Original

Reproductive Toxicity Induced by Tramadol Exposure in Female Albino Rats

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Article history: Received 19 November 2024, Reviewed 03 March 2025, Accepted for publication 06 March 2025

Abstract

Background: Tramadol, a widely abused opioid analgesic, has been linked to various adverse effects, including potential reproductive toxicity. This study evaluated the effect of tramadol on reproductive toxicities in female albino rats.
Methods: Sixty albino rats (40 females and 20 males) were used in a completely randomized design. The 40 females were divided into five groups (eight per group). Group A served as control, while groups B, C, D, and E received 25, 50, 75, and 100 mg/kg BW of tramadol orally for 28 days. After treatment, females were mated with males (1:2 ratio) for seven days until pregnancy confirmation. Pregnant rats were euthanized on days 11–12 of gestation to assess implant counts and induced dominant lethal mutation indices (IDLM). Remaining females completed gestation, and litter size, litter weight at birth and weaning, and offspring survival index were recorded. Data were analyzed using one-way ANOVA, and significant differences were identified using the post hoc Tukey test, assuming that the data were normally distribution and homogeneous variance.
Results: Tramadol exposure resulted in a significant dose-dependent reduction ($p>0.05$) in kidney, liver, lung, heart and spleen weights, as well as decrease in the number of live implants, conception rate, and litter size and weight. The number of dead implants and IDLM rates significantly increased in tramadol-treated groups compared to controls, with all effects dose-dependent.
Conclusion: This study indicates that tramadol can induce reproductive toxicity in female rats, highlighting the need for cautious prescription and awareness campaigns against tramadol abuse.

Keywords: Tramadol, Reproductive toxicity, Conception rate, Litter size, Implantation

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How to cite this article:

Idara S. Esua, Ukam U. Uno, Ekerette E. Ekerette, Reagan B. Agbor, Uduak L. Edem, Ekei V. Ikpeme and Utip B. Ekaluo. Reproductive Toxicity Induced by Tramadol Exposure in Female Albino Rats. The Nigerian Health Journal 2025; 25(1):231 – 239.
https://doi.org/10.71637/tnhj.v25i1.962

Introduction

Opioids, including tramadol, refer to any substance in a group of analgesic agents derived from opium. They are depressants that slow down the transmission of messages through the central nervous system between the body and the brain. While used to treat pain, opioids also induce euphoria and sedation, which can be addictive, leading to widespread abuse.[1] Findings reveal that opioid use can disrupt the hypothalamic–pituitary–gonadal (HPG) axis, leading to opioid-induced hypogonadism, reduced libido, irregular menstruation in women, erectile dysfunction in men, and infertility.[2-3] Opioid abuse and addiction represent a growing social and health crisis worldwide despite efforts to prevent and control it.[4]

Tramadol is a frequently abused narcotic drug that has gained popularity among young men and women. It is a synthetic, prescription opioid analgesic used to treat moderate to moderately severe pain, such as that experienced after surgery or from chronic conditions like arthritis and fibromyalgia. Tramadol is typically available in 50–300 mg tablets and is taken orally. Brand names include Ultram, Ultram ER, ConZip, and Ryzolt, and common street names include "trammies," "chill pills," "tramal," and "ultras"[5]. It delivers analgesia not only by producing 'opioid-like' effects but also by acting as a weak, fast-acting serotonin-releasing agent and norepinephrine reuptake inhibitor.[6] As a centrally acting opioid analgesic, tramadol is considered a weaker opioid. Although prescribed as a pain medication, its stimulant effects can cause people to feel euphoric at dangerously high doses, with effects like heroin.[5-6] Tramadol is one of the most widely prescribed opioids worldwide for the relief and management of acute and chronic pain of moderate to severe intensity, associated with conditions like osteoarthritis, fibromyalgia, and diabetic neuropathy, and is approved for short-term cancer pain management.[7]

