A Placebo-Controlled, Crossover Trial of Granisetron in SRI-Induced Sexual Dysfunction

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Background: Sexual side effects are commonly associated with serotonin reuptake inhibitor (SRI) therapy. The mechanism underlying SRI-induced sexual dysfunction has been hypothesized to be mediated by direct serotonergic effects. Evidence from open-label reports suggests that cyproheptadine, nefazodone, mirtazapine, and mianserin, which block one or more serotonin receptors, may reverse sexual side effects. The current study was a prospective, randomized, crossover trial comparing granisetron, a serotonin-3 antagonist, with placebo in outpatients who developed sexual dysfunction during SRI treatment.

Method: Thirty-one outpatients who were currently experiencing sexual dysfunction associated with SRIs were randomly assigned to double-blind treatment with granisetron (1–1.5 mg) or placebo for use 1 to 2 hours prior to sexual activity. Patients rated sexual symptoms after each trial using the Sexual Side Effect Scale (SSES). After 4 trials of the medication, patients crossed over to the other treatment for 4 more trials.

Results: Twenty patients received at least 1 dose of placebo and granisetron. Analysis by repeated-measures analysis of variance showed no significant effects of granisetron relative to placebo. Significant improvement between baseline and treatment-phase SSES scores was observed for both granisetron ($p = .0004$) and placebo ($p = .0081$). The study medication was generally well tolerated.

Conclusion: The results of this study do not support the efficacy of granisetron (1–2 mg) in the treatment of SRI-associated sexual side effects. A significant placebo response may be associated with the treatment of SRI-induced sexual dysfunction.

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Sexual side effects are commonly associated with serotonin reuptake inhibitor (SRI) therapy.[1–3] Some authors have found the incidence of sexual dysfunction associated with SRIs to be as high as 30%.[4] Moreover, sexual side effects have been shown to decrease compliance with antidepressant treatment.[5] Since noncompliance with medications frequently leads to relapse, new strategies for overcoming sexual side effects have important clinical implications.[4]

Although the mechanism underlying sexual dysfunction associated with SRIs has not been fully characterized, it may be mediated by direct serotonergic effects.[5] However, the specific serotonin receptor(s) involved has not been identified. It has been previously reported that the administration of the nonspecific serotonin antagonist cyproheptadine ameliorated sexual side effects.[6–8] However, this strategy may have led to a recurrence of depression in some patients. Yohimbine has also been used to treat sexual side effects with mixed results.[4] Other medications reported to reverse antidepressant-induced sexual dysfunction in open trials include amantadine,[9] nefazodone,[10] bupropion,[11] sildenafil,[12] mirtazapine,[13] mianserin,[14] and *Ginkgo biloba*.[15] Two recent double-blind, placebo-controlled trials demonstrated some efficacy of sildenafil and bupropion for this problem.[16,17] A double-blind trial of amantadine, buspirone, and placebo showed no difference between placebo and either drug for the treatment of sexual side effects.[18] However, a second study by Landen et al.[19] found that buspirone augmentation of a selective SRI for treatment of depression improved patients' drug-induced sexual dysfunction significantly more than did placebo.

Mirtazapine, the only available antidepressant agent that increases serotonin and blocks the serotonin-2 (5-HT_2) and 5-HT_3 receptor subtypes, has been reported to have a low frequency of sexual side effects despite the fact that it increases serotonergic neurotransmission.[20] This suggests that increased serotonin binding at the 5-HT_2 and/or 5-HT_3 receptor may be involved in producing sexual dysfunction with SRIs. Recently, we reported the case of a woman with severe fluoxetine-induced anorgasmia and decreased libido that were transiently reversed during 3 separate trials of granisetron, a 5-HT_3 antagonist.[21]

The specific aim of the current study was to evaluate the efficacy of granisetron in the treatment of sexual dysfunc-

tion associated with SRIs, including fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, and venlafaxine. This prospective, randomized, crossover trial compared granisetron with placebo in outpatients who developed new-onset sexual dysfunction during SRI treatment.

METHOD

Subjects

Thirty-one outpatients (men and nonpregnant women 18 years or older) who were currently experiencing sexual dysfunction that began while taking an SRI were enrolled in the study. Patients were recruited from advertisements and from outpatient treatment sites at the University of Cincinnati Medical Center. Patients provided written informed consent to participate in the trial.

Sexual dysfunction for men was defined as decreased enjoyment of sex associated with either difficulty achieving or maintaining an erection or delayed ejaculation. For women, sexual dysfunction was defined as decreased overall enjoyment of sexual activity due to either decreased vaginal lubrication or decreased ability to achieve orgasm. Subjects were not included if they had decreased libido but no change in functioning during sexual activity. Subjects were included if they were sexually active on average at least once every 2 weeks and were involved in a stable relationship.

