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Review Article

Effect of antidepressant medications on semen parameters and male fertility

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Abbreviations & Acronyms
BMI = body mass index
FSH = follicle-stimulating hormone
LH = luteinizing hormone
MAOI = monoamine oxidase inhibitor
NDRI = norepinephrine–dopamine reuptake inhibitor
SNRI = serotonin–norepinephrine reuptake inhibitor
SSRI = selective serotonin reuptake inhibitor
TCA = tricyclic antidepressant
TUNEL = transferase dUTP nick end labeling

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Abstract: Antidepressant medications are commonly used in males of reproductive age for long-term treatment of depression, as well as other disorders. Although antidepressants are known to be associated with sexual side-effects, their effects on semen parameters and other markers of male fertility have been less thoroughly described. The majority of available studies have focused on selective serotonin reuptake inhibitors, which have been shown to negatively impact semen quality in *in vitro*, animal and human studies. Fluoxetine, in particular, has been the subject of multiple studies and has been associated with gonadotoxic effects, including decreased sperm concentration and motility, increased deoxyribonucleic acid fragmentation, and decreased reproductive organ weights. Studies of several other selective serotonin reuptake inhibitors have yielded similar results. Reassuringly, this effect does seem to be reversible. The data regarding serotonin–norepinephrine reuptake inhibitors, norepinephrine–dopamine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors and atypical antidepressants are sparse, varied and conflicting. Given the widespread and often long-term use of antidepressant medications, there is a clear need for further data regarding their impact on semen quality and male fertility.

Key words: antidepressant, effects, male infertility, medications, semen.

Introduction

Antidepressants are one of the most commonly used therapeutic drug classes in the USA. While the majority of these medications are taken to treat depression, antidepressants can also be taken to treat other conditions, such as anxiety disorders. The major classes of these are SSRIs, SNRIs, NDRIs, TCAs, MAOIs and atypical antidepressants. Each of these have slightly different mechanisms of action, and therefore can affect sperm in different ways.

According to the National Health and Nutrition Examination Survey, 8.6% of males between the ages of 12 and 18 in the USA took antidepressants between 2011 and 2014.[1] The number of people taking these medications has increased nearly 65% over a 15-year time frame, from 7.7% in 1999–2002 to 12.7% in 2011–2014. Although females are more likely to use these mediations, males have shown a parallel rise in their antidepressant use. Antidepressant use increases with age, from 3.4% among persons aged 12–19 years to 19.1% among persons aged ≥60 years. In addition, these medications are typically taken long term, and between 2011 and 2014, 68.0% of persons aged ≥12 years who took antidepressant medications had been taking these for ≥2 years, and 25% had been taking them for ≥10 years.

There is limited information on the frequency of antidepressant use globally. The Organization for Economic Co-operation and Development has examined this to some degree. Countries with the highest rates of antidepressant use are the USA (110 per 1000 people), Iceland (106 per 1000 people), Australia (89 per 1000 people), Canada (86 per 1000 people) and Denmark (85 per 1000 people). Countries with the lowest reported antidepressant use are Korea (13 per 1000 people), Chile (13 per 1000 people), Estonia (18 per 1000 people), Hungary (27 per 1000 people) and the Slovak Republic (31 per 1000 people).[2] For Japan specifically, although large epidemiological studies are lacking, it is estimated that up to 6 million Japanese suffer from depression, similar to that seen in Western countries.[3]

All classes of antidepressants are known to be associated with some degree of sexual dysfunction in both men and women. In men, the most notable sexual side-effects can include impaired libido, erectile dysfunction, delayed ejaculation or anejaculation. The effects of

antidepressant medications on semen parameters have been less thoroughly studied, although data do exist for some of the medications in each of the classes of antidepressants. We review all available data (*in vitro*, animal and human studies) regarding the use of antidepressants on semen parameters and male fertility (Table 1).

