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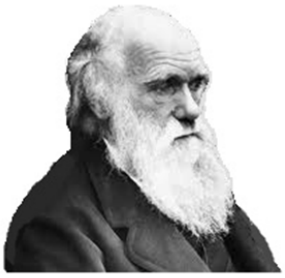

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Histological effects of tramadol on the uterus of albino wistar rat

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ABSTRACT

Tramadol is a synthetic opioid primarily used in pain management. A report by the National Bureau of Statistics (2018) shows that 4.6 million people have misused tramadol in Nigeria. This is due to its availability at cheap prices in pharmacies which do not require prescriptions. Researches has proven and shown that tramadol can be used in the treatment of early ejaculations, extended orgasm and increase performance in men. But the absence of information on the effect of tramadol on the female reproductive system, the concept of fertility is the reason for this study. The present study was undertaken to investigate the histological effects of tramadol on female fertility. The specific objectives were to; A) To evaluate the effect of tramadol misuse on the histology of the Uterus B) To investigate

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the behavioral effect of tramadol abuse on female albino rats. The study adopted the experimental design. Thirty-six (36) healthy female albino wistar rats (100-150g) were used for this study. Following parturition, they were divided into five groups of six rats per group (6) labeled 1- 5. Treatment was carried out as follows: Group 1 (Normal Control) received the normal feed and distilled water. Group 2: Tramadol (25 mg/kg/day), Group 3: Tramadol (25 mg/kg/day), Group 4: Tramadol (50 mg/kg/day), Group5: Tramadol (50 mg/kg/alternate days). Treatment was done for the period of thirty-three day at 11:00 daily. At the end of experiment, animals were sacrificed using cervical dislocation, the uterus organs were harvested, fixed in 10% formal saline and stained with Hematoxylin and Eosin. The Uterus tissues of rats in the control group showed normal uterine features and those treated with 25 mg/kg and 50 mg/kg of only dose of tramadol showed moderate or severe necrotic effects on the endometrial lining. This study affirms that the abuse of tramadol hydrochloride has a deleterious chronic toxic effect on their uterus.

***Keywords*:** Substance Abuse, Tramadol, Opioid, Analgesic, Uterus, Endometrium, Fertility

1. INTRODUCTION

Substance abuse refers to the use of the substances for a purpose that is not consistent with the medical or legal guidelines or using it in a manner or dose other than prescribed. For example, using drugs for sexual stamina, work performance, euphoria and for several purposes other than medical treatment indicates misuse. Substance use and abuse by the youths and adolescents has been on the increase to the extent it has been labeled a global epidemic by the WHO with far reaching adverse effects on both the individual and society at large (Owoaje and Bello, 2010; Duru *et al*., 2017). These substances may include alcohol, tobacco, hallucinogens (alpha-methyltryptamine, ketamine, phencyclidine, D-lysergic acid) and illicit drugs (cocaine, heroin, marijuana, rohypnol and opioids) (Duru *et al*., 2017; Idowu *et al*., 2018). Pederson et al., in 2013, stated that research on human and animal has found that women are generally more vulnerable to the long-term physical effects of drugs and alcohol compared to men. Of growing interest is the increased demand for tramadol which is an opiate analgesic medication. However, the increasing and widespread use of tramadol, especially among youths is worrisome, due to it's availability at cheap prices in pharmacies which do not require prescriptions (Chikezie and Ebuenyi., 2019; Zabihi *et al*., 2011).

However, the increasing and widespread use of tramadol, especially among youths is worrisome (Chikezie & Ebuenyi., 2019; Zabihi *et al*., 2011). Aside from the therapeutic benefits, tramadol use has been strongly associated with drug disorder morbidities (such as addiction, insomnia, and organ damage) and even death (Barahmand *et al.,* 2016; El Wasify *et al*., 2018; Chikezie & Ebuenyi., 2019). The African continent has seen an increase in the opioid crises (Salm-Reifferscheidt., 2018), and tramadol is the top opioid of abuse especially in countries such as Egypt and Nigeria (Mohamed *et al.,* 2015; Iorfa *et al*., 2018). A report by the National Bureau of Statistics (2018), shows that 4.6 million people have misused tramadol in Nigeria.

The high prevalence of tramadol misuse in Nigeria could be attributed partly to non-regulation of tramadol at the international level and its' availability at cheap prices at Nigerian pharmacies which do not require prescription notes before selling out. The belief that tramadol serves as a remedy for premature ejaculation, extends orgasm and increases work performance

has contributed to its popularity and massive use among Nigerian youths (Ibrahim *et al*., 2017; Orhero., 2018; Chikezie & Ebuenyi., 2019). Studies carried out in Nigeria on the widespread use of tramadol showed that 85.2% of sampled drivers in Kano, Northern Nigeria (Yunusa *et al*., 2017), 7% of 'Almajiris' (street children) in Borno, Northern Nigeria (Abdulmalik *et al*., 2009), and 53.4% of university students in Owerri, Southeastern Nigeria (Duru *et al*., 2017) used tramadol.

