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Sexual function and satisfaction in heterosexual couples when men are administered sildenafil citrate (Viagra®) for erectile dysfunction: a multicentre, randomised, double-blind, placebo-controlled trial

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Objective To investigate the effect of improvement in erectile dysfunction (ED) on sexual function and satisfaction measures in heterosexual couples in which the woman reports that sexual intercourse is unsatisfactory at least half of the time.

Design Multicentre, double-blind, placebo-controlled study.

Setting Outpatient medical clinics.

Population Hundred and eighty men with ED and their female partners in whom sexual intercourse was satisfactory about half the time or less (score of ≤3 on the Female Partner of ED Subject Questionnaire question 3 [FePEDS Q3]).

Methods Men were randomised to flexible-dose sildenafil (25, 50, and 100 mg) or placebo as needed for 12 weeks.

Main outcome measures Primary: FePEDS Q3 ('Over the past four weeks, when you had sexual intercourse, how often was it satisfactory for you?') scored as 0 (no sexual activity) and 1 (almost never or never) to 5 (almost always or always). Secondary, partners: Sexual Function Questionnaire, Female Sexual Function Index (FSFI), and ED Inventory of Treatment Satisfaction (EDITS) partner version (EDITS-Partner). Secondary, men: International Index of Erectile Function (IIEF), General Efficacy Questions, event log data, Self-Esteem And Relationship questionnaire, and EDITS. Secondary, partners and men: Dyadic Adjustment Scale.

Results The intention-to-treat population included 85 sildenafil recipients (mean age 59 ± 12 years) and 91 placebo recipients (mean age 57 ± 11 years). Most partners (aged 20–79 years; mean, 54 years) were postmenopausal. Sildenafil compared with placebo couples had greater improvement in the primary outcome (FePEDS Q3 [$P < 0.0001$]) and in sexual function, intercourse success rates, and secondary sexual satisfaction measures (FSFI satisfaction domain [$P < 0.0001$] and IIEF satisfaction domains [$P < 0.001$]) and had higher treatment satisfaction (EDITS and EDITS-Partner; $P < 0.0001$). Several predictors of improvement were identified, and improvement in one member of the couple correlated positively with improvement in the other member.

Conclusions The interdependence of sexual function and sexual satisfaction measures between members of couples consisting of men with ED and sexually healthy women reporting infrequent satisfactory sexual intercourse underscores the importance of including partners in ED treatment discussions.

Keywords Couples, erectile dysfunction, relations, sexual partner, sildenafil citrate.

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Introduction

The sexual problems of a man can directly affect the sexual functioning of his partner.[1] Compared with partners of men who do not have erectile dysfunction (ED), partners of men with ED score significantly lower on measures of sexual function and/or satisfaction.[2] In couples in which the woman reported that her male partner had a sexual problem, 55% were also dissatisfied with their own sex life.[3] When a woman becomes aware of her partner's ED, she may sense him withdrawing, blame herself, may feel less self-confident and less attractive, and even worry that he is having an affair.[4,5] Thus, ED may cause substantial emotional distress to a couple. Furthermore, it is thought that sexual function enhances the pair-bonding of couples,[6] and therefore ED may weaken a relationship.

Despite the availability of sildenafil citrate for the treatment of ED since 1998, and other phosphodiesterase type 5 inhibitors more recently, little information exists regarding the impact on partners of men being treated for ED. Published reports include surveys of partners of men being treated with a phosphodiesterase type 5 inhibitor for ED,[7,8] an open-label, prospective trial that assessed the sexual function of partners of men treated for ED with penile prosthesis implantation or sildenafil compared with that of partners of men without ED,[2] and pooled partner data from placebo-controlled sildenafil clinical trials of ED.[9] A prospective, double-blind, placebo-controlled trial showed improvement in scores on the erectile function domain of the International Index of Erectile Function (IIEF; $P < 0.0001$ versus placebo) in men treated with flexible-dose (5, 10, and 20 mg) vardenafil for ED; their partners showed significant improvement in scores for all domains of the Female Sexual Function Index (FSFI) except pain ($P < 0.01$ versus placebo).[10,11] In this vardenafil trial, the baseline sexual function of the women was relatively high, as showed by least squares (LS) mean FSFI domain scores ranging from 4.0 to 5.0 (active treatment group) and 3.8 to 5.2 (placebo group), respectively, out of a maximum of 6.

We sought, in this heterosexual couples trial of sildenafil, to understand the effect of improved erectile function on measures of sexual function and satisfaction in women who were partners of men with ED, who had no underlying sexual dysfunction, but who reported that sexual intercourse was satisfactory only about half the time or less. Our cohort of women had lower baseline sexual function (e.g. FSFI scores) than the cohort in the vardenafil trial. We also sought to understand the relationship between improvement in the sexual function and satisfaction of men with ED and improvement in the sexual function and satisfaction of women in couples.

Methods

Trial design

This parallel-group, double-blind, placebo-controlled, flexible-dose trial with a 2-week screening phase followed by a 12-week treatment phase was conducted at several outpatient urology and internal medicine clinics in the USA. At screening, the investigator assigned an identification number that, if eligibility criteria were fulfilled, was used to implement randomisation using a pre-existing, computer-generated, blinded schedule. Randomisation was in a 1:1 ratio to ED treatment with sildenafil 50 mg or to matching placebo, adjustable to 25 mg or 100 mg depending upon efficacy and tolerability, to be taken 30 minutes to 1 hour before anticipated sexual activity. Numbered containers were used to maintain treatment allocation blinding of participants, investigators, and those evaluating the study data. Concomitant medications that could have had an effect on erectile function were to remain constant during the trial unless changes were required for safety.

