Review

The Hidden Danger of Amphetamine-Type Stimulants (ATS) and Opioids on Male Reproduction Toxicity: A Narrative Review

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Review

The Hidden Danger of Amphetamine-Type Stimulants (ATS) and Opioids on Male Reproduction Toxicity: A Narrative Review

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Abstract: New psychoactive substances (NPS) pose a global public health challenge. Its ongoing evolution intensifies drug abuse cases, complicates regulation, and makes comprehensive studies difficult to conduct. Emerging studies indicate that these substances may severely impact spermatogenesis, reproductive hormones and male fertility. This review aims to consolidate existing knowledge on the impact of NPS on male reproduction, identify gaps in the literature, and suggest directions for future research. This comprehensive review examines original, peer-reviewed studies and clinical reports from PubMed, Semantic Scholar, AJOL, and Google Scholar. Data collection spanned from 2014 to 2024, using keywords such as "amphetamine-type stimulants", "ATS", "amphetamine", "stimulants", "opioids", "opioid abuse", "opioid addiction", "male reproduction", "male fertility", and "reproductive toxicity". The search encompasses illegal drugs, prescription medications, and over-the-counter (OTC) drugs that induce male reproduction toxicity through chronic use or prolonged exposure. Although current studies have limitations, our findings indicate that both illicit and medicinal ATS and opioids negatively impact male reproduction. These substances can diminish sperm quality, disrupt reproductive hormones, and cause sperm DNA damage. This review highlights further study in formulating public health strategies and supplements that mitigate DNA damage caused by these substances.

Keywords: ATS toxicity; opioids toxicity; male reproduction toxicity; drug-induce male infertility

1. Introduction

The impact of illegal, prescribed, and over-the-counter drug (OTC) abuse has been a global problem with no end in sight. United Nations Office on Drugs and Crime (UNODC), reported that substance abuse is mainly of the psychoactive class. These include opioids and amphetamine-type stimulants [1]. According to the latest statistics, men are the primary consumers of psychotropic drugs [2–4]. This phenomenon prompted concerns about its possible impact on fertility and reproductive function especially among young male adults.

Adolescence is a critical developmental period characterized by increased risk-taking, social pressure, and the emergence of mental health issues [5]. Several interconnected factors may contribute to the prevalence of psychoactive substance use among this specific population. The primary motivation for utilizing synthetic substances and prescription medications for nonmedical

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purposes is to cope with the demands of academic underperformance, work stress, social interaction pressure, and the general challenges of growing up [5,6]. The availability of medicine and the low price of synthetic drugs also significantly influence this circumstance [7,8]. For example, an over-the-counter cough syrup mixture of codeine or prescribed Adderall is easily accessible for treating medical conditions [9]. These medications are legal but harmful if used excessively or incorrectly [10]. Most users are unaware of what they are consuming or what risks are implicated until they become addicted to the psychoactive drugs [11]. Adolescents who start abusing psychotropic substances are more likely to acquire dependence, long-term cognitive impairment, poor educational outcomes, lower life satisfaction, unachieved accomplishments, and an increased risk of psychotic disorders [12–14].

Psychotropic drugs are frequently abused and are known to have adverse effects on various organ systems, including the reproduction system. Several studies have found that psychoactive substances like amphetamine-type stimulants (ATS) and opioids may have a toxic influence on reproductive function in males [15–18]. However, the specific mechanisms and extent of toxicity of each psychoactive drug differ [19], especially on new synthetic substances. Many of these new emerging synthetic substances are made in illegal labs by applying subtle modifications to the chemical structure of existing controlled drugs [20]. Due to this, they no longer fit the classification of traditional opiates or legal psychoactive drugs [21,22]. This modification helps to keep drug traffickers' and users' activities hidden from the authorities and society since psychoactive drugs are scheduled drugs [23].

The overall influence on male reproductive health has been an area of increasing concern, as the global fertility rate has declined over the past several decades [24]. A decline in the fertility rate may have potential implications for a country's economy, society, and overall well-being [25]. This is especially true in countries with a growing base of drug addicts.

