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The Effects of Yohimbine Plus L-arginine Glutamate on Sexual Arousal in Postmenopausal Women with Sexual Arousal Disorder[1]

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This study examined the effects of the nitric oxide-precursor L-arginine combined with the α_2-blocker yohimbine on subjective and physiological sexual arousal in postmenopausal women with Female Sexual Arousal Disorder. Twenty-four women participated in three treatment sessions in which self-report and physiological (vaginal photoplethysmograph) sexual responses to erotic stimuli were measured following treatment with either L-arginine glutamate (6 g) plus yohimbine HCl (6 mg), yohimbine alone (6 mg), or placebo, using a randomized, double-blind, three-way cross-over design. Sexual responses were measured at approximately 30, 60, and 90 min postdrug administration. The combined oral administration of L-arginine glutamate and yohimbine substantially increased vaginal pulse amplitude responses to the erotic film at 60 min postdrug administration compared with placebo. Subjective reports of sexual arousal were significantly increased with exposure to the erotic stimuli but did not differ significantly between treatment groups.

KEY WORDS: yohimbine; L-arginine; female sexual arousal; photoplethysmography; nitric oxide; adrenergic.

INTRODUCTION

Physiological sexual arousal in women involves an increase in pelvic vascular blood flow and resultant pelvic vasocongestion, vaginal engorgement, swelling of the external genitalia, and clitoral erection (Levin, 1992). Vaginal wall engorgement occurs with increased blood flow to the local vascular bed, enabling plasma transudation and subsequent lubrication of the epithelial surface of the vaginal wall (Levin, 1991; Schiavi & Segraves, 1995). Female Sexual Arousal Disorder (FSAD) is defined in the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV*; American Psychiatric Association, 2000) as the "persistent or recurrent inability to attain, or to maintain until completion of the sexual activity, an adequate lubrication-swelling response of sexual excitement" which causes "marked distress or interpersonal difficulty."

Prevalence estimates of FSAD vary widely between studies, likely due to different operational definitions of the disorder. A recent random survey of over 1,600 female respondents, ages 18–59 years, found that approximately 19% of women reported difficulties with lubrication (Laumann, Gagnon, Michael, & Michaels, 1994). Reported risk factors included health and lifestyle factors (e.g., history of STD, poor health, emotional problems), social status, and sexual experience (e.g., low sexual frequency, history of sexual abuse; Laumann, Paik, & Rosen, 1999). The incidence of FSAD is higher among women of peri or postmenopausal years: One study reported 44% of postmenopausal women experience persistent or recurrent lubrication problems (Rosen, Taylor, Leiblum, & Bachmann, 1993). Studies that have used more stringent diagnostic criteria report lower rates. For example, Lindal and Stefansson (1993) reported a lifetime prevalence of 6% in a large random population sample and Fugl-Meyer and Sjogren Fugl-Meyer (1999) reported a 1-year prevalence of 8% in a large Swedish sample. Both of these studies used the earlier *DSM-III* criteria, which did

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not include "marked distress or interpersonal difficulty" (*DSM-IV* criteria) as part of the diagnostic requirements. To our knowledge, there are no prevalence statistics for FSAD based strictly on *DSM-IV* diagnostic criteria.

Female sexual arousal disorder is a clinical diagnosis that rarely presents alone. In fact, several theorists have suggested that the majority of female sexual difficulties reflect disruptions in sexual arousal. Orgasm is impossible without arousal and a lack of arousal commonly leads to a lack of desire simply because sexual activity is not enjoyable or reinforcing. Even sexual pain disorders may be intricately linked to a lack of sufficient sexual arousal. Intercourse without lubrication can be painful, and repeated intercourse without arousal may cause vulvar infections, chronic irritation, and may even lead to secondary vaginismus, fear of sex, or the avoidance of sexual activity altogether (for review, see Everaerd & Laan, 2000).

