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SAFETY AND EFFICACY OF SILDENAFIL CITRATE FOR THE TREATMENT OF FEMALE SEXUAL AROUSAL DISORDER: A DOUBLE-BLIND, PLACEBO CONTROLLED STUDY

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ABSTRACT

Purpose: We evaluated the efficacy and safety of sildenafil citrate in spontaneously or surgically postmenopausal women with female sexual arousal disorder (FSAD).

Materials and Methods: Sildenafil (a 50 mg dose adjustable to 100 or 25 mg) was evaluated in a 12-week, double-blind, placebo controlled study in 202 postmenopausal women with FSAD who had protocol specified estradiol and free testosterone concentrations, and/or were receiving estrogen and/or androgen replacement therapy. Patients were excluded if emotional, relationship or historical abuse issues contributed significantly to sexual dysfunction. Primary end points were questions 2 (increased genital sensation during intercourse or stimulation) and 4 (increased satisfaction with intercourse and/or foreplay) from the Female Intervention Efficacy Index (FIEI). Secondary end points were the remaining questions from this index, the Sexual Function Questionnaire and sexual activity event log questions.

Results: Significant improvements in FIEI questions 2 ($p = 0.017$) and 4 ($p = 0.015$) were noted with sildenafil compared with placebo. For women with FSAD without concomitant hypoactive sexual desire disorder (HSDD) sildenafil was associated with significantly greater improvement in 5 of 6 FIEI items compared with placebo ($p < 0.02$). No significant improvements were shown for women with concomitant HSDD. Most adverse events were mild to moderate with headache, flushing, rhinitis, nausea and visual symptoms reported most frequently.

Conclusions: Sildenafil was effective and well tolerated in postmenopausal women with FSAD without concomitant HSDD or contributory emotional, relationship or historical abuse issues. All patients had protocol specified estradiol and free testosterone concentrations or were receiving estrogen and/or androgen replacement therapy.

KEY WORDS: female; sexual dysfunctions, psychological; hormone replacement therapy; postmenopause; phosphodiesterase inhibitors

The American Foundation of Urological Diseases defines female sexual arousal disorder (FSAD) as "a persistent or recurring inability to attain or maintain sufficient sexual excitement that causes personal distress," which may be experienced as a lack of subjective excitement, genital lubrication/swelling, genital sensation or other somatic responses.[1] FSAD may occur independently of or concurrently with other distinct female sexual disorders, such as hypoactive sexual desire disorder (HSDD), female orgasmic disorder and/or dyspareunia.[1] Although psychosocial factors clearly contribute to the disorder, medical and physiological factors, including reduced vaginal/clitoral blood flow, altered hormonal environment, prior pelvic surgery (for example hysterectomy), vaginal injury from childbirth or use of certain medications, may be the primary basis for the disorder.[2]

Increased clitoral and vaginal vasocongestion during sexual arousal is believed to be mediated by the nitric oxide–cyclic guanosine monophosphate pathway. Findings of nitric oxide synthase in human clitoral tissue[3] and phosphodiesterase 5 (PDE5), the enzyme responsible for cyclic guanosine monophosphate catabolism, in human clitoral[4] and vaginal tissue[5,6] support this theory. Sildenafil citrate, a potent and selective inhibitor of PDE5,[7] causes relaxation of female rabbit clitoral and vaginal smooth muscle strips,[5] and inhibits PDE5 in human clitoral and vaginal smooth muscle.[4,5] Enhanced genital blood flow and vaginal and clitoral engorgement in women with FSAD have been demonstrated with sildenafil.[8] Together these findings suggest that sildenafil may be efficacious for treating FSAD of physiological origin.

