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RESEARCH ADVANCES ON THE ADVERSE EFFECTS OF ANTIBIOTICS ON MALE FERTILITY

Possible Popoola[1], Rasheedat Oniyangi[2], Oluwanifemi Ogunleye[3], Oluwatobi Ojediran[4], Christian Agyei-Acheampong[5], Tosin Olaniran[6], Chinedum Okafor[7], Mercy Opateye[8], Alade Mutolib[9] and Ayodeji Folorunsho Ajayi[10*]

[1,9,10]Department of Physiology, Ladoke Akintola University of Technology, Nigeria.

[2]Department of Regulatory Affairs, Northeastern University, USA.

[3]Department of Microbiology, Ekiti State University, Nigeria

[4]Department of Dentistry, Obafemi Awolowo University, Nigeria.

[5]Department of Pharmacy, Kwame Nkrumah University of Science and Technology, Ghana.

[6]Department of Pure and Applied Biology, Ladoke Akintola University of Technology.

[7]Department of Pathology, Louisiana State University, USA.

[8]Department of Nursing, Babcock University, Nigeria.

[*]Corresponding Author's Email: aajayi22@lautech.edu.ng

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ABSTRACT: *With the widespread use of antibiotics, bacterial infection-related morbidity and mortality have significantly declined, revolutionizing modern medicine. However, concerns have been raised concerning the negative effects of antibiotics on a number of physiological systems, including the health of male reproductive systems. The purpose of this in-depth review is to investigate and summarize the body of knowledge about the effects of antibiotics on male fertility. Antibiotics may have negative impacts on male reproductive characteristics, according to a growing body of studies over the past few decades. Several antibiotic groups, including fluoroquinolones, tetracyclines, and sulfonamides, have been linked to altered sperm quality, lower sperm count, impaired sperm motility, altered DNA integrity and morphology of sperm. Male reproductive health is thought to be negatively impacted by antibiotics in a multifactorial manner. It has been suggested that hormonal imbalances, oxidative stress, and disturbances of the delicate male reproductive system's balance may be the underlying mechanisms for the effects that have been observed. Additionally, changes brought on by antibiotics to the gut microbiota, which is known to be extremely important for overall health, may indirectly affect male fertility by altering systemic inflammation and hormone regulation. Additionally, the timing and length of antibiotic exposure appear to be important variables in determining their effect on male fertility, of which there is proof that repetitive or continued drug use may have more severe side effects. The possible negative effects of antibiotics on male fertility are highlighted in this review. Although the available data support a logical relationship between antibiotic usage and male reproductive health, more, well conducted research on humans are still required to clarify the underlying mechanisms and determine the clinical relevance of these results. Future studies in this field might open the door to stronger protections for male fertility while ensuring efficient control of bacterial infections.*

KEYWORDS: Research Advances, Antibiotics, Male Fertility, Antibiotics, Morbidity, Mortality.

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INTRODUCTION

Background of the Study

Antibiotics have been revealed to have negative effects on spermatogenesis or sperm function throughout the animal kingdom (Luo *et al*., 2022). In humans, these effects have been clearly defined for a few agents and have been linked to the majority of major antibiotic classes, including nitrofurans, macrolides, aminoglycosides, tetracyclines, and sulfa drugs (Roesenberg *et al*., 2020).

Antibiotics' effects on fertility, as well as the implications for infertile couple management, may be greater than previously thought (Schulz *et al*., 2019). Because infertility is potentially multifactorial, it is intended that this review raises as many questions as it answers about the adverse effects of these widely used antibiotics on male fertility (Durairajanayagam, 2018).

Only antibacterial agents will be discussed in this review; the terms antibiotic and antimicrobial will be used interchangeably (Schulz *et al*., 2019; Abuhaimed & Martin, 2018). The antitumor agents have already been discussed. Antiprotozoal, antihelminthic, and other agents are only used on rare occasions in this country and are not covered in this discussion. Approximately 10% to 15% of all couples experience primary infertility, with a male factor identified in approximately 50% of cases. Many extrinsic or environmental factors, such as increased antibiotic use, have been identified as potential causes of male infertility (Schulz *et al*., 2019). However, the precise etiology of male factor infertility is frequently difficult to define due to our limited understanding of spermatozoa biochemistry, spermatogenesis, and sperm maturation (Luo *et al*., 2022).

Drug-related illnesses must be investigated as one of the aetiological factors in male infertility. If a patient is taking a drug, it is important to note when the treatment began, how long it lasted, when it was taken (was it during a critical period of testicular maturation), and the dose (Abuhaimed & Martin, 2018). This information can be very useful if there is a change in spermatogenesis, erectile function, or ejaculatory function. However, with the exception of cancer treatments, very little work has been done to summarize the impact of drugs on male fertility (Schulz *et al*., 2019). It is critical and required to establish levels of scientific proof for each molecule in question in order to determine the actual impact of the treatment in relation to the other risk factors that are frequently associated in the same infertile patient (Luo *et al*., 2022).

Furthermore, the possibility of multifactorial causes of infertility and varying degrees of subfertility adds to the complexities involved in determining the etiology of male infertility (Durairajanayagam, 2018). The time required for spermatogenesis and spermatozoa transport through the reproductive tract, when combined with other confounding systemic factors (local temperature effects, other medications, viral diseases, stress, and increased age), clearly represent additional formidable barriers to delineating the potential antifertility effects of these agents (Durairajanayagam, 2018; Luo *et al*., 2022). Ethical concerns prevent direct evaluation of the negative effects of many environmental agents, including antibiotics, on human fertility and limit critical studies aimed at clarifying the effects of these factors on male reproductive function (Durairajanayagam, 2018).

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However, current research on the effects of antibiotics on human and non-primate male reproductive physiology identifies antibiotics as potential fertility hazards (Durairajanayagam, 2018). To better organize the data, antibiotics will be classified according to drug class and the effects of antibiotics on spermatogenesis and/or sperm function (Durairajanayagam, 2018; Luo *et al*., 2022).

INTRODUCTION TO MALE INFERTILITY

Infertility as defined by the World Health Organization is the inability to conceive after at least one year of constant, unprotected sexual intercourse (Benbella *et al*., 2018). Infertility is a major public health issue that affects 8–12 percent of couples of reproductive age worldwide (Vander Borght & Wyns, 2018). According to a Global Burden of Disease survey, the age-standardized prevalence of infertility increased by 0370 percent in women and by 0291 percent in men between 1990 and 2017 (Sun *et al*., 2019).