The alarming rate of tramadol misuse by young people has posed a serious health challenge globally as it is known to have dire health consequences ranging from mild effects like headache, stomachache, itchy skin and painful urination to severe long-term effects like psychiatric disorder, seizure, serotonin syndrome, cardiovascular collapse and respiratory depression (El-Hadidy & Helaly., 2015; Zwawua *et al.,* 2020). El-Mottaleb *et al*., (2019), observed that opioid therapy leads to impaired endocrine function and dysregulated sex steroid balance in women. Long term opioid use exposes women to unique risks, including endocrinopathy, reduced fertility (El-Mottaleb *et al*., 2019). Abnormal absence of menstruation (amenorrhea) have been reported in more than half of the opioid-taking women aged 30–50 (El-Mottaleb *et al.,* 2019). Tramadol abuse amongst pregnant women has also been reported to produce a variety of neonatal complications ranging from low birth weight to long term development deficits (Bloor *et al*, 2012).

Tramadol is a synthetic opioid analgesic and is chemically trans-2-(dimethylaminomethyl)-1-(mmethoxyphenyl)-cyclohexanolhydrochloride. It is a centrally active analgesic, which possess opioid agonist properties and activates monoaminergic spinal inhibition of pain (Lee *et al*., 1993). Tramadol is used for the relief of moderate to moderately severe acute or chronic pain types, including postoperative pain, gynaecologic and obstetric pain, lower back pain, neuropathic pain, osteoarthritis, fibromyalgia, labour and as well as pain of various other organs, including cancer (Kaye., 2015). Tramadol is available as drops, capsule, tablet, suppositories and solutions. Tramadol is used as an anxiolytic, anti-depressant and anti-shivering (Baraka., 2019). Tramadol modulates the descending pain pathways within the central nervous system through the binding of (+)-tramadol and its primary metabolite (+)-O-desmethyl -tramadol (m1) to μ-opioid receptors and the weak inhibition of the re-uptake of serotonin and norepinephrine (Shine *et al*., 2017) (Martyn St *et al*., 2015). Tramadol is readily absorbed following oral administration and the bioavailability is 75% but is subject to first pass metabolism.

The rate or extent of Tramadol absorption is not significantly affected by food. It is metabolized by N-and O- methylation and glucuroxidation and sulfation in the liver and produce active metabolite O-desmethyltramadol which is pharmacologically active. As also reported by Pederson *et al.,* (2013) females are more susceptible to these adverse reactions of tramadol. The most commonly reported adverse effects are nausea, vomiting, central nervous system depression, seizure, dizziness, agitation, tachycardia, hypertension, reduced appetite, headache, itching, pruritus and rashes, gastric irritation and skin eruption (Marquardt *et al.,* 2005; Shadnia *et al*., 2008; Rahimi *et al*., 2014; Ghoneim *et al.,* 2014; Tsutoaka *et al*., 2015; Dhagudu *et al*., 2019). Increased tremor, irritability and increased deep tendon reflexes has been reported by Shadnia *et al.,* (2008) and Ghamsari *et al*., (2016). Research has proven and shown that tramadol can be used in the treatment of early ejaculations, extended orgasm and increased performance in men (Hossain et al., 2016; El-Baky and Hafez., 2017; Sherein *et al.,* 2020).

In particular, Tramadol use can harm the reproductive system in women. Osadolor and Omo-Erhabor (2016) reported the reduction in luteinizing hormone (LH) and follicle-

stimulating hormone (FSH) levels by opioids in an animal study. Some other reviews reported that tramadol has effects on female fertility (Ahmed and Kurkar., 2014; El-Ghawet., 2015; Vazzana *et al*., 2015; Humphrey and Joseph, 2016). Kallen and Reis reported congenital malformation, and some were relatively severe malformation (Kallen and Reis, 2015). In the female reproductive system, infertility may be caused by a range of abnormalities of the ovary, uterus, fallopian tube and the endocrine system amongst others. De Angelis *et al*., provided an understandable overview on the impact of drug addiction on female fertility, via encompassing the effects on fertility outcomes, on the uterus (De Angelis *et al*., 2020). Although poorly investigated, some evidence suggests that use and abuse of tramadol might adversely affect female reproductive function and reduce couple fertility potential. Therefore, accurate investigation on addictive drugs consumption should be performed in women with fertility disorders and proper counseling should be provided (Collins *et al*., 2009). But the absence of enough information on the effect of tramadol on the female reproductive system, the concept of fertility is the reason for this study.

The uterus is also known as the womb. Anatomically, the uterus is a hollow, pear-shaped organ that is responsible for different kind of functions, such as pregnancy (gestation), menstruation, labour and delivery. The average dimensions of the uterus in an adult female are 8 cm long, 5 cm across, and 4 cm thick. The uterine cavity has an average volume of 80 ml to 200 ml. The uterus is located in the female pelvis immediately posterior to the bladder and anterior to the rectum. Embryologically, the early development of the uterus is quite complex. At about eight weeks of gestation, primordia for both female and male internal genitalia paramesonephric (Mullerian) and mesonephric (Wolffian) duts appears.

The sexual differentiation process involves a series of steps that occur due to growth factors, hormonal signals, and inherited genetic influences. In the female embryo, because of the absence of a Y chromosome and lack of testosterone from any testicular tissue, the typical sequence of developmental events results in canalization and fusion of the paramesonephric (Mullerin) ducts in the middle of the pelvis, which gives rise to the female pelvic organs. At this time, the mesonephric (Wolffian) ducts regress. Histologically, the uterus has three tissue layers which include the following: Endometrium (uterine mucous membrane): the inner is lined by simple columnar epithelium and contain numerous tubular glands. It had a cell-rich connective tissue layer (lamina propria).