Estrogen[9] and testosterone[10] promote nitric oxide synthase expression in human and animal genital tissue. Thus, physiological levels of testosterone and estradiol may potentiate the response to PDE5 inhibitors in women with FSAD. We determined the efficacy and safety of sildenafil in women with FSAD who were postmenopausal or who had undergone hysterectomy and had free testosterone (0.9 pg/ml or greater) and estradiol (40 pg/ml or greater) corresponding to normal values for premenopausal women.[11,12]

METHODS

This randomized, double-blind, placebo controlled study was performed between February 2000 and March 2001 at 31

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centers in the United States. Eligible patients were identified from a population of spontaneously or surgically postmenopausal women with complaints of sexual dysfunction who were recruited from investigator clinical practices or through advertisements. Key inclusion criteria were a minimum age of 18 years, postmenopausal condition or previous hysterectomy with or without oophorectomy and a primary complaint of FSAD at least 6 months in duration. Patients were required to have plasma concentrations of free testosterone 0.9 pg/ml or greater, or be receiving androgen replacement therapy and estradiol 40 pg/ml or greater. If postmenopausal, a minimum of 3 months of stable dosing with conventional hormone replacement therapy (HRT), that is estrogen or estrogen plus progesterone delivered orally or transdermally, was required. The choice of HRT was at the discretion of each patient and the primary physician. HRT was not required for patients who had undergone hysterectomy if protocol specified hormone levels were met. Additional requirements included a stable sexual relationship for at least 6 months and a history of satisfactory sexual function. Secondary diagnoses of female orgasmic disorder, HSDD or superficial/introital dyspareunia due to vaginal dryness were allowed. However, patients were excluded if sexual dysfunction was associated with primary anorgasmia, largely situational or due primarily to any other major psychological or sexual disorder.

Women who had emotional, relationship or historical abuse issues that contributed significantly to sexual dysfunction as determined during the 60-minute semistructured Sexual History Interview (SHI) performed by a qualified sex therapist or psychologist were also excluded from study. SHI was developed in conjunction with sex therapists to standardize sexual dysfunction diagnoses across multiple study sites and assess the relative contribution of potentially confounding psychosexual issues to dysfunction. Other exclusion criteria were significant dyspareunia not due to vaginal dryness; untreated or poorly controlled diabetes, thyroid dysfunction or hyperprolactinemia; major hematological, renal or hepatic abnormalities; major psychiatric disorder; significant cardiovascular disease; previous sildenafil use or current use of nitrates.

Study protocol. The study consisted of a 4-week treatment-free phase followed by a 12-week double-blind treatment phase. During the treatment-free phase baseline sexual function data were collected using patient recorded event logs and the Sexual Function Questionnaire (SFQ).[13] Blood samples were collected for determination of estradiol and free testosterone plasma concentrations at the first visit. Patients who met hormone eligibility requirements attended a second screening visit, during which the SHI was performed. Medical clearance and expert confirmation of FSAD as the most significant aspect of patient sexual dysfunction were required for randomization. Randomization of patients to treatment groups was done by the method of random permuted blocks. Each randomized patient received a bottle of 50 mg sildenafil or matching placebo tablets. Study medication was to be taken approximately 1 hour before sexual activity but not more than once daily. The patient dose could be adjusted to 100 or 25 mg once during the study.

Standard laboratory tests were performed throughout the study. Physical examinations, including gynecologic examination and cervical cytology smear, were done at screening and the end of treatment (that is double-blind phase completion or time of discontinuation). Patients completed the SFQ at baseline and at the study end, and the Female Intervention Efficacy Index (FIEI)[14] at the study end. They maintained an event log in which they recorded information on dosing and sexual activity. Patients were expected to engage in sexual activity (that is any activity that may result in sexual stimulation or sexual pleasure, for example intercourse, caressing, foreplay, masturbation and/or oral sex) an average of once weekly. Adverse events were recorded by the investigators. All patients provided written informed consent.

