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# Aripiprazole cognitive effects on attention deficit hyperactivity disorder (ADHD) in experimental mouse model

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## Abstract

**Background:** Attention deficit hyperactivity disorder (ADHD) is one of children's neurodevelopmental psychological disorders with ideal therapy obscure. Aripiprazole is an antipsychotic medication with a unique mechanism of action that enhances dopamine activity in the prefrontal cortex in turn it might executive function in ADHD patients. This study aimed to clarify the impact of aripiprazole on ADHD using a socially isolated (SI) mice model.

**Methods:** In the current study we used early-life SI mice as models for ADHD and tested three different doses of aripiprazole on attention set-shifting performance. The socially Isolated mice are known to have impairment in attentional set-shifting. Socially housed and isolated reared mice across different doses of aripiprazole for each stage were cross-matched for comparison.

**Results:** Socially isolated mice showed selective great deficits in interdimensional discriminations and extradimensional discriminations. Aripiprazole at 3 and 6mg/kg did greatly mitigate the cognition deficits in comparison with placebo and 1 mg/kg of aripiprazole.

**Conclusion:** The current study results emphasise the positive effect of aripiprazole on cognition. Aripiprazole has the potential to be a treatment for ADHD with a psychostimulatory effect.

## KEYWORDS

aripiprazole, ADHD, dopamine, social isolation, schizophrenia, psychostimulant

**How to cite this article:** Qasim H. O., Jabber I. M., Ahmed S. M., Merkhan M. M. Aripiprazole cognitive effects on attention deficit hyperactivity disorder (ADHD) in experimental mouse model. *Rev. Clin. Pharmacol. Pharmacokinet. Int. Ed.* 38 (2): 197-204 (2024).  
DOI: [10.61873/TOZB6842](https://doi.org/10.61873/TOZB6842)

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## 1. INTRODUCTION

Attentional deficit hyperactive disorder (ADHD) is the most encountered neurodevelopmental psychological in children with an incidence of 2-7% of school-age children. ADHD causes great social, well-being and economic burden on both the family and society [1,2]. Although, ADHD is mainly a childhood psychological disorder, 60-80% of patients continue to show symptoms of ADHD during adulthood [3]. The symptoms of ADHD are not lim-

ited to attention deficit and hyperactivity but also impulsivity and impairment in executive cognition function. The later symptoms are related to the delayed maturation of the prefrontal cortex and circuitry to stria tum. Psychostimulants are the first line treatment for ADHD, as they paradoxically decrease hyperactivity, however, several studies support the concern regarding the long-term effect of using psychostimulants on the developing nervous system, in addition to the potential of causing drug abuse (one of the comorbidities of ADHD) [4,5].

Aripiprazole is an atypical antipsychotic medication that is primarily used to treat schizophrenia, bipolar disorder, and major depressive disorder aripiprazole is a second-generation antipsychotic medicine that was approved by the FDA for the treatment of schizophrenia symptoms in November 2002 [6]. It has very unique mechanism of action it is the first antipsychotic partial D2 receptor agonist which stimulates the D2 receptor in the prefrontal cortex which might enhance both cognitive and negative symptoms. In addition, aripiprazole has several distinctive agonist activities on D3 and serotonin 5-HT1A receptors while blocking the 5-HT2A receptor [7,8]. The selective increase in prefrontal cortex dopamine level by aripiprazole can have the same effect as psychostimulants however without stimulating dopamine receptors in the peripheral or other parts of the central nervous system. The previously mentioned receptor binding profile provides aripiprazole with a favorable adverse effect profile. Although the incidence very low when compared to typical antipsychotics, aripiprazole use has been associated with tardive dyskinesia in some patients has been reported. Several clinical reports showed that aripiprazole can induce hyperprolactinemia in patients but with a much lower incidence in comparison with typical and atypical antipsychotics. Aripiprazole also has a minimum metabolic undue effect when compared with olanzapine, risperidone and other atypical antipsychotics.

The adverse early life events for instant social isolation, maternal separation and abuse affect both structural and functional normal neurodevelopment and their behaviour during their adulthood. Early life social isolation mice have been proposed as an animal model for many neuropsychiatric disorders such as ADHD, depression and anxiety [9,10]. Several studies showed that postweaning social isolation for more the one week induces many behavioural and neurochemical abnormalities including attention deficit, impaired social interaction behaviour, and weakened conditional fear memories [11].

