $^{***}p<0.001$ compared to the Co group; $^{\#}p<0.05$ and $^{\#\#\#}p<0.001$ compared to the Sh group; $^{\ell}p<0.05$ and $^{\ell\ell}p<0.01$ compared to the Dep-WT group.

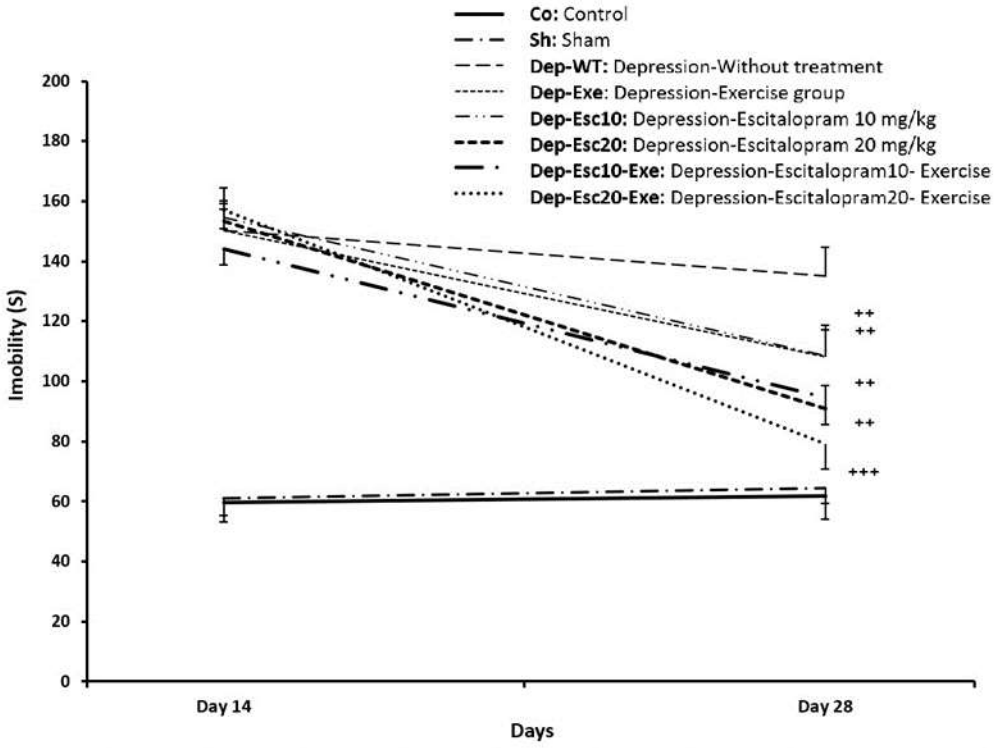


Figure 3. Immobility time on the 14th and 28th day in the FST apparatus before and after depression treatment (within groups). Data represent mean± SEM. $^{++}p<0.01$ and $^{+++}p<0.001$ Immobility time on the 14th day to the Immobility time on 28th day.

3.2 Assessment of open field test

The Dep-WT group exhibited a significant decrease in central time in the OFT compared to the Co group (p<0.05). Conversely, the Dep-Esc10-Exe and Dep-Esc20-Exe groups displayed a significant increase in central time compared to the Co group (p<0.05 for both groups). Furthermore, all treatment groups demonstrated significantly elevated central time compared to the Dep-WT group (p<0.05 in the Dep-Esc10 group, p<0.01 in the Dep-Exe and Dep-Esc20 groups, and p<0.001 in the Dep-Esc10-Exe and Dep-Esc20-Exe groups). These findings suggested that the combination of exercise with both doses of escitalopram had an additive effect on reversing anxiety-like behavior.

