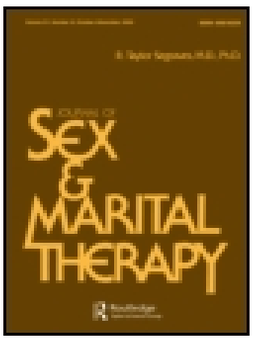

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Placebo Response in the Treatment of Women's Sexual Dysfunctions: A Review and Commentary

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We reviewed the literature to determine the nature and magnitude of therapeutic response associated with placebo treatment in clinical trials for women's sexual dysfunction. We abstracted data from 16 articles to record the effect size associated with placebo treatment. In most of these studies, placebo recipients reported statistically significant improvements on one or more major endpoints relative to baseline. Although placebo responses varied across study populations and methodologies, within-group effect sizes were predominantly in the moderate range. Our findings suggest that postmenopausal women and women with hypoactive sexual desire disorder may be more likely to respond to placebo treatment.

Interest in pharmacological and other biomedical treatments for women's sexual dysfunctions surged after the introduction of phosphodiesterase type 5 (PDE-5) inhibitors in the late 1990s. This prompted a number of clinical investigations aimed at examining the efficacy of vasoactive agents to treat female sexual arousal disorder by facilitating the genital swelling-lubrication response. These trials largely focused on the effects of PDE-5 inhibitors but to a lesser extent also examined the effects of other vasoactive treatments such as nitric oxide precursors (Meston & Worcel, 2002) and adrenergic antagonists (Rubio-Aurioles et al., 2002). In parallel, a number of recent large multi-site trials have investigated the efficacy of testosterone supplementation for treatment of low sexual desire, mainly in post-menopausal populations identified as "androgen deficient." Although resources devoted

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to development of these treatments have been substantial, to date most investigational treatments have failed to meaningfully outperform placebo in the treatment of women's sexual dysfunctions. Consequently, there are no pharmacological treatments for women's sexual desire or sexual arousal disorders that have been approved by the U.S. Food and Drug Administration.

The failure of sildenafil and other vasoactive treatments to outperform placebo in late-phase clinical trials suggests that the target of these treatments (enhancing blood flow to genital tissues) may have a limited effect on women's perceptions of their sexual difficulties. Although laboratory studies indicate that, for the most part, these drugs performed as expected *physiologically* by facilitating genital vasocongestive responses, in most studies they did not effect a comparable increase in psychological sexual arousal (Meston & Worcel, 2002; Basson, McInnes, Smith, Hodgson, & Koppiker, 2002; Laan et al., 2002). Thus, although vasoactive drugs appear to "work" insofar as they promote measurable increases in physical responses to sexual stimuli, the lack of a concomitant subjective response in psychophysiological studies is consistent with the lack of clinical efficacy demonstrated in most clinical trials.

Although clinical trial results indicate testosterone treatment has also largely underperformed initial expectations, some controversy remains about the efficacy of this type of treatment, and efforts to develop testosterone supplementation for sexual desire problems are ongoing. The mechanism by which testosterone might enhance sexual desire in women is not well understood but is thought to be related to central processing of sexual stimuli via steroid receptors in the brain. Androgens, either through a direct mechanism of action or through aromatization to estrogen, are believed to modulate attention to sexual stimuli and cognitive appraisal of sexual stimuli, although other psychological mechanisms such as mood change might better account for their effects (Bancroft, 2002; Scepkowski, Georgescu, & Pfaus, 2006). However, empirical evidence in support of these theories is scant, obscuring a thorough evaluation of the effects of testosterone supplementation on psychological and sexual outcomes.

In summary, pharmacological treatments for women's sexual dysfunction have largely failed to perform as anticipated. The abundance of research and development efforts in this field belies the notion that these treatments have simply received inadequate study. A conspicuous outcome of pharmaceutical research is the finding of a reliable and often substantial response to placebo treatment among women enrolled in these trials, and this effect is worthy of further investigation. To our knowledge, there has been no systematic review of the literature on placebo responses in the treatment of women's sexual dysfunction. We conducted a database search to identify and document placebo responses described in published clinical trial reports for pharmaceutical treatments for sexual desire and arousal problems in women.

METHOD

Our general approach to reviewing literature on placebo responses was to locate published clinical trial reports addressing pharmacological treatment of sexual dysfunctions in women and to qualify (and when possible, quantify) the effect of placebo treatment relative to baseline on some defined endpoint. For the purpose of this review, we defined placebo response broadly as any change occurring after the administration of placebo (Spiro, 1997).