The trial was conducted in compliance with each investigator's Institutional Review Board/Independent Ethics Committee, Good Clinical Practice (i.e. International Conference on Harmonisation Guidelines), the most current version of the Declaration of Helsinki (October 2000), and all applicable local laws and regulatory requirements. Written informed consent was obtained from each man and his partner.

Participants

Enrolled were 180 adult couples (≥21 years of age) in a stable relationship (≥6 months), consisting of men with ED documented by a score of ≤21 out of 25 on the Sexual Health Inventory for Men[12] and their female partners who reported no sexual intercourse or that sexual intercourse was satisfactory 'sometimes, about half the time', 'a few times, much less than half the time' or 'almost never or never' (score of ≤3 on question 3 of the Female Partner of ED Subject Questionnaire question 3 [FePEDS Q3]). A couple was excluded if the woman had significant dyspareunia or lifelong significant sexual dysfunction or if the man had used more than six doses of any phosphodiesterase type 5 inhibitor for the treatment of ED with the current partner, or any dose with any partner within 6 months; if he had used any other commercially available treatment for ED concurrently or within 6 months (other than stable-dose testosterone); if he was using nitrates, nitric oxide donors, or ritonavir; or if the primary investigator determined that the subject had any medical or psychological condition or social circumstances that would have impaired the ability to participate reliably in the trial or would have increased risk to the subject (i.e. significant cardiovascular disease, frequent flares of arthritis that prevent intercourse, or a history of retinitis pigmentosa).

Evaluations and outcomes

The primary outcome was the mean end-of-treatment score for the FePEDS Q3, 'Over the past four weeks, when you had sexual intercourse, how often was it satisfactory for you?' The

FePEDS Q3 is scored on a 6-point scale as 0 (no sexual activity), 1 (almost never or never), 2 (a few times, much less than half the time), 3 (sometimes, about half the time), 4 (most times, much more than half the time), or 5 (almost always or always).

There were several secondary evaluations in women; a description of each follows. The Sexual Function Questionnaire (SFQ) is a validated, self-administered measure of sexual function in women.[13] Higher scores indicate better sexual function and less pain. The FSFI is a validated, 19-item, self-administered questionnaire that assesses key dimensions of sexual function in the domains of desire, arousal, lubrication, orgasm, satisfaction, and pain.[14] Raw scores of the individual items that comprise each domain are summed, and the domain sum is multiplied by a predefined transformation factor to obtain a maximum value of 6, with higher scores indicating better sexual function and less pain.[14] The ED Inventory of Treatment Satisfaction (EDITS), partner version (EDITS-Partner) is a validated, five-item, self-administered scale that measures satisfaction of the partner with the man's ED treatment.[15] Each item is scored from 0 to 4, with higher scores indicating greater satisfaction, and the overall score (EDITS-Partner Index) being 25 times the average of the EDITS-Partner items.

There were several secondary evaluations in men. The IIEF is a validated, self-administered questionnaire designed to detect treatment-related changes in men with ED.[16] The IIEF consists of 15 items that query sexual function over the past 4 weeks, that are rated on either a 6-point or a 5-point scale (with higher scores representing better sexual function), and that compose the domains of erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction. IIEF erectile function domain scores can be used to classify erectile function as no ED (score, 26–30), mild ED (score, 22–25), mild-to-moderate ED (score, 17–21), moderate ED (score, 11–16), and severe ED (score, 6–10).[17] Results are also reported for IIEF Q7 'When you attempted sexual intercourse, how often was it satisfactory for you?', which is scored from 0 (did not attempt intercourse) to 5 (almost always/always). General Efficacy Questions (GEQs), which were posed at the end of treatment, queried whether, compared with no treatment, the medication the man had been taking over the past 4 weeks improved erections (GEQ1; response options, yes/no) and ability to have sexual intercourse (GEQ2; response options, yes/no/did not attempt intercourse). The Self-Esteem And Relationship (SEAR) questionnaire is a validated, 14-item, self-administered, ED-specific instrument, which includes a confidence domain (composed of the self-esteem and overall relationship subscales) and a sexual relationship domain.[18] SEAR items are scored on a 5-point scale from 1 (almost never/never) to 5 (almost always/always) for positive statements and in reverse order for negative statements, such that a higher score represents better self-esteem and confidence. Item scores are separately summed for the two domains and two subscales, and then each component and the total score are transformed into a 0-to-100 scale using the formula: $100 \times [(\text{actual raw score} - \text{lowest possible raw score}) \div (\text{highest possible raw score} - \text{lowest possible raw score})]$. The EDITS is a validated, 11-item, self-administered scale that measures satisfaction with treatment for ED.[15] Each item is scored from 0 to 4, with higher scores indicating greater satisfaction and the overall score (EDITS Index) being 25 times the average of the EDITS items.

The men and their partners completed the Dyadic Adjustment Scale (DAS), a 32-item, validated, self-administered instrument that assesses the components of dyadic satisfaction, dyadic consensus, and dyadic cohesion and affectional expression in cohabitating couples.[19] Total DAS scores range from 0 to 150, with higher scores indicating a more satisfactory, happier general relationship. The men and their partners also completed gender-specific event logs at the occasion of sexual activity.

Most evaluations were completed initially at the screening visit (2 weeks before initiating treatment) or the baseline visit (at the initiation of treatment) and again at the end-of-treatment visit. Questionnaires completed initially at the screening or baseline visit represent baseline values. The FePEDS Q3, IIEF, and DAS were also completed after 8 weeks of treatment. Some outcome measures (EDITS-Partner, EDITS, and GEQs) were only completed at the end-of-treatment visit. Event logs were completed independently by the men and the women at the time of attempted sexual activity to record the date and the corresponding sexual outcome.

