Adverse effect of paroxetine on sperm

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Objective: To assess the effects of a selective serotonin reuptake inhibitor on semen parameters.
Design: Prospective study.
Setting: Academic medical center.
Patient(s): Thirty-five healthy male volunteers, 18–65 years old.
Intervention(s): Paroxetine administration for 5 weeks.
Main Outcome Measure(s): Serum hormone levels, semen analyses, percent sperm DNA fragmentation, and questionnaire assessment of sexual function assessed before, during, and 1 month after drug administration.
Result(s): Mean sperm DNA fragmentation was significantly higher for men while on paroxetine (30.3%) versus baseline (13.8%). Before paroxetine, 9.7% of patients had a terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) score $\geq 30\%$ compared with 50% at week 4 of treatment. The odds ratio (OR) of having abnormal DNA fragmentation while taking paroxetine was 9.33 (95% confidence interval, 2.3–37.9]. Multivariate logistic regression correcting for age and body mass index confirmed this correlation (OR, 11.12). Up to 35% of men noted significant changes in erectile function and up to 47% of men reported ejaculatory difficulties on medication. Recovery to near-normal sexual function was noted after stopping treatment. Standard semen parameters were not significantly altered during paroxetine treatment.
Conclusion(s): In men with normal semen parameters, paroxetine induced abnormal sperm DNA fragmentation in a significant proportion of subjects, without a measurable effect on semen parameters. The fertility potential of a substantial number of men on paroxetine may be adversely affected by these changes in sperm DNA integrity. (Fertil Steril® 2010;94:1021–6. ©2010 by American Society for Reproductive Medicine.)
Key Words: Male infertility, semen analysis, antidepressants, sperm, DNA fragmentation, erectile dysfunction, ejaculation, body mass index

Major depressive disorders affect approximately 10% of American men over their lifetimes (1). Antidepressant medications are the most common form of treatment, with almost 233 million prescriptions written in 2007 (2). Newer agents such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors with equivalent inhibitory action on serotonin reuptake have supplanted older treatment options because of the perceived favorable safety and side effect profiles associated with the newer antidepressants.

Although the majority of antidepressants are prescribed for treatment of depression, they may also be used for treatment of anxiety disorders such as generalized anxiety disorder and obsessive-compulsive disorder. Antidepressant dispensing rates have continued to increase in recent years (3).

Despite the rising use of prescription antidepressants and the known effects of SSRIs on emission and ejaculation (4), few reports have evaluated the effect of antidepressants on male fertility or sperm quality (5). In 2007, we reported two cases of men referred for male infertility evaluation who appeared to have antidepressant medication-associated changes in sperm concentration and motility (6). Both men showed marked improvements in total motile sperm counts within a few weeks after discontinuation of antidepressant medication. This rapid recovery to normal semen parameters suggested to us that SSRIs affect sperm transport, not sperm production which would take months to recover. Given that SSRIs adversely affect emission and ejaculation, it is possible that they could negatively influence sperm transport, as well, with a resultant negative impact on sperm quality and number.

Attempts to assess sperm DNA integrity as determined by sperm DNA fragmentation indices have increasingly been incorporated as part of a male fertility evaluation, although clinical indications for these tests have yet to be defined (7). DNA damage may exist independent of standard semen parameters (8) and the degree of DNA fragmentation correlates with poorer fertility and pregnancy outcomes, even when techniques such as in vitro fertilization and intracytoplasmic sperm injection are applied (9, 10).

We designed the study described herein to assess the potential impact of one SSRI, paroxetine, on standard semen parameters, sperm DNA integrity, endocrine profiles, and sexual function in healthy men. We hypothesize that SSRIs produce a negative impact on semen parameters by exerting an influence on sperm transport, not by disturbing spermatogenesis. An increase in sperm DNA fragmentation that occurs with delayed sperm transport has been observed in men with ejaculatory defects as well as men with obstructive azoospermia (11). Paroxetine was selected for use in this study because it has a relatively short half-life and has been shown previously to exert the strongest effect in delaying ejaculation (12, 13).

