*Available online at* **www.ijmrhs.com**

**ISSN No: 2319-5886**

**International Journal of Medical Research & Health Sciences, 2019, 8(7): 111-121**

# Effects of Haloperidol, Asenapine and Paliperidone on MK-801-Induced Memory Deterioration in Morris Water Maze and Radial Arm Maze Tests in Mice

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## ABSTRACT

***Objective:*** *One of the most important problems of schizophrenic patients is the impairment of cognitive functions.* ***Methods:*** *The aim of this study was to investigate the effects of haloperidol, asenapine and paliperidone on spatial learning and memory using the Morris water maze (MWM) and radial arm maze (RAM) tests; moreover the effects of haloperidol, asenapine, and paliperidone on MK-801 induced cognitive dysfunction were also evaluated in mice.* ***Results:*** *Both asenapine (0.05 mg/kg) and paliperidone reversed MK-801 induced increment in escape latency in 2nd, 3rd, and 4th acquisition sessions while haloperidol failed to reverse MK-801 induced this effect. Time spent in escape platform's quadrant significantly decreased while the mean distance to platform significantly increased in MK-801 group in the probe trial of MWM test and administration of asenapine and paliperidone significantly reversed MK-801 induced these effects while haloperidol had no effect. MK-801 significantly increased the speed of the animals in probe trial of the MWM test while both asenapine and paliperidone reversed this effect. In the RAM test, MK-801 significantly increased the number of errors in the retention trial and haloperidol failed to reverse this effect. Both asenapine (0.075 mg/kg) and paliperidone reversed MK-801-induced increment in a number of errors and improved MK-801 induced prolongation in latency.* ***Conclusions:*** *The results of this study revealed that MK-801 exerted spatial memory impairment in MWM and RAM tests; haloperidol failed to improve MK-801 induced memory deterioration in mice. Moreover both asenapine and paliperidone improved MK-801 induced spatial learning and memory impairment in the MWM and RAM tests.*

**Keywords:** Asenapine, Paliperidon, Schizophrenia, Cognition

## INTRODUCTION

Many schizophrenic patients exhibit impairments in neurocognitive functions such as attention, memory and executive functions [1], as well as prominent positive and negative psychotic symptoms. Cognitive deficits may be present before the onset of psychotic symptoms and may remain stable throughout the course of the illness or show modest progression [2,3]. It has been reported that typical antipsychotic drugs such as haloperidol, have limited or even detrimental influence on cognitive functions [4]. In contrast, some clinical studies suggest that atypical antipsychotic drugs, such as clozapine and olanzapine, may improve memory function in schizophrenics [5]. In a multicenter double-blind study, olanzapine has been shown to have some superior cognitive benefits relative to haloperidol and risperidone [6].

Specifically, novel drugs should alleviate psychotic and/or depressive-like symptoms and not interfere with cognitive or motor performance [7]. In addition, novel drugs such as asenapine and paliperidone have recently become available and remain to be fully characterized [8]. However, no study has been conducted to directly compare the effects of asenapine, paliperidone, and haloperidol on memory functions in animal models. Some antipsychotics are reported to impair spatial learning in the Morris water maze [9]. Haloperidol selectively disrupts working memory after long-term administration and significantly impairs spatial learning in Morris water maze at doses that do not affect the ability

to escape to the visible platform [10,11]. Risperidone and olanzapine improve the consolidation process on a delayed radial maze task in rats, while clozapine, ziprasidone or haloperidol does not [12]. Haloperidol impairs acquisition of the 8-arm radial maze in both young and aging rats [13]. Chronic treatment with haloperidol significantly impairs spatial learning in rats [14].

Paliperidone (9- hydroxyrisperidone) is the main metabolite of risperidone and provides the advantage of being mainly excreted via the kidneys, without requiring processing in the liver. Thus, paliperidone may be safer to use in patients with serious hepatic disease or when receiving other medications (minimal drug-drug kinetic interactions) [15]. An extended-release formulation of paliperidone is also available for patients with schizophrenia [16]. Asenapine is an atypical antipsychotic developed for the treatment of schizophrenia and acute mania associated with bipolar disorder [17]. Preliminary data indicate that it has minimal anticholinergic and cardiovascular side effects, as well as minimal weight gain. Asenapine behaves as a partial agonist at the 5-HT1A receptors [17].

One current hypothesis is that cognitive impairments are caused by hypofunction of the N-methyl-D-aspartate (NMDA) receptor [18]. NMDA receptor antagonists, such as ketamine, phencyclidine, and MK-801 induce schizophrenia-like symptoms in healthy subjects, including positive, negative, and cognitive symptoms [18]. NMDA receptor antagonists also disturb learning and memory functions in animals that are similar to those seen in schizophrenia; these agents are useful for establishing animal models of cognitive impairment [19]. The aim of this study was to investigate the effects of new antipsychotics asenapine and paliperidone on spatial reference and working memory of naive and MK-801-treated mice in MWM and RAM tests and also to compare its effect with classical antipsychotic haloperidol.