We conducted a MEDLINE database search to locate relevant clinical trial reports published between 1997 and 2007. We searched for original research articles that included the search terms "sexual desire" or "sexual arousal" in any field and that were classified as "Randomized Controlled Trial," "Controlled Clinical Trial," "Clinical Trial," "Clinical Trial Phase III," and "Clinical Trial Phase IV." To supplement this search, in a separate search we combined the terms "sexual arousal" and "sexual desire" with "women" in addition to each of three common active treatments described in multiple trials in the literature: "sildenafil," "testosterone," and "bupropion." We searched for articles pertaining to both acute and long-term effects on sexual desire and/or sexual arousal.

The combined search terms yielded a total of 165 articles. We further applied the following exclusion criteria: studies that focused primarily on outcomes other than sexual dysfunction; studies conducted in nonclinical samples (except in laboratory evaluations of acute drug effects); studies that did not include a placebo control group or only assessed placebo response during a pretreatment "lead-in" phase; and studies that were primarily evaluations of safety and side effects rather than efficacy. We applied these criteria by eliminating articles with titles that were unambiguously outside the scope of the study (e.g., studies performed in men), then by reading the abstracts of remaining articles, and finally by obtaining the full text of articles which we were unable to exclude on the basis of information in their abstracts. In addition to the articles identified in our database search, we also evaluated additional articles for inclusion from the reference lists of selected publications.

Forty-one articles met our initial screening criteria, and from these we abstracted data on the participant populations, study designs, active comparison treatments, and effects within the placebo groups (i.e., the difference in outcome scores from baseline to placebo treatment; see Table 1). We further excluded articles that did not provide sufficient information to infer the statistical significance of placebo group effects (e.g., p values, confidence intervals, or standard errors of the mean) as this would obscure interpretation of the magnitude of the effect. However, we retained several articles that provided data for placebo group participants who reached a predetermined clinical endpoint, regardless of data about statistical significance.

TABLE 1. Placebo Group Effect Sizes in Previous Clinical Trials for Sexual Desire and Arousal Problems in Women

Author/Year	Placebo Group Size*	Sample Characteristics	Study Design	Comparison Drug in Active Treatment Group(s)	Outcome Measure	Within-Group Effects of Placebo (Change from Baseline; see Appendix)	Active Treatment > Placebo for 1 or More Outcomes?
Studies of the efficacy of sildenafil in women with sexual arousal difficulties and related problems							
Caruso et al., 2006	32	Pre-menopausal women with type 1 diabetes ages 27–43 complaining of sexual arousal problems	Double-blind, placebo controlled crossover design (8 weeks treatment each phase)	Sildenafil, 100 mg (oral), taken 1 h prior to sexual activity	Personal Experiences Questionnaire (PEQ)	Significant increase in frequency of sexual intercourse compared to baseline, $d = .7$; no significant increase in sexual arousal scores	Yes (PEQ domain scores for arousal, orgasm, and pain)
Berman et al., 2003	98	Post-menopausal women ages 30–71 with sexual arousal problems; excluded women with "emotional" or "relationship" issues contributing to sexual difficulty	Double-blind, placebo-controlled parallel group design (12 weeks of treatment)	Sildenafil, 50 mg adjustable dose (oral), taken before sexual activity	Female Intervention Efficacy Index	44% reported some improvement in genital sensation during sexual activity; 28% reported some improvement in satisfaction with sexual activity	Yes (2 of 6 question-naire items)

(Continued on next page)

TABLE 1. Placebo Group Effect Sizes in Previous Clinical Trials for Sexual Desire and Arousal Problems in Women (*Continued*)

