# The effect of acute and repeated administration of buspirone, 8-OHDPAT and fluoxetine on haloperidol-induced extrapyramidal symptoms

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**Objective:** The aim of this study was to investigate the effect of buspirone, as a partial agonist of 5-$HT_{1A}$ receptors, 8-hydroxy-2-[di-n-propylamino]-tetralin (8-OH-DPAT) as an agonist of 5-$HT_{1A}$ receptors and fluoxetine as a selective serotonin reuptake inhibitor on haloperidol-induced extrapyramidal symptoms (EPS) in male Wistar rats. **Materials and methods:** The experiments were performed on 66 male Wistar rats weighing 200-240g. The rats were divided into 11 groups (n=6). Extrapyramidal symptoms were induced by haloperidol injection 1mg/kg intraperitoneally (i.p.). To investigate the effect of serotonergic drugs on haloperidol-induced extrapyramidal symptoms, 8-OHDPAT (1 mg/kg), buspirone (10 mg/kg), and fluoxetine (1 mg/kg) were injected before haloperidol in an acute and 7 consecutive day's pre-treatment injection(s) mode. Extrapyramidal symptoms such as catalepsy and motor balance were assessed by the bar test and rotarod, respectively. **Findings:** The results demonstrated that i.p. injection of haloperidol induced significant motor imbalance and catalepsy ($p \leq 0.001$) in rats. Data analysis showed that i.p. injection of buspirone (10 mg/kg) significantly decreased catalepsy compared with the control group. The attenuation of haloperidol-induced extrapyramidal symptoms was observed with 8-OHDPAT treatment. Treatment with fluoxetine did not affect the motor coordination caused by haloperidol. **Conclusion:** It may be concluded that buspirone and 8-OHDPAT improves extrapyramidal symptoms in a haloperidol-induced Parkinsonism model probably via activation of 5-$HT_{1A}$ receptors. However, further investigations should be carried out to clarify the exact mechanism of interaction between 5-$HT_{1A}$ and DA receptors.

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**Keywords:** haloperidol, fluoxetine, buspirone, catalepsy, 8-OHDPAT, motor balance, extrapyramidal symptoms

## INTRODUCTION

Generally, 1% of people over 50 years and at least 2% of people over 65 years suffer from Parkinson's disease. One of the prevalent symptoms of this disease is catalepsy that refers to an inability to control and change muscle tightness and stiffness (Field et al., 2000; Nayebi et al., 2010).

Antipsychotic drugs such as haloperidol via blocking brain D2 receptors induce Parkinson-like syndrome. Their favorable clinical effect is thought to be associated with blocking dopamine function in the mesolimbic pathway only. According to the non-selective feature of these drugs, they block D2 receptors in the all dopaminergic pathways. When the nigrostriatal pathway is blocked, Parkinson-like motion disability can be indicated (Costall et al., 1972; Hicks, 1990; Honma and Fukushima, 1978; Nayebi et al., 2010; Silva et al., 1989). This is why catalepsy induced by neuroleptic drugs can be considered for evaluating Parkinson's disease in laboratory models and the corpus striatum is regarded as the most im-

portant brain structure responsible for catalepsy induced by neuroleptic drugs (Honma and Fukushima, 1978). Human neurological defects can be simulated by standard methods in laboratory animals (Sharifi et al., 2014). Among standard methods of developing Parkinson's motor symptoms, haloperidol injection as a neuroleptic drug can be mentioned (Wei and Chen, 2009). Studies conducted by electromyography (EMG) demonstrated that muscle stiffness developed in haloperidol-induced catalepsy had a similar quality to that found in Parkinson's disease (Dunstan et al., 1981).

Dorsal raphe nucleus (DRN) is known as a serotonin releasing source to the basal ganglia, which is the action site of the neuroleptic drugs (Pires et al., 1990). The serotonergic system is in charge of controlling variable physiological procedures such as sensory-motor cognitive, psycho-emotional, and autonomic functions. Serotonin also has a role of hemostatic control in the regulation of neurological complications caused by neuroleptic drugs in the cerebrospinal axis (neuraxis) (Rao et al., 1989). Bilateral serotonin injection effectively weakens the haloperidol-induced catalepsy (Wei and Chen, 2009).