## MATERIALS AND METHODS

### Animals

Male inbred BALB/c ByJ mice (MAM TUBİTAK, Gebze, Kocaeli, Turkey) aged 7-weeks were used in this study upon arrival to the laboratory. Animals (4-5 per cage) were kept in the laboratory at 21 ± 1.5°C with 60% relative humidity under a 12 h light/dark cycle (lights on at 8.00 p.m.) for 2-weeks before experimentation. Tap water and food pellets were available ad libitum. All procedures involving animals were in compliance with the European Community Council Directive of 24 November 1986, and ethical approval was obtained from Kocaeli University Ethics Committee (Number: AEK 3/1-2012, Kocaeli, Turkey). All animals were naive to the experimental apparatus, and different animals were used for each test.

### Morris Water Maze Test (MWM)

The MWM was a circular pool (90 cm diameter and 30 cm height) filled with water (22°C) to a depth of 14 cm and rendered opaque by the addition of small black balls. The pool was located in a dimly lit, soundproof test room with various visual cues, including a white-black colored poster on the wall, a halogen lamp, a camera, and the experimenter. The maze was divided into 4-quadrants and 3 equally spaced points served as starting positions around the edge of the pool. The order of the release positions varied systematically throughout the experiment. A circular escape platform (6 cm diameter and 12 cm high) was located in one quadrant 1 cm above the water surface during the familiarization session and 1 cm below the water surface during the other sessions. Video tracking was conducted with a video camera focused on the full diameter of the pool. Navigation parameters were analyzed by the Ethovision 3.1 video analysis system (Noldus, The Netherlands). The mice were trained in the MWM 5 times daily (Familiarization sessions S1, S2, S3, S4).

One familiarization and 4 acquisition sessions were performed using the MWM. During the familiarization session and acquisition phase of the experiment, each mouse was given 3 trials. The delay between the trials was 60 seconds, and a 1-day interval was used between each session. For each trial, the mouse was taken from the home cage and placed into the water maze at one of three randomly determined locations with its head facing the center of the water maze. After the mouse had found and climbed onto the platform, the trial was stopped, and the escape latency was recorded. If the mouse did not climb onto the platform in 60 seconds, the trial was stopped, and the experimenter guided the mouse to the platform; the escape latency of 60 seconds was recorded.

Twenty-four hours after the last acquisition session, a ‘probe trial’ was used to assess the spatial memory retention of the location of the hidden platform. During this trial, the platform was removed from the maze, and the mouse was allowed to search the pool for 60 seconds. The percent of time spent in each quadrant was recorded.

**Radial Arm Maze test (RAM)**

The experimental device was an elevated maze with 8-open arms (32 cm long and 5 cm wide) leading to 8 cm square platform, which radiated from a central circular platform 44 cm in diameter with 1 cm high sides surrounding each arm. A small cup, 1 cm in diameter, was embedded in each distal platform and contained a hidden 10 mg noodle which was used as reinforcement. The maze was oriented in a small room; on the walls, 4-large black, white or black and white-striped patterns were hung, which provided particularly salient visual extra maze cues [20]. About 24 hours prior to training, the mice were deprived of food but not water; their weight loss reached 15-20% of the initial body weight by the start of testing.

RAM procedure was applied according to Belzung, et al., [21]. The mice were first given two pre-training sessions at 24-hour intervals. Groups of 4 mice were placed on the maze together for 20 minutes per session and could freely explore the 8-arms, which contained abundant food. Following pre-training, mice were given 5 training sessions, at 90-minute intervals.

After baiting the 8 arms with a 10 mg noodle, a mouse was placed on the central platform. The sessions were terminated when the animal had visited all 8 arms and eaten the rewards after 16 arms were visited (regardless of which arms) or after a maximum of 15 min. The maze was quickly cleaned with ethanol to remove fecal deposits and urine after each mouse had completed testing. An error was recorded when the mouse entered an arm previously visited during the retention session. The total number of errors and the latency of retention session (time taken to complete the task) were scored. Because the effects of drugs on locomotor activity of the animals may cause false results, the speed of the animals was recorded using ethovision-XT (Noldus, Netherlands).

**Drug Administration**

Haloperidol, asenapine, paliperidone and MK-801 were purchased from Sigma Chemical Company (Sigma, St. Louis, MO). Haloperidol and MK-801 were dissolved in saline while asenapine and paliperidone were dissolved in saline supplemented with small amounts of DMSO. All drugs were freshly prepared and administered in a volume of 0.1 ml per 10 g body weight. The control groups received the same volume of vehicle. Haloperidol (0.05 and 0.075 mg/kg), asenapine (0.05 and 0.075 mg/kg) and paliperidone (0.125, 0.25 mg/kg) or MK-801 (0.1 mg/kg) alone or concurrently were administered intraperitoneally and subchronically for 6 days 30 min, 30 min, 60 min and 30 min; respectively; before the sessions of MWM test and acutely before the retention trial of RAM test. The number of animals per group ranged from 6-8. Different animals were used for each test. The effective dose of each drug was selected according to previous behavioral and neurochemical studies [22-24].

