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Effects of some commonly used drugs on the male reproductive system and reproduction: A review

Afisu Basiru [1 *], Oluwatobi C. Adetunji [1] and Abdulfatai Aremu [2]

[1] Department of Veterinary Physiology and Biochemistry, Faculty of Veterinary Medicine, University of Ilorin, Ilorin, Nigeria.

[2] Department of Veterinary Pharmacology and Toxicology, Faculty of Veterinary Medicine, University of Ilorin, Ilorin, Nigeria.

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Abstract

The use of certain drugs has been associated with male infertility. This article reviewed the effects of some commonly used drugs on male reproductive system and reproduction. Infertility associated with the use of drugs in males may be due to a direct toxic effect on the gonads or an influence on the hypothalamic-pituitary-gonadal axis that may induce sexual dysfunction, impairment of spermatogenesis, and/or alteration in epididymal sperm maturation. The administration of steroid hormones may impair central control of spermatogenesis or epididymal sperm maturation, and thus lead to a decline in fertility. Steroid hormone usage is common in animals competing in shows, races or hunting, and as stimulants and enhancing drugs before competition. Some anti-fungal medications, including griseofulvin and ketoconazole, which exhibit steroid-like effects by suppressing pituitary gonadotropin release and assisting in the synthesis of steroid hormones has also been associated with male infertility. Some other chemotherapeutic agents such as cimetidine (antacid), amitriptyline (tricyclic anti-depressant), naproxen (non-steroidal anti-inflammatory drug), and sulphasalazine (sulphonamide) may also impair male fertility. The widespread use of these medications in veterinary practice raises significant concerns about their potential impact on male reproductive health and warrants careful consideration by veterinarians and animal owners alike. Awareness of the adverse effects of these drugs on fertility should prompt animal healthcare providers to adopt cautious prescribing practices, considering alternative therapies whenever possible, especially in breeding animals where reproductive health is of paramount importance. To better understand the mechanisms underlying the effects of these medications on male fertility, further research is essential. Additionally, the development of novel therapeutic strategies or preventive measures to mitigate their negative impact on reproductive function should be pursued. This review draws attention to the importance of a cautious approach to the use of medications in veterinary and medical practice, to safeguard the fertility and overall health of male animals and humans.

Keywords: Drugs; Medicines; Male fertility; Spermatogenesis; Reproductive system; Reproduction.

***Correspondence:** Afisu Basiru; Email: basiru.a@unilorin.edu.ng Phone: +2347038047475

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Introduction

The use of certain medicines, such as some anti-neoplastic drugs, anthelmintics, anti-protozoal agents, antimalarials, antibiotics, anti-fungals, and diuretics has been associated with primary infertility in males. This occurrence is believed to be the result of their direct toxic effect on the gonads or their influence on the hypothalamic-pituitary-gonadal axis via inducing sexual dysfunction, impairment of spermatogenesis, and altering epididymal maturation (Koren *et al*., 2020). The effects of drugs on male fertility are sometimes overlooked. Overall, the male reproductive system is a complex and highly coordinated system that involves the interplay of hormones, nerves and various organs and structures to produce and deliver sperm for fertilization. The purpose of this review article is to bring to the fore the reported effects of some drugs on the male reproductive system.

The Male Reproductive Organs

The male reproductive organs can be placed into three categories namely: the primary reproductive organs, which are the testes where spermatogenesis and testosterone production takes place; the secondary reproductive organs, which are various organs such as the epididymis, vas deferens, urethra, and penis (phallus) that are responsible for delivering semen during mating; and the accessory reproductive organs, which are various organs such as the seminal vesicles, prostate gland, and bulbourethral gland that are responsible for the nourishment and protection of sperm released during ejaculation through their various secretions. The combination of sperm and the secretions of the accessory reproductive organs makes up the semen (Ramírez-González and Sansone, 2022).

The testes are the primary male reproductive organs located outside the body in a sac-like structure called the scrotum. They are responsible for producing both sperm and testosterone (Staub and Johnson, 2018). The testes contain various tissues that play varied roles in the production, protection, nourishment and maturation of sperm cells. These tissues include the seminiferous tubules, interstitial tissue (which contains Leydig cells), rete-testis, blood vessels, lymphatic vessels, and supporting cells such as Sertoli cells and myoid cells (Heinrich and DeFalco, 2020; Major *et al*., 2021; Nakata *et al*., 2021).

