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Review

Can antidepressants compromise sperm quality? A comprehensive review of preclinical evidence

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Abstract

Introduction: Infertility is a significant global health concern, particularly among individuals of reproductive age. At the same time, psychiatric disorders—especially depression and anxiety—are increasingly prevalent, leading to a growing global demand for antidepressants.

Objectives: The present review aimed to compile and analyze preclinical studies evaluating the effects of antidepressant exposure on sperm parameters and fertility outcomes in animal models.

Methods A comprehensive literature search was conducted in April 2023 using the PubMed/Medline, Web of Science, and Scopus databases. The search strategy combined terms such as "fertility," "sperm," and "semen" with keywords related to various classes of antidepressants and their specific compounds. Eligible studies included experimental research assessing sperm and/or fertility parameters following antidepressant administration in male animals. Data extracted from the selected studies included drug class, specific compound, dosage, treatment duration, animal species, subject age, and reproductive outcomes.

Results: A total of 32 studies met the inclusion criteria. Among the antidepressants investigated, selective serotonin reuptake inhibitors were the most frequently studied, with venlafaxine, fluoxetine, and paroxetine being the most commonly evaluated compounds. Most studies reported adverse effects on sperm parameters, such as concentration, motility, and morphology. However, evidence regarding fertility outcomes remains inconclusive due to the limited number of studies and considerable heterogeneity in experimental designs and treatment protocols.

Conclusion: These findings suggest that several antidepressants may impair sperm quality in animal models, with possible implications for male fertility. Nonetheless, further research is warranted to clarify these effects, particularly for less-studied antidepressant classes.

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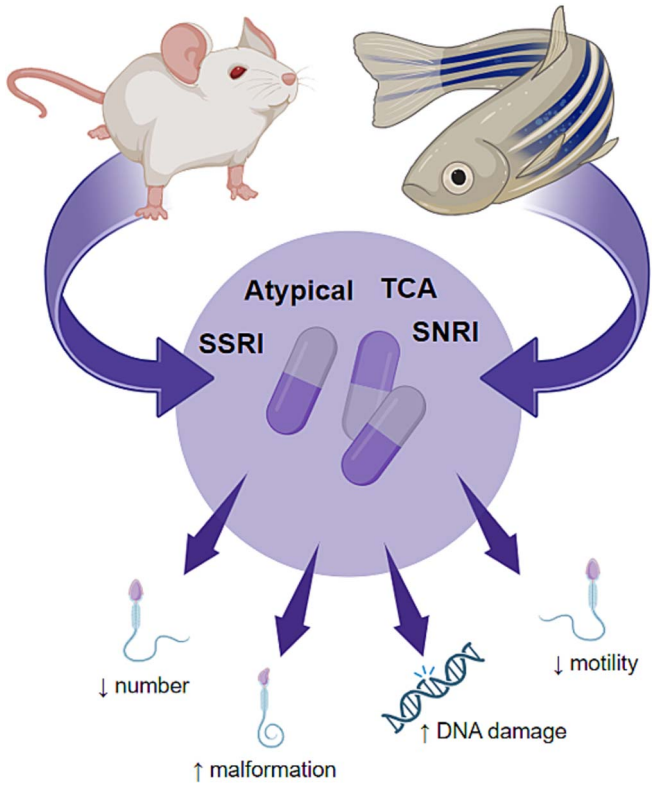
Graphical Abstract



Keywords: male fertility; spermatozoa; depressive disorder; drug; animal models; review.

Introduction

Infertility is recognized as a major global health challenge affecting couples of reproductive age, with an estimated prevalence of 17.5%.[1] Various factors have been implicated in this reproductive disorder, including exposure to stressors, environmental pollutants, sedentary lifestyles, and poor dietary habits. In men, these factors have been associated with declining semen quality, characterized by reduced sperm motility, increased sperm DNA fragmentation, and abnormal sperm morphology.[2] In addition to lifestyle-related influences, psychiatric disorders and psychological stress have been implicated in the deterioration of male reproductive health.[3-6]

In the United States, 13.2% of adults reported using antidepressant medications in the past 30 days (2015-2018).[7] In high-income countries, these drugs are primarily prescribed for the treatment of anxiety and depression. In low- and middle-income countries, their use is also associated with sleep-related disorders.[8] In this context, the most commonly prescribed classes of antidepressants include monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and atypical antidepressants.[9]

Emerging evidence indicates a decline in reproductive health among individuals using antidepressants. Sexual dysfunction is among the most frequently reported adverse effects, with its prevalence varying across different classes of antidepressants and demonstrating a dose-dependent pattern.[10,11] Additionally, these medications have been associated with reductions in sperm count and quality, as well as increased sperm DNA damage.[12,13] Our previous findings highlight a scarcity of studies investigating the effects of antidepressants on semen quality in men of reproductive age.[14] In contrast, animal studies are more numerous and offer clearer insights into the mechanisms through which antidepressants affect sperm parameters. Accordingly, this review aims to synthesize the current evidence on the impact of antidepressant medications on sperm parameters and male fertility, with particular emphasis on findings derived from animal models.