Knowledge of the long-term effects of psychoactive substances is limited. Despite this, a report by Ahmadnia et.al [26] indicated that long-term exposure to psychoactive can have a negative impact on spermatogenesis and testicular health, which leads to infertility. However, due to a lack of detailed investigation, the result demonstrated may raise inconclusive evidence to support if the damage to the reproduction has occurred due to psychoactive substances. Therefore, more study needs to be explored as there are still gaps in understanding the impact of ATS and opioid drugs on male reproductive health, particularly in terms of continuous or repeated exposure to these drugs over a certain period and lasting consequences after stopping or continuing drug use, and mechanistic pathways.

Henceforth, this review aims to understand the implications of ATS and opioids on sperm biology, such as sperm quality, reproduction hormones, testicular function, sperm DNA (deoxyribonucleic acid) integrity, and fertility potential due to DNA mutation.

2. Classification of Psychoactive Drugs

Psychoactive drugs are substances that contain various active compounds that affect the brain and alter mood, perception, cognition, and behavior [27]. The active chemicals in each psychoactive substance differ from one another, natural or synthetic, and have various action pathways [19,28]. They are broadly categorized into several distinct classes based on their psychopharmacological effects, which include, stimulants, depressants, hallucinogens, and cannabis [29,30] (Table 1). The most widely recognized classes within this categorization are stimulants and depressants [31]. Each class affects the central nervous system differently [19], leading to varying impacts on mood, cognition, and behaviors [22].

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Table 1. 0 Psychoactive drugs classification based on psychopharmacological effects.

Stimulants	Depressants	Hallucinogens	Cannabis
Amphetamines-Types Stimulants (ATS)	Opioids	Ketamine	Cannabidiol (CBD)
Cocaine	Alcohols	Lysergic dimethylamine (LSD)	Hashish
Caffeine	Benzodiazepines	Dimethyltryptamine (DMT)	Tetrahydrocannabinol (THC)
Nicotine	Kratom	Mescaline	Cannabis sativa

2.1. Stimulants

Stimulants are a class of drugs that increase the activity of the central nervous system [32]. Stimulants use different neurotransmitter systems, called monoaminergic pathways, involving the action of neurotransmitters norepinephrine, dopamine, and serotonin to exert their effect [33]. These drugs act as agonists to mimic the action of the neurotransmitter [34] and bind with neurotransmitter receptors on the transporter protein [19,35]. This action inhibits the reuptake of neurotransmitters into the presynaptic neuron [35,36]. The neurotransmitter will stay in the synaptic cleft longer and cause an increased release of neurotransmitters from the presynaptic neuron [19,37]. Consequently, it induces the overflow and accumulation of neurotransmitters into the synapse [38].

Elevated neurotransmitters in the nucleus accumbens and prefrontal cortex lead to heightened alertness, increased energy, improved focus, and sometimes euphoria [39,40]. Due to that, stimulants are used to treat conditions such as attention deficit hyperactivity disorder (ADHD) and narcolepsy [37]. Unfortunately, they are also abused for recreational purposes [10]. These drugs can be classified into medical stimulants and illicit stimulants. ATS is one of the broad classes of drugs with stimulant properties [20]. Stimulant properties can be natural or synthetic. Nicotine and caffeine are natural stimulant substances derived from plants such as coffee beans and tobacco [41,42]. These substances are the most popular used in combination with club drugs such as ecstasy to increase or prolong stimulating effects [43] for recreational purposes. Despite their natural origins, these substances can contribute to the rise of addiction and other negative consequences on human health [44]. Synthetic stimulants are lab-created substances, commonly including amphetamine, methamphetamine, 3,4-methylenedioxymethamphetamine (MDMA), and methylphenidate hydrochloride [2,20]. These substances are typically made by modifying the structure of naturally occurring stimulant chemicals or creating entirely new substances that have similar effects on the central nervous system (CNS) [45,46].

2.2. Depressants

Depressant drugs are a class of psychoactive substances that reduce the activity of the central nervous system (CNS) [47], leading to a calming effect on the mind and body [48]. The most often used or misused depressive drugs are opioids [1]. Opioids consist of chemical compounds from either poppy plants or semisynthetic compounds with similar properties that can interact with opioid receptors in the brain [49,50]. Opioid derivatives are heroin, morphine, codeine, methadone, and Tramadol [49,51].