Tramadol is considered the safest analgesic among opioids because it has fewer side effects though it has less clinical efficacy than other opiates with about one-tenth of pain-relieving qualities of morphine.[6]. However, when abused, tramadol produces effects like other opiates, such as euphoria, numbness, lethargy, and calmness.[8]. Tramadol primarily works by acting directly on the brain, modifying the processing of pain signals traveling between the nerves and the brain. Its effects on norepinephrine and serotonin in the brain also lend it to antidepressant-like qualities.[9-10] Tramadol is metabolised into o-desmethyltramadol, a more potent activator of opioid receptors, which can produce stimulating effects in users even if that was not the initial intention.[11] The misuse of tramadol has become a significant aspect of substance abuse in recent years and is rapidly evolving into a health crisis. In Nigeria, the prevalence of tramadol and substance abuse was reported among internally displaced persons (IDPs), largely as a coping mechanism for food scarcity in displacement camps.[12,13] Tramadol is known for its analgesic properties, as well as its ability to induce euphoria and a perceived increase in physical strength. Within IDP camps, it is often marketed as a 'magic drug' that enhances mood and boosts confidence, contributing to its widespread use and subsequent addiction.[14]

In a related survey, [15] reported that a study on drug use in various countries found significant abuse in Nigeria, where 14.3 million people aged fifteen to sixty-four reported using drugs. The survey, conducted by the National Bureau of Statistics (NBS) and the Centre for Research and Information on Substance Abuse (CRISA) in collaboration with the United Nations Office on Drugs and Crime (UNODC) and the European Union (EU), revealed a gap in awareness, treatment options, and support for people affected by drug abuse. Although tramadol has fewer side effects compared to other opioids, it is potent enough to cause euphoria, comparable to heroin.[15-17] Cases of addiction, respiratory depression, dependency, intentional overdose, and poisoning have been documented.[18-23]

Reproductive toxicity refers to biologically adverse effects on the reproductive system and functions in both males and females, as well as developmental toxicity in offspring due to exposure to chemicals or other environmental agents.[24] Reproductive toxicity may manifest as adverse effects on puberty onset, gamete production, reproductive cycle regularity, sexual behavior, fertility, pregnancy, lactation, or other reproductive functions. Manifestations of developmental toxicity include the death of the developing organism, structural abnormalities, altered growth, and functional deficiencies.[25] Reproductive toxicity affects sexual behavior and fertility in both females and males.[26] In women, substance abuse is reportedly related to hormonal imbalances, menstrual irregularities, fertility issues, pregnancy complications, breastfeeding difficulties, and menopausal symptoms.[27] In a previous study, we reported that tramadol has a dose-dependent adverse effect on semen quality and quantity.[28]. Given the increasing abuse of tramadol among women of reproductive age, this study was conducted to assess the effects of tramadol treatment on reproductive toxicity in female rats.

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Materials and Methods

Materials collection

Tramadol (Tramadol HCL), 200 mg tablets obtained from by Bliss GVC Pharma Limited, India.

Experimental animals

Sixty (60) sexually matured albino rats comprising forty females and twenty males with body weight ranging from 200-230g were used in this experiment. Wistar rat, a popular choice for scientific research, has its roots in a wild rat population from the early 20th century. Wistar rats are selected for research based on specific age and weight criteria, typically between 8-12 weeks. Wistar albino rats are renowned for their docility and ease of handling, making them an ideal choice for research. Their stable characteristics and consistent reproductive data make them a popular choice for toxicology, pharmacology, and nutritional studies. The inclusion criteria were the sex of the animals, age and body weight. The animals were kept in steel cages covered with wire mesh under a standard laboratory environment. They had free access to food and water daily. The food was a commercial feed from Top Feed Limited (crude protein: 18 per cent; metabolizable energy: 2800 kcal/kg). Animals were allowed to adapt to their environment for one week before treatment. Animals were handled in line with the Helsinki protocol for care of experimental animals.[29] Their bedding (wood shavings) was changed every three days. Humane endpoints for this study include clinical symptoms of distress and disease and behavioural changes and were monitored regularly. Some mortalities (adverse effects) were observed during the duration of the treatment.

