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A Randomized, Placebo-Controlled, Crossover Study of Ephedrine for SSRI-Induced Female Sexual Dysfunction

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The objective of this study was to determine whether ephedrine, an alpha- and beta-adrenergic agonist previously shown to enhance genital blood flow in women, has beneficial effects in reversing antidepressant-induced sexual dysfunction. Nineteen sexually dysfunctional women receiving either fluoxetine, sertraline, or paroxetine participated in an eight-week, double-blind, placebo-controlled, cross-over study of the effects of ephedrine (50 mg) on self-report measures of sexual desire, arousal, orgasm, and sexual satisfaction. Although there were significant improvements relative to baseline in sexual desire and orgasm intensity/pleasure on 50 mg ephedrine 1-hr prior to sexual activity, significant improvements in these measures, as well as in sexual arousal and orgasmic ability also were noted with placebo. These findings highlight the importance of conducting placebo-controlled trials for this condition.

Several reviews have documented a high prevalence of sexual side effects secondary to almost all antidepressant drugs currently being prescribed (Demyttenaere & Vanderschueren, 1995; Gitlin, 1994; Meston & Gorzalka, 1992; Rosen, Lane, & Menza, 1999; Segraves, 1992). The causative role of antidepressants has been documented by studies in which decreases in dosage or cessation of the medication was accompanied by a reversal of both sexual dysfunction and depressive symptoms (Segraves, 1992). The estimates of incidence noted in these reviews generally range between 20% to 40% in men and women. Anecdotal data from case reports suggest that men spontaneously report antidepressant-induced sexual side effects more

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frequently than do women (Demyttenaere & Vanderschueren, 1995; Meston & Gorzalka, 1992) and that women are more likely than men to falsely attribute their sexual side effects to interpersonal problems rather than to their medication (Segraves, 1992). However, studies that have systematically assessed the prevalence of sexual dysfunction by gender reveal a higher prevalence of antidepressant-induced side effects for women than for men (Balon, Yeragani, Pohl, & Ramesh, 1993). Moreover, women are prescribed antidepressant medications more frequently than are men, given that major depressive disorder has a prevalence rate two to three times higher in women than in men (Hensley & Nurnberg, 2002). Sexual side effects noted in women include loss of sexual desire, impaired arousal and lubrication, vaginal anesthesia, delayed orgasm, and anorgasmia (Demyttenaere & Vanderschueren, 1995; Gitlin, 1994; Meston & Gorzalka, 1992; Rosen et al., 1999; Segraves, 1992).

Given the high reported incidence of adverse sexual side effects noted with antidepressant use and the fact that such side effects negatively impact medication compliance (Sussman, 1994), it is surprising that little controlled research has been conducted in this area. If sexual dysfunction occurs with antidepressant treatment, the general management strategy of clinicians has been either to reduce the medication dosage, to recommend that patients take a 2–4 day drug “holiday,” to wait for tolerance to occur, or to switch antidepressant medications (Gitlin, 1994; McElory, Keck, & Friedman, 1995). Although these strategies are helpful for some patients, dosage reduction and drug holidays, particularly with shorter acting agents, can lead to a reemergence of depressive symptoms (Harvey & Balon, 1995; Rothschild, 1995).

Although the precise mechanism of action by which antidepressants influence sexual function is unknown, central serotonergic and dopaminergic systems have been implicated most frequently. Accordingly, the most successful antidotes for sexual dysfunction are believed to exert their effects through central nervous system enhancement of dopamine neurotransmission or reduction of serotonergic neurotransmission (Gitlin, 1994; Harvey & Balon, 1995). Consistent with this viewpoint, antiserotonergic drugs such as cyproheptadine, buspirone, mirtazapine, and granisetron and dopaminergic agents such as amantadine, dextroamphetamine, bupropion, methylphenidate, and pemoline recently have been prescribed as a means of counteracting antidepressant-induced sexual side effects. Findings from case reports and open label studies suggest that these and other drugs, such as the α_2 -blocker yohimbine, the cholinergic agent bethanechol, and the selective cyclic-GMP catabolism inhibitor sildenafil, are marginally successful in alleviating certain specific types of antidepressant-induced sexual side effects (for a review, see Woodrum & Brown, 1998). Findings from the few placebo-controlled studies published are less optimistic. In a well-designed study, Michelson, Bancroft, Targum, Yongman and Tepner (2000) examined the comparative effects of 8 weeks of treatment with either buspirone (20 mg/day), amantadine (50 mg/day), or placebo on fluoxetine-induced