The efferent ducts collect and store spermatozoa before transporting them from the rete testis to the epididymis' head. They are found within the epididymal fat pad in rodents (Knoblaugh and Hukkanen, 2018).

The epididymis is a tubular structure located behind and above each testis in the male reproductive system. It is responsible for accumulating, maturing, and storing mature sperm. It is made up of three parts - the head, body, and tail (Knoblaugh and Hukkanen, 2018).

The vas deferens is a paired muscular tube that moves sperm from the epididymis' tail to the ampulla, which then connects to the urethra at the colliculus. It is part of the spermatic cord, which also contains blood vessels and nerves (Jiménez-Reina *et al*., 2016; Knoblaugh and Hukkanen, 2018).

The seminal vesicles are two glandular structures situated near the base of the urinary bladder in the male reproductive system. They produce a fluid that is high in fructose, which provides energy for sperm, and prostaglandins, and which helps to induce contractions in the female reproductive tract, assisting the movement of sperm towards the egg. The seminal vesicles also contain enzymes, amino acids, and other substances that supply nutrition and protection for the sperm (Bromfield, 2014).

The prostate gland is an androgen-regulated gland that surrounds the urethra, located beneath the urinary bladder, responsible for producing fluid that helps to protect and nourish sperm. This fluid contains enzymes, proteins, and other substances that create an alkaline environment, neutralizing the acidic conditions of the female reproductive tract (Verze *et al.*, 2016).

The bulbourethral glands are accessory glands in rodents that are similar to Cowper's glands in humans (Knoblaugh and Hukkanen, 2018). They are located around the base of the penis, and produce mucous fluid that lubricates the urethra during ejaculation, neutralize acidity, and facilitate the coagulation and liquefaction of semen. The fluid may also play a role in the development of plugs after copulation in rodents (Tortora and Derrickson, 2017).

Hormonal Control of the Male Reproductive System

Gonadotropins, including luteinizing hormone (LH) and follicle stimulating hormone (FSH), are produced by the pituitary gland and help regulate male reproductive function by binding to receptors on Leydig and Sertoli cells in the testis. Additionally, various local factors and hormones, such as peptides, neurotransmitters, cytokines, and prostaglandins, influence testicular function through paracrine and autocrine processes (Rudolph *et al.*, 2016). The male reproductive system is under the control of a complex network involving the central nervous system, hypothalamus, pituitary gland, and testis (Figure 1).

The male reproductive system is regulated by a pulsatile mechanism involving the rhythmic release of gonadotropin releasing hormone (GnRH) from the hypothalamus, which controls the secretion of LH and FSH from the pituitary gland (Dutta *et al.*, 2019). The sensitivity of the pituitary gland to GnRH is crucial in maintaining normal levels of LH and FSH. The pulsatile mechanism also regulates testosterone production by stimulating the Leydig cells with LH pulses, where higher frequency pulses are more effective in stimulating testosterone synthesis than lower-frequency pulses (Dutta *et al.*, 2019). The timing of pulsatile GnRH pulses is important for normal LH secretion and testosterone production. Long-term exposure to constant GnRH or LH can cause desensitization, and continuous exposure to long-acting GnRH analogues has been studied as an anti-fertility treatment. Pulsatile GnRH can restore fertility in cases of hypothalamic infertility. LH and FSH stimulate testosterone and sperm production in the testes (Behre, 2019).

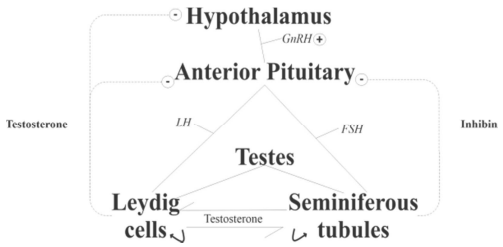

Figure I: Hormonal control of male reproduction: Hypothalamic-pituitary-gonadal axis.