Most commonly, the treatment of FSAD involves administering topical lubricants (e.g., K-Y Jelly, Astroglide), vitamin E, or mineral oils that help to mask the impairment in vaginal lubrication associated with FSAD. These treatments are, however, ineffective in enhancing genital/clitoral blood flow or in alleviating the decrease in genital sensations that often accompanies FSAD. In postmenopausal women, estrogen creams, tablets, or rings are sometimes recommended to alleviate vasomotor symptoms and vaginal atrophy. The impact of testosterone administration on sexual arousal is unclear. Supraphysiologic doses of testosterone have been shown to increase sexual arousal more than placebo or estrogen alone in surgically menopausal women (Sherwin, Gelfand, & Brender, 1985). However, recently, in a study of 75 surgically menopausal women treated with estrogen, neither 50 μg or 300 μg of testosterone/day transdermally for 12 weeks showed a significant improvement in sexual arousal beyond placebo (Shiffrin et al., 2000). In a group of women with androgen insufficiency and sexual dysfunction, 50 mg/day of dehydroepiandrosterone (DHEA; a precursor for testosterone) was shown to significantly improve ratings of sexual arousal and lubrication (Munarriz et al., 2001). However, among sexually functional, premenopausal women, 300 mg DHEA had no significant effect on vaginal pulse amplitude (VPA; a measure of moment to moment changes in vasocongestion) or subjective sexual arousal responses to erotic stimuli at 30 min postdrug administration compared to placebo (Meston & Heiman, 2002). In a comparable study among postmenopausal women, 300 mg DHEA also had no significant effect on VPA responses when measured 60 min postdrug administration, but significantly increased self-reported sexual arousal (Hackbert, Heiman, & Meston, 1998). To our knowledge, no studies have examined the effects of DHEA on women specifically diagnosed with FSAD. A device called EROS, which consists of a small suction cup that fits over the clitoral region, was recently approved by the Food and Drug Administration (FDA) as a treatment for FSAD. Studies report its success in drawing blood into the genital tissue, but anecdotal reports indicate that some women find the external aid decreases sexual spontaneity.

To date, there are no FDA-approved pharmacological agents for the treatment of FSAD. Sildenafil (Viagra) has been highly effective in alleviating erectile dysfunction resulting from organic, psychogenic, and mixed causes (Derry et al., 1998; Dinsmore et al., 1999; Giuliano et al., 1999; Goldstein et al., 1998; Marks, Duda, Dorey, Macairan, & Santos, 1999; Montorsi et al., 1999; Padma-Nathan, Steers, & Wicker, 1998) and might also be effective for treating FSAD. Sildenafil acts on nitric oxide (NO) systems by prolonging the action of cGMP (thus inhibiting the metabolism of cGMP by cyclic nucleotide phosphodiesterase isozymes [PDE_5]; Boolell et al., 1996). In men, sexual stimulation leads to the production of NO and the subsequent release of guanylate cyclase. Guanylate cyclase converts guanosine triphosphate to cyclic guanosine monophosphate (cGMP) and cGMP produces relaxation of the smooth muscles of the penile arteries and corpus cavernosum, resulting in increased blood flow into the penis (Burnett, 1995, 1997). Recent evidence suggests that this may also occur in the clitoris. Immunohistochemical evaluation of the human clitoris revealed that NO is produced in this tissue (Burnett, Calvin, Silver, Peppas, & Docimo, 1997) and, with the exception that the clitoris does not contain a subalbugineal layer (which contributes to the rigidity of the penis), the clitoris may be considered the homologue of the male penis (Toesca, Stolfi, & Cocchia, 1996). Arterial blood inflow is delivered via the clitoral cavernosal arteries and is regulated by helicine arteriolar smooth muscle tone (Park, Moreland, Goldstein, Anthony, & Traish, 1998). Thus, impaired smooth muscle function may adversely impact the process of clitoral erection and vaginal engorgement and lubrication.

Some studies have found Sildenafil reverses antidepressant-induced sexual dysfunction in women (e.g., Ashton, 1999; Ashton & Bennett, 1999; Nurnberg, Hensley, Lauriello, Parker, & Keith, 1999). However, the lack of a placebo control in these studies severely limits the interpretation of findings. Preliminary results from a double-blind, placebo controlled study showed a significant increase in VPA with a single dose of Sildenafil (50 mg) among 12 sexually functional women. Subjective reports of sexual arousal were not, however, significantly altered with Sildenafil in this study (Laan, van Lunsen, Everaerd, Heiman, & Hackbert, 2000).

Since the presence of adrenergic nerves has been demonstrated in cavernosal and helicine arteries as well as in the cavernosal smooth muscle of human penile tissue (Andersson & Wagner, 1995), it is not unreasonable to assume that the modulation of adrenergic activity may also impact the contractile state of the clitoral cavernosal and vaginal tissue. Adrenergic systems are active in women as they become sexually aroused. Vanillylmandelic acid, an epinephrine and norepinephrine metabolite, increases prior to intercourse and remains elevated over baseline up to 23 hr following sexual activity (Ende, Gertner, Hwang, & Kadi, 1989). Sympathetic nervous system activity, indexed by plasma norepinephrine, increases during sexual arousal in women, reaches a peak during orgasm, and returns to baseline levels following orgasm (Exton et al., 1999; Wiedeking, Ziegler, & Lake, 1979).

