Effects of separate and combined chronic ingestion of promethazine and haloperidol on learning behaviour among female Wister albino rats

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Abstract

Increase in the use of neuroleptic medications and reported discrepancies in their effects on cognitive and psychomotor function are a research concern. Haloperidol and promethazine are used commonly and are among the over-the-counter prescribed drugs in Nigeria. This study examined the effects of chronic administration of haloperidol and promethazine on spatial learning behavior and memory among female albino rats. A total of 24 female Albino rats weighing between 180 to 200g were randomly assigned into four groups of control containing 6 rats each. Promethazine, haloperidol and promethazine combined with haloperidol, were used for this study. 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. Promethazine did not significantly affect spatial learning behavior and memory of female Albino Rats $F(1, 332) = .13$, $p > 0.05$, $\eta^2 = .00$ as well as haloperidol $F(1, 332) = 53$, $p > 0.05$, $\eta^2 = .00$. Combined treatment of haloperidol and promethazine significantly affected spatial learning behavior and memory among the female albino rats $F(1, 332) = 4.58$, $p < 0.05$, $\eta^2 = .02$. Female albino rats in the control (148.24) had slower learning time compared to female rats ingested with a combination haloperidol and Promethazine (118.01). It is concluded that combined treatment of haloperidol and promethazine significantly affected learning behaviour but none with separate treatment. The dose of exposure of the haloperidol and promethazine should be studied further to establish the memory and learning deficit claims for the drugs.

Keywords: Haloperidol, promethazine, learning behaviour, female albino rats

Introduction

The ability to learn is held by all animals, including human beings, and there is evidence that certain plants can learn (de Houwer et al., 2013). Learning is defined by de Houwer et al., (2013) as an adaptive function in which the neural system changes in reaction to environmental stimuli, hence modifying behavioral responses and allowing humans and animals to function in their environment. 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 part of learning. The nervous system initiates the learning process in response to environmental cues. Our behavioral reactions can be changed when neural circuits are strengthened, pruned, activated, or rerouted. Learning is a continual process that begins at birth and continues until one's death. To put it another way, education never ends. Humans and animals alike are involved in learning activities in order to build adaptive abilities in response to changing environmental conditions.

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 (Lang et al., 2020; Sawamoto et al., 2008). 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; Gemperle et al., 2003; Houthoofd et al., 2008).

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).

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 these parts of the brain are however 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 step-through test (

Abdel-Salam & Nada, 2011; Hou et al., 2006; Terry et al., 2002)

Promethazine is a histamine (H1) receptor antagonist and phenothiazine derivative. It is also a direct antagonist at the muscarinic (M1) and dopamine (D2) receptors (Cookson, 2008; Sharma & Hamelin, 2005). 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 histamine (H1) and muscarinic (M1) 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). 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 minimal but critical changes in executive performance caused by drugs at multiple time points challenging. Studies on gender differences on the effect of haloperidol and promethazine are scanty. In one study, Arenas et al., (1995) established the existence of gender differences in haloperidol effects on avoidance conditioning in mice and suggested that these differences are related to the learning process and not only to the impairment of motor behavior characteristic of neuroleptic drugs. This study therefore was designed to experimentally investigate the effect of separate and combined chronic ingestion of promethazine and haloperidol on learning behaviour among female Wister albino rats. Specifically, the research will provide answers to the following questions:

(i) Will chronic administration of Promethazine have an effect on

learning behavior especially in female albino rats?

(ii) Will chronic administration of Haloperidol have an effect on learning behaviour especially in female albino rats?

(iii) Will chronic administration of a combination of both drugs (promethazine and haloperidol) have an effect on learning behavior especially in female albino rats?

The following hypotheses were tested to answer the research questions;

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

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. The animal laboratory is a controlled environment for feeding, observations and twenty-four-hours night and day light control for animal experiments.

Subjects

A total of 24 female Albino rats weighing between 180 to 200g were used. 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 learning behaviour. 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 was 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 is 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 chronic administration of promethazine and haloperidol on 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 would significantly affect learning behaviour of female Wister albino rats exposed to the drugs was tested using the Randomized Block ANOVA and the result is presented in Table 1.

Table 1: Summary Randomized Block ANOVA table showing the influence of exposure to acute intake of anti-psychotic drugs (Promethazine) on learning behavior

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial η^2
Block	263681.449	1	263681.449	13.029	.000	.038
Weight	21728.594	1	21728.594	1.074	.301	.003
Treatment	2561.227	1	2561.227	0.127	.722	.000
Error	6719015.664	332	20237.999			
Corrected Total	7103234.640	335				

The result from Table 1 shows that exposure to chronic intake of anti-psychotic drugs (Promethazine) did not significantly affect the learning behavior of female Albino Rats $F(1, 332) = 0.13$, $p > 0.05$, $\eta^2 = .00$. Further analysis on the mean differences was carried out with descriptive statistics and LSD post hoc multiple comparison Test. The result presented in Table 2.