**Statistics**

A two-way analysis of variance (ANOVA) post-hoc Tukey test was used to analyze the time spent in escape platform's quadrant, mean distance to the platform and the speed of the animals in the probe trial of MWM test and the number of errors and latency of animals in the RAM test. The data are expressed as the mean values ± SEM, $p<0.05$ was accepted as statistically significant.

## RESULTS

**Effects of Haloperidol, Asenapine, Paliperidone, and MK-801 on Learning and Memory in the MWM Test**

In the MWM test, there was a significant difference between groups when escape latency of haloperidol, MK-801 and haloperidol+MK-801 groups were evaluated during 5 acquisition sessions [$F(5,30)=4.86$; $p=0.002$; $F(5,30)=4.74$; $p=0.002$; $F(5,30)=15.70$; $p<0.0001$; $F(5,30)=8.11$; $p<0.0001$; $F(5,30)=27.98$; $p<0.0001$)] (Figure 1a). MK-801 significantly increased escape latency starting from the 2$^{nd}$ acquisition session compared to the control group ($p<0.001$) and haloperidol failed to reverse this effect (Figure 1a). There was a significant difference between groups when the effects of haloperidol, MK-801 and haloperidol+MK-801 groups on time spent in escape platform's quadrant in the probe trial were evaluated [$F(5,30)=21.94$; $p<0.0001$)] (Figure 1b). Time spent in escape platform's quadrant

significantly decreased in MK-801 ($p<0.001$), haloperidol (0.05 and 0.075 mg/kg; $p<0.001$), and haloperidol+MK-801 treated animals ($p<0.001$) compared to control group (Figure 1b). There was also a significant difference between groups when the effects of haloperidol, MK-801, and haloperidol+MK-801 groups on the mean distance to the platform was evaluated [$F(5,30)=12.31$; $p<0.0001$] (Figure 1c). Mean distance to the platform in the probe trial significantly increased in MK-801 ($p<0.01$), haloperidol 0.05 ($p<0.01$) and haloperidol+MK-801 treated animals ($p<0.001$) compared to control group (Figure 1c). There was no significant difference between the speed of the animals in the MWM test [$F(5,30)=1.18$; $p=0.34$] (Figure 1d).

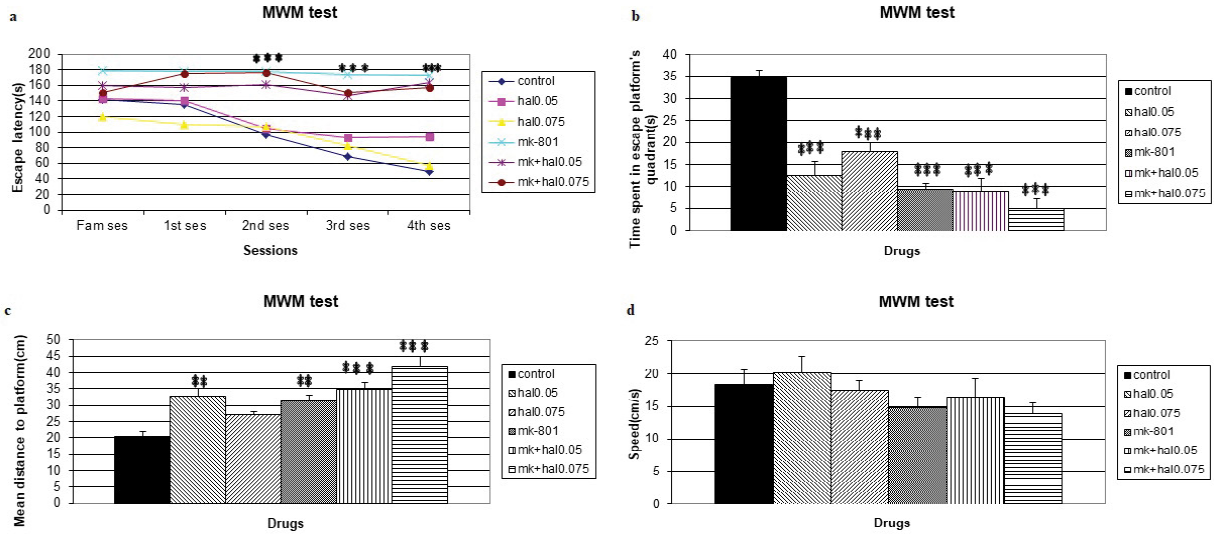


**Figure 1 Effect of haloperidol (0.05 mg/kg and 0.075 mg/kg) and MK-801 (0.1 mg/kg) administered alone or concurrently on: a) escape latency; b) time spent in escape platform's quadrant; c) mean distance to platform; d) speed in the Morris water maze test in mice (n=6). The data are expressed as mean ± SEM values of animals. **p<0.01, ***p<0.001 compared to control group**

