

Dietary supplements for female sexual dysfunction

Female sexual dysfunction (FSD) is complex and poorly understood. The pathways that lead to arousal and orgasm have been mapped in men but not in women. A number of factors can affect female sexual response, including family relationships, financial difficulties, fear, and sexual identity.¹ It is currently estimated that sexual dysfunction is somewhat more common in women (43%) than in men (31%).² The *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)* recognizes four types of FSD:

those affecting desire, arousal, and orgasm and a type associated with sexual pain.³ These categories are not mutually exclusive (a sexual-desire disorder may develop secondary to an orgasmic disorder, for example).

Objectively measuring and assessing FSD is difficult. While vaginal photoplethysmography and pelvic magnetic resonance imaging have been used, they are expensive and invasive.⁴ Several quality-of-life questionnaires have been developed and validated to assess treatment efficacy, including the Female Sexual Function Index (FSFI),^{5,6} the Female Sexual Distress Scale (FSDS),⁷ and the Sexual Function Questionnaire.⁸

There are currently no FDA-approved treatments for FSD, although there are a number of agents in trials. To fill this void, women may choose to self-treat with dietary supplements that are readily available on store shelves and via the Internet. However, clinical data supporting the use of these products are limited. This article reviews the literature on some of the supplements used for FSD. Dehydroepiandrosterone (DHEA), *Ginkgo biloba*, and arginine have been studied as single-product ingredients for FSD. Ephedrine alkaloids have also been

studied and have shown promise,⁹ but these products will not be discussed because FDA recently banned their sale.¹⁰

DHEA. DHEA is an endogenously produced steroid precursor that is converted in the body to androstenedione and then to estrogens and androgens. DHEA supplementation has gender-specific effects. In women, levels of androgens increase more than levels of estrogens, while in men the opposite occurs. DHEA may also have some estrogenic effects without conversion. Decreased estrogen and androgen levels have been associated with FSD; therefore, DHEA supplementation may help treat the disorder.¹¹

DHEA appears to be well tolerated, with few reported adverse effects. Reported adverse effects include hypertension, acne, hair loss, insulin resistance, voice deepening, mild insomnia, and changes in menstrual patterns. Three cases of mania have been reported in patients with and without a history of mental illness, so DHEA should be avoided in those with psychiatric disorders. Along with its estrogenic activity, DHEA interferes with aromatase inhibitors, so women with breast or endometrial cancer should avoid DHEA. Because of theoretical inhibition of cytochrome P-450 isoenzyme 3A4, caution is warranted when using DHEA in combination with drugs metabolized by that enzyme. DHEA may affect liver function and cholesterol levels.¹¹

Studies of DHEA efficacy conducted in a variety of patient populations have shown differing results. Many of these trials were conducted in small populations in which FSD was not a primary criterion for inclusion. Also, studies have used non-standardized or nonvalidated tools to measure efficacy. Trials in some popula-



The Alternative Therapies column features short reviews of herbals and other “nutraceuticals” for which there is some scientific evidence of effectiveness. The contributing editor for Alternative Therapies is Joseph Pepping, Pharm.D., Codirector, Integrative Medicine Service, Kaiser Permanente, Honolulu, HI 96814. Readers are invited to send ideas for the column to AJHP at 7272 Wisconsin Avenue, Bethesda, MD 20814 (301-657-3000) or ajhp@ashp.org.

Continued on page 577

Continued from page 574

tions, including generally healthy adults¹² and androgen-deficient women,¹³ have such severe limitations that they cannot support clinical recommendations.

Twenty-four women with adrenal insufficiency were enrolled in a randomized, double-blind, placebo-controlled crossover trial to evaluate the effects of DHEA.¹⁴ Inclusion criteria were not specified, but the women were considered healthy. The women received DHEA 50 mg orally daily for four months, followed by a one-month washout period and a four-month placebo period. Sexual function was measured with four 100-mm visual analogue scales (VASs) (0 mm = never, 100 mm = always) assessing the frequency of sexual thoughts, sexual interest, and satisfaction with mental and physical sexual experience. By the end of the study, all measures showed significant increases from baseline. The frequency of sexual thoughts and sexual interest increased significantly at one month (mean \pm S.D. VAS scores increasing from 29 ± 14 mm to 44 ± 23 mm and from 31 ± 15 mm to 48 ± 23 mm, respectively), while physical and mental sexual satisfaction scores improved at four months. The researchers concluded that DHEA improved sexual function. While the study's design was good, the outcome measure chosen has not been validated.