Author/Year	Placebo Group Size*	Sample Characteristics	Study Design	Comparison Drug in Active Treatment Group(s)	Outcome Measure	Within-Group Effects of Placebo (Change from Baseline; see Appendix)	Active Treatment > Placebo for 1 or More Outcomes?
Basson et al., 2002	217	Pre- and post-menopausal women with female sexual arousal disorder; 577 were receiving estrogen	Double-blind, placebo-controlled parallel group design (12 weeks of treatment)	Sildenafil, 10, 50, or 100 mg (oral) taken before sexual activity (nonestrogenized started at a 50 mg adjustable dose)	31-item sexual function questionnaire and 2 global efficacy items	44% of women endorsed improvement in physical sexual response; 33.3% of estrogenized and 41.9% of estrogen-deficient women endorsed improved ability to participate in sexual activity	No
Caruso et al., 2001	51	Pre-menopausal women ages 22–38 with "normal" sexual desire complaining of sexual arousal and orgasm problems	Double-blind, placebo-controlled crossover design (4 weeks treatment each phase)	Sildenafil, 25 and 50 mg (oral), taken before sexual activity	Personal Experiences Questionnaire (PEQ)	No significant improvement over baseline for arousal and enjoyment scores, though there was a significant improvement in orgasm scores ($d = 3.3$).	Yes (all PEQ domain scores)
Studies of the efficacy of testosterone in women reporting low sexual desire and other sexual difficulties							
Barton et al., 2007	131	Post-menopausal cancer survivors complaining of low sexual desire (mean age 52)	Double-blind, placebo-controlled crossover design (4 weeks treatment each phase)	2% testosterone topical cream applied to thigh or abdomen (dosing not specified)	Changes in Sexual Functioning Questionnaire (desire subscales)	Increase in sexual desire/frequency and sexual desire/interest subscales after 4 weeks of treatment with placebo; no significant difference compared with active treatment	No

Shifren et al., 2006	264	Post-menopausal women ages 40–70 complaining of low sexual desire	Double-blind, placebo-controlled parallel group design (24 weeks of treatment)	Transdermal testosterone patch, 300 μg qd	Sexual activity log, Profile of Female Sexual Function (PFSF), Personal Distress Scale	Increase in sexual desire outcome score ($d = .28$); decrease in personal distress score ($d = -.46$)	Yes (sexually satisfying events, PFSF desire domain, and Personal Distress Scale score)
Braunstein et al., 2005	81	Women ages 24–70 who reported low sexual desire following hysterectomy and oophorectomy	Double-blind, placebo-controlled parallel group design (24 weeks of treatment)	Transdermal testosterone patch, 150, 300, or 450 μg qd	Sexual activity log, Profile of Female Sexual Function desire score, Personal Distress Scale	Increase in sexual desire score ($d = .35$); 43% increase in number of sexually satisfying activities per week; reduction in personal distress score	Yes (all outcomes)
Simon et al., 2005	273	Women ages 26–70 who reported low sexual desire following oophorectomy	Double-blind, placebo-controlled parallel group design (24 weeks of treatment)	Transdermal testosterone patch, 300 μg qd	Sexual activity log, Profile of Female Sexual Function desire score, Personal Distress Scale	Increase in satisfying sexual events ($d = .26$), Profile of Female Sexual Function sexual desire score ($d = .36$), and decrease in Personal Distress Scale score ($d = -.55$)	Yes (all outcomes)

(Continued on next page)

TABLE 1. Placebo Group Effect Sizes in Previous Clinical Trials for Sexual Desire and Arousal Problems in Women (*Continued*)

Author/Year	Placebo Group Size*	Sample Characteristics	Study Design	Comparison Drug in Active Treatment Group(s)	Outcome Measure	Within-Group Effects of Placebo (Change from Baseline; see Appendix)	Active Treatment > Placebo for 1 or More Outcomes?
Buster et al., 2005	206	Women who reported low sexual desire following oophorectomy (mean age 49)	Double-blind, placebo-controlled parallel group design (24 weeks of treatment)	Transdermal testosterone patch, 300 μg qd	Sexual activity log, Profile of Female Sexual Function, Personal Distress Scale	Significant increases in sexual desire score and number of sexually satisfying events	Yes (all outcomes)
Goldstat et al., 2003	34	Pre-menopausal women ages 30–45 with Sabbatsberg Sexual Self-Rating Scale scores < 42	Double-blind, placebo-controlled crossover design (12 weeks treatment each phase)	Testosterone 1% cream, 10 mg qd, administered topically	Sabbatsberg Sexual Self-Rating Scale (SSSS)	No significant increase in domain scores for sexual interest, sexual pleasure, or sexual fantasy; 19% achieved a 50% or greater increase in their overall sexual self-rating scores	Yes (all SSSS domain scores except "Importance of sex")
Shifren et al., 2000	65	Women ages 31–65 who reported sexual difficulties following hysterectomy and oophorectomy	Double-blind, placebo-controlled crossover design (12 weeks treatment each phase after a 4-week baseline period)	Transdermal testosterone patch, 150 μg qd and 300 μg qd	Brief Index of Sexual Functioning for Women (BISF-W)	Improvement in sexual thoughts/desire (d = .53), arousal (d = .61), receptivity/initiation (d = .58), and composite score (d = .61)	Yes (BISF-W composite score and domain scores for frequency of sexual activity and pleasure-orgasm)