Table 2: Summary of descriptive statistics and LSD post hoc comparison analysis showing the mean difference in learning behaviour between rats exposed to chronic intake of anti-psychotic drugs (Promethazine) and those exposed to normal saline

	Mean	S.E.M	LSD POST HOC	Sig.
Promethazine	155.489[a]	11.033	5.58	.72

Control	149.910[a]	11.033

**. 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, mean differences showed that rats ingested with Promethazine (155.489[a]) displayed slower spatial learning and memory function compared to rats in the control (149.910[a]). The mean difference was not significant. Based on this, hypothesis which states that there will be a significant difference in learning behaviour among females' rats ingested with different drugs is thus rejected.

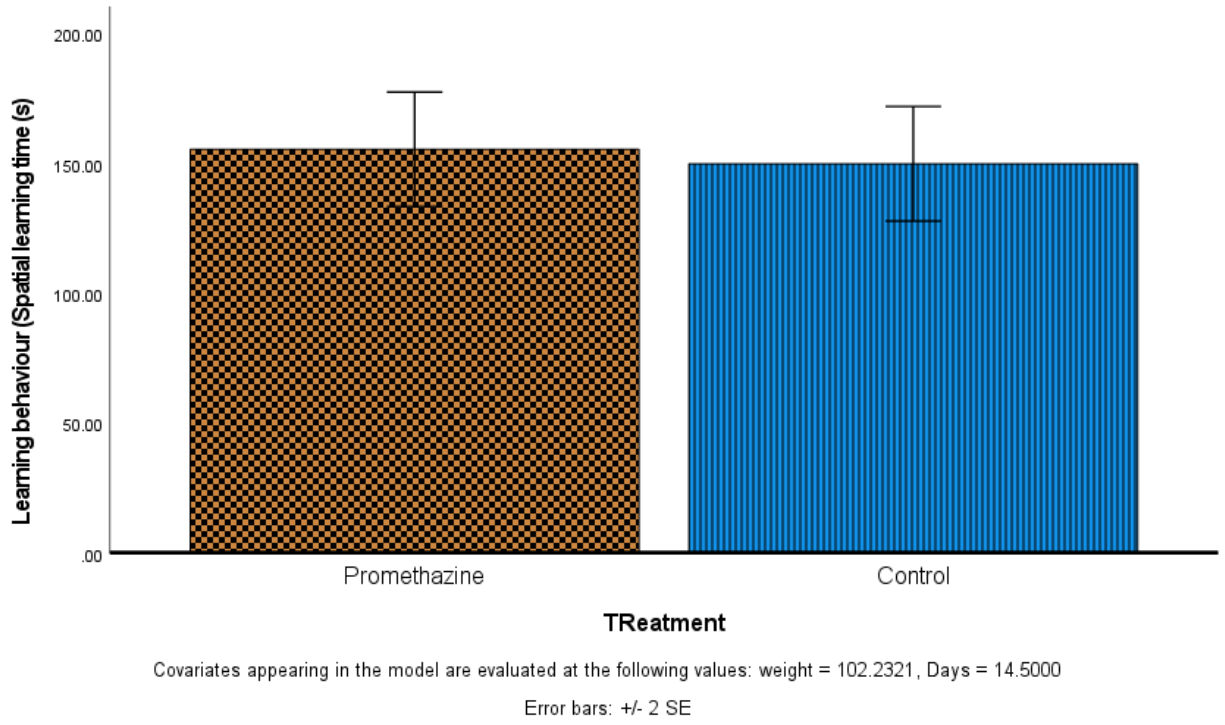

Fig1: Bar chart showing the effect of chronic intake of anti-psychotic drugs (Promethazine) on learning behaviour among Albino rats

The bar chart showed that, despite exposure to acute intake of anti-psychotic drugs, there was no significant difference between Promethazine and control in learning behavior.

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

Table 3: Summary Randomized Block ANOVA table showing the influence of exposure to chronic intake of anti-psychotic drugs (Haloperidol) on learning behaviour

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial η^2
Block	25120.609	1	25120.609	1.330	.250	.004
Weight	259238.499	1	259238.499	13.723	.000	.040
Treatment	9931.308	1	9931.308	0.526	.469	.002
Error	6271917.691	332	18891.318			
Total	6564777.952	335				

The result from Table 3 shows that exposure to acute intake of anti-psychotic drugs (Haloperidol) did not have significant effect on the learning behavior among female albino rats F (1, 332) = 0.53, $p > 0.05$, η^2= .00. Further analysis on the mean differences was carried out with descriptive statistics and LSD post hoc multiple comparison test and the result is presented in Table 4.