In a separate group of animals, there was a significant difference between groups when escape latency of asenapine, MK-801 and asenapine+MK-801 groups were evaluated during familiarization, 2nd, 3rd, 4th acquisition sessions [$F(5,41)=2.95$; $p=0.02$; $F(5,41)=3.59$; $p=0.0087$; $F(5,41)=8.13$; $p<0.0001$; $F(5,41)=9.14$; $p<0.0001$] (Figure 2a). MK-801 significantly increased the escape latency in the 2nd, 3rd and 4th acquisition sessions compared to the control group ($p<0.05$; $p<0.001$; $p<0.001$); asenapine (0.075 mg/kg) also increased the escape latency in the 3rd session ($p<0.05$) (Figure 2a). Asenapine (0.05 mg/kg) reversed MK-801 induced increment in the escape latency in the 2nd, 3rd and 4th acquisition sessions ($p<0.05$; $p<0.01$; $p<0.01$; respectively) (Figure 2a). There was a significant difference between groups when the effects of asenapine, MK-801, and asenapine+MK-801 groups on time spent in escape platform's quadrant in the probe trial were evaluated [$F(5,41)=8.82$; $p<0.0001$] (Figure 2b). The time spent in escape platform's quadrant significantly decreased in MK-801 ($p<0.001$) and asenapine (0.075 mg/kg; $p<0.01$) treated animals while concurrent administration of asenapine (0.05 mg/kg; $p<0.05$) with MK-801 significantly reversed this effect (Figure 2b). There was also a significant difference between groups when the effects of asenapine, MK-801, and asenapine+MK-801 groups on the mean distance to the platform was evaluated [$F(5,41)=5.01$; $p=0.0011$] (Figure 2c). Mean distance to platform significantly increased in MK-801 ($p<0.001$) and asenapine (0.075 mg/kg; $p<0.05$) treated groups while concurrent administration of asenapine (0.05 mg/kg, $p<0.05$) with MK-801 significantly decreased MK-801-induced increment in the mean distance to the platform (Figure 2c). There was a significant difference between groups when the effect of drugs on swimming speed in the probe trial is evaluated [$F(5,41)=6.34$; $p=0.0002$] (Figure 2d). MK-801 partially increased the speed of the animals in the MWM test ($p<0.05$) while asenapine (0.05 mg/kg, $p<0.01$) reversed this effect (Figure 2d).

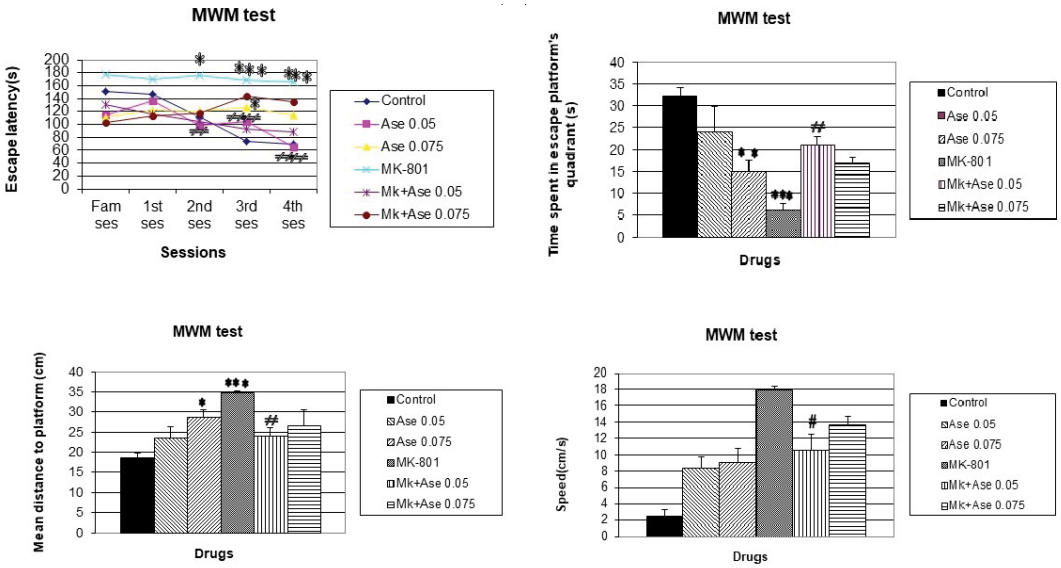


**Figure 2 Effects of asenapine (0.05 mg/kg and 0.075 mg/kg) and MK-801 (0.1 mg/kg) given alone or concurrently on: a) escape latency; b) time spent in escape platform's quadrant; c) mean distance to platform; d) speed in the Morris water maze test in mice (n=8). The data are expressed as mean ± SEM values of animals. *p<0.05, **p<0.01, ***p<0.001 compared to control group. #p<0.05, ##p<0.01 compared to MK-801 alone group**