sexual dysfunction in women. The authors reported that all groups experienced an improvement in sexual dysfunction during treatment, however, neither buspirone nor amantadine was more effective than placebo in restoring sexual function. At a higher dose level (mean daily dose = 47 mg), buspirone showed a marginally significant alleviation, compared with placebo, of sexual side effects in women taking either citalopram or paroxetine, (Landen, Eriksson, Agren, & Fahlen, 1999). In a randomized, double-blind, parallel, placebo-controlled study of mirtazapine (30 mg/day), yohimbine (10.8 mg/day), olanzapine (.5 mg/day), or placebo for fluoxetine-induced sexual dysfunction, Michelson, Kociban, Tamura, and Morrison (2002) found no significant improvements in sexual interest, arousal, lubrication, or orgasm beyond placebo in 107 women with either impaired orgasm or vaginal lubrication. Results from a randomized, double-blind study of 150 mg/day bupropion showed no significant improvements in sexual desire, arousal, orgasm, or satisfaction beyond placebo (Masand, Ashton, Gupta, & Frank, 2001).

The present study provides the first placebo-controlled examination of a peripherally acting vasoactive drug on sexual responses in women with selective serotonin reuptake inhibitor (SSRI)-induced sexual dysfunction. Several uncontrolled trials have demonstrated positive effects of sildenafil, a peripherally acting selective inhibitor of cyclic GMP catabolism, in women with sexual dysfunction associated with SSRI use (for a review, see Rosen, 2002). However, to date, no controlled studies have been published. To the extent that vasoactive agents may have a positive impact on physiological sexual arousal in women (Rosen, 2002), and several researchers have argued that sexual arousal may be integrally linked to all stages of sexual responding in women (for a review, see Meston, 2000), such agents may prove beneficial for treating antidepressant-induced sexual side effects. Moreover, given that treatment using centrally acting serotonergic agents may diminish an antidepressant's therapeutic effectiveness (e.g., Gitlin, 1994), targeting peripheral rather than central mechanisms may be a more viable treatment approach. In theory, this would circumvent the reversal of antidepressants' therapeutic effects on depression that are presumably centrally mediated.

The present study examines whether ephedrine, an alpha- and beta-adrenergic agonist that increases sympathetic outflow, will counteract the adverse sexual side effects associated with antidepressant therapy. Ephedrine was chosen based on past research that has demonstrated a significant facilitatory impact of ephedrine on vasocongestion in women. Using a double-blind, placebo-controlled design, Meston and Heiman (1998) found that 50 mg of ephedrine significantly increased vaginal pulse amplitude responses to an erotic film among sexually functional women. The facilitation of physiological sexual arousal by ephedrine is consistent with research that has shown increased sympathetic nervous system (SNS) activity, induced via intense acute exercise, enhances plethysmograph (vaginal pulse amplitude, vaginal blood volume) measures of sexual arousal in women (Meston &

Gorzalka, 1995, 1996a, 1996b) and that shows that clonidine, a drug which blocks peripheral sympathetic outflow, decreases these responses (Meston, Gorzalka, & Wright, 1997).