Findings from recent controlled studies corroborate these laboratory observations. Ephedrine, an α- and β-adrenergic agonist, significantly increases VPA responses to erotic stimuli compared to placebo (Meston & Heiman, 1998). Clonidine, an antihypertensive medication that acts as a selective α_2-adrenergic agonist and blocks sympathetic nervous system activation, suppresses receptive and proceptive behaviors and increases rejection behaviors in female rats (Meston, Moe, & Gorzalka, 1996). In women, clonidine significantly diminished VPA responses to erotic stimuli compared to placebo under conditions of heightened nervous system arousal (Meston, Gorzalka, & Wright, 1997). Exercise, at a level shown to increase adrenergic activity, increased VPA responses in women (Meston & Gorzalka, 1995; 1996). Yohimbine, an alkaloid that has a mechanism of action opposite to that of clonidine (it selectively blocks α_2-adrenergic receptors pre- and postsynaptically), is clinically more effective than placebo for treating erectile dysfunction (for review, see Tam, Worcel, & Wyllie, 2001). To our knowledge, there have been no controlled studies on the effects of yohimbine on sexual arousal in women.

Evidence suggests that combining drugs that inhibit adrenergic-mediated vasoconstriction with drugs that act as vasodilators to induce direct smooth muscle relaxation may be a highly effective means for treating erectile dysfunction (Govier et al., 1993; Saenz de Tejada et al., 1999). The present study examined the efficacy of L-arginine, a nonessential amino acid and natural precursor of NO, combined with yohimbine, a selective α_2-adrenergic blocker, on physiological and subjective measures of sexual arousal in postmenopausal women with FSAD. It has been shown that blockade of presynaptic α_2-adrenergic receptors by yohimbine enhances NO release from penile nonadrenergic noncholinergic (NANC) nerves (Simonsen, Prieto, Hernandez, de Tejada, & Garcia-Sacristan, 1997) and that NO donors enhance the erectile effects of yohimbine (Saenz de Tejada et al., 1999). Recently, Lebret, Herve, Barre, Lugagne, and Botto (2000) demonstrated a significant facilitatory effect of combined L-arginine and yohimbine on the erectile responses of patients with mild to moderate erectile dysfunction. Given the evidence that both NO and adrenergic systems may also be important in facilitating sexual arousal in women, it was hypothesized that the simultaneous administration of L-arginine and yohimbine would have a synergistic facilitatory effect on vaginal vasodilation. We chose to examine the effects of this drug combination among postmenopausal women because of the high incidence of FSAD noted in this population and because FSAD in older women is often associated with clitoral or vascular insufficiency (Goldstein & Berman, 1998).

METHOD

Participants

Participants were recruited via advertisements placed in the local newspapers and on local radio stations which called for volunteers to take part in a study aimed at developing new methods of treatment for postmenopausal women who are experiencing sexual arousal difficulties. Women who inquired about the study were informed of the purpose of the study, the procedures involved, the potential risks, and were told they would be paid $100 for their participation. Those interested in participating were asked a series of questions to determine whether or not they met the initial selection criteria: at least 21 years of age; postmenopausal (absence of menstruation for at least 6 months); experiencing difficulty attaining or maintaining lubrication during sexual activity for at least the past 6 months; not using antidepressants, clonidine or alpha blockers; absence of any medical disorder known to affect sexual functioning; and absence of participation in another study with an investigational drug or device during the prior 30 days.

Women who met the initial screening criteria were then interviewed by a trained Master's level clinical psychologist to assess whether or not they met the *DSM-IV* criteria for Acquired, Generalized, FSAD. Women who reported difficulty attaining or maintaining lubrication during all sexual situations for at least the past 6 months, who had been previously sexually functional or experienced sexual arousal at some point in the past, who were distressed by their sexual arousal difficulties, and whose difficulties with arousal were not due specifically to a substance, medical disorder, other Axis I disorder, or exclusively to dyspareunia, were invited to participate

in the study. Thirty-seven women (approximately one in 10 women who inquired about the study) met these selection criteria and were scheduled for Visit 1.