The human body has a built-in system to regulate pain, mood, stress, and multiple physiological processes. This system is called the endogenous opioid system [52,53]. It consists of endogenous opioids, a neuropeptide that acts as a chemical messenger, synthesized and released by neurons [52]. There are three types of endogenous opioids: endorphins, enkephalins, and dynorphins [54]. They exert their effects on the brain by acting on five types of receptors, namely the mu receptor (MOR)

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[55], kappa receptor [56], delta receptor [57], nociception receptor (NOR) [34], and zeta receptor (ZOR) [58,59].

On the other hand, exogenous opioids are introduced into someone's body from an external source for medical purposes or recreational purposes. Examples of this exogenous are morphine, heroin, or another synthetic opioid [60]. It mimics the action of endogenous opioids [59] because it binds to the opioid receptor on the presynaptic neuron [61]. This binding activates an intracellular signalling cascade through the G-protein-coupled receptor mechanisms [62]. It inhibits excitatory neurotransmitter release [63], such as glutamate and substance P [64]. This binding complex inhibits adenylyl cyclase [59], which reduces cyclic AMP (adenosine monophosphate) levels [62,65] and calcium influx into the presynaptic cleft [66], thus decreasing synaptic transmission [67]. The consequences of reduced synaptic transmission led to less stimulation, hence depressing the activity. Additionally, opioid receptor activation causes potassium channels in the postsynaptic neuron to open [62], increasing the efflux of potassium ions or inhibiting calcium channels [63,68], making the inside of the neuron less positively charged [67] and causing hyperpolarization of the neuron membrane [69]. Hyperpolarisation of postsynaptic neurons requires more powerful stimulation to reach the threshold to initiate an action potential [61]. As a result, the postsynaptic neuron becomes less excitable [67], which reduces its ability to transmit signals [69].

The inhibition of excitatory neurotransmitter releases may lead to disinhibition of GABAergic neurons (gamma-aminobutyric acid) [69]. This inhibition further suppresses excitatory neurotransmission [69], reduces pain perception, and promotes feelings of calmness and drowsiness that contribute to euphoria [70]. The outcome effects explain why these drugs are the choice for various therapeutic conditions, such as anxiety, insomnia, and seizures [71]. Although heroin, morphine, codeine, methadone, and tramadol are prescribed to treat illnesses, they are also often widely abused globally [72,73]. Due to the possibility of abuse, long-term use of depressants may produce psychological dependence and tolerance [72], leading to an impact on male reproductive health consequences [74,75].

3. Male Reproductive Toxicity

Reproductive toxicity is a complex and heterogeneous area of concern in reproduction health. It encompasses the potential adverse effects of various chemical, physical, and biological agents on the male reproductive system [76]. Previous studies have demonstrated that exposure to chemicals, such as psychoactive drugs, ATS, and opioids is associated with reproduction toxicity that will affect reproduction parameters in males (Table 2.0).

Table 2. 0 Effect of stimulant and depressant drugs on male reproductive health.

Effect on the male reproductive system	Drugs	Author (year)
Reduced sperm quality	Methamphetamine	Sabour et.al (2017)
	Heroine	Farag et.al (2018)
Imbalance of hormone	Methamphetamine	Allaeian Jahromi et.al (2020)
	Tramadol	Salah et.al (2019)

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Testicular function	Methylphenidate hydrochloride	Abdollahifar et.al (2020)
	Codeine	Akhigbe et.al (2020)
Sperm DNA damage	Methamphetamine	Aryan et.al (2022)
	Morphine	Chasemi-Esmailabad et.al (2022)

3.1. Amphetamine-Type Stimulants (ATS) and Male Reproductive Health

ATS, including methamphetamine and ecstasy, causes neurotransmitters such as norepinephrine, serotonin, and specifically dopamine to become more active in the brain [37]. These neurotransmitters are essential in the hypothalamic-pituitary-gonadal axis (HPG) [77]. They control male reproductive function through hormonal regulation [78].