Table 4: Summary of descriptive statistics and LSD post hoc comparison analysis showing the mean difference in learning behavior between rats exposed to chronic intake of anti-psychotic drug (Haloperidol) and those exposed to normal saline

	Mean	S.E.M	LSD POST HOC	Sig.
Haloperidol	135.971[a]	10.706	11.08	.469
Control	147.052[a]	10.706		

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

a. Covariates appearing in the model are evaluated at the following values: weight = 100.0476, Days = 14.5000.

From the analysis, mean differences showed that rats in the control (147.05) significantly displayed slower spatial learning and memory compared to rats ingested with Haloperidol (135.97). The mean difference however was not significant. Based on this, the hypothesis that states that there will be a significant difference in learning behaviour among females rats ingested with different drugs is thus rejected.

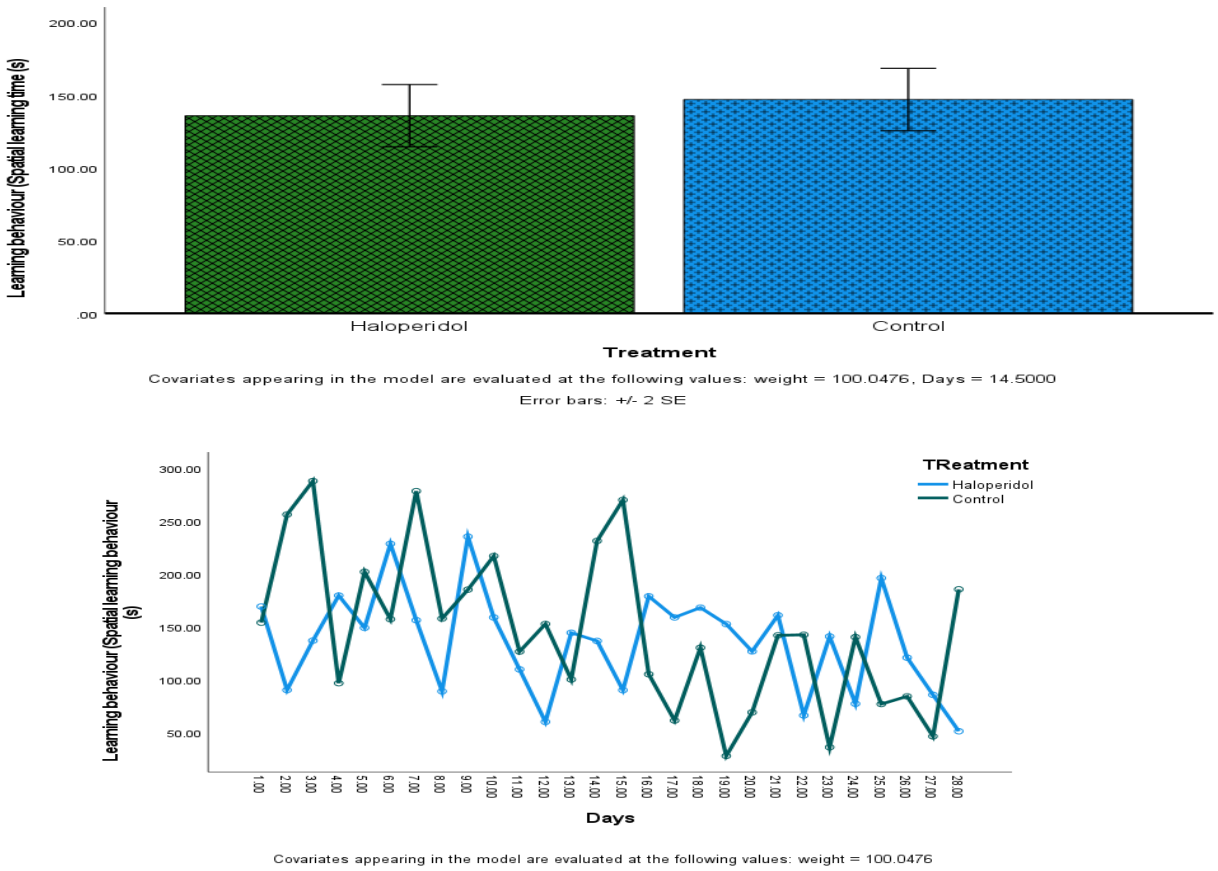

Fig 3: *Line graph showing the effect of chronic intake of anti-psychotic drugs (Haloperidol) on learning behaviour among female Wister albino rats*

The line graph shows that the exposure to chronic intake of anti-psychotic drugs demonstrated that there was no significant difference between haloperidol and control in learning behaviour.

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 is presented in Table 5.