Visit 1 was conducted at a local women's medical facility. After signing the standard consent form, participants completed a detailed medical history questionnaire and the Brief Index of Sexual Functioning in Women (BISF-W; Taylor, Rosen, & Leiblum, 1994), and underwent the following assessments: complete physical examination, pelvic examination including Pap smear, standard 12-lead ECG, clinical laboratory measurements including serum chemistry (glucose, sodium, potassium, chloride, blood urea nitrogen, creatinine, uric acid, phosphorus, calcium, cholesterol, triglycerides, protein, albumin, globulin, alkaline phosphatase, gamma glutamyl transferase, total bilirubin, lactate dehydrogenase, amylase, leutinizing hormone, follicle stimulating hormone, estradiol, beta human chorionic gonadotropin), hematology (white blood cell count with differential, red blood cell count, hemoglobin, hematocrit, platelet count), urinalysis (pH, specific gravity, ketones, protein, glucose, bilirubin, blood, leukocytes, WBC count, RBC count, microscopic examination of urine), and vital sign measurements (height, weight, respiration, standing and supine blood pressure and pulse). Further exclusion criteria based on laboratory tests were: untreated endocrine disease, history of chronic urinary or pelvic infection, significant vaginal atrophy, dyspareunia not due to vaginal dryness, cervical dysplasia, or significant cervicitis; symptomatic coronary disease or recent myocardial infarction; systolic hypertension; bleeding disorders or sickle cell anemia; and any abnormal test result that may place the woman at risk.

Based on Visit 1 results, 12 women were excluded from the study. Twenty-five women met all the selection criteria and were randomized by an outside source (Target Health, Inc.) for further study participation. Nineteen of these women were naturally postmenopausal; six were surgically menopausal. Twelve women were on hormone replacement therapy. One woman discontinued after Visit 2. The mean age of the remaining 24 participants was 53.7 years (range 27–69 years). Ethnic breakdown of the sample was: Caucasian (88%), Hispanic (4%), African American (4%), and Asian (4%). Mean weight was 155.8 lbs and mean height was 62.8 in. The data from one participant were excluded from all psychophysiological analyses due to technical difficulties that occurred during one of the psychophysiological test sessions that may have rendered the results unreliable.

Mean ($\pm SD$) participant BISF-W dimension scores (based on the revised BISF-W scoring procedure detailed in Mazer, Leiblum, & Rosen, 2000) for thoughts/desire, frequency of sexual activity, receptivity/initiation, and pleasure/orgasm were: 5.02 (2.5), 3.18 (1.4), 8.20 (3.6), 4.01 (1.8), respectively. These scores are within 1 *SD* of the means reported for healthy women with sexual partners (Mazer et al., 2000).

Design and Procedure

Visit 2 occurred within 2 weeks of Visit 1 (medical screening visit) and was conducted at the Female Sexual Psychophysiology Laboratory at the University of Texas at Austin. During this visit, vital sign measurements were taken and any medications taken by the participant since Visit 1 were recorded. The participant was then seated and instructed in the use of the vaginal photoplethysmograph. Vaginal photoplethysmograph recordings of VPA were taken continuously while the participant viewed a 3-min neutral film (i.e., travel film) followed immediately by a 5-min erotic film. Before the neutral video and after the erotic video, the participant was asked to complete self-report rating scales about her perceptions of sexual arousal and affect. The participant then received a double-blind oral dose of test medication.

Approximately 27 min after drug administration the participant viewed a new 3-min neutral video followed immediately by a new 5-min erotic video while plethysmograph monitoring of VPA resumed. Prior to viewing the neutral film and at the completion of the erotic film the participant again completed the self-report questionnaires. The same sequence of photoplethysmograph monitoring of VPA during the viewing of a neutral and then an erotic videotape with administration of questionnaires before and after the videos was repeated at 57 min and at 87 min. Following the completion of the last video, vital signs were reassessed. The participant was observed for up to 2 hr and then discharged from the clinic.

Visits 3 and 4 occurred at 5–14 day intervals and were also conducted at the Female Sexual Psychophysiology Laboratory. During these visits, the participant was crossed over to her randomized alternate treatments. The events at these visits were identical to those at Visit 2, except that upon completion of the last visit, an exit ECG was conducted and clinical laboratory samples were collected at the women's medical facility. The erotic films used in this study depicted heterosexual couples engaging in foreplay and intercourse and were matched on sexual content. The film clips were selected from erotic films produced specifically for women (Femme Productions, Inc.) and included segments of kissing, caressing, intercourse male superior position, intercourse female superior position, oral sex female to male, and oral sex male to female. The order in which the erotic films were viewed was counterbalanced across participants. All procedures used in this

study were approved of by the University of Texas Internal Review Board.