It is now known that among 5-HT receptors, 5-$HT_{1A}$ receptor play a crucial role in modulating extrapyramidal motor disorders, including antipsychotics-induced extrapyramidal symptoms (EPS) (Dunstan et al., 1981; Honma and Fukushima, 1978). On the other hand, 5HT1A receptors are widely distributed throughout the basal ganglia, which results in their inhibitory effect on releasing of dopamine and play an important role in the neuroleptic drugs induced catalepsy (Hicks, 1990; Nayebi et al., 2010; Silva et al., 1989; Zubkov et al., 2009). The agonists of these receptors reduce serotonergic activity, which can inhibit the dopaminergic pathway of nigrostriatal neurons, which results in an increase in the amount of dopamine in the dorsal striatal region, which can be incompletely overcome by blocking of D2 receptors (Bantick et al., 2005). It should be noted that dorsal striatum is considered the most important brain structure responsible for extrapyramidal disorders caused by neuroleptic drugs (Costall et al., 1972; Dunstan et al., 1981; Honma and Fukushima, 1978; Ossowska et al., 1990).

Our study aimed to investigate the effect of 8-OH-DPAT and buspirone as an agonist and partial agonist of 5-$HT_{1A}$ receptors respectively, and fluoxetine as a serotonin reuptake inhibitor on haloperidol-induced EPS in male Wistar rats.

## MATERIALS & METHODS

### *Animals*

In the current study male Wistar rats, weighing 200-230g, were obtained from institutional animal facilities, Hamadan University of medical sciences. Animals were randomly divided into 10 groups as follows: 1: normal rats (intact without any injection), 2: control (normal saline), 3: sham (polyethylene glycol), 4: haloperidol (1 mg/kg), 5: haloperidol & acute buspirone (10 mg/kg) (Rao et al., 1989), 6: haloperidol & 7 days pre-treatment with buspirone, 7: haloperidol & acute fluoxetine (1 mg/kg) (Sharifi et al., 2014), 8: haloperidol & 7 days pre-treatment with fluoxetine, 9: haloperidol & acute 8-OH-DPAT (1 mg/kg) (Aristieta et al., 2014; Rao et al., 1989) and 10: haloperidol & 7 day pre-treatment with 8-OH-DPAT. Each group included six rats. Animals were housed in standard plastic cages, 3 per cage and had free access to food and water under a 12:12 h light/dark (Lights on 7:00 AM) schedule at an ambient temperature of 22±2 °C.

Animals were adjusted to laboratory conditions one hour before each test. This study was approved by the ethical committee of the Hamadan University of Medical Sciences with the ethical code of IR.UMSHA.REC.1395.417 and all procedures were conducted under the ethical instructions of the committee for the consideration and use of laboratory animals.

### *Chemicals*

Haloperidol, 8-OHDPAT, buspirone and fluoxetine were obtained from Sigma–Aldrich (St. Louis, MO, USA). Haloperidol, 8-OHDPAT and fluoxetine was dissolved in normal saline 0.9% and buspirone was dissolved in polyethylene glycol. All drug solutions were prepared freshly on the days of experimentation and were injected i.p.

### *Haloperidol-induced extrapyramidal symptoms*

As it was approved in the previous studies, extrapyramidal signs such as catalepsy and motor imbalance can be induced by intraperitoneal injection of haloperidol (1mg/kg) (Field et al., 2000).

### *Behavior study*

*Assessment of catalepsy*

Catalepsy was assessed by bar test, following the method in which the rat is maintained in an imposed

gesture with both forelimbs expanded and remains on a 9-cm high horizontal wooden bar (0.9 cm in diameter). The end point of catalepsy was considered the time that one of the forepaws was removed from the bar or if the rat moved its head in an exploratory manner. The cut-off time was 720 seconds. Haloperidol-induced catalepsy was measured by bar test, at 3 consecutive times, 60, 120 and 180 min after haloperidol injection (Haddadi et al., 2015; Haddadi et al., 2013; Kheradmand et al., 2016a).

*Assessment of motor balance*

Motor balance was evaluated by standard rotarod test. The appliance has a horizontal metal rod (6 cm in diameter) fastened to a motor with alterable speed. The rod is divided into four sections by a separation disc (10.5 cm in diameter). The rod was located at a height of 50 cm to avoid the animals jumping from the rotating rod. The animals were trained on the rotarod at a fixed speed of 18 rpm until they could stay on the device for 300 s without falling 24 h before the experiments. The motor imbalance was assessed by rotarod test at 3 consecutive times, 60, 120 and 180 min after haloperidol injection (Haddadi et al., 2014; Haddadi et al., 2018; Kheradmand et al., 2016b).

