

Sildenafil Treatment of Women With Antidepressant-Associated Sexual Dysfunction

A Randomized Controlled Trial

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TREATMENT-EMERGENT SEXUAL dysfunction is a frequent adverse effect occurring with medication use and is a major influence for premature discontinuation of antidepressant treatment, which leads to treatment failure and costly disease management outcomes. Sexual dysfunction is recognized as being associated with selective and nonselective serotonin reuptake inhibitor (SRI) antidepressants, which are the most frequently prescribed medications for outpatients aged 18 to 65 years and represent 90% of the 180 million antidepressant prescriptions filled in the United States.¹

Antidepressant treatment-associated sexual dysfunction is estimated to occur in 30% to 70% of men and women treated for major depression with first- or second-generation agents,² a principal reason for a 3-fold increased risk of nonadherence that approaches 70% in the first months of treatment and leads to increased relapse, recurrence, disability, and resource utilization by affected patients.³ However, the literature in this field is less developed for women with more highly variable prevalence rates and less conclusive data compared with

Context Antidepressant-associated sexual dysfunction is a common adverse effect that frequently results in premature medication treatment discontinuation and for which no treatment has demonstrated efficacy in women.

Objective To evaluate the efficacy of sildenafil for sexual dysfunction associated with selective and nonselective serotonin reuptake inhibitors (SRIs) in women.

Design, Setting, and Participants An 8-week prospective, parallel-group, randomized, double-blind, placebo-controlled clinical trial conducted between September 1, 2003, and January 1, 2007, at 7 US research centers that included 98 previously sexually functioning, premenopausal women (mean [SD] age 37.1 [6] years) whose major depression was remitted by SRIs but who were also experiencing sexual dysfunction.

Intervention Forty-nine patients were randomly assigned to take sildenafil or placebo at a flexible dose starting at 50 mg adjustable to 100 mg before sexual activity.

Main Outcome Measures The primary outcome measure was the mean difference in change from baseline to study end (ie, lower ordinal score) on the Clinical Global Impression sexual function scale. Secondary measures included the Female Sexual Function Questionnaire, the Arizona Sexual Experience scale-female version, the University of New Mexico Sexual Function Inventory-female version, a sexual activity event log, and the Hamilton Depression Rating scale. Hormone levels were also assessed.

Results In an intention-to-treat analysis, women treated with sildenafil had a mean Clinical Global Impression–sexual function score of 1.9 (95% confidence interval [CI], 1.6-2.3) compared with those taking placebo (1.1; 95% CI, 0.8-1.5), with a mean end point difference of 0.8 (95% CI, 0.6-1.0; $P = .001$). Assigning baseline values carried forward to the 22% of patients who prematurely discontinued resulted in a mean end point in the sexual function score of 1.5 (95% CI, 1.1-1.9) among women taking sildenafil compared with 0.9 (95% CI, 0.6-1.3) among women taking placebo with a mean end point difference of 0.6 (95% CI, 0.3-0.8; $P = .03$). Baseline endocrine levels were within normal limits and did not differ between groups. The mean (SD) Hamilton scores for depression remained consistent with remission in both groups (4.0 [3.6]; $P = .90$). Headache, flushing, and dyspepsia were reported frequently during treatment, but no patients withdrew because of serious adverse effects.

Conclusion In this study population, sildenafil treatment of sexual dysfunction in women taking SRIs was associated with a reduction in adverse sexual effects.

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men. In women, sexual dysfunction is associated with decreased sexual interest, genital sensitivity, and vaginal lubrication; delayed or absent orgasm; dyspareunia; reduced sexual activity; and overall dissatisfaction or loss of pleasure in sexual relations.

Among the numerous strategies proposed for managing sexual dysfunction associated with SRI treatment, selective phosphodiesterase type 5 inhibitors, which have been limited to studies involving men, have demonstrated the best evidence-based data to support broad-based and clinically meaningful treatment efficacy.⁴ However, to our knowledge, no randomized controlled trial (RCT) has demonstrated effectiveness for women experiencing sexual dysfunction associated with SRI treatment. Compared with men, women are prescribed antidepressants at rates of 2 to 1 and can be expected to represent a significant number of patients needing relief.⁵ Without evidence-based data to treat sexual function associated with SRIs in women, clinicians may lack the confidence to manage it effectively, which leaves patients exposed to excess random pharmacology.⁶

Although sexual dysfunction is a major influence in determining the selection or switching of antidepressants, it is frequently overlooked because clinicians fail to inquire, misattribute it as a symptom of depression that will improve with treatment, or because 80% of women do not discuss adverse sexual effects with their physician.^{7,8} Sexual dysfunction associated with SRIs is dose related, usually occurs early in treatment, and rarely remits spontaneously.

Selective phosphodiesterase type 5 inhibitors (sildenafil, vardenafil, tadalafil), which are effective and well tolerated for treatment of erectile dysfunction in men,⁹ including men with depression¹⁰ and associated with SRI treatment,¹¹ are not approved by the US Food and Drug Administration (FDA) for women with sexual dysfunction. However, interest in their potential use in women was encouraged by reports that nitric oxide synthase isoforms, nitric oxide, and phosphodiesterase type

5 inhibitors are present in female genital tissue, and phosphodiesterase type 5 inhibitor enhancement of nitric oxide-cyclic guanosine monophosphate in nonadrenergic-noncholinergic signaling for women seems similar to men.¹² When several trials involving premenopausal and postmenopausal women treated with sildenafil failed to demonstrate significant improvements for sexual arousal disorder,¹³ the manufacturer abandoned pursuit of FDA approval for treating women.

Subsequent RCTs narrowed their focus on more specific hormonal factors and demonstrated efficacy with improved frequency of sexual intercourse, arousal, orgasm, and satisfaction. One trial involved premenopausal women with sexual arousal disorder but with normal sexual desire. They were randomized to receive 1 of 3 treatments: 25 mg or 50 mg of sildenafil or placebo.¹⁴ A protocol-specified trial involved premenopausal or postmenopausal women with sexual arousal disorder without concomitant hypoactive sexual desire disorder. Women with low baseline estrogen and androgen levels received therapy, so their hormone levels would be within the range of normal therapy and were randomly assigned to receive either a flexible dose of between 25 mg and 100 mg of sildenafil or placebo.¹⁵ In a third trial, postmenopausal women receiving estrogen hormone therapy and who had acquired sexual arousal disorder and impaired orgasm found that a single dose of 50 mg of sildenafil compared with placebo reduced orgasm latency and increased subjective arousal in those having the lowest vaginal pulse amplitude percentage change.¹⁶ In a fourth trial involving asymptomatic premenopausal women, a sildenafil-placebo crossover reported increased arousal and orgasm function.¹⁷ Case reports¹⁸ and open-label studies¹⁹ have also suggested efficacy for phosphodiesterase type 5 inhibitor treatment of women with sexual dysfunction associated with SRI treatment.