SSRIs

SSRIs act by inhibiting the reuptake of serotonin, and include citalopram, escitalopram, fluvoxamine, paroxetine, fluoxetine and sertraline. These medications are currently considered first line for the treatment of depression and anxiety disorders. However, SSRIs in particular are known to be associated with significant sexual side-effects, including decreased libido, increased ejaculation latency, alteration of circulating hormones and erectile dyfunction.[4,5] Studies estimate that 25–73% of people treated with an SSRI will experience some type of sexual dysfunction, higher than that of other antidepressants.[4] Studies looking at the impact of these medications on male reproduction and semen parameters are not as robust, but there are some available data. This is the class of antidepressants with the most available data for their effects on semen parameters and male fertility (Table 2).

In vitro studies

There is a single *in vitro* study investigating SSRIs and human sperm. Kumar *et al*. incubated human semen with varying doses of paroxetine, fluoxetine, sertraline, citalopram and fluvoxamine *in vitro*. All SSRIs showed some degree of spermicidal activity, whereas serotonin showed no negative effect on sperm counts. Fluoxetine, which showed the highest spermicidal activity, had a minimal effective concentration comparable to nonoxynol-9, a contraceptive utilized for its spermicidal properties.[6]

Animal studies

Multiple studies carried out in animal models have shown the negative effects of SSRIs on male fertility. Most studies of SSRIs are on fluoxetine, and most do show some degree of gonadotoxic effect. Male rats treated with oral fluoxetine for 60 days were found to have decreased spermatogenesis on histology, as well as significantly decreased sperm density and motility. Treated male rats also had decreased pregnancy and implantation rates with untreated female rats, and had decreased reproductive organ weights, including testes, epididymes, prostates and seminal vesicles.[7] A similar study of rats treated with varying doses of oral fluoxetine for 5 days found a dose-dependent decrease in sperm counts and motility in rats exposed to fluoxetine. At the highest dose (13 mg/kg), sperm count and motility were fourfold less that that observed in controls.[8] Long-term administration of fluvoxamine has also been shown to negatively affect semen parameters, and induce oxidative stress and apoptosis in the testes of rats, which were treated with both low therapeutic doses (9 mg/kg) and high therapeutic doses (27 mg/kg) for 8 weeks.[9] Oxidative stress might mediate and enhance the negative impact that these drugs seem to have on semen parameters. Rats exposed to chronic unpredictable mild stress showed signs of oxidative stress, including increased levels of malondialdehyde and corticosterone, and decreased anti-oxidants, sperm count and motility. These effects were exaggerated in animals treated with

Table 1 Studies carried out on different antidepressant classes

Antidepressant class	*In vitro* studies	Case studies	Animal studies	Human studies
SSRIs	Kumar *et al*.[6]	–	Bataineh and Daradka[7] Alzahrani[8] Galal *et al*.[9] Sakr *et al*.[10] Atli *et al*.[11] Attia and Bakheet[12] Ilgin *et al*.[13] Ayala *et al*.[14] Vieira *et al*.[15]	Tanrikut and Schlegel[16] Elnazer and Baldwin[18] Tanrikut *et al*.[19] Akasheh *et al*.[20] Koyuncu *et al*.[21] Safarinejad[22] Relwani *et al*.[23]
SNRIs	Bandegi *et al*.[24]	–	Bandegi *et al*.[24]	–
NDRIs	–	–	Urra *et al*.[25] Cavariani *et al*.[26] Fazelipour *et al*.[28] Cansu *et al*.[29] Adriani *et al*.[30] Bellentani *et al*.[31]	–
TCAs	Levin *et al*.[32]	–	Bandegi *et al*.[24] Chowdary and Rao[34] Hassanane *et al*.[35]	Levin *et al*.[32] Padrón and Nodarse[33]
MAOIs	–	–	Kalász *et al*.[36] Mihalik *et al*.[37]	–
Atypical antidepressants	Cassidy and Pearson[39]	Elnazer and Baldwin[18]	Ilgin *et al*.[38] El-Sisi *et al*.[40]	–