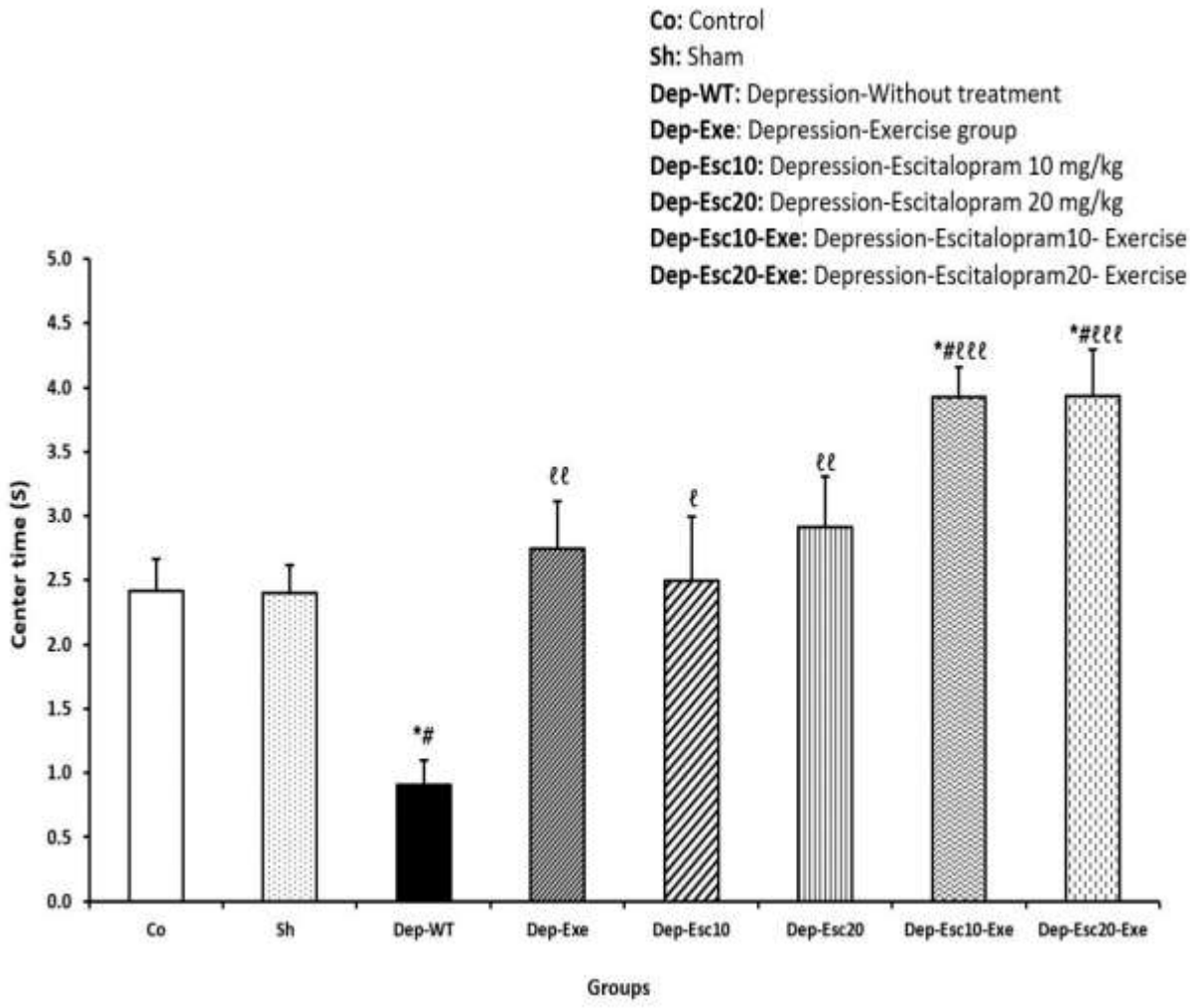


Figure 4. The center time in the OFT in all experimental groups. Data represent mean± SEM (One-way Analysis of variance (ANOVA) followed by Tukey's post hoc test). $^{*}p<0.05$ compared to Co group; $^{\#}p<0.05$ compared to Sh group; $^{\ell}p<0.05$, $^{\ell\ell}p<0.01$ and $^{\ell\ell\ell}p<0.001$ compared to the Dep-WT group.