The objective of our current trial was to use a protocol—similar to our previous RCT¹¹ involving men with sexual

dysfunction associated with SRI treatment—to assess the efficacy of sildenafil in the treatment of women, specifically women whose major depressive disorder is in remission while taking a stable dose of SRI antidepressants and who did not have a preexisting sexual dysfunction but due to the treatment had sexual dysfunction manifest as dysfunction of orgasm (delay) or arousal (lubrication).⁵ Recognizing the importance of the hormonal variability on nitric oxide signaling in sexual function in women²⁰ and depression on hypothalamic-pituitary-adrenal axis regulation,²¹ we also examined endocrine measures. The following were our specific aims: (1) to compare the efficacy of sildenafil with placebo for treatment of sexual dysfunction associated with SRI treatment in women with remitted major depressive disorder; (2) to determine whether sildenafil treatment is associated with change in depression severity; and (3) to compare adverse events occurring with sildenafil and placebo treatment.

METHODS

Trial Design

This prospective, parallel group, randomized, double-blind, placebo-controlled, 8-week trial to test the efficacy of a flexible dose of between 50 mg and 100 mg of sildenafil for sexual dysfunction in women was conducted from September 2003 to January 2007, at 7 US outpatient clinic medical centers. Each center's institutional review board approved the protocol. Before enrollment, each woman provided written informed consent to the investigator, who had explained the nature, purpose, and risks of the trial and who provided her with a copy of the information sheets. The study received an investigational new drug approvable letter from the FDA. Participants did not receive financial compensation.

Patients

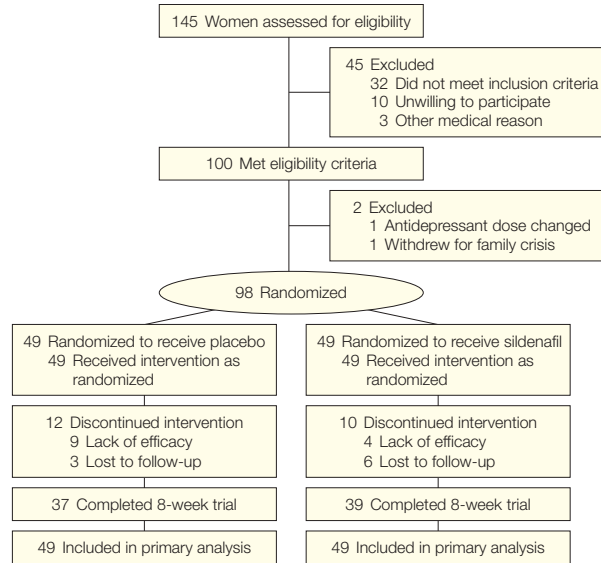
Women were eligible if they (1) were between 18 and 50 years, (2) were premenopausal, (3) had a diagnosis of major depressive disorder in remission, (4) were taking an antidepressant with a se-

lective or nonselective SRI mechanism for at least 8 weeks (at a stable dose for at least 4 weeks), and (5) were experiencing persistent sexual dysfunction for at least 4 weeks. Other eligibility criteria were good health, some form of regular sexual activity (ie, masturbation, oral sex, intercourse) at least twice monthly before the antidepressant treatment, willingness to continue efforts at sexual activity at least once weekly for the duration of the study, and satisfactory sexual function before onset of depression or antidepressant treatment. In addition, any prior sexual dysfunction must have been limited to previous episodes of depression or antidepressant treatment and must have remitted on clinical improvement and discontinuation of medication.

Major depressive disorder in remission was diagnosed according to *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) (*DSM-IV*) criteria.²² Women had to score no more than 10 points on the Hamilton Rating Scale for Depression, which consists of 17 items that are clinician rated on a 5-point scale from 0 (absent) to 4 (severe).²³ The remission threshold score of 10, rather than 7, was selected to adjust for sexual dysfunction associated with SRI treatment potentially inflating the score.²⁴ In addition, women had to score no more than 10 on the Hamilton Rating Scale for Anxiety, indicating absence of significant symptomatic anxiety.²⁵

Sexual dysfunction associated with SRI antidepressant treatment is defined by *DSM-IV* criteria for substance-induced sexual dysfunction,²² which includes impaired desire, arousal (lubrication), and orgasm and sexual pain. Women had to have substantial impaired sexual function defined by at least 1 of the following criteria that caused significant distress: (1) inability to have an orgasm (anorgasmia), according to the woman's opinion; (2) clinically significant orgasm delay with masturbation or intercourse that, according to the woman's opinion, represents a meaningful delay compared with her usual time to achieve orgasm in response to sexual stimulation before antidepressant

Figure. Flow of Patients Through the Trial



medication interfered with her sexual function; or (3) inability to attain or maintain until completion of sexual activity an adequate lubrication or swelling response of sexual excitement that, according to the woman's opinion, interferes with her sexual function (compared with before taking antidepressant medication).

Women were excluded for any of the following reasons: diagnosis of a sexual disorder other than one associated with SRI treatment or onset of major depressive disorder, genital anatomical deformity, hysterectomy with or without oophorectomy, and at least 6 months of established normal sexual function after the procedure and before onset of depression and antidepressant treatment, uncontrolled psychiatric disorder, diabetes mellitus, cardiovascular disease, alcohol or substance abuse or dependence, stroke, unstable cardiac condition, arrhythmia, or myocardial infarction within the last 6 months, current or anticipated use of nitrate or nitric oxide donor in any form, major relationship changes, proliferative retinopathy, investigational drug use within 3 months, current use of other therapies or medications to treat sexual dysfunction, a sexual partner who has or is receiving treatment for sexual dys-

function, or change in SRI antidepressant agent or prescribed dose during the study. Additional exclusion criteria were use of hormone therapy; pregnancy; lactation; planning to become pregnant during the trial; of child-bearing potential and unwilling, unprepared, or judged unreliable to use an acceptable and verifiable form of contraception during the trial; Papanicolaou test results indicating further assessment; dyspareunia due to anatomical, inflammatory, infection condition, or clinical estrogen deficiency; amenorrhea over 1 year; or situational sexual dysfunction.

Study Protocol

Women were recruited and enrolled from outpatient settings, newspaper advertisements, postings, and referrals. One hundred forty-five patients were assessed for eligibility at screening (FIGURE). In addition to an assessment of medical history with detailed sexual history and recording of last menstrual period, all patients received a physical examination including blood pressure, 12-lead electrocardiogram, standard biochemistry and hematological laboratory tests, and pelvic examination with Papanicolaou test

(unless documented within the last 12 months). Blood samples for determination of plasma concentrations of free testosterone, thyroid-stimulating hormone, tetraiodothyronine thyroxin, follicle-stimulating hormone, luteinizing hormone, cortisol, progesterone, estradiol, sex hormone-binding globulin, total testosterone, and prolactin were collected at the first and eighth week before 11 AM on days 1 to 10 of the menstrual period.

