

## Short- and Long-term Effects of Ginkgo Biloba Extract on Sexual Dysfunction in Women

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**Abstract** Ginkgo biloba extract (GBE) facilitates blood flow, influences nitric oxide systems, and has a relaxant effect on smooth muscle tissue. These processes are important to the sexual response in women and, hence, it is feasible that GBE may have a therapeutic effect. The present study was the first to provide an empirical examination of the effects of both short- and long-term GBE administration on subjective and physiological (vaginal photoplethysmography) measures of sexual function in women with Sexual Arousal Disorder. A single dose of 300 mg GBE had a small but significant facilitatory effect on physiological, but not subjective, sexual arousal compared to placebo in 99 sexually dysfunctional women. The long-term effects of GBE on sexual function were assessed in 68 sexually dysfunctional women who were randomly assigned to 8 weeks treatment of either (1) GBE (300 mg/daily), (2) placebo, (3) sex therapy which focused on training women to attend to genital sensations, or (4) sex therapy plus GBE. When combined with sex therapy, but not alone, long-term GBE treatment significantly increased sexual desire and contentment beyond placebo. Sex therapy alone significantly enhanced orgasm function compared with placebo. Long-term GBE administration did not significantly enhance arousal responses beyond placebo. It was concluded that (1) neither short- or long-term administration of GBE involving restricted vascularity, only recently has its use in alone substantially impacts sexual function in women, (2) the treatment of sexual dysfunction and DeLuca (1998) reported a case of a 37-year-old woman with sexual concerns, and (3) teaching women to focus on genital sensations during sex enhances certain aspects of women's sexual functioning.

**Keywords** Ginkgo biloba Female sexual dysfunction Sex therapy Vaginal photoplethysmography

**Introduction** The Ginkgo biloba is an ancient tree that the Chinese have cultivated and held sacred for its health-promoting properties for over two millennia (Christen, Courtois, & Droy-Lefaix, 1995; DeFeudis, 1991). In recent decades, concentrated extracts from Ginkgo biloba leaves (GBE) have been sold in Western countries as herbal medicines for treating peripheral vascular disease and for enhancing cerebral blood flow (Smith, MacLennan, & Darlington, 1996). Indeed, a number of clinical trials have shown that GBE is effective in treating a wide range of problems associated with impaired circulation, including hearing problems, visual disturbances, edema, varicose veins, leg ulcers, stroke, and intermittent claudication (Cohen & Bartlik, 1998), as well as symptoms of cerebrovascular insufficiency, such as difficulties of concentration and memory, confusion, lack of energy, depressed mood, dizziness, and tinnitus (for review, see Kleijnen & Knipschild, 1992). Although GBE has long been used to treat disorders that (1) neither short- or long-term administration of GBE involving restricted vascularity, only recently has its use in alone substantially impacts sexual function in women, (2) the treatment of sexual dysfunction been suggested. Ellison and DeLuca (1998) reported a case of a 37-year-old woman who was experiencing fluoxetine-induced sexual dysfunction (i.e., decreased sexual desire and arousal, decreased lubrication, delayed orgasm, vaginal anesthesia) that was relieved after 2 weeks of daily use of GBE (180–240 mg/day). In a 4-week, open trial in 33 women and 30 men, Cohen and Bartlik (1998) examined the effects of GBE (40 or 60 mg/twice daily) on antidepressant-induced sexual dysfunction. GBE was 84% effective in alleviating the antidepressant-induced sexual symptoms, with success rates being slightly

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higher in women than in men (91% and 76% for women and men, respectively). Detailed outcome measures or results were not provided in the report, but Cohen and Barlik did note that all phases of the sexual response cycle, including desire, arousal (erection and lubrication), orgasm, and resolution were favorably enhanced.

To our knowledge, there has been only one placebo-controlled trial of GBE for antidepressant-induced sexual dysfunction (Kang, Lee, Kim, & Choo, 2002), and no studies examining the effects of GBE for sexual problems not induced by antidepressant medications. In the one placebo-controlled study published, 27 men and 10 women were randomly assigned to receive either GBE (120 mg/daily for 2 weeks or 160 mg/daily next 2 weeks; 240 mg/day remaining 4 weeks) or placebo for 2 months using a double-blind protocol. Sexual function was assessed by asking participants to rate a number of sexual items on a 5 point rating scale from 1=severe impairments, to 5=normal or the level of sexual function prior to antidepressant medication. The following four items were directly relevant to women's sexual function: sexual desire, overall sexual function, orgasm frequency, and satisfaction. Comparisons with baseline levels were made for each item at weeks 2, 4, and 8. Results indicated there were no statistically significant differences on any items between GBE and placebo except for the item of satisfaction with orgasm at week 8, which showed an improvement with GBE. Although a well-controlled study, the findings from this study do not allow conclusions to be drawn regarding the effectiveness of using GBE to treat women's sexual dysfunction given the limited sample size, that the results were not reported separately by gender, and that sex related changes were not measured using a validated questionnaire.

There are many active agents found in GBE and it is unknown whether the therapeutic benefits of GBE are attributable to single active ingredients or the combined, or perhaps even synergistic, action of many ingredients. Ginkgo biloba leaves contain two major groups of substances: flavonoids (e.g., kaempferol, quercetin, isorhamnetin derivatives) and terpenes (e.g., ginkgolides, bilobalide) (van Beek, Scheerlinck, Rantio, Melger, & Lelyveld, 1991). Ginkgolides, which have not been found in any other living species, can be divided into several types (i.e., A, B, C) which differ only in the number and position of hydroxyl groups (Kleijnen & Knipschild, 1992). Although there may be differences in the composition of ginkgo preparations depending on the manufacturing process used, most preparations are standardized based on the amount of flavone glycosides (24%) and terpenoids (6%).

There are several viable means by which GBE might enhance women's sexual function. One is via the vasoregulatory activity of GBE. Clinical and pharmacological studies have shown that GBE promotes increased blood flow both in the arteries and capillaries (Tylet, 1993). In a randomized

double-blind study (Koltrane, Eber, Lind, Langsteger, & Wakonig, 1989) conducted on 60 patients, GBE (200 mg) given over four consecutive days led to increased skin perfusion and a decrease in blood viscosity and elasticity. Similarly, GBE significantly increased blood flow in nail-fold capillaries in a randomized single-blind crossover study, although conclusions from this study are limited given the small sample size ( $n=10$ ) (Jung, Morowietz, Kiesewetter, & Wenzel, 1990). Clinical reports also indicate GBE is effective in treating a variety of conditions responsive to improved circulation (Cohen & Bartlik, 1998). Genital vasocongestion is a marker of sexual arousal in women, and is the crucial process by which plasma transudation and subsequent lubrication of the epithelial surface of the vaginal wall occur. Given GBE's ability to facilitate peripheral blood flow to various bodily regions (e.g., arms, legs, hands), it is reasonable to speculate that it might also be effective in facilitating blood flow to the genital region, thus enhancing sexual arousal mechanisms, particularly among women with sexual dysfunction who have subnormal capillary vascularization. Indeed, research indicates that sexual arousal problems are associated with vascular and clitoral insufficiency in some women (Park et al., 1997). A second means by which GBE might facilitate sexual function is via the relaxation of the muscular cells of blood vessels. Several studies conducted on isolated rabbit aorta have shown that GBE induces a dose-dependent relaxing effect on vascular smooth muscle (e.g., Auguet & Clostre, 1983; Auguet, DeFeudis, & Clostre, 1982). More recently, Paick and Lee (1996) studied the effect of GBE on human rabbit corpus cavernosal tissue. Both human and rabbit corpus cavernosal tissue, precontracted by norepinephrine, showed a potent relaxation response to subfractions of non-flavonoid fraction, the component of ginkgo biloba extract believed to have the most potent relaxing effect on vascular smooth muscle. In addition to the above mechanisms, Cohen and Bartlik (1998) speculated that GBE could enhance vascular flow to the genitals through inhibition of platelet-activating factor, in a similar manner to the mechanism by which it enhances cerebral perfusion, and by having a direct effect on prosta-glandins, which are known to enhance sexual arousal in men. Recent research has also shown GBE to have nitric oxide-scavenging abilities (Marcocci, Maguire, Droy-Lefaix, & Sacker, 1994), which point to its potential therapeutic value in treating conditions in which nitric oxide (NO) reactivity is important. In men, sexual stimulation leads to the production of NO and the subsequent release of guanylate cyclase. Guanylate cyclase converts guanosine triphosphate to cyclic guanosine monophosphate (cGMP) and cGMP produces relaxation of the smooth muscles of the penile arteries and corpus cavernosum, resulting in increased blood flow into

the penis (Burnett 1997). Evidence suggests that this may disorder with or without desire and/or orgasm concerns. The also occur in the clitoris.

