

# The Effects of SSRIs on Male Fertility

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## ABSTRACT

**BACKGROUND:** It is estimated that by 2020, depression will be the second leading cause of world disability with predictions that by 2030 it will be the largest contributor to disease burden. While treatments for depression can vary, selective serotonin reuptake inhibitors (SSRIs) are currently the most prescribed antidepressants. Despite an increase of studies documenting the effects of antidepressants, there exists a limited number of studies on male SSRI use and the resulting effects on their fertility.

**OBJECTIVE:** A structured review of the literature was conducted to assess the evidence regarding the effects of SSRI antidepressants on male fertility. Recent epidemiological studies were identified from the databases PubMed, Scopus, and Ovid.

**METHODS:** The search was limited to publications in English and included the keywords SSRI, antidepressants, sperm, fertility, and male. In total, nine studies were found to be relevant to the structured literature review.

**RESULTS:** One study on male rats observed an association of SSRI use and decreased fertility. Five studies concluded that there may be an association between the use of selective serotonin reuptake inhibitors and decreased sperm quality in both humans and rats. In studies where the discontinued use of SSRIs was evaluated, improvements in sperm concentration and motility were observed. Certain studies showed that changes in DNA fragmentation were observed in men taking paroxetine, allowing the potential for the change in DNA integrity to negatively impact male fertility.

**CONCLUSION:** At this time, the literature shows evidence of the effect of certain SSRI antidepressants on male fertility in both rats and humans. Further study, including long term and large scale research, is needed to advance the validation of this conclusion.

## BACKGROUND

**Objective:** A structured review of the literature was conducted to assess the evidence regarding the effects of SSRI antidepressants on male fertility. These findings can affect prescribing practices of SSRIs.

**Research question:** Is there an association between the use of SSRI antidepressants and male fertility when compared to men not using SSRIs?

### Why SSRIs?

- SSRIs are the first line of defense in the treatment of depression as they have the lowest known number of side effects, making them the most prescribed antidepressant.<sup>[1]</sup>
- The main prescribed SSRIs are fluvoxamine, fluoxetine, citalopram, escitalopram, sertraline and paroxetine.<sup>[1]</sup>

### Why male fertility?

- There is a lack of research on their effects on male fertility.
- Male factors are responsible for approximately half of the cases of infertility.<sup>[2]</sup>
- The underlying cause of infertility not discovered in many cases.

### How do SSRIs work?

- SSRIs inhibit the reuptake of serotonin through the blockage of the serotonin channel allowing serotonin to remain in the synapse for a longer period of time, thus accounting for the longer lasting effects of serotonin.