Evaluation of efficacy. Primary efficacy end points were FIEI questions 2 (increased sensation/feeling in the genital area during intercourse or stimulation) and 4 (increased satisfaction with intercourse and/or foreplay). Secondary efficacy end points included the remaining items from this index, SFQ and the sexual activity event log. Results on individual FIEI questions were tabulated for each treatment group. All items were dichotomized with option a—an increase/enhancement considered the positive outcome and all other options considered negative. The exception was question 3, for which option d—other, please describe was treated as missing, resulting in a decrease in the number of respondents. Most SFQ questions were scored on a scale from 1 to 5. In all cases a higher score represented a more positive response. Responses of not applicable were entered as missing. Efficacy was also assessed for the 7 SFQ domains, including sexual desire (questions 1 to 4, 13 and 26 with a score range of 5 to 31), arousal-sensation (questions 7 to 10 with a score range of 4 to 20), arousal-lubrication (questions 11 and 12 with a score range of 2 to 10), orgasm (questions 22 to 24 with a score range of 3 to 15), pain (questions 15, 16 and 20 with a score range of 2 to 15), partner (questions 30 and 31 with a score range of 2 to 10) and enjoyment (questions 6, 16, 20, 21, 23 and 27 with a score range of 6 to 30). From patient recorded event logs the percent and frequency of successful intercourse attempts; the number of times patients experienced sufficient lubrication, physical sexual arousal or emotional sexual arousal; and the number of satisfactory attempts at orgasm/climax were determined.

Statistical analysis. A 132 patient sample size was estimated to be sufficient to provide 80% power to detect a 25% difference in response rates for the primary end points (FIEI questions 2 and 4) between the placebo (estimated to be 25%) and active treatment (estimated to be 50%) groups. To allow for 20% of patients not completing FIEI and/or not receiving treatment after randomization a minimum sample size of 166 was deemed necessary. Intent to treat analyses were performed on data on all randomized patients who completed efficacy assessments after receiving at least 1 dose of study medication. The last observation carried forward algorithm was applied to patients discontinuing after the baseline period. Derived FIEI binary variables (improvement or no improvement) were analyzed by logistic regression to determine the OR and 95% CI for sildenafil compared with placebo. The 95% CI for the observed percent improved was calculated using a normal approximation for binomial data. Mean scores for each item and domain of the SFQ were calculated for each treatment group and analyzed using ANCOVA for normally distributed data. Standard statistical methods were used to verify the assumption of normality of the residuals from the ANCOVA model. The significance of each covariate was assessed using the F tests and type 3 sums of squares. The significance of treatment (sildenafil and placebo) was also assessed using the F test. Frequency and proportion data from event logs were analyzed using the Mann-Whitney U test. Assessment of the treatment effect in each parametric analysis was adjusted for baseline (SFQ as appropriate for the item analyzed), age, body mass index, FSAD duration, dyspareunia (yes/no), female orgasm disorder (yes/no), hypertension (yes/no), hysterectomy (yes/no), smoking classification (never smoked/ex-smoker/current smoker) and HSDD (yes/no with this covariate not included in HSDD subgroup analyses). All statistical tests and 95% CIs were 2-sided. Software (SAS Institute, Cary, North Carolina) was used to perform statistical analyses.

RESULTS

Of the women who were screened but not randomized 82% had low estradiol and/or free testosterone plasma concentra-

tions, and/or were not receiving hormone therapy (fig. 1). Of the randomized patients 83% reported at least 1 other sexual function disorder in addition to primary FSAD, and 89% and 70% were receiving estrogen and androgen replacement therapy, respectively. Although an oral combination of esterified estrogens and methyltestosterone was most common, other estrogen and androgen formulations were also used (table 1).

Effects on sexual function. A significantly greater percent of patients reported improvement for FIEI questions 2 (assessing genital sensation/feeling, $p = 0.017$) and 4 (satisfaction with intercourse/foreplay, $p = 0.015$) with sildenafil compared with placebo treatment (table 2). Statistical analysis of covariates identified a priori indicated a highly significant interaction between treatment and HSDD status for these primary end points (likelihood ratio chi-square $p < 0.001$ and 0.007, respectively). A highly significant interaction between treatment and HSDD was also found for the other FIEI questions (likelihood ratio chi-square $p < 0.05$) and for 12 items of the SFQ (F test $p < 0.05$).