Physiological the endometrium consists of the functional (superficial) and basal endometrium. The functional layer responds to reproductive hormones (Alimi *et al.*, 2018). Myometrium (uterine musculature): these consist of three muscle layer and are composed of smooth muscle cells. These layers are microscopically difficult to separate (from inside to outside). The subvascular layer, vascular layer and supravascular layer. Serosa/Perimetrium: the thin outer layer composed of epithelial cells (Lüllmann, 2009). The uterus gets its blood supply from the uterine and ovarian arteries, which arise from the anterior branch of the internal iliac artery.

The uterine arteries are the main blood supply vessels that supply blood to the uterus. As the blood supply enters the myometrium, it branches into the arcuate arteries, which branch into the radial arteries. As they enter the level of the endometrium, they branch into the basal and spiral arteries. The fundal part of the uterus chiefly drains into para-aortic lymph nodes along with the ovarian and fallopian tube lymphatic drainage. Some of it also drains into superficial inguinal lymph nodes along the round ligament. The lower part of the uterus drains along the uterine blood vessel into external and internal iliac lymph nodes.

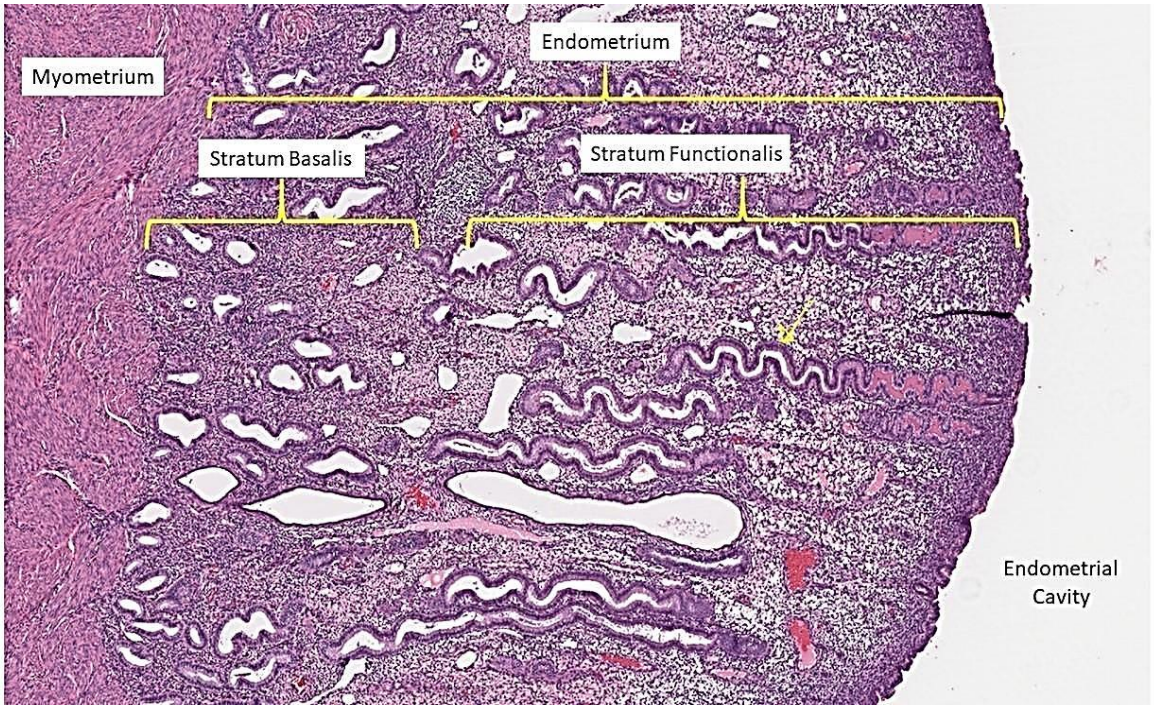

Figure 1. Histological structure of the uterus. Adapted with permission from ref 32, Copyright 2020, *PathologyOutlines.Com,Inc.*

The present study was undertaken to investigate the histological effects of tramadol on female reproductive function relating to fertility by examining the morphology of the uterus of Albino Wistar rats exposed to tramadol. The specific objectives were to; To evaluate the effect of tramadol misuse on histology of the uterus (endometrial tissue). To investigate the behavioral effect of tramadol abuse on female Albino Wistar rats.

2. MATERIALS & METHODS

This study is an experimental animal study involving mostly female Wistar rats of reproductive age group. This present study was carried out in the animal laboratory of Enugu State University College of Medicine (ESUCOM), Enugu. This present study will be carried out in Enugu State University College of Medicine (ESUCOM) Parklane, Enugu State University of Science and Technology (ESUT), Enugu. The study will last for five weeks and five days.

Sundry consumables and other materials; Iron cages, bowl plates, sawdust, gavages, animal feeds (growers mesh pellets from Ogbete market), water, normal saline, improvised feeder (set up with plastic bottles and pen cover), dissecting kits, syringes, organs containers, trays, laboratory coats, protective gloves, goggles, nose mask, mob, buckets, dustbin, disposable bags and electrical weighing machine (Salter, HoMedics Group Ltd. Production No: IB-1066-1011-03).