Hypothalamus secretes gonadotropin-releasing hormone (GnRH) in a pulsatile manner [79]. This in turn stimulates the anterior pituitary gland to release two hormones in male reproduction [80], follicle-stimulating hormone (FSH), and luteinizing hormone (LH) [81]. ATS are agonists to neurotransmitter systems [34]. They enhance or mimic the action of dopamine, norepinephrine, and sometimes serotonin [19]. The action may either directly or indirectly facilitate their release, blocking their reuptake, or influencing their receptor activity [82]. These actions will alter the hypothalamus's pulsatile rhythm of GnRH release [83]. Dysregulation may suppress or overstimulate the GnRH pulse generator [83,84].

Prolonged use of ATS substances like amphetamine or MDMA can lead to the depletion or desensitization of dopamine receptors [36]. Subsequently, dopamine will not be able to bind to its receptor, disrupting normal control of prolactin releases [85], leading to hypoprolactinemia or hyperprolactinemia [86]. The abnormal level will suppress GnRH pulse frequencies [87], and cause an inhibition of FSH and LH release from the pituitary gland [88]. The alteration of FSH and LH secretion reduces testicular function [89], resulting in decreased testosterone synthesis in the testes [90]. This is characterized as hypogonadism [91]. Hypogonadism in males can lead to various symptoms, including reduced libido, erectile dysfunction, fatigue, depression, and infertility due to impaired spermatogenesis and testicular dysfunction [57,87,92,93].

3.2. Opioids and Male Reproductive Health

Chronic use of opioids disrupts neurotransmitter activity [59,61], which directly and indirectly affects the hypothalamus-gonadal (HPG) axis [94]. Opioids primarily interact with inhibitory neurotransmitter systems, GABA (gamma-aminobutyric acid) [95,96], affecting neurotransmitters that regulate gonadotropin-releasing hormone (GnRH) secretion and related hormonal pathways [59], resulting in reproductive toxicity [97].

GnRH secretion plays a key role in male reproduction [98]. The hypothalamus regulates GnRH secretion by a delicate balance of excitatory and inhibitory neurotransmitter signals (glutamate and GABA) [65]. When opioids bind to the presynaptic opioid receptors in the hypothalamus, specifically the mu (μ)-receptor [67], they activate to diminish GABA activity and modulate glutamate action by inhibiting adenylyl cyclase and lowering cAMP levels [63,99,100]. The reduced cAMP level prevents calcium from entering the presynaptic neuron [55]. Since calcium is essential for vesicular dopamine release [101,102], low calcium levels decrease dopamine release into the synaptic cleft [99]. Consequently, it suppressed pulsatile release and decreased GnRH levels [94].

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In addition, chronic opioid exposure may lead to stress response and induce adrenal glands to dysregulate cortisol secretion [103,104]. An imbalance level of cortisol leads to opioid-induced suppression of GnRH production or signaling leading to hypogonadism [105,106], a condition in which gonads fail to produce a sufficient amount of testosterone and oestradiol [75], or gonadotropins (FSH and LH) [80]. Hypogonadism may be considered a marker for reproductive toxicity in males [107], as it involves disruptions to normal reproductive function, including infertility, impaired sexual function, and hormonal imbalance [17,103].

4. Evidence of ATS on Male Reproductive Toxicity

Exposure to amphetamine-type stimulants, including medicinal drugs or a recreational drug, such as amphetamine, methamphetamine, ecstasy, khat, and others, has been associated with various impacts on male reproductive health [16,108–110]. However, evidence is still emerging due to insufficient knowledge of ATS toxicity on the human reproduction system, while new derivatives of ATS keep emerging in the recreational drug market [20]. On the other hand, several studies demonstrated that ATS has potential toxicity and disruptions to reproductive function in males [111–113].

4.1. Sperm Quality

Recent studies have shown that exposure to amphetamine and other ATS impaired sperm count, motility, and morphology [114,115]. Studies from Sabour et.al [116] & Mobaraki et.al [117] prove that chronic methamphetamine and ecstasy exposure may associated with decreased sperm motility and increased sperm DNA fragmentation, both of which can have an impact on male fertility. In addition, there is evidence that ATS chronic consumption can affect spermatogenesis, resulting in decreased testosterone levels and poorer semen quality [108,112,118].