Table 2 SSRI effects on semen and other fertility parameters

Drug	*In vivo* effects on semen parameters	Other effects on fertility
SSRIs		
Fluoxetine	*Rats:* Decreased spermatogenesis, sperm density and motility	*Rats:* Decreased pregnancy and implantation rates, decreased reproductive organ weight
Fluvoxamine	*Rats:* Decreased sperm concentration and motility, increased abnormal forms	*Rats:* Oxidative stress and apoptosis in testes, decreased FSH, LH, testosterone and estrogen
Sertraline	*Human case study:* Decreased sperm concentration and motility *Human prospective:* Decreased sperm count, increased abnormal morphology and DNA fragmentation *Rats:* Increased DNA damage and abnormal forms, decreased sperm count	*Rats:* Testicular degeneration, oxidative stress
Citalopram	*Human case study:* Decreased sperm count and motility, increased abnormal morphology *Rats:* Increased DNA strand breaks and oxidative damage, increased abnormal forms	*Rats:* Decreased seminal vesicle mass, decreased volume of seminiferous tubules
Paroxetine	*Human prospective:* Increase in DNA fragmentation	–
Escitalopram	*Human prospective:* Decreased sperm concentration and motility, increased abnormal morphology	–

fluoxetine (10 mg/kg/day for 28 days), and mitigated in groups treated with either resveratrol (20 mg/kg/day for 28 days) or fluoxetine plus resveratrol.[10]

One study examined the effects of sertraline on the reproductive system of rats treated with 5, 10 or 20 mg/kg for 4 weeks. There was a dose-dependent increase in DNA damage (measured using the Comet assay), testicular degeneration and abnormal sperm forms, as well as a decrease in sperm count in treated animals. Decreased levels of glutathione and increased levels of malondialdehyde suggested oxidative stress as a main mechanism for the testicular toxicity observed.[11]

Citalopram has also been shown to exert toxic effects on sperm and testicles, largely through oxidative stress. Attia and Bakheet saw a dose- and duration-dependent increase in DNA strand breaks, oxidative DNA damage, and abnormal primary spermatocytes in male rats treated with citalopram.[12] A study by Ilgin *et al*. found similar results, with citalopram-administered rats showing reduced sperm counts, increased abnormal sperm morphology and increased DNA damage.[13]

These drugs might affect pre- and postpubertal animals differently, and a study examining pre- and postpubertal rats treated with fluoxetine for 30–53 days found that these two populations had different responses. Although all animals had a decrease in LH, FSH, progesterone and testosterone, prepubertal rats were more likely to show decreased sperm membrane integrity, density, motility and morphology versus their adult counterparts.[14] This might have implications for males taking these medications beginning at young ages.

Maternal use of SSRIs during pregnancy and lactation might also impact semen quality in male offspring. Rat offspring exposed to fluoxetine *in utero* and while nursing have been shown to have decreased seminal vesicle mass and sperm counts, as well as reduced height and diameter of seminiferous tubules.[15]

Human studies

Human data consistently support an association between male infertility (semen parameters and sperm DNA fragmentation) and SSRI use. In 2007, Tanrikut and Schlegel described cases of oligospermia, impaired motility and abnormal morphology in two patients taking SSRIs for depression. The first patient presented on citalopram with "marked oligospermia and 1% motility." Semen analysis 1 month after citalopram discontinuation showed a marked improvement in all parameters to within the normal range. Bupropion was started for depression shortly thereafter, and a semen analysis while on bupropion again showed a decrease in sperm concentration to 21 million/mL with 10% motility. After two failed *in vitro* fertilization attempts, the patient was reassessed (still on bupropion). His DNA fragmentation (tested by the sperm chromatin structural assay) was 76%. He was weaned from the bupropion and his follow-up semen analysis 1 month after bupropion discontinuation showed a normal sperm concentration of 41 million/mL with 75% motility. A second semen analysis carried out 2 months after bupropion discontinuation showed normal sperm concentration and motility. A similar pattern (impaired semen parameters on sertraline [sperm concentration of 20 000 with 0% motility]), with dramatic improvement after SSRI discontinuation (3 months after discontinuation 40 million motile sperm) was seen for the second patient described taking sertraline.[16] Human spermatogenesis takes 72 days, and therefore this marked improvement within weeks of antidepressant discontinuation suggests that SSRIs might exert their effects on post-testicular processes rather than spermatogenesis itself.[17] Similarly, Elnazer and Baldwin described a patient with markedly improved sperm concentration, progressive motility and morphology after discontinuation of citalopram.[18]