2. 1. Laboratory Animals

The experiment will be performed on thirty (30) mature female and five (5) males for mating. Their body weight ranged from 100-150 grams upon arrival and of age 7 weeks were obtained from the Animal Facility Centre (AFC). They were housed in the animal laboratory of the Department of Anatomy, Enugu State University College of Medicine (ESUCOM), for the period of the study. The animals were allowed a week to acclimatize and housed in metallic cages. The animals were allowed 12 hours' light and 12 hours' dark cycles at 27 °C – 30 °C room temperature. They were fed with standard rat pelletized diet (Grand cereals ltd, Nigeria) and water. Strict care and hygiene were maintained to keep them in normal and healthy conditions following the guidelines for care and use of laboratory animals. Drug: Tramadol (Ultram®) containing 50 mg produced by Novartis India Ltd, and was sourced from Eva-pharmacy, Enugu state, Nigeria. License No.: 6516262711, NAFDAC Reg. N0.: 51655018520. The chemical name is Cis-2 [(dimetylamino)methyl]-1-(3-melhoxyp-enyl) cyclohexanol hydrochloride.

2. 2. Ethical Approval

The study's experimental protocol and technique were by the International Animal Use and Care Principles. Ethical clearance was provided by the Research Ethics Committee of the Enugu States University of Science and Technology, college of medicine, Enugu. Before commencement ethical and project registration numbers were assigned to the research project.

2. 3. Experimental Design

After a week of acclimatization, the rats were randomly regrouped or selected into five (5) groups with six (6) female rats. Tramadol doses were given once a day between 11:00 am to 1:00 pm for 4 weeks and 5 days. This was administered orally using a gavage.

Group 1 rats: They served as the negative control group, received only water and feed for 4 weeks and 5 days.

Group 2 rats: which are the first experimental group received 25 mg of tramadol hydrochloride mixed in 1 ml of injection water orally by gavage for 2 weeks (Moore *et al*., 2016; Subramanian *et al*., 2020).

Group 3 rats: which are the second experimental received 25 mg of tramadol hydrochloride mixed in 1ml of injection water orally by gavage for complete 4 weeks and 5 days (Moore *et al*., 2016; Subramanian *et al*., 2020).

Group 4 rats: which are the third experimental group received 50 mg of tramadol hydrochloride mixed in 1ml of injection water orally by gavage for complete 4 weeks and 5 days. These doses of tramadol are designed according to a previous study (Bloor *et al*., 2012; Lopopolo *et al.*, 2014).

Group 5 rats: which are the fourth experimental group received 50 mg of tramadol hydrochloride mixed in 1 ml of injection water alternatively every 72 hours starting from the first day of induction, orally by gavage. This lasted for eleven (11) days.

The male wistar rats will be introduced into the five (5) different cages to initiate mating with the females. The mating is a blind test to find out if there will be any pregnancy at the end

of the experiment and it lasted for 7 days, while the female rats were still administered tramadol. They were sacrificed through cervical dislocation and the uterus was harvested and fixed.

Figure 2. Inducing the rat with tramadol hydrochloride using a gavage

Sampling technique**:** Sampling is a technique for selecting individual member or a subset of the population in order to make statistical inferences and estimate population characteristic (Berndt., 2020). In this research different databanks including PubMed, Google scholar, research gate etc. were accessed. Determination of physical parameters: Individual body weights of rats were determined using a weighing balance, three days after arrival before the

start of the experiment. The general physical appearance and behavior of the rats was also observed throughout the experiment period. Determination of physical parameters: Individual body weights of rats were determined using a weighing balance, three days after arrival before the start of the experiment. The general physical appearance and behavior of the rats was also observed throughout the experiment period.

Table 1. Administration Schedule

Group	Number of rats	Dosages	Duration
Group 1	6	Normal saline/water	4 weeks & 5 days
Group 2	6	25 mg/kg of tramadol in 1 ml of injection water.	2 weeks
Group 3	6	25 mg/kg of tramadol in 1 ml of injection water.	4 weeks & 5 days
Group 4	6	50 mg/kg of tramadol in 1 ml injection water.	4 weeks & 5 days
Group 5	6	50 mg /kg of tramadol in 1 ml of injection water every 72 hours.	A weeks & 4 days

2. 4. Histopathological Examination

The animal was all sacrificed after 24 hours of administering the last dose, through cervical dislocation and their uterus were excised, cleared of the adherent connective tissue immediately fixed in 10% formal saline, dehydrated through grades of ethanol (30, 50, 70, 90, 100%) in 45% interval. Tissues were cleared on absolute xylene three times for 45 minutes each and infiltrated in paraffin wax for about 30 minutes at 56 °C – 60 °C. embedding of the tissue in paraffin wax using tissue Tek embedding mold filled with the molten paraffin wax which was allowed to solidify in the cold compartment of the embedding center. Sections were obtained on a rotary microtome at 5 µm thickness, fixed on clean slides to which Mayer's egg albumin which had been coated to cement the sections to the slides properly and were subjected to hematoxylin and eosin (H&E) staining (Gujral *et al*., 2001). The processed slide will be examined with a light microscope under X10 and X40 photomicrographs will be taken with a computer assisted digital microscope, model Buc2-5ooc camera (Bancroft and Gamble, 2002). Image software will be used to determine the cellular population.

3. RESULTS & DISCUSSION

The concept of fertility has been the paramount of misunderstanding in most homes, causing emotional, psychological, societal and financial difficulties. Infertility is a global problem affecting people around the world and this problem can come from both parties but it

is often times said to be the woman's fault. According to WHO, in 37% of infertile couples, female infertility was the cause; in 35% of couples, both male and female causes were identified; in 8%, there was male factor infertility. Infertility can result from many causes. Women tends to use tramadol (painkiller) more than men (Kallen and Reis. 2015).