DHEA 50 mg orally daily was evaluated in a randomized, double-blind, placebo-controlled, three-month trial in 66 perimenopausal women.¹⁵ Primary outcome measures included the Daily Symptom Rating scale, the Hamilton Depression Rating Scale (HAM-D), and the Profile of Mood scale. Libido was assessed with the HAM-D. Vaginal dryness was also assessed by an unspecified method. There were no significant changes in libido or vaginal dryness in either group. The researchers concluded that, in perimenopausal women, DHEA does not improve libido or vaginal dryness. The study was appropriately designed for the population studied, and, although it is not all-inclusive, the HAM-D

is appropriate for determining libido. The sample size necessary to achieve statistical power was calculated and met. From this study, it appears that DHEA has little or no effect on sexual dysfunction.

The effects of DHEA replacement on sexual function in 44 patients (24 of them women) with Addison's disease were evaluated in a double-blind, placebo-controlled, crossover trial.¹⁶ The patients (ages 18–70 years) had had a diagnosis of Addison's disease for at least four years and had no other significant current medical or psychiatric illness. The Golombok Rust Inventory of Sexual Satisfaction questionnaire was used to evaluate sexual interest and arousal, frequency of intercourse, and vaginal lubrication. Participants were randomized to receive either DHEA 50 mg orally daily or placebo for three months, followed by the opposite treatment after a one-month washout period. There were no differences from baseline in any measure of sexual function. The researchers concluded that DHEA has no effect on sexual function in Addison's disease patients. The study design and duration were appropriate for the population evaluated, and the Golombok questionnaire was adequate to assess changes in sexual function. However, the sample was small, and the size needed to achieve statistical power was not calculated.

Most DHEA studies have not specifically focused on impact on FSD; however, some trials have shown a benefit with respect to sexual function. The best studies have shown little to no benefit for FSD patients, the one exception being a possible benefit in patients with adrenal insufficiency. Overall, DHEA may not be an effective choice for most patients.

Ginkgo. The flavanoid, terpenoid, and acid components of ginkgo are believed to act alone or in combination to improve regulation of vascular tone, although the exact mechanism is not understood. It is possible that inhibition of phosphodiesterase causes an increase in cellular cyclic adenosine monophosphate and the release of epinephrine, norepinephrine, and dopamine. In addition, ginkgo appears to relax vascular

smooth muscle, increasing blood flow to peripheral capillary beds.¹¹

At normal dosages, the most common adverse effects of ginkgo include gastrointestinal upset, lightheadedness, palpitations, and constipation. Large doses have produced nausea, vomiting, diarrhea, and weakness. Spontaneous bleeding has also been reported. Patients with bleeding disorders, those receiving anticoagulant or antiplatelet therapy, and those going into surgery should not take ginkgo. Ginkgotoxin, a trace component, may cause seizures; therefore, patients with seizure disorders and those taking drugs that affect seizure threshold should avoid ginkgo. Diabetics should monitor blood glucose carefully while taking ginkgo, since it may alter insulin secretion.¹¹

Ginkgo has been studied for the treatment of sexual dysfunction caused by selective serotonin-reuptake inhibitors (SSRIs). Most studies have been small and poorly designed.^{17–19} Many studies finding a benefit of ginkgo therapy have not used a standardized or validated tool to assess changes in sexual function or did not have a control group.^{17,18} One fairly well-designed, double-blind, randomized, placebo-controlled trial evaluated the efficacy of ginkgo over two months in 37 patients (10 of them women) with SSRI-induced sexual dysfunction.¹⁹ The patients received either placebo or ginkgo 120 mg orally daily adjusted upward to 240 mg daily. Efficacy was measured with a sexual-function questionnaire based on a 5-point scale, with 5 representing normal sexual function. The questionnaire was administered at baseline and two, four, and eight weeks. There were no differences between the groups, except for a significantly higher satisfaction-with-orgasm score in the control group (mean \pm S.D., 2.72 ± 1.10 versus 3.84 ± 1.14) ($p < 0.05$). The applicability of these results to FSD patients is limited by the small number of patients and the use of a nonvalidated outcome measure. However, ginkgo appears not to affect SSRI-induced sexual dysfunction.