In a subsequent prospective study, Tanrikut *et al*. examined the effects of paroxetine on semen parameters and DNA fragmentation in 35 healthy male volunteers with normal baseline semen parameters and DNA fragmentation (measured by the TUNEL assay). Study participants (mean age 34 years, range 19–58 years) were treated with therapeutic paroxetine for 5 weeks. Semen parameters and sperm DNA fragmentation were tested before treatment and again post-treatment after a 1-month washout period. Use of paroxetine was associated with a significant increase in DNA fragmentation, from 14% at baseline to 30% post-treatment. In

addition, the number of men having elevated sperm DNA fragmentation of >30% increased from 10% at baseline to 50% post-treatment (odds ratio 9, confidence interval 2.3–38). In contrast to some other studies, these authors did not identify a change in semen parameters with SSRI use.[19] This suggests that although raw semen parameters might be affected by SSRI use, sperm DNA fragmentation might also be affected even in the absence of changes in semen parameters and could represent an alternative means for impaired male reproductive potential.

Prospective data have also supported a relationship between SSRI use and markers of male infertility. In a randomized, single-blinded clinical trial, 60 men were treated for primary premature ejaculation with either sertraline or non-pharmacological behavioral therapy. The sertraline group was treated with sertraline 25 mg/day for 1 week, followed by 50 mg/day for 3 months. Both sperm concentration (reduction by 10^5/mL) and percent normal morphology were significantly decreased in the sertraline group versus controls. DNA fragmentation (sperm chromatin dispersion method) was also increased in the treatment group (31% *vs* 16%).[20] Another prospective study by Koyuncu *et al*. showed decreased sperm concentration (26.4×10^6/mL *vs* 68.9×10^6/mL), motility (23.4% *vs* 58.2%) and morphology (23.4% *vs* 58.2%) after 3 months of exposure to escitalopram for the treatment of premature ejaculation.[21]

Other factors, including duration of SSRI use and BMI, might synergistically adversely affect semen parameters. One cross-sectional study compared semen parameters and sperm DNA fragmentation in men taking SSRIs versus those of healthy men, and also included an evaluation of the duration of antidepressant use. Men taking SSRIs were found to have significantly lower sperm counts (61 million *vs* 184 million), motility (49% *vs* 66%) and normal morphology (8% *vs* 20%), as well as significantly increased amounts of fragmented sperm DNA versus controls (43% *vs* 21%). All differences in semen parameters and sperm DNA fragmentation correlated with the duration of antidepressant use (6–12 months *vs* 1–2 years), although no differences were observed between specific antidepressants within the SSRI class.[22] Another study of 530 men aged 18–50 years examining the effect of BMI found that use of combination SSRIs was associated with a significant decrease in sperm motility, independent of BMI.[23]

In vitro, animal and human studies all showed a decline in semen quality with SSRI use, as manifested by both impaired semen parameters and increased DNA fragmentation rates. The duration of recovery (<73 days, the time required for spermatogenesis) to baseline semen parameters and DNA fragmentation suggests that these effects might be due to some type of post-testicular process. Given the wide prevalence of the use of this class of medications, there is a clear need for further large-scale, randomized, placebo-controlled trials to further characterize the role of SSRIs in infertility, and their effect on semen parameters and other markers of male fertility.