The major role of tramadol, used as an analgesic when treating mild to severe pain is publically known, but when abused it can result to some lethal effects on the uterus of the woman. A research done by El-Ghawet in 2015, stated that chronic misuse of tramadol leads to reproduction dysfunctions and decreased average of fertility. The goal of this research is to investigate the effect of tramadol hydrochloride (TrHCl) on female reproductive function and examine the morphology of the uterus of Albino Wistar rats exposed to tramadol. And also to identify the behavioral effect of tramadol abuse on the rats. Discussion on Histological Findings: The objective of the study was to evaluate the effect of tramadol misuse on histology of the uterus (endometrial tissue).

The histological reports showed variation in levels of impact from the tramadol hydrochloride, differences in the level of impact could be attributed to the dose of tramadol. A comparison of the uterine section of the control group with that of the tramadol administered groups.

Effects of tramadol on the rat tissues harvested.

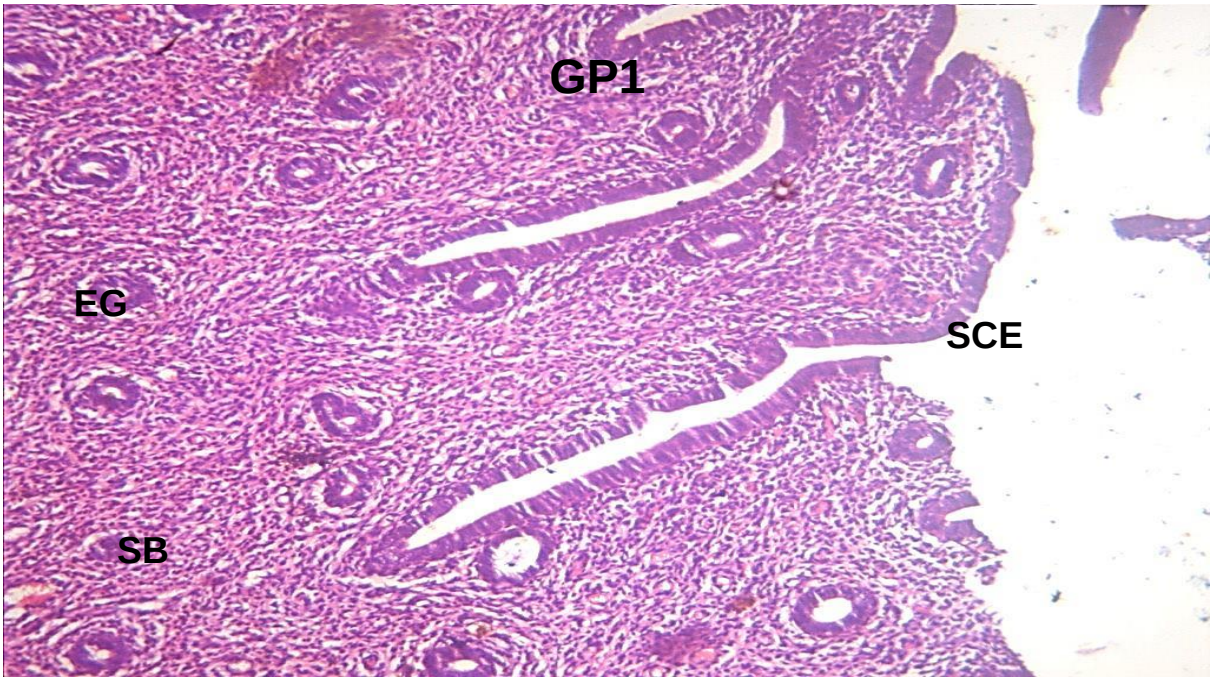

Figure 3. Photomicrograph the control section of uterus (x400) (H/E) shows normal uterine tissue with stratum basal (SB), endometrial gland (EG). The stratum functionalis is lined by simple cuboidal epithelium (SCE) the overall features appear normal.

On the endometrium of the female rats in the control group, it was observed that the histology of the uterine tissue, were lined with stratum basal (SB), stratum functionalis and endometrial gland (EG). The stratum functionalis is lined by simple cuboidal epithelium (SCE)

the overall features appear to be normal. This is similar to the work done by Ambedkar, 2006 which showed the same result (Figure 3).The histological presentation of the group two (2) of female rats that were administer with 25 mg/kg of Tramadol two weeks after mating (Moore *et al*., 2016), showed moderate effect on the uterine tissue with mild dilated gland (DG) and infiltration of inflammatory cell. (Figure 4).