MATERIALS AND METHODS

Participants

Normal, healthy male volunteers (18–65 years old) were recruited to identify men with normal semen parameters and physical examinations. Exclusion criteria included: known sexual dysfunction, tobacco use, illicit drug use, alcohol intake greater than 2 ounces daily, prescription medications, history of psychiatric disorder, previous chemotherapy or radiation, history of seizure disorder, clinically detected varicocele, oligoasthenospermia or azoospermia or ongoing attempts to initiate pregnancy. Volunteers were excluded if suspicion of an Axis I psychiatric disorder was found on Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders IV (14). Brief sexual function inventory (BSFI) (15), and a screening semen analysis were done at the outset. A total of 35 volunteers were enrolled after the initial screening process. All participants granted written informed consent before enrollment in the study and initiation of testing.

Study Design

A second semen sample before medication initiation was obtained at least 3 weeks later, and semen parameter results were averaged together as baseline values for each patient. Hormonal parameters were drawn between 8:00 and 10:30 AM. Specimens were obtained before starting medication to assess baseline T, FSH, LH, E_2, and PRL levels. Interassay and intraassay coefficients of variation for all hormones tested ranged from 4.4–11.6%.

Paroxetine was administered for 5 weeks using an escalating dosing schedule: week 1, 10 mg daily; week 2, 20 mg daily; weeks 3 and 4, 30 mg daily; week 5, 20 mg daily. Semen analyses were performed at the end of weeks 2 and 4. Serum blood samples and the BSFI were repeated at the end of week 4. One month after cessation of medication, each subject provided a final ejaculated specimen and again completed the BSFI. Sperm DNA integrity (deoxyuride-5′-triphosphate biotin nick end labeling [TUNEL]) assays were performed on one baseline semen sample and on the week 4 sample. Subjects were instructed to abstain from ejaculation for 2–5 days before semen analysis.

This research protocol was approved and monitored by the Weill Cornell Medical College Institutional Review Board and entered into the National Institutes of Health clinical trials database before initiation of the study.

Laboratory Testing

All laboratory personnel were blinded to samples.

Semen analyses Semen samples were collected into a sterile container and allowed to liquefy at 37°C for 30 minutes. A single technician in a New York State–certified laboratory assessed standard semen parameters using World Health Organization standards (16).

Hormonal evaluation Approximately 8 mL of peripheral blood was obtained via venipuncture and serum was separated immediately by centrifugation. Serum samples were stored at –20°C, and all samples were run in duplicates using commercially available enzyme immunoassay kits for T (TE080S) and E_2 (ES071S) and enzyme-linked immunosorbent assay kits for PRL (PR063F), FSH (FS046F), and LH (LH049F; Calbiotech, Inc., Spring Valley, CA).

Sperm DNA integrity analysis For TUNEL assays of sperm, four smears from each semen sample were prepared on glass slides and air-dried. The In Situ Cell Death Detection Kit with Fluorescein isothiocyanate (FITC; Roche Diagnostics GmbH, Mannheim, Germany) was used with modifications. Each slide was fixed with 4% paraformaldehyde (1 mL) in phosphate-buffered saline (PBS) solution and incubated at room temperature for 1 hour. Slides were washed with ice-cold PBS then permeabilized with TritonX in 0.1% sodium citrate for 5 minutes. Slides were again washed with PBS then incubated with a mixture of the TUNEL enzyme solution containing terminal deoxynucleotidyl transferase plus TUNEL labeling solution containing deoxyuridine triphosphate. A Parafilm M strip (Alcan Packaging, Darien, CT) was applied to each slide, and the slides were incubated in a dark, moist chamber at 37°C for 1 hour. After labeling, slides were taken out of the chamber, the Parafilm M was removed, and the cells were washed with PBS. Vectashield (Vector Laboratories, Burlingame, CA) with 4',6-diamidino-2-phenylindole (DAPI) was applied to each slide for DNA counterstaining, and a cover slip was applied. Cells were allowed to stain overnight. Two negative and two positive controls were tested with each batch.
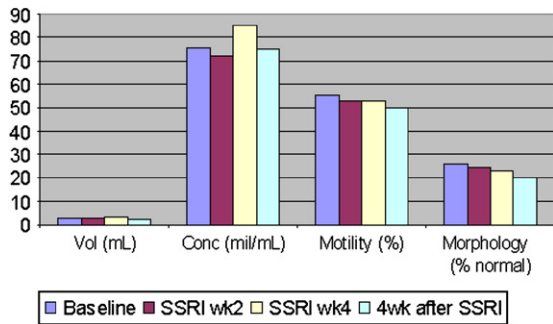
Slides were analyzed using an epifluorescent microscope at ×400 magnification. The number of DAPI-positive cells were counted then, in the same field, the number of FITC-positive cells were recorded. At least 100 DAPI-positive cells were counted for one single tally. The number of FITC-positive cells detected were divided by DAPI-positive cells × 100 to produce the percentage of TUNEL-positive cells (containing fragmented DNA), and at least four separate fields were analyzed.