Spermatogenesis

Spermatogenesis, which is the process in which haploid spermatozoa develop from germ cells in the seminiferous tubules to become mature spermatozoa, occurs in four stages: undifferentiated spermatogonia development by mitosis, spermatocyte development by meiosis, spermiogenesis (differentiation of spermatids), and spermiation (release of spermatid). The process of spermatogenesis occurs in the seminiferous tubules of the testes, where stem cells (spermatogonia) divide to produce spermatogonia and differentiated cells (spermatocytes). Spermatocytes further

undergo meiosis, resulting in the formation of haploid spermatids. The spermatids then develop into spermatozoa during spermiogenesis and are released during spermiation (Dalia *et al*., 2019).

Different Classes of Drugs

Drugs that have similar properties and mechanisms of action are grouped together as a drug class (Nickel *et al*., 2014). A prototype drug serves as the benchmark for comparison with other drugs in the same class (Harel and Radinsky, 2018). Drugs can be classified based on the chemical type of the active ingredient, as done with β-lactam antibiotics, benzodiazepines, cardiac glycoside, fibrate, thiazide diuretic, steroids, and triptan (Ullah and Ali, 2017). Drugs can also be classified based on their mechanism of action; this depends on their ability to bind to specific biological targets and the type of behaviour they exhibit, such as agonist, antagonist, inverse agonist, or modulator (Marc, 2008). Examples of drugs classified based on mechanism of action include beta blockers, angiotensin II receptor antagonists, and non-steroidal anti-inflammatory drugs (NSAIDs) - cyclooxygenase inhibitors (Barreras and Gurk-Turner, 2003). Classification based on the mode of action refers to the anatomical and functional changes that drugs cause. Examples of drugs classified based on the mode of action are antimicrobial, anti-thrombotic, bronchodilators, chronotropes (positive and negative), decongestants, diuretics, and inotropes (positive or negative) (Prasad *et al*., 2016; Olivier *et al*., 2021). Based on their therapeutic use and the pathology they treat, drugs can be classified as analgesics, antibiotics, anti-coagulants, anti-depressants, anti-neoplastic, antiulcer, anti-diabetics, anti-epileptics, anti-psychotics, antispasmodics, cardiovascular drugs, reproductive drugs, CNS depressants, sedatives, CNS stimulants, etc (Prasad *et al*., 2016). Other drug classification formats exist, such as legal classifications, the biopharmaceuticals classification system, etc (Farah *et al*., 2020).

Effects of Different Classes of Drugs on Male Reproduction

Antibiotics and Anti-fungal agents: Some antibiotics have been linked to negative effects on sperm parameters and spermatogenesis (Olayemi, 2010). Tetracycline hydrochloride, tylosin, ceftriaxone, ampicillin, cloxacillin, gentamycin, neomycin, and metronidazole have all been shown to have varying degrees of impact on sperm count, motility, morphology, viability, and testicular function (Kumari and Singh, 2013). These effects may be due to direct toxic effects on spermatozoa and/or inhibition of gonadotropin-releasing hormone (Olayemi, 2010). A summary of the reported effects of different antibiotics and anti-fungal agents on male reproduction are shown in Tables 1 and 2, respectively.

Anthelmintics: Anthelmintic drugs are used to treat infections caused by parasitic worms (Chai *et al*., 2021). Niclosamide has been shown to cause aberrant sperm morphology but no change in sperm count (Drobnis & Nangia, 2017). Pyrantel pamoate and niridazole increased sperm-head abnormalities in a dose-dependent manner, suggesting that both substances may be mutagenic (Otubanjo & Mosuro, 2001). A combination of ivermectin and verapamil induced hazardous effects on sperm motility, sperm count, and abnormality in male rats (Gada *et al*., 2018). Further details of the reported effects of anthelmintics on male reproduction are presented in Table 3.

Anti-protozoal drugs: Anti-protozoal drugs are used to treat infections caused by protozoan parasites, and they can have varying effects on male fertility. Diminazene aceturate treatment has been shown to significantly reduce sperm concentration, volume, and motility when

compared to untreated controls (Onakpa, 2010). Details of the reported effects of other anti-protozoal agents such as chloroquine and metronidazole on male fertility is presented on Table 4.

Table 1. Effects of antibiotics on male reproductive system and reproduction.