Immunohistochemical evaluation of the human clitoris revealed that NO is produced in this tissue (Burnett 1997) and, with the exception that the clitoris does not contain subalbugineal layer (which contributes to the rigidity of the penis), the clitoris may be considered the homologue of the penis (Toesca, Stolp, & Cocchi 1996). Arterial blood flow is delivered via the clitoral cavernosal arteries and is regulated by helicine arteriolar smooth muscle tone (Park, Moreland, Goldstein, Atala, & Traish 1998). NO has been implicated as a vasodilator in clitoral corpus cavernosum and vaginal muscularis smooth muscle relaxation (Azad et al., 1992; Burnett, 1997). Thus, impaired smooth muscle function may adversely impact the process of clitoral erection and vaginal engorgement and lubrication. Sildenafil (Viagra) acts on NO systems by prolonging the action of cGMP (thus inhibiting the metabolism of cGMP by cyclic nucleotide phosphodiesterase isozymes (PDE)) (Boolell et al., 1996) and has been highly effective in alleviating erectile dysfunction (e.g., Dinsmore et al., 1999; Goldstein et al., 1998; Marks, Duda, Dorey, Macairan, & Santoro et al., 1999).

Evidence from placebo-controlled research is conflicting as to whether sildenafil may also be beneficial in treating sexual arousal dysfunction in women. Among pre-menopausal women with Sexual Arousal Disorder (SAD), Caruso, Intelisano, Lupo, and Agnelli (2001) reported increased self-reported sexual arousal, orgasm, and enjoyment of sexual activity with sildenafil. Among post-menopausal women with SAD, Basson and Brotto (2003) reported decreased latency to orgasm, and increased subjective sexual arousal and perceptions of genital arousal with sildenafil, but only among women with low baseline levels of laboratory-induced genital arousal. In a large sample of 577 estrogen-dependent 204 estrogen-deficient women with SAD, Basson, McInnes, Smith, Hodgson, and Koppik (2002) reported no significant impact of sildenafil on self-report measures of sexual arousal function.

In summary, GBE facilitates blood flow, influences NO systems, and has a relaxant effect on smooth muscle tissue. These processes are integral to sexual response in women.

From a pharmacological perspective then, it is highly feasible that GBE may be effective in enhancing sexual function in women. GBE is extremely well tolerated (Maitra, Marcocci, Method Droy-Lefaix, & Packer, 1995), and animal studies suggest that GBE may exert anti-stress effects that are not explained by either classical antidepressant or anxiolytic activity (Porsolt, Martin, Lenegere, Fromage, & Driedonck, 1990; Rapin, Lamproglou, Drieu, & DeFeudis, 1994).

The present study was designed to provide a comprehensive examination of the potential effectiveness of using GBE to treat sexual dysfunction in women with sexual arousal and orgasmic disorders. Women ( $n = 99$ ) aged 18–65 who were currently experiencing Sexual Arousal Disorder, with or without coexistent Hypoactive Sexual Desire Disorder and/or Orgasmic Disorder were recruited through radio public service announcements and advertisements in local newspapers. Of these 99

women, 36 reported sexual side effects secondary to another blood thinning pharmaceutical agents, and would use antidepressant medication (fluoxetine, sertraline, or paroxetine) as a medically accepted form of birth control. This latter criterion was required by the University of Texas Internal Review Board to protect participants against the potential unknown induced sexual dysfunction if they reported an onset of Hypertensive negative consequences of GBE on pregnancy. Participants with active Sexual Desire Disorder, Sexual Arousal Disorder, or Orgasmic Disorder no less than one week and no more than 3 months after beginning treatment with either fluoxetine, sertraline, or paroxetine; they had been receiving antidepressant treatment for a minimum of 10 weeks prior to beginning the study; and they described the sexual dysfunction as being distinctly different from any sexual dysfunction they may have noticed prior to starting antidepressant treatment. In an effort to increase the homogeneity of input variables, potential participants receiving antidepressant medications other than fluoxetine, sertraline, or paroxetine were not included in the study (approximately 20).

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There is wide variability in the mechanisms of action by which the antidepressants exert their effects, and also in the reported sexual side effects associated with antidepressant medications (e.g., Meston & Gorzalka 1992). Side effects secondary to fluoxetine, sertraline, and paroxetine were chosen for examination in the present study because these drugs have a similar serotonergic mechanism of action in that they selectively inhibit the uptake of serotonin but, unlike some of the newer antidepressants (e.g., mirtazapine), they do not act on noradrenergic systems (Stimmel, Doppeide, & Stimmel 1997). In addition, fluoxetine, sertraline, and paroxetine have been associated with similar sexual side effects in women (e.g., Meston & Gorzalka 1992; Rosen, Lane, & Menza 1999).

Table 1 describes participants' enrollment. As illustrated in Table 1, a total of 443 women were excluded from the study. Of the women who did not meet criteria ( $n = 342$ ), the majority was not in a relationship ( $n = 81$ ) or did not meet diagnostic criteria for sexual dysfunction ( $n = 80$ ), 45 women were on medications known to affect sexual dysfunction, and 40 had either undergone total hysterectomy or had a health condition that excluded them from the study (i.e., high blood pressure, diabetes, or thyroid disorder). Fewer women ( $n = 12$ ) were breast feeding or pregnant and four reported a history of psychosis. Of the 43 women who chose not to participate, 13 reported feeling uncomfortable with the psychophysiological assessment procedures used in the study and 19 did not want to make the time commitment required for the treatment.

During the entry interview, inclusion and exclusion criteria were assessed. Participants were accepted in the study if they were between the ages of 18 and 65, were currently involved in a heterosexual relationship, and agreed that during the course of the study they would engage in at least two sexual encounters with their partners per week, would not use any form of birth control, and would use antidepressant medication (fluoxetine, sertraline, or paroxetine) as a medically accepted form of birth control. This latter criterion was required by the University of Texas Internal Review Board to protect participants against the potential unknown induced sexual dysfunction if they reported an onset of Hypertensive negative consequences of GBE on pregnancy. Participants with active Sexual Desire Disorder, Sexual Arousal Disorder, or Orgasmic Disorder no less than one week and no more than 3 months after beginning treatment with either fluoxetine, sertraline, or paroxetine; they had been receiving antidepressant treatment for a minimum of 10 weeks prior to beginning the study; and they described the sexual dysfunction as being distinctly different from any sexual dysfunction they may have noticed prior to starting antidepressant treatment. In an effort to increase the homogeneity of input variables, potential participants receiving antidepressant medications other than fluoxetine, sertraline, or paroxetine were not included in the study (approximately 20).

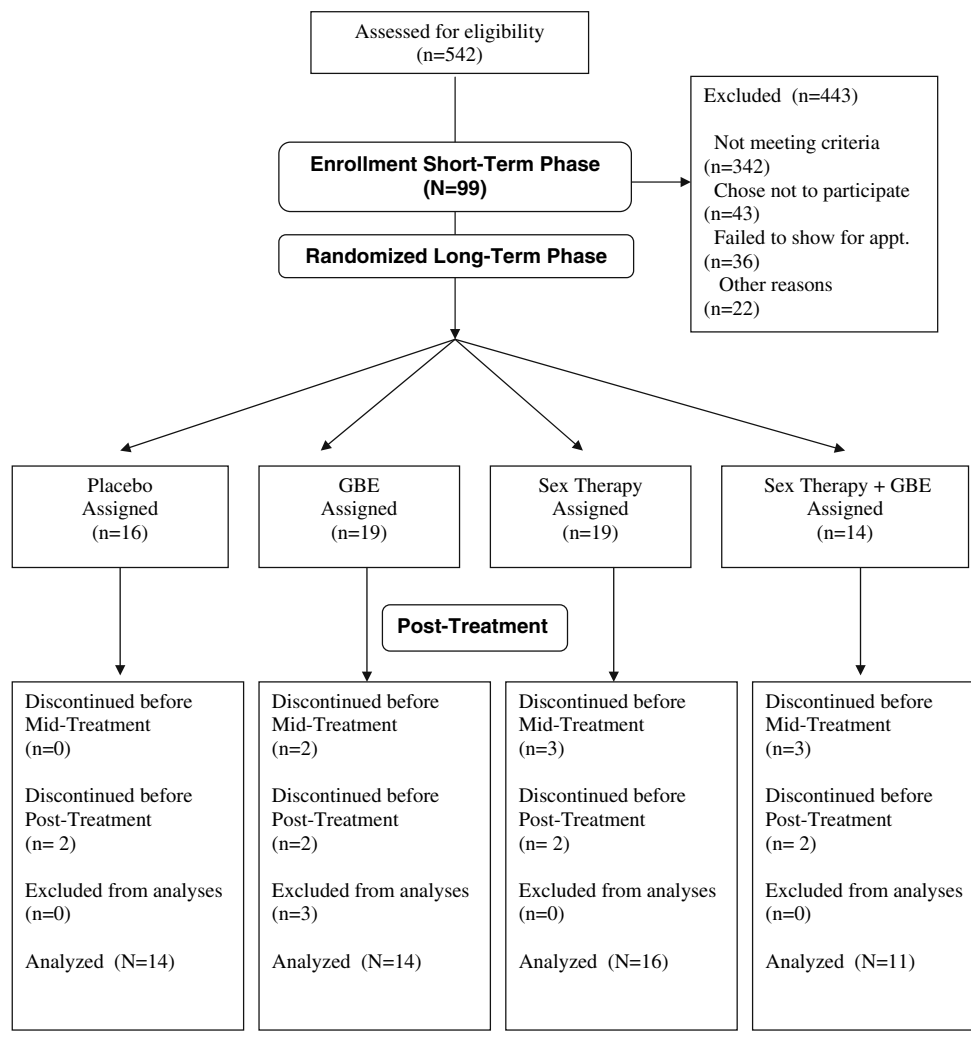
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Table 1 Participants flow-chart