Because of the contradictory study findings and the adverse effects, more

Alternative Therapies

study is needed before ginkgo can be recommended for FSD.

Arginine. Arginine is an essential amino acid found in animal products. In vascular epithelium, arginine is converted to nitric oxide, which causes smooth-muscle dilation and increased blood flow. Arginine applied topically to the genitalia is purported to increase blood flow to the vagina.¹¹

When taken orally, arginine can cause gastrointestinal complaints, increases in blood urea nitrogen (BUN) and serum creatinine, hyperkalemia, allergic responses, and bronchial inflammation. Patients with asthma should avoid arginine. When taken with drugs that can increase serum potassium levels, patients should be monitored for potassium changes. Arginine may have an additive effect with drugs causing vasodilation, resulting in hypotension. Arginine is contraindicated for patients with renal failure because of its effects on potassium and BUN.¹¹

Twenty-five women were enrolled in a double-blind, randomized, placebo-controlled trial of the effects of arginine and yohimbine on female sexual arousal disorder (FSAD).²⁰ Study participants met *DSM-IV* criteria for FSAD, were postmenopausal, were not taking any medications, and had no diseases known to cause FSD. The subjects received each of three treatments in random order: (1) yohimbine 6 mg orally daily, (2) yohimbine 6 mg and arginine 6 g orally daily, and (3) placebo, all separated by a wash-out period of at least one week. Before product ingestion and 30, 60, and 90 minutes afterward, participants watched a number of short films containing both neutral and erotic segments. During the viewing, a vaginal photoplethysmograph was used to measure vaginal pulse amplitude (VPA); after viewing, a sexual self-assessment questionnaire was administered. Yohimbine plus arginine produced a significantly larger increase in VPA (over placebo-associated readings) than yohimbine alone (mean \pm S.D. increase, $2.6 \pm 3.7 \mu\text{V}$ and $1.6 \pm 3.1 \mu\text{V}$, respectively). There were no changes in self-reported sexual function in any group. The authors concluded that the

yohimbine–arginine combination is effective at increasing genital blood flow during erotic stimulation. This study was well designed to examine objective sexual responses, but subjective responses would have been better assessed with a validated instrument. The study's value was limited by its inadequate power and small sample. An arginine-only group would give a better picture of this amino acid's specific role in female arousal.

Combination products. The mechanism of action of combination products is often poorly known. In studies of the combination products for FSD discussed here, no attempts were made to elucidate a mechanism of action.

There are similar difficulties in determining the safety of combination products, because the specific quantities of components are usually not stated. Adverse effects are unpredictable, and patients should be monitored closely.

Avlimil. Avlimil (Berkeley Premium Nutraceuticals, Inc., Cincinnati, OH) is a combination of 11 herbal extracts: sage leaf, red raspberry leaf, kudzu root, red clover, bayberry fruit, capsicum pepper, damiana leaf, ginger root, licorice root, valerian root, and black cohosh root. None of these ingredients have been studied for the treatment of FSD.

The effects of Avlimil on FSD were evaluated in a randomized, double-blind, placebo-controlled, parallel-group trial lasting three months.²¹ Sixty-five women ages 25–65 years were enrolled. The subjects received one tablet of Avlimil or placebo orally twice a day. They passed a compliance screening, had no current medical illnesses, and expressed an interest in increasing their sexual satisfaction. The FSFI and John Ware's Functional Survey (SF-12) were used to assess sexual satisfaction and overall well-being at baseline and at study's end. Satisfaction increased 3.6 points for the placebo group and 14.6 points for the treatment group (the total possible increase was 95 points). The researchers concluded that Avlimil was effective at improving sexual function. The methodology was incomplete and at times misleading. The authors indicated in the text that there were equal numbers

of participants in both groups, while the report's tables indicated that 40 women were enrolled in the treatment group and 25 in the placebo group. Only 49 subjects completed the trial; no reasons for the withdrawals were given. Baseline scores were not provided, only mean changes from baseline. The results are therefore of very little clinical utility.

