Mindfulness-based cognitive-behavioral treatments have also shown excellent promise for sexual desire problems. Brotto et al,[140] in one of the few empirically tested outcome studies of psychotherapy, demonstrated that a brief mindfulness-based cognitive-behavioral intervention was successful in improving sexual desire and arousal problems in gynecologic cancer survivors.[140]

Office-based counseling

Although psychotherapy/sex therapy is recommended for most women who present to their HCPs with HSDD, it may also be helpful for the HCPs to consider using the previously described PLISSIT model to offer some office-based counseling as well. For some, basic office counseling may be sufficient. For others, it may be partially helpful until they take the step of following through on a referral for psychotherapy. It is often useful to remind women in long-term relationships that committed couples are at risk for desire problems caused by boredom and complacency. Counseling suggestions may include ideas for rekindling energy and interest, such as planning romantic interludes/dates, changing sexual scripts/patterns, and incorporating erotic literature or films.

Testosterone treatment and desire

The evidence that low testosterone levels are not directly associated with loss of sexual desire may create confusion because, at first pass, it seems inconsistent with the evidence from multiple treatment trials indicating that exogenous testosterone improves sexual desire. The confusion arises from the fact that serum levels of testosterone do not necessarily correlate with women's sexual function[141] and have not been independently associated with well-being in postmenopausal women.[142] This may be explained by the known imprecision of testosterone assays at the lower end of the female range and the fact that measuring circulating testosterone levels may not reflect true tissue concentrations.[25] Compelling evidence suggests that testosterone plays a role in female sexual desire in some premenopausal and postmenopausal women. Premenopausal women with androgen insufficiency or low levels of androgens due to hypopituitarism, premature ovarian failure, adrenal insufficiency, or oophorectomy experience a diminished sense of well-being, fatigue, and decreased sexual desire.[25] Numerous studies involving postmenopausal women also showed that low testosterone levels were associated with loss of sexual desire and sexual pleasure, decreased physical well-being, and persistent fatigue.[25] Furthermore, current research is examining a genetic component for androgen receptors that may help explain this variation in women's sensitivity and response to testosterone treatment.[143]

The relationship between androgens and sexual desire was established nearly 75 years ago and was further validated by clinical research on postmenopausal women in the 1980s and 1990s (for review, see Traish et al[144] and Segraves and Woodard[29]). It was during this time that the benefit of testosterone with estrogen was identified, and this combined therapy reportedly resulted in improved sexual activity, satisfaction, pleasure, and orgasm.[145-147] Routes of administration during that time included oral administration, intramuscular injection, and subcutaneous implants.

Many of the key randomized clinical trials that studied the effects of exogenous testosterone on postmenopausal women with HSDD are presented in Table 7. These studies demonstrated efficacy as established by significant changes in satisfying sexual events (SSEs) and desire compared with placebo (in surgically and naturally postmenopausal women with and without exogenous estrogen).[148-150,152-156]

Although the absolute change in SSEs from baseline to the end of treatment may seem modest (eg, Buster et al[150]; the baseline SSE per month was 3, and the mean increase was 2.1 SSEs/month in the testosterone group vs 0.98 SSEs/month in the placebo group), the change was statistically significant, and, more importantly, the women reported clinically meaningful benefit.[157]

More recently, results from two large randomized, placebo-controlled, phase 3 trials of transdermal testosterone gel did not demonstrate the efficacy of testosterone compared with placebo among surgically and naturally postmenopausal women with and without estrogen.[158,159] These surprising results may actually represent an overly robust placebo response more than an actual lack of efficacy.

Although testosterone plays a role in drive, motivation, and sexual sensation, it is important to understand that, because there is little correlation between HSDD and serum androgen levels, they should not be used as a diagnostic measure of sexual dysfunction.[141] When hormone assays are used, it is important to include the measurement of SHBG and to calculate the free androgen index (total testosterone/SHBG), which is a more accurate reflection of the hormonal milieu than total testosterone or bioavailable/free testosterone alone. An example of a free and bioavailable testosterone calculator can be found at

TABLE 7. *Randomized, placebo-controlled, clinical trials demonstrating the efficacy of transdermal testosterone patch in postmenopausal women*