S/N	Drugs.	Class of the drug.	Species studied, and the reported effects on male reproduction.	References.
1	Gentamicin	Aminoglycoside	**Rats:** Reduction in sperm count, motility and viability; reduction in libido, impairment of spermatogenesis, and reduction in testosterone level.	Khaki, 2015.
2	Neomycin	Aminoglycosides	**Rats:** Marked reduction in sperm count, motility, and viability.	Khaki, 2015.
3.	Ofloxacin	Fluoroquinolone	**Rats:** Reduction in sperm count and viability, degeneration of seminiferous tubules, decrease of spermatozoa in the testis, epididymis and vas deferens.	Khaki, 2015.
4	Enrofloxacin	Fluoroquinolone	**Chickens (Rooster):** Decrease in sperm volume, reduction in sperm count, reduction in sperm motility, increased abnormal spermatozoa.	Aral *et al*., 2008; Mohammedi *et al*., 2022.
5	Ampicillin	Beta-lactam antibiotic	**Rats:** Reduction of sperm count, sperm motility, fertility ratio and serum testosterone level. **Chickens (Rooster):** Decrease in sperm count, Increased in sperm volume.	Gupta *et al*., 2013; Mohammedi *et al*., 2022.
6	Sulphamethazine	Sulphonamide	**Chickens (Rooster):** Enhances sperm motility and viability by increasing testosterone production. However, reduction in sperm count and concentration.	Mohammedi *et al*., 2022.
7	Metronidazole	Imidazole	**Rats:** Decreases sperm motility, sperm viability, sperm count of epidermal spermatozoa.	Kumari and Singh, 2013.
8	Colistin	Polymyxin	**Chickens (Rooster): -** Reduction in sperm volume, sperm count, sperm motility, sperm viability, increase in the presence of abnormal sperm cells.	Mohammedi *et al*., 2022.

Table 2. Effects of anti-fungal drugs on male reproductive system and reproduction.

S/N	Drugs.	Class of the drug.	Species studied, and the reported effects on male reproduction.	References.
1	Ketoconazole	Imidazole	**Humans:** Reduction in testosterone level. **Rats:** Hyperprolactinemia; reduction in testosterone level, GNRH, LH level and sperm count; increase in abnormal sperm morphology, oligospermia and azoospermia.	Olayaki *et al*., 2020.
2	Fluconazole	Triazole	**Cocks:** Reduction in serum testosterone level, sperm motility and live/dead ratio, increase in percentage of abnormal sperm cells.	Hammad *et al*., 2021.
3	Griseofulvin	Antibiotics	**Rabbits:** Reduction in serum testosterone level, semen volume, sperm count, sperm live/dead ratio and sperm motility, and increase in abnormal sperm morphology.	Mohamed *et al*., 2020.

Table 3. Effects of anthelmintic drugs on male reproductive system and reproduction.

S/N	Drugs.	Class of the drug.	Species studied, and the reported effects on male reproduction.	References.
1	Pyrantel Pamoate	Pyrimidine	**Mice:** Increase in sperm-head abnormalities.	Otubanjo & Mosuro, 2001.
2	Albendazole, Mebendazoles and Thiabendazole	Benzimidazole, Nitrotiazole and Benzimidazole respectively.	**Mice:** No significant effects observed.	Otubanjo and Mosuro, 2001.
3	Ivermectin	Macrocyclic lactone	**Rams:** Decrease in semen volume, sperm motility, testosterone level as well as follicle stimulating hormone level.	Onakpa, 2010.

Table 4. Effects of anti-protozoal drugs on male reproductive system and reproduction.