Secondary outcomes defined *a priori* included the change from baseline to end of treatment in scores for SFQ domains, FSFI domains, IIEF domains and questions, SEAR components, and DAS, as well as the end-of-treatment EDITS-Partner Index, EDITS Index, and the percentage satisfied with ED treatment (where satisfaction with treatment was defined as an EDITS Index score ≥50 out of 100). GEQ data were used to calculate percentage responses, and event log data were used to calculate the percentage of attempts with sexual stimulation at which an erection that lasted long enough for successful intercourse was achieved.

All observed or volunteered adverse events were recorded, regardless of treatment group or suspected causal relationship to study drug.

Statistical methods

Sample size computation was based on an estimate for the SD of FePEDS Q3 of approximately 1.8 (as determined in previous analyses of a pool of ten sildenafil clinical trials)[20] and on 90% power to detect a mean sildenafil versus placebo difference of 1.0 point using a two-sided test conducted at 5% level of significance. Assuming that 80% of the randomised men (and their partners) would contribute to intent-to-treat (ITT) end-of treatment analyses, a total sample size of 90

subjects per treatment group were to be enrolled and randomised.

Descriptive statistics were used to summarise baseline characteristics, premature discontinuation, adverse events, vital signs, and concomitant medication use by treatment group. Efficacy variables were analysed within the ITT population, defined as men who took at least one dose of active or placebo study medication and who provided sufficient data for at least one efficacy analysis. Last observation carried forward was used as a method of imputation for missing data.

Within the ITT population, all efficacy variables except for the GEQs and event log response rates were analysed using an analysis of covariance (ANCOVA) model with terms for baseline value (except for EDITS-Partner and EDITS), treatment group, investigator site, and the following prognostic factors: age (women and men), smoking status (former, never, current; men only), ED duration, ED aetiology (organic, psychogenic, mixed), and baseline DAS score (women and/or men). The ANCOVA model for all efficacy variables in the partners included the baseline DAS score for the partners and the men, whereas the ANCOVA model for all efficacy variables in the men included only the baseline DAS score for the men. Two-factor interactions between treatment group and the other model terms were explored; if treatment by baseline interaction was statistically significant ($P < 0.05$), then an ANCOVA model consisting of treatment group, prognostic variables, and treatment by baseline interaction was used and P values based on the heterogeneous model at baseline were reported. LS means from the ANCOVA model were used to determine treatment effects. GEQs and event log response rates were analysed with a logistic regression model containing terms for treatment group, age, smoking status, baseline DAS score (men), ED duration, and ED aetiology; treatment effects were estimated using predicted percents from the model evaluated at the overall mean for continuous covariates (age, ED duration) and the overall distribution of participants for categorical covariates (smoking status and ED aetiology). All statistical tests were two-sided and performed at the 5% significance level.

Variables that might predict improvement in sexual function (FSFI domain scores in women and IIEF domain scores in men) and in measures of sexual satisfaction (FSFI satisfaction domain and FePEDS Q3 in women and the IIEF intercourse satisfaction and overall satisfaction domains in men) between baseline and the end of treatment were determined based on the generalised linear model described above.

Correlations were explored for each treatment group separately using Pearson product-moment correlation. The corresponding 95% confidence interval was constructed using a back transformation based on Fisher's Z transformation of Pearson's correlation coefficient. Safety was evaluated in all men who took at least one dose of study medication.

Results

Population

Between June 2003 and April 2004, 86 men (sildenafil) and 94 men (placebo) were randomised and treated, of whom 85 (mean 59 ± 12 years) and 91 (mean age 57 ± 11 years), respectively, were included in the ITT population and 79 (91.9%) and 76 (80.9%), respectively, completed the trial. Only three discontinuations, all in the placebo group, were for lack of efficacy. Remaining discontinuations were because of adverse events unrelated to treatment (two men in the sildenafil group and one in the placebo group), loss to follow up, withdrawal of consent, and protocol violations.

Baseline characteristics were similar between treatment groups (Table 1). Women were aged 20–79 years (mean, 54 years), and most of them had intact ovaries and uterus and were postmenopausal. Men were aged 30–86 years (mean, 58 years), with ED for 0.1–34.7 years that was of organic aetiology, as rated by study investigators, in most cases.

Responses in partners of men treated for ED (Table 2)

According to end-of-treatment FePEDS Q3 scores, the partners of men who were treated with sildenafil compared with placebo found sexual intercourse to be satisfactory more frequently. LS mean ± standard error (SE) FePEDS Q3 scores were 3.6 ± 0.2 in the partners of men treated with sildenafil (average of two points improvement from baseline) compared with 2.4 ± 0.2 in the partners of men treated with placebo (average of less than one point improvement from baseline) ($P < 0.0001$). Based on median scores, sexual intercourse was satisfactory 'most times, much more than half the time' (score = 4) for partners of men treated with sildenafil versus 'a few times, much less than half the time' (score = 2) for partners of men treated with placebo.

The partners of men treated with sildenafil compared with placebo also had significantly better responses as indicated by greater baseline to end-of-treatment improvement in scores for the SFQ enjoyment domain ($P = 0.006$), but not the other SFQ domains, and for the FSFI satisfaction ($P < 0.0001$), arousal ($P < 0.05$), orgasm ($P = 0.006$), and pain ($P = 0.0007$) domains, but not the desire or lubrication domains, and indicated by higher end-of-treatment EDITS-Partner Index ($P < 0.0001$) and estimated percentage satisfied with ED treatment (OR = 5.0, $P < 0.0001$). The baseline to end-of-treatment change in DAS scores was similarly small for the partners of men treated with sildenafil or placebo. LS mean ± SE end-of-treatment scores across the FSFI domains in the partners of men treated with sildenafil versus placebo ranged from 4.2 ± 0.2 to 5.5 ± 0.3 versus 3.9 ± 0.2 to 4.5 ± 0.3.