In a separate group of animals, there was a significant difference between groups when escape latency of paliperidone, MK-801 and paliperidon+MK-801 groups were evaluated during 1st, 2nd, 3rd, 4th acquisition sessions [F (5,41)=12.69; p<0.0001; F (5,41)=9.79; p<0.0001; F (5,41)=4.11; p=0.004; F (5,41)=6.01; p=0.0003] (Figure 3a). MK-801 significantly increased the escape latency in the 2nd, 3rd and 4th acquisition sessions compared to the control group (p<0.05; p<0.001; p<0.001) (Figure 3a). Paliperidone (0.125, 0.25 mg/k) reversed MK-801 induced increment in the escape latency in the 2nd (p<0.001), 3rd (p<0.01; p<0.05) and 4th (p<0.05; p<0.001) acquisition sessions (Figure 3a). There was a significant difference between groups when the effects of paliperidone, MK-801 and paliperidon+MK-801 groups on time spent in escape platform's quadrant in the probe trial were evaluated [F (5,41)=6.14; p=0.0002] (Figure 3b). The time spent in escape platform's quadrant significantly decreased in MK-801 (p<0.001) treated animals while concurrent administration of paliperidone (0.125 and 0.25 mg/kg; p<0.05, p<0.01 respectively) with MK-801 significantly reversed this effect (Figure 3b). There was also a significant difference between groups when the effects of paliperidone, MK-801, and paliperidon+MK-801 groups on the mean distance to the platform was evaluated [F (5,41)=4.95; p=0.0012] (Figure 3c). Mean distance to platform significantly increased in MK-801 (p<0.001) treated groups while concurrent administration of paliperidone (0.125 mg/kg and 0.25 mg/kg, p<0.05) with MK-801 significantly decreased MK-801-induced increment in the mean distance to the platform (Figure 3c). There was a significant difference between groups when the effect of drugs on swimming speed in the probe trial was evaluated [F (5,41)=7.99; p<0.0001] (Figure 3d). MK-801 (p<0.05) increased the speed of the animals in the MWM test (p<0.05) while paliperidone (0.125 and 0.25 mg/kg; p<0.001, p<0.05 respectively) reversed this effect (Figure 3d).

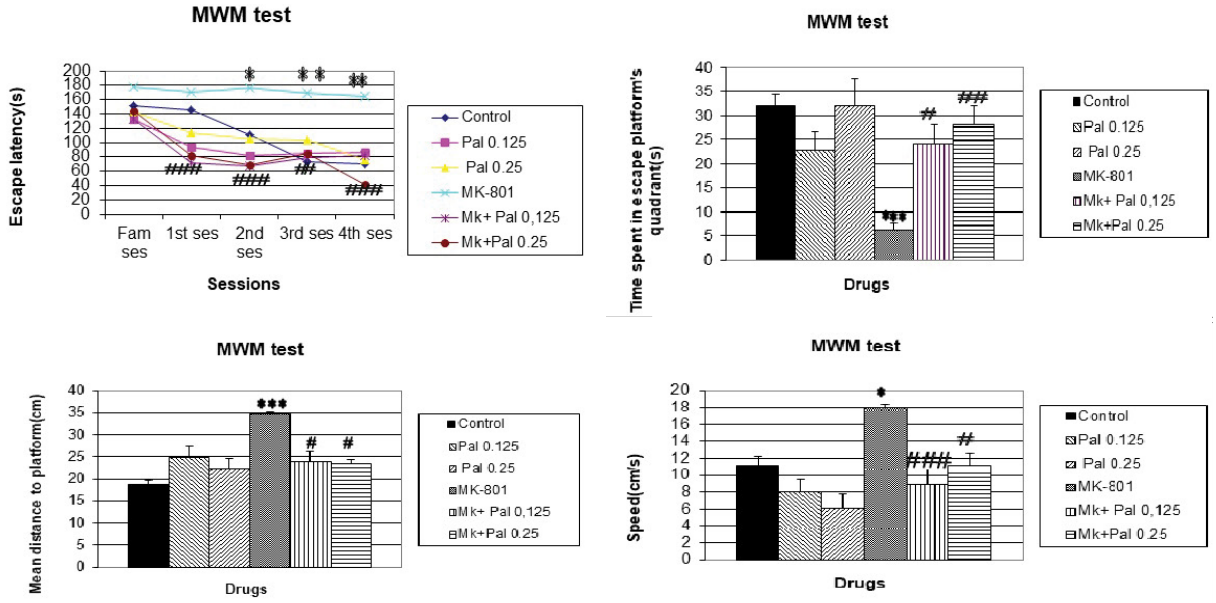


**Figure 3 Effects of paliperidone (0.25 mg/kg and 0.50 mg/kg) and MK-801 (0.1 mg/kg) given alone or concurrently on a) escape latency; b) time spent in escape platform's quadrant; c) mean distance to platform; d) speed in the Morris water maze test in mice (n=8). The data are expressed as mean ± SEM values of animals. *p<0.05, **p<0.01, ***p<0.001 compared to control group. #p<0.05, ##p<0.01, ###p<0.001 compared to MK-801 alone group**

### Effects of Haloperidol, Asenapine, Paliperidone and MK-801 on Learning and Memory in the RAM Test

In the RAM test, there was a significant difference between groups when the effects of haloperidol, MK-801 and haloperidol+MK-801 groups on a number of errors in the retention trial were evaluated [F (5,30)=12.45; p<0.0001] (Figure 4a). MK-801 significantly increased the number of errors in the retention trial (p<0.001) compared to control group and haloperidol failed to reverse this effect (Figure 4a). There was no significant difference between the retention latency of the animals [F (5,30)=2.30; p=0.06] (Figure 4b) and number of correct arm choices [F(5,30)=1.69; p=0.16] (Figure 4c).