	Testosterone dose (μg/d)	Participants	n	Concomitant estrogen
Shifren et al[148]	150/300	Surgically postmenopausal	75	Yes
Braunstein et al[149]	150/300/450	Surgically postmenopausal	447	Yes
Buster et al[150]	300	Surgically postmenopausal	533	Yes
Simon et al[151]	300	Surgically postmenopausal	562	Yes
Davis et al[152]	300	Surgically postmenopausal	61	Yes (patch)
Davis et al[153]	300	Surgically postmenopausal	76	Aromatase inhibitor
Shifren et al[154]	300	Naturally postmenopausal	486	Yes
Davis et al[155]	150/300	Naturally postmenopausal/surgically postmenopausal	814	No
Panay et al[156]	300	Naturally postmenopausal	272	(Predominantly no)

http://www.issam.ch/freetesto.htm.[159a] Evidence for the efficacy of TTP use in premenopausal women with HSDD exists but is less vigorous, and conclusions for use in this population remain undecided.[160] In addition, the potential risk of fetal exposure to androgen therapy among women of reproductive age remains a concern.

Adverse effects and safety data on testosterone use

Only limited long-term safety data on testosterone use for the treatment of HSDD are available. This was the reason that the Food and Drug Administration (FDA) Advisory Committee failed to approve in December 2004 the use of a testosterone product for women.[161] After reviewing the data from the clinical trials of TTP in postmenopausal women, the committee accepted the efficacy of TTP but deemed the safety data inadequate.[162]

As result of this decision, the new drug application was withdrawn in the United States. It was subsequently submitted to and approved in the European Union but has recently been discontinued by the company that markets it. The major concerns regarding safety included the potential effects of long-term androgen exposure on the cardiovascular system, breast, endometrium, liver, and psychological well-being. The minor concerns included the known adverse effects of increased hair growth and acne. Postmenopausal women already have a high testosterone-to-estrogen ratio, and the effects of promoting this profile for the long term is unknown.

The short-term adverse effects and safety data for TTP were well documented in the randomized patch studies, but these data do not go beyond 2 years. Nachtigall et al[163] demonstrated a 4-year open-label extension safety summary of data from more than 900 surgically postmenopausal women receiving estrogens who participated in a study of 300 μg of TTP. In this study, again no increase in the rate of major adverse effects was found. The most common adverse events were application site reactions and unwanted hair growth.

In 2012, Davis and Braunstein[25] addressed some of these safety concerns in their review of the current literature. The most common adverse effects of testosterone in clinical studies were acne and increased body and facial hair with increased depilation rates, but the finding of virilization had not been observed. With respect to cardiovascular disease, they cited both observational and prospective studies in postmenopausal women that have examined the association between testosterone levels, atherosclerosis, cardiac events, and death, and have not demonstrated a causal role.[164,165]

For exogenous doses of testosterone at treatment levels consistent with those described for HSDD, there seems to be no adverse effects on the cardiovascular system, and any lipid alteration is dependent on the route of administration.[25] By avoiding the first-pass liver effects, TTPs, sprays, and other nonoral approaches do not alter the lipid profile and do not increase viscosity, as determined by plasma concentrations of fibrinogen and triglycerides. In transdermal patch studies, basal insulin and glucose levels remained unchanged, suggesting that physiologic levels of testosterone do not lead to insulin resistance.[25] Davis and Braunstein[25] even cited data from a study of 293 female-to-male transsexuals who received male doses of testosterone for 2 months to 41 years and had no increased cardiovascular mortality.

Testosterone can potentially exert an effect on the endometrium via local aromatization to estrogen; however, because aromatase activity has not been detected here, there should be no adverse uterine effects. Endometrial biopsies of postmenopausal women given oral testosterone alone for 3 months did not show any growth or proliferative changes.[166] In the APHRODITE study,[155] 12 months or two doses of TTP did not yield any adverse endometrial effects.

