Original Article

# Neurotoxicity of Isotretinoin in Mice: Behavioral and Tissue Neurological Function Assessment

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## ABSTRACT

**Background:** Isotretinoin is used to treat some skin disorders in dogs and cats by reducing the size and activity of their sebaceous glands, although it may have some neurobehavioral side effects.

**Objectives:** To evaluate isotretinoin's effects on the brain and neurotransmitters, as well as its impact on neurobehavior and motor activity.

**Methods:** Fifteen mice were divided into three groups: the first group was a control group, the second group received 125 mg/kg isotretinoin, and the third group received 250 mg/kg orally.

**Results:** The $LD_{50}$ for isotretinoin is 4841.2 mg/kg. Neurobehavioral measurements of mice revealed significant effects on changes in open-field activity, time spent in dark areas, and negative geotaxis behaviors across different dosage levels of isotretinoin. Both doses of isotretinoin (125 and 250 mg/kg) significantly altered serotonin levels. Mice treated with 125 mg/kg isotretinoin exhibited a decrease in serotonin levels compared to the control group. Both doses of isotretinoin resulted in significant changes in acetylcholine levels. Isotretinoin (125 mg/kg) slightly increased in acetylcholine levels. The data indicated a significant increase in catechol-O-methyltransferase (COMT) enzyme levels. A histopathological study of the brain revealed that 125 mg/kg isotritinoin induced mild vacuolization, blood vessel congestion, and mild perivascular edema. A high dose (250 mg/kg) resulted in vacuolization, gliosis, blood vessel congestion, hemorrhage and satellitosis.

**Conclusion:** High oral doses of isotretinoin influence animal neurobehavioral behavior due to its effect on brain tissue, as evidenced by its effects on serotonin, acetylcholine and the COMT enzyme.

**Keywords:** Catechol-O-methyltransferase (COMT) enzyme, Isotretinoin, Neurobehavior, Neurotransmitters,

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## Introduction

Isotretinoin is prescribed to treat Schnauzer comedone syndrome, ichthyosis, feline acne, sebaceous adenitis, epithelial lymphoma, keratoacanthoma, sebaceous gland hyperplasia and adenomas (Koch et al., 2010).

Other names for this medicine include accutane®, claravis®, sotret®, isotretinoin and retinoids. retinoids are a family of vitamin A-derived chemicals that belong to the nuclear receptor superfamily and regulate gene transcription (Gudas, 2012). They play several roles. This signaling molecule binds to particular retinoic acid receptors in the brain, including glucocorticoids and thyroid hormone receptors (Gudas, 2012).

Research into retinoic acid in the central nervous system has concentrated on brain development, spurred partly by the discovery that isotretinoin, an isomer of retinoic acid, is used in therapy (Jimenez et al., 2017). Recent research has revealed that retinoic acid may alter the adult brain, and animal studies have shown that isotretinoin administration causes behavioral abnormalities and inhibition of neurogenesis in the hippocampus. Isotretinoin inhibits fat cell growth and stimulates apoptosis, reducing sebaceous gland output and size. It also inhibits the migration of multinucleated white blood cells to the skin (Jimenez et al., 2017).

Isotretinoin affects the collection of nuclear receptors that control the expression of several receptors into the skin. Retinoic acid is derived from vitamin A and regulates cell proliferation and differentiation in several body organs, including bones, blood vessels, the heart and immunity (Szymański et al., 2020).

Recent studies have highlighted the effects of isotretinoin on neural health, particularly nerve cell proliferation, differentiation, and adaptability. Elevated or reduced isotretinoin levels significantly impact these processes (Melnik, 2019). Studies in companion animals, specifically dogs and cats, have indicated psychological changes associated with isotretinoin use, including increased anxiety, aggression and notable behavioral shifts (Camps et al., 2019).

Evidence suggests that isotretinoin influences mood and behavior in experimental studies on rodents. For example, O'Reilly et al. (2008) demonstrated that a dosage of 1 mg/kg/day over six weeks in rats induced depression-like symptoms, as observed in behavioral tests, such as the forced swim test and tail suspension test, in which affected animals exhibited decreased activity. Additionally, isotretinoin has been associated with memory and learning impairment. Bremner (2021) reported hippocampal shrinkage, which aligns with the findings on isotretinoin's negative impact on cognitive function.