Infertility causes significant psychological and social distress as well as a significant economic burden on patients and health care systems (Kiesswetter *et al*., 2020). These factors can be mitigated by early diagnosis and appropriate management. Glazer *et al*. (2019) discovered a higher risk of mortality among men with male factor infertility than among men who were fertile in a prospective study of 384,419 Danish men. Ventimiglia *et al*. (2015) discovered that poor male reproductive health (including poorer semen parameters and lower testosterone levels) was associated with a higher Charlson Comorbidity Index, a proxy for poor general health state (Kiesswetter *et al*., 2020). Severe male infertility is also linked to an increased risk of cancer (Hanson *et al*., 2018). Thus, early detection of male fertility problems enables the detection and correction of male infertility as well as other general health issues. There is growing evidence that paternal health at the time of conception, such as oligoasthenoteratozoospermia and asthenozoospermia, can affect the offspring's wellbeing and reproductive possibilities via neurotransmission of epigenetic modifications (Watkins *et al*., 2018).

In most cases, the causes of male infertility are complex and inadequately defined (Fainberg & Kashanian, 2019). Although there are various tests available, their assessment is often indefinite and debatable (Softness *et al*., 2020). Intracytoplasmic sperm injection has enabled pregnancy with very poor semen quality, such as in cases of azoospermia, in which surgically collected testicular sperm is used (Aghajanova *et al*., 2020). Also, interesting new therapies based on sperm cells and *in vitro* sperm maturation are still in the early stages of development.

Prevalence of Male Infertility

In some cases of fertility problems, both partners are to blame. According to the WHO (2010), 5-15 percent of the infertile cohort has an unknown cause for this condition. Male infertility is defined as a male's incapability to conceive naturally in a fecund female (Benbella *et al*., 2018). It is responsible for 40-50 percent of infertility in humans. It affects approximately 7% of all men. In 20–30% of cases, the man is the primary cause of infertility, and a male cause is a contributing factor in another 20% (Jensen *et al*., 2018).

Causes of Male Infertility

Testicular failure, low semen volume, sperm agglutination, obstruction, cryptorchidism, idiopathic infertility, varicocele, erectile or ejaculatory dysfunction, abnormal viscosity,

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endocrine disorder, high sperm density, congenital abnormalities, and environmental causes have been identified as significant causes of infertility (Darmishonnejad *et al*., 2020). According to Sherins, 50% of male infertility cases are idiopathic (unknown) (Panara *et al*., 2019). Male infertility causes can be generally divided into non-genetic and genetic factors. Prior exposure to disease is one of the non-genetic factors that influences fertility either directly or indirectly. Diabetes is linked to increased sperm nuclear and mtDNA damage, which may impair these men's reproductive ability (Darmishonnejad *et al*., 2020).

Genetic Damage

Genetic damage in sperm can occur at multiple levels, each of which has the potential to cause male infertility (Darmishonnejad *et al*., 2020) Sperm DNA is known to contribute one-half of a child's genomic material. Normal sperm genetic material is thus required for fertilization, embryo and fetal development, and postnatal child well-being (Darmishonnejad *et al*., 2020). Several in vivo and in vitro studies have suggested that disruptions in the genomic organization of sperm nuclei are negatively correlated with spermatozoa fertility potential (Middelkamp *et al*., 2019). According to research, these disorders play a significant role in the failure of intracytoplasmic sperm injection (ICSI) and intrauterine insemination (IUI) (IUI). The prevalence of genetic factors appears to be inversely related to sperm count in males (Lopes & Esteves, 2019).

There is a major worry that genetic anomalies may be passed down to male offspring, resulting in a more severe phenotype of infertility. The predominance of chromosome factors in infertile male ranges between 2 and 8%, but has recently increased to 15% in azoospermic males (Ambulkar & Pande, 2018). FSH is an important hormone that is required for the initiation of spermatogenesis and must be controlled in infertile men from the therapeutic and clinical intervention standpoint (Oduwole *et al*., 2018). Normal FSH levels are indicative of germinal epithelial destruction, but elevated FSH levels are associated with both normal and abnormal spermatogenesis, with testicular histology revealing Sertoli cell only (SCO) syndrome (Oduwole *et al*., 2018).

Hypospermatogenesis is accompanied by a decline in sperm production and is associated with either standard or increased FSH (Ribas-Maynou *et al*., 2020). When DNA-damaged sperm is used in ART, the rate of healthy birth is low. Couples face financial, emotional, and psychological strain as a result of recurrent ART failure. Due to advances in molecular biology, underlying genetic causes of male infertility can now be identified and characterized. Infertile men must be assessed for genetic causes, and affected couples must be informed about the implications of such diagnoses for the outcome of assisted reproductive technology and their potential offspring (Fainberg & Kashanian, 2019). For a long time, there has been a link between human male infertility and chromosomal abnormalities (Dong *et al*., 2022). The genetic structure of infertility is extremely complex and is influenced by a variety of factors. These factors play a part in the development of gametes, the external and internal reproductive organs, their physiology, and the development of the embryo and its further distinctions (Zhang *et al*., 2022). Genetic disorders can be chromosomal, caused by a single gene mutation, or multifactorial. Extensive research has been carried out in order to gain a better understanding of the genetic basis of infertility (Krausz & McElreavey, 2001). However, genetic counseling informs patients about their genetic make-up and any risks that may be passed down to their offspring. It also provides them with reproductive options (Zhang *et al*., 2022).

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ENVIRONMENTAL FACTORS

Individuals are exposed to a wide range of exogenous and endogenous chemicals through different routes. The massive development of chemical industries in both developed and developing countries over the last 50 years has resulted in the release of a multitude of organic pollutants into the environment. The male reproductive system is extremely sensitive to environmental factors that cause infertility (Mesquita *et al*., 2021). Pesticides, herbicides, cosmetics, preservatives, cleaning materials, municipal and private wastes, pharmaceuticals, and industrial byproducts are among the alien molecules that enter our bodies in a variety of ways. Exposure to chemical contaminants, which act as estrogen mimics and endocrine disruptors, has been identified as one of the potential causes of rising male infertility (Mesquita *et al*., 2021).

Heavy Metals

Humans can be exposed to heavy metals at minute quantities through the consumption of contaminated water and food, as well as through exposure to infected air or soil. Heavy metals such as lead (Pd), cadmium (Cd), and mercury (Hg) can harm the male reproductive system by altering the hypothalamic-pituitary-adrenal axis or directly affecting spermatogenesis, resulting in poor sperm quality (Bouabdallah *et al*., 2021). Men exposed to heavy metals have a tendency to have weaker sperm quality and it has been discovered that exposure to lead causes childlessness rather than postponed pregnancy. Pregnancies in which the father worked as a stainless-steel welder had an increased risk of spontaneous abortion, whereas pregnancies in which the father worked as a welder of other metals had no increased risk (Kaur *et al*., 2022).