SNRIs and NDRIs

SNRIs exert their effects by inhibiting the reabsorption of both serotonin and norepinephrine. This class of medications includes desvenlafaxine, duloxetine, levomilnacipran and venlafaxine. The prevalence of sexual dysfunction is 58–70% in patients treated with SNRIs,[4] in general slightly less than that seen for SSRIs. There has only been a single study investigating the effects of any of these medications on semen parameters (Table 3). This group examined 40 adult male mice given oral venlafaxine (2 mg/kg) or venlafaxine (2 mg/

Table 3 Non-SSRI antidepressant effects on semen and other fertility parameters

Drug	*In vivo* effects on semen parameters	Other effects on fertility
SNRIs		
Venlafaxine	*Human prospective:* Improved normal morphology and sperm viability, increased non-progressive motility	–
NDRIs		
Bupropion	*Rats:* Decreased motility at high doses (30 mg/kg)	*Rats:* Increased epididymal duct contractility
Methylphenidate	*Rats:* Increased abnormal sperm tail morphology; increased spermatogonia; reduced round spermatids; increased sperm count	*Rats:* Increased testicular interstitial tissue; decreased germinal epithelium thickness, increased gonadotropins; decreased testicular weight, increase in apoptosis; increased testicular weight
Sibutramine	*Rats:* Decreased sperm number in epididymis, decreased transit time within epididymis	*Rats:* Decreased reproductive organ weight
TCAs		
Desipramine	*Human:* No change in sperm count or motility	–
Amitriptyline	*Human prospective:* Increased ejaculate volume, sperm count and normal morphology; decreased sperm concentration and viability; decreased sperm count and normal forms	*Human prospective:* Increased germ cell mutations
MAOIs		
Selegiline	*Rats:* Increased sperm count and viability	*Rats:* Increase in testis mass
Atypical antidepressants		
Trazodone	*Rats:* Decreased sperm concentration, motility and normal morphology, increased DNA damage	–
Mirtazapine	*Rats:* Protective effect against nitrofurazone-induced decrease in sperm count and viability	–
Agomelatine	*Human case study:* No effect on semen parameters	–

kg) plus vitamin C (10 mg/kg) for 35 days. Mice treated with venlafaxine alone had better sperm morphology (58.50% *vs* 43.71%), non-progressive motility (25.50% *vs* 16.25%) and sperm viability (80.25% *vs* 64.62%) compared with controls. This effect is thought to be a result of the anti-oxidant properties of venlafaxine in protecting against lipid peroxidation. There were no significant differences between semen parameters in mice treated with venlafaxine alone and those treated with combination venlafaxine and ascorbic acid.[24]

NDRIs act by blocking the reuptake of norepinephrine and dopamine from the synaptic terminal, thereby increasing their bioavailability. This class includes bupropion, dexmethylphenidate, diphenylprolinol, ethylphenidate, methylenedioxypyrovalerone, methylphenidate, pipradrol, prolintane and sibutramine. In general, the limited available data for these medications show varied effects on semen parameters (Table 3).

Bupropion is commonly used in combination with other medications in the treatment of depression, as well as for smoking cessation. Although the role of dopamine in reproductive physiology has not been clearly established, there are limited data implicating some role in male reproductive function. Urra *et al*. first identified the presence of functional dopamine transporters in equine sperm. In the present study, high levels of dopamine were associated with decreased total and progressive sperm motility, and this effect was partially reversed by the addition of bupropion. Blocking the dopamine transporter reduced uptake of a dopamine analog, thereby decreasing accumulation of the catecholamine in equine sperm.[25] Another study evaluated the effects of bupropion on semen parameters and epididymal duct contractility in rats. At lower doses (15 mg/kg), bupropion increased epididymal duct contractility, but had no effect on semen parameters. At higher doses (30 mg/kg), the drug was shown to impair sperm motility.[26]