Statistical Analysis

A prospective power calculation assuming a normal distribution of semen analyses with an estimated standard deviation
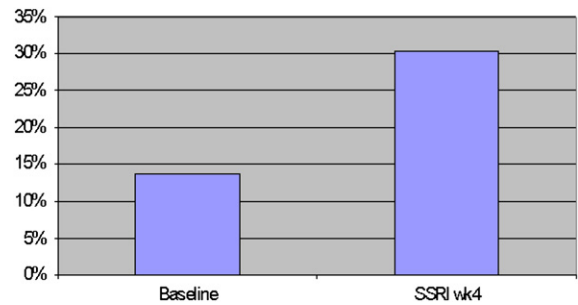
Tanrikut. *Effect of paroxetine on sperm. Fertil Steril 2010.*

FIGURE 2

Comparison of mean TUNEL scores. Mean percentage of sperm DNA fragmentation at baseline was 13.8%; this rose to 30.3% at week 4 of paroxetine administration ($P < 0.001$, t test).

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of 25%, a 20% change in semen parameters when on medication, a two-sided alpha of 0.05, and a beta level of 0.15 yielded a required sample size of 31 subjects. Semen parameters, hormone levels, TUNEL assays, and sexual function scores for each individual were compared at each time point. Continuous data were assessed for normality using the Shapiro-Wilk test. The central limit theorem was invoked for those distributions that approached normality. Continuous data were analyzed using ANOVA and repeated measures t test comparisons for parametric data and Wilcoxon and Kruskal-Wallis tests for nonparametric data. Dichotomous measures using standardized cutoffs were evaluated by contingency table analysis. All statistical analyses were performed using SAS JMP 7.0 software (SAS Institute, Inc., Cary, NC).
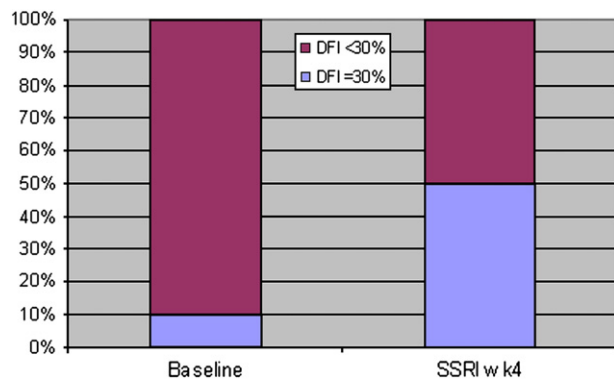
RESULTS

Eighty-four men were screened, and 35 subjects enrolled. Mean age of subjects was 33.9 ± 11.1 years (range, 19–58 years) and mean body mass index (BMI) was 26.9 ± 4.4 (range, 19.4–38.1). Eleven (31.4%) patients had a BMI <25, 15 (42.9%) patients had a BMI of 25–30, and 9 (25.7%) patients had a BMI ≥ 30. Two patients left the study after medication initiation: one because of medication side effects and one was lost to follow-up after completing medication.

Endocrine Effects

Statistically significant decreases in serum T (844 ng/dL vs. 605 ng/dL; $P=0.015$, t test) and E_2 (28.8 pg/mL vs. 20.6 pg/mL; $P=0.019$, t test) were noted with paroxetine. However, the decreased values on medication remained well within the normal reference range for each of these hormones. There were no significant changes in serum concentrations of FSH, LH, or PRL during paroxetine treatment.

Semen Parameters

Semen parameters (volume, concentration, motility, and morphology) were not significantly altered during SSRI treatment (Fig. 1).