Materials and methods

Search strategy and research question

This is a comprehensive review, which includes studies based on varied research designs. The PECO strategy (Population, Exposure, Comparator, and Outcomes) was employed to frame the following guiding question: What are the effects of antidepressant administration on male fertility and sperm parameters in animal models? In 2023/April, a bibliographic search was conducted on the following databases: PubMed/Medline, Web of Science, and Scopus. The Boolean operators "AND" and "OR" were used to combine the terms "fertility," "sperm," and "semen" with the terms associated with the different types of antidepressants and its drugs, resulting in the combinations described in Supplementary Data S1. The generated database was organized using Rayyan software, with automatic and manual exclusion of the duplicated articles.

Studies selection and data extraction

The process of selecting articles for inclusion and exclusion was carried out independently by two researchers, with a third investigator reviewing the results to ensure compliance with the eligibility criteria. Studies were considered for inclusion if they assessed fertility and/or sperm parameters following antidepressant administration in animal models. Exclusion criteria comprised case reports, review articles, and book chapters. Studies with different research focuses (eg, those that did not evaluate sperm or fertility parameters), including those investigating unrelated disorders (eg, rheumatoid arthritis), studies involving human participants, female fertility, in vitro research, and transgenerational studies—where either parent had been exposed to antidepressants—were also excluded.

For the selected studies, the following data were extracted: (1) general information, including the title, first author, and year of publication; and (2) details related to exposure and outcomes, such as the class and specific type of antidepressant, dosage, duration of exposure, species and age of subjects, as well as sperm analysis results and fertility-related parameters. Data extraction was independently conducted by two researchers and subsequently reviewed by a third investigator.

Risk of bias

Risk of bias evaluation was conducted independently by two researchers using the SYRCLE tool (Systematic Review Center for Experimentation with Laboratory Animals) with necessary adaptations.[15] A third investigator reviewed and verified the results.

Results

A comprehensive literature search across PubMed (5470), Scopus (1627), and Web of Science (690) yielded a total of 7787 records. After eliminating 835 duplicate entries and excluding 6913 articles that did not align with the review's scope, 32 articles were selected for inclusion in this review. Notably, 4 of these studies independently assessed two different antidepressants, leading to a separate analysis of the data for each drug. Consequently, a total of 36 studies were analyzed. The included studies are described in Table 1.

Animal model

Among the included studies, 61.11% ($n=22$) used rats as the experimental model. Mice were the second most frequently used species, accounting for 33.33% ($n=12$) of the studies, while fish (*Danio rerio*) were used in two studies (5.56%).

Antidepressant classes and drugs

Among the analyzed studies, 47.22% ($n=17$) investigated the use of SSRIs, 22.22% ($n=8$) examined SNRIs, 16.66% ($n=6$) focused on atypical antidepressants, and 13.89% ($n=5$) assessed TCAs. Venlafaxine was the most frequently studied drug (22.22%, $n=8$), followed by fluoxetine (13.89%, $n=5$) and paroxetine (11.11%, $n=4$). Furthermore, based on the predefined inclusion and exclusion criteria, no studies involving MAOIs were identified.

Sperm parameters evaluation

Sperm parameters were evaluated in 35 (97.22%) of the included studies. Among these, only two studies (5.55%) reported no alterations in sperm analysis; these studies used citalopram and ansofaxine, which are a SSRI and an atypical antidepressant, respectively. The main alteration found is the decrease in the sperm concentration/count/density (72.22%, $n=26$) and involves all of the antidepressant classes. Additionally, 69.44% ($n=25$) of the studies reported some degree of alteration in sperm motility, while 66.67% ($n=24$) observed abnormalities in sperm morphology associated with antidepressant use. Regarding sperm viability or deaths, 27.78% ($n=10$) reported a decrease in this parameter.

Among the included studies, 22.22% ($n=8$) assessed DNA damage or genotoxicity in sperm and/or spermatic lineage across all antidepressant classes. Of these, seven studies (19.44%) reported an increase in DNA damage or genotoxicity following antidepressant exposure. The only study that observed no DNA damage used venlafaxine, an SNRI.

Fertility evaluation and gestation rate

Regarding fertility evaluation, only eight studies (22.22%) investigated this parameter. Among these, five studies used SSRIs including paroxetine, sertraline, citalopram, fluoxetine, and dapoxetine; two studies used atypical antidepressants (bupropion and ansofaxine); and one study used a SNRI (venlafaxine).