According to event log data, an erection lasted long enough for successful intercourse on approximately 25% of occasions at baseline in each group, but there was an estimated increase

Table 1. Baseline characteristics

Characteristics	Placebo	Sildenafil
ITT population	*n* = 91	*n* = 85
Age (years), mean ± SD (range)		
Women	54 ± 12 (28–79)	55 ± 12 (20–79)
Men	57 ± 11 (30–78)	59 ± 12 (30–86)
Race, % white/black/Asian/other		
Women	79/7/2/12	78/7/2/13
Men	80/7/1/12	78/7/3/13
Smoking status (men), % former/never/current	41/41/19	40/45/15
FePEDS Q3, mean score (range, 0–5)	1.5	1.4
SFQ domains, mean score		
Enjoyment (range, 6–30)	19.1	18.9
Desire (range, 5–31)	18.2	18.0
Arousal, sensation (range, 4–20)	10.5	10.3
Arousal, lubrication (range, 2–10)	5.5	5.9
Orgasm (range, 3–15)	8.9	9.6
Pain (range, 2–15)	13.9	13.9
Partner satisfaction (range, 2–10)	8.3	8.8
FSFI, mean score		
Satisfaction domain (range, 0.8–6)	3.1	3.2
Desire domain (range, 1.2–6)	3.8	3.5
Arousal domain (range, 0–6)	3.1	2.9
Lubrication domain (range, 0–6)	3.6	3.3
Orgasm domain (range, 0–6)	2.7	2.9
Pain domain (range, 0–6)	3.7	3.4
DAS, mean total score (range, 0–150)		
Women	112	114
Men	114	114
IIEF, mean score		
Erectile function domain (range, 1–30)	12.6	13.2
Orgasmic function domain (range, 0–10)	5.5	5.6
Sexual desire domain (range, 2–10)	6.3	6.3
Intercourse satisfaction domain (range, 0–15)	6.1	6.7
Overall satisfaction domain (range, 2–10)	5.0	5.0
Q7: frequency of satisfactory intercourse (range, 0–5)	2.1	2.3
SEAR questionnaire, mean score (range, 0–100)		
Sexual relationship domain	43.2	41.7
Confidence domain	56.3	52.7
Self-esteem subscale	54.2	52.4
Overall relationship subscale	60.4	53.3
Total score	48.8	46.3
Randomised population	*n* = 94	*n* = 86
Women		
Ovarian status, % intact/unilateral oophorectomy/ bilateral oophorectomy/other	79/4/17/0	69/10/20/1
Menopausal status, % pre/peri/postmenopausal	30/9/62	20/13/67
Uterine status, % intact/hysterectomy	59/41	62/38
Pregnancies, mean ± SD	2.8 ± 1.8	2.8 ± 1.7
Men		
ED aetiology, % organic/mixed/psychogenic	62/27/12	59/24/16
ED duration (years), mean (range)	6.1 (0.1–34.7)	4.7 (0.2–21.6)

Table 2. Responses in the partners of men treated with sildenafil or placebo for ED

Efficacy measure*	Placebo	Sildenafil	*P* value
FePEDS Q3 score at week 12 LOCF as LS mean ± SE (range, 0–5)			
Over the past four weeks, when you had sexual intercourse, how often was it satisfactory for you?	2.4 ± 0.2	3.6 ± 0.2	<0.0001
SFQ score change from baseline to week 12 LOCF as LS mean ± SE			
Enjoyment domain (score range, 6–30)	1.4 ± 0.6	3.3 ± 0.6	0.006
Desire domain (score range, 5–31)	1.4 ± 0.6	2.2 ± 0.6	NS
Arousal, sensation domain (score range, 4–20)	1.8 ± 0.6	2.1 ± 0.6	NS
Arousal, lubrication domain (score range, 2–10)	0.9 ± 0.3	1.1 ± 0.3	NS
Orgasm domain (score range, 3–15)	0.5 ± 0.5	1.2 ± 0.5	NS
Pain domain (score range, 2–15)**	0.1 ± 0.3	0.3 ± 0.2	NS
Partner satisfaction domain (score range, 2–10)	0.3 ± 0.2	0.6 ± 0.2	NS
FSFI score change from baseline to week 12 LOCF as LS mean ± SE			
Satisfaction domain (score range, 0.8–6)	0.9 ± 0.2	1.6 ± 0.2	<0.0001
Desire domain (score range, 1.2–6)	0.3 ± 0.2	0.6 ± 0.2	NS
Arousal domain (score range, 0–6)	1.2 ± 0.2	1.6 ± 0.2	<0.05
Lubrication domain (score range, 0–6)	1.1 ± 0.2	1.4 ± 0.2	NS
Orgasm domain (score range, 0–6)	0.8 ± 0.3	1.5 ± 0.3	0.006
Pain domain (score range, 0–6)**	1.0 ± 0.3	1.9 ± 0.3	0.0007
EDITS-Partner			
Index at week 12 LOCF as LS mean ± SE (range, 0–100)	38.7 ± 4.6	57.7 ± 4.6	<0.0001
Estimated percentage (95% CI) satisfied at week 12 LOCF as LS mean ± SE	26 (17–37)	63 (51–74)	<0.0001 (OR, 5.0)
DAS total score change from baseline to week 12 LOCF as LS mean ± SE (range, 0–150)	5.1 ± 1.9	2.5 ± 1.9	NS