DNA Fragmentation

Mean TUNEL score was significantly higher on SSRI (30.3%) vs. baseline (13.8%; $P < 0.001$, t test; Fig. 2). At baseline, 9.7% of patients had a TUNEL score $\geq 30\%$, compared with 50% patients with a TUNEL score $\geq 30\%$ at week 4 of SSRI administration ($P=0.001$, Fisher's Exact; Fig. 3). The odds ratio (OR) of having abnormal DNA fragmentation while taking an SSRI was 9.33 (95% confidence interval [CI], 2.3–37.9]. Multivariate logistic regression, correcting for age and BMI, confirmed that SSRI treatment was significantly correlated with increased DNA fragmentation (OR, 11.12; $P < 0.001$).

A subset analysis of men who had a T level decrease ≥ 150 ng/dL was performed to assess whether this decrease correlated with an increase in DNA fragmentation to $\geq 30\%$. No correlation was found ($P=1$, Fisher's exact).

An incidental finding was that men with abnormal TUNEL score had a higher BMI. Analysis of variance revealed a mean BMI of 25.7 for TUNEL score <30% and a mean BMI of 28.2 for TUNEL score $\geq 30\%$ ($P < 0.02$). A similar trend was noted when BMI and TUNEL scores were compared at baseline and on paroxetine ($P=0.05$ and $P=0.13$, respectively), but it did not reach statistical significance.

Sexual Dysfunction

The BSFI results revealed significant sexual dysfunction while taking an SSRI compared with baseline. Four questions

FIGURE 3

TUNEL results with 30% threshold. Only 9.7% of patients had a TUNEL score ≥30% before medication compared with 50% of patients at week 4 of paroxetine ($P=0.001$, χ-square).

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FIGURE 5

Changes in ejaculatory function. Three questions (questions 6, 7, 10) of the BSFI assess ejaculatory function, rated on a scale of 0 (most severe dysfunction) to 4 (no dysfunction). The percentage of patients responding 0, 1, or 2 to the three questions increased significantly while taking paroxetine, from 3–9% to 30–56%. Ejaculatory function approached baseline 1 month after cessation of medication with only 9% of patients complaining of more than mild dysfunction ($P \leq 0.002$, χ-square).
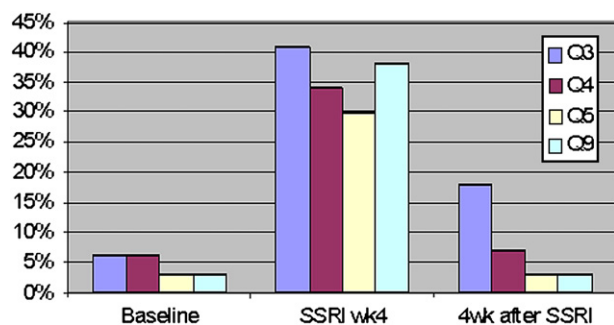

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of the BSFI address erectile function and three address ejaculatory function. Up to 35% of men noted significantly worsened erectile function ($P < 0.003$; Fig. 4), and 47% of subjects reported significant declines in ejaculatory function ($P \leq 0.002$; Fig. 5). These significant changes from baseline returned to near-normal one month after treatment. Several patients experienced severe ejaculatory dysfunction while taking paroxetine and were unsuccessful in providing a semen sample after attempts on three separate days. This occurred in two men during week 2 and in four men during week 4.
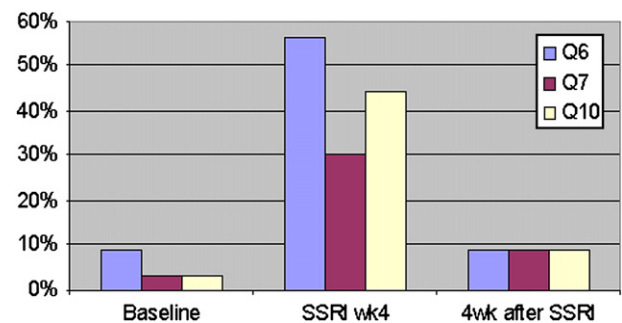
FIGURE 4

Changes in erectile function. Four questions (questions 3, 4, 5, 9) of the BSFI pertain to erectile function, rated on a scale of 0 (most severe dysfunction) to 4 (no dysfunction). The percentage of patients responding 0, 1, or 2 to the four questions increased significantly while taking paroxetine, from 3–6% to 30–41%. Erectile function returned to or approached baseline 1 month after cessation of medication ($P < 0.003$, χ-square).