Of the studies that evaluated fertility, 3 (8.33%) reported impairment in gestation rate or fertility potential, all of which were associated with SSRI administration (paroxetine, fluoxetine, dapoxetine). Additionally, three studies (8.33%) observed an increase in pre-implantation loss and a decrease in the number of live fetuses, also associated with SSRIs (dapoxetine, sertraline, and fluoxetine).

Risk of bias

None of the selected studies provided information on sequence generation, allocation concealment, random housing, blinding, random outcome assessment, or incomplete outcome data. Most of the included studies reported baseline characteristics, selective outcome reporting, and ethical committee approval. All included studies provided information on the species and dose used (Figure 1).

Discussion

Sexual dysfunction induced by antidepressants has long been recognized as a prevalent and distressing adverse effect for many patients, representing a significant factor contributing to medication non-adherence.[48] However, as highlighted in this review, the effects of many antidepressants on sperm parameters and male fertility remain poorly investigated. Furthermore, most of the available studies are descriptive and do not explore the underlying mechanisms of action.

Studies focusing on histopathological parameters of reproductive organs were excluded,[49,50] as these assessments do not directly reflect sperm impairment. Additionally, investigations centered on female fertility or those simultaneously exposing both male and female subjects were not included,[51,52] as they do not allow for the isolated evaluation of antidepressant effects on male reproductive parameters. Furthermore, studies assessing wildlife exposure to antidepressants,[53] as well as those involving comorbid conditions,[54] were beyond the scope of this review.

Table 1. Key characteristics of selected studies evaluating fertility and sperm parameters following antidepressant administration in animal models.

Antidepressant class	Drug and dose	Administration duration	Animal model	Main findings		Reference
				Sperm parameters	Fertility-associated parameters	
Atypical	Ansofaxine (LPM570065) (30, 100, and 300 mg/kg)	9 weeks	Sprague–Dawley rats (age is not available)	No alteration on sperm motility, count, and sperm malformation	No alteration on the gestation rate, number of implantation sites, number of resorptions number of dead and viable fetuses, and percentage of post-implantation loss Increase in the percentage of pre-implantation loss only at the higher dose Decrease in the fertility rate only at the higher dose	16
Atypical	Bupropion (15 and 30 mg/kg)	30 days	Wistar rats (90 days of age)	No alteration on the sperm count, abnormal morphology Increased number of spermatozoa with non-progressive movement	No alteration on the fertility potential	17
Atypical	Bupropion (40 mg/kg)	35 days	Swiss mice (age is not available)	Decreased sperm production Increased morphological alterations of the sperm head and tail	Not performed	18
Atypical	Bupropion (17 mg/kg)	69 days	Sprague–Dawley rats (21 days of age)	Decreased sperm concentration and motility Increased abnormal morphology	Not performed	19
Atypical	Trazodona (5, 10, and 20 mg/kg)	28 days	Sprague–Dawley rats (12 weeks of age)	Decreased sperm concentration, motility, and normal sperm morphology Increased sperm DNA damage	Not performed	20
Atypical	Trazodone (20 mg/kg)	4 weeks	Wistar rats (12 weeks of age)	Decreased sperm normal morphology, motility, and sperm count	Not performed	21
SNRI	Venlafaxine (60 mg/kg)	2 weeks	Balb/C mice (age is not available)	Decreased sperm concentration and sperm motility	Not performed	22
SNRI	Venlafaxine (3.85, 7.7, and 15.4 mg/kg)	20 days	Wistar rats (1-20 gestational days)	Decreased sperm motility at all doses No alteration on the sperm abnormal morphology and sperm count	No alteration on the fertility potential, number of live fetuses, pre-implantation loss, number of resorptions, and post-implantation loss	23
SNRI	Venlafaxine (30 mg/kg)	35 days	Holtzman rats (90 days of age)	Decreased viable spermatozoa	Not performed	24
SNRI	Venlafaxine (2 mg/kg)	35 days	Balb/C mice (8 weeks of age)	No alteration on the sperm concentration Increased non-progressive motility, immotile sperm, normal morphology, and viability	Not performed	25
SNRI	Venlafaxine (30 mg/kg)	35 days	Rats (age and strain is not available)	Decreased sperm concentration and quality	Not performed	26
SNRI	Venlafaxine (30 mg/kg)	35 days	Holtzman rats (90 days of age)	Decreased sperm normal morphology, motility, concentration, and mitochondrial activity	Not performed	27

(continued)

Table 1. Continued.