Table 5: Summary Randomized Block ANOVA table showing the influence of exposure to acute intake of anti-psychotic drugs (Haloperidol & Promethazine) on learning behaviour of female Wister albino rats

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial η^2
Block	639220.008	1	639220.008	38.279	.000	.103
Weight	18944.569	1	18944.569	1.134	.288	.003
Treatment	76429.492	1	76429.492	4.577	.033	.02
Error	5544087.636	332	16699.059			

Corrected Total	6271855.997	335

The result from Table 5 reveals that exposure to chronic intake of anti-psychotic drugs (Haloperidol & Promethazine) has significant effect on the learning behaviour among albino rats F (1, 332) = 4.58, $p < 0.05$, $\eta^2 = .02$. 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 comparisons Test. The result is presented in Table 6.

Table 6: Summary of descriptive statistics and LSD post hoc comparison analysis Reaction time showing the mean difference between rats exposed to chronic intake of anti-psychotic drugs (Haloperidol & Promethazine) and those not exposed (Control)

	Mean	S.E.M	LSD POST HOC	Sig.
CONTROL	148.239[a]	9.981		
COMBINED (HALOPERIDOL PROMETHAZINE)	+118.005[a]	9.981	14.13*	.033

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

a. Covariates appearing in the model are evaluated at the following values: Days = 14.5000, weight = 102.4940.

From the analysis, the rats in the control (148.24) have slower learning time compared to rats ingested with anti-psychotic drugs combination (Haloperidol + Promethazine (118.01). The mean difference was significant. Based on this, hypothesis which states that there will be a significant difference in spatial learning behavior among female albino Wister rats ingested with Haloperidol and Promethazine is thus accepted.

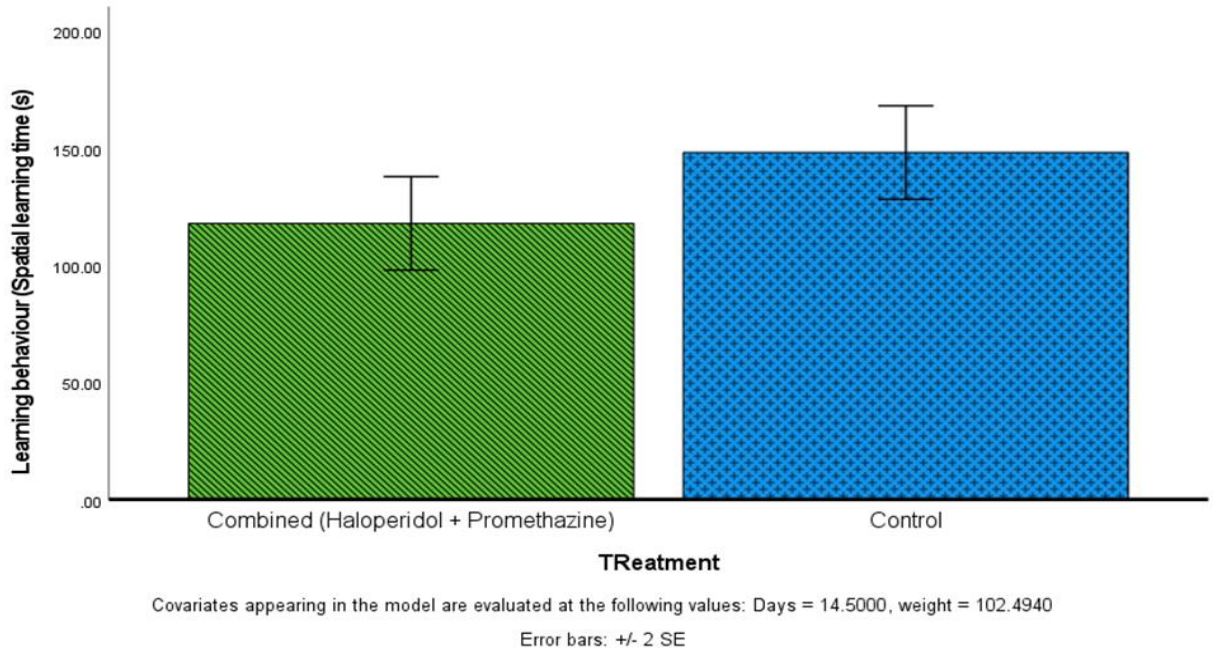

Fig4: Bar graph showing the effect of chronic intake of anti-psychotic drugs (Haloperidol + Promethazine) on learning behavior among albino rats

The bar chart on the exposure to chronic intake of anti-psychotic drugs demonstrated that Haloperidol + Promethazine induced faster spatial learning function compared to the control group.