4.2. Hormonal Imbalance

ATS use can result in hypogonadism, which refers to low testosterone levels [119]. Testosterone is critical for maintaining male reproductive health and fertility [120]. Studies indicate that methamphetamine and MDMA can reduce the testicular size [121], lower serum testosterone levels [118,122], and cause alterations in luteinizing hormone secretions (LH) [121,123] and follicle-stimulating hormone (FSH) [111,124], which are vital for normal spermatogenesis.

4.3. Testicular Function

Long-term or chronic ATS abuse may lead to a decrease in various parameters of male reproductive health. The experiment conducted by Saberi, Sepehri [125] and Peirouvi and Razi [126] demonstrates that methamphetamine leads to a decrease in the Tubular Differentiation Index (TDI), Spermiogenesis Index (SI), Repopulation Index (RI), and Mean Seminiferous Tubule Diameter (MSTD). The low TDI index indicates the impairment of the seminiferous tubule to differentiate [125], leading to a significant reduction in spermatogonia, spermatocytes, and spermatids [111], which are essential stages in sperm production. In addition, results from an in-vitro study show that methamphetamine may induce a decrease in Sertoli cells, leading to diminished capacity in spermatogenesis [127]. This disruption will reflect a reduction in the Spermiogenesis Index (SI). A study by Azizi et.al [128] indicates interference may occur in the maturation process as spermatids and spermatozoa show a significant reduction in spermatogenesis [124]. Furthermore, methamphetamine may lower the Repopulation Index (RI), reflecting compromised regenerative potential in the testes [125]. The damage presents as a disarrangement of the germinal epithelium due to increased spaces between spermatogenic cells [121,128]. Additionally, exposure to amphetamines can result in a reduction in the Mean Seminiferous Tubule Diameter (MSTD), which is indicative of reduced tubular volume [126] and impaired testicular function [129]. Overall, alteration in these measures due to chronic and long-term ATS exposure can negatively affect multiple aspects of spermatogenesis and testicular health, reducing fertility in males.

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4.4. Oxidative Stress and DNA Damage

The chronic use of ATS has proven to be associated with decreased sperm DNA integrity [130], primarily involving oxidative stress [108], mitochondrial dysfunction [127], hormonal imbalance [131], and inflammation in the testis [122]. These factors collectively lead to sperm DNA fragmentation and reduced sperm quality [132]. For example, observation by Aryan et. al [112], and Ghafori et.al [133] showed that methamphetamine and ecstasy increased levels of reactive oxygen species (ROS) in testicular cells, leading to oxidative DNA damage. In this regard, da Costa Nunes Gomes et.al [130] reported that this damage can contribute to infertility in males and increase the risk of genetic defects in offspring that compromise embryo survival. Consequently, this disruption has the potential to decrease fertility in men who use this substance chronically.

5. Evidence of Opioid on Male Reproductive Toxicity

Opioid abuse has been associated with significant negative effects on reproduction, leading to a potential decrease in fertility in males [134]. Research has shown that chronic opioid utilization, such as tramadol [17], heroin [56], codeine [135], morphine [18], and other prescription painkillers [136] can have a significant impact on reproductive parameters. Opioid misuse has been proven to impair overall sperm parameters [137], interfere with the HPG axis [138], and induce oxidative stress [139], which leads to damage to sperm DNA [140] and impair cellular function [26]. Overall, these combined effects were evidence of the deleterious impact of opioid misuse on male fertility. In addition, long–term opioid exposure may potentially cause irreversible damage to overall male reproductive health [137,141]

5.1. Sperm Quality

According to previous studies, chronic opioid use has been associated with reduced sperm parameters [137], with the most significant impact being a decrease in sperm motility [56,142,143]. However, other findings suggest that opioids may also lead to decreases in sperm viability, morphology, count [144], and concentration [145]. In a case-control study conducted by Bassiony et al. [138], the analysis indicates that male patients who developed an opioid disorder due to tramadol misuse exhibited low sperm counts. This condition is linked to high rates of abnormal forms and decreased motility. Additionally, a study by Koohsari et al.[146] observed similar effects on sperm parameters in an animal experiment. The results showed that male rats treated with doses of 50 and 75 mg/kg experienced significant decreases in sperm count, motility, and normal morphology. These identified damages to sperm quality can hinder individuals from successfully conceiving, thereby affecting the continuation of offspring.