during the neutral video. All pulses were included in their attention away from the television screen. Subjective sexual arousal scores were first transformed into a 0–100 scale where 0 on the arousalmeter corresponded to a score of 0 and a 7 on the arousalmeter corresponded to a score of 100. Subsequently, the average of subjective sexual arousal was computed during the exposure to the neutral and erotic videos. Since all participants reported 0.00 subjective sexual arousal during the neutral video, the average of subjective sexual arousal during the erotic video corresponded to the score of subjective sexual arousal used for between-participants analyses. The average subjective sexual arousal for each pulse during the neutral and the erotic video was averaged across every 10 s intervals.

Subjective ratings of the participant's sexual response were measured with a device termed "arousometer." The arousalmeter was a computer optical mouse (Intellimouse by Microsoft) mounted on a wooden track divided into equally spaced intervals from 0.00 to 7.00. At each numeric interval of the relationship between VPA and subjective sexual arousal). Six sets of videos were counterbalanced across participants and used as stimuli for assessing laboratory measures of arousal that they were indicating without having to focus of sexual arousal. Each video comprised 1 min of the word

Table 2 Means and SDs for demographic characteristics for women in the short- and long-term study divided by conditions

	Acute sample ( <i>n</i> = 99)		Chronic sample ( <i>n</i> = 68)							
	<i>M</i>	<i>SD</i>	Placebo ( <i>n</i> = 16)		GBE ( <i>n</i> = 19)		Therapy ( <i>n</i> = 19)		GBE + Therapy ( <i>n</i> = 14)	
			<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Age (in years)	25.30	7.81	24.92	4.14	25.82	6.81	27.82	10.26	25.40	5.36
Length of relationship (in mos)	2.60	1.53	2.75	0.97	2.55	1.44	2.09	1.58	2.70	1.16
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Education										
At least some college	89	89.90	16	100.00	18	94.74	18	94.74	13	92.86
Marital Status										
Currently single	48	48.49	9	56.25	12	63.16	10	52.63	6	42.86
Married	37	37.40	7	43.75	4	21.05	5	26.32	7	50.00
Divorced	14	14.14	0	0.00	3	15.79	4	21.05	1	7.14
Ethnicity										
Caucasian/White	72	72.72	10	62.50	16	84.21	15	78.95	11	78.57
African American	3	3.03	0	0.00	0	0.00	0	0.00	0	0.00
Native American	1	1.01	1	6.25	0	0.00	0	0.00	0	0.00
Hispanic/Latina	13	13.13	1	6.25	2	10.53	3	15.79	2	14.29
Asian American	5	5.05	2	12.50	0	0.00	1	5.26	1	7.14
Other	1	1.01	1	6.25	0	0.00	0	0.00	0	0.00
Mixed ethnicity	4	4.04	1	6.25	1	5.26	0	0.00	0	0.00
Sexual Orientation										
Bisexual	10	10.10	2	12.50	2	10.53	2	10.53	3	21.43
Heterosexual	89	89.90	14	87.50	17	89.47	17	89.47	11	78.57

relax, 3 min of a travel documentary on Russian culture, interviewer first provided a definition of sexual desire, and 10 min of an erotic video showing a heterosexual couple aroused, and orgasm based on the DSM-IV-TR criteria and engaging in foreplay (2 ± 0.5 min), manual stimulation then asked the participants to indicate whether in the pre- (3 ± 0.5 min), oral sex (2 ± 0.5 min), and vaginal penetration (3 ± 0.5 min). To examine whether the videos were to each sexual dimension. The interviewer used a number of comparable in their ability to enhance sexual arousal prompts to further investigate the nature and severity of the women, a one-way ANOVA was computed using videodysfunction. Participants were also questioned as to whether number (1–6) watched during baseline as an independent variable, and VPA and continuous subjective sexual arousal during baseline as dependent variables. No significant differences were observed between the six videos for either percentage of VPA increase ( $F(5, 98) < 1$ , or average subjective sexual arousal during the erotic portion of the videos and the Sexual Satisfaction Scale–Women (SSS-W; Meston & Trapnell, 2005). The FSFI is a 19-item questionnaire divided into six domains: desire (2 items), arousal (4 items), lubrication (4 items), orgasm (3 items), satisfaction (3 items), and pain (3 items). Response options differ by question but are based on a 5-point Likert scale rating system with some questions also including the response option of “no sexual activity.” Several studies on the psychometrics quality of the FSFI have reported adequate inter-item reliability with Cronbach’s computed for the subscales ranging from .89 to .96; appropriate test-retest reliability ( $r = .79–.86$ ) after 2

A semi-structured clinical interview was conducted by an advanced student in clinical psychology with over 300 h of experience assessing sexual dysfunction in women. The and without Hypoactive Sexual Desire Disorder, Sexual

Arousal Disorder, and Orgasmic Disorder (Meston & Rosen et al. 2000). Recently, a cut off score of 26.5 was shown to have adequate sensitivity and specificity for the distinction between women with and without female sexual dysfunction (Wiegel, Meston, & Rose 2005).

The SSS-W (Meston & Trapnel 2005) is a 30-item questionnaire developed on the four domains of sexual satisfaction identified by the literature: compatibility, contentment, communication, and concern (personal, relational). Response options range from 1 strongly agree, to 5 strongly disagree. The psychometrics of this questionnaire indicate that it has good inter-item reliability (Cronbach's  $\alpha \geq .72$ ), acceptable test-retest reliability after a lapse of 1 month ( $r = .62$ – $.79$ ), and the construct validity of the instrument was confirmed with a principal component analysis. The full scale score differentiated between women with and without ( $M = 123.4$ ) sexual dysfunction.

In agreement with the guidelines on clinical trials for sexual treatments provided by the Food and Drug Administration (FDA Guidance document 2000), an event log was created for the assessment of treatment-induced changes in the sexual function of the participants. Participants were provided with event logs and were asked to complete the log after each sexual activity that did or did not include a partner. The log was composed of seven items that addressed satisfaction with the sexual arousal response (physical and mental sexual arousal), satisfaction with orgasm, levels of sexual desire before the sexual activity, and general experience of sexual pleasure during the activity. Each item was scored on a 6-point Likert scale that ranged from "None" or "Not at all" to "Very much" or "Extremely satisfied." An analysis of the psychometrics properties of these event logs has shown that self-report questionnaires such as the FSFI are more sensitive at identifying the clinical changes induced by treatment than are event logs (Rellini & Meston 2006). The results from the events logs were included in this study as a supplement to the descriptions provided by the FSFI and the SSS-W on the changes experienced by the participants in the study.

## Conditions

### *Short-term GBE and Long-term GBE*

**GBE.** The GBE used for this study was a standardized extract of GBE leaves, termed GBE 761, manufactured by Schwabe GMBH in Germany, and distributed in U.S. under Nature's Way Brand. This product contains concentrated (50:1) ginkgo biloba leaf extract standardized to 24% ginkgo flavone glycosides and 6% terpen lactose. It is the most widely used form of GBE in clinical trials. Each pill contained 300 mg of the GBE 761 formula. This dosage was

selected based on studies that have indicated GBE increases peripheral blood flow at acute doses of 200 mg and higher (e.g., Koltringer et al. 1989).

**Placebo.** Both the placebo and GBE capsules were prepared by the University of Texas at Austin Pharmacy and were identical in appearance and texture to ensure double-blind conditions.