Drug Treatments Administered

Yohimbine Hydrochloride and L-Arginine Glutamate. A sachet containing 6 g of L-arginine glutamate was dissolved in a half glass of water and three 2 mg tablets of yohimbine HCl (total 6 mg) were ingested with water. L-arginine glutamate was commercially purchased in France, where it is sold by Novartis Pharma under the brand name Dynamisan®. Yohimbine hydrochloride was purchased commercially in France, where it is sold by Laboratoires Hoechst Houdé under the name Yohimbine Houdé®.

Yohimbine Hydrochloride Only. A sachet containing L-arginine glutamate placebo that was dissolved in a half glass of water and three 2 mg tablets of yohimbine (total 6 mg) were taken with water.

Placebo. A sachet containing L-arginine glutamate placebo that was dissolved in a half glass of water and three yohimbine placebo tablets were ingested with water. The L-arginine placebo sachets and the yohimbine placebo tablets were manufactured to match the active treatments by LCO, France. All participants received a single dose of each of the three drug combinations on three separate visits.

Data Sampling and Reduction

Physiological Measurements. A vaginal photoplethysmograph (Sintchak & Geer, 1975) was used to measure VPA responses. VPA was sampled at a rate of 60 samples/s throughout the entire 180 s of neutral film and 300 s of erotic film, band-pass filtered (0.5–30 Hz), and recorded on a Del Pentium computer using the software program AcqKnowledge III, Version 3.2 (BIOPAC Systems, Inc., Santa Barbara, CA) and a Model MP100WS data acquisition unit (BIOPAC Systems, Inc.) for analog/digital conversion. In accordance with previous studies of this nature (Laan, Everaerd, & Evers, 1995), artifacts caused by movement or contractions of the pelvic muscles were deleted using the computer software program following visual inspection of the data.

Vaginal pulse amplitude scores were computed for both the neutral and erotic films by averaging across the entire 3 min of the neutral and 5 min of the erotic film stimulus at each of the three test periods postdrug administration (approximately 30, 60, 90 min) as well as the predrug baseline for each of the experimental conditions (placebo, yohimbine, yohimbine plus L-arginine). Difference scores were then computed for each test period and experimental condition by subtracting the average VPA score during the neutral film from the average VPA score during the erotic film. This yielded 12 VPA difference scores (three experimental conditions × four test periods).

Subjective Measurements. A self-report rating scale, adapted from Heiman and Rowland (1983), was used to assess subjective measures of physical sexual arousal ("warmth in genitals," "genital wetness or lubrication," "genital engorgement (fullness)," "genital pulsing and throbbing," "any genital feelings"), mental sexual arousal ("sexually aroused," "sexually turned off"), autonomic arousal ("faster breathing," "faster heart beat"), anxiety ("anxious"), positive affect ("pleasure," "interested," "excited") and negative affect ("disgusted," "bored"). Immediately following presentation of the erotic films, participants rated each of these items on a 7-point Likert scale, from *not at all* (1) to *intensely* (7). Mean composite scores for physical sexual arousal, mental sexual arousal, autonomic arousal, anxiety, positive affect, and negative affect were calculated for each test period and experimental condition. This yielded 12 scores for each of the six domains (four test periods: predrug baseline, 30 min, 60 min, 90 min × three experimental conditions: placebo, yohimbine, yohimbine plus L-arginine). Also, prior to viewing the neutral films, participants rated their level of sexual arousal on a 7-point Likert scale, from *not at all* (1) to *intensely* (7).

Baseline participant characteristics including demographics, baseline medications, vital signs, and concurrent illnesses were recorded and summarized. Medical history, physical assessments, clinical laboratory evaluations, and ECG assessments recorded at baseline were displayed as normal or abnormal by individual participants and then summarized. The incidence of study-emergent adverse events was tabulated by treatment, event, and body system. The incidence rates of adverse events with each treatment were compared using Pearson's chi-square test or Fisher's Exact test. Statistical analyses were performed using SAS Version 6.12 (Cary, NC).

RESULTS

Vaginal Pulse Amplitude

A significant increase in average VPA during the erotic videos, relative to the average response during the neutral videos, was observed during each of the treatment conditions. This suggests that the erotic films were effective in facilitating physiological sexual arousal among this group of women. Postdrug administration difference

scores were analyzed for treatment differences after correcting for the predrug baseline and test period (30, 60, 90 min) using a repeated measures analysis of covariance (ANCOVA). In order to account for outcomes being measured at three different visits, a term for visit (2 *df*) was included in the model. A term for sequence (5 *df*) was included to account for the subject being randomized to one of six treatment sequences. In order to account for the repeated measures design, a term for the individual subject nested within sequence (17 *df*) was included in the model. Results revealed an overall significant difference in VPA difference scores between treatment conditions, $F(2, 176) = 3.18$, $p = .04$. Two interaction terms, time postdrug by treatment and visit by treatment, were originally fit into the model. These interaction terms were dropped from the final model since no statistical significance was found.