There is a widespread consensus that increased or even mild levels of lead cause fertility issues in humans. Lead levels in the blood greater than 40 g/dL cause a decrease in sperm count. Furthermore, they found lower motility (50%) and morphology (14%), with >35 g/dL in whole blood. It was also discovered that an elevated lead concentration in the blood reduces sperm concentration and motility (36.7 g/dL) (Javorac *et al*., 2021). High lead concentrations appear to be clearly linked to sperm damage. Cadmium, in high concentrations, may also have an effect on sperm quality. Men with high cadmium concentrations in seminal plasma (65 g/dL) had a lower sperm count and 36% motile sperm (Jain, 2019). Elevated mercury concentrations in the body have been shown to be hazardous to sperm. It was also discovered that high levels of total mercury (inorganic and organic) in whole blood (40.6 mmol/L) resulted in 50% of sperm motility, 14% of normal morphology, and 0% of sperm concentration (Henriques *et al*., 2019). However, according to a study conducted by Lidia *et al*., there is no significant relation between the concentration levels of any of the metals in the three biological samples examined (whole blood, blood plasma, and seminal plasma) (Choi *et al*., 2020).

Lifestyle

Lifestyle factors are modifiable habits and ways of life that can have a significant impact on overall health and well-being, including fertility (Balawender & Orkisz, 2020). As paternal age increases, occupation has been linked to a variety of unusual reproductive and genetic results. Fertility may be influenced by lifestyle factors such as age when starting a family, nutrition, weight management, exercise, psychological stress, cigarette smoking, recreational and prescription drug use, alcohol and caffeine intake (De Jonge & Barrett, 2019).

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- **Age**

Age has a detrimental effect on the basal membrane, seminiferous tubules, and tunica albuginea of the testis. The number of Leydig cells decreases, and the "aging" pigment lipofuscin accumulates (Kakimoto *et al*., 2019). Age causes localized changes in spermatogenesis, such as a decrease in dark type spermatogonia and intratubular clustering of pale type spermatogonia. Spermatogenesis has been halted at the spermatocyte I stage, and numerous spermatid malformations have been observed (Kakimoto *et al*., 2019). Sharma's research also shows that aging is associated with decreased sperm motility and vitality, but has the least effect on sperm count. Normal sperm parameters were observed between the ages of 20 and 30 years, with the most significant reduction occurring after the age of 35 years (Gao *et al*., 2017; Kakimoto *et al*., 2019).

- **Obesity**

Obesity is a global issue, with levels increasing all over the world. Body mass index (BMI) is a simple index of the weight-to-height ratio that is used to classify overweight and obesity in adult populations and individuals. Infertility is more common in men with high BMIs. Excess weight is linked not only to an increased risk of chronic disease (Stenholm *et al*., 2017), but also to an increased risk of reproductive problems (Stenholm *et al*., 2017). Given the pathophysiology of obesity, it has a negative impact on male fertility. Jensen *et al*. (2013) studied 1,558 younger men undergoing paramilitary physicals and discovered that overweight men had lower sperm concentrations than normal weight men (Ramaraju *et al*., 2018).

Several scientific studies have apparently investigated the effect of BMI on sperm parameters, which show that the prevalence of azoospermia or oligozoospermia is associated with increased overweight and obesity (Ramaraju *et al*., 2018). Previous research on BMI and sperm function has revealed that sperm function, including sperm concentration, motility, and vitality, has a significant and negative relationship with BMI; in contrast to the results show a significant declination in sperm concentration, motility, and vitality in overweight and obese males when compared to normal males (Stenholm *et al*., 2017). However, increased BMI has the least effect on sperm morphology (Stenholm *et al*., 2017). When compared to normal weight subjects, underweight men had significantly lower sperm function (Ramaraju *et al*., 2018).

- **Alcohol**

Alcohol consumption in men can have an effect on spermatogenesis and/or sperm physiology, and it can even cause impotence. According to one study, 75% of children with fetal alcohol syndrome have alcoholic fathers (Bai *et al*., 2020). Alcohol intake is accompanied by a decrease in sperm parameters, which may be partially reversible upon cessation of alcohol consumption (Bai *et al*., 2020). Although paternal alcohol intake has been shown to affect offspring growth and behavior, the methods underlying these effects are still unknown. The reduction in cytosine methyltransferase mRNA levels caused by alcohol may reflect altered genomic imprinting caused by decreased DNA methylation, which may lead to the expression of the enzyme (Patil *et al*., 2019).

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- **Use of recreational drugs**

Cocaine inhalation in males before the partner conceives has been linked to abnormal development in the offspring, as cocaine has a high affinity for binding to human spermatozoa. As a result, sperm may serve as a vehicle for cocaine transport to the ovum (Wimmer *et al*., 2019). Methamphetamine, cocaine, and marijuana use are linked to an increased risk of congenital anomalies affecting specific organ systems (Wimmer *et al*., 2019). Marijuana, which contains the chemical 9-tetrahydrocannabinol (THC), has the potential to be directly toxic to the egg. THC has a similar structure to testosterone and binds to the same receptors that testosterone should bind to. A cardiovascular genetic defect has been linked to paternal marijuana use (Slotkin *et al*., 2020).

MSG, a popular flavor booster found in foods such as accent, flavored potato chips, Doritos, Cheetos, meat seasonings, and many packaged soups, was discovered to cause infertility in test animals (Jubaidi *et al*., 2019). It was reported that male rats fed MSG before mating had less than a 50% success rate (5 of 13 animals), whereas those not fed MSG had a 92% success rate (12 of 13 animals). In addition, after 25 days of MSG treatment, the offspring of MSG-treated males had shortened body length, lower testes weights, and evidence of obesity (Jubaidi *et al*., 2019).

- **Smoking**

Tobacco smoke has a negative impact on reproduction. In cigarette smoke, benzo[a]pyrene (B[a]P) is a carcinogen. Its reactive metabolite forms adduct with DNA, causing mutations (Lopez *et al*., 2018). This can lead to infertility in both men and women (Lopez *et al*., 2018). Women who smoke have lower estrogen and progesterone levels, a poor LH surge (causing irregular menstruation and ovulation), a longer time to conceive, an increased risk of miscarriage, bleeding during pregnancy, low birth weight babies during IVF, and menopause at a younger age. Male smokers have lower sperm counts, impaired sperm motility, more abnormal sperm, and lower testosterone levels, which may contribute to genetic anomalies and asthma in their children. Heavy paternal smoking may increase the probability of children developing cancer (Lopez *et al*., 2018).