Experimental design and protocol

The forty female albino rats were divided into five groups (A, B, C, D and E) made up of eight animals under a completely randomized design (CRD). The randomization protocol was executed using GraphPad randomization software. Blinding was implemented so that researchers responsible for administering treatments and conducting laboratory analyses were not informed of the treatment group allocations. The sample size was determined based on previous research findings and relevant literature, adhering to the 3Rs principle of animal research to ensure ethical and efficient use of experimental animals. The lethal dose 50% (LD_{50}) value of oral administration was estimated to be 340 mg/kg BW for rats.[30] The chosen dose was nearly comparable to the human effective therapeutic dose.[31] The daily dose (D) was calculated according to[32] using the formula: D = MRT, where M = maximum recommended daily human dosage in tablets, R = ratio of weight of rats to average human weight of 60 kg and T = weight of each tablet. The test substance tramadol was pulverised, weighed, and dissolved in normal saline and given orally by means of oral gavages to the rat in accordance with Table 1. The dosage was adjusted every week according to changes in body weight.

After 28 days of the treatment, the animals were mated for seven days with the male animals in 1:2 ratios until pregnancy was confirmed. The female rats were euthanised using cervical dislocation after Isoflurane anaesthesia between the 11- and 12-day following exposure to males which was approximately half-way the 21 – 23 days gestation period.[33]. The female rats in the five groups were scored for total implants (embryos) which involved live embryos and early fetal IDLM while the remaining animals were allowed to carry the pregnancy to full for estimation of birth rate, litter size and litter weight.

Weight of organs

Weight of the kidney, liver, lungs and heart were determined using an electronic weighing balance (Scout Pro SPU 601).

Dominant lethal mutation indices

The treated virgin female rats were sired by untreated males. They were co-habited in the ratio of one male: two female for seven days. The female rats were euthanised using cervical dislocation after Isoflurane anaesthesia the 15th and 19th day following exposure to males, which is approximately half-way the 28 days gestation period. Autopsy was carried out on the female rats, and they were scored for implants (embryos) which comprised of live embryos and early fetal deaths. IDLM was calculated using[34] thus:

$$\text{IDLM} = 1 - \frac{\text{Live implant (treated)}}{\text{Live implant (control)}}$$

Birth weight

The litters were weighed on electronic balance (Scout Pro SPU 601) and the results for each group were averaged. The sex of the newborn rats was determined from both the distance that separates the genital papilla and the anal opening and from the general appearance of the urogenital-anal region. The numbers of male and female pups were counted and observed sex ratio recorded. The number of litter alive in the control and treatment groups were recorded and all the litter were re-examined for external malformations in the head, face, nostrils, eyes, external ears (pinna), trunk to tail and limbs.

Litter size at birth and at weaning

The numbers of the pups were counted at birth and weaning (18 days old).

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Litter weight at birth and at weaning

The weight of the pup in each group at birth and weaning was recorded using an electronic balance (Scout Pro SPU 601)

Statistical analysis

Data obtained were tested for normality, homogeneity and independence of observations and the assumptions of the statistical approach were met. The data obtained on all the parameters were analysed using one-way ANOVA and subsequently, post hoc Tukey test at $p < 0.05$ using Statistical Package for the Social Sciences (SPSS) 27 (IBM, New York, USA). All results obtained were presented as mean ± standard error of mean (SEM) (n = 8 replicates).

Results

Weight of organs

Tramadol treatments had a significant effect ($p<0.05$) on the all the organ examined in the treated female rats when compared to the control group increasing from 0.28± 0.08g to 0.75±0.28g for kidney, 2.08±0.35g to 5.04±1.19g for liver, 0.50±0.03 to 0.98±0.37g for lungs, 0.19±0.13 to 0.41±0.15 for heart and 0.20±0.14 to 0.85±0.32g for spleen in the control and group E, respectively in a dose dependent manner (Table 2).