Antidepressant class	Drug and dose	Administration duration	Animal model	Main findings		Reference
				Sperm parameters	Fertility-associated parameters	
SNRI	Venlafaxine (40 and 150 mg/kg)	10 weeks	Albino rats (age is not available)	No alteration on the sperm count and DNA integrity Decreased progressive motility at the higher dose, and the normal morphology at both doses Increased immotile sperm at the lower dose	Not performed	28
SNRI	Venlafaxine (0.1, 1, 10, and 100 μg/L)	2 and 4 weeks	Zebrafish (*Danio rerio*) (180-day exposure, with onset at 2 h post-fertilization)	No alteration on the sperm concentration, viability, and motility	No alteration on the fertility rate Decreased number of egg production	29
SSRI	Citalopram (0.1, 1, 10, and 100 μg/L)	2 and 4 weeks	Zebrafish (*Danio rerio*) (180-day exposure, with onset at 2 h post-fertilization)	No alteration on the sperm concentration, viability, and motility	No alteration on the fertility rate	29
SSRI	Citalopram (5, 10, and 20 mg/kg)	28 days	Wistar rats (12 weeks of age)	Decreased sperm concentration at all doses Increased sperm abnormal morphology and DNA damage at all doses Increased sperm motility at 10 mg/kg dose when compared to 5 mg/kg dose	Not performed	30
SSRI	Dapoxetine (2, 4, and 8 mg/kg)	70 days	Wistar rats (3 months of age)	Decreased sperm count and viability at the higher dose, and the sperm motility at the medium and higher doses Increased head and tail abnormalities at the medium and higher doses, and DNA damage only at the higher dose	Decreased number of live fetuses and the fertility potential at the higher dose Increased percentage of post-implantation loss at the medium and higher doses, and pre-implantation loss only at the higher dose The fecundity index, and the number of dead fetuses did not change.	31
SSRI	Escitalopram (10 and 20 mg/kg)	30 and 60 days	Swiss mice (age is not available)	Decreased sperm count, motility, and viability at both doses and times of treatment	Not performed	32
SSRI	Escitalopram (dose is not available)	6 weeks	Balb/C mice (8-12 weeks of age)	Decreased sperm concentration and motility Increased number of dead sperms	Not performed	33
SSRI	Fluoxetine (1, 5, 10, and 20 mg/kg)	21 days	Wistar rats (1 day of age)	No alteration in the daily sperm production at all doses Decreased daily sperm production per gram of testis at the 5 mg/kg dose	Not performed	34
SSRI	Fluoxetine (5 mg/kg)	21 days	Mice (strain not available) (exposure during lactation; recovery period until DPN 80)	Decreased sperm count, motility, and viability Increased sperm abnormal morphology, immature nucleus, and damaged DNA	Not performed	35

(continued)

Table 1. Continued.

Antidepressant class	Drug and dose	Administration duration	Animal model	Main findings		Reference
				Sperm parameters	Fertility-associated parameters	
SSRI	Fluoxetine (15.63 mg/kg)	28 days	Rats (strain and age are not available)	Decreased sperm concentration, motility, and viability Increased sperm abnormality	Not performed	36
SSRI	Fluoxetine (5, 10, and 20 mg/kg)	30 days	Wistar rats (exposure during gestation and lactation)	Decreased daily sperm production per testis No alteration on the daily sperm production per gram of testicle	Not performed	37
SSRI	Fluoxetine (200 mg/kg)	60 days	Sprague–Dawley rats (age is not available)	Decreased sperm motility and density	Decreased gestation rate, implantation site, and viable fetuses	38
SSRI	Fluvoxamine (9 and 27 mg/kg)	8 weeks	Albino rats (age is not available)	Decreased sperm motility and count at both doses Increased sperm abnormalities in both doses	Not performed	39
SSRI	Paroxetine (10 mg/kg)	2 weeks	Albino mice (age is not available)	Decreased sperm count and acrosome integrity Increased sperm abnormalities	Not performed	40
SSRI	Paroxetine (7 mg/kg)	35 days	NMRI mice (6-8 weeks of age)	Decreased sperm concentration and motility Increased sperm abnormal morphology, lipid peroxidation, immature chromatin, protamine deficiency, and DNA damage	Not performed	41
SSRI	Paroxetine (3.6 mg/kg)	69 days	Sprague–Dawley rats (21 days of age)	Decreased sperm concentration Increased abnormal morphology No alteration in the sperm motility	Not performed	19
SSRI	Paroxetine (4.3, 13, or 43 mg/kg)	10 weeks (males) + 42 days (pregnant and lactating females)	Rat (strain and age information are not available)	Not performed	No alteration in pre-implantation loss and litter size Decreased pregnancy rate at the 13 and 43 mg/kg doses Increased post-implantation loss at the 13 and 43 mg/kg doses.	42
SSRI	Sertraline (5, 10, and 20 mg/kg)	4 weeks	Wistar rats (8-10 weeks of age)	No alteration in the sperm motility Decreased sperm concentration at the higher dose Increased sperm abnormal morphology at the 10 and 20 mg/kg doses Increased sperm DNA damage at all doses, with higher damage at the high dose	Not performed	43
SSRI	Sertraline (1.2 mg/kg)	6 weeks	Wistar rats (28 days of age)	Decreased sperm count, sperm motility, sperm viability, and number of fetuses Increased sperm deformity percentage	Increased pre-implantation loss percentage No alteration in the pregnancy rate and post-implantation loss percentage	44

(continued)

Table 1. Continued.