Garlantézec *et al*. (2019) revealed that heavy smokers had 19% lower sperm counts than nonsmokers. It was discovered that the more a man smokes before his wife's conception, the greater the risk of cancer in the child by the age of five. It has been demonstrated that exposing nonsmokers' spermatozoa to smokers' seminal plasma reduces sperm motility, acrosome reaction, and increases MDA (Kurkowska *et al*., 2020).

Drug Induced Male Infertility

Male fertility is affected by exposure to certain drugs, particularly drugs of abuse. These drugs influence male fertility through a variety of mechanisms, and it has become necessary to consider recreational drug use when determining the cause of male infertility (Durairajanayagam, 2018).

Opioids

Globally, the rise in opioid medication abuse is now a public health issue. Opioids reduce male fertility through a variety of mechanisms. At high doses, testosterone concentrations fall,

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resulting in hypogonadism (Wehbe & Dobs, 2020). This is due in part to increased prolactin and suppression of pituitary gonadotropin secretion. The observed hypogonadism is not affected by androgen levels. Endogenous opioids are produced in the Leydig and germ cells. Their receptors can be found throughout the testis (Abu El-Hamd & Farah, 2018). By inhibiting the Sertoli cell receptors, these opioids reduce the secretion of androgen-binding protein, which plays a role in androgen intra-testicular transport (Abu El-Hamd & Farah, 2018).

Morphine has also been linked to an increase in aromatase expression in the brain and testis, as well as a decrease in testicular function (Ghasemi-Esmailabad *et al*., 2021). Exogenous opioids have been shown to cause DNA fragmentation and lower sperm quality. These effects are associated with all opioids, though lower doses, shorter-acting opioids, and opioids with mixed receptor activity, such as tramadol, cause less damage. Similar findings were observed in heroine-treated experimental mice (Imam *et al*., 2018). Heroin reduced sperm viability, serum testosterone levels, and fertility rate significantly. Long-term opioid use leads to hypogonadism because the hypothalamus suppresses gonadotropin-releasing hormone secretion (Nazmara *et al*., 2021).

Cocaine

Steiner *et al*. (2018) revealed that acute cocaine exposure had no substantial effects on overall sperm motility and fertilizing capability despite an initial decrease in straight line velocity and linearity. In vitro cocaine exposure significantly reduced sperm motility and bovine mucus penetration rates (Steiner *et al*., 2018). Chronic high-dose cocaine administration has been shown to significantly reduce fertility indices, offspring birth weights, as well as the diameter of the seminiferous tubule, thickness of the germinal epithelium, and number of spermatids (Caffino *et al*., 2018). In a study, cocaine caused a rapid disruption of the seminiferous tubules and Sertoli cells, resulting in a decrease in spermatogenesis. Cocaine has been shown to bind to an unidentified testicular tissue protein, causing testicular damage through apoptosis (Verhaeghe *et al*., 2020).

Cannabis

Cannabis sativa's (hemp, marijuana) negative effects have been well recorded. According to animal research, cannabis sativa causes testicular wound as measured by a decrease in the Johnsen score, organo gonadal index, and testicular total antioxidant capacity, down-regulates the hypothalamic–pituitary–gonadal axis, resulting in androgen suppression and hyperprolactinemia (Verhaeghe *et al*., 2020), and Cannabis-induced infertility has been linked to oxidative stress (Verhaeghe *et al*., 2020). Tetrahydrocannabinol, the main organic composition of Cannabis sativa as revealed by GC-MS, also impairs sperm motility in an in vitro study (Alagbonsi & Olayaki, 2018). Cannabis sativa spermatotoxicity was shown to be via cannabinoid receptor 1 (CB 1) rather than CB 2 (Alagbonsi & Olayaki, 2018).

Cannabis sativa spermatotoxicity was shown to be via cannabinoid receptor 1 (CB 1) rather than CB 2 (Alagbonsi & Olayaki, 2018). In the cannabinoid-deficient Benin Republic, Cannabis sativa was found to significantly improve sperm parameters, reduce prolactin levels, and boost antioxidant status (Alagbonsi *et al.,* 2019). Human studies have also found that men who use cannabis have lower sperm quality than men who do not (Carroll *et al*., 2018). This negative effect was observed to persist even four weeks after withdrawal. This supports the

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observation that men who abuse cannabis have a higher risk of abnormal sperm motility and morphology (Carroll *et al*., 2018).