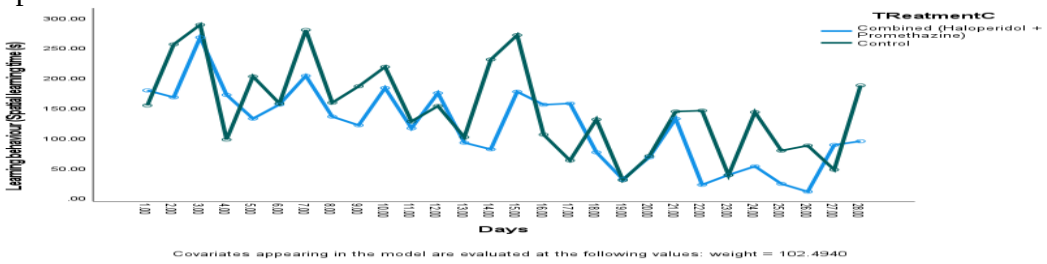

Fig5: *Line graph showing the interaction between time of exposure and treatment to chronic intake of anti-psychotic drugs on reaction time (Haloperidol + Promethazine) among albino rats*

The line graph shows that longer period of exposure to chronic intake of anti-psychotic drugs (Haloperidol + Promethazine) increased the reaction time to the effects of combined treatment on learning and memory. Rat ingested with Haloperidol plus Promethazine exhibited faster reaction time compared to the control group.

Discussion

The results of this investigation revealed that promethazine had no effect on memory or spatial learning behavior in female albino rats. Female rats given Promethazine had weaker spatial learning and memory performance than female rats given a placebo. The difference in means was not statistically significant. This is consistent with the mechanism of action of promethazine. 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 that exposure to acute intake of Haloperidol did not have significant effect on the learning behavior among female albino rats. The female albino rats in the control significantly displayed slower spatial learning and memory compared to female Albino rats ingested with Haloperidol. However, the mean difference was not significant. There are similar research reports in line with the findings of this study. Marwari & Dawe (2019) examined investigated the effects of chronic haloperidol treatment on spatial place learning in a social home cage environment using the IntelliCage system and found that, while haloperidol-treated mice showed reduced water-rewarded reversal place learning compared to control mice, haloperidol-treated mice learned better than control mice when air puff was used to punish incorrect visits. According to the findings of this study, haloperidol medication can improve learning depending on the dosage and treatment settings. The food in one of the arms of the Y-Maze employed for this study functioned as an incentive for appraising the arm.

One possible explanation is that haloperidol inhibits the mechanisms by which reward reinforces learning while having less of an effect on the negative reinforcement of air puff or the absence of food punishment, allowing other underlying mechanisms boosting learning to be disclosed. Haloperidol's ability to modulate reward-reinforced learning is consistent with the involvement of a dopamine-dependent signal in the nucleus accumbens and striatum in reward. The significance of D2 dopamine receptors in the nucleus accumbens and striatum in reward systems has been reevaluated (Soares-Cunha et al., 2016; 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).

Our result as tested in 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 shows that combined treatment of female albino rats with Haloperidol and Promethazine has significant effect on the learning behaviour among the rats. We found that the rats in the control group had slower learning time compared to those treated with a combination of Haloperidol and Promethazine. This is an indication that

combined treatment of Promethazine and haloperidol improved learning.

However, there have been discrepancies in the reported effects of neuroleptic medications on cognitive and psychomotor functions in both patients and healthy controls. The sensitivity of detection of neuroleptic drug effects appears to have been established by the experimental design of our current investigation rather than any specific cognitive or psychomotor test. Several investigations have demonstrated that sedative phenothiazines impair psychomotor function and sustained attention, but not higher cognitive skills. In the majority of investigations of schizophrenia patients, neuroleptic treatment improves both cognitive performance and attention, paralleling clinical recovery. Negative symptoms are rarely exacerbated and usually improve slightly with neuroleptic medication.

Controls are more sensitive to neuroleptic drug-induced deficits than schizophrenia patients. Tolerance has been observed in patients but not in healthy individuals. (Cole et al., 2018). The mechanism by which neuroleptics exert their therapeutic effects on patients is uncertain. Normalization of attention, supported indirectly by inhibition of 'released' limbic dopamine hyperactivity, and normalization of asymmetrical temporohippocampal function, as well as direct enhancement of attentional processing are thought to be involved. More research is however needed.

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 (Lidow et al., 1997), both of which are critical for executive functions such as attention and working memory (Chudasama & Robbins, 2004). This effect of common drugs may contribute to some of the negative effects of common antipsychotics on cognition (Marwari & Dawe, 2019b; Saeedi et al., 2006). Nonetheless, several studies have found that drug therapy improves cognition (Scheuer et al., 2006; Mishara & Goldberg, 2004). For these reasons, some clinicians have broadened and changed their approach in characterizing and judging clinical appropriateness in the cognitive therapy of schizophrenia (Kern et al., 2009; Nasrallah et al., 2005).

Conclusion and Recommendations

In conclusion, the effect of chronic haloperidol and promethazine administration on spatial learning and memory in female Wister albino rats was investigated. The current study shows that haloperidol and promethazine have no effect on learning behaviour when administered separately, but that the combination of haloperidol and promethazine increases spatial learning and memory in female albino rats subjected to the treatment. Adequate policy on the use of haloperidol and promethazine should be adequately publicized with enough awareness for youths and all stakeholders.