Due to the consistent presence of this interaction subgroup analyses of efficacy by the presence/absence of HSDD were performed. In women with FSAD and concomitant HSDD no significant differences from placebo were found for sildenafil treatment for any efficacy parameter analyzed. However, for women without HSDD sildenafil treatment was associated with a significantly greater percent of patients reporting improvement on FIEI primary end point questions (table 2) and for 3 of the remaining 4 questions from this index. Adjusted ORs were 4.14 (95% CI 1.23 to 13.97, $p = 0.015$) for vaginal lubrication, 3.50 (95% CI 0.86 to 14.20, $p = 0.069$) for a pleasant and satisfying change in genital sensation, 4.33 (95% CI 1.30 to 14.45, $p = 0.012$) for ability to achieve orgasm and 10.99 (95% CI 2.70 to 44.76, $p = 0.0001$) for overall sexual experience compared with placebo.

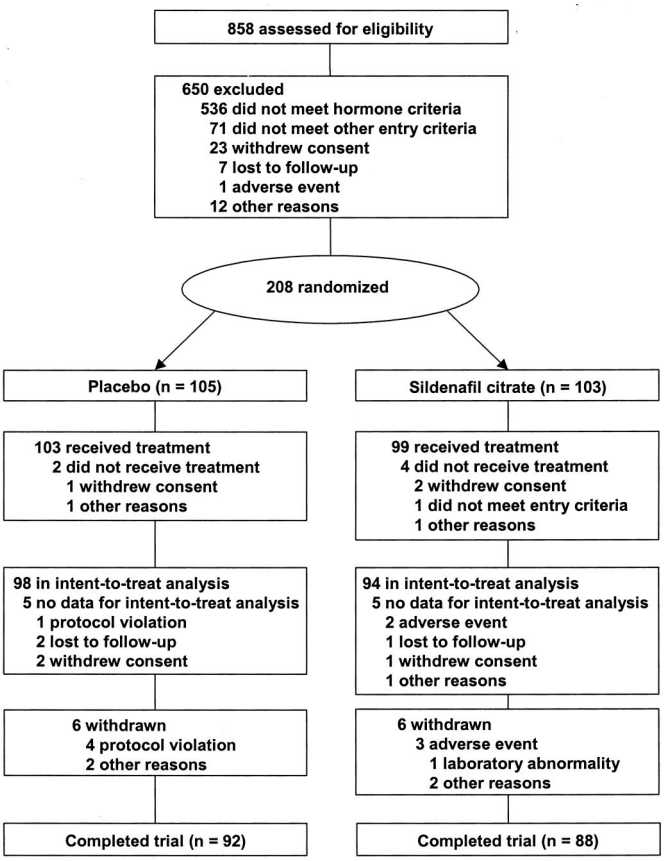

FIG. 1. Number of patients included in or excluded from randomization and subsequent analyses.

TABLE 1. *Patient characteristics*

Characteristic	Placebo	Sildenafil
No. pts	103	99
Mean age (range)	51 (34–71)	50 (30–68)
Mean kg/m^2 body mass index (range)	27.2 (18.7–51.1)	27.2 (19.2–44.0)
No. race or ethnic group:		
White	96	92
Black	5	6
Hispanic	2	0
Other	0	1
Mean yrs FSAD (range)	6.8 (0.51–24.7)	6.6 (0.56–32.8)
No. concurrent HSDD	57	55
No. concurrent female orgasmic disorder	56	56
No. concurrent dyspareunia	26	24
No. postmenopausal	26	26
No. previous hysterectomy	77	73
No. female sex hormone use (%)*	91 (88)	88 (89)
No. male sex hormone use (%)†	69 (67)	73 (74)

* Esterified estrogen in 65% of patients, estradiol in 22%, conjugated estrogen in 17%, conjugated estrogen/medroxyprogesterone in 5%, progesterone in 22% and other in 4%, including estrone, unspecified estrogen, estriol, norethisterone and phytoestrogen.