Attentional-set shifting performance in ADHD adult patients reported by Luna-Rodriguez et al.

(2018) study on behavioural brain function journal, patients with ADHD showed slowness in task with switch trials in comparison with control subjects with a simultaneous shift of attention between global and local attentional set [12]. Another study on children with ADHD showed executive functioning deficits represented by the impaired performance of shifting set tasks [13]. One of the face validity of socially isolated mice for modelling ADHD is the attentional set-shifting task impairment [14]. In a study conducted by Ouchi et al. (2013), who confirmed that social isolation-induced attention and hyperactivity deficits indicated by impaired latent learning performance in the water-finding test, impaired mice cognitive performance in a way which is similar to ADHD symptoms, the researchers also found out that methylphenidate-HCl and caffeine monohydrate reduced these deficits compared to mice in the control group [15]. Moreover, several studies have reported that social isolation-induced symptoms that mimic ADHD confirmed by novel object recognition test, 3-chamber test, social interaction test in the open field, and a resident-intruder-based social interaction test [16-20].

Aripiprazole is not typically used as a treatment for attention deficit hyperactivity disorder (ADHD), as other medications are more commonly used for this condition. However, some studies have explored the use of aripiprazole in the treatment of ADHD. Earlier studies reviewed studies conducted on children adolescents, and adults, who were unresponsive to other ADHD medications, and responded efficiently to aripiprazole in reducing ADHD symptoms [21], moreover, similar outcomes were reported in youth (8-12 years) study [22], despite their efficacy, aripiprazole used in ADHD is off-label.

In the current study, we used the attentional set-shifting paradigm to verify the adverse effect of social isolation rearing on cognition flexibility and then tested the hypothesis of aripiprazole's potential treatment for ADHD by using early-life socially isolated mice as an animal model for ADHD.

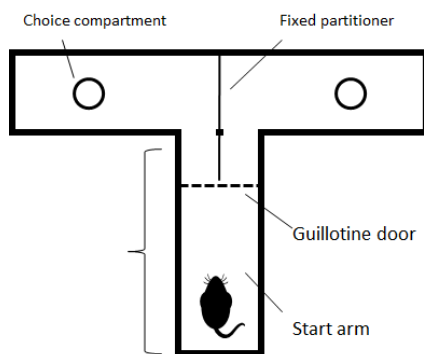
## 2. MATERIALS AND METHODS

*Subjects:* In total 49 mice involved in this study were divided into 5 groups. All mice that participated in this study were 3 months white Albino male BALB/c weighing 30-45g. The mice were kindly provided by the Center of Technical Research (Northern Technical University, Mosul). The registration and approval of the present study have been recorded in the Technical Institute of Polytechnic University (Department of Pharmacy (Approval Letter 16 on 06 July 2022)). Before starting the experiments, the

mice were housed under standard conditions of free access to food and water *ad libitum*, 12h-light-dark cycle, the temperature was controlled other the day between 21-24C°, and humidity about 45-50%.

The first group consists of 9 socially reared mice, and the rest of the groups consist of 10 mice housed individually in non-transparent cages. The socially isolated mice were individually housed after weaning (at age 21 days after birth). All mice were housed in a temperature-controlled environment between 21-24 C° and humidity of 45-50% were maintained. All experiments were performed in dim light to reduce anxiety after habituating mice to a testing room for one hour. Isolation-reared mice could hear and smell other mice in the same room but could not see or come into any physical or social interaction with other mice. Mouse body weight was reduced to 90% of their original body weight by restricting the food intake while water access was *ad libitum*. Aripiprazole was commercially purchased and crushed using mortar and pestle then suspended and diluted in 5% of hydroxypropyl beta cyclodextrin solution. All doses (saline, 1, 3, 6 mg/kg) of aripiprazole were given by gavage 1 hour before commencing the test each day for each stage of the attentional set-shifting test. Each mouse was tested once and the result mean of mice was averaged.