METHOD

Subjects

Study participants were currently receiving fluoxetine ($n = 7$), sertraline ($n = 7$), or paroxetine ($n = 5$) treatment for depression. In an effort to minimize the likelihood of spontaneous remission of sexual side effects during the course of the study, I required that participants have received the SSRI for a minimum of 10 weeks prior to enrolling in the study. Only participants who reported no sexual dysfunction prior to beginning SSRI treatment and who reported an onset of sexual dysfunction no less than 1 week and no more than 3 months after beginning SSRI treatment were included in the study (See Table 1 for breakdown of retrospectively reported sexual side effects secondary to SSRI treatment). Because many patients describe diminished sexual desire or functioning as a symptom of depression, I only considered SSRI-induced sexual dysfunction to occur only if it was described by the participant as following the otherwise successful treatment with the SSRI

TABLE 1. Percentage of Subjects Reporting Changes in Sexual Functioning Following Antidepressant Treatment

	Markedly decreased (%)	Mild-moderate decrease (%)	No change (%)	Mild-moderate increase (%)	Markedly increased (%)
1. Thinking about sex with interest or desire	38	56	—	6	—
2. Enjoyment of sex	19	62	13	6	—
3. Ability to become sexually aroused	31	69	—	—	—
4. Ability to have an orgasm during masturbation	38	56	6	—	—
5. Ability to have an orgasm during sexual intercourse	47	53	—	—	—
6. Length of time to reach orgasm	13	25	6	25	31
7. Frequency of kissing and romantic touching	13	50	25	12	—
8. Frequency of masturbation	50	38	12	—	—
9. Frequency of sexual intercourse	38	50	12	—	—
10. Overall level of sexual satisfaction	44	56	—	—	—

and as being distinctly different from any sexual dysfunction noticed during the depressed state. Participants were required to be currently involved in a sexually active heterosexual relationship.

Individuals were excluded from participating in the study if they met Diagnostic and Statistical Manual of Mental Disorders (DSM-IV American Psychiatric Association, 1994) criteria for an Axis I disorder; if they had a history of thyroid disorder, cardiovascular dysfunction, high or low blood pressure, heart disease, neurological disease, diabetes, or were considered at risk for suicide; if they were currently receiving any medication (other than fluoxetine, sertraline, or paroxetine) or if they engaged in excessive alcohol consumption; if they had any other medical illness known to affect vascular or sexual functioning; or if they were currently receiving any form of psychological therapy that addressed sexual or relationship issues. A registered nurse screened all potential participants for confounding medical illnesses or cardiovascular anomalies; participants were excluded if any abnormalities were detected.

Of the 29 qualified participants entering the study, 19 completed the study (M age = 28 years, range = 18–50 years). Of the ten women who failed to complete the study, one was discharged because she began asthma medication, 8 were discharged because they failed to mail in their weekly assessment questionnaires, and 1 dropped out because of side effects. The study was approved by the University of Texas institutional review board. Participants were recruited by local advertisements and were paid \$75.00 for their participation.

Design and Procedure

I obtained written informed consent from the participants after providing them with a complete description of the study. In order to assess the women's current levels of sexual functioning, I administered to those who met the screening criteria a demographics questionnaire, a questionnaire designed to assess their subjective reports of sexual function in comparison with their pre-SSRI levels (Table 1), and a modified version of the Brief Index of Sexual Functioning for Women (BISF-W; Taylor, Rosen, & Leiblum, 1994). The modified BISF-W requested information about sexual desire, arousal, orgasm, and satisfaction during the prior 1-week period. Between 1 and 2 weeks later, participants returned for their second visit and again filled out the modified BISF-W and were randomized for 3 weeks of double-blind treatment with 50 mg of ephedrine or placebo. This dosage of ephedrine was chosen because it has previously been reported to increase sexual arousal in women without causing adverse side effects (Meston & Heiman, 1998). Participants were dispensed either 21 capsules of placebo or 21 capsules of ephedrine and instructed to self-administer one medication capsule orally at the same time daily. The time of day that subjects were instructed to take the capsule was

approximately 1 hour prior to the time at which sexual activity usually occurs for them. Participants also were given three modified BISF-W questionnaires in self-addressed, stamped envelopes and instructed to complete and mail one questionnaire at the end of each 1-week period. I conducted telephone interviews with participants on a weekly basis to assess any potential side effects and to remind participants to complete and mail the questionnaires.