Other efficacy studies							
Caruso et al., 2004	55	Pre-menopausal women ages 26–45 with low sexual desire and sexual arousal problems; study limited to nonresponders to initial treatment with study drug	Double-blind, placebo-controlled crossover design (2 weeks treatment each phase)	Apomorphine, 2 mg qd and 3 mg qd, administered sublingually	Personal Experiences Questionnaire (PEQ)	No significant increase in desire or arousal scores or frequency of intercourse; significant increase in satisfaction with intercourse frequency	Yes (all PEQ domain scores)
Meston, 2004	19	Pre-menopausal women ages 18–50 reporting sexual problems secondary to anti-depressant treatment	Double-blind, placebo-controlled crossover design (3 weeks treatment each phase)	Ephedrine, 50 mg daily (oral)	Brief Index of Sexual Functioning for Women	Significant improvement in sexual desire (d = .62) and arousability (d = .53) scores compared to baseline	No
Padma-Nathan et al., 2003	23	Pre-menopausal women ages 21–50 with sexual arousal problems	Double-blind, placebo-controlled parallel group design (6 weeks of treatment)	Alprostadil cream, 500 μg, 1000 μg, or 1500 μg applied to the vulva prior to intercourse	Female Sexual Encounter Profile ("arousal success rate")	52.2% achieved an "arousal success rate" of >50% (median success rate = 57%)	No

(Continued on next page)

TABLE 1. Placebo Group Effect Sizes in Previous Clinical Trials for Sexual Desire and Arousal Problems in Women (*Continued*)

Author/Year	Placebo Group Size*	Sample Characteristics	Study Design	Comparison Drug in Active Treatment Group(s)	Outcome Measure	Within-Group Effects of Placebo (Change from Baseline; see Appendix)	Active Treatment > Placebo for 1 or More Outcomes?
Michelson et al., 2002	39	Pre-menopausal women ages 18–50 with lubrication or orgasm problems secondary to fluoxetine	Double-blind, placebo controlled parallel group design (6 weeks of treatment following a 4-week baseline)	Mirtazepine 15 m/day, yohimbine 5.4 mg/day, or olanzepine 2.5 mg/day (dose doubled after 1 week unless poorly tolerated)	Patient-rated visual analog scale; 5-item sexual function questionnaire; computer assisted structured interview	No change in sexual function as assessed by questionnaire; significance of other changes could not be assessed with the available data	No
Michelson et al., 2000	20	Women ages 50 or younger with sexual arousal or orgasm problems secondary to fluoxetine	Placebo controlled parallel group design (8 weeks of treatment following a 4-week baseline)	Amantadine 50 mg/day, or buspirone 20 mg/day (oral), flexible dosing	Patient-rated visual analog scale; sexual function interview	Overall patient-rated sexual function significantly improved ($d = .61$); clinician-rated global impressions were also higher at the end of treatment	No

*Number of treatment completers or number of subjects represented in intent-to-treat analysis. When number of subjects varied by outcome measure reported, the highest number was used. Placebo group size includes the total sample size for studies using crossover designs.

When possible, we computed effect sizes (Cohen's *d* (Cohen, 1977)) for the within-group placebo response by dividing the change score associated with placebo treatment by the standard deviation (SD) of scores. We used the pooled SD when the SDs were reported for both baseline and placebo treatment scores; otherwise, we used the SD of the change score. Some authors reported standard errors of the mean (SEMs) instead of SDs; in this case, we transformed SEMs to SDs by dividing the SEM by the square root of the number of subjects represented in the analysis (see Appendix 1 for detailed information on derivation of effect sizes when applicable).

RESULTS

Placebo Response in Studies of Acute Reactions to a Study Drug

We located 16 articles matching our initial selection criteria that described studies of acute drug effects (e.g., physiological and/or subjective sexual responses in a clinic or laboratory setting). Of these, only two studies compared responses to placebo to responses under identical baseline conditions without any study drug; the majority of the studies only compared responses during administration of placebo versus the active comparison drug. Thus, in most of the acute phase trials we located, we were unable to determine whether placebo treatment itself appeared to enhance acute physiological or subjective responses above baseline. Of the two studies that did measure acute responses under baseline "no drug" conditions, neither reported sufficient information to determine the magnitude and/or statistical significance of placebo response relative to responses under baseline conditions.