5.2. Hormonal Imbalances

Opioids chronic use, including heroin, morphine, and prescription painkillers, may suppress the hypothalamic-pituitary-gonadal (HPG) axis [147,148]. This suppression causes an imbalance in the HPG axis, disrupting the testosterone and gonadotropin secretion essential in normal spermatogenesis [17]. Disruption may occur in any stage of spermatogenesis [149], leading to a decline in sperm production [26]. A study by Norioun et.al [150] proves that chronic exposure to morphine and methadone may present a decrease in testosterone secretion, and elevated FSH and LH. This condition is linked to causing CatSper1 expression to decrease, an indicator of disruption that had occurred during spermatogenesis. The increase in gonadotropins indicates there is a disruption in the HPG, suggesting due to a problem in the feedback loop owing to testes dysfunction. In addition, the analysis of reproductive hormones in studies by Ajayi et.al [134] and Soliman et.al [137], showed codeine and tramadol cause a decrease in testosterone production and hypersecretion of prolactin. The imbalance of these hormones affects sperm parameters which compromises its function and contributes to infertility in individuals.

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5.3. Testicular Function

Spermatogenesis is the most vital process in the male reproduction system because it is responsible for sperm production and fertilization [151]. As described by Chojnacka and Mruk [152], spermatogenesis occurs in the seminiferous tubules, coiled structures that fill most of the interior of the testes. These tube structures are very delicate and vulnerable to opioids [153]. Exposure to opioids may suppress testosterone and induce apoptosis that leads to testicular cell death and dysfunctions [140].

A study by Salah et.al [154] showed that tramadol interferes with hormone systems, causing dysregulation in gonadotropins and testosterone levels. While on histopathological, endocrine disruption causes damage to seminiferous tubules. The damage appears as the disorganization of spermatogenic cells, displaying numerous desquamations and vascular degeneration. Abundant apoptotic cells and multinucleated giant cells also appeared, and countless spermatogenic cells occurred as pyknotic cells. Furthermore, the absence of spermatozoa was notable in the prepared tissue section, along with oedematous and congested interstitial tissue. A decrease in mature sperm histologically can be an indicator of diminished spermatogenesis [149]. Another study on methadone, a synthetic opioid [155], has been shown to cause dysfunction in sexual hormones, leading to the suppression of sperm parameters. The experiment exposing male rats to morphine, which was done by Takzare et.al [149] similarly produced the same outcome on sperm parameters. The results show cells at the spermatogenesis cycle, at the phase of spermatogonia, spermatocyte, spermatid, and spermatozoa were markedly decreasing. The destruction manifested on the testicular can be the plausible factor for decreased potential in fertilization.

5.4. Oxidative Stress and DNA Damage

Sperm cells are vulnerable and have limited antioxidant defense systems [156]. Excessive use or long-time exposure to either synthetic or natural opioids has proven to increase reactive oxygen species (ROS) in the testicular [134,139]. ROS are unstable molecules that can damage sperm cells via mitochondrial dysfunction [156]. Opioid misuse diminishes mitochondrial function [157] and consequently leads to excessive ROS generation, depleted superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase [158]. An imbalance in antioxidant defense to neutralize ROS creates a condition called oxidative stress [159]. Oxidative stress causes damage to sperm membrane cells, protein, and DNA fragmentation [134], resulting in decreased sperm motility that negatively impacts male fertility [148]. An in-vitro study [135] was performed on human sperm cells exposed to different concentrations of codeine (0, 0.1, 1, 5, and 10 mM). Codeine at concentrations 1, 5, and 10 mM pronounced high levels of sperm 8OHdG (8-hydroxy-2’-deoxyguanosine), indicating increased DNA damage in sperm cells due to oxidative stress.

Furthermore, a study by Nazmara et.al [56] was carried out among 24 volunteer men with heroin dependency symptoms. Sperm from heroin users showed significantly low motility and survival rates and increased white blood cells. Data collected showed a high DNA fragmentation index (DFI) and alteration in seminal RNA (Ribonucleic acid) Profile (HDAC1 and HDAC2). These findings confirm that opioids can have adverse effects on sperm, causing DNA damage and genetic mutation. This adverse effect of opioids can reduce the genetic quality of sperm and may increase the risk of miscarriage or congenital abnormalities.

