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Case Report

Treatment with citalopram, but not with agomelatine, adversely affects sperm parameters: a case report and translational review

Elnazer HY, Baldwin DS. Treatment with citalopram, but not with agomelatine, adversely affects sperm parameters: a case report and translational review.

Background: Adverse effects of antidepressant drug treatmenton sexual function are well documented but the effects of antidepressants on sperm production have not been researched extensively.
Methods: A narrative of an interventional case report of sperm parameters in a 30-year-old Caucasian man with a diagnosis of mixed depressive and anxiety disorder, who underwent citalopram treatment, followed by agomelatine treatment. Clinical observations prompted a review of the pre-clinical and clinical literature on the effects of antidepressant administration or treatment on sperm production and parameters. Findings from the review are discussed to suggest potential underlying mechanisms.
Results: Abnormal sperm parameters were associated with treatment with the SSRI citalopram. There was an improvement in sperm concentration, motility, progressive motility and sperm morphology following its withdrawal. There was no similar association during subsequent treatment with agomelatine. The clinical observations reflect findings from animal studies, which indicate that antidepressants can have untoward effects on spermatogenesis.
Conclusions: SSRI treatment can be associated with impaired semen quality. Potential underlying mechanisms include changes in sperm DNA integrity, activation of IDO and shifting tryptophan metabolism. Further studies of the effects of antidepressants on spermatogenesis might benefit from including investigation of changes in IDO activity during antidepressant administration.

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Introduction

The adverse effects of antidepressant drug treatment on sexual function and satisfaction in men and women are well documented (1), but the effects of antidepressants on sperm production and male fertility have not been researched extensively. Pre-clinical investigations in experimental animals indicate that a range of antidepressants can have untoward effects on spermatogenesis and sperm viability (2–7). Observations from a limited number of case series and case reports together suggest that antidepressant drug treatment can be associated with abnormal spermatogenesis and male infertility (8–13). We report the case of a 30-year-old man who was found to have abnormal sperm parameters during treatment with the selective serotonin reuptake inhibitor (SSRI) citalopram, which resolved once citalopram was withdrawn: subsequent treatment with the novel antidepressant agomelatine (a melatonin agonist and 5-HT2C receptor antagonist) was not found to be associated with abnormal sperm

parameters. We place these findings in the context of pre-clinical investigations and highlight areas of current uncertainty.

Case narrative

A 30-year-old Caucasian man with a diagnosis of mixed depressive and anxiety disorder had been undergoing citalopram treatment (at a daily dosage of 40 mg mane) for almost 3 years. He was known to be a carrier of β-thalassaemia but there was no history of physical illness or sexual dysfunction. Alcohol consumption was minimal and there was no history of drug misuse: he exercised regularly and maintained a healthy diet. There was a positive family history of anxiety disorder, hypertension and diabetes mellitus, but no family history of infertility. He and his partner were referred to the fertility clinic for investigation of their failure to conceive after 2 years of regular sexual activity: the female partner was investigated thoroughly, with normal results. His physical examination was normal, and serum hormone levels were unremarkable.

Sperm analysis revealed abnormal sperm parameters: concentration 11 million/ml (normal range >15 million/ml); motility 25% (normal range >40%), progressive motility 15% (normal range >32%), and abnormal morphology 99% (normal range <96%). With the support of his partner, the patient decided to stop citalopram treatment, and experienced a number of discontinuation symptoms including dizziness, 'head shocks', disturbed sleep and increased anxiety. He declined alternative antidepressant drug treatment, in the hope of improving sperm parameters.

Four months after stopping citalopram, further sperm analysis indicated an improvement in sperm parameters, with a sperm concentration of 16 million/ml, motility of 60% and progressive motility of 35%: but with a persisting abnormal morphology of 98%. The couple underwent *in vitro* fertilisation (IVF) and intra-cytoplasmic sperm injection treatment, but this was not successful because of a failure of implantation. A second frozen embryo cycle failed in the thawing process because of embryo denaturation.

Anxiety symptoms and insomnia worsened and 16 months later he started treatment with the novel antidepressant agomelatine (at a daily dosage of 25 mg nocte, increased to 50 mg nocte after 2 weeks), with an ensuing improvement in symptoms. Blood monitoring revealed no abnormalities in liver function tests. After 3 months of agomelatine treatment, a further sperm analysis was performed, the parameters being sperm concentration 15 million/ml, sperm motility 62%; progressive motility 22%; and abnormal morphology 95% (Tables 1 and 2). An ultrasound scan found evidence of a small unilateral subclinical varicocoele: this was considered to be clinically insignificant, but the patient preferred to undergo elective surgery. The couple are now considering putting themselves forward for a second round of IVF.