Antidepressant class	Drug and dose	Administration duration	Animal model	Main findings		Reference
				Sperm parameters	Fertility-associated parameters	
SSRI	Fluoxetine (15.63 mg/kg)	28 days	Rats (strain and age are not available)	Decreased sperm concentration, motility, and viability Increased sperm abnormality	Not performed	36
SSRI	Fluoxetine (5, 10, and 20 mg/kg)	30 days	Wistar rats (exposure during gestation and lactation)	Decreased daily sperm production per testis No alteration on the daily sperm production per gram of testicle	Not performed	37
SSRI	Fluoxetine (200 mg/kg)	60 days	Sprague–Dawley rats (age is not available)	Decreased sperm motility and density	Decreased gestation rate, implantation site, and viable fetuses	38
SSRI	Fluvoxamine (9 and 27 mg/kg)	8 weeks	Albino rats (age is not available)	Decreased sperm motility and count at both doses Increased sperm abnormalities in both doses	Not performed	39
SSRI	Paroxetine (10 mg/kg)	2 weeks	Albino mice (age is not available)	Decreased sperm count and acrosome integrity Increased sperm abnormalities	Not performed	40
SSRI	Paroxetine (7 mg/kg)	35 days	NMRI mice (6-8 weeks of age)	Decreased sperm concentration and motility Increased sperm abnormal morphology, lipid peroxidation, immature chromatin, protamine deficiency, and DNA damage	Not performed	41
SSRI	Paroxetine (3.6 mg/kg)	69 days	Sprague–Dawley rats (21 days of age)	Decreased sperm concentration Increased abnormal morphology No alteration in the sperm motility	Not performed	19
SSRI	Paroxetine (4.3, 13, or 43 mg/kg)	10 weeks (males) + 42 days (pregnant and lactating females)	Rat (strain and age information are not available)	Not performed	No alteration in pre-implantation loss and litter size Decreased pregnancy rate at the 13 and 43 mg/kg doses Increased post-implantation loss at the 13 and 43 mg/kg doses.	42

(continued)

Table 1. Continued.

Antidepressant class	Drug and dose	Administration duration	Animal model	Main findings		Reference
				Sperm parameters	Fertility-associated parameters	
SSRI	Sertraline (5, 10, and 20 mg/kg)	4 weeks	Wistar rats (8-10 weeks of age)	No alteration in the sperm motility Decreased sperm concentration at the higher dose Increased sperm abnormal morphology at the 10 and 20 mg/kg doses Increased sperm DNA damage at all doses, with higher damage at the high dose	Not performed	43
SSRI	Sertraline (1.2 mg/kg)	6 weeks	Wistar rats (28 days of age)	Decreased sperm count, sperm motility, sperm viability, and number of fetuses Increased sperm deformity percentage	Increased pre-implantation loss percentage No alteration in the pregnancy rate and post-implantation loss percentage	44
TCA	Amitriptyline (1, 2, or 4 mg/kg)	1 month	Swiss albino mice (age is not available)	Decreased meiotic activity and sperm count Increased sperm morphological alterations and genotoxicity in spermatocytes in a dose-dependent manner	Not performed	45
TCA	Amitriptyline (4 mg/kg)	35 days	Balb/C mice (8 weeks of age)	No alteration in the sperm normal morphology Decreased sperm concentration, progressive motility, and viability Increased immotile sperm	Not performed	25
TCA	Amitriptyline (dose is not available)	6 weeks	Balb/C mice (8-12 weeks of age)	Decreased sperm concentration and motility Increased number of dead sperms	Not performed	33
TCA	Clomipramine (9.75, 13, and 32.5 mg/kg)	35 days	Swiss mice (3 months of age)	Decreased sperm count at all doses, in a dose-dependent manner Increased sperm abnormalities at all doses, in a dose-dependent manner	Not performed	46
TCA	Clomipramine (2.25 mg/kg)	8 weeks of treatment 4 weeks of recovery	Wistar rats (age is not available)	Decreased sperm count and motility, immediately after treatment, and after discontinuation Increased sperm abnormalities immediately after treatment and after discontinuation	Not performed	47

Abbreviations: MAOIs, monoamine oxidase inhibitors; TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor.