After the initial 3-week period, participants returned for their third visit. Using a double-blind cross-over protocol, I dispensed to them either 21 capsules of placebo or 21 capsules of ephedrine. As in the first phase, they were instructed to self-administer 1 medication capsule orally at the same time daily. They were given a second set of three modified BISF-W questionnaires to complete and mail in on a weekly basis. At the end of the second 3-week period, participants presented for their fourth and final visit. They filled out a brief questionnaire that asked them to guess during which 3-week period they had received the ephedrine capsules, were debriefed, and paid for their participation.

Measures

I used the BISF-W, a brief 22-item self-report inventory, to measure sexual desire, arousal, orgasm, and satisfaction. Test-retest reliability, concurrent validity, and the ability to discriminate between women with and without sexual complaints have been demonstrated for the BISF-W (for a review, see Meston & Derogatis, 2002). Recently, the BISF-W was shown to be sensitive to detecting treatment-induced changes on the overall composite score and two of seven BISF-W subscales (Shiffrin et al., 2000). The BISF-W asks questions about sexual functioning over the prior 1-month period. The BISF-W was adapted for the purposes of this study to ask questions about sexual functioning over the prior 1-week period.

I measured sexual desire using the following questions: "During the past week, how frequently have you had sexual thoughts, fantasies, or erotic dreams?" (0 = not at all to 4 = more than once a day), and "Using the scale to the right, indicate how frequently you have felt a desire to engage in the following activities during the past week (kissing, masturbation, petting and foreplay, vaginal penetration or intercourse [individually scored])?" (0 = not at all to 4 = more than once a day). Sexual arousability was assessed with the question, "Using the scale to the right, indicate how frequently you have become aroused by the following sexual experiences during the past week (kissing, masturbation, petting and foreplay, vaginal penetration or intercourse [individually scored])?" (0 = not at all to 4 = more than once a day). I measured lack of vaginal lubrication using the question, "During the past week, how frequently have you experienced a lack of vaginal lubrication?" (0 = not at all, 1 = seldom, less than 25% of the time, 2 = sometimes, about 50% of the time, 3 = usually, about 75% of the time, 4 = always). Orgasm

ability was measured with the question, "Using the scale to the right, indicate how often you have reached orgasm during the past week with the following activities (kissing, masturbation, petting and foreplay, vaginal penetration or intercourse [individually scored])?" (0 = have not engaged in this activity, 1 = not at all, 2 = seldom, less than 25% of the time, 3 = sometimes, about 50% of the time, 4 = usually, about 75% of the time, 5 = always reached orgasm). I added the following question regarding orgasm intensity/pleasure to the BISF-W; "This past week, how intense or pleasurable would you rate your orgasms as being?" (0 = I have not had an orgasm this week, 1 = not very intense or pleasurable to 3 = very intense and pleasurable). I measured sexual dissatisfaction using the BISF-W item: "Over the past week, how satisfied have you been with your sexual relationship with your partner?" (0 = very satisfied to 4 = very dissatisfied).

I calculated levels of sexual functioning during baseline, placebo, and ephedrine administration using mean responses to the above questions recorded on the two baseline, three placebo, and three ephedrine weekly modified BISF-W questionnaires, respectively. Participants who reported no sexual activity at baseline ($n = 3$) were excluded from the analyses comparing orgasmic ability between baseline and drug treatments.

The Beck Depression Inventory (Beck & Beamesderfer, 1974) was administered at each of the four visits to assess whether levels of depression fluctuated across the 8-week study and, if so, whether they might account for any potential changes in sexual functioning.