All tests were made between 9:00 AM and 15:00 PM in a silent ambience by an observer who was blind to treatments.

*Data analysis*

Descriptive analysis and comparison of differences between each data set were calculated using SPSS 16 software. The data were expressed as Mean ± SEM, and were analyzed by ANOVA in each experiment. In the case of significant variation ($p<0.05$), the values were compared by Tukey test. Statistical significance was accepted at the level of $p<0.05$.

## RESULTS

### *Acute injection of haloperidol-induced catalepsy*

The results indicated that haloperidol (1mg/kg, i.p.) was able to induce catalepsy significantly ($p\leq0.001$; $F=15.325$, $df=6$) compared with sham and normal groups, that is, the duration of standing on the bar was increased significantly (Figure 1).

### *Acute injection of haloperidol induced motor imbalance*

The results of current study demonstrated that haloperidol (1mg/kg, i.p.) was able to induce motor imbalance significantly ($p\leq0.001$; $F=17.124$, $df=6$) compared to sham and normal groups. That is, the duration of walking on the rotating rod was decreased significantly (Figure 2).

### *Effect of 8-OHDPAT on haloperidol-induced catalepsy*

To evaluate improving effect of 8-OHDPAT on haloperidol-induced catalepsy, three groups of animals were compared: haloperidol group (Hal group), acute 8-OHDPAT group which was treated by a single injection with 8-OHDPAT (1mg/kg, i.p) before haloperidol injection and 7-day pre-treatment with 8-OHDPAT (1mg/kg, i.p.) before haloperidol injection. Catalepsy was assessed by bar test after

**Figure 1.** Effect of haloperidol administration (1mg/kg) on catalepsy.
Each bar represents the mean±SEM of elapsed time (s) in bar test. n=6 rats for each group.†: p<0.001

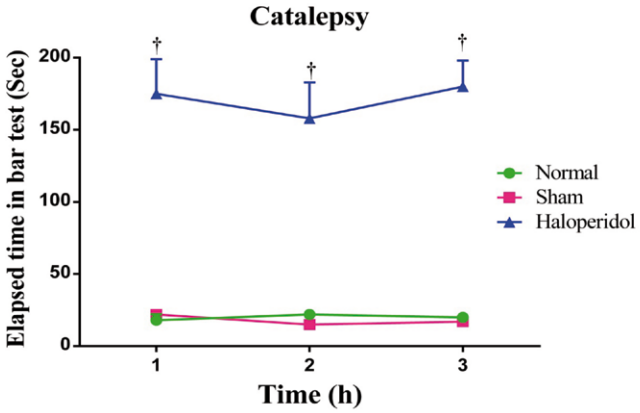


**Figure 2.** Effect of haloperidol administration (1mg/kg) on motor balance.
Each bar represents the Mean±SEM of elapsed time (s) in rotarod. n=6 rats for each group.†: p<0.001

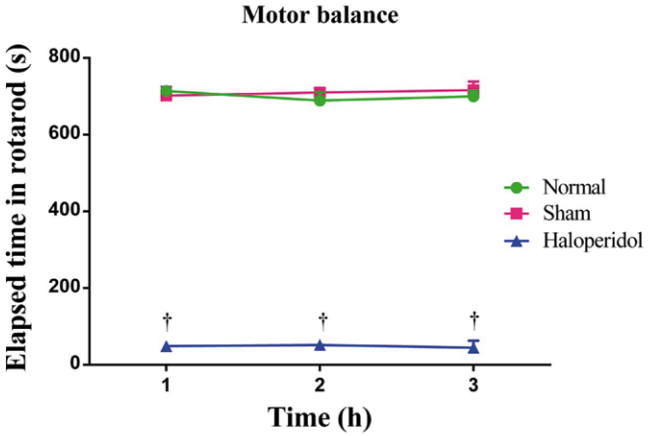



**Figure 3.** Effect of 8-OH-DPAT administration (1mg/kg) on haloperidol-induced catalepsy.
Each bar represents the mean±SEM of elapsed time (s) in bar test. n=6 rats for each group. **: p<0.01, ***: p<0.001 vs haloperidol group.