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DISCUSSION

This study sought to further evaluate the effect of SSRIs on male fertility potential after previously published anecdotal observations identified dramatically affected total motile sperm counts associated with SSRI use (6). In this study, we have demonstrated that marked changes in sperm DNA fragmentation occur during paroxetine treatment that are not reflected by changes in standard semen parameters. Not only did mean DNA fragmentation levels increase from 13.8 to 30.3% on paroxetine, but the percentage of patients with abnormal DNA fragmentation (≥30%) rose from 9.7–50%. Integrity of DNA is important to normal fertility (17, 18) and affects the success of intrauterine insemination. Abnormal sperm DNA integrity also affects pregnancy outcomes with the most advanced assisted reproductive technologies (10, 19, 20). The threshold of ≥30% sperm DNA fragmentation has been suggested as a cut-off point to identify men with poorer fertility (21). The fivefold increase in the number of patients who developed abnormal sperm DNA integrity while taking paroxetine in this study is unsettling. Although fertility was not directly assessed in this study, these marked changes in the DNA integrity of sperm suggest an adverse fertility effect related to paroxetine use.

Both serum T and E_2 levels decreased significantly during treatment in this study. Two other studies that have included hormonal assessment of patients who were receiving an SSRI (fluoxetine) for major depressive disorder have not shown any significant changes in serum T during treatment (22, 23). Because the lower values in our study were well within the normal range for each hormone, the differences are likely

of little clinical relevance in healthy men. However, low or low-normal serum testosterone levels are often found in men examined for a fertility evaluation. In those men, an approximately 28% decrease in serum T level levels could have clinical relevance with symptoms of hypogonadism and/or potential negative impacts on spermatogenesis. The drop in T and E_2 levels that was noted in our study may partially explain recent reports of increased fractures in older patients using SSRIs (24, 25).

Of note, changes to sperm DNA quality occurred without changes in standard semen parameters with paroxetine. For patients taking SSRIs and desiring fertility, the standard semen analysis would not show sperm DNA damage. Serotonin affects the ejaculatory response and sperm transport. The extent of this effect may vary from patient to patient. Whereas limited changes in serotonin-related effects may moderately slow sperm transport resulting only in altered sperm DNA integrity without changes in sperm numbers, a limited number of men may experience more dramatic effects on sperm transport causing deterioration of standard semen parameters, such as those patients reported in our prior publication (6). Again, the rapid recovery of semen parameters in the initial case reports coupled with the lack of change of FSH in this study supports a mechanism of impact via sperm transport rather than sperm production, although basic science studies would be warranted to confirm this concept.

Patients already taking an SSRI were not considered for this study, as we could not test for changes in semen parameters if subjects were already taking medication. Furthermore, for patients who are clinical candidates for treatment of anxiety or depression with SSRIs and have not yet started medication, their inherent psychiatric condition could affect sperm production, thereby creating confounding variables in evaluating the effects of paroxetine. As an initial investigation of our case study findings, this was a proof-of-principle study and a placebo arm was not included because of the additional significant expense that would have been incurred for the study. Future studies may incorporate a placebo-controlled design.

The incidental finding of a relationship between BMI and sperm DNA fragmentation is of interest. Although other studies have reported that increased BMI is associated with lower sperm concentration and decreased motility (26, 27), we are aware of only one other study that identifies an association between high BMI and elevated sperm DNA fragmentation (28). This relationship will be evaluated further in future studies.

The potential compromise of male fertility caused by increased sperm DNA fragmentation associated with paroxetine use is an important concern, given the prevalence of depressive disorders and the upward prescribing trends for SSRI antidepressants. It remains to be seen whether similar degrees of DNA fragmentation occur with alternative SSRIs or other classes of antidepressants. We plan future larger-scale, randomized, placebo-controlled trials with other SSRIs to further explore these findings and possibilities.

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