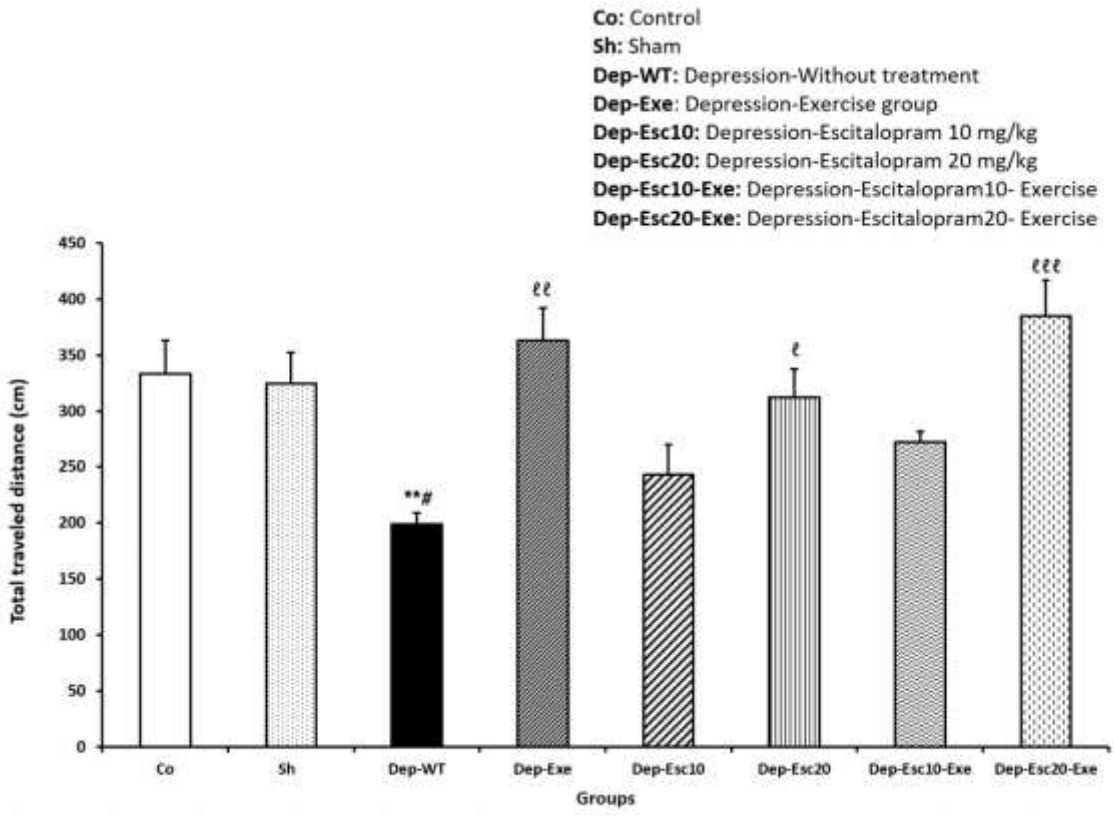


Figure 5. The total traveled distance in the OFT in all experimental groups. Data represent mean± SEM One-way Analysis of variance (ANOVA) followed by Tukey's post hoc test. $^{**}p<0.01$ compared to the Co group; $^{\#}p<0.05$ compared to the Sh group; $^{\ell}p<0.05$, $^{\ell\ell}p<0.01$ and $^{\ell\ell\ell}p<0.001$ compared to the Dep-WT group.

The Dep-WT group exhibited a significant decrease in total travelled distance in the OFT compared to the Co group (p<0.01). This finding suggested that depression without treatment resulted in reduced locomotor activity in rats. The Dep-Exe, Dep-Esc20, and Dep-Esc20-Exe groups demonstrated significant enhancements in total travelled distance compared to the Dep-WT group (p<0.01, p<0.05, and p<0.001, respectively) (Figure 5).

4. Discussion

This study aimed to evaluate the effects of exercise, escitalopram (at dosages of 10 and 20 mg/kg), and the combination of exercise with escitalopram on anxiety and depressive-like behavior in male rats.

The increased immobility time observed in the FST after 14 days of chronic stress exposure indicated the manifestation of depression-like behavior in the subjects (Figure 2), consistent with previous findings (14). Furthermore, our previous study confirmed elevated corticosterone levels in depression without treatment (15), thereby confirming the induction of depression. Another study also reported that corticosterone levels (a main hormone involved in depressive and anxiety behaviors) tend to decrease following the removal of the stressor (11).

In the present study, escitalopram treatment (20-mg/kg/day) and a combination of exercise with both doses of escitalopram showed improvements in depression-like behavior in the subjects. However, exercise and escitalopram treatment (10mg/kg/day) alone did not effectively reverse the effects of chronic stress on depressive subjects (16). Previous research has demonstrated the antidepressant and anxiolytic properties of escitalopram in animal models (17). Moreover, the lack of efficacy of escitalopram (10-mg/kg) in treating depression may be attributed to its delayed onset of action (approximately two weeks for escitalopram 10mg/kg), which is required for the therapeutic and efficacious effects of SSRI medications (18). Conversely, exercise alone improved anxiety and depression induced by repeated restraint stress (2-h/day/14 consecutive days) (19). Present findings suggested that exercise might not effectively improve depression induced by longer periods of restraint stress (6h/day) (Figure 2). It is possible that the severity of chronic stress (6h/day) disrupted mood and exercise could not increase serotonin levels in the brain enough to improve it. Additionally, it demonstrated that the timing of induced stress appears to be one of the most critical factors in causing depression (20).