RESULTS

First, I conducted a doubly-multivariate ANOVA with sexual desire, arousal, lubrication, orgasmic ability, orgasm intensity, and sexual satisfaction as the dependent measures and assessment time (baseline, placebo, ephedrine) as the repeated measures variable. Results revealed an overall significant effect of time, $F(6,32) = 2.93$, $p = .02$ (F values reported here and throughout the results section are approximations from Roy's Largest Root). Next, follow-up multivariate repeated-measures ANOVAs were conducted separately for each of the dependent variables. There was a significant effect of assessment time (baseline, placebo, ephedrine) for sexual desire, $F(2, 17) = 7.41$, $p = .005$, arousal, $F(2, 17) = 6.13$, $p = .01$, and orgasm intensity/pleasure, $F(2, 17) = 7.34$, $p = .005$, and a trend toward significance for orgasmic ability, $F(2, 17) = 3.18$, $p = .07$.

Planned, follow-up simple contrasts were conducted between measures taken at baseline and placebo, baseline and ephedrine, and placebo and ephedrine conditions. Using Bonferonni correction for multiple comparisons, I considered only p values less than or equal to .01 significant ($p.05/3$). There were significant increases in sexual desire between baseline and placebo,

TABLE 2. Means and SEM of Reported Sexual Function by Experimental Condition

Questionnaire item	Baseline 1 (weeks 1–2)	Placebo (weeks 3–5)	Ephedrine (weeks 6–8)
1. Sexual desire	1.49 (.16)	1.95 (.18) ^a	1.79 (.18) ^a
2. Sexual arousability	.99 (.15)	1.37 (.18) ^a	1.21 (.18)
3. Lack of vaginal lubrication	1.34 (.29)	1.44 (.34)	1.36 (.29)
4. Orgasm ability	1.09 (.14)	1.39 (.14) ^a	1.29 (.19)
5. Orgasm intensity/pleasure	.89 (.18)	1.39 (.17) ^a	1.25 (.19) ^a
6. Sexual dissatisfaction	2.18 (.17)	1.86 (.20)	1.91 (.19)

Means are based on the following response format: Items 1 and 2, 0 = (not at all) to 4 = (more than once a day); items 3 and 4, 0 = (not at all) to 4 = (always); item 5, 0 = (did not attain orgasm) to 3 = (very intense and pleasurable); item 6, 0 = (very satisfied) to 4 = (very dissatisfied).

^aSignificantly different from Baseline at $p < .01$. Higher numeric values correspond to improvements in sexual function for sexual desire, sexual arousability, orgasm ability, and orgasm intensity/pleasure. Lower numeric values correspond to improvements in sexual function for lack of vaginal lubrication and sexual dissatisfaction. There are no significant differences between Placebo and Ephedrine conditions.

and baseline and ephedrine. Sexual arousal and orgasmic ability both significantly increased between baseline and placebo. Orgasm intensity/pleasure significantly increased between baseline and placebo and between baseline and ephedrine. There were no significant improvements beyond the placebo response with ephedrine for any of the sexuality variables. Means and SEMs of sexuality variables by experimental condition are reported in Table 2.

BDI scores did not significantly change across the four visits ($F < 1.0$). The mean BDI scores at study entry and completion were 15.38 and 15.75, respectively. Of the 11 women who completed the follow-up questionnaire at Visit 4, nine correctly guessed during which 3-week period they had received the ephedrine capsules. Reported side effects of ephedrine administration were insomnia (4 women), anxiety/irritability (4 women), decreased appetite (1 woman), racing heart (1 woman), and nausea (1 woman). Reported side effects of placebo were insomnia (1 woman) and anxiety (1 woman).