Given the abundance of retinoid receptors in various brain regions, isotretinoin has been implicated in inhibiting brain growth in several animal models. However, few studies have explored its specific neurobehavioral effects in adult animals, particularly regarding learning, memory and anxiety. This study aims to fill this gap by examining the impact of isotretinoin on these neurobehavioral mechanisms in adult models, thereby addressing a critical void in the current literature. This study aims to comprehensively assess the effects of isotretinoin on neurobehavioral functions, including learning, memory, and anxiety, in adult animal models.

## Materials and Methods

Isotretinoin was obtained as an oil capsule from Ajanta Company, Jordan. The dose was determined based on the animal's weight and was delivered orally using a gavage needle).

### Animals

Male mice measuring 25-30 g and aged two months were raised in laboratory conditions that were temperature, and humidity-controlled. They were kept in dedicated cages inside the animal home.

### Diagnostic kits

All kits using Eliza for measuring: 1) A kit for measuring acetyl choline from Elabscience Company; 2) A kit for measuring serotonin 5-HT from the Elabscience Company; 3) A kit to measure (catechol-O-methyltransferase [COMT]) from the Elabscience Company, Lot Number: E202311045

### Experiment design

### Lethal dose ($LD_{50}$) experiment

To determine the median $LD_{50}$, an initial dose was administered to a single animal based on preliminary experiments. The survival or death of the animal was observed after 24 hours. If the animal died, the dose was decreased by a fixed amount; if the animal survived, the dose was increased by the same fixed amount. This process is repeated until a change occurs, usually indicated by a reversal in the outcome (i.e. a live animal followed by a dead one, or vice versa).

After this turning point, observations were recorded for three additional animals over three days. The results are noted in binary format, where "X" represents the animal's death, and "0" indicates survival. The final $LD_{50}$ value was calculated according to the table described in Dixon's (1980) study.

A wide range of dosages were employed to calculate $LD_{50}$. The $LD_{50}$ was calculated using a formula that includes the first orally provided dose (Xf), a coefficient (K) indicating the rise or decrease in dose, and the last orally delivered dose. Based on the number supplied, the first orally administered dose (Xf) was 4000 mg/kg, the coefficient (K) was 0.701, and the dose increase or decrease was 1200 mg/kg.

Substituting these values into the $LD_{50}$ formula (Equation 1), we obtain:

1. $LD_{50}=Xf+Kd$

## Evaluation of various doses of isotretinoin on nervous system

In this investigation, 15 mice were divided into three groups: The first group received no therapy, the second group received 125 mg/kg isotretinoin, and the third group received 250 mg/kg orally.

### Dose selection

Isotretinoin doses of 125 and 250 mg/kg were selected based on several factors. First, the selection was guided by an $LD_{50}$ value of 4841.2 mg/kg in rats, which indicates the median $LD_{50}$. Choosing doses well below this level minimizes the risk of acute toxicity and ensures safety.

Second, previous studies have reported these doses on the effects of isotretinoin. These studies demonstrated notable neurobehavioral effects at doses lower than the $LD_{50}$. Thus, the 125 and 250 mg/kg doses allowed observing behavioral and neurological impacts within a safe range while revealing any significant sub-acute toxicity effects relevant to the study. The therapy session lasted for 14 days.

Neurobehavioral assessments were performed following the treatment period as follows:

The open field test is performed by counting the number of rearing and squares the mouse passes within an open field box diameter of 40×40×30 cm (length×width×height) (Gould et al., 2009).

The light and dark test uses specific equipment in the shape of a box divided into two rooms: Dark and light. After placing the mouse inside the box for 3 minutes, the time spent by each mouse inside each chamber was measured and the percentage remaining in the dark room was determined using the Equation 2:

2. *Dark time=(Dark time)/(Total time)×100* (Kulesskaya & Voikar, 2014).

The negative geotaxis test involves placing the animal on a device with a sloping surface at a 45-degree angle and then calculating the time tacit takes to turn and change direction within seconds (Kulesskaya & Voikar, 2014).

The pocking test involves utilizing a device in the shape of a perforated surface with numerous holes and the size of the mouse's head. The mouse was then placed on the surface and left for three minutes. The number of holes in which the mouse places its head during a period is counted (Hurst & West, 2010).

After behavioral and neurological tests were completed, the mice were anesthetized with ether to allow blood to be drawn. The blood was then placed in glass tubes containing the anticoagulant ethylenediaminetetraacetic acid (EDTA), to separate the plasma for future biochemical assays. Brains were removed and stored in clean containers containing 10% neutral formalin.