In addition to the overall analysis, separate ANCOVAs were performed for each of the three postdrug test periods. A series of *t* tests using LSMEANS to examine pairwise differences were made within the framework of ANOVA. *p* values $\leq .05$ were considered statistically significant. A difference that approached significance was noted between treatment groups at 60 min postdrug, $F(2, 41) = 2.85$, $p = .07$. No significant differences were noted between treatment groups at either 30 min, $F(2, 40) = 0.91$, $p = .41$, or 90 min, $F(2, 40) = 0.27$, $p = .77$, postdrug administration. At 60 min postdrug administration, there was a statistically significant difference between the yohimbine plus L-arginine versus placebo conditions ($p = .02$, based on least-square adjusted means from the ANCOVA model).

Pairwise comparisons of VPA difference scores between placebo and experimental conditions, collapsed across the three test periods postdrug administration, were conducted within the framework of the ANCOVA model. Results revealed a significantly higher mean VPA change during the yohimbine plus L-arginine glutamate (2.6 ± 3.73 μV) versus placebo (1.6 ± 3.11 μV) conditions, $t(176) = 2.52$, $p = .01$. There were no significant differences between the mean VPA change (collapsed across the three postdrug administration periods) between yohimbine alone (2.1 ± 2.68 μV) and placebo, $t(176) = 1.25$, $p = .21$, or between the yohimbine and yohimbine plus L-arginine conditions, $t(176) = 1.30$, $p = .19$. Effect sizes for the difference between pairs of treatments in standard deviation units were calculated using adjusted means from the repeated measures ANCOVA model. The effect sizes for yohimbine plus L-arginine glutamate versus placebo, yohimbine versus placebo, and yohimbine plus L-arginine glutamate versus yohimbine were 0.44, 0.21, 0.23, respectively.

Table 1. Mean Vaginal Pulse Amplitude Difference Scores ($\pm SD$s) at 30, 60, and 90 min Postdrug Administration

	Placebo ($N = 23$)	Yohimbine ($N = 23$)	Yohimbine plus L-arginine ($N = 23$)
30 min	1.70 (3.6)	2.54 (2.7)	2.50 (3.9)
60 min[a]	1.03 (2.1)	1.56 (2.6)	2.66 (3.1)
90 min	2.00 (3.5)	2.12 (2.6)	2.61 (4.3)

Note. Units are in microvolts ($V \times 10^{-6}$).
[a] Yohimbine plus L-arginine versus placebo comparison statistically significant ($p < .05$).

The effects of L-arginine glutamate plus yohimbine and of yohimbine alone appeared to occur as early as 30 min. In the L-arginine glutamate plus yohimbine-treated participants, mean ($\pm SD$) VPA increased from a predrug value of 0.5 ± 9.4 μV to 2.5 ± 3.9 μV 30 min after dosing. In the yohimbine-treated participants, mean VPA increased from a predrug value of 1.7 ± 2.5 μV to 2.5 ± 2.9 μV 30 min postdrug administration. Sixty minutes after dosing, the response in participants treated with L-arginine glutamate plus yohimbine peaked at 2.7 ± 3.1 μV. Adjusting for the predrug difference, this response was significantly greater than that observed in participants treated with placebo (1.0 ± 2.07 μV), $t(41) = 2.34$, $p = .02$. At no time point measured did yohimbine alone result in a change in VPA that was significantly greater than that seen in the placebo condition (see Table 1 for VPA means and *SD*s by experimental condition).

Because previous studies have shown that VPA levels often do not return to baseline levels between sequential measurement periods (e.g., Laan et al., 1995), a repeated measures ANCOVA was used to test for differences in VPA scores during the neutral films across the four test periods (predrug, 30 post, 60 post, and 90 post). Terms included in the model were: Time (3 *df*), Treatment (2 *df*), Visit Number (2 *df*), Sequence (5 *df*), and Subject was nested within sequence (17 *df*). The time effect for average VPA during the neutral films was not statistically significant, $F(3, 245) = 0.08$, $p = .97$. This suggests that VPA levels had returned to baseline between the test periods. Mean ($\pm SD$) VPA responses (μV) during the neutral film presentations were: 5.89 (5.8), 5.89 (3.8), 6.12 (4.0), 5.87 (3.6), during the predrug, and 30, 60, 90 min postdrug test periods, respectively.