S/N	Drugs.	Class of the drug.	Species studied, and the reported effects on male reproduction.	References.
1	Diminazene aceturate	Trypanocidal drug (Pentamidine analogue)	**Rams:** Decrease in semen volume, sperm motility, sperm concentration, reduction in testosterone level as well as follicle stimulating hormone levels.	Onakpa, 2010
2	Chloroquine	Amebicides and Antimalarial (Quinoline)	**Rat:** Testicular and epididymal weight reduction. Reduction in Leydig cells, sperm count and sperm motility, reduction in testicular morphology and a resultant reduction in testosterone level.	Ekaluo *et al*., 2008
3	Metronidazole	Anti-protozoal (Imidazole)	**Rats:** Decreases sperm motility, sperm viability, sperm count of epidermal spermatozoa.	Kumari and Singh, 2013

Anti-neoplastic agents: Gonadotoxicity of anti-neoplastic drugs is dependent on the drug used, the dose delivered, the dosage size (dose/m^2), the time between doses, the kind of cancer being treated, and whether or not other substances are being used concurrently (such as immunosuppressants) (Samplaski and Nangia, 2015). Antineoplastic chemotherapy-induced sperm diploidy has been reported in men treated for testicular cancer with bleomycin, etoposide, and cisplatin (BEP) for up to two years after the end of treatment. Procarbazine-containing regimens have been reported to cause permanent infertility in men (Hassan and Jasim, 2020). Further details on the reported effects of anti-neoplastic agents on male reproduction is shown in Table 5.

Table 5. Effects of anti-neoplastic drugs on male reproductive system and reproduction.

S/N	Drugs.	Class of the drug.	Species studied, and the reported effects on male reproduction.	References.
1	Doxorubicin	Anthracycline antibiotic	**Rat:** Acute loss of spermatogonia stem cells (SSCs), impaired germ cells development, increase expression of apoptotic markers on SSCs.	Lopes *et al*., 2021
2	Cisplatin	Alkylating like platinum-based	**Rat:** Acute loss of SSCs, impaired germ cells development, increase expression of apoptotic markers on SSCs.	Lopes *et al*., 2021

Anti-hypertensive drugs: The alpha-blockers antagonize the α1-adrenergic receptors in the body, including the urinary tract, and are used to treat hypertension and benign prostatic hyperplasia (Mari *et al*., 2021). Tamsulosin, a sulphonamide derivative alpha-blocker, has been shown to cause reversible changes in sperm parameters, including decreased ejaculate volume, sperm count, motility, and shape, potentially due to its interaction with central neurotransmitters. Both Tamsulosin and Silodosin can lead to ejaculatory abnormalities such as retrograde or an-ejaculation, which could be due to decreased smooth muscle tone at the bladder neck (Semet *et al*., 2017). The detailed reported effects of the above and other anti-hypertensive agents on male reproduction are shown in Table 6.

Cimetidine: Cimetidine is an anti-histamine drug used to treat peptic ulcers. It has been shown to have anti-androgenic properties due to its competition with dihydrotestosterone receptors; it has also been proven to cause oxidative stress in testicular tissue as well as hyperprolactinemia (Liu *et al*., 2018) [Table 7].

Digoxin: Digoxin is a cardiac glycoside used in the treatment of heart conditions such as atrial fibrillation, atrial flutter and heart failure. Digoxin may impair erectile function by lowering serum testosterone levels (Table 7). Additionally, it has anti-cholinergic effects that inhibit smooth muscle relaxation through its ability to block sodium/potassium adenosine triphosphatase (sodium pump), a necessary component of *corpora cavernosa* enlargement (Oyedeji *et al*., 2020)

Anti-inflammatory drugs and salicylates: Prolonged use of anti-inflammatory drugs like sulphasalazine is spermato-toxic, causing alterations in sperm count, motility, and morphology. Aspirin, a common drug used to treat inflammation, has also been observed to have negative effects on sperm development and motility in rats (Banihani, 2020) [Table 7].

Anabolic Steroids and Testosterone: Hormone therapy based on testosterone has been shown to inhibit the hypothalamic-pituitary-gonadal axis, resulting in hypogonadotropic hypogonadism and partial or complete inhibition of spermatogenesis, leading to conditions such as oligospermia, cryptozoospermia, or azoospermia (Semet *et al*., 2017).

Diuretics: Diuretics such as spironolactone and hydrochlorothiazide can affect sexual function through their actions on the sympathetic vasculature (Samplaski and Nangia, 2015). Spironolactone has been reported to exhibit an anti-androgen effect by inhibiting testosterone biosynthesis and increasing it conversion to estrogen while hydrochlorothiazide can impair penile blood flow. Spironolactone has been observed to cause gynecomastia and a decrease in sperm motility and density in humans and rats (Samplaski and Nangia, 2015; Semet *et al*., 2017).