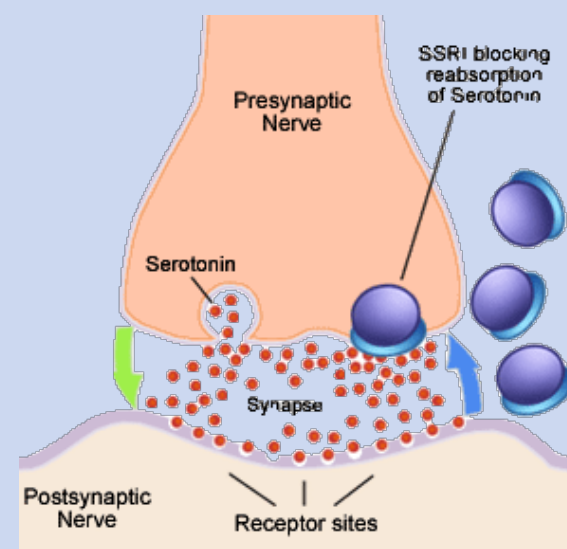


Figure 1: Mechanisms of action of SSRIs<sup>[3]</sup>

## RESULTS

Study	Study type	Population	SSRI type	Purpose	Findings	Association
<b>Rats</b>						
Galal et al. (2016) <sup>[4]</sup>	Experimental	-Rats: 60 male adults -8 weeks	Fluvoxamine -control, low dose (LTD): 9mg/kg & high dose (HTD): 27mg/kg	-Investigate adverse effects of long term administration of fluvoxamine on fertility -Evaluate the state recovery after the cessation of SSRI treatment	Both doses for 8 weeks resulted in: - Significant (p<0.05) reduction in percentage of sperm motility, % sperm count, serum levels of FSH, LH, testosterone and estrogen -Increased apoptosis and % sperm abnormalities compared to control group - All effects reversed after an 8-week recovery period	-Fluvoxamine Might Lead to risk of male infertility
Monteir et al. (2013) <sup>[5]</sup>	Experimental	-Rats: 35 male adults -gestation day 13 to lactation day 21	Fluoxetine -5mg/kg, 10 mg/kg, 20 mg/kg, control group	- Analyze safe doses during prenatal period and lactation as well as extent of damage that fluoxetine brings to the testicles of the male rat offspring in adulthood	- Those exposed to 20 mg/kg showed a decrease in testicular weight, daily sperm production and seminiferous tubule length, reduced by 16%, 18% and 17%, respectively -The volume of Leydig cells were reduced by 29% and 30% respectively in rats exposed to 5mg/kg and 20mg/kg respectively.	-Exposure to fluoxetine may change testosterone and testicular parameters
Lyons et al. (2016) <sup>[6]</sup>	Experimental	-Rats: 87 male adults	Fluoxetine, sertraline (Zoloft)	- Identify the mechanism in which SSRI elevates serum prolactin	-The SSRIs in this study can inhibit hypothalamic dopamine neurons that would normally suppress secretion of prolactin -Inhibit due to an increase of serotonin activity -Hyperprolactinemia (excess prolactin) is a common cause of infertility in males	- Zoloft and Fluoxetine have ability to elevate circulating prolactin
<b>Humans</b>						
Tanrikut et al. (2010) <sup>[7]</sup>	Prospective Cohort	-Human: 35 males -aged 18-65yrs	Paroxetine -10mg, 20mg ,30mg & 40mg	- evaluate the effects of the SSRI Paroxetine on semen parameters	- Mean sperm DNA fragmentation significantly higher for men on paroxetine 30.3% VS 13.8 % at baseline. -Odds ratio of abnormal DNA fragmentation with paroxetine is 9.33 (95% confidence interval) - the percentages of men that noted significant (P<0.003) changes in their erectile function as well as significant (P<0.002) ejaculatory difficulties were 35% and 47%, respectively - Stopping treatment led to a return of close to normal sexual function	In men taking Paroxetine, Changes in the DNA integrity may adversely affect fertility potential.
Elnazer et al. (2014) <sup>[8]</sup>	Case Report	-Human: 1 Caucasian male -3 years SSRI -Mixed depressive and anxiety disorder	Citalopram -40mg	- Review the effects antidepressants by review of the case report and literature.	-Sperm concentration: 11 million/ml (normal range >15 million/ml) -Sperm motility %: 25% (normal range >40%) -Abnormal Sperm morphology: 99% (normal range <96%) -Improvement in sperm concentration, motility and sperm morphology when discontinuing Citalopram. -After SSRI cessation, patient took agomelatine (non-SSRI antidepressant) which did not affect semen parameters	- SSRI treatment can be associated with reduced semen quality
Safarinejad et al. (2008) <sup>[9]</sup>	RCT	-Human: 74 men -Aged 20-50 years - clinically depressed for over 6 months	Escitalopram, Citalopram, Fluoxetine, Paroxetine, Sertraline -Dosage N/A	- Evaluate semen parameters and sperm DNA in patients receiving SSRIs	-Standard error of total sperm count in patients administered SSRI was 61.2 million and 186.2 million in controls (p = 0.001) -60.8% of cases and 9.1% of controls had abnormal sperm concentration (p=0.001) -Significant increase of damaged DNA found in patients administered SSRIs (43.2%) compared to controls (10.6%) -Length of use of SSRI use positively correlated with DNA damage, and abnormal sperm parameters. -Type of SSRI used showed no differences	-SSRIs can impair semen quality and damage sperm DNA

Table 1: Results from the peer-reviewed articles

## METHODS

A structured literature review was conducted using databases such as PubMed, Ovid and Scopus. All three databases were used to find peer-reviewed articles only, with specific keywords, such as "SSRI", "antidepressant", "sperm", "fertility" and "male", limiting our findings to publications between 2007 and 2017. By entering the keywords "SSRI" and "male" into all three databases, a total of 28,722 peer-reviewed articles were generated; to narrow the search to scientific articles that show a direct correlation between both variables, an assembly of keywords were used in each database. By combining keywords "SSRI", "male", "sperm" OR "SSRI", "antidepressants", "male" and "fertility", a total of 9 relevant articles were found. Publications were limited to cases that involved male humans and male rats. Upon further analysis of each article, only 6 out of 9 articles were accessible to us.