Methylphenidate is a psychostimulant that inhibits norepinephrine and dopamine reuptake. It is currently most commonly used in the treatment of attention-deficit/hyperactivity disorder in children and adolescents. In the past it was used as an antidepressant, and there are some conflicting data on its effect on semen parameters. Motagnini *et al*. studied the effects of methylphenidate administration on rats during childhood and young adult development. An increase in abnormal sperm tail morphology was observed, as well as an increase in testicular interstitial tissue in treated animals.[27] A different rat study found that treatment with methylphenidate was associated with decreased germinal epithelium thickness, as well as an increase in the number of spermatogonia, likely secondary to increases in serum gonadotropin levels.[28] Finally, a rat study by Cansu *et al*. showed a dose-dependent association between 90-day exposure to methylphenidate and reduced numbers of round spermatids, decreased testicular weight, and an increase in apoptosis (TUNEL method) and expression of p53.[29] Conversely, Adriani *et al*. found that adolescent rats exposed to methylphenidate had increased testicular weights and increased sperm count as adults.[30] These data are conflicting, and there are no human data, making it difficult to truly know the effect of methylphenidate on semen parameters and male fertility.

Sibutramine, initially developed for use in the treatment of depression, is a monoamine reuptake inhibitor commonly used today for weight loss. There are no human studies for sibutramine, and only a single animal study. Bellentani *et al*. found that exposure to 10 mg/kg of sibutramine for 28 days decreased weights of reproductive organs in male rats, including the ventral prostate and epididymis, although there were no histological changes noted in these organs. The sperm number within the epididymis (180.98×10^6/organ *vs* 276.16×10^6/organ) and transit time within the epididymis (4.73 days *vs* 7.85 days) were also significantly decreased. There was no change in spermatid number within testes, daily sperm production, sperm motility or morphology between groups.[31]

There is a clear lack of data for many of these medications. No studies exist for duloxetine, desvenlafaxine, levomilnacipran, dexmethylphenidate, diphenylprolinol, ethylphenidate, methylenedioxypyrovalerone, pipradrol or prolintane. Scant data exist for venlafaxine, bupropion, methylphenidate and sibutramine. No prospective clinical studies have yet been carried out exploring the effects of SNRIs and NDRIs on semen quality. Given the contradictory results found in preliminary animal studies, there is a clear need for additional research in this area.

TCAs

TCAs, including amitriptyline, nortriptyline, amoxapine, desipramine, doxepin, imipramine, protriptyline and trimipramine, were one of the earliest medications used to treat depression. However, they are generally no longer used as first-line medications because of significant side-effect profiles. The estimated prevalence of sexual dysfunction in men and women taking TCAs is comparatively low, at approximately 30%.[4] Evidence regarding the effects of TCAs on semen quality is scant (Table 3). There is a small number of studies on desipramine and amitriptyline, but no studies on nortriptyline, amoxapine, doxepin, imipramine, protriptyline or trimipramine.

A 1981 study by Levin *et al*. described both *in vitro* and clinical studies examining the effect of desipramine on semen parameters. *In vitro*, desipramine was associated with dose-dependent inhibition of sperm motility. However, *in vivo* clinical evaluation found no difference in sperm count or motility between treatment and control groups. Treatment with desipramine was associated with decreased sperm viability (defined as the percentage of motile spermatozoa, no true viability testing was carried out). Other semen parameters did not significantly differ between treatment and control groups.[32]

There have been four studies examining amitriptyline, yielding conflicting results. A small study on the effects of amitriptyline in 20 infertile men with oligospermia found increased ejaculate volume, sperm count and normal morphology after treatment with amitriptyline. Sperm count was increased in 50% of patients, and motility was increased in 35% of patients.[33] In contrast, Bandegi *et al*. found negative effects of amitriptyline on semen parameters in rats treated with amitriptyline alone versus amitriptyline and ascorbic acid. Rats treated with amitriptyline alone had lower sperm

concentration (18.11 million *vs* 22.41 million) and viability (31.25% *vs* 64.62%) compared with controls. These results were also seen when comparing the group receiving amitriptyline plus ascorbic acid and controls, and the addition of ascorbic acid did not seem to mitigate this effect.[24] Two studies suggest that amitriptyline has a mutagenic effect on sperm. A study by Chowdary and Rao showed mutagenic effects of amitriptyline in germ cells of mice treated with various oral doses of the antidepressant.[34] Similar results were obtained in an animal study in which amitriptyline was found to increase chromosome abnormalities, and decrease sperm count and normal morphology.[35]