Table 1. Hormonal assay

Free testosterone	0.183 nmol/l	Reference range: >0.245 nmol/l
Testosterone	11.2 nmol/l	10.0–27.6 nmol/l
SHBG	43 nmol/l	10–50 nmol/l
LH	2.1 IU/l	1.2–8.6 IU/l

LH, leutinizing hormone; SHBG, steroid hormone-binding globulin.

Potential causality?

We report the association of abnormal sperm parameters during treatment with the SSRI citalopram, and an improvement in sperm concentration, motility, progressive motility and sperm morphology following its withdrawal. There was no similar association during subsequent treatment with agomelatine. The association with citalopram is therefore both temporally related and specific to the drug. Using the scoring criteria proposed by Naranjo (14), the probability of

Table 2. Changes of sperm parameters and normal ranges

	Patient on citalopram	4 months medication free	3 months agomelatine	Reference range
Sperm concentration (million/ml)	11	16	15	>15
Total spermatozoa in ejaculate ($\times 10^6$ million)	85	70.4	78	39–928 U
Motility (%)	25	60	62	>40
Progressive motility (%)	15	35	22	>32
Abnormal morphology (%)	99	95	95	<96
Volume (on 3 days abstinence)	7.8 ml	4.4 ml	5.2 ml	1.5–10 U
Liquefaction	Yes	Yes	Incomplete	
Viscosity	No	Yes	Yes	

First diagnosis of fertility problem and investigations, January (year 1); second fertility investigation, mid May (year 1); started agomelatine, October (year 2); third fertility investigation, January (year 3). The timing of stopping citalopram is subject to 2–3 weeks error as the patient stopped the medication abruptly and cannot remember the exact date of stopping medication.

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causality for the observation with citalopram was rated as 5 (probable). In accordance with Bradford Hill Criteria (15), this observation is coherent with findings from animal and human studies, which provide some evidence of a plausible mechanism, through possible damage to DNA integrity.

Potential limitations inherent in this report are the presence of a varicocoele and the carrier state of β-thalassaemia. The patient is merely a carrier of the β-thalassaemia gene, and is and has always been asymptomatic from this condition. The varicocoele was also asymptomatic and considered to be sub-clinical, and persisted throughout treatment, both with citalopram then with agomelatine. There is current uncertainty about the extent to which a varicocoele might affect semen parameters, which usually vary from normal to mild-to-moderate asthenospermia, teratospermia or asthenoteratospermia. The detection of a sub-clinical varicocele is not usually an indication for surgical repair, as prospective controlled studies that have included men with a sub-clinical varicocoele have found no increase in the post-operative fertility rate (16–18).

Previous clinical observations

Tanrikut and Schlegel described two cases of patients on citalopram and sertraline referred for evaluation of male infertility, who were found to have antidepressant-associated changes in sperm motility and/or concentration. In each case physical examination and endocrine studies were unremarkable, but analysis of initial semen specimens revealed oligospermia, impaired motility and abnormal morphology. Repeated semen analyses 1–2 months after discontinuation of the serotonin reuptake inhibitor antidepressant revealed marked improvements in sperm concentration and motility (8).

Male patients treated with combinations of SSRI with other psychotropic drugs were found to have significantly reduced sperm motility, after controlling for body mass index, leutinizing hormone, follicle-stimulating hormone (FSH), testosterone, steroid hormone-binding globulin and the free androgen index (9). Administration of escitalopram (daily dosage 10 mg) to patients with lifelong premature ejaculation for 12 weeks has been associated with a significant decrease in sperm concentration, motility and morphology, when compared with baseline semen measures (10). Further investigations suggest that SSRIs can impair semen quality and damage sperm DNA integrity in depressed fertile men (11). Mean sperm DNA fragmentation was significantly more frequent in men after treatment with paroxetine (30.3%) than at baseline (13.8%). In men with normal semen parameters, paroxetine administration was associated with abnormal sperm DNA fragmentation in a significant proportion of subjects, without a measurable effect on semen parameters. It has been argued that the fertility potential of a substantial number of men undergoing paroxetine treatment may be adversely affected by changes in sperm DNA integrity (12).