References

Abdel-Salam, O. M. E., & Nada, S. A. (2011). Effect of piracetam, vinpocetine and Ginkgo biloba extract on antipsychotic-induced impairment of learning and memory. Czech and Slovak Neurology and Neurosurgery;74/107(1):29-35. https://www.researchgate.net/publication/298894333_Effect_of_Piracetam_Vinpocetine_and_Ginkgo_Biloba

_Extract_on_Antipsychotic-Induced_Impairment_of_Learning_and_Memory

Arenas, M. C., Parra, A., & Simón, V. M. (1995). Gender differences in the effects of haloperidol on avoidance conditioning in mice. *Pharmacology, Biochemistry, and Behavior*, 51(4), 601–609. https://doi.org/10.1016/0091-3057(94)00382-S

Babin, S. L., Hood, A. J., Wassef, A. A., Williams, N. G., Patel, S. S., & Sereno, A. B. (2011). Effects of Haloperidol on Cognition in Schizophrenia Patients Depend on Baseline Performance: A Saccadic Eye Movement Study. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 35(7), 1753–1764. https://doi.org/10.1016/J.PNPBP.2011.06.004

Beuzen, J.-N., Taylor, N., Wesnes, K., & Wood, A. (2016). A comparison of the effects of olanzapine, haloperidol and placebo on cognitive and psychomotor functions in healthy elderly volunteers. Journal of Psychopharmacology, 13(2), 152–158. https://doi.org/10.1177/0269881199013000207

Bohannon, J. (2002). Animal models. To build a better mouse cage. *Science*, 298(5602), 2320-2321. https://doi.org/10.1126/science.298.5602.2321

Boslaugh, S. E. (2016). WHO Model Lists of Essential Medicines.. *The SAGE Encyclopedia of Pharmacology and Society page 433*. https://doi.org/10.4135/9781483349985.n433

Burns, J. M., & Boyer, E. W. (2013). Antitussives and substance abuse. *Substance Abuse and Rehabilitation*, 4, 75-82. https://doi.org/10.2147/SAR.S36761

Carney, T., Wells, J., Parry, C. D. H., McGuinness, P., Harris, R., & Van Hout, M. C. (2018). A comparative analysis of pharmacists' perspectives on codeine use and misuse - A three country survey. *Substance Abuse: Treatment, Prevention, and Policy*, 13(1), 13011-13018. https://doi.org/10.1186/s13011-018-0149-2

Carr, B. C. (2006). Efficacy, abuse, and toxicity of over-the-counter cough and cold medicines in the pediatric population. *Current Opinion in Pediatrics*, 18(2), 184–188. https://doi.org/10.1097/01.mop.0000193274.54742.a1

Chesler, E. J., Wilson, S. G., Lariviere, W. R., Rodriguez-Zas, S. L., & Mogil, J. S. (2002a). Influences of laboratory environment on behavior [1]. *Nature Neuroscience*, 5(11), 1101–1102. https://doi.org/10.1038/nn1102-1101

Chesler, E. J., Wilson, S. G., Lariviere, W. R., Rodriguez-Zas, S. L., & Mogil, J. S. (2002b). Identification and ranking of genetic and laboratory environment factors influencing a behavioral trait, thermal nociception, via computational analysis of a large data archive. *Neuroscience and Biobehavioral Reviews*, 26(8), 907–923. https://doi.org/10.1016/S0149-7634(02)00103-3

Chudasama, Y., & Robbins, T. W. (2006). Functions of frontostriatal systems in cognition: Comparative neuropsychopharmacological studies in rats, monkeys and humans. *Biological Psychology*, 73(1), 19–38. https://doi.org/10.1016/J.BIOPSYCHO.2006.01.005

Chudasama, Yogita, & Robbins, T. W. (2004). Dopaminergic modulation of visual attention and working memory in the rodent prefrontal cortex. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, 29(9), 1628–1636. https://doi.org/10.1038/SJ.NPP.1300490

Clatts, M., Giang, L. M., Goldsamt, L., & Colón-López, V. (2010). Nonmedical use of promethazine hydrochloride among heroin injectors in vietnam: Unrecognized risks and unintended consequences. *Substance Use and Misuse*, 45(4), 515–527. https://doi.org/10.3109/10826080903452520

Cole, S. L., Robinson, M. J. F., & Berridge, K. C. (2018). Optogenetic self-stimulation in the nucleus accumbens: D1 reward versus D2 ambivalence. *PLOS ONE*, 13(11), e0207694. https://doi.org/10.1371/JOURNAL.PONE.0207694

Cookson, J. (2008). Atypical antipsychotics in bipolar disorder: the treatment of mania. *Advances in Psychiatric Treatment*, 14(5), 330-338. https://doi.org/10.1192/apt.bp.107.004150