MAOIs

MAOIs are typically reserved for patients who have failed other first-line medications for the treatment of depression. Medications belonging to this class include selegiline, isocarboxazid, phenelzine and tranylcypromine. Approximately 40% of male and female patients taking MAOIs will experience some degree of sexual dysfunction.[4] Data on semen parameters are scant (Table 3). There have been two rat studies examining the effects of selegiline, but no studies examining the effects of other MAOIs, including isocarboxazid, phenelzine and tranylcypromine, on semen parameters or other markers of male fertility.

Selegiline, used to treat major depressive disorder and parkinsonism, might actually have a favorable effect on male fertility. A small rat study found an increase in testis mass, sperm number and viability (defined as the ratio of live to dead sperm) in rats treated with oral selegiline for 4 weeks.[36] These findings were corroborated in a study of rats treated with intraperitoneal selegiline. Treated rats had significantly higher sperm counts (137.73×10^6/mL *vs* 115.09×10^6/mL on semen analysis) than those receiving intraperitoneal saline.[37] The mechanism for this increase in sperm counts and viability is unclear.

Atypical antidepressants

Atypical antidepressants are those that act by mechanisms separate from those discussed above. These medications include mirtazapine, trazodone, nefazodone, tianeptine, agomelatine, vilazodone and vortioxetine. There are limited data regarding the effects of these medications on fertility through semen parameters, although the available data do suggest a negative effect on semen quality (Table 3).

One study of rats receiving vehicle (control), 5, 10 or 20 mg/kg/day of trazodone for 28 consecutive days found decreased sperm concentration (4.68×10^6/mL, 3.04×10^6/mL, 2.84×10^6/mL and 2.68×10^6/mL, respectively), sperm motility (86.49%, 80.06%, 78.85% and 76.23%, respectively) and normal morphology (18.00%, 28.90%, 31.20% and 37.08% abnormal forms, respectively), as well as increased DNA damage in treated rats. Increased malondialdehyde levels suggested that oxidative stress contributed to the testicular toxicity in these animals.[38] Similarly, Cassidy and Pearson showed that trazodone had an inhibitory effect on motility in *in vitro* samples of human sperm.[39]

Mirtazapine has been shown in one study to have a protective effect against oxidative stress and testicular damage. In that study, testicular damage in rats was induced by administration of nitrofurazone. Rats exposed prophylactically to mirtazapine 1 week before the initiation of nitrofurazone had a significantly less pronounced decline in sperm count and viability than those receiving only nitrofurazone, as well as decreased indicators of oxidative damage.[40]

One case study suggested that agomelatine (*vs* citalopram) does not negatively impact semen quality (at least in one patient). Elnazer and Baldwin described a case of decreased sperm concentration, motility, progressive motility and normal morphology in a patient treated with citalopram for mixed depression and anxiety. These effects resolved after withdrawal of citalopram. The patient was subsequently treated with agomelatine, which was not associated with a decline in semen parameters.[18]

There have been no studies to date regarding the effects of nefazodone, tianeptine, vilazodone or vortioxetine on semen parameters or other markers for male fertility.

Conclusions

Given the relatively common use of antidepressant medications, the limited data on their use is worrisome. This is particularly concerning, given that these medications are taken by young men, generally on a long-term basis. We do not have pregnancy or live birth data on any of these medications. All of them have the potential to affect sexual performance to varying degrees.