6. Conclusions

These findings imply that both amphetamine-type stimulants (ATS) and opioids cause damage to reproductive health in individual males. This study adds to the body of knowledge about the contribution of ATS and opioids on reproductive toxicity in males through distinct mechanisms. The use of these psychoactive drugs either as therapeutic or in recreational consumption has been shown to disrupt the hypothalamic-pituitary-gonadal (HPG) axis, induce oxidative stress, and disrupt the

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spermatogenesis process. This will lead to infertility and sexual dysfunction in males, particularly in chronic and long-term use.

The detrimental effects of these drugs on reproduction are particularly significant in younger individuals, as they are at the peak of their reproductive years. The potent effects of ATS and opioids come with significant risks, including dependency, substance adaptation, and overdose, especially in conditions where this drug is misused or abused. Chronic exposure to these psychoactive drugs is destructive, as the cumulative impacts on sperm quality and overall reproductive function may have the potential to cause lasting infertility. Thus, this is why ATS and opioids must be used carefully under medical supervision.

Nevertheless, even though ATS and opioids have been shown to induce a negative impact on male reproduction, there is limited knowledge that may connect these detrimental effects to human reproduction. For instance, the response dose or exposure duration that may induce reproductive toxicity has yet to be recognized as a reference standard in humans. Therefore, any appropriate approach needs to be explored, as there is an increase in new synthetic drug cases globally every year, while knowledge about the harmful effects of established illicit is still sparse on human health. Thus, to further understand the adverse consequences on human reproduction, more comprehensive methods and alternative approaches must be explored, particularly in terms of spermatogenesis, testosterone regulation, and sexual function.

Finally, individuals who use these substances should be mindful of the potential risks to reproductive health. Those planning to start a family or facing fertility challenges are especially encouraged to seek appropriate medical guidance. Reducing or withholding these substances can improve reproductive outcomes and overall health. For the authority and community, the options for addressing this crisis must include stricter regulations, better access to addiction treatment, and enhanced public awareness campaigns.

Author Contributions: MFMR conceptualized and designed the study, formulated the research question, and played a key role in data collection. KO, SFI, and FZMY contributed to the methodology, including designing the experimental framework, and provided supervision throughout the writing of the manuscript. KO was responsible for the data interpretation and drafting of the results section. MFMR contributed to the writing of the initial manuscript, including the introduction and discussion, and made significant revisions based on feedback. KO and SFI were involved in providing study materials and revising the manuscript for clarity and coherence. AAAN and SFI secured funding for the project. Also, SFI, KO and FZMY ensured the timely execution of the study. All authors contributed to the critical review and approval of the final manuscript.

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Abbreviations

The following abbreviations are used in this manuscript:

ADHD	Attention deficit hyperactivity disorder
AMP	Adenosine monophosphate
ATS	Amphetamine-type stimulants
CBD	Cannabidiol
CNS	Central nervous system
DFI	DNA fragmentation index
DMT	Dimethyltryptamine
DNA	Deoxyribonucleic acid
DOR	Delta receptor
FSH	Follicle-stimulating hormone
GABA	Gamma-aminobutyric acid
GnRH	Gonadotropin-releasing hormone
GPx	Glutathione peroxidase
HPG	Hypothalamic-pituitary-gonadal
KOR	Kappa receptor
LH	Luteinizing hormone
LSD	Lysergic dimethylamine
MDMA	3,4-methylenedioxymethamphetamine
MOR	mu receptor
MSTD	Mean Seminiferous Tubule Diameter
NOR	Nociception receptor
NPS	New psychoactive substance
OTC	Over-the-counter drug
RNA	Ribonucleic acid
RI	Repopulation Index
ROS	Reactive oxygen species
SI	Spermiogenesis Index
SOD	Superoxide dismutase
TDI	Tubular Differentiation Index
THC	Tetrahydrocannabinol
UNODC	United Nations Office on Drugs and Crime
ZOR	Zeta receptor

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