LOCF, last observation carried forward; NS, not statistically significant; OR, odds ratio.
*LS mean ± SE and *P* value based on an ANCOVA model with terms for treatment, investigator site, baseline value (except for EDITS), DAS total score at baseline (for men and women), duration and aetiology of ED, and age (of men and women).
**Higher score indicates less pain.

of 42 percentage points in the men treated with sildenafil compared with 20 percentage points in the men treated with placebo ($P = 0.038$). Concomitantly, the partners found intercourse satisfying on fewer than 25% of occasions at baseline in each group, but there was an estimated increase of 38 percentage points in the partners of men treated with sildenafil compared with 16 percentage points in the partners of men treated with placebo ($P < 0.0001$).

Responses in men treated for ED (Table 3)

Men treated with sildenafil compared with placebo had greater baseline to end-of-treatment improvement in scores for IIEF Q7 (frequency of satisfactory intercourse) and the IIEF domains of erectile function, intercourse satisfaction, and overall satisfaction ($P < 0.001$ for all comparisons), but not orgasmic function or sexual desire. At the end of treatment, 46% (38/82) of sildenafil recipients compared with 15% (13/86) of placebo recipients had an IIEF erectile function (EF) domain score indicating no ED (score, 26–30). A greater estimated percentage of men treated with sildenafil, versus placebo, responded that treatment improved their erections (OR = 6.8, $P < 0.0001$) and that treatment improved their ability to have sexual intercourse (OR = 5.9, $P < 0.0001$). During the last 4 weeks of treatment, sildenafil recipients more frequently achieved an erection that lasted long enough for successful intercourse than did placebo recipients (OR = 3.4, $P < 0.01$).

Men treated with sildenafil, compared with placebo, had greater baseline to end-of-treatment improvement in scores for the SEAR sexual relationship domain ($P < 0.0001$), confidence domain ($P = 0.01$), self-esteem subscale ($P = 0.006$), and total score ($P = 0.0003$), but not the overall relationship subscale, and had higher end-of-treatment EDITS Index ($P < 0.0001$) and estimated percentage satisfied with ED treatment (OR = 4.4, $P < 0.0001$). The baseline to end-of-treatment change in total DAS scores was similarly small for men treated with sildenafil or placebo.

Predictors of improvement in satisfaction and sexual function in couples

The generalised linear model (ANCOVA) identified several predictors of improvement in measures of sexual satisfaction and function. In the women, greater baseline to end-of-treatment improvement in sexual satisfaction was predicted by higher baseline DAS score (which predicted improvement

Table 3. Responses in men treated with sildenafil or placebo for ED

Efficacy measure*	Placebo	Sildenafil	*P* value
IIEF score change from baseline to week 12 LOCF as LS mean ± SE			
Erectile function domain (range, 1–30)	3.4 ± 1.0	8.9 ± 1.0	<0.0001
Orgasmic function domain (range, 0–10)	0.9 ± 0.4	1.5 ± 0.4	NS
Sexual desire domain (range, 2–10)	0.1 ± 0.2	0.4 ± 0.2	NS
Intercourse satisfaction domain (range, 0–15)	1.3 ± 0.5	3.8 ± 0.5	<0.0001
Overall satisfaction domain (range, 2–10)	0.8 ± 0.3	2.1 ± 0.3	0.0003
Q7: frequency of satisfactory intercourse (range, 0–5)	0.3 ± 0.2	1.5 ± 0.2	<0.0001
GEQs: estimated percentage (95% CI). 'Compared with no treatment, has the medication you have been taking over the past four weeks improved your			
erections?' (GEQ1)	25 (16–36)	69 (57–79)	<0.0001 (OR, 6.8)
ability to have sexual intercourse?' (GEQ2)	30 (20–41)	71 (60–80)	<0.0001 (OR, 5.9)
Event log estimated percentage (95% CI) at week 12 LOCF			
Attempts with sexual stimulation at which an erection that lasted long enough for successful intercourse was achieved	49 (35–63)	77 (64–86)	0.004 (OR, 3.4)
DAS total score change from baseline to week 12 LOCF as LS mean ± SE (range, 0–150)	1.7 ± 1.8	2.1 ± 1.8	NS
SEAR questionnaire score change from baseline to week 12 LOCF as LS mean ± SE (range 0–100)			
Sexual relationship domain	5.5 ± 3.4	20.8 ± 3.5	<0.0001
Confidence domain	7.0 ± 3.6	17.1 ± 3.8	0.01
Self-esteem subscale	7.2 ± 3.9	18.8 ± 4.1	0.006
Overall relationship subscale	6.8 ± 4.0	13.3 ± 4.2	NS
Total score	6.1 ± 3.3	19.1 ± 3.4	0.0003
EDITS			
Index at week 12 LOCF as LS mean ± SE (range, 0–100)	43.4 ± 4.1	64.1 ± 4.3	<0.0001
Estimated percentage (95% CI) satisfied at week 12 LOCF as LS mean ± SE	31 (21–42)	66 (55–76)	<0.0001 (OR, 4.4)

LOCF, last observation carried forward; NS, not statistically significant; OR, odds ratio.
*LS mean ± SE and *P* value are derived from an ANCOVA model with terms for treatment, investigator site, baseline value, DAS total score at baseline (men), duration and aetiology of ED, age, and smoking status. Estimated percentages (95% CI) are computed from logistic regression with terms for treatment, percent at baseline (for event log only), DAS total score at baseline (men), duration and aetiology of ED, age, and smoking status.