Using SPSS version 10 (SPSS Inc, Chicago, Illinois), an unrestricted, computer-generated randomization schedule was developed by the study statistician (S.P.) and given to the independent pharmacy. The randomization assigned 49 patients to receive active sildenafil and 49 to receive identical placebo. The only restriction to this randomization was that the groups be of equal size. The largest difference in numbers assigned to the 2 groups at any point in the trial was 4 (excludes completions). At baseline, patients were allocated to the next available number that randomly assigned them to receive sildenafil or matching placebo (50-mg starting dose). Medications were sealed in sequentially numbered identical containers according to allocation sequence, and all study personnel and participants were blinded to treatment assignment for the duration of the study. Patients were instructed to take 1 tablet of trial medication approximately 1 to 2 hours before anticipated sexual activity, not more than once daily over the 8-week trial period and were required to make at least 1 attempt but were asked to try to make at least 2 attempts at sexual activity per week. The dose of study drug could be adjusted from 1 (50 mg) to 2 (100 mg) tablets based on investigator judgment of efficacy and tolerability, including the recording of the findings that resulted in any study drug dosage change and adverse events. Patients were given diaries with instructions for recording trial medication use and sexual activity. Sildenafil and placebo were provided by Pfizer Inc, New York, New York.

Drug accountability, concomitant antidepressant treatment, vital signs, and

self-rated and physician-rated symptom reports were assessed at each visit (weeks 2, 4, and 8), which included diary review and return of unused medication. A urine pregnancy test was administered to all women of childbearing potential at each visit. Investigators monitored, collected, and followed up on any spontaneous reports of adverse events, and they assessed and categorized the severity of the events and their relationship to the study drug throughout the trial.

Outcome Measures

Efficacy was assessed using 4 validated measurements. The primary efficacy outcome measure was the difference between the 2 treatment groups in end point mean improvement scores (ie, lower ordinal score) on the Clinical Global Impression Scale adapted for sexual function.²⁶ Secondary outcome measures were baseline to end point mean scores on the Sexual Function Questionnaire,²⁷ the Arizona Sexual Experience scale—female version,²⁸ and the University of New Mexico Sexual Function Inventory—female version.²⁹ Patient-recorded event logs were reviewed for the frequency and percentage of successful intercourse attempts, the number of satisfactory attempts at orgasm or climax, and used to corroborate ratings. Participants were seen at baseline and at weeks 2, 4, and 8 (or last visit) for assessments that included measures of change from baseline to weeks 2, 4, and 8 (or last visit).

The Clinical Global Impression scale is a clinician-rated severity improvement scale derived from a review of the diary and discussion with the patient for measuring sexual function with changes measured from baseline to weeks 2, 4, and 8 (final or last visit) with anchored scores from 1 (normal) to 7 (most extreme sexual dysfunction).²⁶ The sexual function questionnaire is a 34-item, multidimensional, patient-rated, self-report, outcome measure of female sexual function developed and validated in English and several other languages.²⁷ It quantifies sexual function in 7 functional domains (desire, arousal-sensation, arousal-lubrication, orgasm,

enjoyment, pain, partner) of the female sexual response cycle to detect change in and distinguish between the presence and absence of female sexual dysfunction consistent with the *DSM-IV* diagnostic criteria. Anchored 5- or 7-point individual item response scales are scored, ascending or descending, from 0 or higher to 6 or lower (most are 1 to 5) with the higher scores indicating better sexual function. The 7 domain composite-section scores add to a total score range of 30 to 167: sexual desire (range, 5-31), arousal-sensation (range, 4-20), arousal-lubrication (range, 2-10), orgasm (range, 3-15), pain (range, 2-15), partner (range, 2-10), and enjoyment (range, 6-30). Responses of not applicable were entered as missing.

To provide concurrent validity, we used the Arizona Sexual Experience and the University of New Mexico Sexual Function Inventory scales. Both are shorter and well-established instruments that have been validated in patients with psychiatric disorders. They weight sexual function domains equally with different wording and anchors at administration.

The Arizona scale is a 5-item, patient-rated questionnaire that quantifies sexual drive, arousal (subjective excitement), lubrication (physiological excitement), ability to reach orgasm, and orgasm satisfaction using anchored 6-point scales from 1 (good function) to 6 (poor function) for each item with a total score ranging from 5 to 30 (higher scores indicate greater sexual dysfunction).²⁸

The University of New Mexico scale²⁹ is a 5-item, clinician-rated—for this study—questionnaire derived from and similar to the Arizona²⁸ and the Massachusetts General Hospital-Sexual Function questionnaires.³⁰ It uses anchored 6-point scales from 1 (good function) to 6 (poor function) for each item (desire, sexual arousal, ability to achieve lubrication, ability to achieve orgasm, and overall satisfaction) to quantify presence and changes in sexual dysfunction independent of disease state or medication (lower scores indicate better or improvement in sexual function).

The 17-item Hamilton depression rating²³ was administered at baseline and at weeks 2, 4, and 8 (or last visit) to monitor depression severity to ensure that the severity of depression had not changed to be more than 10 (relapse of major depression excluded study continuation). A second Hamilton anxiety rating²⁴ occurred at week 8.

The clinical assessment of each patient and medical record was used to confirm DSM-IV–defined major depressive disorder in remission, substance-induced sexual dysfunction, and any exclusionary diagnoses.

Biochemical Measures

Serum blood samples drawn at baseline and at study end, before 11 AM on days 1 to 10 of the menstrual period (follicular phase), were stored at -80°C until assayed and measured following prescribed procedures (eg, chemiluminescent enzyme immunoassay, micro-particle enzyme immunoassay, radioimmunoassay) at the Reproductive Endocrine Reference Laboratory at Massachusetts General Hospital, Boston. Levels of cortisol, progesterone, estradiol, total testosterone, free testosterone, follicle-stimulating hormone, luteinizing hormone, prolactin, sex hormone-binding globulin, thyroid-stimulating hormone, and total thyroxine were determined. Full analysis procedures with lower limits of detection reported for assays performed at the Massachusetts General Hospital General Clinical Research Center core laboratory using commercially available kits are published by the manufacturer and available on request.

Statistical Analysis

Baseline demographics, safety, and tolerability evaluations were compared using descriptive statistics by χ^2 and Fisher exact tests (when cell sizes were <5). Independent samples *t* tests compared baseline patient characteristics and Clinical Global Impression sexual function scores between the study groups at end point. The χ^2 analyses were used to evaluate group differences in categorical measures. Analy-

ses were based on intent-to-treat with the last-observation-carried-forward analyses performed on all variables and included data from all protocol-treated patients. All randomized patients received and took at least 1 dose of study trial medication, had at least 1 efficacy assessment, and were included regardless of protocol deviations or whether they completed the study. The final analysis included women who completed the trial, but for the women who did not complete the trial, their baseline value was carried forward in separate analyses. The change in sexual functioning by Clinical Global Impression sexual function score and all other questionnaires from baseline to each patient's own end point were the dependent measures of efficacy.