ArginMax. ArginMax (Daily Wellness Company, Sunnyvale, CA) contains arginine, *Panax ginseng*, ginkgo, damiana, calcium, iron, vitamins (A, C, E, and B complex), and zinc. A randomized, double-blind, placebo-controlled, four-week trial looked at the effects of ArginMax on female sexual function, as measured by the FSFI.²² Seventy-seven women who expressed a desire to increase their sexual enjoyment were enrolled; there were no other inclusion criteria. In terms of overall satisfaction with sex life, 73.5% of ArginMax-treated patients reported improvement, compared with 37.2% of placebo recipients ($p < 0.01$). The ArginMax group also reported increased frequency of intercourse and improved sexual desire. The researchers concluded that ArginMax was effective in increasing sexual desire and satisfaction. No adverse effects were noted. The authors did not indicate the dosage of ArginMax. Findings were reported for baseline and four weeks for the treatment group but only four weeks and nine weeks for the placebo group, making it impossible to compare data points and base clinical decisions on this study.

Zestra. Zestra (QualiLife Pharmaceuticals, Inc., Charleston, SC), a topical massage oil, contains borage seed oil, evening primrose oil, angelica extract, coleus extract, vitamin C, and vitamin E. Little is known about the topical efficacy of any of these components. However, the dosage form (massage oil) may provide benefit in aiding in female arousal.

A randomized, double-blind, placebo-controlled trial studied the effects of Zestra in 20 women with and without FSAD.²³ Applicants were evaluated with the FSFI and FSFS questionnaires. Women with FSAD had baseline

Continued on page 580

Alternative Therapies

Continued from page 578

scores of 40–60 on the FSDS, and non-FSAD women had baseline scores of <40 on the FSDS. (The FSDS ranges from 0 to 80, with lower scores generally indicating normal function.) All participants were allowed to continue current medications, including antidepressants, nutritional supplements, and hormone replacement therapy. Sexual pain or an FSDS score of >60 would exclude patients from participation. Each patient was given five vials of Zestra or placebo and a diary (the Female Sexual Encounter Profile [FSEP]). After the patients used all five vials, they returned and completed the FSFI, the FSDS, two global assessment questionnaires (GAQs), and the QualiLife Consumer Testing Survey (QCTS). Then they received the crossover vials and a new diary and returned to complete the questionnaires again. Zestra produced significant improvement in FSEP, FSFI, GAQ, and QCTS scores. The primary outcome measure, sexual arousal, showed a mean \pm S.D. improvement (on a 0–1 scale) of 0.22 ± 0.28 ($p = 0.03$). There were no significant changes in FSDS scores. In addition, the researchers compared data between patients taking and not taking SSRIs; there was no significant difference. It was concluded that Zestra improved sexual function in all subjects, regardless of FSAD diagnosis or SSRI use. Some patients reported that Zestra caused mild burning or tingling that resolved within 30 minutes. No other adverse effects were reported.

Overall, this study was well done. Sexual function was assessed with approved questionnaires. The short duration, lack of power calculation, and small sample could have affected the results, however. Although the results look promising, a larger study should be done to provide more definitive results.

Discussion and conclusion. There is limited information about the use of dietary supplements for FSD. DHEA seems to have little or no effect on sexual function, except perhaps in patients with adrenal insufficiency. Ginkgo appears to

offer no benefit in FSD, and arginine requires more study.

While three of the myriad of combination dietary supplement products for FSD have been studied in human clinical trials, many trials are flawed to the point where it is impossible to accurately interpret the data. Of the three products assessed, Zestra seems the most promising; however, the safety data on Zestra are fairly limited.

In general, patients should not expect the available dietary supplements to provide relief from FSD, although some patients may benefit from some products. The existing data simply are not robust enough to provide clear evidence of efficacy or safety for any of these products.