in the FSFI satisfaction domain, $P = 0.0184$), and greater baseline to end-of-treatment improvement in sexual function was predicted by younger age of the men (which predicted improvement in the FSFI desire domain, $P = 0.0237$) and higher baseline DAS score in the women (which predicted improvement in the FSFI lubrication domain, $P = 0.0119$). In the men, greater baseline to end-of-treatment improvement in sexual satisfaction was predicted by younger age (which predicted improvement in the IIEF intercourse satisfaction domain, $P = 0.0342$), and greater baseline to end-of-treatment improvement in sexual function was predicted by shorter ED duration (which predicted improvement in the IIEF erectile function domain, $P = 0.0287$) and lower baseline DAS score (which predicted improvement in the IIEF orgasmic function domain, $P = 0.0292$).

Correlations between sexual satisfaction and sexual function within couples

Correlation coefficients were estimated for sexual satisfaction outcomes and sexual function outcomes between the women and the men treated with sildenafil (Table 4) or placebo (Table 5) for ED. There were statistically significant positive correlations for all sexual satisfaction outcomes, for approximately half the sexual satisfaction outcomes in one gender versus the sexual function outcomes in the other gender and for several of the sexual function outcomes. Further evidence for association between change in sexual function and satisfaction within couples is provided by positive correlation between the change score for the IIEF EF domain and the end-of-treatment EDITS-Partner Index (sildenafil: $r = 0.52$ [95% CI, 0.33–0.66]; placebo: $r = 0.49$ [95% CI, 0.31–0.64]).

Safety

Sildenafil was generally well tolerated. Eighteen (21%) of the 86 sildenafil recipients experienced a total of 29 treatment-related adverse events, compared with 11 treatment-related adverse events in 10 (11%) of 94 placebo recipients. All treatment-related adverse events were mild or moderate in intensity, except for a severe case of rhinitis in a sildenafil recipient and a severe headache in a placebo recipient. The most

Table 4. In couples in which the man was treated with sildenafil for ED, correlations between measures of satisfaction in one gender and measures of satisfaction and sexual function in the other gender at week 12

	Pearson's correlation coefficients, *r* (95% CI)*				
	Men: IIEF domains				
	Satisfaction measures		Sexual function measures		
Women: FePEDS Q3 and FSFI domains	Intercourse satisfaction	Overall satisfaction	Erectile function	Orgasmic function	Sexual desire
Satisfaction measures					
FePEDS Q3	**0.33 (0.12–0.51)**	**0.28 (0.07–0.47)**	**0.51 (0.32–0.65)**	**0.29 (0.08–0.48)**	−0.05 (−0.26 to 0.17)
FSFI satisfaction domain	**0.28 (0.06–0.47)**	**0.28 (0.06–0.47)**	**0.26 (0.04–0.45)**	**0.24 (0.02–0.44)**	−0.06 (−0.28 to 0.16)
Sexual function measures					
FSFI desire	0.16 (−0.06 to 0.36)	0.12 (−0.10 to 0.33)	**0.26 (0.05–0.46)**	0.16 (−0.06 to 0.37)	0.02 (−0.20 to 0.24)
FSFI arousal	**0.22 (0.00–0.42)**	**0.23 (0.01–0.43)**	**0.25 (0.03–0.45)**	**0.21 (−0.01 to 0.41)**	−0.07 (−0.28 to 0.16)
FSFI lubrication	**0.22 (0.00–0.42)**	0.15 (−0.07 to 0.36)	**0.24 (0.02–0.43)**	0.17 (−0.05 to 0.37)	−0.00 (−0.22 to 0.22)
FSFI orgasm	**0.22 (0.00–0.42)**	0.14 (−0.08 to 0.35)	**0.30 (0.09–0.49)**	0.17 (−0.05 to 0.38)	−0.09 (−0.30 to 0.14)
FSFI pain	**0.29 (0.08–0.48)**	0.08 (−0.15 to 0.29)	**0.31 (0.10–0.50)**	0.07 (−0.16 to 0.28)	−0.07 (−0.28 to 0.16)

*Change scores (baseline to end of treatment) for the IIEF domains were correlated with the end-of-treatment FePEDS Q3 score and change scores (baseline to end of treatment) for the FSFI domains. Bold text indicates $P < 0.05$ for the correlation.

common treatment-related adverse events were headache ($n = 6$ [sildenafil] and $n = 5$ [placebo]), vasodilatation ($n = 6$ and $n = 3$), rhinitis ($n = 6$ and $n = 0$), dyspepsia ($n = 2$ and $n = 0$), and abnormal vision or chromatopsia ($n = 3$ and $n = 1$). No treatment-related adverse event was serious or caused permanent discontinuation or death.