Conception rate

Results showed a significant decrease in the conception rate of tramadol treated female rats as compared to control group. The control group had a conception rate of 100% while it reduced dose-dependently in the tramadol treatment to 40% (Fig. 1, Table S1)

Induced dominant lethal mutation indices

The IDLM obtained in tramadol treated female rats sired by untreated males showed a dose-related response on the lethality as the treatment increased (Fig. 1). Results revealed a significant decrease in weight of implant and number of live embryos in treated animals with the highest value recorded in group E females treated with 100 mg/kg BW of tramadol compared to the control (Fig. 2). The IDLM also increased significantly in the treatment groups against the control group with concomitant dose dependent increase in the frequency of IDLM (Table S2).

Litter size and weight at birth and at weaning

No external malformations in the tramadol treated group as well as in the control. However, there was a significant difference in the litter size of the pubs at birth and weaning with an increase in the treatment when compared to the control group (Table 3). The average litter size reduced from 4.00 (control) to 0.75 (group D) at birth and weaning, respectively. In the same vein, litter weight at birth and weaning reduced significantly in the tramadol treated animals in a dose-dependent manner when compared to the control as presented in Table 3, from 20.31±3.00 to 3.08±1.09 at birth and 150.62±12.08 to 29.72±10.56 at weaning for the control and group D, respectively. Furthermore, there was a significant decrease in the offspring survival index from 47.92±9.00 in the control to 12.50±3.15 in group D (Table 3).

Discussion

The administration of tramadol had a significant effect on the organ weights of treated female rats, with significant increases in the kidney, liver, lungs, heart, and spleen when compared to the control group. These increases suggest a dose-dependent effect. The changes observed in organ weights are critical because they can reflect underlying alterations in physiological or pathological states, potentially due to pharmacological impact of tramadol on various bodily systems. The significant increase in the weight of the kidney could be associated with renal hypertrophy or tissue accumulation as the kidney attempts to metabolize and excrete the drug. This aligns with findings from previous studies suggesting that tramadol and other opioids may lead to renal stress and alter kidney function over time.[35-37]

Similarly, the liver, a primary organ involved in drug metabolism, showed an increase in weight, which may indicate hepatic hypertrophy or even mild hepatotoxicity due to the metabolic demands of the drug on liver enzymes and tissues.[38] Consistent with these findings, other studies have documented that chronic administration of tramadol can lead to increased liver enzyme activity, indicative of hepatocellular stress or adaptation to increased metabolic processing demands.[38-40] The tramadol-induced increase in lungs and heart could be due to congestion, inflammation, or even early signs of tissue damage induced by systemic effects of the drug. Tramadol has been associated with respiratory complications, and these findings may reflect initial physiological adjustments or potential adverse effects on pulmonary tissues.[41-43] This increase aligns with research on opioids that suggests possible alterations in respiratory tissues with prolonged use, even at sub-toxic levels.[44]

The female rats treated with tramadol had lowered conception rates which were dose-dependent, and this agrees with [43], suggesting that opioids are likely to interfere with female reproductive systems. This may be attributed to the presence of opioid receptors in human oocytes, granulosa cells, and the endometrium.[45]. In line

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with the findings of this study, [46] noted that tramadol interference may result in lowered conception. A possible mechanism of action is the effect on the preparation for egg release by the body, influenced by follicle-stimulating hormone (FSH) or luteinizing hormone (LH) production, regulated by the pituitary gland. Since opioids affect the endocrine system, especially the hypothalamus and pituitary, they lead to a drop in gonadotropins like FSH and LH, key hormones in female reproduction. [47-48] These hormones play vital roles in oogenesis, and tramadol-induced disruption in hormone levels can significantly impact fertility, resulting in reproductive dysfunction.[31,49-53] The findings of this study contradict those of [30], who reported that tramadol has no effect on fertility, conception, and lactation processes in rats and subsequently had no effects on the fetus.