A case-controlled study of the effects of the tricyclic antidepressant clomipramine (which is principally a non-SSRI) found that it had pathological effects on all spermiograms evaluated, especially with regard to volume, sperm motility and sperm morphology; whereas pathological findings were present in only 37% of a control group, which is a proportion similar to that in healthy individuals in this age range. Clomipramine did not appear to alter sex hormone profiles but had a significant negative effect on ejaculate parameters (13).

Potential underlying mechanisms

Investigations of the effects of antidepressant drug and lithium administration on sperm production and motility provide some suggestions about possible underlying mechanisms. In male rats, long-term (60 days) administration of the SSRI fluoxetine (at a concentration of 200 mg/kg) is associated with decreased spermatogenesis in the seminiferous tubules, and with reduced sperm motility and density in the cauda epididymides and testes. In addition, there was a decrease in number of primary and secondary spermatocystes and spermatids, decrease in reproductive organ weight, decreases in testosterone and FSH levels and reduction in number of female rats impregnated by fluoxetine-administered male rats. Furthermore, the number of implantations and number of viable foetuses were also decreased in female rats impregnated by male rats that had been administered fluoxetine (2). In mice, fluoxetine administration was found to induce sperm abnormalities and reduce sperm count and sperm motility in a dose-dependent manner (3). A study in rats of maternal exposure to fluoxetine and the herbal preparation St John's Wort (which has some SSRI properties) showed a decrease in weight of the full seminal vesicle and in the number of spermatozoa. Moreover, pups exposed to fluoxetine were found to have a reduction in height of the seminiferous epithelium and in diameter of the seminiferous tubules (4). In male hamsters, administration of tricyclic antidepressants appeared to be without effect, except for dosing with desipramine, which significantly decreased whiplash motility after spermatozoa were added to eggs, and dosing with clomipramine, which decreased motility and whiplash

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motility in epididymal sperm suspensions. Mianserin and viloxazine were also without effect, but nomifensine significantly decreased sperm motility and whiplash motility, and inhibited egg penetration almost completely (5).

The role of serotonin and the influence of SSRIs on sperm development appears complex. Serotonin, which is derived from dietary tryptophan, may stimulate sexual development in male rats during the pre-pubertal period, this activating effect occurring earlier in domesticated than in aggressive male rats (6). A short period of sterility associated with oligospermia in adult male Swiss strain mice following whole body gamma irradiation could be significantly reduced by pre-administration of the combination of the serotonin precursor 5-hydroxy-L-tryptophan (5-HTP, 100 mg/kg) and 2-aminoethyl isothiuronium bromide hydrobromide (AET, 20 mg/kg) (7).

Indoleamine 2, 3-dioxygenase (IDO) is a rate-limiting enzyme in the tryptophan–kynurenine pathway, and may play a pivotal role in any untoward effects of antidepressant drugs on spermatogenesis. Normal IDO activity may play an important role in sperm quality control in the epididymis, involving the ubiquitination (protein inactivation resulting from attachment of the small molecule ubiquitin, and subsequent passage of tagged proteins towards the proteosome and subsequent degradation) of defective spermatozoa, and in their subsequent removal (19).

Immune activation may increase tryptophan metabolism in both the periphery and central nervous system, with a subsequent reduction in 5-HT (20,21). Activation of IDO shifts tryptophan metabolism from serotonin synthesis to the formation of kynurenines, which have apoptotic, neurotoxic and pro-oxidative effects, and towards upregulation of inducible nitric oxide synthase, phospholipase A2, arachidonic acid, prostaglandin, 5-lipoxygenase and the leukotriene cascade. The other rate-limiting enzyme of the tryptophan–kynurenine pathway, tryptophan 2,3-dioxygenase, is activated by tryptophan and cortisol (22). Therefore, the balance of tryptophan–kynurenine metabolism may be important in the development of abnormal spermatogenesis during antidepressant treatment.

Conclusion

This case report indicates that citalopram treatment can be associated with impaired semen quality, with particular effects on motility and morphology; whereas agomelatine treatment was not associated with similar effects. Further pre-clinical and clinical studies of the effects of antidepressants on spermatogenesis might benefit from including investigation of changes in IDO activity during antidepressant administration.

Conflicts of Interest

The authors declare that they have no conflicts of interest relevant to this report.

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