Effects of Separate and Combined Chronic Ingestion of Promothazine and Haloperidol on Memory and Learning Behaviour of Male Wister Albino Rats

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Abstract
The recent increase in the use and abuse of substances such as antipsychotic drugs like haloperidol and promethazine, is a source of research concern. This study, therefore, examined the effects of chronic exposure to separate and combined ingestion of haloperidol and promethazine on memory and spatial learning behaviour in albino rats. Twenty-four (24) male albino rats weighing between 180-200g were used for this study. They were divided into 4 experimental groups of haloperidol, Promethazine combined haloperidol and promethazine and control groups with 6 rats in each group. The rats were exposed to chronic treatment of haloperidol and promethazine at doses of 1mg/kg and 1.1mg/kg bodyweight respectively for 28 days and run on the Y-Maze for spatial learning and memory on each day of the experiment. Randomized block ANOVA was used to analyse the data. Promethazine did not significantly affect spatial learning behavior and memory of rats F (1, 332) = .21, p > 0.05, ç²= .00. Haloperidol had significant effect on learning, F (1, 332) = 4.89, p < 0.001, ç²= .02. Combined treatment of haloperidol and promethazine did not significantly affect learning in the male rats F (1, 332) = .766, p >0.05, ç²= .00. On the average, the male rats in the control group learning time were ($\bar{x} = 49.45$), While the fastest learning average was recorded for haloperidol group (34.37), followed by the group in combined drugs situation (41,25) and Promethazine alone (52.29) It was concluded that chronic exposure to Promethazine and haloperidol has implications for exploratory learning and memory deficits.

Keywords: Memory, Learning Behavior, Promethazine, Haloperidol, Male albino rats

Introduction

Studies have documented the effects of drugs on behaviours generally (e.g. Balogun et al 2025, a, b; Balogun, et al, 2020a,b) These behaviours range from grooming, feeding, learning and to aggression, just to mention a few. They also involve use of different drugs singularly or in combination. The general concern in the modern world is the use of combination of drugs effects, otherwise known as synergism, among adolescents and youths which is on the increase (Jentsch, & Taylor, 1999; Everitt, & Robbins, 2005). Use of single drugs seems not to be having desired effects by these young ones, hence the resort to use of multiple drugs.

Balogun, et al, (2020 a, b), and Balogun et al (2025a, b), have demonstrate the effects of these practices of separate and combined effects on learning behaviour, feeding behaviour, aggressive behaviour and so on. Another concern, in the present study, is the gender differentials on how these separate and combined use of drugs affect behaviour, particularly on learning among male rats. The effects on combined ingestion of codeine and tramadol on learning among female rats has been reported elsewhere by Balogun, et al (2020a). We know that gender reactions to drugs in behavioural and physiological compositions do exist (Dunne et al., 1993). For example, Frezza et al. (1990) observed that women become intoxicated after drinking smaller quantities of alcohol than men because of physiological differences between the genders (women have less total body water than men).

Balogun et al (2025a) observed that combining drugs, especially psychoactive drugs, do have their physiological, physical and psychological consequences, and this is worrisome enough to warrant continuous interrogation by every stakeholder in human health. This is because certain behavioural reactions to substance use can become habitual (addictive), tending towards compulsive-obsessive, as observed by Grant et al. (2010).

Several behaviours, besides psychoactive substance ingestion, produce short-term rewards that may engender persistent behaviour, despite knowledge of adverse consequences, i.e., diminished control over the behaviour.

Learning involves consciously or nonconsciously attending to relevant aspects of incoming information, mentally organizing the information into a coherent cognitive representation, and integrating it with relevant existing knowledge activated from long-term memory (APA, 2018) Learning is an important aspect of human behavior; all living persons interact with and are influenced by their surroundings on a daily basis, making the environment an important role in learning.

Memory, or the ability to remember and recall prior experiences and learned information, is critical to human survival. Memory problems can develop as a result of natural aging (mild cognitive impairment), neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease (Lang et al., 2020), or psychiatric disorders such as severe depressive illness and schizophrenia (Sawamoto et al., 2008; Lang et al., 2020). Medication-induced memory loss is also possible. In this context, antipsychotic drugs used to treat schizophrenia have been linked to memory impairment; this is more noticeable with traditional antipsychotics like haloperidol, as opposed to atypical or newer generation antipsychotics that are thought to act via both D2 and 5HT2A receptor antagonism (Beuzen et al., 2016; Houthoofd et al., 2008; Gemperle et al., 2003).