DISCUSSION

This study represents the first placebo-controlled examination of a peripherally acting vasoactive substance for treating SSRI-induced sexual dysfunction in women. Administration of 50 mg ephedrine approximately 1 hr prior to sexual activity was associated with significant improvements in sexual desire and orgasm intensity/pleasure. Significant improvements in these same measures, as well as improvements in sexual arousal and orgasmic ability were, however, also noted with placebo. A robust placebo response, such as that noted here, is often reported in studies assessing the effects

of agents or therapeutic interventions on sexual functioning. With regard to studies specifically examining the effects of pharmacological agents on SSRI-induced sexual dysfunction, a paucity of placebo-controlled trials have been published. Woodrum and Brown (1998) described the findings from studies on the pharmacological management of antidepressant-induced sexual dysfunction published between 1986 and 1998. Of the 21 studies retrieved using an extensive MEDLINE search, 20 claimed improvements in sexual functioning. These studies consisted of two open-label studies, twelve case series, and seven case reports; there were no controlled studies retrieved. Since 1998, to my knowledge, only four placebo-controlled studies have examined the effects of agents for counteracting antidepressant-associated sexual dysfunction in women. One of these reported no significant effect of either buspirone (20 mg/day) or amantadine (50 mg/day) beyond placebo (Michelson et al., 2000), one reported a marginally significant effect of buspirone (47 mg/day) beyond placebo (Landen et al., 1999), one reported no significant effect of mirtazapine (30 mg/day), yohimbine (10.8 mg/day), or olanzapine (5 mg/day) versus placebo (Michelson et al., 2002), and one reported no significant effect of bupropion (150 mg/day) versus placebo (Masand et al., 2001). Clearly, the findings noted above and the findings reported here highlight the importance of using placebo-controlled trials when examining the effects of pharmacological intervention on antidepressant-related sexual dysfunction.

The mechanisms by which placebos enhance treatment outcome effects have been discussed extensively elsewhere (Kirsch, 1997; Straus & von Ammon, 1996). Expectancies for improvement may have influenced participants' experiences of sexual responding once drug treatment began. Simply enrolling in a study of this nature, talking to a professional about one's sexual difficulties, and/or monitoring one's sexual responses may also have impacted aspects of participants' sexual function. Although it is possible that the improvements noted between baseline and treatment visits were simply due to the passage of time, this seems unlikely in the present study given that all participants were required to have received antidepressant treatment for a minimum of 10 weeks prior to enrolling in the study to help control for spontaneous remission of symptoms.

I hypothesized that ephedrine would serve as an effective antidote for antidepressant-induced sexual dysfunction based partly on the results of Meston and Heiman (1998), which showed a significant effect of 50 mg ephedrine on genital responses to erotic stimuli. Unlike the participants tested in this study, the women in Meston's and Heiman's study were sexually functional, were not receiving any medication, and reported no history of depression. These participant differences may account for the discrepant findings of ephedrine on sexual responding between studies. It should be noted, however, that although physiological responses were significantly facilitated in the Meston and Heiman study, there were no significant increases

reported in subjective perceptions of sexual arousal. The authors speculated that this may have been because of the contrived laboratory setting or the use of erotic films to induce sexual arousal. It cannot be determined from this data whether the women in this study experienced an increase in vaginal responses that did not impact their subjective perceptions of sexual responding, as was the case in Meston's and Heiman's study, or whether ephedrine did not facilitate vaginal responses in this study because of concurrent SSRI use.

The results of this study do not definitively rule out the possibility that enhancing peripheral SNS activity might help counteract SSRI-associated sexual difficulties. A number of women reported side effects of ephedrine such as insomnia and anxiety, which may have overshadowed any beneficial effects of ephedrine on sexual responding. In addition, most of the women questioned successfully guessed which 3-week arm they received ephedrine, which raises the possibility that the rather apparent drug effects may have comprised study blinding. The similarity of outcome results with placebo and ephedrine administration suggests, however, that this was not an important factor in this study.

In summary, these data suggest that ephedrine is no more effective than placebo in the treatment of SSRI-induced female sexual dysfunction and that nonspecific factors can contribute to substantial improvements in female sexual function. Additional placebo-controlled studies are needed to explore the effectiveness of other vasoactive substances for alleviating antidepressant-induced sexual dysfunction.

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