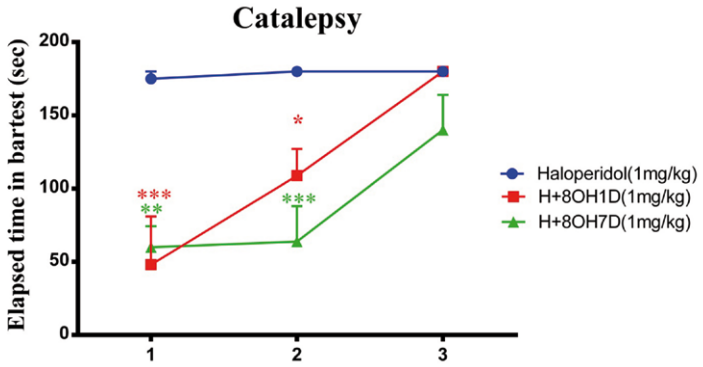



**Figure 4.** Effect of 8-OH-DPAT administration (1mg/kg) on haloperidol-induced motor imbalance.
Each bar represents the mean±SEM of elapsed time (s) in rotarod. n=6 rats for each group.

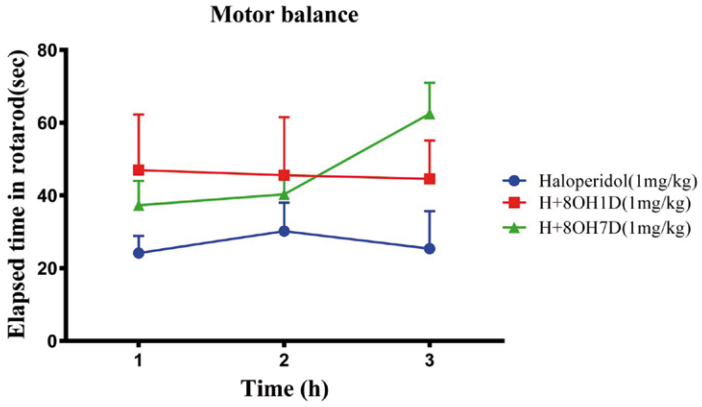


**Figure 5.** Effect of buspirone administration (1mg/kg) on the haloperidol-induced catalepsy.
Each bar represents the mean±SEM of elapsed time (s) in the bartest. n=6 rats for each group. *: p<0.05, ***: p <0.001 vs haloperidol group.

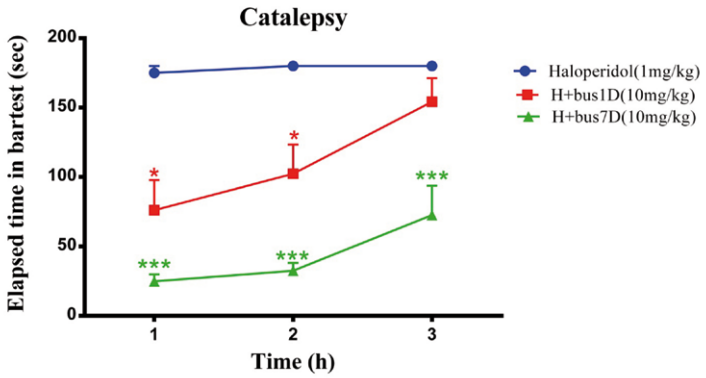



**Figure 6.** Effect of buspirone administration (1mg/kg) on haloperidol-induced motor imbalance.
Each bar represents the mean±SEM of elapsed time (s) in rotarod. n=6 rats for each group.