Haloperidol decreases learning and memory function in both humans and animals. Chronic use of haloperidol, a high-affinity D2 postsynaptic receptor blocker, has been linked to behavioral changes. Despite improving positive symptoms in schizophrenia, haloperidol concurrently decreases dopaminergic function in the already hypodopaminergic frontal cortex and decreases the expression of D1 receptors in the prefrontal cortex (Babin et al., 2011), both of which are essential for executive functions such as attention and working memory (Chudasama & Robbins, 2006). Thus, studies have shown that haloperidol impairs spatial working memory performance and planning ability in healthy volunteers (Rosengarten & Quartermain, 2002; Lustig et al., 2005) and worsens recent autobiographical memory scores in Alzheimer's disease patients (Lustig et al., 2005). Haloperidol reduced memory recall in experimental rats both in water-maze challenge and a step-through test (Terry et al., 2002; Hou et al., 2006; Abdel-Salam & Nada, 2011)

Promethazine is a histamine (H1) receptor antagonist and phenothiazine derivative. It is also a direct antagonist at the muscarinic (M1) and dopamine (D2) receptors (Sharma & Hamelin, 2005; Cookson, 2008). Promethazine is a medication that can be taken alone or in combination with additional components such as dextromethorphan, paracetamol, and/or expectorants. It is a widely available medicine with considerable variations among nations, primarily in Europe and beyond, where some promethazine-containing pharmaceutical treatments can be acquired over-the-counter (OTC).

Promethazine is often used to treat the symptoms of nausea and vomiting, allergic diseases, motion sickness, and the common cold, as well as for the short-term treatment of sleeplessness in adults or as a paediatric sedative ((EMC), 2019). It is classed as a first-generation antihistamine molecule, which penetrates the blood-brain barrier more easily than second-generation antihistamines and is associated with side effects such as moderate/intense drowsiness (Jensen et al., 2017). As a result of its inhibiting action at H1 and M receptors, promethazine could be employed in acute tranquilization (Cookson, 2008). Toxicity may induce severe impairment of cognitive and psychomotor functioning as a result of central nervous system (CNS) depression/ reduced levels of consciousness, and may result in fatalities (Jensen et al., 2017). Promethazine has been linked to a variety of CNS adverse effects, including confusion, disorientation, drowsiness, cardiovascular symptoms, and respiratory depression (Burns & Boyer, 2013; Ellen Tsay et al., 2015).

Promethazine is a drug that is commonly abused and misused, particularly among young adults. Promethazine abuse in co-formulation with various components of OTC cough treatments has been reported to be on the rise among young adult populations (Carney et al., 2018; Carr, 2006). Because of its soothing and sedative properties, first-generation antihistamines such as promethazine and cyclizine have a significant misuse potential (Cookson, 2008; Jensen et al., 2017), and augmentation of other co-ingested compounds, particularly those engaging with gamma-aminobutyric acid (GABA), opiate, and muscarinic acetylcholine receptors, resulting to psychedelic experiences (Clatts et al., 2010 ;Lynch et al., 2015).

Haloperidol is a well-known antipsychotic medication that is commonly used to treat schizophrenic symptoms, manage agitation in patients with acute illness and delirium, and control delusions, hallucinations, agitation, and other disruptive behavioral symptoms associated with Alzheimer's disease. The medicine works by inhibiting dopamine D2 receptors in the prefrontal brain, which causes extrapyramidal side effects. Haloperidol is still a widely used antipsychotic medication. It is on the World Health Organization's (WHO) list of essential medications (Boslaugh, 2016).

Because of the high prescription rate, haloperidol and promethazine research is still important. Only a few rodent studies have looked at the long-term effects of antipsychotic medication on cognition (Bohannon, 2002); (Chesler et al., 2002b; Chesler et al., 2002a) This makes assessing tiny but critical changes in executive performance caused by drugs at multiple time points challenging. This study therefore was designed to experimentally investigate the effect of separate and combined chronic ingestion of promethazine and haloperidol on memory and learning behaviour among male Wister albino rats. The reason for this has been provided by Balogun et.al (2025b), apart from the fact that female behaviour on learning has been documented by Balogun et al (2020a)

Against this background, , the concern in the present study, as a follow-up to Balogun et al. (2020a), was to establish gender differences in reaction to learning behaviour using haloperidol and promethazine. Research indicates that women and men can experience different reactions to substance abuse, with women often reporting greater impairment and a higher risk of relapse, even though men generally have higher rates of substance use overall. These differences can be attributed to biological factors like hormone fluctuations, as well as social and environmental influences impacting how women access and utilize substances compared to men. Men are more likely than women to use almost all types of illicit drugs (NIDA, 2020), but women may be light users of drugs, especially alcohol, and so be binge drinkers, but suffer more psychiatric disorders (Grant et al., 2010; Dunne et al., 1993; Brady & Randall, 1999; Frezza et al. 1990).