During the screening interview, a sexual history was taken to rule out causes of sexual dysfunction other than SRI treatment. Subjects were included in the study only if it was determined that sexual dysfunction began after treatment with an SRI and no other medication or medical condition was contributing to the problem. Specifically, patients were excluded if they were taking thiazide diuretics, spironolactone, β-blockers, clonidine, methyldopa, prazosin, phenoxybenzamine, verapamil, antipsychotics, cimetidine, digoxin, or disopyramide.

Procedure

At the screening visit, patients were rated using the Hamilton Rating Scale for Depression (HAM-D).[22] Patients were excluded if their HAM-D total score was ≥ 10 in order to minimize the possibility that depressive symptoms were contributing to sexual dysfunction. Patients were also asked to provide a baseline self-rating on the Sexual Side Effect Scale (SSES; Appendix 1). This scale, which was designed for the purpose of this study, asked patients to rate the severity of 3 sexual side effects: (1) decreased overall pleasure during sex, (2) difficulty maintaining an erection or decreased lubrication, and (3) delayed ejaculation or orgasm. Patients estimated the severity of these symptoms on a scale from 0 (no symptoms) to 5 (total dysfunction on the particular item). At baseline, patients were asked to report the average severity of these symptoms for their recent sexual activity. Patients were included in the study if they had a minimum total score of 3 for the 3 items on the SSES with at least 1 item being rated 2 or higher.

Patients were randomly assigned in double-blind fashion to 1 of 2 sequences of crossover treatment between granisetron and placebo: granisetron-placebo or placebo-granisetron. Patients were given an unmarked bottle, containing seven 1-mg tablets of granisetron or 7 matching placebo tablets. Patients were instructed to take 1 tablet on an empty stomach 1 to 1.5 hours before anticipated sexual activity. After each trial of taking the medication and subsequent sexual activity, patients rated their sexual functioning using the SSES. Patients were instructed to rate any type of sexual activity as long as it involved clitoral or penile stimulation. Patients were asked to rate the same type of sexual activity in all trials to decrease variability in the severity of sexual side effects that might be due to differences in the degree of stimulation between sexual practices. If the patient noticed no improvement or only partial improvement with the first trial, they were asked to increase to 2 tablets for 3 more trials (total of 4 trials). If they had complete resolution of sexual side effects with the first trial, they were instructed to try the medication 2 more times using 1 tablet. Patients returned for a second visit after they had completed the trials with the first bottle. They were then given a second bottle containing the other study medication (either placebo or granisetron) depending on which they had received initially. Patients were given 3 weeks to complete the trials with each bottle. Patients were evaluated at the end of each trial period to obtain the SSES rating sheets and report any side effects of the medication. A HAM-D rating was performed at each visit to ensure that depressive symptoms had not recurred during the preceding trial period.

Of the 31 patients who received medication in this study, a total of 23 returned for the first follow-up appointment. Three more patients did not return for the second follow-up, leaving 20 patients who completed both arms of the trial and received at least 1 dose of both study medications. Of the 3 patients who received only 1 dose of study medication, 2 received granisetron and 1 received placebo. The reasons that these patients dropped out of the trial were not established, since they were lost to follow-up. The 20 patients who completed the study received a total of 68 trials with granisetron (mean ± SD = 3.4 ± 1.15 trials per patient) and 73 total trials with placebo (3.7 ± 1.30 trials per patient). Eleven patients started with granisetron and 9 patients received placebo first. Clinical and demographic characteristics of the patient population are given in Table 1.

Statistics

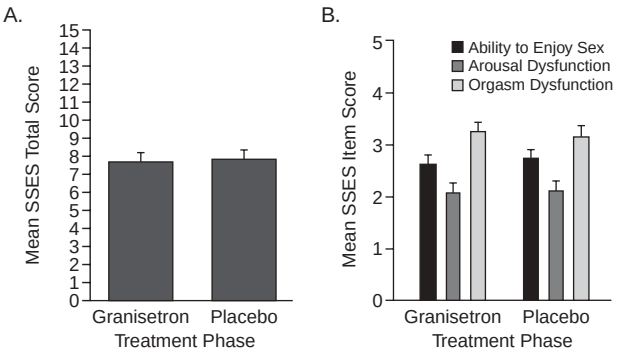
A repeated-measures analysis of variance (ANOVA) incorporating trials nested within each treatment phase for each patient was used to test the effect of granisetron

Table 1. Demographics of Patients Who Completed at Least 1 Trial of Granisetron and Placebo[a]

Variable	Value
Study completers, total N	20
Age, y, mean	45
Female, N (%)	18 (90)
White, N (%)	20 (100)
Daily SRI dose in fluoxetine mg equivalents, mean	27.1
SRI used, % of patients	
Fluoxetine	34.8
Sertraline	17.4
Paroxetine	26.1
Venlafaxine	17.4
Citalopram	4.3

[a]Abbreviation: SRI = serotonin reuptake inhibitor.