† Methyltestosterone in 82% of patients, dehydroepiandrosterone in 12% and other in 8%, including testosterone cream, gel or injection.

TABLE 2. *Patients reporting improvement on FIEI questions 2 and 4**

Treatment	No. Pts	Observed No. Improved (%)†	Adjusted OR	95% CI	p Value
		Question 2			
Overall:					0.017
Placebo	98	43 (44)			
Sildenafil	94	54 (57)	2.14	1.14–4.03	
No HSDD:					0.0004
Placebo	44	18 (41)			
Sildenafil	42	29 (69)	7.98	2.22–28.64	
HSDD:					0.84
Placebo	54	25 (46)			
Sildenafil	52	25 (48)	1.09	0.47–2.54	
		Question 4			
Overall:					0.015
Placebo	98	27 (28)			
Sildenafil	94	39 (42)	2.24	1.16–4.32	
No HSDD:					0.0001
Placebo	44	9 (20)			
Sildenafil	42	21 (50)	10.95	2.84–42.20	
HSDD:					0.77
Placebo	54	18 (33)			
Sildenafil	52	18 (35)	1.14	0.47–2.78	

* FIEI question 2 is, "After taking study medication, the sensation/feeling in my genital (vagina, labia, clitoris) area during intercourse or stimulation (foreplay) seemed to be: (a) more than before, (b) less than before, or (c) unchanged" and question 4 is, "After taking the study medication, intercourse and/or foreplay was: (a) pleasant and satisfying; better than before taking the study medication, (b) unpleasant; worse than before the study medication, (c) unchanged; no difference, or (d) pleasant; but still not like it used to be or I would like it to be."

† Defined as patient answer of a to FIEI questions with not improving defined as any other response.

Significantly higher mean scores were recorded for SFQ questions pertaining to satisfaction with overall sexual life, sexual arousal (warmth, sensation and wetness during sexual activity), enjoyment of penetrative sexual activity orgasm, sexual confidence and less disappointment with sexual response for patients with no concurrent HSDD receiving sildenafil vs placebo ($p < 0.02$). Significant improvements in 3 SFQ domains (arousal-sensation, arousal-lubrication and orgasm) were also noted with sildenafil treatment in women with no concurrent HSDD (fig. 2). Although mean changes from baseline scores were large for some SFQ domains, no significant differences from placebo were found for women with concurrent HSDD for individual questions or domains of the SFQ. Consistent with the clinical diagnosis of HSDD, baseline scores for the desire domain were substantially