Discussion

The results of this trial show that men treated with sildenafil compared with placebo had improved erectile function, increased frequency of successful and satisfactory sexual intercourse, and improvement in IIEF measures of sexual satisfac-

Table 5. In couples in which the man was treated with placebo for ED, correlations between measures of satisfaction in one gender and measures of satisfaction and sexual function in the other gender at week 12

	Pearson's correlation coefficients, *r* (95% CI)*				
	Men: IIEF domains				
	Satisfaction measures		Sexual function measures		
Women: FePEDS Q3 and FSFI domains	Intercourse satisfaction	Overall satisfaction	Erectile function	Orgasmic function	Sexual desire
Satisfaction measures					
FePEDS Q3	**0.34 (0.13–0.51)**	**0.40 (0.20–0.57)**	**0.37 (0.17–0.55)**	0.17 (−0.4 to 0.37)	0.15 (−0.06 to 0.36)
FSFI satisfaction domain	**0.34 (0.13–0.51)**	**0.29 (0.08–0.48)**	**0.24 (0.03–0.44)**	**0.25 (0.04–0.45)**	0.18 (−0.04 to 0.38)
Sexual function measures					
FSFI desire	0.30 (0.09–0.49)	**0.22 (0.00–0.42)**	**0.24 (0.03–0.44)**	0.11 (−0.11 to 0.32)	0.14 (−0.08 to 0.35)
FSFI arousal	**0.33 (0.12–0.51)**	0.22 (−0.01 to 0.42)	0.19 (−0.03 to 0.39)	**0.27 (0.05–0.46)**	0.20 (−0.02 to 0.40)
FSFI lubrication	0.22 (−0.00 to 0.42)	0.10 (−0.12 to 0.32)	0.11 (−0.11 to 0.33)	**0.22 (0.00–0.42)**	**0.25 (0.03–0.44)**
FSFI orgasm	0.20 (−0.02 to 0.40)	**0.27 (0.06–0.46)**	0.07 (−0.14 to 0.29)	0.14 (−0.07 to 0.35)	**0.27 (0.06–0.46)**
FSFI pain	**0.31 (0.11–0.50)**	0.16 (−0.06 to 0.37)	**0.33 (0.12–0.51)**	**0.24 (0.03–0.43)**	0.02 (−0.19 to 0.24)

*Change scores (baseline to end of treatment) for the IIEF domains were correlated with the end-of-treatment FePEDS Q3 score and change scores (baseline to end of treatment) for the FSFI domains. Bold text indicates $P < 0.05$ for the correlation.

tion and SEAR measures of emotional wellbeing. Their partners, compared with the partners of men treated with placebo, had greater frequency of satisfactory sexual intercourse, an increase in sexual satisfaction assessed by the FSFI and enjoyment assessed by the SFQ, and improvement in some measures of desirability, arousal, and orgasm. The men treated with sildenafil, and their partners, were also more satisfied with the ED treatment, according to the EDITS Index and EDITS-Partner Index. Baseline affectional expression and dyadic satisfaction, consensus, and cohesion assessed by the DAS were high at baseline and showed no significant change with treatment.

Greater improvement in sexual satisfaction measures was predicted in the women by higher baseline DAS score and was predicted in the men by younger age. Greater improvement in sexual function measures was predicted in the women by younger age of the men and higher baseline DAS score and was predicted in the men by shorter ED duration and lower baseline DAS score. Thus, in the women, higher baseline DAS score predicted greater improvement in measures of sexual satisfaction and function, whereas in the men, lower baseline DAS score predicted greater improvement in measures of sexual function. This suggests, that in women, a more satisfactory, happier general relationship provides a good basis for sexual improvement, whereas in men, sexual and relationship problems are closely linked.

Change in measures of sexual satisfaction and function (arousal, orgasm, and pain) in the women correlated positively with change in measures of sexual satisfaction and erectile function in their male partners with ED. Specifically, change in intercourse satisfaction in the women correlated positively with change in erectile function and with change in intercourse satisfaction in their male partners. Change in erectile function in men with ED also correlated positively with change in satisfaction of the partners with the ED treatment. The fact that the correlations were shown in the sildenafil group and in the placebo group adds strength to the association between sexual function and satisfaction between members of a couple.

The results of the current trial support previous outcomes reported by partners of men treated with a phosphodiesterase type 5 inhibitor for ED. There have been two reports of survey results.[7,8] In a Japanese survey, the partners of 98 men being treated with sildenafil for ED were queried as to their satisfaction; 63% of the responding women reported satisfaction with their own sex life and 67% with the man's sildenafil treatment, but these results are compromised by a low survey response rate (31%) and high rate of underlying female sexual dysfunction (47%).[7] In the Female Experience of Men's Attitudes to Life Events and Sexuality study, 293 partners of men with ED who had participated in the Men's Attitudes to Life Events and Sexuality study responded to a mail or internet questionnaire; a higher proportion of partners of men with ED who were currently using a phosphodiesterase type 5 inhibitor to treat their ED, compared with partners of untreated men with ED, responded that they 'almost always' or 'most times' experienced sexual desire (54 versus 43%), arousal (56 versus 40%), orgasm (46 versus 30%), and pain (7 versus 2%) ($P < 0.05$ for all comparisons).[8] Clinical trial data in female partners have provided additional information.[2,9] In an open-label, prospective trial conducted in Turkey, measures of sexual function were assessed in partners, before and after 3–24 (mean, 9 ± 7) months of treatment of men with penile prosthesis implantation ($n = 17$) or oral sildenafil ($n = 13$) for ED, and compared with the sexual function in the partners of 49 men without ED (control group).[2] In this open-label study, scores on the FSFI total score and on the domains of arousal, lubrication, orgasm, satisfaction, and pain, but not desire, were lower (indicating poorer function and greater pain) in the partners of the men with ED than that in the control group partners at baseline ($P < 0.05$) but improved after treatment of the men's ED ($P < 0.01$) to a level equal to or slightly greater (≤8%) than that of the control group partners at baseline. Placebo-controlled FePEDS Q3 data were pooled from 11 sildenafil clinical trials of ED ($n = 611$ men and 426 partners), and EDITS-Partner data were pooled from 6 of these ($n = 410$ men and their partners).[9] The partners of men taking sildenafil compared with placebo reported more frequent satisfactory intercourse (FePEDS Q3; $P < 0.0001$) and greater satisfaction with the ED treatment (EDITS-Partner Index; $P < 0.0001$). Positive correlations were found between the end-of-treatment frequency of satisfactory intercourse reported by the women (FePEDS Q3) and the change from baseline to end of treatment in frequency of erection (IIEF Q1), maintained erection (IIEF Q4), and satisfactory intercourse (IIEF Q7) reported by the men and between the end-of-treatment satisfaction with ED treatment in the women (EDITS-Partner Index) and the men (EDITS Index) ($P < 0.0001$ for all correlations).[9] However, unlike the results of the current trial, these placebo-controlled data provide no specifics of the sexual function of the women before the men's use of sildenafil to treat their ED, nor do they provide any specific information as to what contributed to the women's increased frequency of satisfactory intercourse, for example, improvement in measures of sexual relationship, overall relationship satisfaction, or her own sexual response. Thus, previous outcomes reported by partners of men treated with a phosphodiesterase type 5 inhibitor for ED had left many unanswered questions regarding sexual function and sexual satisfaction.