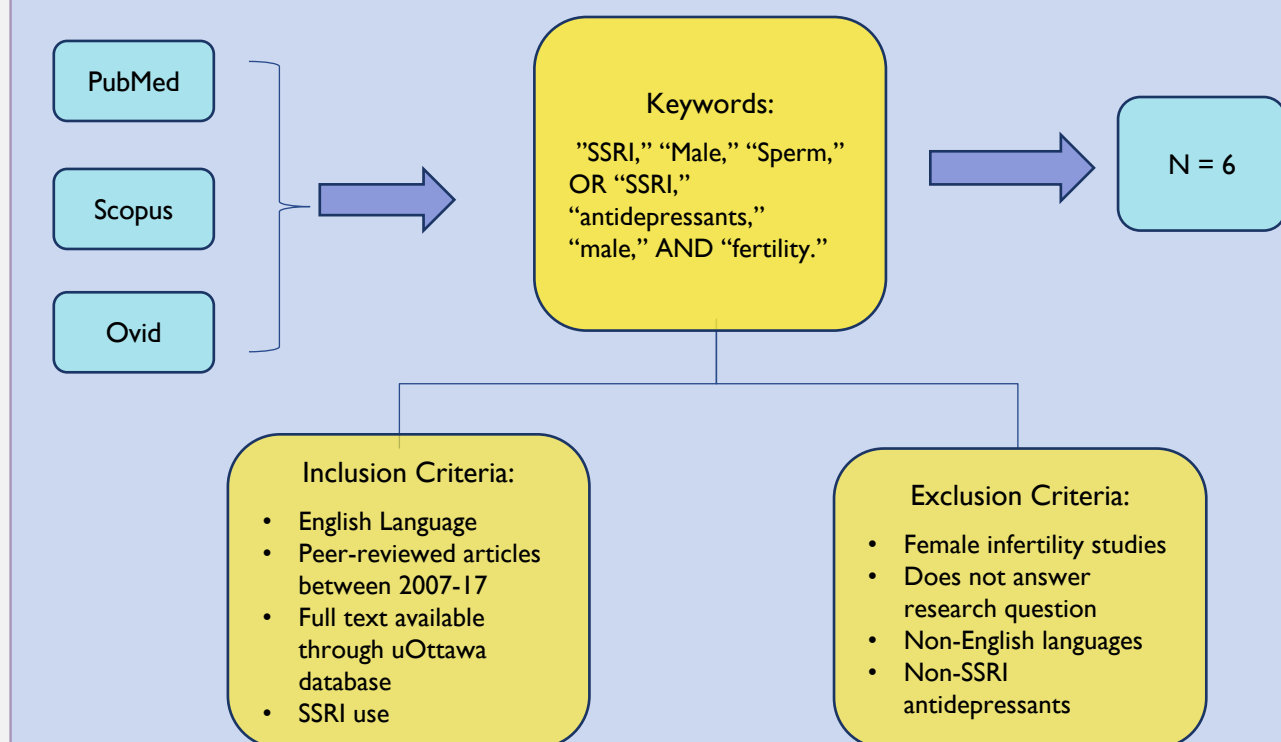


Figure 2: Methodology of the structured literature review of the association between SSRIs and fertility in males.

## DISCUSSION

The results of these studies suggest that SSRI use leads to significant changes on male fertility in both men and rats. Altered semen parameters, increased DNA fragmentation, increased oxidative stress, decreased testicular weight were all observed. Moreover, in multiple studies, once the population stopped being administered SSRIs, all negative alterations on male fertility were reversed.

### Limitations:

In order to have access to 3 of the desired articles, we were required to pay. This being said, articles were not included. This left us with six studies in total. A limitation in our selection of studies is the inclusion of both rats and humans as the study population. These are two different study populations; however there was still some similarities found. We included a case report on one SSRI user and his infertility, which has potential to generalize findings.

Another limitation of the study is that different articles evaluated different factors to determine if there is an association. This is not optimal because it limits comparison of verdicts regarding factors that can influence fertility in SSRI use. I.e.: Oxidative stress link to infertility was only measured in one study.

### Strengths:

Inclusion criteria for gender was limited to males which allowed us to limit our search to a fair amount of studies as well as to focus on the effects of SSRIs solely on the male reproductive system. Focusing on males regarding the association between SSRI use and fertility is also strength, considering there is not enough reviews regarding this association. Included various SSRIs to better understand the general effect of SSRI use on male fertility. Analyzed the effects of SSRIs on male rats when they were exposed in placenta or via breast milk

### Future research

Considering the limitations of these studies, Future research studies should be of larger scale, longer duration, include different races, different SSRIs, a wider range of doses to further evaluate dose response relation as well as a control group.

### What do these findings mean?

These findings can influence the way we prescribe SSRIs in males. A detrimental effect on male fertility can influence prescribing protocol in healthcare. If a male using an SSRI presents himself at a clinic experiencing difficulties in conceiving a child, the use of SSRIs should be a cause to consider in determining the factors leading to infertility.

## CONCLUSION

At this time, the literature shows evidence of the effect of certain SSRI antidepressants on male fertility in both rats and humans. Further studies, including long-term and large scale, research is needed to advance the validation of this conclusion.

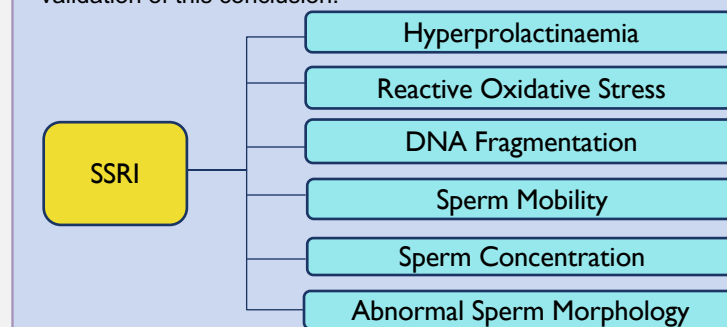


Figure 3: Potential consequences of the use of SSRI on male fertility

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