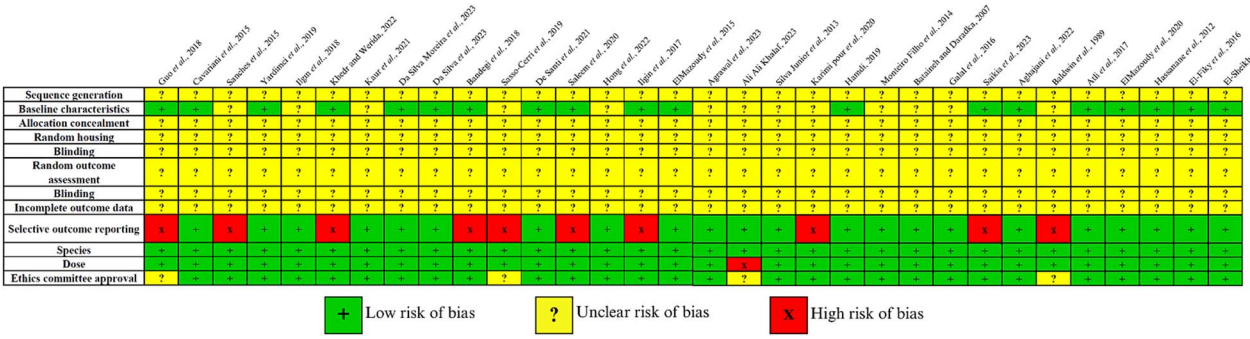


Figure 1. Risk of bias in each included study, assessed using the SYRCLE (Systematic Review Center for Laboratory Animal Experimentation) tool. Assessments were categorized as "yes" (low risk of bias, +), "no" (high risk of bias, x), or "unclear" (not reported, resulting in an unknown risk of bias, ?).

Selective serotonin reuptake inhibitor

Many studies have identified SSRIs as the most frequently prescribed class of antidepressants.[55–57] Accordingly, this class has the most extensive available data on fertility and sperm-related parameters in animal studies. These drugs share the same mechanism of action, which increases serotonin levels in the extracellular space by inhibiting serotonin (5-HT) reuptake.[58] SSRIs appear to exert the most consistent adverse effects, with fluoxetine, paroxetine, and sertraline frequently associated with decreased sperm parameters across different doses and treatment durations.

Within this class, fluoxetine was the most extensively investigated drug. Notably, even at lower doses (5 mg/kg), during short exposure periods (21 or 30 days), and at different life stages (lactation or adulthood), exposure to this compound adversely affected sperm parameters.[34,35,37] At a higher dose (200 mg/kg) and with prolonged exposure, sperm quality and density were also impaired.[38] As with fluoxetine, paroxetine has also demonstrated a significant adverse effect on sperm quality. Even at lower doses (3.6 mg/kg) and after prolonged exposure (69 days), this compound has been shown to affect sperm parameters.[19] Sperm alterations have also been observed following higher doses over shorter exposure periods.[40]

Fertility-associated parameters were evaluated in five studies involving SSRIs. Among these, only citalopram[29] and sertraline[44] were not associated with decreased fertility or gestation rate. Hong *et al*.[29] reported no alterations in sperm or fertility-related parameters in zebrafish exposed to citalopram. In contrast, ElMazoudy *et al*.[44] observed spermatic changes and increased pre-implantation loss associated with sertraline exposure; however, these impairments did not affect the gestation rate. These findings suggest that the choice of experimental model may influence the extrapolation of results to human contexts.

Dapoxetine,[31] fluoxetine,[38] and paroxetine[42] were associated with fertility impairment. ElMazoudy *et al*.[31] and Bataineh and Daradka[38] reported that dapoxetine and fluoxetine, respectively, negatively impacted sperm quality, which led to a decrease in the number of live fetuses and impaired fertility potential. Baldwin *et al*.[42] also documented fertility impairment associated with paroxetine exposure; however, this study did not assess sperm parameters. It is important to point out that the animals were exposed to paroxetine during the gestation and lactation period, in addition to the exposure experienced by the fathers.

Several mechanisms have been proposed to explain the impairment of reproductive outcomes following SSRI administration. Fluoxetine, similar to other SSRIs, has been shown to impair oxidative phosphorylation, thereby compromising ATP production and reducing sperm motility. Additionally, SSRIs may interact with sulfhydryl groups in gamete membranes, causing direct cellular damage.[59]

In this class, several compounds can also affect CatSper channels, impairing Ca^{2+} influx into sperm cells. This disruption may hinder the ligand-induced acrosome reaction and reduce the ability of sperm to penetrate viscous media.[60] SSRIs are also capable of increasing the production of reactive oxygen species in reproductive tissues, leading to cellular damage and compromising sperm quality and DNA integrity.[43] Oxidative damage may further disrupt steroidogenesis, altering hormone levels and potentially affecting fertility outcomes.[61] As shown in this review, these effects are often dose- and duration-dependent, with higher doses and longer exposures producing more pronounced impairments. In many cases, sperm parameters appear to recover after discontinuation, suggesting a potential for reversibility.