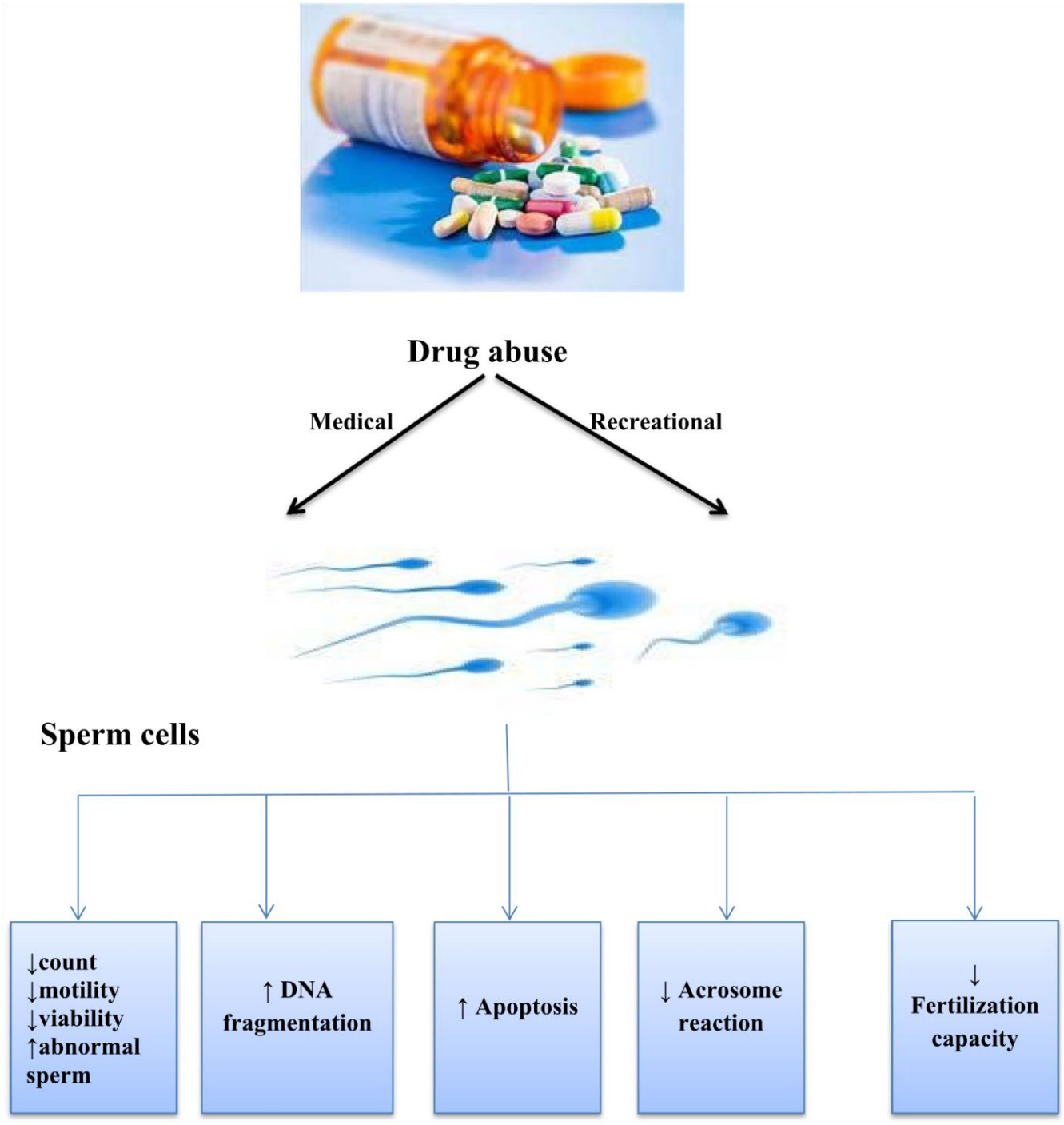

Figure Effects of Drugs on Male Fertility

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Methamphetamine

Methamphetamine, an N-methylated amphetamine, abuse has been linked to detrimental consequences on male sexual system. It has been shown to reduce sperm motility and testosterone levels in the blood and to induce apoptosis in the seminiferous tubules of experimental mice (Khan *et al*., 2021). The exposure of methamphetamine whether rapid or slow results in a significant decrease in sperm count and percentage of normal sperm morphology via apoptosis (Khan *et al*., 2021). Nudmamud-Thanoi *et al*. (2016) found that methamphetamine had a negative effect on sperm cells, causing a significant decrease in sperm count, motility, and normal morphology. This was linked to a decrease in the expression of progesterone receptor and estrogen receptor (both ER- and ER-) and their respective mRNA in male germ cells and Sertoli cells caused by methamphetamine. Methamphetamine has been shown to, partially, halt spermatogenesis by stimulating GABAergic activity in the testis (Kaewman *et al*., 2018). Following methamphetamine exposure, there was a significant increase in GABA concentration as well as expression of the GABA-AI receptor and glutamate decarboxylase I genes. This stimulant has also been linked to a significant decrease in testes index, as well as mRNA and protein expressions of glucose transporter 1 (GLUT1), hexokinase 1 (HK 1), and lactate dehydrogenase C (LDHC) (Kaewman *et al*., 2018).

This could imply that the molecule also prevents spermatogenesis by interfering with glycolysis. Methamphetamine also caused DNA damage in sperm and disrupted the normal testicular histoarchitecture, according to research (Yang *et al*., 2019). A study revealed that prenatal methamphetamine exposure in female rats resulted in an evident delay in oocyte development, poor sperm quality, and increased sperm DNA damage in the male offspring (Zhang *et al*., 2021).

ANTIBIOTICS

Antibiotics' introduction into clinical use was arguably the greatest medical breakthrough of the twentieth century (Torres *et al*., 2020). Antibiotics, in addition to treating infectious diseases, enabled many modern medical procedures, such as cancer treatment, organ transplants, and open-heart surgery. Misuse of these valuable compounds, on the other hand, has resulted in a rapid rise in antimicrobial resistance (AMR), with some infections now effectively untreatable (Torres *et al*., 2020). The dangers of a post antibiotic era have prompted policymakers to recognize this threat to human health and promise additional grant funding, resulting in a gradual resurgence of interest in antibiotic discovery and development (Kim *et al*., 2018).

According to the UK Government-commissioned O'Neill report, without immediate action, ten million people per year will die from drug-resistant infections by 2050 (Sandmann *et al*., 2021). One of the most important recommendations is to encourage early-stage drug discovery. Given the relative lack of success in bringing effective synthetic antibiotics to the clinic, discovering new microbial natural products is the best hope for developing a new generation of anti-infective drugs because these compounds are unrivaled in their chemical diversity and antibiotic effectiveness (Baquero *et al*., 2021). Filamentous actinomycetes produce 64% of known antibiotic classes, with the remainder produced by other bacteria and fungi. In this

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section, we provide a brief history of antibiotics as well as our prospects for discovering, developing, and safeguarding a new generation of antibiotics (Alrahimi, 2021).

DISCOVERY OF ANTIBIOTICS

Antibiotic-producing microbes have been used to prevent disease for thousands of years, with moldy bread cataplasm being used to treat open wounds in Serbia, China, Greece, and Egypt more than two thousand years ago (Tomas *et al*., 2021). The oldest preserved medical document is Ebers papyrus from 1550 BC, which includes moldy bread and medicinal soil among its list of remedies (Popko, 2018). A 1000-year-old Anglo-Saxon recipe was also recently shown to kill MRSA (methicillin-resistant Staphylococcus aureus) (Yang *et al*., 2018). However, Paul Ehrlich is widely credited with developing the synthetic arsenic-based prodrugs salvarsan (salvation arsenic) and neo-salvarsan around 100 years ago to treat *Treponema pallidum*, the causative agent of syphilis (Addetia *et al*., 2020). This was one of the first systematic drug discovery screens that used a library of synthetic compounds, and it was inspired by Ehrlich's work on dyes that specifically stained bacterial cells. Salvarsan was surpassed by the sulfonamide prodrug Prontosil, which was discovered by Gerhard Domagk, a Bayer bacteriologist who used the drug to save his daughter's arm from amputation (Addetia *et al*., 2020). Because the sulfa drugs were inspired by dyes used to selectively stain bacterial cells, Domagk and colleagues were effectively carrying on Paul Ehrlich's work (Addetia *et al*., 2020). Sulfonamides were the first truly effective, broad-spectrum antimicrobials in clinical use, and they are still used today, but they were largely superseded by the discovery of penicillin, which Alexander Fleming discovered in 1928 on a contaminated Petri dish (Angeli *et al*., 2019).