### *Long-term*

**Sex Therapy.** A standardized 8-session sex therapy protocol was administered by an advanced student in clinical psychology supervised by a licensed clinical psychologist with more than 20 years of experience in therapy and clinical trials. A therapist manual was developed to ensure the treatment was standardized across participants and all sessions were videotaped to check for protocol compliance. The client manual with definitions, descriptions of aim and goals, treatment agenda, and forms to complete in session and during home assignments was also developed to help clients follow the standardized treatment. Each participant was required to attend the eight 55 min individual sessions with the therapist and to set aside 20 min every two days to complete exercises assigned by the therapist. The primary treatment goal was to increase women's focus on the sexual pleasure and physiological sexual responses during sexual activity. Cognitive-behavioral techniques were used to identify cognitive distortions that created a distraction from sexual pleasure during sexual activities. Exposure interventions were used to help participants to practice focusing on their bodies and explore different behaviors and different sensations during sexual activities.

Our rationale for selecting this type of sex therapy was that if GBE enhanced genital blood flow, by having women attend to those genital changes and interpret them in a positive sexual manner, psychological levels of arousal might also be enhanced. This hypothesis is rooted in the cognitive model originally proposed by Barlow (for a review, see Wiegel, Scepkowski, & Barlow 2006). According to this model, people with sexual dysfunction are less aware of how aroused they are. Additionally, individuals with sexual dysfunction are more likely to focus on their performance rather than their sexual responses. We expected the combined effect of, on one hand, increasing women's genital response with GBE and, on the other hand, helping them to attend their genital sensations and identify variables that increased their sexual arousal to increase sensations of both subjective and physiological sexual arousal.

<sup>1</sup> The therapist manual is available from the corresponding author upon request.

The first four sessions of therapy used exercises to help participants refrain from engaging in any strenuous physical activity for 2 h prior to the visits. In addition, because rate of GBE absorption may be influenced by food in the stomach, participants were asked to refrain from eating for 4 h prior to the sessions. These two sessions were conducted over two consecutive days scheduled during the 12th and 28th day of the participant's menstrual cycle. During the first session, participants completed two psychophysiological assessments: a baseline measure of the participant's sexual response to the neutral-erotic video sequence and an assessment after the administration of either GBE or placebo. During all physiological assessments, the participants were in a private internally locked room and they were asked to follow a standardized protocol. First, participants inserted the vaginal photoplethysmograph and relaxed on a recliner chair on their own pleasure during sexual activities with a partner for 10 min (habituation time). Then, the first video sequence started and during this time participants indicated their level of subjective sexual arousal by moving the arousal meter. Shortly after the end of this first video sequence (baseline), a GBE or a placebo pill was administered. The time from GBE/placebo ingestion to the onset of the second video sequence was approximately 90 min. This time period was chosen based on research which indicates the times to peak concentration for ginkgolide A, ginkgolide B, ginkgolide C, and bilobalide are 1.5, 1, 1, 2 h, respectively (Kleijnen & Knipschild, 1992). Participants were scheduled for a second assessment session in 28 days.

*Sex therapy plus GBE.* Participants received a combination of GBE plus the standardized 8-session sex therapy protocol described above.

## Procedure

### *Short-term Effects of GBE versus Placebo*

After an initial assessment interview, participants who qualified were scheduled for a two-session physiological assessment that took place at the Female Sexual Psychophysiology Laboratory. During the first session, participants were given a detailed informed consent form to complete. The form stated that the purpose of the study was to learn whether ginkgo biloba and/or sexual education could help alleviate sexual difficulties. The form included a detailed description of the two parts of the study (short-term effects; long-term effects) and an extensive list of the potential discomforts and risks associated with GBE use. To this regard, the following statements were included in the informed consent, "You should be aware that ginkgo biloba has been associated with mild gastrointestinal complaints, headaches, and allergic skin reactions. There have been isolated reports of cerebral bleeding, and prolonged bleeding associated with ginkgo biloba use and this may be intensified with antidepressant use. Also, there is a mild risk for bleeding of the eye and increased bleeding during surgery."

Participants who chose to participate in the long-term GBE treatment portion of the study were randomly assigned to one of four groups: GBE, Sex Therapy, Placebo, and Sex Therapy plus GBE. The Placebo and GBE groups were conducted using a double-blind protocol and the Sex Therapy plus GBE was conducted using a single blind protocol.

The treatment lasted for 8 weeks and participants completed

During the second physiological assessment session, participants viewed a video sequence after the ingestion of the pill they did not receive during their first session. As in the first session, a 90 min waiting period was used from the ingestion of the pill to the onset of the erotic video. At the

end of the video, participants were instructed on how to complete the event logs and asked to do so after each sexual activity occurring in the following 2 weeks. Participants received \$50 as compensation for their two physiological assessment sessions. After 2 weeks, participants were contacted and asked to mail in their event logs. Upon receiving the event logs, participants were scheduled for an orientation to the second part of the study that investigated the long-term (8 weeks) effects of GBE.

### *Long-term Effects of GBE, Placebo, Sex Therapy, Sex Therapy plus GBE*

Participants who chose to participate in the long-term GBE treatment portion of the study were randomly assigned to one of four groups: GBE, Sex Therapy, Placebo, and Sex Therapy plus GBE. The Placebo and GBE groups were conducted using a double-blind protocol and the Sex Therapy plus GBE was conducted using a single blind protocol.

The treatment lasted for 8 weeks and participants completed

a mid-treatment at week 4, and a post-treatment assessment at week 8.

Prior to the beginning of treatment, participants were asked to attend an orientation visit. The orientation lasted 30 min and participants were asked to bring their partners. Of the women in the Placebo, GBE, Sex Therapy, and Sex Therapy plus GBE conditions, 13, 17, 15, and 10 partners respectively, participated in the orientations. During this time, participants were shown a video explaining the rationale for using GBE and/or sex therapy for the treatment of sexual problems. Participants receiving GBE or placebo were told that GBE was expected to increase blood flow in the vaginal walls, which was expected to facilitate sexual arousal. Participants assigned to a sex therapy condition were told that the therapy was designed to increase one's comfort and knowledge with one's body and to decrease thoughts that distracted one from attending to pleasurable sexual sensations. Both rationales were given to women in the Sex Therapy plus GBE condition. The orientation was also used to assess participants' motivation, to clarify the requirements of the study, and to answer any study-related questions. An additional goal of the orientation visit was to increase participants' commitment and minimize potential drop out rates. At the end of orientation, participants in the GBE, Sex therapy plus GBE, or the Placebo conditions were given a bottle of 28 pills and instructed to take one pill orally once per day approximately 1 h before they would normally engage in sexual activities. Participants in the Sex Therapy and in the Sex Therapy plus GBE conditions met with the therapist to arrange their first session of individual sex therapy. Women in the Sex Therapy plus GBE group were told that their pill may be either placebo or GBE. Participants were instructed to complete the event logs after every sexual activity and mail it in every week in the self-addressed, stamped envelopes that were provided. Telephone calls were made every week to remind participants to mail in their event logs.

After 4 weeks, participants were scheduled for a mid-treatment visit during which they completed the FSFI, the SSS-W, the sexual function interview, and laboratory measures of subjective and physiological sexual responses to the neutral/erotic video sequence. This visit lasted approximately 50 min and participants received \$50 upon completion. After 8 weeks from the beginning of treatment, a post-treatment assessment was conducted identical to the 4 week mid-treatment assessment. Participants were compensated \$50.00 for this visit. In order to check treatment compliance for both the 4 week mid-treatment and 8 week post-treatment assessment visits, participants were asked to bring all the pills that they had not used to their session. Participants who used less than 50% of the pills (>28 returned pills) or either visit were excluded from further analyses; this included three women in the GBE condition.

## Results Short-term Effects of GBE versus Placebo

Figure 1 shows the means and SDs of the differences between neutral and erotic videos in VPA responses during the baseline, placebo, and GBE conditions. Women ranged between minus 0.11% to plus 61.57% of increase in VPA from neutral to erotic videos. A repeated-measures ANOVA on Condition (baseline, GBE, placebo) was conducted to assess whether there were differences among baseline, GBE, and placebo in VPA percentage increase in responses to erotic videos. There was a significant main effect of Condition ( $F(2, 196) = 3.44, p < .05$ ). Two-way contrasts revealed significant differences between GBE and baseline ( $F(1, 97) = 5.99, p < .01$ ), placebo and baseline ( $F(1, 97) = 4.32, p < .05$ ), and GBE and placebo ( $F(1, 97) = 4.33, p < .05$ ), with GBE being the condition