A repeated measures analysis of variance was used to determine differences between placebo and sildenafil in the change from baseline to end point for the measures of efficacy and depression severity (time \times group interaction). In addition, exact nonparametric methods were applied to the efficacy measures to substantiate results that rely on distributional assumptions. Findings were also confirmed with analysis of covariance and Wilcoxon rank sum tests for primary analyses.

All statistical tests were 2-sided, and all hypotheses were evaluated at the 5% significance level. The *F* test of the overall hypothesis test was first conducted before multiple comparisons analyses.

Sample-size calculations were based on detecting a difference in full response rates at 8 weeks, assuming a response rate of 70% for sildenafil and 35% for placebo. Thus, a sample size of 82 evaluable patients (41 per group) was expected to detect a significant difference with 90% power for a type I error rate of $\alpha = .05$ between sildenafil and placebo (2-sided). Assuming 20% attrition, 100 patients were planned to be randomized and 98 patients were entered. The sample size determination assumed no interactions of treatment with site or antidepressant.

The primary analysis was according to assignment at randomization. In addition to determination of this narrow measure of efficacy based on all randomized patients and imputing the worst rank scores for early exclusions due to protocol violations before and without taking the trial drug, there was a general efficacy analysis for all protocol-treated patients and all trial completers.

Adjusted means (SDs) were determined and reported. Where applicable, 95% confidence intervals (CIs) are provided. Analyses were performed with SAS version 9.1.3 (SAS Institute Inc, Cary, North Carolina).

RESULTS

One hundred women (Figure) of the 145 screened met eligibility requirements. Among the most frequent causes for exclusion were ineligible protocol criteria (ie, lack of acceptable and verifiable form of contraception, perimenopausal with irregular cycles or amenorrhea, non-SRI sexual dysfunction augmentation, switching antidepressant agent, other treatments for sexual dysfunction), and other miscellaneous reasons (partner issues, abnormal Papanicolaou test results, medical comorbidity, excessive alcohol use, or relationship or partner problems). Two eligible participants were withdrawn after they were screened but before they were randomized. One patient had a change in antidepressant dose made by her primary care physician. The other patient withdrew due to her partner's serious injuries. The 2 nonrandomized and untreated women did not differ on any demographic characteristics from those who entered the trial and were not included in the analyses. A total of 98 women were randomly assigned to receive active sildenafil ($n=49$) or placebo ($n=49$). The mean (SD) age of the women was 36.7 (7.1) years. They had been taking antidepressant medication for 27.7 (34.6) months. Distribution of prescribed antidepressants was comparable between groups. There were no statistically significant differences between

baseline demographics in the assigned treatment groups (TABLE 1).

Systematic review for any protocol deviations in patient enrollment was undertaken before unbinding. The 98 randomized women constituted the last-observation-carried-forward analysis. Seventy-six women (77.6%) completed the study: with 75.5% (37 of 49) in the placebo group and 79.6% (39 of 49) in the sildenafil group and constituted the completer population. Nine women in the placebo group and 4 in the sildenafil group discontinued prematurely for lack of efficacy. The other 6 in sildenafil and 3 in the placebo groups were lost to follow-up. No discontinuations for intolerable or serious adverse events were reported (Figure).

Baseline Prevalence of Sexual Dysfunction

As determined by the inclusion criteria, the prevalence of sexual problems was high and the mean (SD) number of problems reported was 3.0 (0.7) for the sildenafil group and 2.8 (0.7) the placebo group ($P = .21$), with 95.8% of women reporting more than 1 complaint. They reported disturbances in desire (87.8%), subjective arousal (80.6%), lubrication (79.6%), orgasm delay (98.7%), and other difficulties (23.6%), which included anorgasmia, lack of pleasure, and pain. Prior to study entry, the women self-reported a mean (SD) of 6.0 (5.2) sexual attempts per month, of which 1.4 (2.0), or 29.6% (34.9%), were considered successful. There were no statis-

tically significant differences between treatment groups in number or type of sexual problems or in number or percentage success of sexual attempts at baseline (Table 1).

Efficacy Measures

Clinical Global Impression. The difference from baseline to end point in the mean (SD) change in the Clinical Global Impression scale sexual function improvement by intent-to-treat last-observation-carried-forward analyses (ie, lower ordinal score) was 4.8 (0.7) to 2.8 (1.0) with a difference of 1.91 (95% CI, 1.57-2.26) for the sildenafil group vs 4.7 (0.9) to 3.6 (0.9) with a difference of 1.10 (95% CI, 0.75-1.46) for the placebo group, which showed a significant difference of 0.8 (95% CI, 0.6-1.0, $P = .001$) between groups (TABLE 2). To adjust for potential bias introduced by patients who prematurely discontinued, a more conservative intent-to-treat analysis assigning return-to-baseline values carried forward of those who did not complete the study showed a baseline-to-end point mean difference in the Clinical Global Impression scores of 1.5 (95% CI, 1.1-1.9) among women taking sildenafil vs 0.9 (95% CI, 0.6-1.3) for women taking placebo and a significant 0.6 (95% CI, 0.3-0.8) mean change difference between groups ($P = .03$). Clinically, 73% of women taking placebo compared with 28% of women taking sildenafil reported no improvement with treatment (Clinical Global Impression score >3 was rated as no improvement).

Sexual Function Questionnaires. Table 2 shows the mean (SD) scores on the secondary outcome measures from baseline to study end for both treatment groups. In comparing the baseline sexual function questionnaire domain scores with those at the end of the study, women in the sildenafil group had a higher mean (SD) improvement (orgasm, $P = .01$) than women taking placebo for all domains except for pain. In the Arizona and the University of New Mexico ques-