**Apparatus:** The apparatus used in the attentional-set shifting is a modification of those previously described by Young et al. (2011), attentional-set shifting task [23]. Mice were trained to retrieve food pellets by digging into small cups. The apparatus is a T-maze with black plexiglass walls and transparent dividers (Figure 1). Two equal-sized choice arms (10\*30) which can be accessed through a guillotine-like door from the starting arm. Two identical cups were used in this apparatus, one cup in each choice arm which could be baited with a small food pellet and covered with a non-scented medium.



**Figure 1.** Apparatus used for attentional-set shifting task.

All mice were trained in the attentional set-shifting procedure as reported in previous studies with few modifications [23-25]. After mice reach 90% of their free feeding weight due to diet restriction, they are exposed to a T maze (which is used for an additional set shifting arena) over three days for habituation and training in the baited ceramic cups to get their tasty sugar-coated cheerios cereal (approximately 5 mg) which used as reward latter, in addition to the olfactory cues or visual and somatosensory cues (shape and texture of digging media). The odours used for the olfactory cue are (Table 1) extracts of vanilla, caramel, orange, lemon, almond and mint while for somatosensory and visual cues we used small pieces of Polystyrene, Cotton balls, Aquarium stone, Coarse Sand, feather, and rubber pellets. The testing arena was made using black Plexiglas and was cleaned by spring diluted bleach between trials to eliminate an odour cue.

**Table 1.** Exemplars (odour, and media) pairs are used for attentional-set shifting tasks.

Stimulus pairs			
Pair	Exemplar	Odor	Medium
1	1	Vanilla	Polystyrene
	2	caramel	Cotton balls
2	3	Orange	Aquarium stones
	4	Lemon	Coarse sand
3	5	Almond	Feather
	6	mint	Rubber pellets

In the first four trials, the mice were placed gently in the T maze testing arena for free exploring the two small coffee cups which were fixed to the floor of the T maze double-face adhesive tape, until one bowl to report choice (dig on medium and retrieve it's reward) and their respond was recorded. Wood chips were mixed with 100 microliters of odour. The mice went through a series of discriminations where the exemplar pair was altered, but the dimension for the correct pick was unaltered. The discriminations (Table 2) were started with simple discriminations where the mouse commenced the trial by being presented to a testing arena containing two resemble cups with different odours in each arm of the T maze one scented cup was the correct choice and its location was changed randomly between left or right arm while the other cup (which is same for the simple discrimination trials) scented with different odour and not baited and considered incorrect choice. The mouse has to choose the correct choice relying on the odor for 6 consecutive trails. The next stage is compound discrimination in which the mice have to find food pellets in the correct choice by associating it with smell when relevant and ignoring the shape and texture of the bowl when it is irrelevant and vice versa. The third stage is the interdimensional shifts

in which the mouse has to do the same as compound discrimination but with totally novel exemplars (odour). The fourth stage is reversal discrimination where the relevant correct exemplar (odour) turned to be relevant and incorrect while the incorrect choice turns incorrect. The fifth stage is the extradimensional shift where the mouse needs to shift its attention from the previously relevant exemplar (odour) to the previously irrelevant exemplar (shape and texture of the coffee cup). All data were reported on how many trials to criterion, latency to choose and count for errors committed for each discrimination.

**Table 2.** This table shows the combinations used as exemplars.

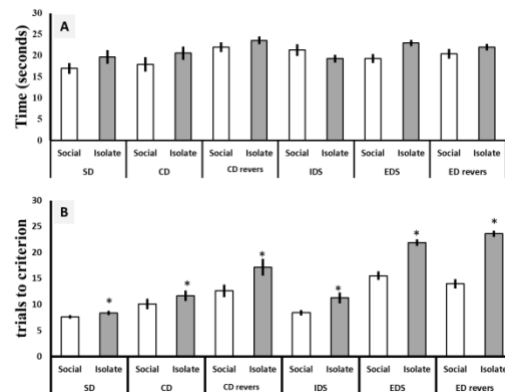
Task	Dimension		Medium	
	Relevant	Irrelevant	Correct	Incorrect
SD	O	M	O1,M1	O2,M1
CD	O	M	O1,M1,M2	O2,M1,M2
CD reversal	O	M	O2,M1,M2	O2,M1,M3
IDS	O	M	O3,M3,M4	O4,M3,M4
EDS	M	O	M5,O5,O6	M6,O5,O6
EDS reversal	M	O	M6,O5,O6	M5,O5,O6

O=Odor, M=Medium, SD=single discrimination, CD=compound discrimination, IDS=intra-dimensional shift, EDS=extra-dimensional shift

**Statistics:** All graphs and data are reported as the mean  $\pm$  SEM. A one-way ANOVA test was used to analyze the difference between isolation-reared and socially housed mice. Also, one-way ANOVA was used to reveal statistical significance between different aripiprazole dose groups, which was followed by Bonferroni correction post hoc analysis. GraphPad software was used to perform this analysis.  $P < 0.05$  is considered as statistical significance.