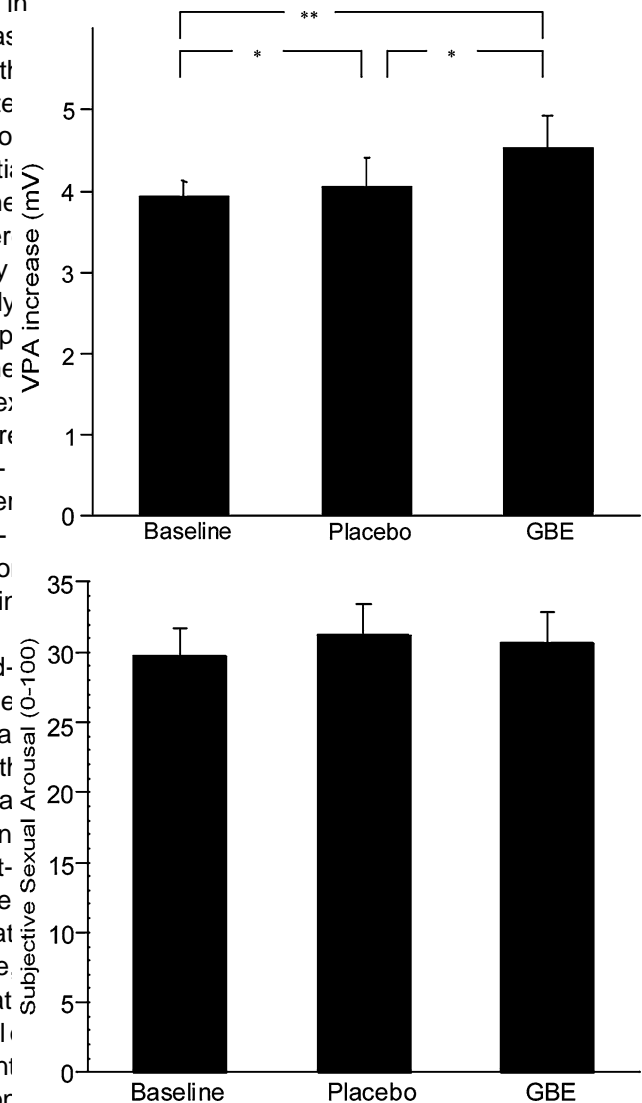


Fig. 1 VPA and subjective sexual responses to the sexual video during Baseline, Placebo, and GBE conditions.  $p < .05$ ,  $** p < .01$

associated with the highest VPA response ( $M = 4.84$ ), followed by placebo ( $M = 4.34$ ), and by baseline ( $M = 4.20$ ). The effect sizes computed by using the original means (Dunlop, Cortina, Vaslow, & Burkett 1996) revealed that, although significant, the difference was of questionable clinical significance. The effect size between baseline and GBE ( $d = -0.19$ ) was below what Cohen defined as a small effect size. Only approximately 14.7% of the VPA values in the GBE condition did not overlap with the VPA values in the level of functioning and physiological response at the post-baseline condition. The effect size between baseline and placebo was even smaller ( $d = -0.04$ ) indicating that <7.7% of the VPA values in the placebo condition did not overlap with the VPA values of the baseline condition (Fig. 1).

Figure 1 shows the means and SDs of the subjective sexual responses to the erotic videos during the baseline, placebo, and GBE conditions. The average subjective rating of sexual arousal during the erotic film varied from plus 0.14 to 90.43 points (possible range, 0–100).

A repeated-measures ANOVA was used to assess differences in average scores of continuous subjective sexual arousal during the erotic video (measured using the arousal meter) between baseline, placebo and GBE. No significant differences between baseline, placebo and GBE were detected with a repeated-measures ANOVA ( $F(2, 128) < 1$ ). Women in each of the conditions showed an increase in subjective sexual arousal during exposure to the erotic video with the overall average increase being approximately 30 units (Fig. 2).

Exploratory analyses were conducted to examine whether a single dose of 300 mg GBE had a differential impact on sexual arousal between women with sexual problems attributable and not attributable to antidepressant medication. Results of two repeated-measures (baseline, placebo, GBE) ANOVAs revealed that women on antidepressants ( $n = 36$ ) showed a trend towards lower physiological sexual responses to the erotic videos ( $F(1, 97) = 3.45, p = .066$ ) compared to women not taking antidepressants ( $n = 63$ ). There were no significant differences between women receiving and not receiving antidepressants in VPA levels of subjective arousal to the erotic videos ( $F(1, 97) < 1$ ). There were no significant interactions between Group and Condition for either VPA ( $F(2, 96) < 1$ ), or subjective arousal ( $F(2, 96) < 1$ ), suggesting that GBE did not have a differential impact on sexual arousal responses between women with sexual dysfunction secondary to, and not secondary to, antidepressant medication.

#### Long-term Effects of GBE, Placebo, Sex Therapy, and Sex Therapy plus GBE

##### Laboratory Measures of Sexual Arousal to Erotic Videos

Three women in the GBE condition were noncompliant in taking the GBE daily and returned more than 50% of their

pills to the mid-treatment or post-treatment assessment visits. In an attempt to standardize amount of GBE in the bloodstream, data from these participants were excluded from further analyses. As per other comparable treatment-outcome clinical studies (e.g., Foa et al. 2005), we used an intent-to-treat approach to the outcome analyses, meaning that people who dropped out after the mid-treatment assessment (4 weeks) were assumed to have maintained the same level of functioning and physiological response at the post-treatment assessment visit. Therefore, mid-treatment data were considered representative of the post-treatment level of function and physiological response.

To examine the physiological effects of 8 weeks daily treatment with GBE, a 3-level hierarchical linear modeling (HLM) analysis was used to test whether VPA increased from baseline to post-treatment (Level 2), and if there was a condition effect (i.e., GBE, Placebo, Sex Therapy, or Sex Therapy plus GBE) (Level 3). We selected HLM to analyze the VPA data because of the high between-participants variance in VPA responses (Prause & Janssen 2005) known to affect statistical analyses and because of the ability of HLM to provide robust results in spite of this variability (for a review, see Rellini, McCall, Randall, & Meston 2005). Given that we compared more than two groups, dummy coding was used to compare GBE, Sex Therapy, and Sex Therapy plus GBE to Placebo. No other comparisons were tested in the following HLM analyses.

Figure 2 shows the average changes in VPA from neutral to erotic films during baseline, mid-treatment, and post-treatment for each of the treatment conditions (Placebo, GBE, Sex Therapy, Sex Therapy plus GBE). There were no significant differences between conditions in VPA responses to erotic films when measured at baseline. Specifically, women in the placebo condition showed a significant increase in VPA between neutral and erotic videos during baseline ( $\beta_{100} = 3.62, t(55) = 2.41, p < .05$ ), and this increase was not significantly different from the increases in VPA levels of subjective arousal to the erotic videos noted among women in the GBE, Sex Therapy, and Sex Therapy plus GBE when measured at baseline. During post-treatment, women in the placebo condition did not show a significant change in VPA responses to erotic films from measures taken at baseline ( $\beta_{110} = 1.01, t(55) = 1.17$ ). When comparing sexual arousal at post-treatment with sexual arousal at baseline, GBE, Sex Therapy, and Sex Therapy plus GBE were not significantly different from placebo ( $t$  range,  $-0.76$  to  $-0.22, t$  range,  $-0.86$  to  $-0.22, p > .05$ ). It is worth noting that the direction of the difference between placebo and the other conditions was opposite to predictions such that treatment-induced increases in VPA responses were higher in the Placebo condition as compared to the GBE, Sex Therapy, and Sex Therapy plus GBE conditions.

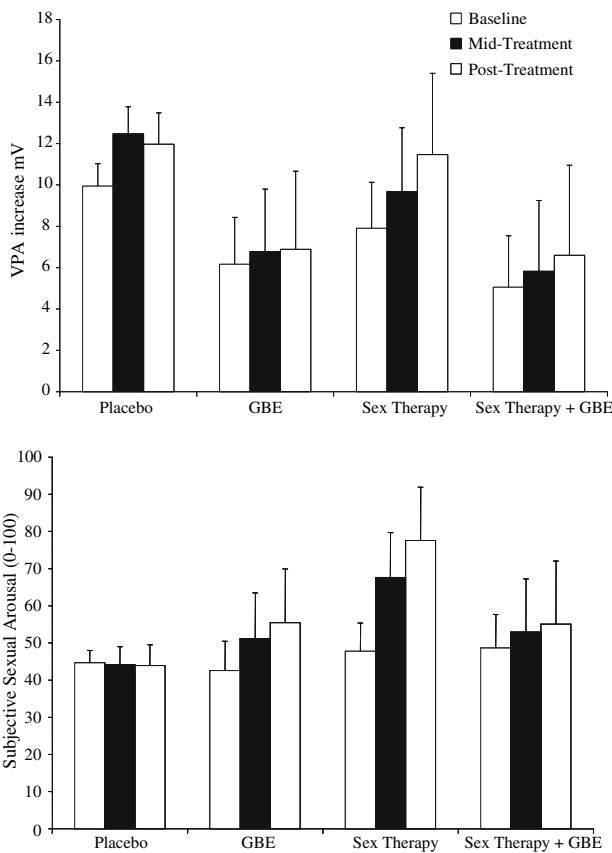


Fig. 2 VPA and subjective sexual response at baseline, mid-treatment, and post-treatment for women in the Placebo, GBE, Sex Therapy, and Sex Therapy plus GBE Conditions

Figure 2 shows the average increases in VPA to erotic films during baseline, mid-treatment, and post-treatment for each of the treatment conditions (Placebo, GBE, Sex Therapy, Sex Therapy plus GBE). Changes in subjective sexual arousal as measured with the arousometer were also assessed with a 3-level HLM analysis. Women in the placebo condition showed an increase in subjective sexual arousal during baseline of approximately 44.61 units by the end of the erotic video,  $\beta_{100} = 0.081, t(55) = 7.32, p < .001$ . No significant differences in subjective sexual arousal during baseline were observed between women in the Placebo, GBE, Sex Therapy, or Sex Therapy plus GBE conditions.