Therefore, these studies demonstrate that most SSRIs are capable of impairing sperm-related parameters, which may potentially affect fertility. These findings shed light on the clear need for further research to investigate the effects of SSRIs on sperm parameters in fertile men, in order to better guide clinicians when prescribing antidepressants to reproductive-aged men.

Serotonin-norepinephrine reuptake inhibitor

The SNRI class of antidepressants is the second most studied in animal models. The mechanism of action of these drugs involves the inhibition of 5-HT and norepinephrine (NE) reuptake. These compounds are used not only for treating mental health conditions but also for managing pain-related disorders.[58]

Among the studies included in this review involving SNRI, all assessed the effects of venlafaxine, and all reported some level of sperm impairment. At lower doses (2 mg/kg), venlafaxine did not affect sperm concentration, but impaired motility-related parameters, normal morphology, and sperm viability.[25] Additionally, exposure during gestation resulted in impaired sperm motility in adult offspring.[23] At intermediate doses (30 mg/kg), venlafaxine was found to decrease viable spermatozoa,[24] sperm concentration,[26] normal morphology, motility, and mitochondrial activity.[27] In a study using a dose

of 40 mg/kg for 10 weeks, an increase in the number of immotile sperm was reported.[28] At higher doses, venlafaxine led to a decrease in sperm concentration and motility (60 mg/kg),[22] and an impairment in normal sperm morphology (150 mg/kg).[28] The only study that assessed DNA integrity found no alterations in Albino rats exposed to 40 or 150 mg/kg for 10 weeks.[28] Taken together, these findings suggest that venlafaxine does not affect sperm concentration at low doses, whereas its detrimental effects on this parameter become more pronounced with increasing doses. Nevertheless, sperm motility and viability appear to be consistently impaired regardless of dose or age at exposure.

Norepinephrine appears to play a role in the acrosome reaction and sperm capacitation,[62–64] while 5-HT receptors have been identified in mammalian sperm.[38] Thus, it is not surprising that SSRI and SNRI antidepressants can interfere with sperm quality and fertility. Kaur *et al*.[22] suggested that venlafaxine-induced alterations in sperm parameters may be associated with increased oxidative stress, as indicated by elevated levels of lipid peroxidation and reactive oxygen species in the testes of exposed animals. Despite this association, available data from animal studies remain limited, particularly for SNRIs, with most research focusing on venlafaxine. Key drugs such as duloxetine, desvenlafaxine, and levomilnacipran have yet to be thoroughly investigated in animal models.

Atypical

This class of antidepressants includes drugs that do not exactly fit into the other categories. The mechanism of action of these drugs, accordingly, is heterogeneous and the molecular targets are diverse.[65]

Among these, bupropion is the most studied in animal models. This unicyclic aminoketone compound acts by increasing the 5-HT and dopamine (DA) levels and is known as the antidepressant drug with less—or none—sexual side effects.[66] In this review, we observed that administration of bupropion at lower doses (15 and 30 mg/kg) and shorter treatment durations appears to have minimal effects on sperm concentration, morphology, and fertility; however, impairments in sperm motility are already evident at these levels.[17] At higher doses (≥40 mg/kg) 18 and/or longer exposure durations19, bupropion induces more pronounced detrimental effects, including decreased sperm production and abnormalities in morphology and motility. Overall, the available evidence suggests that the effects of bupropion on male reproductive parameters are dose- and exposure-dependent. Thus, in the animal model, despite being free from adverse sexual side effects, bupropion administration requires caution when sperm-associated side effects are not intended.

Among atypical antidepressants, trazodone was the other atypical antidepressant evaluated. The mechanism of action of this drug is based on its metabolite *m*-chlorophenylpiperazine, which consists of an agonist of 5-$HT_{2A/2C}$.[67] The two studies included in this review demonstrate that even short-term treatment (4 weeks) with trazodone impairs sperm concentration (or count), motility, and normal sperm morphology, with doses ranging from 5 to 20 mg/kg.[20,21] Additionally, all tested doses of trazodone were associated with increased sperm DNA damage.[20] To date, there are no studies evaluating fertility-related parameters in males receiving trazodone.