Figure 1. Mean (A) Total and (B) Item Scores on the Sexual Side Effect Scale (SSES) Associated With Granisetron and Placebo[a]



[a]Values shown as means and 95% confidence intervals.

relative to placebo. The analysis was performed separately on each of 3 questions on the SSES (see Appendix 1). Correlational measures of internal consistency suggested that it was also reasonable (based on Cronbach $\alpha > 0.7$) to sum these subsets to form a composite scale score. The analysis was performed on this composite score, as well.

RESULTS

Treatment

There was a significant improvement between baseline and treatment-phase SSES for both granisetron and placebo (mean ± SD baseline SSES score = 10.6 ± 2.0, mean change from baseline for granisetron = 2.8 ± 3.1, $p = .0004$; mean change from baseline for placebo = 2.7 ± 4.3, $p = .0081$). There were no significant effects of granisetron relative to placebo on the composite score or any subset. Figure 1 shows the means and 95% confidence intervals for the SSES total and subscale scores by treatment phase. The width of the confidence intervals relative to the range of the scale scores indicates that failure to find significant differences was unlikely to have been due to low statistical power; rather, any true effect of granisetron at the doses studied is likely to have been negligible. Since the scale properties of the SSES have not yet been verified and therefore the ANOVA assumption of interval scaling is uncertain for these data, we verified our results by performing a nonparametric ANOVA based on rank-transformed scores ($p > .5$). Exploratory analyses in which each patient's mean difference (on the composite score) between the 2 treatment phases was regressed on potential covariates (baseline dose of antidepressant, age, gender, order that treatments were received) were also performed, but no relationships were apparent. The mean ± SD dose of granisetron in the study was 1.7 ± 0.5 mg. Eighteen patients (90%) received at least 1 trial with both 1 mg and 2 mg of granisetron. One patient (5%) received only 1 mg and 1 patient (5%) took only 2 mg.

Tolerability and Safety

The study medication was well tolerated in general. One patient (4.5%) reported a recurrence of mood symptoms while taking granisetron (N = 22). Specifically, he experienced depressed mood, anhedonia, decreased motivation, insomnia, and nightmares for approximately 36 hours after taking 2 mg of granisetron on 2 different occasions. He did not experience any mood symptoms after taking placebo. Three patients (13.6%) reported constipation and 1 patient (4.5%) reported abdominal cramping and gas after taking granisetron. One patient reported increased salivation and bruxism (4.8%) and 1 patient complained of dizziness (4.8%) on placebo (N = 21).

DISCUSSION

The results of this study do not support the efficacy of granisetron (1–2 mg) in the treatment of SRI-induced sexual side effects. There was no difference in the mean SSES scores for trials with granisetron and placebo. Although there was a significant reduction in the mean SSES score from baseline with granisetron, there was also significant improvement with placebo. There are several possible explanations for this lack of response. Foremost, it is possible that the 5-HT_3 receptor is not involved in the production of sexual side effects caused by SRIs and, therefore, blocking this receptor may have no therapeutic effect. Although it has not been determined conclusively which, if any, of the 5-HT receptors are involved in SRI-induced sexual dysfunction, there is some evidence that the 5-HT_2 receptor may play a role.[10] However, 5-HT_3 receptor antagonists have been found to increase sexual behavior in animal models, suggesting at least a partial role for this receptor in the modulation of sexual behavior in some animals.[23]

A second possibility is that the 5-HT_3 receptor is important in the etiology of sexual side effects, but that

the dose of granisetron was not sufficient to fully block serotonin binding at this receptor. This explanation appears unlikely, however, since studies have shown that 1 to 2 mg of granisetron is sufficient to reduce other serotonin-mediated symptoms such as nausea[24] and to block serotonin-induced axon-reflex flare.[25] Moreover, it is possible that continuous dosing of granisetron would produce a benefit not seen with the intermittent dosing schedule used in this study. In fact, 1 study of bupropion for sexual side effects showed greater benefit with continuous as opposed to intermittent dosing.[11]