The enzyme COMT is crucial for breaking of catecholamines, such as dopamine, epinephrine, and norepinephrine. COMT transfers a methyl group to catecholamines, inactivating them and playing a crucial role in regulating mood, cognition, and stress responses.

### Statistical analysis

The statistical interpretation of these findings entails determining the significance of the observed differences, as indicated in the tables. Statistical testing using SPSS software for analysis of variance and post-hoc comparisons with the Tukey HSD test revealed significant differences at $P<0.05$.

## Results

The provided data outline the oral $LD_{50}$ for 50% of the test animal) for isotretinoin. The $LD_{50}$ value is crucial in toxicology as it indicates the dosage at which a substance becomes lethal to half of the test animal. In this case, the $LD_{50}$ of isotretinoin was calculated to be 4841.2 mg/kg (Equation 3) (Table 1).

3. *4000+(0.701×1200)=4841.2 mg\kg*

Neurobehavioral measurements of mice treated with isotretinoin for 14 consecutive days revealed significant effects on various parameters compared to the control group. The data in Table 2 illustrate changes in open-field activity, time spent in dark areas, and negative geotaxis behaviors across different isotretinoin dosage levels.

Starting with open field activity, both doses of isotretinoin (125 mg/kg and 250 mg/kg) showed alterations compared to the control group. Mice treated with 125 mg/kg exhibited increased locomotor activity, as indicated by increased crossings and rearing. The higher dose of isotretinoin (250 mg/kg) exacerbated this effect, resulting in a more pronounced increase in crossing and rearing activities than the control and lower dose groups.

The percentage of time spent in the dark areas was significantly different between the control and isotretinoin-treated groups. Mice administered both doses of isotretinoin spent significantly less time in dark areas than the control group.

Significant differences were observed between the control and isotretinoin-treated groups in the negative geotaxis test. Mice receiving isotretinoin, particularly at the higher dose of 250 mg/kg, exhibited impaired performance in negative geotaxis and pocking number compared to the control and lower dose groups (Table 2).

Table 3 records that compared to the control group, both doses of isotretinoin (125 mg/kg and 250 mg/kg) resulted in a significant decrease in serotonin levels. Also, both doses of isotretinoin (125 and 250 mg/kg) significantly increased acetylcholine levels. Mice treated with 125 mg/kg isotretinoin showed a slight increase in acetylcholine levels compared to the control group. In addition, the data indicated a significant increase in COMT levels between the control group and the isotretinoin-treated groups at either dose (125 or 250 mg/kg).

## Histopathological study results

Figure 1 shows histological sections of the brains of mice from different experimental groups. In panels A and B, representing the control group, normal architecture of neurons (indicated by arrows), glial cells (thick arrows), and blood vessels (arrowheads) were observed. No significant abnormalities were observed in any of these sections.

**Table 1.** Oral $LD_{50}$ for isotretinoin

| Variables | Dosage |
|---|---|
| $LD_{50}$ | 4841.2 (mg\kg) |
| First orally dose | 4000 (mg\kg) |
| Last orally dose | 4000 (mg\kg) |
| Increase and decrease in dose | 1200 (mg\kg) |
| Value in table | 0.701 |
| Animal number | 5 (0X0X0) |

Abbreviations: $LD_{50}$: Lethal dose.

Note: Symbol 0 refer to animal alive, X refer to died animal.

**Table 2.** Neurobehavioral measurements of mice treated with isotretinoin for 14 consecutive days

| Groups | Mean±SE | | | Mean±SE | |
|---|---|---|---|---|---|
| | Open Field\3 min | | % Time in Dark\3 min | Negative Geo-taxis\Second | Pocking |
| | Number of Cross Square | Rearing | | | |
| Control | 120±11.2 | 16.21±2.2 | 70 | 2.31±1.52 | 16.83±3.1 |
| Iso 125 mg\kg | 130±15.2 | 19.13±3.5 | 72 | 7.7±4.10* | 13.5±5.11 |
| Iso 250 mg\kg | 180±12.1*A | 30±1.5*A | 30*A | 14.1±3.7*A | 9.4±2.11*A |

Data mean (5 animals±SE), *Significant difference from control, ASignificant difference from isotritinonin 125 mg\kg.