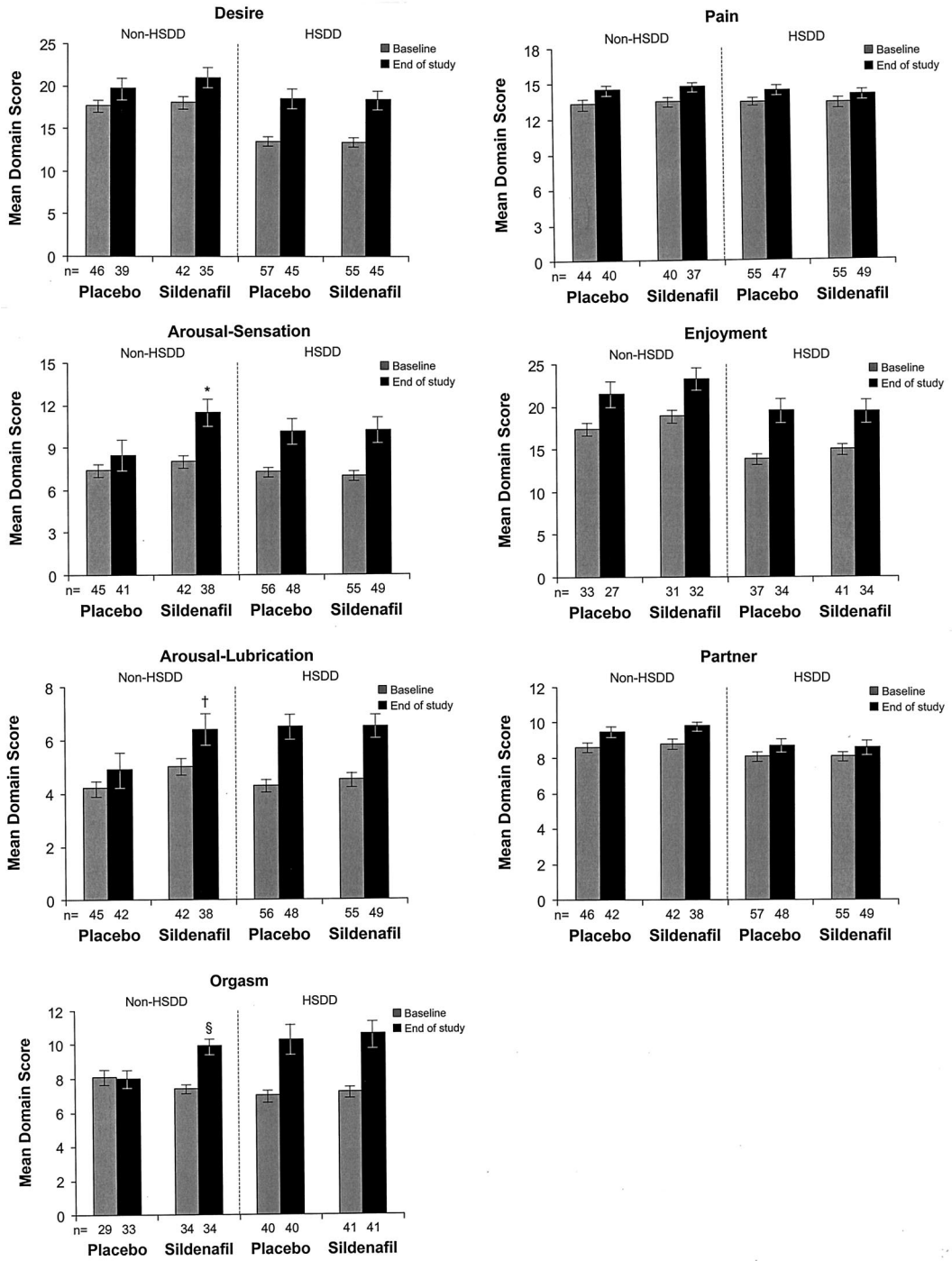

FIG. 2. Mean scores ± SE for 7 SFQ domains for women with or without concomitant HSDD receiving sildenafil or placebo at baseline and study end, including sexual desire (4 questions with possible total score of 5 to 31), arousal-sensation (3 questions with possible total score of 4 to 20), arousal-lubrication (2 questions with possible total score of 2 to 10), orgasm (3 questions with possible total score of 3 to 15), pain (3 questions with possible total score of 2 to 15), enjoyment (6 questions with possible total score of 6 to 30) and partner (2 questions with possible total score of 2 to 10). Women providing responses to all domain questions at baseline or study end, that is end of treatment or time of discontinuation, were included in analysis of that domain. Not applicable responses were treated as missing. Asterisk indicates $p < 0.001$ vs placebo. Dagger indicates $p = 0.003$ vs placebo. Double s indicates $p = 0.01$ vs placebo.

lower for women with concurrent HSDD than for those without this disorder.

A greater proportion of sexual intercourse episodes considered successful during the last 4 weeks of treatment were reported in sexual event logs of women without HSDD receiving sildenafil, although the difference between the placebo and sildenafil groups was not significant (60% and 74%, respectively, $p = 0.07$). Of the remaining event log questions only sufficient vaginal wetness/lubrication was significantly greater with sildenafil treatment (64% and 82%, respectively, $p = 0.03$). Mean responses for feelings of emotional and physical sexual arousal were slightly higher for patients receiving sildenafil. However, the differences between treatment groups were not significant.