Table 1. Demographics and Baseline Characteristics

	Placebo (n = 49)	Sildenafil (n = 49)	P Value
Age, mean (SD), y	36.1 (7.6)	37.4 (6.6)	.36
Demographics, No. (%)			
Married/significant other	41 (83.7)	46 (93.4)	.11
Smoke cigarettes	7 (14.3)	8 (16.3)	.78
Drink alcohol	43 (87.8)	40 (81.6)	.40
≥High school education	42 (85.7)	43 (87.8)	.97
Premenopausal ^b	44 (89.8)	38 (77.6)	.10
Exogenous contraceptive hormone	16 (32.7)	19 (38.8)	.53
Primary diagnosis of depression ^a	48 (98.0)	47 (95.9)	.56
Antidepressant use, mean (SD), mo	25.8 (33.8)	29.3 (35.6)	.62
No. of children, mean (SD)	1.2 (1.2)	1.3 (1.3)	.58
Sexual problems			
No. of problems, mean (SD)	2.8 (0.7)	3.0 (0.7)	.21
Women with problems, No. (%)			
Libido	43 (87.8)	43 (87.8)	>.99
Arousal difficulty, lubrication	38 (77.6)	41 (83.7)	.44
Anorgasmia	8 (16.3)	14 (28.6)	.15
Orgasm delay, No./total (%) ^b	41/42 (97.6)	34/34 (100)	1.00
Sexual attempts within 30 d			
Total, mean (SD)	6.1 (5.6)	6.0 (4.8)	.92
Successful, %	34.7 (37.1)	24.6 (31.9)	.15
Serotonergic antidepressants, No. (%)			
Citalopram hydrochloride	6 (12.2)	6 (12.2)	>.99
Venlafaxine hydrochloride	6 (12.2)	4 (8.2)	.50
Escitalopram hydrochloride	8 (16.3)	7 (14.3)	.44
Fluvoxamine maleate	1 (2.1)	0 (0.0)	>.99
Paroxetine	2 (4.1)	10 (20.4)	.20
Fluoxetine hydrochloride	16 (32.7)	12 (24.5)	.40
Clomipramine, tricyclic	0 (0.0)	1 (2.0)	>.99
Sertraline hydrochloride	10 (20.4)	9 (18.4)	>.99

^aIn the other 3 women, the primary diagnoses were dysthymia, depressive disorder not otherwise specified, or anxiety and depression.

^bWomen who were not able to have an orgasm were not asked about delay.

tionnaires, the ability to reach orgasm and experience orgasm satisfaction was significantly better for those in the sildenafil group than for those in the placebo group for a mean difference from baseline of 0.5 (95% CI, 0.1-1.0; $P=.01$) for reaching orgasm for the Arizona questionnaire and 0.7 (95% CI, 0.1-1.3; $P=.01$) for the New Mexico questionnaire. In measuring depression, at baseline, women in both groups had nearly identical Hamilton scores. At the end of the

study, their scores remained similar ($P=.90$) indicating persisting remission in depression. The difference in change scores between treatment groups did not achieve statistical significance ($P=.86$). Among women who received treatment according to protocol, 3 women in the placebo group and 1 in the sildenafil group developed intermittent Hamilton depression scores of between 10 and 15. These were self-limited, transient, symptomatic changes distinguished

from major depressive disorder relapse and not considered clinically meaningful to warrant intervention. No recurrence or relapse of major depressive disorder occurred in any of the women continuing a stable dose of antidepressants during the trial (Table 2).

Endocrine Levels. Mean (SD) baseline values for all endocrine values were within the normal range without significant differences between groups (TABLE 3). Independent of treatment as-

Table 2. Sexual Function^a

Outcome	Mean (SD)				Change From Baseline Mean (95% Confidence Interval) ^b	P Value ^c
	Placebo (n = 49)		Sildenafil (n = 49)			
	Baseline	Study End	Baseline	Study End		
Primary						
Clinical Global Impression scale						
ITT ^d	4.7 (0.9)	3.6 (0.9)	4.8 (0.7)	2.8 (1.1)	0.8 (0.6 to 1.0)	.001
ITT-BCF ^e	4.7 (0.9)	3.8 (1.2)	4.8 (0.7)	3.2 (1.4)	0.6 (0.3 to 0.8)	.03
Secondary						
SFQ domains ^f						
Desire	13.6 (4.7)	16.4 (5.2)	13.0 (4.7)	17.3 (5.1)	1.4 (−0.9 to 3.8)	.22
Arousal-sensation	8.4 (3.4)	10.4 (4.2)	7.1 (3.6)	10.3 (4.2)	1.1 (−0.8 to 2.9)	.24
Arousal-lubrication	4.9 (2.0)	5.6 (2.3)	4.9 (1.7)	6.2 (2.2)	0.6 (−0.3 to 1.5)	.20
Orgasm	7.9 (2.9)	8.6 (3.0)	5.9 (3.4)	8.6 (3.9)	2.1 (0.5 to 3.6)	.01
Enjoyment	14.3 (5.5)	16.9 (5.4)	13.0 (5.2)	18.0 (5.7)	2.4 (0.01 to 4.73)	.05
Pain	14.1 (1.6)	13.9 (1.8)	13.8 (2.4)	14.1 (1.9)	0.5 (−0.3 to 1.3)	.21
Partner	7.5 (2.0)	7.9 (2.0)	7.0 (1.9)	8.2 (1.6)	0.9 (0.3 to 1.6)	.007
ASEX items						
Sexual drive	4.7 (1.1)	4.2 (1.2)	4.9 (1.2)	4.2 (1.2)	0.2 (−0.2 to 0.6)	.40
Arousal	4.5 (1.0)	4.1 (1.1)	4.5 (0.9)	4.1 (1.1)	0.0 (−0.4 to 0.5)	.81
Lubrication	3.9 (1.1)	3.5 (1.3)	3.8 (1.1)	3.3 (1.1)	0.1 (−0.3 to 0.5)	.64
Ability to reach orgasm	4.8 (0.8)	4.5 (1.0)	5.2 (0.8)	4.3 (1.2)	0.5 (0.1 to 1.0)	.01
Orgasm satisfaction	4.0 (1.4)	3.8 (1.3)	4.5 (1.5)	3.6 (1.4)	0.6 (0.0 to 1.3)	.05
Total score	21.9 (3.6)	20.0 (4.2)	22.9 (3.5)	19.5 (4.6)	1.5 (−0.1 to 3.1)	.06
UNM-SFI items						
Desire	5.0 (1.7)	4.3 (1.6)	5.1 (1.4)	4.1 (1.5)	0.4 (−0.2 to 1.0)	.18
Sexual arousal	5.0 (1.4)	4.4 (1.5)	5.0 (1.3)	4.3 (1.5)	0.2 (−0.5 to 0.8)	.61
Lubrication	4.3 (1.5)	3.9 (1.6)	4.1 (1.4)	3.4 (1.4)	0.3 (−0.3 to 0.8)	.32
Ability to reach orgasm	5.6 (1.2)	5.0 (1.4)	5.9 (1.1)	4.6 (1.6)	0.7 (0.1 to 1.3)	.01
Overall satisfaction	4.9 (1.3)	4.4 (1.5)	5.1 (1.2)	4.0 (1.5)	0.6 (−0.03 to 1.2)	.07
Total score	24.8 (5.6)	22.0 (6.1)	25.2 (4.7)	20.2 (6.4)	2.3 (−0.1 to 4.7)	.06
Hamilton depression score	4.1 (2.5)	3.9 (3.6)	4.1 (2.4)	4.0 (3.5)	0.2 (−1.6 to 1.9)	.86

Abbreviations: ANOVA, analysis of variance; ASEX, Arizona Sexual Experience scale; BCF, baseline carried forward; ITT, intent to treat; LOCF, last observation carried forward; SFQ, Sexual Function Questionnaire; UNM-SFI, University of New Mexico Sexual Function Inventory.