Other findings of the present study showed that escitalopram at 20mg/kg and the combination of

exercise with two doses of escitalopram beneficial effects in improving depression and reducing despair-like behaviors (Figures 2 and 3). It seems that escitalopram effectiveness is dependent on the dosage, as it increases serotonin levels in the brain (21). Therefore, it is proposed that increasing the dose of medication may positively affect depression treatment (21). Furthermore, the beneficial effect of combining exercise with both doses of escitalopram may be attributed to exercise's role in enhancing the basal firing activity of serotonin neurons. In addition, this may reduce the inhibitory effects of SSRIs on serotonin neurons and diminish the delay time in the therapeutic effects of SSRIs in alleviating depression (22).

Within-group comparisons of immobility time between the 14th and 28th days revealed an improvement trend of depression-like behavior by both escitalopram and exercise (separately and together) in this study. However, these effects were particularly pronounced when escitalopram was combined with exercise at a dosage of 20mg/kg (Figure 3). Based on the findings from OFT, anxiety levels persisted at elevated levels in depressive subjects without treatment (the Dep-WT group) after 28 days (Figure 4). This observation suggested that anxiety did not improve without intervention, such as through exercise or medication. In contrast, the other treatment groups exhibited decreased anxiety levels compared to the Dep-WT subjects in this study. This indicates the beneficial effects of various therapies, including exercise as a lifestyle modification, escitalopram at both dosages as medication, and notably, the combination of exercise with escitalopram at both dosages, in mitigating anxiety-related behaviours. Indeed, the combination of exercise and escitalopram demonstrated additive effects in reducing anxiety in the present study. This was supported by some previous research, which found elevated corticosterone levels in anxious subjects (23). On the other hand, exercise and escitalopram could decrease corticosterone levels in anxious subjects (24, 25). Furthermore, conflicting reports exist regarding the effects of exercise and escitalopram. While exercise has been shown to alleviate stress-induced anxiety and improve depressive-like behaviour (26). There are reports suggesting that forced exercise may exacerbate anxiety-like behaviours (27). Chronic escitalopram treatment has been demonstrated to prevent anxiety-like behavioral reactivity, while acute administration of escitalopram may enhance anxiety (18). Based on other OFT findings, locomotor activity decreased in the depressive subjects without treatment (the Dep-WT group) (Figure 5). The impact of chronic stress on motor activity is inconsistent, as indicated by conflicting findings in previous studies, with some reporting a reduction (28), others an enhancement (29), and some observing no changes (16).

In this study, exercise alone, escitalopram 20 mg/kg, and the combination of exercise with escitalopram 20-mg/kg were found to increase locomotor activity in depressive subjects (Figure 5). A previous study reported that treadmill exercise could reverse alteration in locomotor activity induced by chronic stress (30). However, exercise fatigue can also lead to decreased locomotor activity due to a reduction in dopamine secretion in the brain (31). Additionally, various studies reported different effects on locomotor activity with different doses of escitalopram (32, 33). This suggests that escitalopram can either reduce or increase dopaminergic neuron firing which depends on the administered dosage of the medication (34, 35). Additionally, the response to stressors depends on the type and duration of the stressor, as well as the task used to assess behavior (16, 28).

5. Conclusion

Chronic stress caused anxiety and depressive-like behaviors. Various treatments, such as exercise (a lifestyle change) and escitalopram at both doses (a medication), along with combination of them, were beneficial for reducing anxiety. Notably, the combination of exercise and escitalopram exhibited additive effects in improving anxiety, depression, and locomotor activity in the present study. Further research, including biochemical, electrophysiological, and molecular studies is necessary to elucidate the mechanisms underlying depression treatment.

6. Declaration

6.1 Acknowledgment

The authors wish to convey their appreciation for the financial support provided by the Isfahan University of Medical Sciences (Isfahan, Iran).

6.2 Conflict of Interest

The authors declare no conflict of interest.

6.3 Authors' Contributions

M. Radahmadi designed the experiments. M. Zamani performed experiments. M. Radahmadi analyzed all data of experiments. M. Zamani, M. Radahmadi, and P. Reisi wrote the manuscript. All authors approved the final version of the manuscript.

6.4 Funding

Isfahan University of Medical Sciences supported this work.

6.5 Ethical Approval

The ethical committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1398.607) approved this study.

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