Placebo Response in Studies of Long-Term Clinical Efficacy

Although 25 articles met our initial screening criteria, only 16 included sufficient information in determining the magnitude and statistical significance of placebo group effects relative to baseline (or alternatively, included information on the number of subjects who met a predetermined clinical change criterion). Articles that lacked data on the magnitude and significance of placebo group effects were largely focused on comparing placebo and active treatment conditions.

Table 1 summarizes positive placebo-group outcomes that we determined to be statistically significant on the basis of the data provided. The estimated magnitude of effect is provided in cases when sufficient data were available to perform effect size calculations. Also summarized are null findings related to placebo treatment where applicable. We focused our analyses on endpoints that were relevant to the presenting complaints among participants in the included studies, including assessments of domain-specific

symptoms (such as sexual desire and sexual arousal dysfunction). We also noted effects relevant to global indicators of efficacy, such as frequency of sexual activity, overall ratings of sexual function, and reduction in distress related to sexual symptoms. As a reference, we indicated whether outcome measure scores in each study were significantly greater in treatment groups compared to placebo groups.

We obtained estimates of placebo responses in four studies that evaluated the efficacy of sildenafil among women who endorsed sexual arousal problems. The outcomes of these studies were expressed as numerical scores on self-report measures in two studies (Caruso, Intelisano, Lupo, & Agnello, 2001; Caruso et al., 2006) and as a percentage of women reporting any increase in scores in two others (Basson et al., 2002; Berman, Berman, Toler, Gill, & Haughie, 2003). Although in the latter two studies, a substantial percentage of placebo recipients reported some degree of improvement in sexual function, these findings were based on single-item scores that retrospectively assessed treatment efficacy. In contrast, no significant effect of placebo was reported in the two studies that compared mean scores at post-treatment to scores at baseline. Thus, it is possible that differences in outcome assessment methods (e.g., prospective versus retrospective) may have yielded different placebo group outcomes. However, it is also worth noting that the two studies with null findings for the placebo treatment groups enrolled only premenopausal women, whereas the two studies suggesting some degree of placebo treatment efficacy included post-menopausal women and considerably larger samples.

We evaluated placebo group outcomes in seven studies that compared the efficacy of placebo to that of testosterone in the form of a transdermal patch or topical cream (Barton et al., 2007; Braunstein et al., 2005; Buster et al., 2005; Goldstadt, Briganti, Tran, Wolfe, & Davis, 2003; Shifren et al., 2000, 2006; Simon et al., 2005). These studies primarily assessed improvements in sexual desire rather than sexual arousal, and in all but one of the studies the populations consisted of post-menopausal women. Interestingly, the study including premenopausal women was also the only study that reported no significant increase in sexual interest scores following placebo treatment. Among the other six studies, ratings of sexual desire or sexual interest significantly increased from baseline levels among placebo recipients. Estimates of effect size for sexual desire outcomes could be computed in four studies and ranged from 0.28 (Shifren et al., 2006) to 0.53 (Shifren et al., 2000). Reductions in personal distress among placebo groups were also evident in several studies.

The remaining studies we evaluated assessed the efficacy of a variety of treatments in clinically heterogeneous premenopausal populations (Caruso et al., 2004; Meston, 2004; Michelson, Bancroft, Targum, Kim, & Tepner, 2000; Michelson, Kociban, Tamura, & Morrison, 2002; Padma-Nathan et al., 2003).

Of interest, three studies specifically examined treatments for sexual dysfunctions induced by treatment with selective serotonin reuptake inhibitors (Meston, 2004; Michelson et al., 2000, 2002), and two of these reported moderate effects of placebo on global or domain-specific sexual function outcome scores (Meston, 2004; Michelson et al., 2000).