The existing data show that SSRIs exert a harmful effect on semen quality and rates of DNA fragmentation, as well as increase oxidative stress within reproductive organs. Most of these effects do seem to be reversible on cessation of treatment with SSRIs, although this might not be possible for all patients who need these medications to control their depression. There is contrasting evidence regarding whether bupropion (an NDRI), negatively or positively impacts sperm motility. Similarly, the available data for methylphenidate is animal only, and conflicting, making it difficult to know its true effect. Studies on amitriptyline have yielded conflicting results, with one small clinical study suggesting improved semen parameters in patients with baseline oligospermia, but three animal studies finding the opposite effect. The only MAOI that has been studied in this arena is selegiline, which has been shown to increase sperm counts and viability in two rat studies.

Evaluations of the effects of treatment with antidepressant medication on semen parameters should consider the effects of untreated depression and anxiety on fertility as well. Shiraishi and Matsuyama showed that comorbid medical conditions negatively impacted spermatogenesis and that treatment of medical comorbidities, including hypertension, hyperlipidemia, hyperuricemia and skin disease, was associated with a significant increase in motile sperm count.[41] In particular, psychosocial stress has been shown to have an inverse effect on testosterone levels.[42] Furthermore, it is not surprising that a diagnosis of major depression appears to affect gonadal

function. Men with depressive episodes of moderate-to-severe severity have been shown to have lower levels of testosterone[43] as well as lower sex hormone-binding globulin and DHEA-S, higher secretion of cortisol and prolactin, and lower semen volume and sperm density.[44]

Given the widespread and often long-term use of antidepressant medications, there is a clear need for further data regarding their impact on semen quality and male fertility. The existing data are often based on animal studies or human studies with low numbers of patients. There is a stark absence of prospective data. At this point, it is difficult for clinicians to counsel patients on the effect that these medications might have on their fertility. We would recommend an informed discussion with patients attempting parenthood and taking these medications. Checking a baseline semen analysis and sperm DNA fragmentation might provide some level of guidance. If possible, a trial of discontinuation of antidepressants is advised, although this should be carried out in conjunction with the patient's mental health provider.

Conflict of interest

None declared.

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Editorial Comment

Editorial Comment to Effect of antidepressant medications on semen parameters and male fertility

The paper by Beeder and Samplaski is a review article of antidepressant medications and male fertility.[1]

Antidepressant medications are widely applied for patients in the psychological field. As the authors mentioned, it is well known that antidepressant medications cause male sexual dysfunction, including erectile dysfunction and late-onset hypogonadism syndrome.

A few previous studies have reported a relationship between male fertility factors and antidepressants, mainly in basic research besides the references in this article.[2–4] The authors concluded that the existing data show that selective serotonin reuptake inhibitors exert harmful effects on semen quality and rates of DNA fragmentation. This conclusion might almost be acceptable. However, at present, there are insufficient data to clearly show relationships between male fertility factors and antidepressants, because we did not find adequate and decisive results from previous reports. The effects of antidepressants on male infertility are still equivocal and the mechanisms are unclear. In addition, there are so many variations of antidepressants, and each selective serotonin reuptake inhibitor might have their own mechanisms and characteristics, as mentioned in this review.

Although there is still not enough evidence in the content of this review to generally and widely accept the influence of antidepressants on male infertility, this article is significant in that it raises urologists' concerns about the risks of antidepressants in regard to male infertility.

Another interesting point is that this harmful effect seems to be reversible upon cessation. In clinical practice, we sometimes experience reversible testicular function (spermatogenesis) in patients with male hypogonadotropic hypogonadism. Spermatogenesis is often observed in male hypogonadotropic hypogonadism patients when luteinizing hormone and follicle-stimulating hormone treatment are commenced, even after testosterone replacement therapy. A normal to nearly normal testis itself seems to have a high potential for spermatogenesis function.

It is almost impossible to clarify which antidepressants affect which level of spermatogenesis. It is most important that we pay attention to the risks posed to male infertility by antidepressants, and avoid overprescribing antidepressants.

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Conflict of interest

None declared.

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