**Table 3.** Effect of isotretinoin dose on serotonin and acetylcholine and COMT enzyme

| Groups | Mean±SE | | |
|---|---|---|---|
| | Serotonin (ng/mL) | Acetylcholine (ng/mL) | COMT (nmol/mL) |
| Control group | 213.458±0.31 | 187.5±20.13 | 0.156±28.13 |
| Iso 125 (mg\kg) | 157.876±65.12* | 230.021±41.35* | 0.200 ±25.60* |
| Iso 250 (mg\kg) | 113.701±67.25*A | 280.116±19.6*A | 0.231±30.40* |

COMT: Catechol-O-methyl-transferase.

Data mean (5 animals±SE), *Significant difference from control, ASignificant difference from isotritinonin 125 mg\kg.

In panels C and D, corresponding to the low-dose (125 mg) isotritinoin group, mild vacuolization (arrows), blood vessel congestion (thick arrows), and mild perivascular edema (arrowheads) were evident. These changes suggest some degree of tissue alteration, although they are relatively minor compared to the control group.

Panels E and F, representing the high-dose isotritinoin (250 mg) group show more pronounced histological changes. Vacuoles (indicated by arrows), gliosis (indicated by arrows), congested and hemorrhaged blood vessels (marked by arrowheads), and satellitosis (shown with curved arrows) are visible. These changes suggest tissue damage and an inflammatory response is underway.

Both low and high doses of isotretinoin seem to alter mice's brain tissue, with severe changes observed at higher doses. The figures in the panel are magnified at 100x, providing a view of the tissue structure, while those in the right panel are magnified at 400x, offering a closer look at the cellular details.

Histological sections were stained with hematoxylin and eosin (H&E) to visualize the shapes and tissue structures. These histopathological findings offer insights into the neurotoxic effects of isotretinoin at varying doses, underscoring the need for further research on its safety profile and possible impact on the central nervous system.

A specialized pathologist with expertise in brain tissue analysis was used to ensure the accuracy and reliability of the results. The pathologist evaluated the tissue samples using advanced methods and standardized criteria, allowing for a comprehensive analysis of histopathological changes. This evaluation included examining cellular structures, assessing the degree of damage, and monitoring changes that may indicate the treatment effects or toxicity.

## Discussion

This study examined isotretinoin's effects on animal behavior, motor activity, neurotransmitter interactions, and brain tissue. The $LD_{50}$ was 4841.2 mg/kg, indicating toxicity risks at high doses. Neurobehavioral tests showed that isotretinoin increases motor activity, such as standing time and square crossing, suggesting brain effects that manifest as anxiety (Gould et al., 2009). The light and darkness experiment also indicated that the mouse preferred staying in the light to the dark, indicating stress experienced by the animals, possibly due to nerve receptor stimulation in the brain. Similarly, findings from the negative geotaxis test showed that it took longer for the animal to turn around, suggesting an impairment in its vestibular brain functions. The brain plays a role in maintaining balance, and a decreased interest level implies that animals may not be fully aware of their environment (Kulesskaya & Voikar, 2014).

In this study, we explored how certain brain neurotransmitters influence behavioral changes. The rise in anxiety and tension observed in the animals could be due to disturbances in the levels of neurotransmitters, such as Ach and serotonin (Hurst & West, 2010). Serotonin, a neurotransmitter that impacts mood, cognition, and behavior, has been linked to mental health conditions, such as sadness and anxiety. The decrease in levels after isotretinoin treatment raises concerns about the mood-related side effects of therapy (Dopheide & Morgan, 2008). These results highlight isotretinoin's influence on neuropsychiatric side effects, including altered acetylcholine levels after treatment (Kontaxakis et al., 2009). Acetylcholine is crucial for neurotransmission, muscle movement, and cognition. The observed increase in acetylcholine may indicate effects on cholinergic mechanisms (Bacqué-Cazenave et al., 2020), although the exact process, whether through production, release, or breakdown in the peripheral nervous system, remains unclear (Ding et al., 2023).