DISCUSSION

Our review of the available data from the literature indicates that statistically significant and often substantial placebo responses are not uncommon in the biomedical treatment of women's sexual dysfunctions. There are many nuanced explanations for the effects of placebo treatment, but most are organized around two dominant theories. First, a placebo effect can be conceptualized as a response to a conditioned stimulus, whereby the physiological effects of an active treatment, when repeatedly paired with exposure to a procedure or substantive that is itself inert (e.g., a medication bottle, a capsule of a certain color and shape), are eventually elicited by the inert treatment without the active ingredient (Ader, 1997). However, conditioning depends on the presence of an *active, effective* treatment at some point during the conditioning process to provide a reliable schedule of stimulus-effect pairings. Experimental evidence is insufficient in determining whether women's sexual responses can be elicited through classical conditioning. Moreover, classical conditioning in a clinical context is limited by a lack of a known treatment that can reliably elicit a potent "unconditioned response;" hence it is unlikely that conditioning is a plausible mechanism in this case.

Another dominant explanation for placebo effects is that they result from the individual's conscious expectations of the placebo to bring about relief or other change (Kirsch, 1985; Ross & Olson, 1981). Expectancy effects are essentially meaning responses shaped by the participant's interpretation of her problem and her treatment in the context of culture and experience (Moerman, 2002). Laboratory research to date provides some support for the theory that expectancies for enhanced sexual responses are associated with subjective perceptions of heightened sexual arousal in women. For instance, in studies of vaginal vasocongestive responses to sexually explicit film clips, Palace (1995) and Sipski, Rosen, Alexander, and Hager (2000) provided women with false feedback suggesting strong physiological responses. In these studies, women who received false-positive feedback showed enhanced self-reported and physiological sexual responses upon subsequent exposure to other sexually explicit stimuli. McCall and Meston (2007a) replicated these findings and also found that the effect of false-positive feedback on subsequent sexual responses did not differ in magnitude between women with and without sexual arousal disorder. Although expectancies have been linked to pharmacotherapy outcomes in psychiatric contexts (Gaudiano &

Miller, 2006), this mechanism has yet to be established specifically in the treatment of sexual dysfunctions.

No-treatment or wait list groups are conspicuously absent from controlled trials of sexual dysfunction treatments. Although there is reason to believe that placebo treatment might have caused real clinical change, we cannot estimate the proportion of change after placebo administration which may be attributable to favorable responding bias, regression to the mean, or other effects of repeated measurement. Thus, it is still legitimate to question the extent of a true "placebo effect," that is, a direct effect of placebo treatment that does not simply reflect the passage of time and repeated measurement (Hróbjartsson & Gøtzsche, 2001).

Our findings are based on published data from which we could estimate the presence and magnitude of placebo responses. Although a number of clinical trial reports failed to provide adequate data on placebo responses compared to baseline, and others provided insufficient data to estimate treatment effect sizes for placebo recipients, the data available suggest several hypotheses for further exploration. One possibility is that placebo responses may differ between clinical populations. In our analysis, sexual desire outcomes appeared to be somewhat more responsive to placebo treatment than outcomes for sexual arousal. It is possible, then, that the influence of placebo effect mediators such as expectancies might be more potent in enhancing sexual interest than in sexual arousal, the latter being conceptualized more physically in clinical trials for sexual dysfunction. If this is the case, then it is especially critical to understand predictors of placebo response in hypoactive sexual desire disorder in light of ongoing efforts to develop testosterone-based therapies and novel central stimulants to treat low sexual desire.

Another finding revealed in our review was that placebo responses were greater among post-menopausal than premenopausal women. In the clinical trials we analyzed for both sildenafil and testosterone treatments, null placebo effects were reported only for premenopausal women. Although heterogeneity of assessment methods may somewhat confound this observation, underlying differences in sexual responsiveness and sexual behavior between pre- and post-menopausal women (McCall & Meston, 2007b) might influence the extent to which these populations respond to placebo treatment. For example, responses may have differed among older women who were in relationships of a longer duration, or placebo effects may have been more potent in women for whom sexual difficulties were of a more longstanding nature. On the other hand, post-menopausal women may have been better represented in studies examining treatments for sexual desire problems, which appeared to have larger placebo responses; thus, age and presenting problem might be confounded in comparing these studies.

Methodological influences on placebo responses cannot be underemphasized. Investigator effects, assessment strategies, duration of treatment, dosing schedule (e.g., daily versus as needed), selection criteria, and treatment procedures are several factors that may influence participant expectancies and other possible mediators of placebo effects. It is worth noting that four methodologically similar studies in our review (Shifren et al., 2006; Braunstein et al., 2005; Simon et al., 2005; Buster et al., 2005), which were similar or identical in treatment duration, treatment modality, outcome measures, and study population, were also highly similar in placebo group responses on the primary outcome measures.