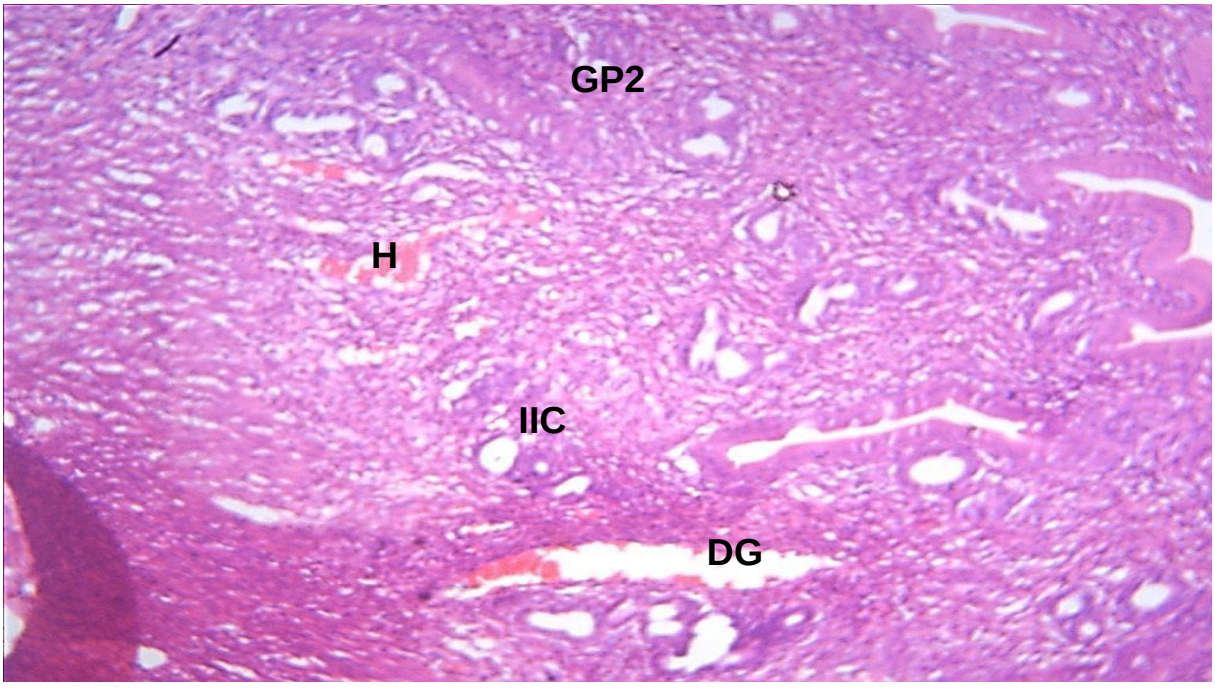

Figure 4. Photomicrograph of group 2 uterus section administered with 25 mg/kg of tramadol (X400) (H/E) shows moderate effect on the uterine tissue with mild dilated gland (DG) and infiltration of inflammatory cell (IIC).

On the group that was administered with 25 mg/kg of the test drug (Moore *et al*., 2016), for four (4) weeks and five days which is the group three(3), we observed moderate effect on the uterine tissue lining with endometrial hyperplasia (EH) and with necrotic fragment (NF) within the epithelia (Figure 5). The group four (4) histological presentation of the group of female rats that were administered with 50 mg/kg of tramadol hydrochloride (Bloor *et al*., 2012; Lopopolo *et al*., 2012) for four (4) weeks and five days, showed sever effect on the uterine tissue lining with necrotic epithelia (NE) and sever dilated gland (DG) filled with hemorrhage (H) (Figure 6). Finally, the last group (group 5) was administered with 50 mg/kg of tramadol hydrochloride at the interval of 72 hours till the end of the experiment (This happened for eleven days within the duration of the experiment). The histological representation showed sever effect on the uterine tissue with sever endometrial hyperplasia, with dilated gland and ground-glass appearance of the cytoplasm. (Figure 7). The evaluation of the uterine section of the groups given low dose of tramadol hydrochloride and that of the group give high dose showed significant variation in the degeneration. Group three and four (Figure 5 & 6) showed that when tramadol is misused for a long duration can cause necrotic effects, resulting to lesion on the endometrial lining. This can affect the possible implantation.