It is interesting to note that there was a significant decrease in SSES score from baseline during trials with placebo in this study. A significant placebo effect was also seen in 1 other published controlled study of SRI-induced sexual dysfunction.[18] This raises the question of whether SRI-induced sexual dysfunction has a high placebo response rate. It is also possible that sexual dysfunction was incorrectly attributed to SRI treatment and instead may have been due to random variation in sexual functioning, which could also have contributed to placebo response. However, this seems unlikely given the severity of sexual dysfunction reported and efforts during the patients' initial evaluation to link the onset of sexual dysfunction to the initiation of SRI therapy. This high placebo response rate underscores the importance of conducting placebo-controlled trials with the various treatments that have been reported to be beneficial for sexual dysfunction in open-label studies.

One of the significant limitations of this study was the high rate of patient dropout. Unfortunately, the reasons for these discontinuations are unknown, since patients who did not complete the study also did not respond to our follow-up inquiries. Although the loss of subjects undoubtedly reduced the power of the findings, it would appear that this would have had an impact on the response to granisetron only if patients selectively dropped out in one study condition over the other, thus creating a bias in the data. For instance, if some patients decided not to return for the second arm of the study on the basis of having a positive response to granisetron and the assumption that they would receive placebo in the next set of trials, a true response to granisetron could be obscured. Barring this eventuality, a type II error does not appear likely since the confidence intervals were narrow, with little separation between the mean SSES scores for drug and placebo.

Other limitations of this study include the lack of validation of the SSES in previous studies. It is also a highly subjective measure that relies on patients' ability to rate their sexual side effects soon after trials of medication in order to maximize the accuracy of their reporting. Although it is generally presumed that increased serotonin is the underlying mechanism of SRI-induced sexual dysfunction, it is still conceivable that there are some differences in the etiology of sexual side effects among SRIs. Given this possibility, the fact that patients in this protocol were on treatment with 1 of 5 different SRIs may have distorted the results as well. Moreover, the fact that patients only received 4 trials of study medication in each treatment arm also diminishes the power of the findings. Another limitation is that the secondary efficacy evaluation of change in SSES score from baseline was based on retrospective measures of sexual functioning. This is less meaningful than had these measures been obtained through a prospective baseline evaluation. Furthermore, only 3 male subjects completed the study, making it difficult to detect any effects of granisetron that may be specific to men. Also, all completers in the study were white, making it impossible to generalize any findings to other ethnic groups.

Drug names: amantadine (Symmetrel and others), bupropion (Wellbutrin), buspirone (BuSpar), cimetidine (Tagamet and others), citalopram (Celexa), clonidine (Catapres and others), cyproheptadine (Periactin), digoxin (Lanoxin and others), fluoxetine (Prozac), fluvoxamine (Luvox), methyldopa (Aldomet and others), mirtazapine (Remeron), nefazodone (Serzone), paroxetine (Paxil), prazosin (Minipress and others), sertraline (Zoloft), sildenafil (Viagra), verapamil (Calan and others), venlafaxine (Effexor), yohimbine (Aphrodyne and others).

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Appendix 1. Sexual Side Effect Scale

A. (All Subjects)
- 0 = normal ability to enjoy sex
- 1 = questionable loss of ability to enjoy sex
- 2 = mild but definite loss of ability to enjoy sex
- 3 = moderate loss of ability to enjoy sex
- 4 = marked loss of ability to enjoy sex
- 5 = complete loss of ability to enjoy sex

B. (Females only)
- 0 = normal ability to achieve an orgasm
- 1 = questionable loss of ability to achieve orgasm
- 2 = mild loss of ability to achieve orgasm
- 3 = moderate loss of ability to achieve orgasm
- 4 = marked loss of ability to achieve orgasm
- 5 = complete loss of ability to achieve orgasm

- 0 = normal vaginal lubrication
- 1 = questionable decrease in vaginal lubrication
- 2 = mild decrease in vaginal lubrication
- 3 = moderate decrease in vaginal lubrication
- 4 = marked decrease in vaginal lubrication
- 5 = complete absence of vaginal lubrication

C. (Males only)
- 0 = normal ability to obtain an erection
- 1 = questionable decrease in ability to obtain an erection
- 2 = mild decrease in ability to obtain an erection
- 3 = moderate decrease in ability to obtain an erection
- 4 = marked decrease in ability to obtain an erection
- 5 = complete inability to obtain an erection

- 0 = normal time to ejaculation
- 1 = questionable delay in ejaculation
- 2 = mild delay in ejaculation
- 3 = moderate delay in ejaculation
- 4 = marked delay in ejaculation
- 5 = complete inability to ejaculate