Dawe, G. S., Huff, K. D., Vandergriff, J. L., Sharp, T., O'Neill, M. J., & Rasmussen, K. (2001). Olanzapine activates the rat locus coeruleus: in vivo electrophysiology and c-Fos immunoreactivity. *Biological Psychiatry*, 50(7), 510–520. https://doi.org/10.1016/S0006-3223(01)01171-4

de Houwer, J., Barnes-Holmes, D., & Moors, A. (2013). What is learning? On the nature and merits of a functional definition of learning. *Psychonomic Bulletin & Review* 20(4), 631–642. https://doi.org/10.3758/S13423-013-0386-3

EMC, E. M. C. (2019). Phenergan Injection - Summary of Product Characteristics (SmPC) - (emc). https://www.medicines.org.uk/emc/medicine/1669#gref

Ellen Tsay, M., Procopio, G., Anderson, B. D., & Klein-Schwartz, W. (2015). Abuse and intentional misuse of promethazine reported to US poison centers: 2002 to 2012. *Journal of Addiction Medicine*, 9(3), 233–237. https://doi.org/10.1097/ADM.0000000000000124

Gemperle, A. Y., McAllister, K. H., & Olpe, H. R. (2003). Differential effects of iloperidone, clozapine, and haloperidol on working memory of rats in the delayed non-matching-to-position paradigm. *Psychopharmacology*, 169(3–4), 354–364. https://doi.org/10.1007/s00213-003-1459-1

Harvey, P. D., Rabinowitz, J., Eerdekens, M., & Davidson, M. (2005). Treatment of cognitive impairment in early psychosis: a comparison of risperidone and haloperidol in a large long-term trial. *The American Journal of Psychiatry*, 162(10), 1888–1895. https://doi.org/10.1176/APPI.AJP.162.10.1888

Hou, Y., Wu, C. F., Yang, J. Y., & Guo, T. (2006). Differential effects of haloperidol, clozapine and olanzapine on learning and memory functions in mice. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 30(8), 1486–1495.

https://doi.org/10.1016/j.pnpbp.2006.06.001

Houthoofd, S. A. M. K., Morrens, M., & Sabbe, B. G. C. (2008). Cognitive and psychomotor effects of risperidone in schizophrenia and schizoaffective disorder. *Clinical Therapeutics*, 30(9), 1565–1589. https://doi.org/10.1016/j.clinthera.2008.09.014

Jensen, L. L., Rømsing, J., & Dalhoff, K. (2017). A Danish Survey of Antihistamine Use and Poisoning Patterns. *Basic and Clinical Pharmacology and Toxicology*, 120(1), 64–70. https://doi.org/10.1111/bcpt.12632

Keefe, R. S. E., Seidman, L. J., Christensen, B. K., Hamer, R. M., Sharma, T., Sitskoorn, M. M., Lewine, R. R. J., Yurgelun-Todd, D. A., Gur, R. C., Tohen, M., Tollefson, G. D., Sanger, T. M., & Lieberman, J. A. (2009). Comparative effect of atypical and conventional antipsychotic drugs on neurocognition in first-episode psychosis: a randomized, double-blind trial of olanzapine versus low doses of haloperidol. *American Journal of Psychiatry*, 161(6), 985–995. https://doi.org/10.1176/APPI.AJP.161.6.985

Kern, R. S., Glynn, S. M., Horan, W. P., & Marder, S. R. (2009). Psychosocial treatments to promote functional recovery in schizophrenia. *Schizophrenia Bulletin*, 35(2), 347–361. https://doi.org/10.1093/SCHBUL/SBN177

Lang, S., Gan, L. S., Yoon, E. J., Hanganu, A., Kibreab, M., Cheetham, J., Hammer, T., Kathol, I., Sarna, J., Martino, D., & Monchi, O. (2020). Cognitive deficits and striato-frontal dopamine release in Parkinson's disease. Theta-Burst Stimulation for Cognitive Enhancement in Parkinson's Disease With Mild Cognitive Impairment: A Randomized, Double-Blind, Sham-Controlled Trial. *Frontiers in Neurology*, 11; 584374-395. https://doi.org/10.3389/FNEUR.2020.584374/PDF

Lidow, M., Elsworth, J., & Goldman-Rakic, P. (1997). Down-regulation of the D1 and D5 dopamine receptors in the primate prefrontal cortex by chronic treatment with antipsychotic drugs. *The Journal of Pharmacology and Experimental Therapeutics*, 281(1):597-603.