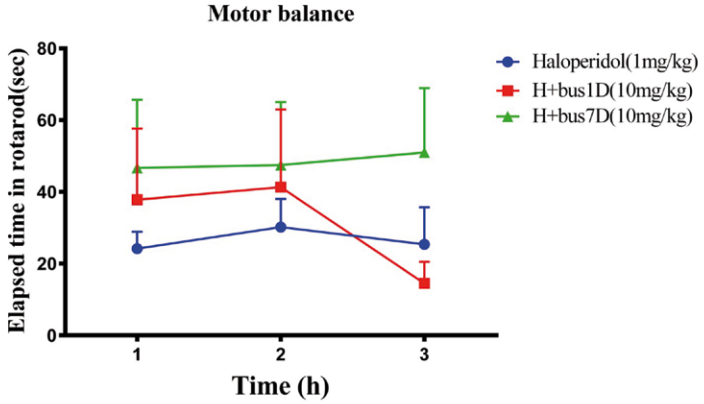



**Figure 7.** Effect of fluoxetine administration (1mg/kg) on haloperidol-induced catalepsy.
Each bar represents the mean±SEM of elapsed time (s) in bar test. n=6 rats for each group.

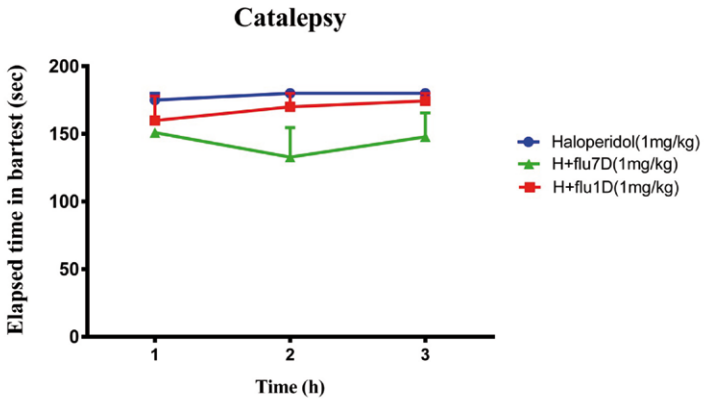


**Figure 8.** Effect of fluoxetine administration (1mg/kg) on haloperidol-induced motor imbalance. Each bar represents the mean±SEM of elapsed time (s) in rotarod. n=6 rats for each group.

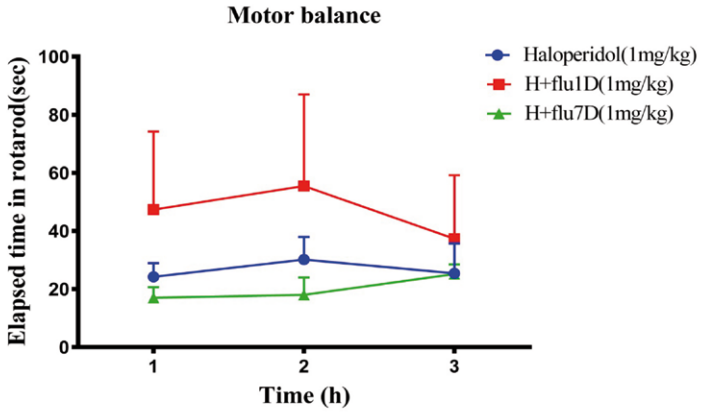



**Figure 9.** The effect of 8-OH-DPAT (1mg/kg), buspirone (10mg/kg) and fluoxetine (1mg/kg) administration alone for 1 or 7 day on catalepsy in intact animals. Each bar represents the mean±SEM of elapsed time (s) in bar test. n=6 rats for each group.

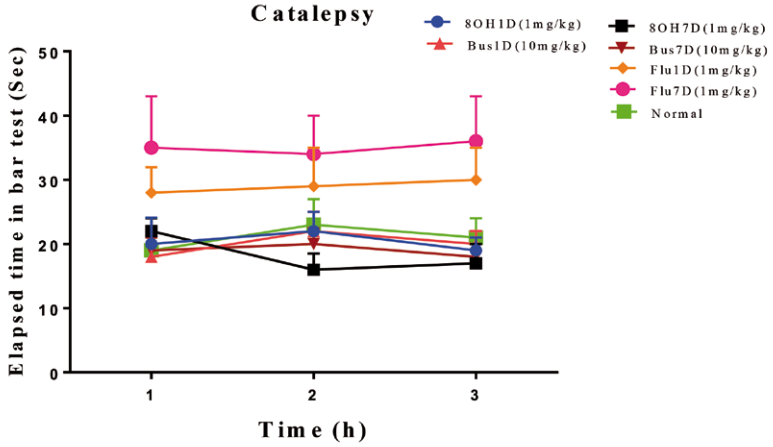
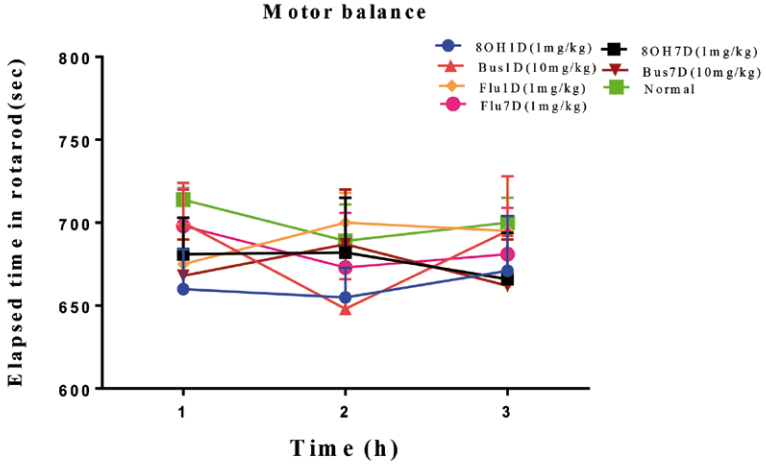