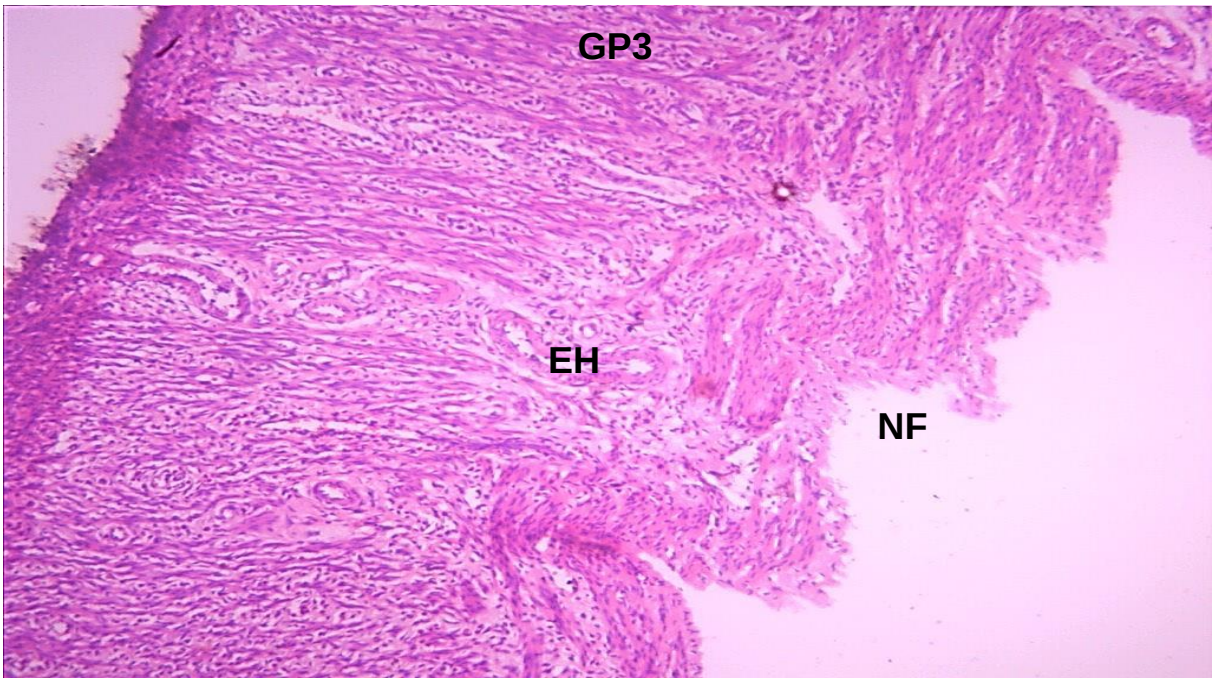

Figure 5. Photomicrograph of group 3 uterus section administered with 25 mg/kg of tramadol (X400) (H/E) shows moderate effect on the uterine tissue with endometrial hyperplasia (EH) with necrotic fragment (NF) within the epithelia.

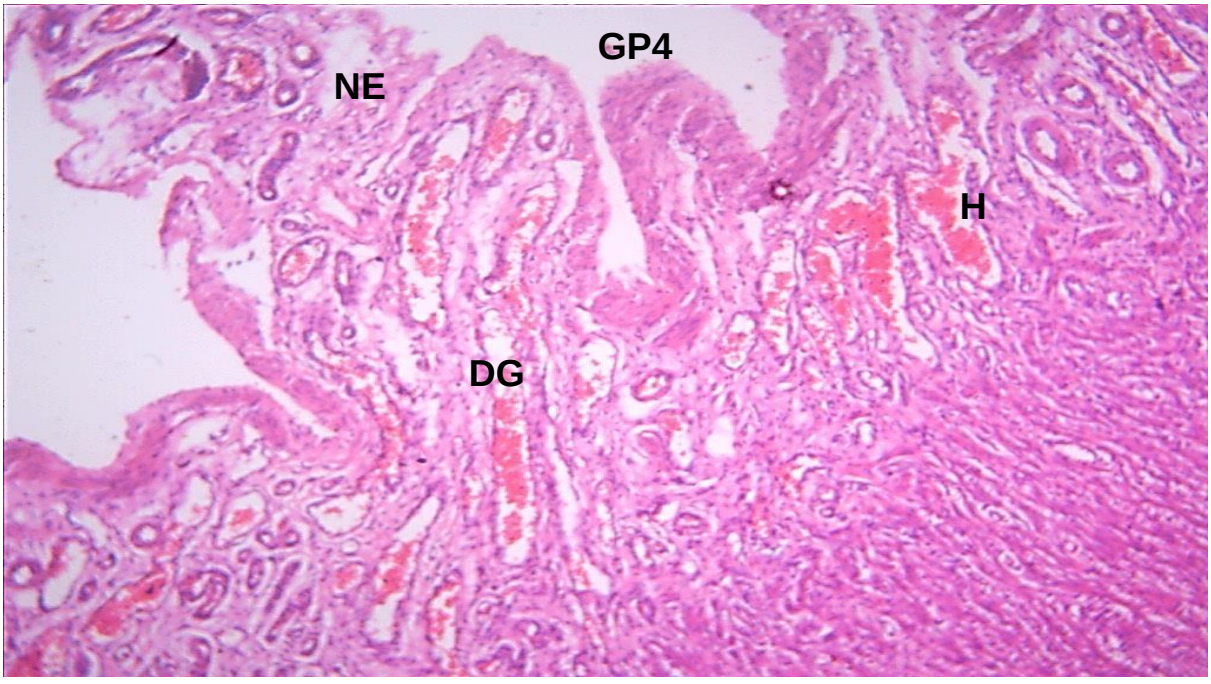

Figure 6. Photomicrograph of group 4 uterus section administered with 50 mg/kg of tramadol (X400) (H/E) shows sever effect on the uterine tissue with necrotic epithelia (NE) and sever dilated gland (DG) filled with hemorrhage (H).