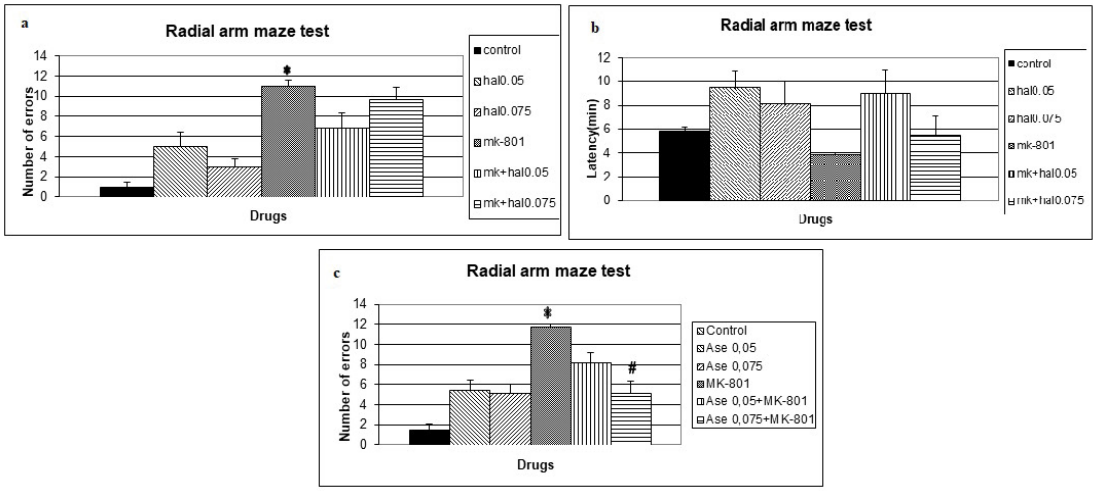


**Figure 4 Effect of haloperidol (0.05 mg/kg and 0.075 mg/kg) and MK-801 (0.1 mg/kg) administered alone or concurrently on: a) number of errors; b) latency; c) number of correct arm choices. The data is expressed as mean ± SEM values of animals. *p<0.001 compared to control group**

In a separate group of animals, there was a significant difference between groups when the effects of asenapine, MK-801 and asenapine+MK-801 groups on number of errors, retention latency and number of correct arm choices were evaluated [F (5,41)=12.94; p<0.0001; F (5,41)=9.70; p<0.0001; F (5,41)=5.41; p=0.0006] (Figure 5). Asenapine

exerted no effect on a number of errors, latency, and the number of correct arm choices in naive mice. Asenapine (0.075 mg/kg) improved MK-801 induced increment in number of errors ($p<0.05$) (Figure 5a), asenapine (0.05 mg/kg and 0.075 mg/kg) (Figure 5b) reversed MK-801 induced prolongation in latency ($p<0.001$) but it failed to reverse MK-801 induced decrement in number of correct arm choices (Figure 5c).

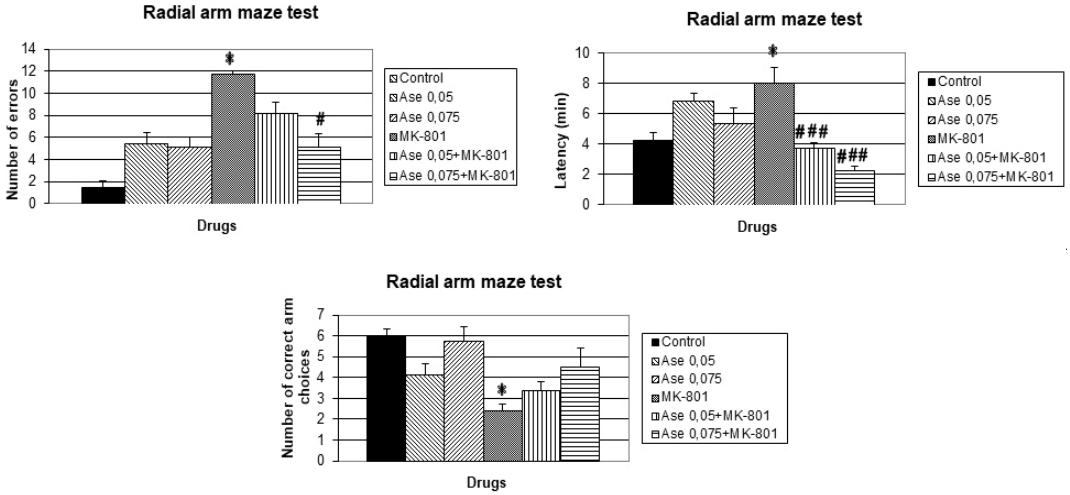


**Figure 5 Effect of asenapine (0.05 mg/kg and 0.075 mg/kg) and MK-801 (0.1 mg/kg) administered alone or concurrently on: a) a number of errors; b) latency; c) a number of correct arm choices in the radial arm maze test in mice (n=8). The data are expressed as mean ± SEM values of animals. *$p<0.001$ compared to control group. $^{\#}p<0.05$, $^{\#\#\#}p<0.001$ compared to MK-801 alone group**