Penicillin was later purified by Norman Heatley, Howard Florey, Ernst Chain, and workmates at Oxford, who were helpful in the drug's advancement (Cozzoli, 2019). Dorothy Hodgkin solved the beta-lactam structure of penicillin, resolving the popular controversy between Robert Robinson, who advocated for a thiazolidine-oxazolone structure, and several other notable chemists, including Chain, Abrahams, and Woodward, who thought it was a beta-lactam (Wlodarchak *et al*., 2018). This was a major advancement because it allowed the development of semi-synthetic derivatives that could circumvent penicillin resistance. Antibiotics between microbes was explained long before penicillin's discovery, including by Louis Pasteur, who proposed that microbes could secrete material that killed other bacteria (Bottalico *et al*., 2022). Bacterial production of diffusible and heat-stable compounds had been reported by the turn of the twentieth century, and their utility in combating infectious diseases had been investigated (Liu *et al*., 2019).

Pyocyanase was found to be an enzyme but was actually active against multiple pathogens. Instead, the active components of pyocyanase were most likely a mixture of pyocyanin, a quorum sensing phenazine, and 2-alkyl-4-hydroxyquinolines. The majority of clinically relevant classes of antibiotics are derived from natural products. The discovery of penicillin, tyrocidine, and numerous reports of microorganisms producing antimicrobial compounds prompted Selman Waksman to begin a systematic study of microbes as producers of antimicrobial compounds in the late 1930s. Waksman described an antibiotic as "a compound made by a microbe to decimate other microbes" and was helpful in finding soil-dwelling filamentous Actinomycetales ('actinomycetes') as renowned manufacturers of antimicrobial substances (Chattopadhyay *et al*., 2015)

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CLASSES AND FUNCTIONS OF ANTIBIOTICS

Aminoglycosides

One of the earliest antibiotic classes, aminoglycosides, can have broad spectrum activity but are associated with widespread resistance in Gram-negative bacteria. They also have safety concerns, such as nephrotoxicity and ototoxicity, which make them less preferable treatment options than other antibiotics (Rosenberg *et al*., 2020). A new class of aminoglycosides known as 'neoglycosides' has recently been introduced in an attempt to circumvent the most common resistance mechanisms and improve the class's safety profile (Krause *et al*., 2016). Plazomicin (ACHN-490), the lead candidate in the neoglycoside subclass, has completed two Phase 1 clinical trials in which the drug was well tolerated with no ototoxicity or nephrotoxicity reported, as well as a Phase II clinical trial for the therapies of complex urinary tract infections (cUTI) (Bilinskaya *et al*., 2020).

This novel aminoglycoside has antibacterial activity in vitro against many multidrug-resistant (MDR) Gram-negative bacteria, including carbapenem-resistant Enterobacteriaceae (Livermore *et al*., 2011), as well as MRSA (MIC90 of 2 mg/ml) (Matsushita *et al*., 2019). Pseudomonas aeruginosa and Acinetobacter spp. activity was slightly lower, with a MIC50 of 8 mg/ml. Although plazomicin is resistant to most aminoglycoside-modifying enzymes, it is ineffective against Gram-negative strains that carry the ArmA and RmtC 16S rRNA methylases, which are found in the majority of NDM-1-producing Enterobacteriaceae, limiting its spectrum against some MDR Gram-negative bacteria (Matsushita *et al*., 2019).

b-Lactams

Since the use of benzylpenicillin in World War II, b-lactam antibiotics have been effective antimicrobial agents. Despite the fact that resistance to older members of this class is spreading, new b-lactams and related b-lactamase inhibitors are still being developed to combat b-lactam resistance mechanisms in both Gram-positive and Gram-negative bacteria (Vena *et al*., 2019). Some of these newer agents have impressive anti-MDR activity. However, all of them have gaps in their activities that will almost certainly necessitate the use of multiple agents to provide broad-spectrum coverage (Vena *et al*., 2019).

Cephalosporins

Anti-MRSA cephalosporins have been the most prominent newer b-lactam-containing agents, with antibacterial activity against multidrug-resistant Gram-positive pathogens (Tang *et al*., 2017). Ceftobiprole was the first anti-MRSA b-lactam to successfully complete Phase III clinical trials, but it was not approved by the FDA. Ceftaroline, an anti-MRSA cephalosporin, was approved by the FDA in 2010 for the treatment of community-acquired bacterial pneumonia (CABP) and complicated skin and skin structure infections (cSSSI) (Stryjewski *et al*., 2015; Tang *et al*., 2017). Ceftaroline had a 2-fold greater potency than ceftobiprole against staphylococci (MIC90 1 mg/ml) in a recent large Canadian surveillance study, with comparable potency against streptococci (MIC100 0.03 mg/ml); ceftaroline was less active than ceftobiprole against most Gram-negative pathogens (Stryjewski *et al*., 2015).

Ceftolozane is a cephalosporin with powerful anti-activity (MIC90 of 8 mg/ml) and interaction against several enteric bacteria, but only moderate activity against Gram-positive and anaerobic bacteria (Sheffield *et al*., 2020). Particularly, all three cephalosporins are susceptible to the

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action of extended-spectrum b-lactamases (ESBLs) and carbapenemases, including the common KPC serine carbapenemases, limiting their possible role as monotherapy agents (Ogbolu *et al*., 2018; Sheffield *et al*., 2020).

Quinolones

Fluoroquinolones are now benchmark empiric therapy in the community setting, particularly now that ciprofloxacin and levofloxacin are generic. Despite the fact that these broad-spectrum agents cover a wide range of therapeutic indications, they have recently encountered resistance and safety issues, making new topoisomerase inhibitors appealing (Kocsis *et al*., 2021).

Delafloxacin, nemonoxacin (a nonfluorinated quinolone), and JNJ-Q2 are all quinolones with enhanced activity against Gram-positive bacteria, including MDR S. pneumoniae and ciprofloxacin-resistant MRSA (MIC90 0.5 mg/ml, 1 mg/ml, and 0.5 mg/ml, respectively) (Bassetti *et al*., 2018; Kocsis *et al*., 2021). Resistance in staphylococci was particularly difficult to pick with JNJ-Q2, especially when compared to resistance selection with ciprofloxacin, levofloxacin, or moxifloxacin (Bassetti *et al*., 2018; Wang *et al*., 2019). Nemonoxacin has also been shown to be active against Nocardia, with MIC90 values of 1 mg/ml and 0.25 mg/ml, respectively. Delafloxacin has completed two Phase II clinical trials for the treatment of cSSSI, whereas nemonoxacin has completed Phase II studies for CAP and diabetic foot infections; recruitment for a Phase III trial in CAP is currently underway. When administered once daily, nemonoxacin was found to be as safe and effective as levofloxacin in the Phase II CAP trial (Wang *et al*., 2019). JNJ-Q2 recently completed a randomized, double-blind, multicenter noninferiority study in 161 patients for the treatment of acute bacterial skin and skin structure infections. Using the 2010 FDA guidance, JNJ-Q2 was found to be noninferior to linezolid in terms of clinical cure rates (Wang *et al*., 2019).