1. Phillips N. Female sexual dysfunction: evaluation and treatment. *Am Fam Physician*. 2000; 61:127-42.
2. Laumann E, Paik A, Rosen R. Sexual dysfunction in the United States: prevalence and predictors. *JAMA*. 1999; 281:537-44.
3. Diagnostic and statistical manual of mental disorders (DSM-IV). 4th ed. Washington, DC: American Psychiatric Association; 1994.
4. Fourcroy J. Female sexual dysfunction: potential for pharmacotherapy. *Drugs*. 2003; 63:1445-57.
5. Rosen R, Brown C, Heiman J et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. *J Sex Marital Ther*. 2000; 26:191-208.
6. Meston C. Validation of the Female Sexual Function Index (FSFI) in women with female orgasmic disorder and in women with hypoactive sexual desire disorder. *J Sex Marital Ther*. 2003; 29:39-46.
7. Derogatis L, Rosen R, Leiblum S et al. The Female Sexual Distress Scale (FSDS): initial validation of a standardized scale for assessment of sexually related personal distress in women. *J Sex Marital Ther*. 2002; 28:317-30.
8. Quirk F, Heiman J, Rosen R et al. Development of a sexual function questionnaire for clinical trials of female sexual dysfunction. *J Womens Health Gend Based Med*. 2002; 11:277-89.
9. Meston C, Heiman J. Ephedrine-activated physiological sexual arousal in women. *Arch Gen Psychiatry*. 1998; 55:652-6.
10. Food and Drug Administration. FDA issues regulation prohibiting sale of dietary supplements containing ephedrine alkaloids and reiterates its advice that consumers stop using these products. www.cfsan.fda.gov/~lrd/fpephed6.html (accessed 2004 Jun 7).
11. Therapeutic Research Faculty. Natural medicines comprehensive database. www.naturaldatabase.com (accessed 2004 Mar 9).
12. Morales A, Nolan J, Nelson J et al. Effects of replacement dose of dehydroepiandroster-

one in men and women of advancing age. *J Clin Endocrinol Metab*. 1994; 78:1360-7.

13. Johannsson G, Burman P, Wiren L. Low dose dehydroepiandrosterone affects behavior in hypopituitary androgen-deficient women: a placebo-controlled trial. *J Clin Endocrinol Metab*. 2002; 87:2046-52.
14. Arlt W, Callies F, Vlijmen J et al. Dehydroepiandrosterone replacement in women with adrenal insufficiency. *N Engl J Med*. 1999; 341:1013-20.
15. Barnhart K, Freeman E, Grisso J et al. The effect of dehydroepiandrosterone supplementation to symptomatic perimenopausal women on serum endocrine profiles, lipid parameters, and health-related quality of life. *J Clin Endocrinol Metab*. 1999; 84:3896-902.
16. Hunt P, Gurnell E, Huppert F et al. Improvement in mood and fatigue after dehydroepiandrosterone replacement in Addison's disease in a randomized, double blind trial. *J Clin Endocrinol Metab*. 2000; 85:4650-6.
17. Cohen A, Bartlik B. *Ginkgo biloba* for antidepressant-induced sexual dysfunction. *J Sex Marital Ther*. 1998; 24:139-43.
18. Cohen A. Brief report: long term safety and efficacy of *Ginkgo biloba* extract in the treatment of anti-depressant-induced sexual dysfunction. www.mhsanctuary.com/rx/ging.htm (accessed 2004 Mar 19).
19. Kang BJ, Lee SJ, Kim MD et al. A placebo-controlled, double-blind trial of *Ginkgo biloba* for antidepressant-induced sexual dysfunction. *Hum Psychopharmacol Clin Exp*. 2002; 17:279-84.
20. Meston C, Worcel M. The effects of yohimbine plus l-arginine glutamate on sexual arousal in postmenopausal women with sexual arousal disorder. *Arch Sex Behav*. 2002; 31:323-32.
21. Blum JM, Blum RI. Executive summary: prospective, randomized, double-blind, placebo-based, parallel-group clinical trial. www.avlimil.com/avlimiltrials.html (accessed 2004 Mar 8).
22. Ito T, Trant A, Polan M. A double-blind placebo-controlled study of ArginMax, a nutritional supplement for enhancement of female sexual function. *J Sex Marital Ther*. 2001; 27:541-9.
23. Ferguson D, Steidle C, Singh G et al. Randomized, placebo-controlled, double blind, crossover design trial of the efficacy and safety of Zestra in women with and without female sexual arousal disorder. *J Sex Marital Ther*. 2003; 29(15):33-44.

Sarah A. Boone, Pharm.D. Degree Candidate

Kelly M. Shields, Pharm.D., Assistant Professor of Pharmacy Practice and Assistant Director of the Drug Information Center
k-shields@onu.edu

Raabe College of Pharmacy
Ohio Northern University
Ada, OH 45810