Specifically, the research provides answers to the following questions:

(i) Could there be influence of promethazine on learning among the male albino rats?
(ii) Could there be influence of haloperidol on learning among the male albino rats?
(iii) Could there be combined influence of haloperidol and promethazine on learning among male albino rats? g behavior especially in male albino rats?

The following hypotheses were tested to answer the research questions;

1. There will be a significant effect of Promethazine on learning among male albino rats.
2. There will be a significant effect of Haloperidol on learning among male albino rats.
3. There will be a significant combined effect of Promethazine and Haloperidol on male albino rats.

MATERIALS AND METHOD

Research design

The design employed for this research is the independent group randomized design. The independent variables are promethazine and haloperidol, administered at a dose of 1.1mg/kg for promethazine and 1mg/kg for haloperidol. The dependent variable is learning behavior.

Setting

The experimental animal laboratory of the Department of Psychology, University of Ibadan was used for this study.

Participants

A total of 24 female Albino rats weighing between 180 to 200g were used for this study. The rats were randomly assigned into 4 groups with 6 rats in each group of control, Promethazine, haloperidol and promethazine combined with haloperidol. The rats were brought into the laboratory three weeks before the commencement of the study for the purpose of acclimatization. They were housed in North Kent plastic cages and properly fed with adequate food and water. For easy identification, the rats were numbered with markers according to the groupings.

Instruments

The following materials were used in conducting the experiment:

1. Recording sheets
2. Laboratory hand Gloves
3. Nose masks
4. Oral cannula
5. Distilled water
6. Weighing balance
7. North Kent plastic cages
8. Stopwatch/ Timer
9. Mouse cubes
10. Y-maze
11. Promethazine
12. Haloperidol
13. Disinfectants (Dettol)

Procedure

The rats were housed in cages in the laboratory and acclimatized for 21 days before the commencement of the experiment. During this period, food and water were freely available without any form of deprivation. The study commenced with baseline data collection on learning for eight (8) days before treatment started, to erase any plausible explanation for the outcome of the experiment. The rats were randomly assigned into four (4) groups; the control group, the promethazine group, the haloperidol group, the promethazine and haloperidol group, with 6 (six) female rats in each group.

The rats were weighed on each day of the experiment and exposed to the drugs in each of the groups according to their body weight with oral cannula. The rats in the control group were given distilled water. After treatment, the rats were allowed a period of 30 minutes before they were introduced into the Y-Maze to measure memory and learning. This is to allow for enough time for the onset of the action of the drugs. The process was repeated each day for a period of 28 days which was the duration of the experiment.

The rats were allowed to run the maze as a measure of their memory and learning. They were deprived of food a day before the experiment to make them sufficiently hungry to learn the location of food in the Maze. Food was placed in a corner of a Y- maze and the rats were then placed at the starter point of the Y-maze and allowed to run the Maze. Each rat was allowed 10 minutes to run the Maze and were given 3 trials on each day of the experiment. The amount of time the rat spends before reaching the food within the 10 minutes' period was recorded. A period of 24 hours was allowed before the next treatment and data collection. All rats were properly disposed at the end of the experiment.

Results

The effects of separate and combined acute administration of promethazine and haloperidol on memory and learning behaviour among female Wister Albino rats were investigated by this study. The results are presented according to the hypotheses proposed for the study.

The first hypothesis which stated that promethazine ingestion will significantly affect learning behaviour of female Albino Wister rats exposed to the drugs was tested using the Randomized Block ANOVA and the result presented in Table 1.

Table 1a: Summary Randomized Block ANOVA showing the influence of exposure to Chronic intake of Promethazine on Learning behavior

Source	Type III Sum of Squares	Df	Mean Square	F	Sig.	Partial η^2
Block	2668.951	1	2668.951	.568	.452	.002
Weight	293.020	1	293.020	.0624	.803	.000
Treatment	980.942	1	2980.942	.209	.648	.001
Error	1559409.069	332	4697.015			
Corrected Total	71563583.973	335				

The result from Table 1a shows that exposure to chronic intake of anti-psychotic drugs (Promethazine) did not significantly affect the learning behavior of male Albino Rats F (1, 332) = .21, $p > 0.05$, $ç^2$= .00. Further analysis on the mean differences was carried out with descriptive statistics and LSD post hoc multiple comparison Test and the result presented in Table ib.