The IDLM of groups treated with tramadol showed dose-dependent increases, which may be attributed to abnormalities induced in the egg cells, as suggested by.[54] The increase in mutation indices suggests aberrations during oogenesis, as reported by.[55-56] The increase in the dominant lethal mutation index of tramadol-treated rats corroborates results obtained regarding the number of dead implants in rats in the same group. This agrees with,[57] who reported that a genetic abnormality can give rise to early embryonic and fetal mortality. These findings suggest that the effects observed in this present study in the treatment group might have occurred in the early stages of pregnancy. This can also be attributed to genetic defects induced in the oocytes due to the treatment. Anderson [58] reported that dominant lethal mutations, congenital malformations, and heritable translocations were associated with heritable damage and that IDLM were responsible for gamete dysfunction, which is lethal to fertilized eggs or developing embryos, resulting in stillbirths and early fetal lethality. This increased frequency of IDLM, increased number of dead implants (embryos), and the lowered conception rate could be due to oxidative stress, mitochondrial functional abnormalities, and impaired production of antioxidant enzymes.[57]

Results obtained also indicated a significant decrease in litter size and weight at birth and weaning in tramadol-treated animals when compared to the control. Litter size and weight are considered sensitive indicators of responses to toxicants of an animal [59]. The significant dose-dependent decrease in litter size and weight in the treatment groups further supports our results on conception rate and the number of live implants, in line with [48], who suggested that maternal toxicity adversely affects offspring. Furthermore,[48,59-60] reported the generic effect of certain therapeutics, noting that opioids affect fetal outcomes and litter size in rats. In contrast to our findings,[52] reported that morphine-treated rats showed no significant differences in litter size and weight, although the offspring of opioid-treated rats exhibited significant behavioral changes.

Strengths and limitations

The study presents a well-structured and scientifically rigorous investigation into a significant health-related issue, offering valuable insights on effects of drug abuse. A major strength lies in its comprehensive methodology, which ensures high reliability and reproducibility of findings. The use of appropriate data collection techniques and robust statistical analysis enhances the credibility of the study, making its conclusions both statistically sound and practically relevant. Furthermore, the research addresses critical gaps in existing knowledge tramadol abuse. The findings are relevant to both researchers and practitioners, thereby increasing their potential impact on policy and practice.

While all studies have inherent limitations including sample size and scope, these have been carefully managed through methodological precision and analytical rigor, ensuring that the conclusions remain highly relevant. Additionally, any potential biases have been minimized through strategic research design, making the results broadly applicable and significant.

Conclusion

This study revealed that chronic tramadol exposure has significant toxic effects on the reproductive system of female albino rats, including reduced body weight, lowered conception rates, increased mutation frequency and reduced gestational outcomes. These findings underscore the potential for both prescription and illicit substance abuse to severely impact fertility and reproductive health, with some effects possibly reversible upon cessation, while others may result in permanent reproductive damage.

Declaration

Funding: This research has no external funding.

Author contributions: Utip Ekaluo: Writing – original draft, Methodology, Investigation, Formal analysis. Idara Esua: Writing – original draft, Methodology, Investigation, Formal analysis. Ekerette Ekerette: Methodology, Investigation, Formal analysis. Reagan Agbor: Investigation, Formal analysis. Uduak Linus: Formal analysis. Ekei Ikpeme: Data curation, Conceptualization. Ukam Uno: Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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Table 1. Treatment protocol

Treatment groups	Description of treatments
A	Control group was given 2 ml of normal saline orally daily for 28 days.
B	Tramadol at 25 mg/kg BW was given to them in 2ml of normal saline orally for 28 days
C	Tramadol at 50 mg/kg BW was given to them in 2ml of normal saline orally for 28 days
D	Tramadol at 75 mg/kg BW was given to them in 2ml of normal saline orally for 28 days
E	Tramadol at 100 mg/kg BW was given to them in 2ml of normal saline orally for 28 days.