**Figure 10.** The effect of 8-OH-DPAT (1mg/kg), buspirone (10mg/kg) and fluoxetine (1mg/kg) administration alone for 1 or 7 day on motor balance in intact animals. Each bar represents the mean±SEM of elapsed time (s) in rotated rod. n=6 rats for each group.



haloperidol (1 mg/kg i.p.) injection in the final day of each phase of experiment. Data analysis demonstrated the improving effect of 8-OHDPAT on haloperidol-induced catalepsy. Acute injection of 8-OHDPAT could significantly ($p \leq 0.001$; $F=9.689$, $df=6$, $p<0.05$; $F=3.673$, $df=6$) reduce haloperidol-induced catalepsy during the first and second tests, respectively, but in the last test (3 hours after haloperidol injection) its effect was not significant. Pretreatment with 8-OHDPAT could reverse haloperidol effect and it was in a significant ($P<0.01$; $F= 4.721$, $df=6$, $p \leq 0.001$; $F=5.841$, $df=6$) manner 1 and 2 hours after haloperidol injection, respectively (Figure 3).

One-way ANOVA revealed that 8-OHDPAT pretreated group was not able to improve muscle coordination and cataleptic sign in comparison to acute group.

***Effect of 8-OHDPAT on haloperidol-induced motor imbalance***

To detect therapeutic aspects of 8-OHDPAT on haloperidol-induced motor imbalance, three groups of animals were compared: haloperidol group (Hal group), acute 8-OHDPAT group which was treated by a single injection with 8-OHDPAT (1mg/kg, i.p) and 7-days pre-treatment with 8-OHDPAT (1mg/kg, i.p) group. All these groups were tested after haloperidol (1 mg/kg i.p) administration in the final day of each phase of experiment to assess motor balance. Improving manifestation effect of 8-OHDPAT on haloperidol-induced motor imbalance was seen in both acute and pre-treated 8-OHDPAT groups 60, 120 and 180 min. after haloperidol injection but it wasn't statistically significant (Figure 4).

One-way ANOVA revealed that the 8-OHDPAT pre-treated group was more effective in improving muscle coordination than the acute group, without any significant difference (Figure 4).

***Effect of buspirone on haloperidol-induced catalepsy***

As shown in the figure 5, acute administration of buspirone could decrease haloperidol-induced catalepsy in a significant ($p \leq 0.05$; $F= 2.81$, $df=6$) manner in the first and second tests (1 and 2 hours after haloperidol injection). Our results showed that 7 days pretreatment with buspirone significantly ($p \leq 0.001$; $F= 8.501$, $df=6$) prevented haloperidol-induced catalepsy in the all tests (Figure 5).

***Effect of buspirone on haloperidol-induced motor imbalance***

Treatment with buspirone in both phases, acute and pre-treatment, could increase motor balance following haloperidol injection, but no significant difference was seen between different groups (Figure 6).

***Effect of fluoxetine on haloperidol-induced catalepsy***

Our data demonstrated that fluoxetine in both phases, acute and pre-treatment, could not diminish haloperidol-induced catalepsy, so that there is no significant difference was seen between different groups (Figure 7).