After 4 weeks (mid-treatment) and 8 weeks (post-treatment) of treatment, women in the placebo condition showed no significant changes in their subjective sexual arousal response to the erotic video compared to their baseline,  $\beta_{100} = -0.000, t(55) < 1$ . At post-treatment, compared to baseline, women in the Sex Therapy condition reported a significantly greater increase in subjective sexual arousal to the erotic video than did women in the placebo condition,  $\beta_{112} = 0.016, t(55) = 2.65, p < .01$ . There were no significant changes in subjective sexual arousal from baseline to post-treatment in women in the GBE condition,  $\beta_{111} = -0.0004, t(55) < 1$ , or

in the Sex Therapy plus GBE condition,  $\beta_{113} = 0.0026, t(55) < 1$ , meaning that they did not show significantly greater subjective sexual arousal responses as treatment progressed.

A 3-level HLM analysis was computed to assess the relationship between VPA and subjective sexual arousal and potential differences in this relationship during baseline, GBE, and placebo conditions. This analysis computed at Level 1 a regression line between VPA and continuous subjective sexual arousal for each participant during each of the three conditions. The slope and intercept coefficients were then used as outcome variables for the Level 2 analysis used to test whether there was a difference between conditions. Level 3 is usually used to conduct between participants analyses but, because in this part of the study, the research question was exclusively about within participants differences, we left Level 3 empty. In order to compare the three conditions, we used dummy coding to compare both placebo and GBE to baseline, leaving untested differences between placebo and GBE.

HLM coefficients of a 3-level HLM model were computed using subjective sexual arousal as the outcome variable, VPA as the within-participants predictor (Level 1), time as the covariate (Level 1), session (baseline versus post-treatment) as the Level 2 predictor (within-participants), and Condition as the Level 3 predictor (between-participants). The OLS analysis of the coefficients revealed that, during baseline, women in the placebo group showed a significant relationship between subjective sexual arousal and VPA,  $\beta_{100} = 10.97, t(56) = 2.45, p < .05$ , indicating that for each increase in 1 mV in VPA women overall responded with an increase in 10.97 subjective units of sexual arousal. The VPA/subjective sexual arousal relationship noticed during baseline in women from the placebo group was not significantly different from the VPA/subjective sexual arousal in women from the other groups (Fig. 3). At post-treatment, there was a trend for women in the Sex Therapy,  $\beta_{112} = 6.70, t(56) = 1.78, p = .08$ , and in the Sex Therapy plus GBE,  $\beta_{111} = 6.55, t(56) = 1.84, p = .07$ , conditions towards a stronger VPA/subjective sexual arousal relationship as compared to women in the placebo group. By contrast, at post-treatment, women in the placebo group showed a trend towards a weaker VPA/subjective sexual arousal relationship,  $\beta_{110} = -4.91, t(56) = -1.77, p = .08$ , compared to baseline.

#### Sexual Function Measures

Figures 4 and 5 show the mean and SDs for several of the FSFI and SSS-W subscales measured at baseline, mid-treatment, and post-treatment for each of the treatment conditions (Placebo, GBE, Sex Therapy, Sex Therapy plus GBE). Analyses of sexual function were conducted using data from the FSFI, the SSS-W, and event log entries to

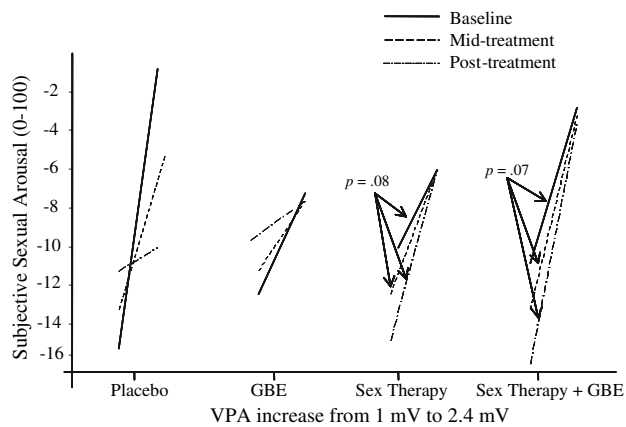


Fig. 3 Subjective sexual responses estimated when VPA increased from 1 mV to 2.4 mV during baseline, mid-treatment, and post-treatment visits for women in the Placebo, GBE, Sex Therapy, and Sex Therapy plus GBE conditions

compare the impact of Placebo, Sex Therapy, GBE, and Sex Therapy plus GBE on levels of sexual function in the women in the placebo condition (contrast estimate = 5.78, domains of sexual desire, arousal, orgasm, and satisfaction,  $p = .062$ ). Follow-up analyses were conducted to investigate

A univariate ANOVA was used to test group differences whether the difference observed between women in the Sex in levels of sexual desire (FSFI desire domain) in the intent-Treatment plus GBE condition and Placebo was due to speto-treat sample while controlling for baseline levels of ciBc subfactors of the SSS-W. Indeed, only Factor 1, Consexual desire. A significant condition effect on sexual desire at post-treatment was observed ( $F(3, 59) = 6.36, p < .001$ ). A two-way comparison indicated that women in the Sex for baseline scores (Fig. 5). In particular, women in the Sex Therapy plus GBE condition showed a significantly greater level of sexual desire at post-treatment compared to placebo (contrast estimate = 1.52,  $p < .05$ ). This difference was characterized by a large effect size ( $d = -0.88$ ), indicating that approximately 50% of the desire scores of women in the Sex Therapy plus GBE group did not overlap with the desire scores of the placebo condition. Sexual desire at post-treatment was higher in women in the Sex Therapy condition as compared to placebo but it was not statistically significant (contrast estimate = .881) (see Fig. 4). The lack of significance despite the large effect size may be a consequence of the small sample size. Also, there was no interaction effect between condition and time (baseline and post-treatment) ( $F(3, 59) = 1.82$ ).

The same model was used to test the arousal, lubrication, and orgasm domains of the FSFI (see Fig. 4). When controlling for baseline scores of sexual arousal, post-treatment levels of psychological arousal measured with the FSFI (arousal domain) were higher for women in the Sex Therapy group, 13 in the Sex Therapy plus GBE condition ( $M = 14.90$ ), followed by Sex Therapy plus GBE group ( $M = 14.35$ ), GBE ( $M = 13.56$ ), and placebo ( $M = 12.81$ ), but these differences were not statistically significant ( $F(3, 59) = 1.82, p > .05$ ). Physiological arousal measured with the FSFI Lubrication subscale indicated that women in the Sex Therapy plus GBE condition showed the highest scores at post-treatment ( $M = 15.58$ ), followed by Sex Therapy

( $M = 15.18$ ), placebo ( $M = 15.96$ ), and GBE ( $M = 14.92$ ),  $F(3, 59) < 1$ .

When controlling for baseline measures, orgasm (measured using the FSFI Orgasm domain) at post-treatment showed a significant difference between the Sex Therapy and Placebo conditions (contrast = 2.48,  $p < .05$ ), although no overall difference was detected in the between-participants analysis ( $F(3, 57) = 1.77$ ). The effect size for orgasm difference was medium ( $d = 0.76$ ), indicating that, at post-treatment, approximately 43% of scores on orgasm in the placebo condition did not overlap with orgasm score in the Sex Therapy condition (see Fig. 4).