Ansofaxine (LY03005, also named toludesvenlafaxine) is the most recent drug among those reviewed. This compound exhibits high affinity for DA, 5-HT, and NE transporters, significantly inhibiting the reuptake of these monoamines. Accordingly, ansofaxine is a potential triple reuptake inhibitor[68] and seems to lack sexual adverse effects.[16] Guo *et al*.[16] demonstrated that administration of ansofaxine at doses of 30 and 100 mg/kg for 9 weeks did not adversely affect sperm parameters such as count, density, morphology, or motility. However, at a higher dose of 300 mg/kg, ansofaxine was associated with increased pre-implantation loss and reduced fertility rate. It is noteworthy that the no observed adverse effect level (NOAEL) for fertility identified by these authors is 300 mg/kg. In Phase 3 trials of ansofaxine[69](p3), doses of 80 and 160 mg/day were used, which approximately convert to 1.3 to 2.6 mg/kg (using a reference body weight of 60 kg). According to human equivalent dose conversion,[70] the 300 mg/kg dose in rats equates to ∼16 mg/kg in humans—eight times higher than the maximum dose used in Phase 3 trials. Accordingly, ansofaxine warrants further investigation as a potential antidepressant with minimal sexual and fertility-related side effects at therapeutic doses, at least in animal models.

Information regarding sperm and fertility issues related to other atypical antidepressants, such as mirtazapine and nefazodone, is lacking in experimental models.

Tricyclic antidepressant

The mechanism of action of TCAs involves inhibiting the reuptake of 5-HT and NE without affecting DA reuptake.[58] Beyond their efficacy in treating depressive disorders, TCAs are known for their numerous side effects due to their ability to interact with a wide range of receptors and ion channels. As a result, TCAs are generally not considered first-line treatments for depression. However, this class of drugs remains valuable for managing severe or treatment-resistant depression.[71]

The TCA with more available information regarding sperm-associated parameters is amitriptyline. Evidence indicates that amitriptyline can impair sperm concentration, motility, and viability at doses of 1, 2, or 4 mg/kg administered over 30-35 days.[25,45] In addition, amitriptyline exhibits dose-dependent genotoxic effects at these doses[45] and increases malondialdehyde levels in seminal plasma, suggesting that oxidative stress may contribute to the observed alterations. These findings indicate that amitriptyline adversely affects male reproductive parameters in a dose-dependent manner.

The other TCA evaluated was clomipramine. One study indicated that the adverse effects on sperm were dose-dependent. The authors tested doses of 9.75, 13, and 32.5 mg/kg over 35 days, finding that sperm count decreased and sperm abnormalities increased with higher doses.[46] At a lower dose of 2.25 mg/kg administered over 8 weeks, sperm count was impaired, and sperm abnormalities were increased. These changes persisted even after 4 weeks of clomipramine discontinuation.[47] In summary, clomipramine induces dose-related impairments in sperm quality, and that such effects may persist even after treatment cessation, highlighting its potential long-term impact on sperm quality.

Despite the available information, the effects of TCA on sperm parameters and fertility are still poorly explored. There is no information about important drugs of this class, such as imipramine, desipramine, nortriptyline, and doxepin.

Limitations

This review compiled a large number of studies with diverse experimental designs and species, evaluating sperm-related parameters through various methodologies. These discrepancies make it challenging to properly compare and align the studies to reach definitive conclusions. However, we provide valuable insights into which antidepressant drugs warrant further investigation and should be evaluated in clinical trials and large cohorts of men. We also highlight existing knowledge gaps and identify key drugs for which no data are currently available, even in animal models. Importantly, no precise dose or threshold has been established above which sperm quality may be compromised. Expanding research in this area is particularly relevant for men of reproductive age. Future studies should prioritize mechanistic investigations and employ multi-omic approaches to more comprehensively capture the complexity of epigenetic regulation in spermatogenesis.

Conclusion

Current evidence suggests that most available antidepressants affect sperm quantity and/or quality in animal models. However, the impact on fertility remains inconclusive due to the limited number of studies, which have employed varying drugs and experimental designs. Although few studies have assessed DNA damage, most indicate that all classes of antidepressants can impact sperm DNA integrity, highlighting the need for further research in this area. Thus, despite the abundance of literature on the relationship between antidepressants and male reproductive function, this topic remains far from fully explored.

Author contributions

L.O.P.S.: Literature search, data analysis, Writing—original draft. P.R.Q.S.: Data analysis. N.C.G.: Data analysis. G.M.O.R.: Data analysis. H.F.P.: Data analysis, Supervision, Writing—review & editing. G.E.M.L.S.: Conceptualization, Funding acquisition, Project administration, Supervision, Writing—review & editing.

Supplementary material

Supplementary material is available at *Sexual Medicine Reviews* online.

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Conflict of interest

The authors have no relevant financial or non-financial interests to disclose.

Data availability

The authors confirm that all relevant data are included in the article and/or its supplementary information files. Some data sets generated and/or analyzed during the present study are not publicly available but could be shared on reasonable request to the corresponding author.

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