Subjective Ratings

To examine whether the erotic films increased self-reported levels of sexual arousal, a repeated measures ANCOVA was conducted on subjective ratings of sexual

Table II. Mean ($\pm SD$) Subjective Ratings to Erotic Stimuli During the Predrug Baseline and Averaged Across the Three Postdrug Test Periods (30, 60, 90 min) for Each Experimental Condition

	Placebo ($N = 24$)			Yohimbine ($N = 24$)			Yohimbine plus L-arginine ($N = 24$)		
Domain	Predrug	Postdrug	Diff[a]	Predrug	Postdrug	Diff[a]	Predrug	Postdrug	Diff[a]
Physical sexual arousal									
M	2.1	3.0	0.9	2.2	3.1	0.9	2.0	2.9	0.9
SD	1.40	1.77		1.18	1.46		1.50	1.82	
Mental sexual arousal									
M	4.4	5.0	0.6	4.6	4.9	0.3	4.5	4.9	0.4
SD	0.94	0.94		0.65	0.95		0.85	1.12	
Anxiety									
M	0.9	0.9	0.0	1.1	1.0	−0.1	1.1	1.0	−0.1
SD	1.14	1.52		1.44	1.20		1.18	1.52	
Autonomic arousal									
M	1.6	2.2	0.6	1.4	2.0	0.6	1.4	2.1	0.7
SD	1.26	1.68		1.26	1.43		1.37	1.73	
Positive affect									
M	2.4	3.1	0.7	2.4	3.2	0.8	2.3	3.0	0.7
SD	1.14	1.80		1.26	1.49		1.32	1.79	
Negative affect									
M	0.6	0.4	−0.2	0.7	0.5	−0.2	0.8	0.4	−0.4
SD	0.96	0.79		0.92	0.82		1.15	0.67	

Note. Means are based on an item response format of 0 (*not at all*) to 7 (*intensely*).

[a]Differences refer to the mean postdrug domain score averaged across 30, 60, 90 min test periods minus the mean predrug baseline domain score. There were no significant differences between experimental conditions for any of the composite difference scores.

arousal between the preneutral and posterotic films. In these models, the sexual arousal rating score was the outcome variable. Terms included in the model were: Film (1 *df*), to account for preneutral/posterotic differences; Time (2 *df*), to account for outcome being measured at three postdrug time points (30, 60, and 90 min); Drug (2 *df*), to account for the three treatments; Visit Number (2 *df*), to account for the outcome being measured at three different visits; Sequence (5 *df*), to account for the subject being randomized to one of six treatment sequences; and Subject nested within sequence (18 *df*), in order to account for the repeated measurements. Results indicated an overall significant difference in sexual arousal ratings between the preneutral and posterotic films, $F(1, 399) = 503.97$, $p < .001$. Mean ($\pm SD$) ratings of self-reported sexual arousal during the preneutral and posterotic assessments were 0.94 (1.26) and 3.38 (1.66) respectively. These results suggest that the erotic films used were effective in enhancing participants' subjective experience of sexual arousal.

For each subjective domain (physical sexual arousal, mental sexual arousal, autonomic arousal, anxiety, positive affect, negative affect), a repeated measures analysis of covariance (ANCOVA) was used to assess treatment differences after adjusting for the predrug domain score and time postdrug. Terms included in the model were: Visit Number (2 *df*), Sequence (5 *df*), and Subject nested within sequence (18 *df*). The overall among group treatment difference was not statistically significant for any of the domains: Physical Sexual Arousal, $F(2, 184) = 0.39$, $p = .68$, Mental Sexual Arousal, $F(2, 184) = 0.38$, $p = .69$, Anxiety, $F(2, 184) = 0.32$, $p = .73$, Autonomic Arousal, $F(2, 184) = 0.20$, $p = .82$; Positive Affect, $F(2, 184) = 0.58$, $p = .56$; Negative Affect, $F(2, 184) = 0.83$, $p = .44$. None of the pairwise comparisons between treatments were statistically significant for any of the domains ($p < .05$). Table II summarizes the differences in subjective responses (organized by domain) from pre- to posttreatment during the viewing of erotic videos. Two interaction terms, postdrug time by treatment and visit by treatment, were originally fit into the model. No statistically significant interactions were found and these interaction terms were removed from the final model.