^aThirty-seven of 49 women (75.5%) in the placebo group and 39 of 49 women (79.6%) in the sildenafil group completed all 8 end point assessments.

^bDifferences in the change from baseline to each patient's own end point for the change in sexual functioning measured by Clinical Global Impression of Sexual Function improvement.

^cCalculated as part of the repeated measures ANOVA and using the last-observation-carried-forward algorithm.

^dThe intent-to-treat analysis using the last observation carried forward measured by the mean difference in baseline to study end improvement in placebo-treated group was 1.1 (95% confidence interval [CI], 0.8-1.5) vs sildenafil-treated group 1.9 (95% CI, 1.6, 2.3). The effect size was 0.7 (95% CI, 0.5-0.9).

^eFor patients not completing trial the mean difference in baseline to end point in placebo-treated group was 0.9 (95%CI, 0.6-1.3) vs sildenafil-treated 1.5 (95% CI, 1.1-1.9). The effect size was 0.5 (95%CI; 0.3,0.7).

^fSee the "Methods" section for the 7 SFQ domain scoring ranges. All randomized women providing responses to all domain questions at baseline or study end of treatment, or time of discontinuation, were included in analysis of that domain. Nonapplicable responses were treated as missing.

Table 3. Endocrine Levels at Baseline (Total n = 98)^a

Hormones	Normal Range	Mean (SD)		P Value ^b	Mean (SD)		P Value ^b
		Placebo (n = 49)	Sildenafil (n = 49)		Nonresponders (n = 46)	Responders (n = 52)	
Cortisol, µg/dL	5-25	11.40 (4.90)	13.62 (8.11)	.45	11.77 (5.34)	13.30 (7.97)	.30
Estradiol, pg/mL	<20-60	66.93 (56.08)	68.23 (52.73)	.94	72.44 (58.40)	62.62 (49.45)	.40
FSH, mIU/mL	2.8-8.9	8.91 (7.95)	7.53 (3.90)	.45	9.11 (7.89)	7.30 (3.77)	.18
LH, mIU/mL	1.0-8.2	6.95 (5.83)	8.12 (12.51)	.47	8.45 (9.58)	6.62 (9.91)	.39
Progesterone, ng/mL	<0.2	0.38 (0.16)	1.18 (3.16)	.46	0.41 (0.30)	1.17 (3.19)	.13
Prolactin, µg/L	1.4-23.1	13.21 (8.47)	13.26 (5.38)	.31	13.59 (8.35)	12.87 (5.45)	.64
SHBG, nmol/L	21-139	67.45 (49.42)	85.95 (76.94)	.47	73.07 (50.93)	80.64 (77.44)	.60
Testosterone							
Total, ng/dL	5-63	32.2 (33.47)	26.77 (12.59)	.91	29.43 (30.83)	29.41 (17.88)	.99
Free, pg/mL	0.4-3.1	1.18 (0.77)	1.29 (0.74)	.42	1.04 (0.69)	1.44 (0.76)	.01
TSH, µIU/m	0.5-4.7	1.68 (0.99)	2.02 (1.40)	.32	1.92 (1.29)	1.78 (1.15)	.58
T ₄ µg/dL	4-12	8.10 (1.63)	8.47 (2.13)	.56	7.75 (1.44)	8.83 (2.15)	.01

Abbreviations: ANOVA, analysis of variance; FSH, follicle-stimulating hormone; LH, luteinizing hormone; SHBG, sex hormone-binding globulin; T₄, tetraiodothyronine (thyroxine); TSH, thyroid-stimulating hormone; T₄, thyroxine.

SI Conversion factors: To convert cortisol to nmol/L, multiply by 27.588; estradiol to pmol/L, multiply by 3.671; FSH to IU/L, multiply by 1.0; LH to IU/L, multiply by 1.0; progesterone to nmol/L, multiply by 3.18; prolactin to pmol/L, multiply by 43.478; SHBG to nmol/L, multiply by 8.896; testosterone to nmol/L, multiply by 0.0347; TSH to IU/L, multiply by 1.0; and T₄ to pmol/L, multiply by 12.871.

^aSee the "Methods" section for the hormone analysis assays.

^bCalculated as part of the repeated measures analysis of variance and using the last-observation-carried-forward algorithm.

Table 4. Most Common Adverse Events^a

Adverse Event	No. (%)		P Value
	Placebo (n = 49)	Sildenafil (n = 49)	
Total, No.	55	104	
Headache	13 (27)	21 (43)	.09
Dyspepsia	0	6 (12)	.01
Flushing	0	12 (24)	<.001
Visual disturbance	1 (2)	7 (14)	.03
Nasal congestion	3 (6)	18 (37)	<.001
Palpitations	1 (2)	4 (8)	.17
Restless/anxious	3 (6)	1 (2)	.31
Insomnia	1 (2)	4 (8)	.17
Diarrhea	3 (6)	2 (4)	.65
Nausea	8 (16)	1 (2)	.01
Dizziness	2 (4)	3 (6)	.65
Other ^b	6 (12)	12 (24)	.84

^aOf the 100 patients eligible for the study, 2 women were excluded prior to randomization and did not receive study drug.

^bUrinary, psychiatric symptoms, dry mouth, fatigue, body warmth, gastrointestinal tract, infection. The adverse events that were more common in women treated with placebo than with sildenafil were nausea (15% vs 1%) and anxiety (7% vs 1%).

signment, a comparison of women whose sexual function improved with those whose sexual function did not improve showed higher mean baseline levels of free testosterone ($P \leq .01$) and thyroxine ($P \leq .01$) among SRI-associated sexual dysfunction treatment responders.

Study Drug Use. At study end, 76.9% (30 of 39) of women took a mean (SD)

dose of 91.7 (19.8) mg of sildenafil and 86.5% (32 of 37) took 93.1 (17.5) mg of placebo. The maximum dose for the study was 100 mg. The mean (SD) number of doses per 2-week interval was 5.0 (2.5) mg for sildenafil and 5.2 (2.5) for placebo, which supports the notion that the lack of efficacy in placebo patients was not due to a lack of attempts ($P = .67$).

Adverse Events. The most common adverse event was headache, reported by 43% of women taking sildenafil and 27% taking placebo ($P = .09$). Less frequent were flushing, 24% vs 0% ($P < .001$); dyspepsia, 12% vs 0% ($P = .01$); nasal congestion, 37% vs 6% ($P < .001$); and transient visual disturbances, 14% vs 2% ($P = .03$), respectively. Adverse events more common in the placebo group than in the sildenafil group were nausea 16% vs 2% ($P = .01$) and anxiety 6% vs 2% ($P = .31$). No serious adverse events related to trial medication were reported (TABLE 4).