Lim, E. P., Verma, V., Nagarajah, R., & Dawe, G. S. (2007). Propranolol blocks chronic risperidone treatment-induced enhancement of spatial working memory performance of rats in a delayed matching-to-place water maze task. *Psychopharmacology*, 191(2), 297–310. https://doi.org/10.1007/S00213-006-0664-0

Lustig, C., Matell, M. S., & Meck, W. H. (2005). Not "just" a coincidence: Frontal-striatal interactions in working memory and interval timing. *Memory*, 13(3–4), 441–448. https://doi.org/10.1080/09658210344000404

Lynch, K. L., Shapiro, B. J., Coffa, D., Novak, S. P., & Kral, A. H. (2015). Promethazine use among chronic pain patients. *Drug and Alcohol Dependence*, 150, 92. https://doi.org/10.1016/J.DRUGALCDEP.2015.02.023

Marwari, S, Dawe, G. S.(2019a). Effects of haloperidol on cognitive function and behavioural flexibility in the IntelliCage social home cage

environment. Behavioural Brain Research, 3;371:111976. doi: 10.1016/j.bbr.2019.111976. Epub 2019 May 25. PMID: 31136773.

Marwari, S., & Dawe, G. S. (2019b). Effects of haloperidol on cognitive function and behavioural flexibility in the IntelliCage social home cage environment. *Behavioural Brain Research*, 371. https://doi.org/10.1016/J.BBR.2019.111976

Mishara, A. L., & Goldberg, T. E. (2004). A meta-analysis and critical review of the effects of conventional neuroleptic treatment on cognition in schizophrenia: opening a closed book. *Biological Psychiatry*, 55(10), 1013–1022. https://doi.org/10.1016/J.BIOPSYCH.2004.01.027

Nasrallah, H. A., Targum, S. D., Tandon, R., McCombs, J. S., & Ross, R. (2005). Defining and measuring clinical effectiveness in the treatment of schizophrenia. *Psychiatric Services* (Washington, D.C.), 56(3), 273–282. https://doi.org/10.1176/APPI.PS.56.3.273

Rosengarten, H., & Quartermain, D. (2002). The effect of chronic treatment with typical and atypical antipsychotics on working memory and jaw movements in young and aged rats. European *Neuropsychopharmacology*, 12, 285–286. https://doi.org/10.1016/S0924-977X(02)80399-6

Saeedi, H., Remington, G., & Christensen, B. K. (2006). Impact of haloperidol, a dopamine D2 antagonist, on cognition and mood. *Schizophrenia Research*, 85(1–3), 222–231. https://doi.org/10.1016/J.SCHRES.2006.03.033

Sawamoto, N., Piccini, P., Hotton, G., Pavese, N., Thielemans, K., & Brooks, D. J. (2008). Cognitive deficits and striato-frontal dopamine release in Parkinson's disease. *Brain*, 131(5), 1294–1302. https://doi.org/10.1093/brain/awn054

Scheuer, C., Boot, E., Carse, N., Clardy, A., Gallagher, J., Heck, S., Marron, S., Martinez-Alvarez, L., Masarykova, D., Mcmillan, P., Murphy, F., Steel, E., Ekdom, H. Van, & Vecchione, H. (2006). Long-term neurocognitive effects of olanzapine or low-dose haloperidol in first-episode psychosis. *Biological Psychiatry*, 59(2), 97–105. https://doi.org/10.2/JQUERY.MIN.JS

Sharma, A., & Hamelin, B. (2005). Classic Histamine H1 Receptor Antagonists: A Critical Review of their Metabolic and Pharmacokinetic Fate from a Birds Eye View. *Current Drug Metabolism*, 4(2), 105–129. https://doi.org/10.2174/138920003348952 3

Soares-Cunha, C., Coimbra, B., Sousa, N., & Rodrigues, A. J. (2016). Reappraising striatal D1- and D2-neurons in reward and aversion. *Neuroscience and Biobehavioral Reviews*, 68, 370–386. https://doi.org/10.1016/J.NEUBIOREV.2016.05.021

Stein, R. A., & Strickland, T. L. (1998). A Review of the Neuropsychological Effects of Commonly Used Prescription Medications. *Archives of Clinical Neuropsychology*, 13(3), 259–284. https://doi.org/10.1016/S0887-6177(97)00027-9

Terry, A. V., Hill, W. D., Parikh, V., Evans, D. R., Waller, J. L., & Mahadik, S. P. (2002). Differential effects of

chronic haloperidol and olanzapine exposure on brain cholinergic markers and spatial learning in rats. *Psychopharmacology*, 164(4), 360–368. https://doi.org/10.1007/S00213-002-1230-Z

Valentine, U. A., Paul, O., & -Ossai, U. (2016). Promethazine injection do not modulate spatial learning effects of haloperidol injection in long Evan rats. *Sky Journal of Medicine and Medical Sciences*, 4(5), 38–45. http://www.skyjournals.org/SJMMS

Verma, V., Lim, E. P., Han, S. P., Nagarajah, R., & Dawe, G. S. (2007). Chronic high-dose haloperidol has qualitatively similar effects to risperidone and clozapine on immediate-early gene and tyrosine hydroxylase expression in the rat locus coeruleus but not medial prefrontal cortex. *Neuroscience Research*, 57(1), 17–28. https://doi.org/10.1016/J.NEURES.2006.09.002