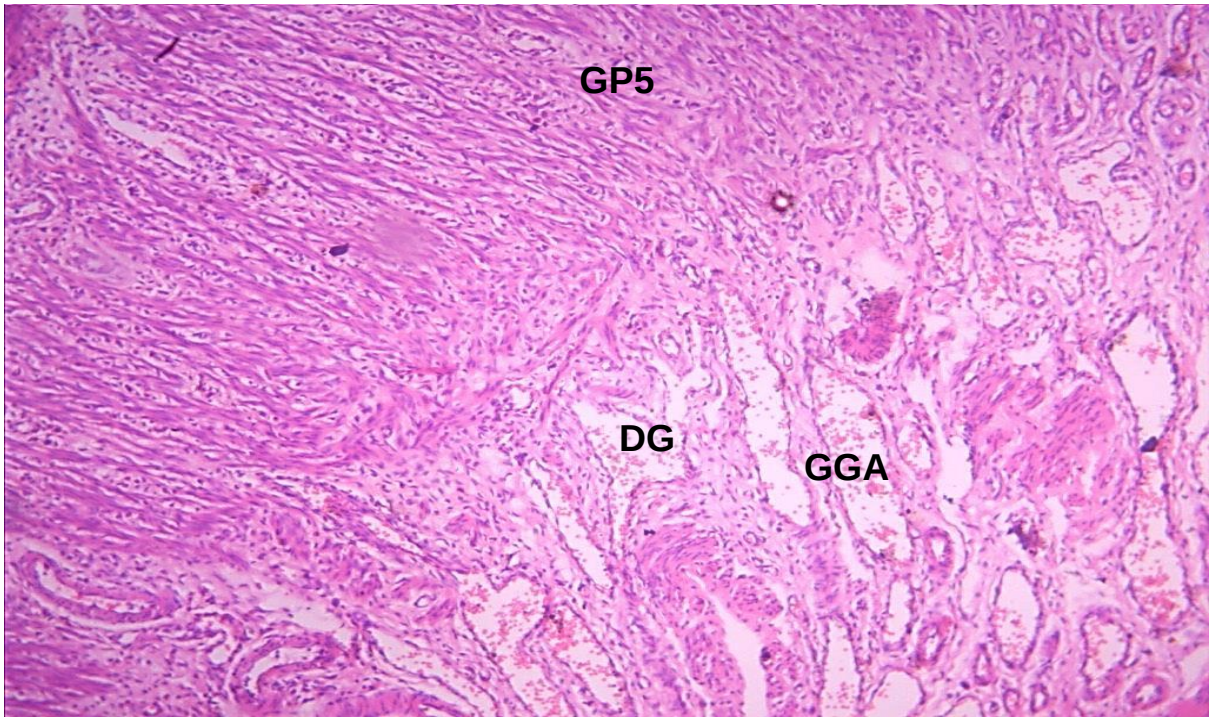

Figure 7. Photomicrograph of group 5 uterus section administered with 50 mg/kg of tramadol (X400) (H/E) shows sever effect on the uterine tissue with sever endometrial hyperplasia. With dilated gland and ground-glass appearance of the cytoplasm.

The sign of inflammation and endometrial hyperplasia present in the histological results can also affect the chances of conception. At the end of this experiment there was no pregnancy achieved, my results showed similar alterations similar to some reported works (El-Mounem *et al.*, 2018; El-Mottaleb *et al*., 2019).

While some reported not only does it affect female fertility and men also (El-Ghawet, 2015; Salah *et al*., 2022; Moussa *et al.,* 2020). Though some of the results seemed to differ a bit though to some environmental factors and duration.

Discussion on the behavioral effect of tramadol abuse on female Albino Wistar rats. The control group that were not administered with tramadol hydrochloride showed normal characteristics, they had a glossy coat, good appetite and were active throughout the experiment.

The groups that got either low dose or high dose of tramadol were hyperactive and very aggressive, they drank more water than food. After the administration they became very itchy, running from one corner of the cages to another, until they eventually huddle to a corner of the cages. Some bite through the iron net lid of the cage. I noticed hair loss in the 25mg groups and massive hair loss in 50 mg groups.

Group two and three that received 25 mg of tramadol were actively normal, had good appetite and gained weight. However, after three weeks and four days of administration became hyperactive, had poor appetite and started reducing in their size. The remaining ones that received 50 mg of tramadol were very hyperactive, aggressive and had too much appetite for food.

4. CONCLUSIONS

The use of the potent opioid painkiller, Tramadol, for nonmedical purposes and self-medication cuts across all strata, which in the world has been indicated to be on the rise in recent years. Tramadol can have various histological effects on the uterus. Studies have shown that it may alter uterine structure, potentially affecting endometrial morphology. These changes can include variations in glandular development and stromal composition, as well as possible inflammatory responses. However, the extent and significance of these effects can vary based on dosage, duration of use, and individual responses. Sherein *et al*., (2020), affirmed that the abuse of tramadol has deleterious chronic toxic effects on the reproductive system and that it should be used with caution with appropriate dose monitoring to avoid its undesirable side effects on male fertility. Although Azari *et al*., (2014), stated that the negative effects of tramadol on testes are reversible. Women are at more risk of the toxicity (Pederson et al, 2013).

This result revealed the histological adverse effect of tramadol, at 25mg and 50 mg dose on the uterine morphology in adult female wistar rats.

The histological results showed that the abuse of tramadol has histopathological effects (such as Inflammation, deterioration and degeneration) on the reproductive organs of the female wistar rats. Duration of the different dosages determined how intensified the damage was too. Thus this possibly leads to female infertility which has high prevalence in our environment. This study has shown that tramadol when abused has a deleterious effect on the reproductive system, this may result in failure in conception in women of childbearing stage, therefore, reducing fertility. This study can serve as an insight for educationists, physicians and other health professionals, in diagnosing tramadol. More research is needed to fully understand its implications on uterine histology.

Raising awareness on the effects of tramadol abuse on the uterus, the government should structure an organization that will do campaigns and create initiatives enlightening women especially at the child bearing stage of the danger involved because it is an indisputable fact that most women indulge in this abuse due to ignorance of the negative effects. They can do this through the use of the medias, electronics, seminars and direct contact. The organization should also endeavor that it reaches the rural areas. Post-operative anesthesia is also another means that can result in dependence and abuse, since women have shown to be more susceptible therefore putting them at more risk. It is better to consult the patient on the risks involved in taking unprescribed dosages without a doctor's prescription.

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