Macrolides

Telithromycin, a ketolide, was the most newly introduced macrolide into clinical practice; it has an enhanced activity against erm-containing Streptococcus pneumoniae and Staphylococcus aureus strains with the MLSBphenotype, as well as against streptococci with mef-mediated macrolide efflux (Zheng *et al*., 2020). Ketolides, which are distinguished by the presence of a 3-keto group in place of a cladinose moiety in early macrolides, have a tarnished reputation as a result of the events that led to the approval and subsequent (partial) withdrawal of telithromycin in the United States. A mechanistically unexplained, transient, blurred vision in some patients was observed as a safety issue in the telithromycin trials (Fermandes *et al*., 2020).

Cethromycin is a ketolide with greater activity than telithromycin against many macrolide-resistant *S. pneumoniae* strains, has lower activity against enterococci and *Streptococcus pyogenes* isolates that produce an Erm methylase constitutively (Fernades *et al*., 2020). Cethromycin successfully completed Phase III clinical trials for the treatment of community-acquired pneumonia (CAP) and was deemed safe by the FDA Advisory Committee and the FDA after dosing over 5000 patients in 53 clinical studies (Fernades *et al*., 2020).

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Antibiotics, Spermatogenesis and Sperm Quality

Antibiotics have been shown to have a negative impact on spermatogenesis or sperm function (Barbagallo *et al*., 2020). The effects of antibiotics on fertility and the implications for infertile couple management may be greater than commonly presented. W. Nelson and R. Bunge conducted a study on the effect of nitrofurantoin on spermatogenesis in humans in 1957 (Nasrallah *et al*., 2018). Nitrofurantoin is the most commonly used antibiotic for treating urinary tract infections and genital infections. They gave nitrofurantoin at a dose of 10 mg/kg per day to 36 young healthy white males. Nitrofurantoin was found to temporarily cause mild to moderate spermatogenic arrest in some unpredictable cases (O'Connor *et al*., 2022). The study found that out of 36 volunteers who took the antibiotic for 14 days, 23 had significant changes in testicular biopsies or sperm counts, 13 had a partial decrease in sperm counts, and 6 had no changes in testicular biopsies. The incidence of arrest is even less likely to occur at the reduced clinical doses currently in use, and they proposed that drugs may tamper with fertility significantly (Luo *et al*., 2022).

This was one of the first studies to look into the negative effects of antibiotics on male fertility. The germinal epithelium is the most rapidly increasing tissue, producing millions of sperms per hour. Because it is a very sensitive tissue and the regulation of spermatogenesis and testicular function is a very complex process, chemicals and drugs are very likely to interfere with the process, potentially leading to infertility (Barbagallo *et al*., 2020). There are drugs and chemicals that either directly or indirectly inhibit testosterone synthesis. They may restrict testosterone's effect on target organs, interfering with the growth and development of sperm and the function of other sexual glands. Several animal studies have been conducted to investigate the effect of various antibiotics on male fertility (Singh & Singh, 2019). Investigation on the effect of cefonicid and other cephalosporins on male rat sexual development was performed because the researchers wanted to see how cefonicid (a type of cephalosporin antibiotic) with a modified Nmethylthiotetrazome (MTT) side chain affected prostate toxicity in male rats. Rats aged 636 days postpartum were given 50-1000 mg/kg of cefonicid antibiotics daily. With the same dose, the positive control is Moxalactam antibiotic, which also contains the Nmethylthiotetrazome (MTT) side chain, and the negative control is Cephalothin antibiotic, which lacks the N-methylthiotetrazome (MTT) side chain. Moxalactam significantly reduced testicular and seminal vesicle weight in 37-day-old rats, and histological examination revealed damage to the seminiferous tubules at all dose levels, but cefonicid did not cause any significant damage in the same age group (Rosenfeld *et al*., 2018).

Some researchers are attempting to understand the effect of antibiotics on sperm in vitro in order to study this phenomenon in humans. Amoxicillin, ofloxacin, ciprofloxacin hydrochloride, nitrofurantoin monohydrate, doxycycline hyclate, and cefuroxime axetil were tested on cryopreserved-thawed sperm (Luo *et al*., 2022). They discovered that ciprofloxacin affects sperm hyperactivation by altering the sperm membrane, ofloxacin did not harm the sperm and actually improved sperm fertilization capacity, nitrofurantoin decreased sperm motility and fertilization capacity, cefuroxime affected sperm motility, amoxicillin also affected the motility, and doxycycline affected the sperm capacitation process (Luo *et al*., 2022).

An experiment was conducted a similar experiment with fresh sperm samples and various antibiotics such as co-trimoxazole, erythromycin, amoxicillin, tetracycline, and chloroquine and discovered that tetracycline at a concentration as low as 2.5 mg/ml can inhibit sperm

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motility and that at a dose of 50 mg/ml all spermatozoa became immotile (Luo *et al*., 2022). Erythromycin also had an effect on motility. Amoxicillin had no effect on sperm movement, but it did have an effect on sperm viability at high doses. Co-trimaxazole had no effect on sperm movement at low concentrations, but it reduced movement by 34% at 500 mg/ml. Chloroquine had no negative effects on sperm (Luo *et al*., 2022). Antibiotics' importance in modern health care and lifestyle cannot be overstated. To treat urogenital tract infections, antibiotics are required. These infections are thought to be one of the factors interfering with male fertility. Doxycycline is one of the most commonly prescribed antibiotics to males with leukocytospermia (Hou *et al*., 2019; Eini *et al*., 2021). Male fertility is negatively impacted by leukocytospermia, and antibiotic therapy for the condition may improve male fecundity (Hou *et al*., 2019).

Antibiotics and Sexual/Erectile Function

Numerous antibiotics, many of which are often administered, have been found to negatively impact fertility. Historically, it has been demonstrated that excessive doses of nitrofurantoin can halt the development of the testicles. It is most usually related to the testicular cells' incapacity to utilize oxygen and carbohydrates (Pergialiotis *et al*., 2018). These detrimental impacts have not been demonstrated to occur with minimal, brief nitrofurantoin treatment.

