

Impact of Duloxetine on Male Fertility

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Protocol 001	10/25/2016	Protocol was submitted to IRB for review and eventually approved. Please refer to protocol summary below. Subsequent amendments submitted to IRB do not reflect changes in protocol background, study design, methods, or statistical analysis.

Background and Clinical Significance

Antidepressant medications are commonly prescribed in the USA not only for depression, but also for anxiety disorders such as generalized anxiety disorder and obsessive-compulsive disorder, premature ejaculation, post-traumatic stress disorder, and neuropathic pain. In fact, prescriptions for antidepressants in American men increased by 28% between 2000 and 2010 (Medco, 2010). Despite being widely prescribed in the United States in men of reproductive age, the impact of antidepressants on fertility has not been extensively studied. After noticing worsened semen parameters in men on anti-depressants (Tanrikut and Schlegel 2007), the investigators performed the first prospective study to demonstrate a deleterious impact of selective serotonin reuptake inhibitors (SSRI) on sperm DNA integrity, which has been linked to reproductive outcomes (Tanrikut and Schlegel, 2010). Further small studies have corroborated the negative impact of SSRIs on male fertility, as assessed by semen parameters and/or sperm DNA integrity (Safarinejad, 2008 and Koyuncu et al, 2011). While the exact mechanism for the negative impact of SSRIs on male fertility is not yet known, animal studies have suggested the potential spermicidal action of SSRIs mediated through the binding of SSRIs to sulfhydryl groups on spermatozoa (Wolf et al, 1992; De Lamirande et al., 1998, and Kumar et al., 2006). Tanrikut and Schlegel suggested an impact on post-testicular sperm transport as the mechanism for sperm DNA damage (Tanrikut and Schlegel, 2010). An increase in sperm DNA fragmentation commonly occurs in men with delayed sperm transport, as has been shown in those with ejaculatory dysfunction or obstructive azoospermia. No studies have examined the impact of a newer, but similar, class of antidepressant - the serotonin-norepinephrine reuptake inhibitor (SNRI). Like SSRIs, SNRIs inhibit the reuptake of serotonin, but also act on norepinephrine. The use of SNRIs has increased recently due to their slightly improved efficacy profile when compared to SSRIs. Duloxetine (trade name Cymbalta) is an SNRI and is one of the most commonly prescribed anti-depressants in the United States. The most common side effects for duloxetine at its optimal treatment dose of 60mg daily include nausea (23-25%), dry mouth (13-15%), headache (13-14%), somnolence (10-12%), and fatigue (10-11%). Significant side effects include the activation of mania/hypomania in those with bipolar disorder and the potential for serotonin syndrome in those concurrently taking SNRIs with other serotonergic medications.

Primary and Secondary Objectives

The primary objective of the research study is to determine the administration of duloxetine on sperm DNA fragmentation, and the secondary objective is to determine the impact of duloxetine administration on semen parameters such as serum hormone levels, and sexual function.

Study Design

The hypothesis is that administration of duloxetine will result in a deterioration in sperm DNA fragmentation in healthy, fertile men. To evaluate the hypothesis, the investigators conducted a placebo-controlled, randomized control trial with duloxetine in healthy, fertile men not previously on any antidepressants. Patients will be randomized to either the duloxetine (60mg PO daily) or placebo groups for 6 weeks. In the sixth and last week of therapy, the drug dosage will be halved to 30mg PO daily as a taper. Changes in sperm DNA fragmentation were assessed at numerous time points before, during, and after drug administration (semen analyses at baseline before administration, at 2-weeks, 6-weeks, and then at 2-weeks and 4-weeks after drug cessation). Other outcomes measured include semen parameters (sperm concentration, motility, morphology), hormone levels (testosterone, estrogen, prolactin, LH, FSH collected at baseline, at 2-weeks, 6-weeks, and at 2-weeks and 4-weeks after discontinuation of medication), and sexual function (IIEF and MSHQ) surveys (collected at baseline, at 6-weeks, and at 4-weeks after discontinuation of medication).