DISCUSSION

Based on previous research which suggests that both NO and adrenergic systems play a role in female sexual arousal, this study was the first to examine the effects of a natural precursor of NO (L-arginine) combined with a selective α_2-adrenergic blocker (yohimbine) on

physiological and subjective measures of sexual arousal in postmenopausal women with FSAD. This drug combination facilitated VPA responses compared with placebo at 60 min postdrug administration and showed a nonsignificant facilitatory effect at 30 and 90 min postdrug administration. There were no acute adverse events associated with either of the active medications. The fact that VPA responses were maximally increased at 60 min postdrug administration is consistent with the pharmacokinetic profile of the L-arginine plus yohimbine combination (Worcel, 2000). When administered to humans orally, both L-arginine and yohimbine are rapidly and simultaneously absorbed and attain maximal plasma concentration at approximately 40 min postdrug administration.

The finding of a significant facilitation of L-arginine plus yohimbine on vaginal vasocongestion is consistent with recent findings in males that showed this same drug combination facilitated erectile responding (Lebret, Herve, Barre, Lugagne, & Botto, 2000). Using a randomized, double-blind, placebo-controlled, 3-way crossover design comparable to that used here, Lebret et al., demonstrated that the combination of 6 g of L-arginine and 6 mg of yohimbine hydrochloride (taken orally 1–2 hr prior to intercourse) significantly improved erectile function in participants with mild to moderate erectile dysfunction. Measured using color duplex ultrasonography, Padma-Nathan (2000) reported an increase in penile arterial diameters among males with mild to moderate erectile dysfunction at 60 min postadministration of this same drug combination. Like that noted in this study, there were no adverse events reported with the combined administration of L-arginine and yohimbine in males (Lebret et al., 2000; Padma-Nathan, 2000).

Yohimbine alone did not significantly increase VPA responses at any of the test periods. Although it has been suggested that an L-arginine supplement might enhance genital blood flow in men, the few studies that have been conducted to date do not confirm this assertion (Chen et al., 1999; Klotz, Mathers, Braun, Bloch, & Engelmann, 1999; Zorgniotti & Lizza, 1994), although to a large extent these studies have been poorly designed, inadequately powered, and have employed nonvalidated efficacy measures. Although speculative, this suggests that the facilitation of genital blood flow noted in the current study was due to the combined efforts of NO and adrenergic systems. As noted earlier, α adrenergic receptor antagonists have been shown to potentiate the effects of other vasodilator drugs (e.g., papavarine) on genital responding in men, and we speculate that it is a similar mechanism of action working here to facilitate genital arousal in women.

Despite increases in physiological measures of sexual arousal, the L-arginine glutamate/yohimbine combination had no significant impact on subjective measures of sexual arousal. That is, like sildenafil (Laan et al., 2000), ephedrine (Meston & Heiman, 1998), and clonidine (Meston et al., 1997), this drug combination facilitated VPA responses but did not enhance the women's experience of sexual arousal. Possibly, the contrived nature of the laboratory settings used in this and comparable studies limited the degree to which women could "feel" sexually aroused. Alternatively, or in addition, it may be the case that women estimate their degree of sexual arousal according to standards other than genital cues. For women, external stimulus information such as relationship satisfaction, mood state, and sexual scenarios may play a more important role in assessing feelings of sexual arousal than do internal physiological cues (for a review of these issues, see Meston, 2000). If this is the case, drugs that target increasing vasocongestion are likely to be most effective in women whose primary complaint is decreased genital response, experienced as decreases in lubrication, or feelings of not achieving vaginal fullness or engorgement. These symptoms are most likely to occur in women who are postmenopausal, who have undergone oophorectomy, or who suffer from arterial vascular problems. For some women, if the drug increases vaginal engorgement to the extent that it is detected and labeled as a "sexual feeling," this may also enhance their feelings of more general, psychological arousal. However, women who experience FSAD secondary to an overall decrease in sexual desire, or describe their lack of arousal primarily in psychological rather than physiological terms, may benefit more from psychological intervention (possibly combined with vasodilator drug treatment) or from drugs currently under investigation that focus on activation of more central brain mechanisms.

In conclusion, the results of this study suggest that administering a drug that inhibits adrenergic-mediated vasoconstriction (yohimbine) with a drug that acts as a vasodilator to induce direct smooth muscle relaxation (L-arginine) may be a safe and effective means for enhancing genital vasocongestion in postmenopausal women diagnosed with FSAD. Before implications for treatment are suggested, follow-up studies are required to assess whether administering this drug combination in a more realistic, at-home setting might also impact a woman's cognitive experience of feeling sexually aroused.

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