Sperm motility and density may be affected by erythromycin (Barbagallo *et al*., 2020). Tetracyclines attach to developed sperm cells and may have an impact on motility (Barbagallo *et al*., 2020). Although studies conducted in vitro have not demonstrated a difference in mature sperm cells, gentamicin and neomycin may directly reduce sperm production (Barbagallo *et al*., 2020). Further research will be necessary to make sure that minor changes in spermatogenesis or activity are not brought on by routinely used antibiotics such the penicillins and quinolones, despite the minimal data suggesting that these drugs negatively impair male fertility (Barbagallo *et al*., 2020).

Although there is little in vivo data, the majority of antibiotics decrease sperm movement in vitro. According to its possible gonadotoxic effects at the level of initial spermatocytes and spermatids (a reduced level of nucleic acid in the affected germ cells), nitrofurantoin may be detrimental to sperm production (Luo *et al*., 2022). By blocking the intake of the carbohydrates and oxygen needed for the proper activity of the cells present in sperm production, nitrofurantoin may impede germ cell development when used in high doses (Pacholak *et al*., 2019). After ceasing the antibiotic therapy, the effects on sperm parameters—which are marked by a decline in testosterone levels and motility—can be reversed. However, because antibiotic therapy has a positive effect on semen quality in the setting of penile diseases and epididymitis, it is advised (Alyethodi *et al*., 2021).

The steroidogenesis-related cytochromes P450 enzymes are inhibited by the antifungal medication ketoconazole. Thus, there is a decreased production of androgens and intratesticular testosterone as a result of the inhibition of the enzyme complexes 17α-hydroxylase and 17-20 Desmolase. It is conceivable for sperm parameters to change in a reversible way. Prior to being pregnant, it is advised that men discontinue using ketoconazole (Pacholak *et al*., 2019; Alyethodi *et al*., 2021). The protease inhibitor and lysosome stabilizer chloroquine is used to treat malaria. It has the potential to impede spermatozoa's acrosome response and lessen their ability to fertilize. However, there is currently a lack of information in the literature about how chloroquine affects male fertility (Alyethodi *et al*., 2021).

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Germ cell changes caused by ribavirin, a medication used to treat chronic hepatitis C, are reversible. Reversible changes in sperm movement and structure happen four months after stopping the medications (Alyethodi *et al*., 2021). This nucleoside synthesis analog prevents the production of guanosine triphosphate in DNA and RNA by inhibiting inosine monophosphate dehydrogenase. As a result, it prevents cell growth. As a result, the seminal epithelium's germ cells experience a higher rate of cell death, insufficient multiplication, and cellular differentiation. (Barbagallo *et al*., 2020).

Zidovudine and Stavudine are nucleoside reverse transcriptase inhibitors that may prevent spermatozoa from reproducing mitochondrial DNA (polymerase c), despite the fact that healthy mitochondria are essential to the energy supply needed for their motility. Protease inhibitors are believed to stop the apoptosis that affects the quality of sperm (Wen *et al*., 2021).

Premature ejaculation (PE) is a common condition, although accurate population-based data are lacking. Despite the fact that it is normally associated with less inconveniences than ED, this disorder can be extremely distressing in some cases (Wen *et al*., 2021). In most cases, the cause of PE is unknown, however it is thought to be a combination of organic and psychogenic causes. Low serum testosterone, seminal plasma magnesium levels, hyperthyroxinemia, significant neurological diseases, and short frenulum of prepuce, penile hypersensitivity, and reflex hyperexcitability have all been linked to PE (Shin *et al*., 2019; Wen *et al*., 2021). PE was found to be more common in patients with chronic prostatitis in two recent investigations. Initial research into the effectiveness of antibiotics in treating PE found positive results (Davidov, 2020).

The use of culture-specific antibiotics in the treatment of patients with PE and chronic bacterial prostatitis was found to have a very beneficial effect in our study (Davidov, 2020). The mechanism underlying antibiotics' severe influence on ejaculation time is unknown. Except with PE, prostatitis is thought to fester in a moderate form for years without visible or clear symptoms (Yepes *et al*., 2020). One of the pathogenetic mechanisms of PE is sensory impairment that occurs before orgasm (Rowland *et al*., 2022). In research conducted, about 64 percent of males who complained of PE were diagnosed with neurophysiologic PE. By modifying sensation and influencing the ejaculatory reflex, prostate inflammation may contribute to this theory. All of our patients with PE had bacterial chronic prostatitis with no signs of prostatitis (Culha *et al*., 2020). It is still unknown if the type of organism—bacterial or nonbacterial—influences the development of PE. Our patients with PE and chronic bacterial prostatitis improved significantly in both ejaculation time and prostatic infection after a one-month antibiotic treatment. Prostatitis infection and the onset of prostatitis-related symptoms can take a long time, according to Metz and Pryor (Culha *et al*., 2020). As a result, it is plausible to assume that germs that cause chronic prostatitis have a long incubation period. We believe that our short course of antibiotics' high success rate in treating chronic prostatitis is due to an "early" interference with the etiology of chronic prostatitis. The absence of prostatitis-related symptoms in all treated patients supports this (Xiong *et al*., 2020). In cases of PE and chronic bacterial prostatitis, the lack of improvement in ejaculation time or prostatic infection in the control group patients clearly supports the positive effect of antibiotics (Neymark *et al*., 2022).

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CONCLUSION

In conclusion, although antibiotics are germ killers, chronic use of these drugs can have a deleterious impact on male reproductive health. The majority of research highlights the risk factors that people utilizing drugs—primarily antibiotics—can be exposed to. Antibiotics are necessary for treating infections and enhancing general health, but their inappropriate use and possible adverse effects on reproduction cannot be disregarded. Studies have emphasized the detrimental effects of antibiotics on the function of the male reproductive system, including alterations in sperm quality, decreased sperm motility, and increased DNA damage. These outcomes may result in diminished fertility and poor sperm activity, which may affect the ability to conceive and add to reproductive problems. Medical practitioners must be cautious when writing prescriptions for antibiotics and, whenever practical, take into account alternate therapeutic approaches. The possible implications of antibiotic usage on male fertility should also be discussed with patients, and they should be urged to take precautions.

Additional investigation is required to fully comprehend the underlying mechanisms by which antibiotics impact the health of the male reproductive system and to find solutions to these negative consequences. In order to encourage careful antibiotic usage and protect male fertility, outreaches and information efforts can also be very helpful. Medical practitioners, scientists, governments, and individuals must work to resolve the negative effects of antibiotics on male fertility. By cooperating, we can find a middle ground between the advantages of antibiotics and the protection of male reproductive health, assuring a better lifestyle for succeeding generations.

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