COMMENT

To our knowledge, this is the first randomized trial to demonstrate a significant reduction in adverse sexual effects, measured by the Clinical Global Impression sexual function, that compared sildenafil with placebo among women with SRI-associated sexual dysfunction, specifically including delayed orgasm responses and inadequate lubrication, while continuing stable-dose antidepressant treatment. These findings support earlier open-label reports involving women with SRI-associated sexual dysfunction and builds on the results of previous trials involving men, with benefits not lim-

ited to erectile function, and including delayed ejaculation or orgasm and satisfaction.¹¹ These findings are important not only because women experience major depressive disorder at nearly double the rate of men⁵ and because they experience greater resulting sexual dysfunction than men³¹ but also because it establishes that selective phosphodiesterase type 5 inhibitors are effective in both sexes for this purpose. By treating this bothersome treatment-associated adverse effect in patients who have been effectively treated for depression, but need to continue on their medication to avoid relapse or recurrence, patients can remain antidepressant-adherent, reduce the current high rates of premature medication discontinuation, and improve depression disease management outcomes.

Baseline pituitary, thyroid, adrenal, ovarian hormone, and sex hormone-binding globulin levels were within normal limits and were not different to a statistically significant extent between groups. It should be noted that the endocrine levels, especially those of the menstrual cycle, are estimates of general levels because they were taken in the follicular phase, when levels are at their nadir.³² Within this restriction, there were treatment differences due to assignment suggesting phosphodiesterase type 5 inhibitor treatment likely benefitted women with SRI-associated sexual dysfunction by reducing some of the confounds that women encountered in other trials; for example, low free-testosterone and hypoactive sexual desire,¹⁵ low estrogen-decreasing secretory lubrication,¹³ exogenous estrogen-increasing sex hormone-binding globulin and decreasing free testosterone, hypothyroid hyperprolactinemia-inhibiting neuronal nitric oxide-cyclic guanine monophosphate,^{33,34} mixed menopausal status, and other conditions that reportedly interfere with nitric-oxide synthase isoforms activating nitric oxide-cyclic guanine monophosphate and phosphodiesterase type 5 in female genital tissue.³⁵ Independent of treatment assign-

ment, a positive treatment response was associated with higher free testosterone and thyroxine.

Secondary efficacy measures revealed improved orgasm delay with sildenafil treatment, which is considered a central feature of SRI-associated sexual dysfunction. Orgasm function has received far less attention than sexual arousal, perhaps due to erectile dysfunction being the only FDA indication and primary marketing focus for selective phosphodiesterase type 5 inhibitors. Significant improvement in orgasm function found in this trial is consistent with findings of improved orgasm in trials involving premenopausal and postmenopausal women with sexual arousal disorder,^{14,15,17} in open-label studies reporting reversal of delayed orgasm in SRI-associated sexual dysfunction,^{18,19} in trials involving men with erectile dysfunction,⁹ in trials that include treated or untreated depression,^{10,11} and in reports showing that enhanced nitergic activity (direct or indirect) can improve inadequate smooth muscle relaxation involved in orgasm delay with SRIs and serotonin norepinephrine reuptake inhibitors.³⁶ Another consideration is whether the dose range of 50 mg to 100 mg of phosphodiesterase type 5 inhibitor was sufficient because reports on treating ejaculatory delay in men with SRI-associated sexual dysfunction suggest that higher doses of between 100 mg and 200 mg can be more effective.^{37,38} Independent of a significant effect on arousal in women with SRI-associated sexual dysfunction, it would seem unlikely for sexual function to globally improve without some effect on physiological sexual arousal, ie, lubrication, or tumescence.

This study may not be generalizable to women who did not meet the criteria of this study. The specific entry criteria requirements in this trial, including study participation, which can contribute to encouraging sexual interest, selecting women with SRI-associated sexual dysfunction who were highly motivated to improve, including improved relationship changes, can promote differences between treat-

ment measures. Lack of a significant sildenafil treatment effect for sexual desire is consistent with reports that selective phosphodiesterase type 5 inhibitors do not directly enhance libido or that it might reflect a bias for selecting patients highly motivated to recover preexisting sexual function that attenuates effects on desire.³⁹ The limitation of the trial to 8 weeks is also a consideration and it is unknown whether women would be willing to continue treatment over time.

Although the protocol designs between this trial and the trial involving men with SRI-associated sexual dysfunction¹¹ share features and limitations (eg, lack of biological criterion for female sexual dysfunction, assessment instruments with high correlation, and use of analysis-of-variance models for samples assigning integers to ordinal categories of an outcome measure when the phenomenon in question has an underlying continuous scale),⁴⁰ the mechanism of action or specific treatment effects cannot be assumed to be the same. Both trials relied on scoring based on subjective responses to different questions for men and women, so the roles of expectations and adverse effects, as well as treatment response, influencing subjective report measures cannot be ruled out. However, it seems clear that effective evidence-based treatments for treatment-associated adverse effects can lead to improved outcomes for major depressive disorder and other conditions requiring extended medication treatment.

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Study concept and design: Nurnberg, Hensley, Paine.
Acquisition of data: Nurnberg, Hensley, Heiman, Croft, Debattista.

Analysis and interpretation of data: Nurnberg, Hensley, Paine.