Conclusion

This review sheds light on the interactions between various classes of drugs and the male reproductive system. The male reproductive organs, governed by a complex hormonal control system, are essential for spermatogenesis. The drugs discussed in this review, spanning antibiotics, anti-fungals, anthelmintics, anti-protozoal drugs, anti-neoplastic agents, anti-hypertensives, anti-inflammatory drugs, diuretics, etc. exhibit diverse effects on male reproduction. The impact of these drugs on male fertility is substantial, ranging from alterations in sperm parameters to hormonal disruptions and impairment of spermatogenesis.

Understanding the potential adverse effects of these drugs on male reproduction is crucial for clinicians. This review emphasizes the need for a more comprehensive assessment of drug

safety, particularly concerning their impact on male reproductive health. As research in this field continues to evolve, it is imperative to consider these findings when prescribing medications to animals and humans of reproductive age.

Table 6. Effects of anti-hypertensive drugs on male reproductive system and reproduction.

S/N	Drugs.	Class of the drug.	Species studied, and the reported effects on male reproduction.	References.
1	Clonidine	Anti-hypertensive	**Rats:** Decreased sperm reserves and diminished epidermal transit time in the caput and cauda epidermis.	da Silva Júnior *et al*., 2014.
2	Methyldopa	Anti-hypertensive	**Humans and Rats:** Reduction in sperm motility, increased prolactin level, erectile dysfunction and reduction in libido in males.	Adeleke *et al*., 2017.
3	Tamsulosin	α1-Blocker	**Rats:** Retrograde ejaculation by decreasing smooth muscle tone at the bladder neck. Reduction in sperm motility and count through.	Ratnasooriya and Wadsworth, 1994.
4	Doxazosin	α_1-Adrenergic blocker	**Rats:** Decreased serum testosterone level.	Drobnnis and Nangia, 2017.
5	Propranolol	Non-selective β-adrenergic antagonist	**Rats:** Decreased sperm motility, increased sperm abnormality and disrupted seminiferous tubule architecture.	Mohammadi *et al*., 2020.
6	Atenolol	Peripheral β_1-adrenergic antagonist.	**Humans:** Erectile dysfunction, Reduction in sperm count, sperm motility, testosterone level and inhibition of spermatogenesis.	Abbas and Khalil, 2017.
7	Metoprolol succinate	β_1-Adrenergic antagonist.	**Humans and Rats: -** Reduction in testosterone level, inhibition of spermatogenesis, decreased sperm morphology and motility.	Drobnis and Nangia, 2017.
8	Amlodipine	Calcium channel blocker	**Rats:** Reduction in sperm motility, increase sperm abnormality and reduction in sperm count.	Oyedeji *et al*., 2018.
9	Diltiazem	Calcium channel blocker (Nondihydropyridine).	**Humans and Rats:** Reduction in sperm motility and viability within a very short period of usage, prevented sperm passage through cervical mucus.	Morakinyo *et al*., 2009.
10	Nifedipine	Calcium channel blocker (Dihydropyridine; mineralocorticoid blocker).	**Rats:** Reduction in serum testosterone level, decreased epididymal weight, reduction in sperm count and motility.	Drobnis and Nangia, 2017; Hamid *et al*., 2019.

Table 7. Effects of cimetidine (anti-histamine), digoxin (cardiac glycoside) and aspirin (NSAID – salicylate) on male reproductive system and reproduction.

S/N	Drugs.	Class of the drug.	Species studied, and the reported effects on male reproduction.	References.
1	Cimetidine	Anti-histamine	**Rats:** Competes with dihydrotestosterone receptor and causes a decline in spermatozoa and overall sperm count.	Beltrame *et al*., 2019.
2	Digoxin	Cardiac glycoside	**Rats:** Anti-cholinergic effects that inhibit smooth muscle relaxation and corpora cavernosa enlargement.	Oyedeji *et al*., 2020.
3	Aspirin	NSAID: Salicylate	**Rats:** Reduction in sperm density, sperm count, and sperm motility; histopathology on sperm cells.	Vyas *et al*., 2016.

Conflict of Interest

The authors declare no conflict of interest regarding this article.

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