The findings of our review should be interpreted with caution in light of several limitations. First, we did not include unpublished clinical trial report data, and it is possible that unpublished data may have revealed other patterns of placebo response. Second, although the selected studies represent a broad population of women, we reviewed only studies published in English. Third, we limited our review to the data that could be readily extrapolated from the text of the published reports. Due to a lack of analyzable data, we had to exclude almost one-third of the clinical trial reports we located from any assessment of placebo response. Furthermore, as a number of publications did not include numeric values for group means and/or standard deviations, we were able to estimate placebo group effect sizes using data from only half of the 16 studies we reviewed. The quantity and quality of data available in the existing literature preclude any attempt to systematically analyze methodological or other moderators of placebo response through meta-analysis. Moreover, the limited data on placebo responses in clinical trials may obscure the relative magnitude of active treatment effects.

We argue that it is important to take into consideration the magnitude of the placebo effect when considering the magnitude of the treatment effect. Consider, for instance, the outcomes reported by Shifren and colleagues' (2000) study of testosterone supplementation in women after oophorectomy. To what extent is the 56% increase in the composite outcome score over baseline in the high-dose treatment group *meaningfully* larger than the 38% increase in the placebo group? Although most clinical trial reports understandably focus on the effect of an active treatment over and above that of placebo, statistical significance alone is not a satisfactory criterion for evaluating the difference between placebo and active treatments. If effects were reported in more robust terms, such as the percentage of participants no longer meeting criteria for sexual dysfunction after treatment, then the relative effects of placebo and active treatments would have greater relevance to clinical practice.

Repeated drug development failures in the area of women's sexual dysfunction warrant a more careful focus on placebo response. The

difficulties presented by moderate-to-large placebo responses in sexual dysfunction treatment are likely to persist until these effects are better understood. A more comprehensive understanding of placebo responses has the potential to improve active treatments with insight into the psychological processes involved in clinical improvement. In most pharmacological trials, there is likely some degree of overlap in the processes of change between active treatment and placebo groups, as the study procedures responsible for placebo effects are necessarily embedded within the active treatment. In the absence of an active ingredient, improvement in symptoms may reflect any number of clinically relevant processes, from the provider-patient relationship to the manner in which the patient's partner approaches treatment. Basic research on the nature of placebo response in sexual outcomes may answer some questions, but it is also necessary to continue to monitor placebo group outcomes in large clinical trials with better data on the magnitude of placebo response.

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Appendix 1. Notes on Calculation of Effect Sizes

Braunstein et al., 2005: Authors reported a mean sexual desire change score of 8.4 ± 2.2 (standard error of the mean (SEM)) and noted this represented a 48% change from baseline. We inferred that the average baseline score was 17.5 and computed the standard deviation as $2.2/\sqrt{119}$ (SEM divided by square root of the given sample size of 119 for the placebo group). Mean scores were not reported for change in sexually satisfying events from baseline in the placebo group.

Caruso et al., 2001: Authors reported a mean baseline orgasm score of 1 with no standard deviation (SD), which was inferred to be zero. During the placebo treatment crossover phase, the mean orgasm score was reported to be 2.4 (SD = 0.6).

Meston, 2004: Author reported mean baseline sexual desire and sexual arousability scores of 1.49 (SEM = .16) and 0.99 (SEM = .15), respectively. After the placebo crossover phase, these scores had increased to 1.95 (SEM = .18) and 1.37 (SEM = .18), respectively. We transformed the SEMs to standard deviations for all scores by dividing them by the square root of the given sample size of 19 for treatment completers.

Michelson et al., 2000: The authors reported means and standard deviations for patient-rated sexual function scores at the beginning of treatment and the means and standard deviations for change scores pre- to post-treatment (we added the mean change score to the score at baseline to determine the post-treatment score and used the standard deviation of the change score to compute the effect size). Significance level was reported only for the overall sexual function score.

Shifren et al., 2000: Used means and SDs as reported for scores on the outcome measure during baseline and placebo periods.

Shifren et al., 2006: The authors reported means and SEMs for baseline and change scores. We computed the placebo treatment outcome score by adding the mean change score to the mean baseline score. We transformed the SEMs to SDs for all scores by dividing SEMs by the square root of the given sample size (264 for the sexual desire domain score and 263 for the personal distress score).