Adverse events and treatment discontinuation. Most adverse events were generally mild to moderate in severity and resolved spontaneously. Headache, flushing, rhinitis, nausea and abnormal vision were reported most frequently in the sildenafil treated group (table 3). No treatment related serious adverse events were reported during the study. Four

TABLE 3. *Adverse events*

	No. Placebo (%)	No. Sildenafil (%)
Overall	103	99
Adverse events	52 (50)	70 (71)
Most common adverse events in more than 5% of any treatment group:		
Headache	7 (7)	29 (29)
Flushing	5 (5)	20 (20)
Rhinitis	3 (3)	13 (13)
Nausea	1 (1)	6 (6)
Abnormal vision*	0	5 (5)
Limiting adverse events:	0	6 (6)
Treatment related	0	4 (4)
Not treatment related†	0	2 (2)

* Changes in brightness perception and blurry vision.
† Vaginitis in 1 patient and a laboratory abnormality of elevated serum glutamate pyruvate transaminase in 1.

patients discontinued sildenafil due to treatment related adverse events, including headache in 1, rhinitis in 1, anxiety reaction in 1, and fatigue, headache, nausea, dizziness, rhinitis and paresthesia in 1.

DISCUSSION

In the current study postmenopausal women diagnosed with a primary complaint of FSAD reported substantial positive effects on sexual function. Although sexual function improved with placebo treatment, significantly more women reported improvement with sildenafil treatment. However, there were no significant positive effects of sildenafil treatment on sexual function in the subgroup of women who had associated HSDD.

The occurrence of a strong placebo response in the current study is similar to that reported in previous trials in women with sexual dysfunction.[15,16] Entry criteria and study requirements probably resulted in the selection of women who were highly motivated to improve sexual function. Study participation may have further encouraged increased communication and sexual interest, contributing to the large placebo response.

Significant improvements in arousal, orgasm and frequency, and enjoyment of sexual intercourse were previously reported in a double-blind, placebo controlled study evaluating sildenafil in premenopausal women with FSAD without HSDD.[17] In contrast, no significant improvement in sexual arousal was found in a randomized trial of sildenafil in a more heterogeneous population of postmenopausal women with FSAD, including only 46% with a primary diagnosis of FSAD, who were receiving estrogen but not androgen therapy.[15] These findings suggest that adequate testosterone may be necessary for subjective improvement in sexual function and response with sildenafil treatment. However, a recent study in ovariectomized rabbits showed that sildenafil caused a significant increase in genital hemodynamics irrespective of hormonal status.[18] Studies have demonstrated that testosterone has a significant role in female sexual arousal, genital sensation orgasm and libido.[16,19,20] However, determinations of normative testosterone values for women throughout the life cycle and appropriate therapeutic doses are still evolving,[16]

Because medical/physiological factors and psychological/emotional factors may contribute to the development of sexual dysfunction, use of a combined medical and psychosexual evaluation for women seeking treatment for sexual dysfunction, as in the current study, may result in more efficient identification of potential causes and selection of appropriate treatment. In particular, unresolved emotional or relational issues should be addressed before beginning medical therapies. Further research is needed to develop effective psychosexual diagnostic tools for application by general practitioners. In conclusion, sildenafil treatment was associated with significant improvements in sexual arousal, orgasm, intercourse and overall satisfaction with sexual life in postmenopausal women with FSAD without concurrent HSDD who had protocol specified estradiol and free testosterone concentrations or were receiving estrogen and/or androgen replacement therapy.

Dr. Mitradev Boolell reviewed the manuscript. Dr. Janet Matsuura assisted with manuscript preparation. The study drug was provided by Pfizer, Inc.

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