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REFERENCES

- Trends in antidepressant use. AHRQ News and Numbers. Rockville, MD: Agency for Healthcare Research and Quality; May 16, 2005. <http://www.ahrq.gov/news/nn/nn051605.html>.
- Montejo AL, Llorca G, Izquierdo JA, Rico-Villademor F. Incidence of sexual dysfunction associated with antidepressant agents: a prospective multicenter study of 1022 outpatients. Spanish Working Group for the Study of Psychotropic-Related Sexual Dysfunction. *J Clin Psychiatry*. 2001;62(3)(Suppl 3):10-21.
- Lin EHB, Von Korff M, Katon W, et al. The role of the primary care physician inpatients' adherence to antidepressant therapy. *Med Care*. 1995;33(1):67-74.
- Rudkin L, Taylor MJ, Hawton K. Strategies for managing sexual dysfunction induced by antidepressant medication. *Cochrane Database Syst Rev*. 2004;(4):CD003382.
- Kessler RC, Berglund P, Demler O, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA*. 2003;289(23):3095-3105.
- Zimmerman M, Posternak M, Friedman M, et al. Which factors influence psychiatrists' selection of antidepressants? *Am J Psychiatry*. 2004;161(7):1285-1289.
- Alex J, Mitchell AJ, Selmes T. Why don't patients take their medicine? reasons and solutions in psychiatry. *Adv Psychiatr Treat*. 2007;13(5):336-346.
- Ekselius L, von Knorring L. Effect on sexual function of long-term treatment with selective serotonin reuptake inhibitors in depressed patients treated in primary care. *J Clin Psychopharmacol*. 2001;21(2):154-160.
- Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA; Sildenafil Study Group. Oral sildenafil in the treatment of erectile dysfunction. *N Engl J Med*. 1998;338(20):1397-1404.
- Rosen R, Shabsigh R, Berber M, et al. Efficacy and tolerability of vardenafil in men with mild major depressive disorder and erectile dysfunction: the depression related improvement with vardenafil for erectile response (DRIVER) study. *Am J Psychiatry*. 2006;163(1):79-87.
- Nurnberg HG, Hensley PL, Gelenberg AJ, Fava M, Lauriello J, Paine S. Treatment of antidepressant-associated sexual dysfunction with sildenafil: a randomized controlled trial. *JAMA*. 2003;289(1):56-64.
- Park K, Moreland RB, Goldstein I, Atala A, Traish A. Sildenafil inhibits phosphodiesterase type 5 in human clitoral corpus cavernosum smooth muscle. *Biochem Biophys Res Commun*. 1998;249(3):612-617.
- Basson R, McInnes R, Smith MD, Hodgson G, Koppiker N. Efficacy and safety of sildenafil citrate in women with sexual dysfunction associated with female sexual arousal disorder. *J Womens Health Genet Based Med*. 2002;11(4):367-377.
- Caruso S, Intelisano G, Lupo L, Agnello C. Premenopausal women affected by sexual arousal disorder treated with sildenafil: a double-blind, crossover, placebo-controlled study. *BJOG*. 2001;108(6):623-628.
- Berman JR, Berman LA, Toler SM, Gill J, Haughey S; Sildenafil Study Group. Safety and efficacy of sildenafil citrate for the treatment of female sexual arousal disorder: a double-blind, placebo controlled study. *J Urol*. 2003;170(6 Pt 1):2333-2338.
- Basson R, Brotto LA. Sexual psychophysiology and effects of sildenafil citrate in oestrogenised women with acquired genital arousal disorder and impaired orgasm: a randomised controlled trial. *BJOG*. 2003;110(11):1014-1024.
- Caruso S, Intelisano G, Farina M, Di Mari L, Agnello C. The function of sildenafil on female sexual pathways: a double-blind, crossover, placebo-controlled study. *Eur J Obstet Gynecol Reprod Biol*. 2003;110(2):201-206.
- Nurnberg HG, Hensley P, Lauriello J, Parker L, Keith SJ. Sildenafil for women patients with antidepressant-induced sexual dysfunction. *Psychiatr Serv*. 1999;50(8):1076-1078.
- Fava M, Rankin MA, Alpert JE, Nierenberg AA, Worthington JJ. An open trial of oral sildenafil in antidepressant-induced sexual dysfunction. *Psychother Psychosom*. 1998;67(6):328-331.
- Min K, Munarriz R, Kim NN, Goldstein I, Traish A. Effects of ovariectomy and estrogen and androgen treatment on sildenafil-mediated changes in female genital blood flow and vaginal lubrication in the animal model. *Am J Obstet Gynecol*. 2002;187(5):1370-1376.
- Musselman DL, Evans DL, Nemeroff CB. The relationship of depression to cardiovascular disease: epidemiology, biology, and treatment. *Arch Gen Psychiatry*. 1998;55(7):580-592.
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; 1994.
- Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23:56-62.
- Frank E, Prien RF, Jarrett RB, et al. Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse, and recurrence. *Arch Gen Psychiatry*. 1991;48(9):851-855.
- Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol*. 1959;32(1):50-55.
- Guy W. *ECDEU Assessment Manual for Psychopharmacology*. Washington, DC: National Institute of Mental Health; 1976.
- Quirk FH, Heiman JR, Rosen RC, Laan E, Smith MD, Boolell M. Development of a sexual function questionnaire for clinical trials of female sexual dysfunction. *J Womens Health Genet Based Med*. 2002;11(3):277-289.
- McGahuey CA, Gelenberg AJ, Laukes CA, et al. The Arizona Sexual Experience Scale (ASEX): reliability and validity. *J Sex Marital Ther*. 2000;26(1):25-40.
- Nurnberg HG, Gelenberg A, Fava M, Hensley PL, Lauriello J, Paine S. *The Sexual Function Inventory: A Screening Instrument for Antidepressant-Associated Sexual Dysfunction*. New Orleans, LA: American Psychiatric Association; 2001.
- Labbate LA, Lare SB. Sexual dysfunction in male psychiatric outpatients: validity of the Massachusetts General Hospital Sexual Functioning Questionnaire. *Psychother Psychosom*. 2001;70(4):221-225.
- Piazza LA, Markowitz JC, Kocsis JH, et al. Sexual functioning in chronically depressed patients treated with SSRI antidepressants: a pilot study. *Am J Psychiatry*. 1997;154(12):1757-1759.
- Davis SR, Davison SL, Donath S, Bell RJ. Circulating androgen levels and self-reported sexual function in women. *JAMA*. 2005;294(1):91-96.
- Laan E, van Lunsen RH, Everaerd W, Riley A, Scott E, Boolell M. The enhancement of vaginal vasocongestion by sildenafil in healthy premenopausal women. *J Womens Health Genet Based Med*. 2002;11(4):357-365.
- Kilicarslan H, Bagcivan I, Yildirim MK, Sarac B, Kaya T. Effect of hypothyroidism on the NO/cGMP pathway of corpus cavernosum in rabbits. *J Sex Med*. 2006;3(5):830-837.
- Berman JR, Berman LA, Lin H, et al. Effect of sildenafil on subjective and physiological parameters of the female sexual response in women with sexual arousal disorder. *J Sex Marital Ther*. 2001;27(5):411-420.
- Angulo J, Cuevas P, Cuevas B, Bischoff E, Sáenz de Tejada I. Vardenafil enhances clitoral and vaginal blood flow responses to pelvic nerve stimulation in female dogs. *Int J Impot Res*. 2003;15(2):137-141.
- Seidman SN, Pesce V, Roose SP. High dose sildenafil citrate for selective serotonin reuptake inhibitor-associated ejaculatory delay: open clinical trial. *J Clin Psychiatry*. 2003;64(6):721-725.
- Nurnberg HG, Siegel R. Effects of sildenafil citrate treatment on ejaculatory/orgasm delay and erectile dysfunction in serotonergic antidepressant-associated sexual dysfunction [abstract]. *J Urol*. 2006;175(4):300.
- Nurnberg HG, Seidman SN, Gelenberg AJ, Fava M, Rosen R, Shabsigh R. Depression, antidepressant therapies, and erectile dysfunction: clinical trials of sildenafil citrate (Viagra) in treated and untreated patients with depression. *Urology*. 2002;60(2)(suppl 2):58-66.
- Snedecor GW, Cochran WG. *Statistical Methods*. 7th ed. Ames: Iowa State University Press; 1980.