Table 1b: Summary of descriptive statistics and LSD post hoc comparison analysis showing the mean difference in spatial learning and memory between rats exposed to acute intake of anti-psychotic drugs (Promethazine) and those exposed to Normal saline

	Mean	S.E.M	LSD POST HOC	Sig.
Promethazine	52.294[a]	5.435	3.61	.65
Control	48,689[a]	5.435		

*. The mean difference is significant at the .05 level.

a. Covariates appearing in the model are evaluated at the following values:
WEIGHT = 3.1490, Days = 7.5000.

From the analysis, in the table 1b above, the mean differences showed that rats ingested with Promethazine ($\bar{x} = 52.29^a$) displayed slower spatial learning and memory function compared to rats in the control (48.69^a). The mean difference was not significant. Based on this, hypothesis which states that there will be a significant difference in learning behaviour among male rats ingested with different drugs is thus rejected.

The second hypothesis which stated that Haloperidol ingestion will significantly impact on the learning behaviour of female Albino Wistar rats exposed to the drug compared to the control was tested using the Randomized Block ANOVA and the result presented in Table 3.

Table 2a: Summary Randomized Block ANOVA table showing the influence exposure to chronic intake of on spatial learning behaviour.

Source	Type I II Sum of Squares	Df	Mean Square	F	Sig.	Partial η^2
Block	36661.825	1	36661.825	9.365	.002	.027
Weight	13277.649	1	13277.649	3.392	.006	.010
Treatment	19132.856	1	19132.856	4.887	.4028	.015
Error	1299676.413	332	3914.688			
Corrected Total	1352615.702	335				

The result from table 2a shows that exposure to chronic intake of anti-psychotic drugs (Haloperidol) significantly affected learning behavior among male Albino Rats F (1, 332) = 4.89, $p < 0.001$, $ç^2 = .02$. Further analysis on the mean differences was carried out with descriptive statistics and LSD post hoc multiple comparison Test and the result presented in Table 2b.

Table 2b: Summary of descriptive statistics and LSD post hoc comparison analysis showing the mean difference in learning behavior between rats exposed to acute intake of anti-psychotic drug (Haloperidol) and those exposed to Normal saline

	Mean	S.E.M	LSD POST HOC	Sig.
Haloperidol	34.371[a]	4.898	15.53	.000
Control	49.903[a]	4.898		

*. The mean difference is significant at the .05 level.

a. Covariates appearing in the model are evaluated at the following values: weight = 108.7113, Da = 14.5000.

From the analysis in the table 2b above mean differences showed that rats in the control ($\bar{x} =$ 34.37) significantly displayed slower spatial learning and memory compared to rats ingested with Haloperidol (49.90). The mean difference was significant. Based on this, hypothesis states that there will be a significant difference in learning behaviour among males rats ingested with different drugs is thus accepted.

The third hypothesis which stated that Promethazine and Haloperidol ingestion will jointly interact to affect the learning behaviour of female Wister Albino rats exposed to the drugs was tested using the Randomized Block ANOVA and the result presented in Table 3a.

Table 3a: Summary Randomized Block ANOVA table showing the influence of exposure to acute intake of anti-psychotic drugs (Haloperidol & Promethazine) on learning behaviour of male Wister Albino rats

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial η^2
Block	10341.648	1	10341.648	2.233	.136	.001
Weight	28838.096	1	28838.096	6.228	.013	.002
Treatment	3549.026	1	3549.026	.766	.382	.001
Error	1537288.638	332	4630.387			
Corrected Total	1577795.988	335				

The result from table 3a reveals that exposure to chronic intake of anti-psychotic drugs (Haloperidol & Promethazine) did not significantly affect learning behaviour among Albino Rats F (1, 332) = .766, $p > 0.05$, $ç^2 = .00$. As demonstrated spatial learning time improve by 2% with ingestion of anti-psychotic drugs. Further analysis on the mean differences was carried

out with descriptive statistics and LSD post hoc multiple comparison Test and the result presented in Table 3b.

Table 3b: Summary of descriptive statistics and LSD post hoc comparison analysis Reaction time showing the mean difference between rats exposed to acute intake of anti-psychotic drugs (Haloperidol & Promethazine) and those not exposed (Control).