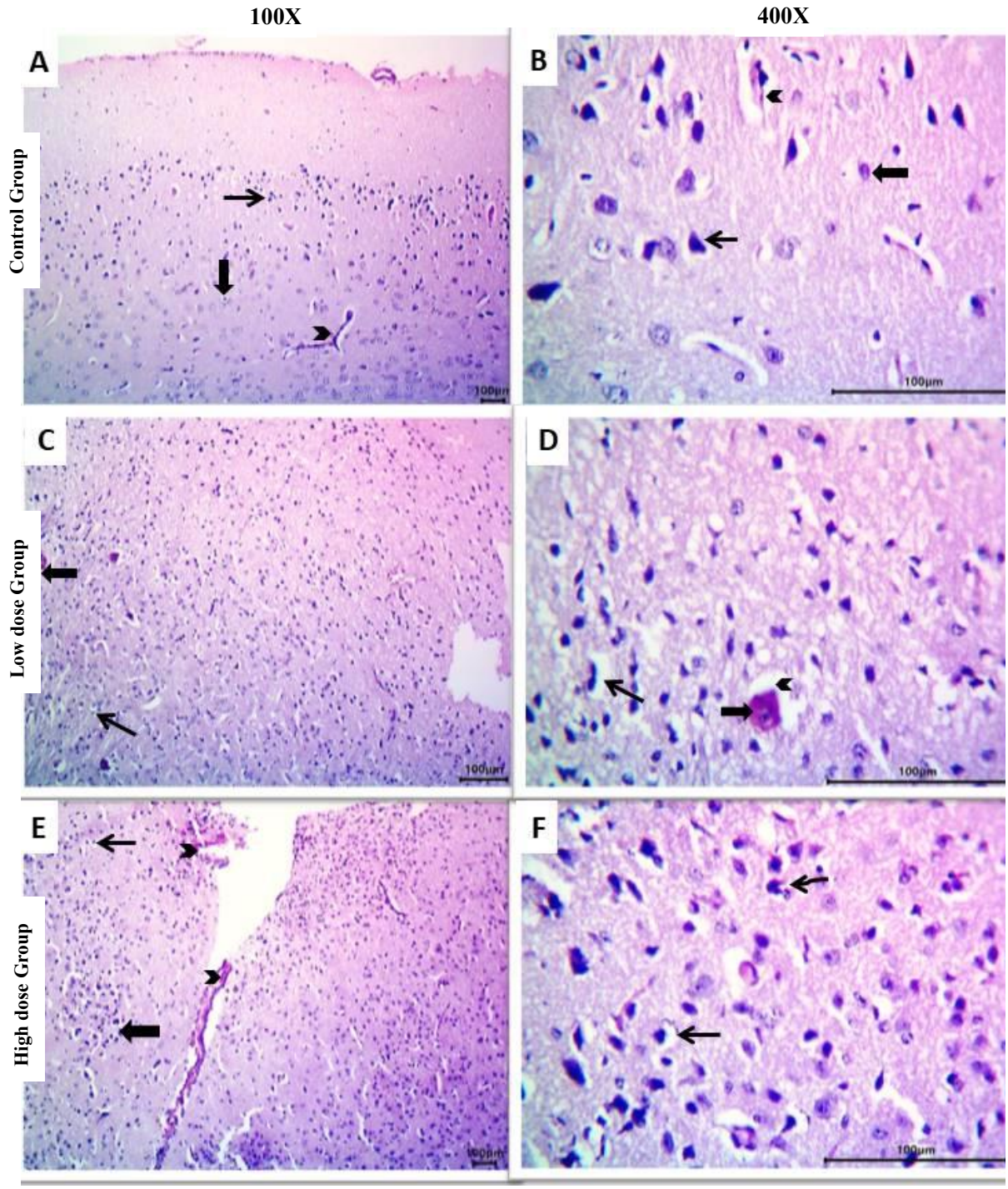


**Figure 1.** Sections of the mice brain under a microscope

Note: In images A and B representing the control group we observe the structure of neurons (pointed by an arrow) glial cells (indicated by an arrow) and blood vessels (marked with an arrowhead). Moving on to images C and D related to the low dose (125 mg/kg) isotretinoin group we notice vacuolization (arrow) congestion, in blood vessels (arrow) and mild perivascular edema (arrowhead). Images E and F depict the high dose isotretinoin group (250 mg/kg) which display vacuolization (arrow) gliosis (arrow) congestion and hemorrhage in blood vessels (arrowhead) along, with satellitosis indicated by an arrow. The left panel represents ×100 magnification while the right panel represents ×400 magnification. Stained with H&E.