The overall SSS-W score for sexual satisfaction at post-treatment was used as an outcome variable in a univariate ANOVA, where baseline sexual satisfaction was used as a covariate. The two-way contrasts compared Placebo to GBE, Sex Therapy, and Sex Therapy plus GBE (Fig. 5). Women in the Sex Therapy plus GBE condition showed a trend towards a

higher score in overall sexual satisfaction as compared to Therapy plus GBE on levels of sexual function in the women in the placebo condition (contrast estimate = 5.78,  $p = .062$ ). Follow-up analyses were conducted to investigate

whether the difference observed between women in the Sex in levels of sexual desire (FSFI desire domain) in the intent-Treatment plus GBE condition and Placebo was due to speto-treat sample while controlling for baseline levels of ciBc subfactors of the SSS-W. Indeed, only Factor 1, Consexual desire. A significant condition effect on sexual desire at post-treatment was observed ( $F(3, 59) = 6.36, p < .001$ ). A two-way comparison indicated that women in the Sex for baseline scores (Fig. 5). In particular, women in the Sex Therapy plus GBE condition showed a significantly greater level of sexual desire at post-treatment compared to placebo (contrast estimate = 1.52,  $p < .05$ ). This difference was characterized by a large effect size ( $d = -0.88$ ), indicating that approximately 50% of the desire scores of women in the Sex Therapy plus GBE group did not overlap with the desire scores of the placebo condition. Sexual desire at post-treatment was higher in women in the Sex Therapy condition as compared to placebo but it was not statistically significant (contrast estimate = .881) (see Fig. 4). The lack of significance despite the large effect size may be a consequence of the small sample size. Also, there was no interaction effect between condition and time (baseline and post-treatment) ( $F(3, 59) = 1.82$ ).

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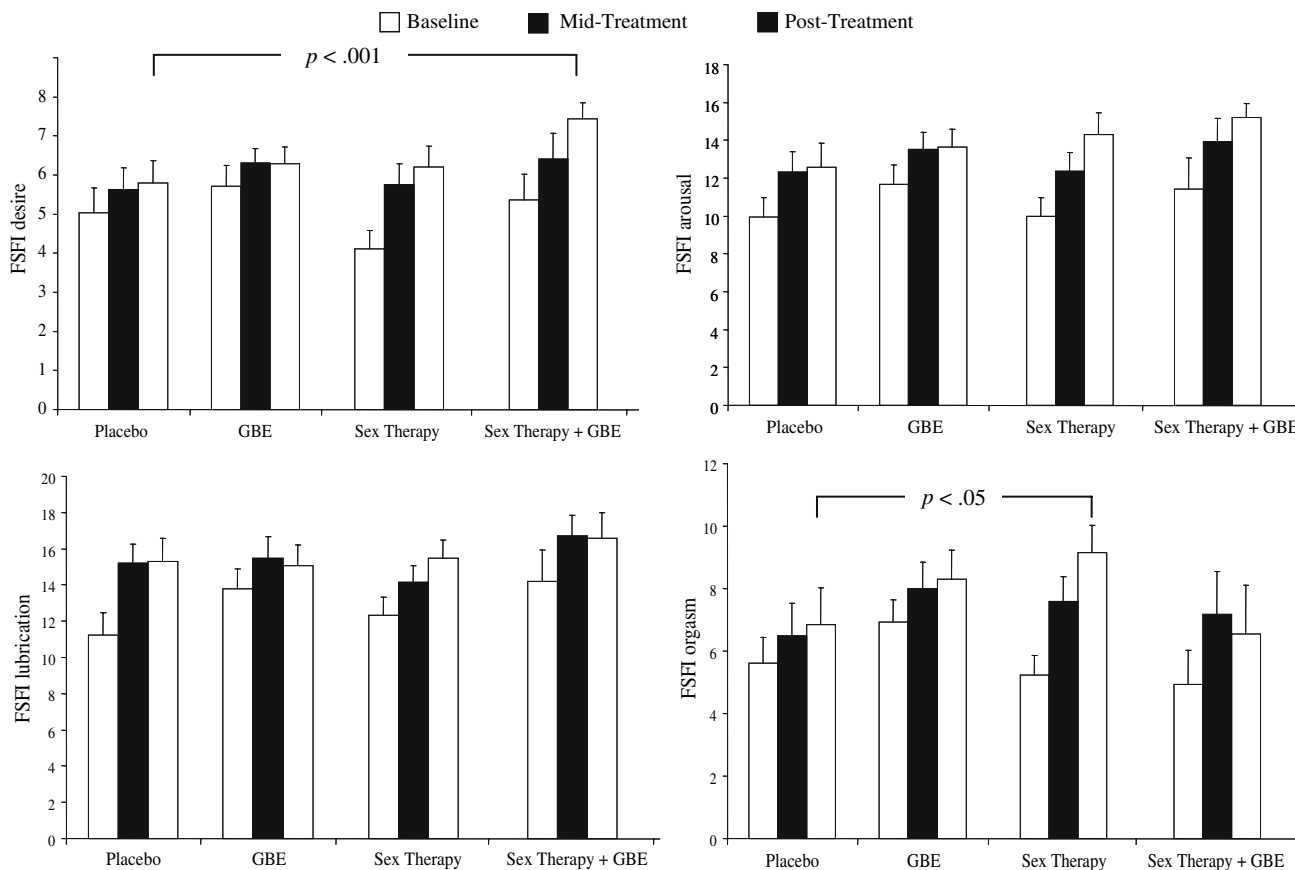


Fig. 4 Scores on the FSFI domains (Desire, Arousal, Lubrication, Orgasm) at baseline, mid-treatment, and post-treatment for women in the Placebo, GBE, Sex Therapy, and Sex Therapy plus GBE conditions. Note: *p* values refer to contrast differences calculated for post-treatment scores when controlling for baseline scores as part of univariate ANOVAs computed separately for each of the FSFI factors indicated

HLM results are known to be robust to missing data (Bryk, Raudenbush, & Congdon, 1996).

Results indicated a trend towards an increase in percentage of satisfying sexual encounters for women in the Placebo group,  $\beta_{01} = 0.03, t(41) = 1.93, p = .061$ . No significant differences were observed between women in the GBE,  $\beta_{11} = -0.001, t(41) < 1$ , Sex Therapy,  $\beta_{21} = -0.022, t(41) < 1$ , and Sex Therapy plus GBE,  $\beta_{31} = 0.014, t(41) < 1$ , conditions compared to placebo, indicating that all women showed a tendency towards improvement in frequency of satisfying sexual behaviors at post-treatment independent of the condition to which they were assigned.

Discussion

This study provided a comprehensive examination of the short-term and long-term effects of GBE for treating women's sexual dysfunction. The short-term effects of GBE were examined using a double-blind, placebo-controlled, within subjects design in which laboratory measures of

subjective and physiological sexual arousal to neutral and erotic film stimuli were measured 90 min after ingestion of either 300 mg GBE or placebo. It was predicted that women would attain higher levels of sexual arousal in response to the erotic videos after having received GBE versus placebo. This was based, in part, on speculation that GBE could enhance vascular flow to the genitals in a similar manner to the mechanism by which it enhances cerebral perfusion, and by having a direct effect on prostaglandins which are known to enhance sexual arousal in men (Cohen & Barlow, 1998). Consistent with prediction, VPA responses to erotic stimuli were significantly higher in women who received GBE compared with women who received placebo. The effect size was small, however, and, combined with the fact that, contrary to prediction, subjective reports of arousal were not significantly higher with GBE versus placebo, this leads one

to question the clinical significance of this finding. Whether the positive impact of GBE on sexual arousal would have been greater among sexually dysfunctional women with subnormal capillary vascular function is a topic for future study.