Methods

Selective serotonin reuptake inhibitors (SSRI) are known to affect post-testicular sperm transport and adversely impact male fertility, but no studies have examined the impact of a newer, but similar, class of antidepressant - the serotonin-norepinephrine reuptake inhibitor (SNRI). Duloxetine (trade name Cymbalta) is an SNRI and is one of the most commonly prescribed anti-depressants in the United States. An increase in sperm DNA fragmentation commonly occurs in men with delayed sperm transport, as has been shown in those with ejaculatory dysfunction or obstructive azoospermia. The research hypothesis is that administration of duloxetine will result in a deterioration in sperm DNA fragmentation in healthy, fertile men. To test the hypothesis, a placebo-controlled, randomized control trial will be conducted with duloxetine in healthy, fertile men not previously on any antidepressants. Patients will be randomized to either the duloxetine or placebo groups for 6 weeks. Changes in sperm DNA fragmentation will be assessed at numerous time points before, during, and after drug administration. Other outcomes measured will include semen parameters (sperm concentration, motility, morphology), hormone levels (testosterone, estrogen, prolactin, LH, FSH), and sexual function (IIEF and MSHQ) surveys.

Study Population

Study participants will be screened and recruited if they meet the selection criteria. Participants who are healthy males aged 18-65 years, with normal or borderline (concentration >10 million/mL, motility >30%, morphology >3%) semen parameters on semen analysis, and are willing to engage in sexual activity, alone or with a partner, at least weekly for the duration of the study, and are capable of providing semen sample will be included in the study. Participants will be excluded if they have clinically detected varicocele, diagnosed with oligoasthenospermia or azoospermia on screening semen analysis, ongoing attempts to initiate pregnancy, current sexual dysfunction, indicated by moderate or worse dysfunction on any International Index of Erectile Function (IIEF) domain, history of seizure disorder, history of previous chemotherapy or radiation, current psychiatric disorder or history of bipolar disorder, family history (including cousins and grandparents) of bipolar disorder (manic depressive disorder) or suicide, use of any psychotropic agents (prescription or herbal) or anticonvulsants, use of sleeping pills more than once per week, use of any hormonal medications on a daily or intermittent basis including glucocorticoid pills, inhalers, or creams during the preceding 3 months, use of medications which may affect hormonal measures or sexual function, use of any prescription or non-prescription medications to enhance sexual function, inability to read, follow instructions or complete questionnaires in English, consumption of more than 2 ounces of alcohol daily, and consumption of tobacco or illicit drugs.

Statistical Analysis Plan

After consultation with a biostatistician, the required sample size for a proportion difference of 5% of patients with abnormal sperm DNA fragmentation in the control group and 30% of patients with abnormal sperm DNA fragmentation in the treatment group with 80% power, two-sided alpha 5% is 35 patients per group. Descriptive statistics (including mean, standard deviation, median, range, frequency, and percent) for demographic and clinical factors of interest will be calculated for the placebo and treatment groups separately. The two-sample t-test (or Wilcoxon rank-sum test) and chi-square test (or Fisher's exact test) will be used to compare 1) mean (median) TUNEL values and 2) proportions of patients with TUNEL values >25%, respectively, between the treatment and placebo groups, at each time point. Analysis of covariance (ANCOVA) and multiple logistic regression will also be used to compare mean TUNEL value and proportion of patients with TUNEL values > 25%, respectively, between the two groups, after adjustment for baseline value (i.e., assuming any remaining imbalance in the baseline assessment between the two groups after randomization). The paired t-test and McNemar's chi-square test will be used to compare change in mean TUNEL value and change in proportion of abnormal results,

respectively, between the time points, within each group separately. The secondary outcomes of interest will also be compared between the two groups using similar statistical tests as noted above. All p-values will be two-sided with statistical significance evaluated at the 0.05 alpha level. Ninety-five percent confidence intervals (95% CI) will be calculated to assess the precision of the obtained estimates. All analyses will be performed in SAS Version 9.4 (SAS Institute, Inc., Cary, NC) and Stata Version 14.0 (StataCorp, College Station, TX).