	Mean	S.E.M	LSD POST HOC	Sig.
Control	47.763[a]	5.256	6.51	.32
Combined(Haloperidol + Promethazine)	41.249[a]	5.256		

*. The mean difference is significant at the .05 level.

a. Covariates appearing in the model are evaluated at the following values: Days = 7.7000, weight = 3.1490.

From the analysis, the rats in the control ($\bar{x} = 47.76$) have slower learning time compared to rats ingested with anti-psychotic drugs combination (Haloperidol + Promethazine (41.25). The mean difference was not significant. Based on this, hypothesis which states that there will be a significant difference in spatial learning behavior among male Albino Wister rats ingested with Haloperidol and Promethazine is thus rejected.

Discussion

Results in this study revealed that there was no significant effect of promethazine on learning. This is in line with the findings of Balogun, et.al.(2022) where the same drug (Promethazine) did not affect learning in female rats. This goes to show that there was no gender differences in learning when it comes to use or abuse of antipsychotic drugs.

Promethazine is used as a muscle relaxant and in the treatment of motion sickness, among other things. Because of its antimuscarinic and relaxant actions, it may be utilized to treat severe cases of motor rigidity and mobility problems in patients experiencing haloperidol motor side effects in some cases. Promethazine is a histamine H1 receptor antagonist that has been shown to perform actions that are not induced by histamine blockage (Valentine et al., 2016; Stein & Strickland, 1998), including substantial antimuscarinic effects, which are required for the treatment of Parkinson's motor symptoms.

We observed from this study also, that exposure to chronic intake of haloperidol have significant effect on the learning behavior among male Albino Rats. The male Albino rats in the control (x = 49.90) significantly displayed slower spatial learning and memory compared to male Albino rats ingested with haloperidol (x = 34.37). There are similar research reports in line with the findings of this study. Marwari & Dawe, (2019), investigated the effects of chronic haloperidol treatment on spatial place learning in a social home cage environment and found that, haloperidol-treated mice learned better than control mice. It can then be concluded that haloperidol medication can improve learning particularly when there is the presence of motivational object (like the food placement in the Y-maze). As observed by Balogun et. al (2022), one possible explanation is that haloperidol inhibits the mechanisms by which reward reinforces learning, as confirmed by Soares-Cunha et al., (2016) and Cole et al., (2018). Meanwhile, haloperidol's other activities may be mediating the gain in learning. Some studies have found that haloperidol at 4 mg/kg/day produces similar increases in locus coeruleus tyrosine hydroxylase activity and immediate early gene activation as atypical antipsychotics (Verma et al., 2007). Atypical antipsychotics have been demonstrated to boost locus coeruleus activity and tyrosine hydroxylase expression (Dawe et al., 2001), as well as locus coeruleus-mediated enhancements in long-term potentiation and noradrenergic-mediated improvements in spatial working memory (Lim et al., 2007). The mechanisms of haloperidol-induced cognitive function remain unknown, but they may be clinically relevant because haloperidol-associated improvements in cognitive function have been described in first-episode patients treated with lower haloperidol dosages (Keefe et al., 2009; Harvey et al., 2005).

The combined effect of promethazine and haloperidol enhanced learning (X= 41.25) when compared to the control group (X= 49.96), this difference was negligible a it did not approach

significant level. Though Balogun, et al (2022) reported a significant enhancement capacity of the combined drugs, on learning, among females rats, the difference observed in the present study was not significant , probably confirming gender differentials in reaction to the two drugs as expected (Balogun, et al 2025b) as a result of physiological composition of females and males. There have been discrepancies in the reported effects of neuroleptic medications on cognitive and psychomotor function in both patients and healthy controls. (Balogun, et al 2022; Cole et al., 2018) More research is however, needed as studies(e.g. Scheuer et al., 2006; Mishara & Goldberg, 2004) have demonstrated the encouraging effects of some drugs on cognitive and motor activities sucg as the design of the present study adopted.

Conclusion

In conclusion, the effect of chronic haloperidol and promethazine administration on spatial learning and memory in male wister albino rats was investigated. The current study shows that promethazine alone and/or a combination of haloperidol and promethazine promethazine have no effect on learning behaviour when administered but haloperidol alone increased learning behaviour. A cursory look at the means across board revealed that the drugs either singularly or in combination affected learning but in different degrees. Promethazine lowered memory and learning more than combined drugs, followed by haloperidol alone respectively. It was like haloperidol alone group enhanced learning than all other groups including the control group. No matter the supposed advantage in learning by using haloperidol group, the long term effect of drug itself should not be encouraged, Adequate policy on the use of haloperidol and promethazine should be adequately publicized with enough awareness for youths and all stakeholders.

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