There was a significant difference between groups when the effects of paliperidone, MK-801 and paliperidon+MK-801 groups on number of errors, retention latency and number of correct arm choices were evaluated [$F(5,41)=16.37$; $p<0.0001$; $F(5,41)=9.91$; $p<0.0001$; $F(5,41)=6.97$; $p<0.0001$] (Figure 6). Paliperidone exerted no significant effect on a number of errors, latency, and a number of correct arm choices in naive mice. Paliperidone (0.125 and 0.25 mg/kg) reversed MK-801-induced increment in number of errors ($p<0.001$) (Figure 6a); improved MK-801 induced prolongation in latency ($p<0.05$; $p<0.001$; respectively) (Figure 6b) and reversed MK-801 induced decrease in number of correct arm choices ($p<0.01$; $p<0.05$; respectively) (Figure 6c).

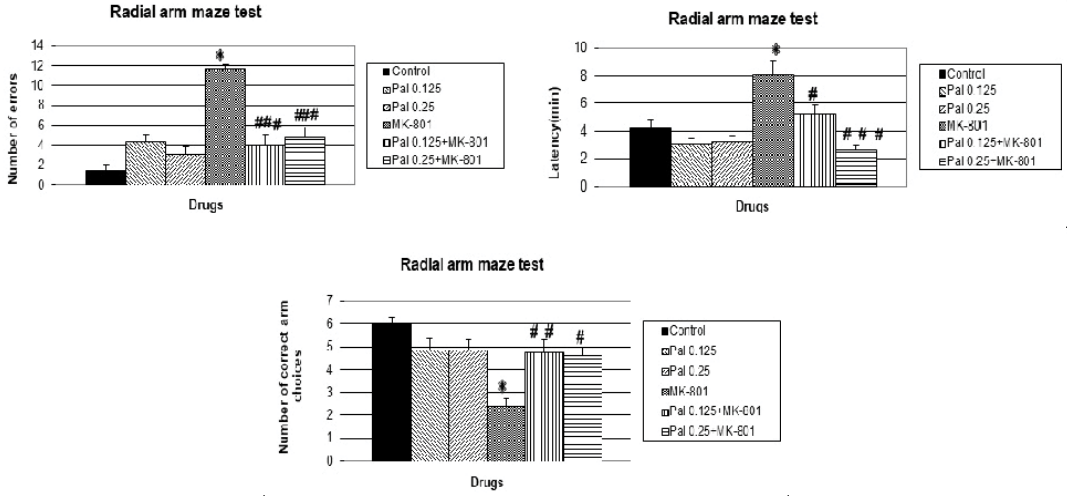


**Figure 6 Effect of paliperidone (0.125 mg/kg and 0.25 mg/kg) and MK-801 (0.1 mg/kg) administered alone or concurrently on: a) number of errors; b) latency; c) number of correct arm choices in the radial arm maze test in mice (n=8). The data are expressed as mean ± SEM values of animals. *$p<0.001$ compared to control group. $^{\#}p<0.05$, $^{\#\#}p<0.01$, $^{\#\#\#}p<0.001$ compared to MK-801 alone group**

## DISCUSSION

The results of our study showed that MK-801 significantly increased escape latency starting from the 2nd acquisition session and haloperidol failed to reverse this effect while both asenapine and paliperidone reversed MK-801 induced increment in the escape latency in the 2nd, 3rd and 4th acquisition sessions in the MWM test. The time spent in the escape platform's quadrant in the probe trial significantly decreased while the mean distance to platform significantly increased in MK-801 group while concurrent administration of asenapine and paliperidone with MK-801 significantly reversed this effect. MK-801 significantly increased the speed of the animals in the MWM test while both asenapine and paliperidone reversed this effect. In the RAM test, MK-801 significantly increased the number of errors and haloperidol failed to reverse this effect while paliperidone and asenapine reversed MK-801-induced increment in a number of errors; improved MK-801 induced prolongation in latency. Paliperidone also reversed MK-801 induced decrement in a number of correct arm choices.