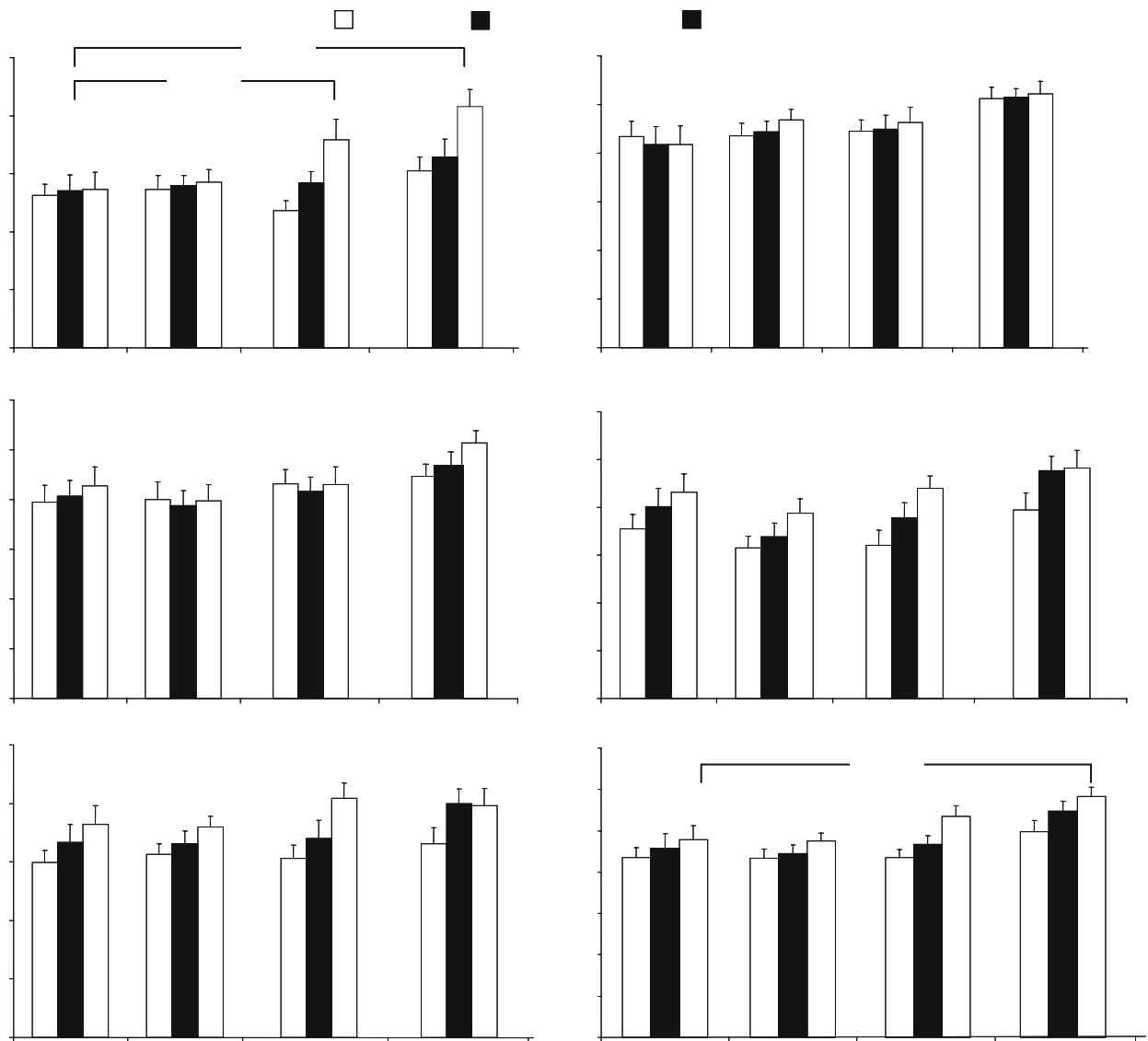


Fig. 5 Scores on the SSS-W factors (Contentment, Communication, Compatibility, Relational Concern, and Personal Concern) and full treatment scores when controlling for baseline scores as part of the univariate ANOVAs computed for each SSS-W factors and the full Placebo, GBE, Sex Therapy, and Sex Therapy plus GBE conditions. Note: *p* values refer to contrast differences calculated for post-treatment scores when controlling for baseline scores as part of the univariate ANOVAs computed for each SSS-W factors and the full Placebo, GBE, Sex Therapy, and Sex Therapy plus GBE conditions

GBE did not differentially impact physiological or subjective sexual arousal responses among women with sexual difficulties secondary to and not secondary to antidepressant medication. Interestingly, VPA responses to erotic videos showed a trend towards being lower among women receiving antidepressant medication, compared with women not on antidepressants but who also reported arousal difficulties secondary to antidepressant medication. This finding should, of course, be interpreted with caution given that it is well known that wide variability exists between women on laboratory measures of arousal between these groups of women. The finding that VPA responses and between groups comparisons may not be especially reliable (Janssen 2001). Future research that is consistent with the literature indicating a high incidence of sexual responses before, during, and even after antidepressant treatment (e.g., Meston & Gorzalka 1992, Rosen et al., 1999). While speculative, the fact that levels were lower on sexual responding in women.

It was predicted that, independent of any potential short-term effects of GBE on arousal, long-term treatment with GBE would enhance sexual function in women. This was based on research showing chronic GBE has a relaxing effect on vascular smooth muscle (e.g., Auguet & Clostre, 1983), and has NO scavenging properties (e.g., Marcocci et al., 1994), both of which are known to play a role in the measures. Findings did not reach significance, but several female sexual arousal response, and on limited findings from the present study, the long-term effects of GBE were examined by comparing the effects of 8 weeks treatment with GBE to 8 weeks of either Placebo, Sex Therapy, or Sex Therapy plus GBE. Outcome measures included sexual arousal to erotic videos, validated measures of sexual function and satisfaction, and daily event log entries.

Contrary to prediction, 8 weeks daily treatment with GBE did not significantly increase VPA or subjective sexual arousal responses to erotic stimuli. The finding that a time dose of 300 mg GBE (90 min prior to viewing the videos) enhanced VPA responses compared with placebo, albeit a small effect, and long-term GBE (daily for 8 weeks) did not, suggests that any facilitatory effect of GBE on VPA and subjective sexual arousal is to continuously and vasocongestion occurs shortly after GBE is absorbed into the bloodstream. In other words, the tendency for long-term treatment with GBE to increase overall peripheral blood flow (Smith et al., 1996) does not seem to translate into a sexual arousal specific increase in genital engorgement. Using this technique, Rellini et al. (2005) reported significant increase in genital engorgement. This finding may, of course, be limited to a laboratory setting and not generalizable to a real life sexual context.

Women in the Sex Therapy condition showed a significant increase in subjective reports of sexual arousal to erotic videos compared with placebo. Women in the Sex Therapy plus GBE condition also showed an increase in subjective responses to the erotic stimuli compared with placebo but the increase did not reach significance. The fact that GBE did not have an additive effect on outcome measures suggests that any beneficial impact of these interventions on laboratory measures of subjective sexual arousal was due to the sex therapy component of treatment. In both conditions, the primary focus of the sex therapy was on training women to attend to genital changes and to interpret them in a positive sexual manner. Whether due to an increased concordance between genital and psychological arousal or a fort with experiencing and/or expressing feelings of sexual arousal, being less distracted by negative thoughts, or feeling more in tune with sexual sensations, the type of therapy intervention used in the present study seems to have enhanced the women's psychological experience of being aroused to the erotic videos.

We predicted that a higher concordance between laboratory measures of subjective and physiological arousal, as measured by the FSFI domains of desire, arousal, lubrication, and orgasm, and by the SSS-W satisfaction

domains. Partly consistent with predictions, women who received sex therapy plus GBE showed significant and substantial increases in sexual desire and contentment, and significant increases in arousal and lubrication from baseline compared with women in the Placebo condition. Inconsistent with predictions, women who received GBE alone, did not show a significant increase in these measures beyond placebo. Women receiving sex therapy alone showed a trend towards increased desire, arousal, lubrication and contentment, but not of the same magnitude as that seen

women receiving a combination of treatments. Orgasm function was significantly and substantially improved from baseline only in the Sex Therapy compared with Placebo condition. Together, these findings suggest that sex therapy contributed substantially to enhancing desire, arousal, and orgasm, and contentment in women, and combining GBE with therapy had an additive effect on all but one (i.e., orgasm) of these outcome measures. The fact that orgasm function was significantly higher in the Sex Therapy versus Placebo condition, but not in the Sex Therapy plus GBE versus Placebo condition is noteworthy and may suggest that long-term treatment with GBE had a negative impact on women's orgasm ability. Because women receiving Sex Therapy plus GBE were told the pill was either GBE or Placebo, we were unfortunately, unable to determine whether the additive effect of GBE with sex therapy was the result of specific pharmacological properties of GBE or, alternatively, the result of a placebo effect.

In the present study, a placebo effect was noted with short-term administration on subjective measures of sexual arousal in the laboratory, and with long-term administration on validated measures of desire, arousal, lubrication, and orgasm function, and on event log records of satisfying sexual encounters. Several studies examining the impact of sildenafil on women's sexual dysfunction have also noted substantial placebo effects (e.g., Basson & Brotto 2003; Basson et al., 2002), and it is now well known that the placebo effect is a strong agent in managing sexual dysfunction (for a discussion of the mechanisms by which placebos enhance treatment outcome effects, see Kirsch 1997; Straus & von Ammon, 1996). Future research that attempts to parse out the potential components of placebo treatment on sexual function in women would provide enormous insight into developing effective treatments for women's sexual dysfunction.

Three overall conclusions can be drawn from this study. First, neither short- or long-term administration of GBE alone substantially impacts sexual function in women with sexual difficulties beyond the improvements seen with placebo. Second, the results confirm past findings that indicate a substantial placebo effect on sexual function exists in women with sexual concerns, and suggest the placebo effect is operative with both short term and long term treatment. Third, the present findings indicate

that sex therapy, designed to train women to attend to genital issues, has a positive impact on women's sexual function, including measures of desire, arousal, orgasm and contentment. Limitations of the present study include sample sizes that limited the ability to examine potential predictor variables of outcome success (e.g., coexistent sexual dysfunction), and the absence of a Sex Therapy plus Placebo condition which preclude interpretation of the differences between women in the Sex Therapy plus GBE and Sex Therapy alone conditions. Speculative.

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