Table 2: Weight of organs of female rats treated with tramadol

Organs	Group A	Group B	Group C	Group D	Group E
Kidney	0.28±0.08^{a}	0.33±0.08^{a}	0.37±0.14^{a}	0.45±0.29^{b}	0.75±0.28^{c}
Liver	2.08 ±0.35^{a}	2.08 ±0.40^{a}	2.63 ±0.73^{b}	4.59 ±1.75^{c}	5.04 ±1.9^{c}
Lungs	0.50 ±0.03^{a}	0.53 ±0.06^{a}	0.81 ±0.53^{b}	0.90 ±0.33^{b}	0.98 ±0.37^{c}
Heart	0.19 ±0.13^{a}	0.21 ±0.15^{a}	0.21±0.14^{a}	0.39 ±0.15^{b}	0.41 ±0.15^{b}
Spleen	0.20 ±0.14^{a}	0.23 ±0.06^{a}	0.34 ±0.23^{b}	0.59 ±0.22^{c}	0.85 ±0.32^{d}

Values are presented as mean ± standard error. Means with similar case letters across vertical array are not significantly different at p>0.05

Table 3: Litter size and weight at birth and at weaning of female rats treated with tramadol

Parameter	Group A	Group B	Group C	Group D	Group E
Litter size at birth	4.00±1.57^{a}	1.50±1.0^{b}	1.55±1.16^{b}	0.75±0.75^{b}	0.00±0.00^{d}
Litter size at weaning	4.00±1.52^{a}	1.50±1.00^{b}	1.50±0.98^{b}	0.75±0.75^{c}	0.00±0.00^{d}
Litter weight at birth	20.31±3.00^{a}	9.22±1.34^{b}	6.8±1.55^{c}	3.08±1.09^{d}	0.00±0.00^{e}
Litter weight at weaning	150.62±12.08^{a}	60.60 ±10.00^{b}	57.23±11.00^{b}	29.72±10.56^{c}	0.00±0.00^{d}
Offspring survival index after seven days	47.92±9.00^{a}	25.00±4.50^{b}	21.88±4.00^{c}	12.50±3.15^{d}	0.00±0.00^{e}

Values are presented as mean ± standard error. Means with similar case letters across horizontal array are not significantly different at p>0.05

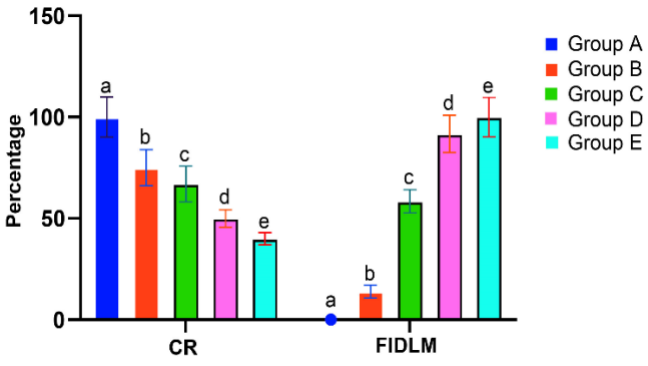

Fig1. Effect of tramadol on conception rate (CR) and frequency of IDLM (FIDLM) of female albino rats

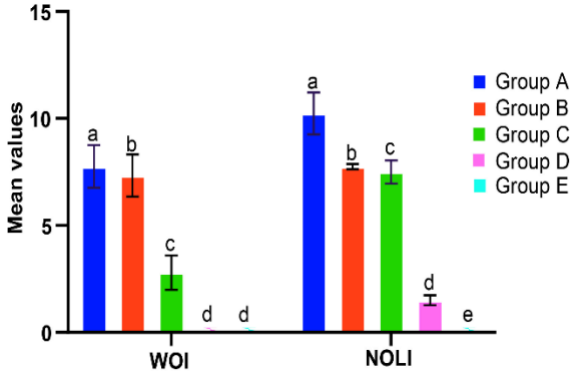

Fig. 2. Effect of tramadol on weight of implants (WOI) and number of live embryos (NOLI) of female albino

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