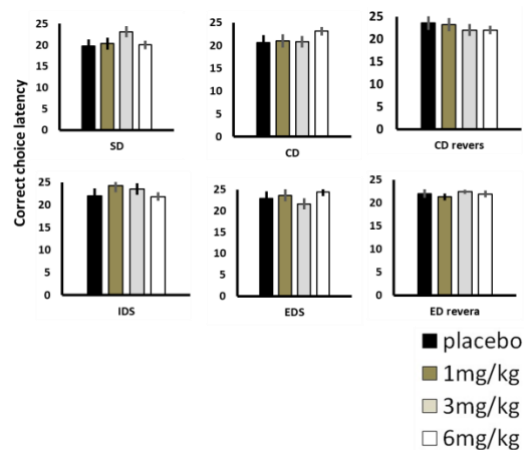
### 3. RESULTS

**Isolation reared effect on attentional set-shifting:** As shown in Figure 2A, two-way mixed model ANOVA analysis results showed no significant difference interaction between the discrimination stage and rearing condition ( $F(5, 85) = 1.166$ ;  $P = 3.333$ ), however, the discrimination stage shown a significant difference ( $F(1, 17) = 13.30$ ;  $P < 0.05$ ) also rearing condition as a factor shown a significant difference in the time required to choose the baited (correct) bowl ( $F(5, 85) = 2.932$ ;  $P < 0.05$ ). The result of the two-ANOVA test for trials to criterion (Figure 2B) showed a significant difference in the rearing condition ( $F(1, 17) = 54.92$ ;  $P < 0.05$ ) and discrimination stage ( $F(5, 85) = 52.02$ ;  $P < 0.05$ ) also the analysis showed a significant interaction between rearing condition and discrimination set ( $F(5, 85) = 6.607$ ;  $P < 0.05$ ). Mice reared in isolation showed a deficit in reversing the set of discrimination.



**Figure 2.** (A) The differences in correct choice latency in second between socially housed and isolation-reared mice. (B) The difference between socially reared mice and isolation reared mice in the attentional set-shifting task. A Significant difference in interdimensional reversal and extradimensional reversal. Data expressed as mean $\pm$ SD. \*indicates significant differences at  $p < 0.05$  compared to other groups using one-way ANOVA followed by Bonferroni post hoc analysis. SD=single discrimination, CD=compound discrimination, IDS=intra-dimensional shift, EDS=extra-dimensional shift.

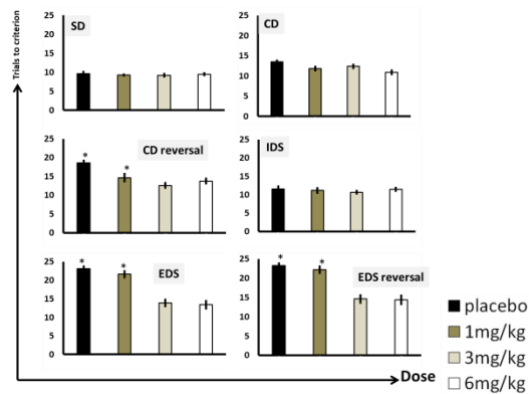
**Aripiprazole effects on socially isolated mice deficit on attentional set-shifting:** As mentioned earlier, all mice which were involved in the experiment are socially isolated. Different doses of aripiprazole (Figure 3) didn't significantly affect the time needed to pick the correct bowl ( $F(2.675, 144.5) = 0.3312$ ;  $P = 0.7798$ ).