***Effect of fluoxetine on haloperidol-induced motor imbalance***

Our result demonstrated that in both phases, acute and pre-treatment, fluoxetine could not increase motor balance following haloperidol injection. So that, there is no significant difference was seen between different groups (Figure 8).

***Effect of 8-OHDPAT, buspirone and fluoxetine alone on catalepsy***

To evaluate the primary effect of 8-OHDPAT, buspirone and fluoxetine on catalepsy, these drugs were injected alone to intact animals. As shown in the figure 9, acute (1 day) and repeated (7 day) injection of 8-OH-DPAT (1mg/kg) and buspirone (10mg/kg) alone in the intact animals were not able to induce catalepsy compared with normal groups. On the other hand, acute and repeated injection of fluoxetine (1mg/kg) alone to healthy animals could increase catalepsy but not in a significant manner compared to the normal group. However, repeated administration of fluoxetine increased catalepsy more than in the acute group. So that, the duration of standing on the bar was increased (Figure 9).

***Effect of 8-OHDPAT, buspirone and fluoxetine alone on motor balance***

To evaluate the primary effect of 8-OHDPAT, buspirone and fluoxetine on motor balance, these drugs were injected alone to intact animals. The results of current study demonstrated that acute (1 day) and repeated (7 day) injection of 8-OH-DPAT (1mg/kg), buspirone (10mg/kg) and fluoxetine (1mg/kg) alone

to the intact animals were not able to induce motor imbalance significantly ($p>0.05$) compared with normal groups (Figure 10).

## DISCUSSION

The results of the current study demonstrated that haloperidol injection induced obvious motor disorders in rats. Data analysis showed that i.p. injection of buspirone at the dose 10 mg/kg decreased extrapyramidal symptoms compared with the control group. The attenuation of haloperidol-induced extrapyramidal symptoms was observed with 8-OHDPAT treatment. Treatment with fluoxetine did not affect motor coordination impairment caused by haloperidol.

Regarding to the mechanism of Parkinson's disease development and previous laboratory findings, neuroleptic drugs and D2 antagonists such as haloperidol have a potential to induce movement-related disorders. Dorsal striaum is considered the most important brain structure responsible for extrapyramidal disorders caused by neuroleptic drugs (Hicks, 1990; Mahmoudi et al., 2011; Nayebi et al., 2010; Pires et al., 1990). On the other hand, 5HT1A receptors are widely distributed throughout the basal ganglia, which results in their inhibitory effect on releasing of dopamine and play an important role in the neuroleptic drug-induced catalepsy (Pires et al., 1994; Prinssen et al., 2002; Rao et al., 1989; Wei and Chen, 2009). The agonists of 5HT1A receptors increase the amount of dopamine in the dorsal striatal region (Prinssen et al., 2002; Zubkov et al., 2009), which may be incompletely overcome by blocking of D2 receptors. But agonists of 5HT2A receptors can inhibit the dopaminergic pathway in nigrostriatal neurons, which results in the cataleptogenic effect (Zubkov et al., 2009).

Therefore, the present study examined the effects of serotonergic drugs buspirone, fluoxetine and 8-OHDPAT on acute haloperidol-induced extrapyramidal symptoms and also the effect of pretreatment with these drugs on the administration of haloperidol. Result of our study demonstrated that 8-OHDPAT can diminish extrapyramidal symptoms caused by acute haloperidol injection. Moreover, pretreatment with 8-OHDPAT was also effective in preventing extrapyramidal symptoms. In agreement with our results, it has been reported that 8-OHDPAT reduces catalepsy via serotoninergic receptors in the raphe nucleus (Invernizzi et al., 1988). Furthermore, buspirone was able to reduce acute haloperidol-induced extrapyramidal symptoms probably through the effect on the 5HT1A serotonin receptor. In addition, positive results were obtained in the pretreatment with this drug. This confirms the previous findings of the protective effect of buspirone on 6-hydroxy dopamine injected rats via acting on nigral 5HT1A receptors (Nayebi et al., 2010). To evaluate the effects of fluoxetine, acute injection and pre-treatment with this drug were applied. Fluoxetine wasn't able to prevent extrapyramidal symptoms in either acute and pre-treatment phases in a significant manner. However, injection of fluoxetine (1 mg/kg) alone to intact rats in both acute and repeated phase increased catalepsy compared with the normal group, but not in a significant manner. This is entirely in line with previous findings regarding the creation of fluoxetine-based catalepsy (Aristieta et al., 2014; Tatara et al., 2012). Aristieta et al. have shown that fluoxetine in high doses (more than 10 mg/kg) increases subthalamic nucleus neuron activity in chronically fluoxetine-treated rats, which may explain the role of this nucleus in fluoxetine-induced extrapyramidal side effects. That is, chronic administration of fluoxetine increased 5HT levels in the frontal cortex and decreased dopamine levels in the striatum which lead to induction of catalepsy (Aristieta et al., 2014; Tatara et al., 2012). In another study, chronic administration of fluoxetine in low doses (1mg/kg) has not only increased catalepsy but has also been able to decrease 6-OHDA-induced catalepsy (Sharifi et al., 2014). This result is inconsistent with our findings. Differences in fluoxetine effects can be attributed to the dose and period of treatment. This drug, in low doses and long periods of therapy improves extrapyramidal disturbances and in high doses the effect is reversed.