Patients on isotretinoin should be monitored for side effects, such as muscle weakness, digestive issues, or cognitive concerns (Rose & Goldberg, 2013). Both doses of isotretinoin significantly raised COMT levels, an enzyme that metabolizes neurotransmitters, such as dopamine, serotonin, norepinephrine, and epinephrine, which may explain the serotonin decline observed in this study. COMT regulation affects mood, stress, and cognitive function (Brandt & Flurie, 2020), and altered COMT activity is associated with conditions, such as schizophrenia, depression, and Parkinson's disease (Clayton et al., 2020). Histopathological analysis showed dose-dependent effects on brain tissue consistent with prior studies showing isotretinoin's impact on nerve cell development and repair (Balch et al., 2012).

Isotretinoin has been linked to delays in brain development, affecting mental and nervous system growth (Meloto et al., 2015). Research shows that isotretinoin impairs neuron growth in the hippocampus, crucial for memory and learning, by impacting gene activity that regulates nerve cell growth, survival, and repair, accelerating neuron death in this area (Bremner et al., 2011). As an anti-inflammatory, isotretinoin reduces skin inflammation by inhibiting leukocyte migration and likely functions through retinoic acid receptor activation, affecting gene expression (Clark et al., 2020; Isoherranen & Zhong, 2019). Retinoic acid from vitamin A is essential for cell differentiation across various systems, including the hippocampus, which relies on neuronal plasticity and neurogenesis for memory formation (Dabrowska & Thaul, 2018). Histopathology confirmed isotretinoin's dose-dependent toxicity in the brain tissue, consistent with previous findings showing restricted nerve cell formation and repair (Nurjanti, 2019).

In addition to damage to synapses and the communication points between nerve cells, there are brain developmental issues, such as delayed mental and nervous development (Huang et al., 2014).

Researchers have also discovered that isotretinoin inhibits the development of new neurons in the hippocampus, a brain region critical for memory and teaching (Clark et al., 2020).

Isotretinoin alters the expression of several genes in nerve cells, including those involved in nerve cell growth and death, thus slowing the repair of damaged nerve cells in this brain region (Ormerod, 2021; Moini & Piran, 2020).

Researchers have also discovered that isotretinoin causes nerve cell loss in the hippocampus (Al-Abdaly et al., 2023; Khodabakhshi Rad et al., 2023).

Our research on the effects of isotretinoin on behavior and biochemistry matches what previous studies have found that isotretinoin can affect neurotransmitter levels and brain function. Previous studies conducted by Bremner et al. (2021) and O'Reilly et al. (2006) also reported changes in pathways and behavioral patterns after administering isotretinoin. This explains why we observed serotonin levels in mice administered 125 mg/kg in our study. The disturbance of this chemical messenger is acknowledged as an element in alterations to patterns, and research has connected these shifts to emotional disorders and cognitive limitations while also heightening the stress response.

However, there are differences between these studies. For instance, previous investigations have mostly concentrated on low-level application of isotretinoin, whereas our study assessed sudden dosages. Our findings particularly concern increased acetylcholine levels. Intensified COMT enzyme function is fresh and indicates that immediate isotretinoin exposure could provoke distinctive biochemical reactions, perhaps using increased oxidative stress or acetylcholine pathway adjustment. These findings enhance our knowledge of the impacts of isotretinoin. This emphasizes the necessity for further exploration of dose-related neurochemical alterations.

Addressing experiments presents difficulties and suggestions to consider moving forward when dealing with the careful monitoring required for high doses of isotretinoin due to the potential toxicity risks involved in the process. A notable challenge arises from the varying neurobehaviors exhibited by mice, which could be influenced by factors affecting the experiments' outcomes.

Future research should investigate the impact of doses over time to mimic real-world usage patterns. It would be beneficial to study the long-term effects of isotretinoin on neurotransmitters, such as serotonin and acetylcholine, as COMT in diverse populations across different age groups and sexes. Additionally, exploring the benefits of using substances, such as antioxidants or enzyme inhibitors, to mitigate the neurotoxic effects of isotretinoin could be valuable for future research.

## Conclusion

We conclude that orally administered doses of isotretinoin influence animal neurobehavior due to its effect on brain tissue, as evidenced by its effects on serotonin, acetylcholine and COMT.

## Ethical Considerations

### Compliance with ethical guidelines

This study was approved by the Ethics Committee of University of Mosul, Mosul, Iraq (Code: M.VET.2023.036).

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### Authors' contributions

All authors contributed equally to the conception and design of the study, data collection and analysis, interception of the results and drafting of the manuscript. Each author approved the final version of the manuscript for submission.

### Conflict of interest

The authors declared no conflict of interest.

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