**Figure 3.** Effect of aripiprazole on correct choice latency. Data expressed as mean $\pm$ SD. \*indicates significant differences at  $p < 0.05$  compared to other groups using one-way ANOVA followed by Bonferroni post hoc analysis. SD=single discrimination, CD=compound discrimination, IDS=intra-dimensional shift, EDS=extra-dimensional shift

On the other hand, there is a significant difference

between different aripiprazole doses ( $F(5,54)=64.02$ ;  $P<0.05$ ). The post hoc analysis showed that isolation-rearing mice administering aripiprazole (at doses 3mg/kg and 6mg/kg) needed significantly fewer trials to reach the criterion in both CD reversal, EDS, and EDS reversal with no differences in trial criterion for SD, CD, and IDS (Figure 4).



**Figure 4.** The effect of different doses of aripiprazole on different stages of attentional set-shifting. Data expressed as mean $\pm$ SD. \*indicates significant differences at  $p<0.05$  compared to other groups using one-way ANOVA followed by Bonferroni post hoc analysis. SD=single discrimination, CD=compound discrimination, IDS=intra-dimensional shift, EDS=extra-dimensional shift

#### 4. DISCUSSION

In the current study, isolation-reared mice showed a significant deficit when tested in the attentional set-shifting task, especially in both interdimensional reversal and extradimensional reversal which might resemble deficits in patients with ADHD. In addition, aripiprazole at both 3 mg/kg and 6 mg/kg doses mitigates this deficit.

ADHD is the most encountered neurodevelopmental psychological disorder in children. The first line treatment of for ADHD is psychostimulants, however, there is a significant percentage of these patients do not respond well to psychostimulants. Psychostimulants' paradoxical effects on ADHD patients are due to the elevation of dopamine in the ADHD prefrontal cortex but not serotonin or norepinephrine [26]. The later result implies that a selective increase in dopamine activity in the prefrontal cortex is essential for the mitigation of ADHD symptoms while an increase in dopamine release in the striatum and other tissues might be responsible for psychostimulants and verse effects [5,27].

Consistently several treatments were developed like guanfacine and atomoxetine which are

not psychostimulants, however, with less efficacy. Indeed, the development of new treatments is of great need. One of the intriguing findings of this study was the pattern of attentional set-shifting task deficit in socially isolated mice was in parallel with another model of ADHD spontaneous hypertensive rat [28], while the model for schizophrenia is more about extradimensional discrimination in attentional set-shifting task [29].

Research has shown that aripiprazole may have a positive effect on cognitive function in the phencyclidine model for schizophrenia in a 5-choice serial reaction task [30]. A study conducted by Keck (2006) has found that aripiprazole improved cognitive function, including memory, attention, and executive function, in patients with schizophrenia who were experiencing cognitive defects [31]. Another study by Riedel et al. (2010) found that aripiprazole improved cognitive flexibility and working memory in patients with schizophrenia [32]. The study also found that aripiprazole improved social cognition, which is the ability to understand and respond to social cues, in patients with schizophrenia. In addition to its effects on cognition in patients with schizophrenia, aripiprazole may also enhance cognition in patients with bipolar disorder. A study found that aripiprazole improved cognitive function, particularly attention and processing speed, in patients with bipolar disorder who were experiencing cognitive deficits [33].

The hyperactivity in children with ADHD is an additional upsetting feature, so drug therapy should tackle the hyperactivity alongside attention deficit. Aripiprazole (to a lesser extent cariprazine which is an analogue of aripiprazole) has both reduced hyperactivity [22,30,34]. This impact has been explained in the context that aripiprazole and cariprazine have diverse pharmacological activity related to their receptor interaction at dopamine and serotonin receptors. Since, unlike absolute serotonin and dopamine receptor blockers (clozapine, quetiapine, and olanzapine) [35-38], both aripiprazole and cariprazine partial agonists at dopamine receptors and serotonin 5-HT<sub>1A</sub> receptors and antagonists at 5-HT<sub>2A</sub> receptors [39]. Moreover, aripiprazole has shown a great impact on schizophrenia-associated cognitive deficits [32] and bipolar-associated cognitive deficits [33].

#### 5. CONCLUSION

Social isolation impairs male mice's performance in attentional set-shifting tasks. Specifically on reversal stages which indicate the impairment of the ability of reversing the set of attention after they were formed. On the other hand, aripiprazole par-

tially this deficit. Aripiprazole has a potential for ADHD treatment through enhancing cognition flexibility.

#### CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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