According to our findings, fluoxetine is not able to prevent extrapyramidal symptoms in pretreatment and acute therapy but administration of buspirone and 8-OHDPAT is effective in treating haloperidol-induced extrapyramidal symptoms. Pre-treatment with these drugs can also be effective in the preventing of extrapyramidal symptoms in animals treated with haloperidol. To prove this, we need more clinical investigation. Also, the authors suggested to investigate the effect of fluoxetine on extrapyramidal symptom induced by neuroleptic drugs in lower doses to detect its mechanism of action.

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**Conflict of Interest:** The authors declare that they have no conflict of interest.

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# Akut és ismételt buspiron-, 8-OHDPAT- és fluoxetinkezelés hatása a haloperidol-indukálta extrapiramidális tünetekre

**Célkitűzés:** Jelen kutatás célja az 5-$HT_{1A}$ parciális agonista buspiron, az 5-$HT_{1A}$ agonista 8-hidroxi-2-[di-n-propilamino] tetralin (8-OH-DPAT), és a szelektív szerotoninvisszavétel-gátló fluoxetin haloperidol-indukálta extrapiramidális tünetekre (EPS) gyakorolt hatásának vizsgálata volt hím Wistar patkányokban. **Módszer:** A kísérletet 66, 200-240 g súlyú hím Wistar patkányon végeztük. A patkányokat 11 csoportra osztottuk (n=6). Az extrapiramidális tüneteket 1mg/kg intraperitoneális (i.p.) haloperidolinjekció segítségével indukáltuk. A szerotonerg szerek haloperidol-indukálta extrapiramidális tünetekre gyakorolt hatásának vizsgálatához a patkányok 8-OHDPAT (1mg/kg), buspirone (10mg/kg) és fluoxetin (1mg/kg) injekciót kaptak akutan, illetve hét egymás utáni napon a haloperidolkezelést megelőzően. Az extrapiramidális tüneteket, köztük a katalepsziát és a motoros egyensúly zavarait rúdteszttel illetve rotarod módszerrel vizsgáltuk. **Eredmények:** Az eredmények szerint az i.p. haloperidol injekció jelentős motoros egyensúlyvesztést és katalepsziát váltott ki ($p \leq 0.001$) az állatokban. Az adatok szerint az i.p. buspiron (10mg/kg) szignifikánsan csökkentette a katalepsziát a kontrollcsoporthoz képest. A haloperidol-indukálta extrapiramidális tünetek csökkenése 8-OHDPAT kezelés mellett is megfigyelhető volt. A fluoxetinkezelés nem befolyásolta a haloperidol által okozott motoros koordinációs zavart. **Következtetés:** A buspiron és a 8-OHDPAT javítja az extrapiramidális tüneteket a haloperidol-indukálta parkinzonizmus állatmodellen, mely hatást valószínűleg az 5-$HT_{1A}$ receptorok aktivációja közvetíti. További vizsgálatok szükségesek azonban az 5-$HT_{1A}$ és DA receptorok közti interakció pontos mechanizmusának tisztázására.

**Kulcsszavak:** haloperidol, fluoxetin, buspirone, katalepszia, 8-OHDPAT, motoros egyensúly, extrapiramidális tünetek