In a double-blind, placebo-controlled trial of flexible-dose vardenafil (5, 10, and 20 mg), 229 couples selected for long-standing (more than 6 months) ED in the men and the absence of underlying sexual dysfunction in their partners (documented by an FSFI total score >26.55 out of a maximum of 36) were randomised.[10,11] In this vardenafil trial, baseline

sexual function of the women was relatively high according to FSFI scores, with LS mean domain scores ranging from 4.0 to 5.0 out of a maximum of 6 in the partners of men randomised to vardenafil and ranging from 3.8 to 5.2 in the partners of men randomised to placebo. From baseline to end of treatment, IIEF EF domain scores improved in the men treated with vardenafil ($P < 0.0001$ versus placebo) and FSFI scores in their partners improved slightly across the domains (from a score of 4.2 to 4.3 [desire], 4.0 to 4.4 [orgasm], 4.3 to 4.9 [satisfaction], 4.5 to 4.9 [arousal], 5.00 to 5.01 [lubrication], and 4.9 to 5.2 [pain]). In contrast, IIEF EF domain scores were unchanged in the men treated with placebo, and FSFI scores decreased slightly in their partners. Consequently, the difference between vardenafil and placebo in FSFI change scores was statistically significant for all domains except pain ($P < 0.01$).[10,11,21]

In comparison with this vardenafil trial, the current sildenafil trial randomised couples selected for ED in the men and self-reported frequency of satisfactory sexual intercourse 'sometime, about half the time' or less in their partners, excluding couples in which the partner had significant dyspareunia or lifelong significant sexual dysfunction. Consequently, our cohort of partners of men treated with sildenafil for ED had baseline FSFI domain scores that were lower (range, 2.9–3.5) than those of the partners of men randomised to vardenafil treatment for ED in the vardenafil trial (range 4.0–5.0). Nevertheless, end-of-treatment FSFI scores were almost identical (4.2–5.5 and 4.3–5.2, respectively) because of greater improvement in the sildenafil trial. Thus, in partners of men who received an efficacious treatment for their ED (vardenafil) and who had no underlying sexual dysfunction of their own, sexual function improved significantly relative to placebo but with modest absolute gains. However, in partners of men who received an efficacious treatment for their ED (sildenafil) and who had no underlying dyspareunia or lifelong significant sexual dysfunction of their own but had lower baseline sexual function because of differences in entry criteria, sexual function improved to a clinically significant extent, attaining levels similar to those of women whose baseline sexual function was much higher. In these two trials, FSFI domain scores in the partners of men who received placebo for their ED showed different trends, decreasing slightly in the vardenafil trial and increasing slightly in the current trial.

The results of the current trial are important because they showed, for outcomes on measures of sexual function and satisfaction, the interdependence between partners in a stable couple. It may be intuitive that efficacious treatment of ED, which improved measures of sexual function and satisfaction in men, would also improve measures of sexual function and satisfaction in their partners. Our results show that this association was significant, although neither universal across domains nor strong. An implication of the interaction in responses within couples is that partners may play a significant role in the success or failure of the man's ED treatment and may influence decisions regarding treatment and even its continuation. Consequently, inclusion of partners in discussions of ED treatment may improve outcomes, a supposition that warrants further study in controlled clinical trials. There are many other topics that warrant further study, such as the adjustments in sexual activity that couples make in response to an unsatisfactory intercourse attempt and the role of sildenafil in that context. The demonstrated value of certain baseline characteristics (e.g. age, DAS scores) in predicting improvement in measures of sexual function and sexual satisfaction in men treated with sildenafil for ED, and in their partners, suggests the potential to identify candidate couples who might have an increased likelihood of benefit from this therapy and the potential to determine how these predictive variables might compare with other medication or psychological therapies.

Conclusions

The results of this trial can be generalised to couples in which a man with ED is in a long-standing relationship with a woman who is sexually healthy but reports infrequent satisfactory sexual intercourse. In such men, sildenafil treatment improved erectile function; increased the frequency of successful and satisfactory sexual intercourse; and improved measures of sexual satisfaction, emotional wellbeing, and satisfaction with the ED treatment. In their partners, the frequency of satisfactory sexual intercourse improved, as did measures of sexual satisfaction and enjoyment; some measures of desirability, arousal, and orgasm; and satisfaction with the ED treatment. The interdependence between outcomes on measures of sexual function and sexual satisfaction of men and those of women in such couples suggests a significant role for partners in treatment outcomes and continuation decisions and highlights the importance of including partners in discussions of ED treatment. The prognostic factors identified in the current study may begin to suggest candidate couples who may better benefit from sildenafil therapy.

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