The behavioral syndrome induced by PCP and MK-801 treatment has been suggested to be an animal model of cognitive deficits in schizophrenia [25]. NMDA receptor antagonists produce various dose-dependent motor dysfunctions in rats, which are characterized by locomotor hyperactivity at lower doses and behavioral stereotypes and ataxia at higher doses [26]. All second-generation antipsychotics share potent antagonistic effects at the 5-HT2A, 5-HT2C, and α1-adrenergic receptors. Selective ligands that affect these receptors inhibit locomotor hyperactivity induced by PCP or by the prototypical NMDA antagonist MK-801 [27]. In addition, most typical and atypical antipsychotics reduce hyperactivity and many other behavioral abnormalities produced by non-competitive NMDA receptor antagonist treatment [28]. Antipsychotics with potent 5-HT2A and α1-adrenergic antagonistic activity also readily block PCP- or MK-801-induced hyperactivity [27]. The ability of asenapine and paliperidone to reverse the effects of MK-801 treatment can be explained by a combination of these mechanisms.

Paliperidone, also known as 9-hydroxyrisperidone, is a dopamine antagonist and 5-HT2A antagonist of the atypical antipsychotic class of medications. Paliperidone is used to treat mania and at lower doses as maintenance for bipolar disorder. It is also used for schizophrenia and schizoaffective disorder. Paliperidone is the primary active metabolite of the older antipsychotic risperidone [16]. While its specific mechanism of action is unknown, it is believed paliperidone and risperidone act via similar pathways. Paliperidone has antagonist effect at α1 and α2 adrenergic receptors and at H1 histamine receptors [16]. It does not bind to muscarinic acetylcholine receptors. In addition, it binds with dopamine and serotonin receptors. Asenapine is an atypical antipsychotic developed for the treatment of schizophrenia and acute mania associated with bipolar disorder [17]. Preliminary data indicate that it has minimal anticholinergic and cardiovascular side effects, as well as minimal weight gain. Asenapine shows high affinity for numerous receptors, including the serotonin 5-HT1A, 5-HT1B, 5-HT2A, 5-HT2B, 5-HT2C, 5-HT5A, 5-HT6, and 5-HT7 receptors, the adrenergic α1, α2A, α2B, and α2C receptors, the dopamine D1, D2, D3, and D4 receptors, and the histamine H1 and H2 receptors. It has a much lower affinity for the muscarinic acetylcholine receptors. Asenapine behaves as a partial agonist at the 5-HT1A receptors [17]. Haloperidol is an antipsychotic medication used in the treatment of schizophrenia, acute psychosis, mania, delirium, tics in Tourette syndrome, chorea, nausea and vomiting in palliative care, intractable hiccups, agitation, and severe anxiety [29]. Haloperidol is a butyrophenone derivative and functions as an inverse agonist of dopamine. It is classified as a typical antipsychotic and has pharmacological effects similar to the phenothiazine [29].

The effects of antipsychotics on learning and memory are controversial. Haloperidol and risperidone impair cognition at doses used to treat psychosis, whereas clozapine and sertindole effectively treat psychosis without producing detrimental effects on cognition [9,30]. Haloperidol was also shown to disturb performance in the water maze and delayed-non-match to position performance in rats [30]. It is proposed that atypical antipsychotics are more effective at improving cognitive functions in comparison to classical antipsychotics; however, some studies report no effect of the drugs [31]. The majority of studies show that atypical antipsychotic drugs improve cognitive function [32]; however, studies of typical antipsychotics are controversial [33]. For example, atypical antipsychotics, such as clozapine and olanzapine, attenuate cognitive deficits in schizophrenic patients in comparison to the effects of haloperidol [34].

Antipsychotics targeting the DA D2 receptor may affect the positive symptoms of schizophrenia; however, the actions on non-DA D2 receptors (DA D1, D3, and D4), serotonin receptors (5-HT2A, 5-HT1A, 5- HT3,6,7) and alpha-adrenergic receptors, as well as other neurotransmitter receptors, are hypothesized to be effective against the negative

symptoms of schizophrenia [35]. Effects on several of these receptors and, in particular, the balance between these effects is important for the reversal of MK-801-induced cognitive impairment by asenapine and paliperidone.

The 5-HT2A receptor regulates mesocortical dopamine projections, and the efficacy of atypical antipsychotics to block 5-HT2A receptors within the prefrontal cortex may cause an increase in dopamine transmission and diminish cognitive dysfunctions in schizophrenic patients. Higher 5-HT2A/dopamine D2 receptor affinity is correlated with the successful treatment of the negative symptoms of schizophrenia [36], and these effects may be important for the relief of cognitive deficits. In recent studies, selective ligands for serotonin and adrenoceptors have been examined in various NMDA receptor antagonist-induced animal models of cognitive impairment [37]. In addition, post-training administration of the specific 5-HT7 receptor antagonists SB-269970 and DR-4004 improved MK-801-induced memory impairment in the rat autoshaping task [38]. In our study, asenapine and paliperidone reversed MK-801-induced deficits, possibly through interaction with serotonin receptors and adrenoceptors.

## CONCLUSION

In conclusion, our study revealed that MK-801 exerted spatial memory impairment in MWM and RAM tests; haloperidol failed to improve MK-801 induced memory deterioration in mice. Moreover, both asenapine and paliperidone improve MK-801 induced spatial learning and memory impairment in the MWM and RAM tests.

## DECLARATIONS

### Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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