Although the hyperandrogenism seen in women with polycystic ovarian syndrome has not been associated with an increased risk of breast cancer, the breast does contain the aromatase enzyme complex and androgen receptors.[167] This leads to concern over exogenous testosterone therapy, especially in light of the results of combined estrogen-progestin therapy in the postmenopausal population of the Women's Health Initiative study[168]; however, similar increases in breast cancer risk were not seen in the estrogen-only treatment group, which is more relevant to the current context.[169] Davis and Braunstein[25] stated that, collectively, the data on breast cancer risk with exogenous testosterone therapy suggest a neutral or possibly protective effect. In fact, although the available safety data are not conclusive, they are reassuring with respect to cardiovascular, breast, and endometrial outcomes.[25] This has also been maintained by Bitzer et al,[170] who essentially stated in a review in 2008 that the available literature does not allow for conclusions to be drawn about the safety of testosterone therapy. However, long-term published data from large clinical trials of testosterone use are not available. In the APHRODITE trial[155] of 814 postmenopausal women not receiving estrogen, four cases of breast cancer were detected in the testosterone group, whereas there was none in the placebo group. The authors of the APHRODITE study suggested that the excess of cases in the testosterone group may have been attributable to chance. Yet, they acknowledged the possibility of a causal relationship.[154]

To address the long-term safety issues raised by the FDA, BioSante conducted a large phase 3 long-term safety study focusing on cardiovascular and breast cancer risks using a testosterone transdermal gel.[171] This safety trial was a randomized, placebo-controlled, multicenter, cardiovascular events–driven adaptive design comparison of a testosterone gel 300 μg/day (LibiGel) versus a placebo gel for the treatment of HSDD in naturally and surgically postmenopausal women with known cardiovascular risk. Enrollment at the end of approximately 4 years reached 3,656 randomized postmenopausal women with HSDD and cardiovascular risk, with accumulated exposure of more than 5,000 women-years.[171] Although the efficacy studies for LibiGel did not show any improved outcome over placebo, the data from their large safety trial helped to support the safety of using exogenous testosterone in postmenopausal women—even in women at risk for cardiovascular disease.[25,171]

INVESTIGATIONAL TREATMENTS ON THE HORIZON

On September 24, 2012, the FDA announced, as part of the Prescription Drug User Fee Act (PDUFA V), that female sexual dysfunction is one of 20 disease areas to be focused on regarding its impact on women's daily lives, the types of treatment benefit that matter most to women, and women's perspectives on the adequacy of available therapies.[172]

Centrally acting agents

Flibanserin is another nonhormone agent undergoing investigation with three completed phase 3 pivotal trials.[173-175]

As described by the dual control model of Bancroft et al,[14] HSDD has been hypothesized to be caused by an imbalance in excitatory and inhibitory activities that regulate sexual response within the central nervous system.[14] The prefrontal cortex is involved in the inhibitory control of motivational behavior, including sexual behavior. Dopamine and norepinephrine have been shown to be excitatory factors, whereas serotonin has been shown to be inhibitory. Flibanserin acts as a postsynaptic serotonin receptor 1A (5-HT_{1A}) agonist/serotonin receptor 2A antagonist (5-HT_{2A}). Stimulating the 5-HT_{1A} seems to have prosexual effects, and inhibiting serotonin receptor 2A (5-HT_{2A}) may also have prosexual effects. Three pivotal randomized controlled trials have been conducted—all comparing flibanserin 100 mg with placebo in premenopausal women. The first two trials used SSEs and an e-diary (an electronic diary that prompts women to assess their desire daily) as co–primary endpoints. Although there was a statistically different improvement in SSEs from baseline in the flibanserin group versus the placebo group, the e-diary did not show a statistical difference. The third pivotal trial used SSEs and the Female Sexual Function Index desire domain as co–primary endpoints. In this trial, the mean (SE) change in SSEs from baseline to the end of study (24 wk) for the treatment group was 2.5 (SE 4.6) versus 1.4 (SE 4.5) for the placebo group ($P < 0.001$). The mean (SE) Female Sexual Function Index desire domain score change from baseline was 1.0 (0.1) for the treatment group, versus 0.7 (0.1) for placebo ($P < 0.001$).[172,173,175]

Flibanserin has been studied in more than 11,000 women and has been resubmitted to the FDA for consideration.

Bremelanotide, a melanocortin receptor 4 agonist, is a synthetic peptide analog of the naturally occurring hormone α-melanocyte-stimulating hormone. Bremelanotide has shown benefit in improving sexual desire and arousal in postmenopausal women. It was initially formulated as a nasal spray, but development was stopped because of adverse blood pressure effects.[176]

It has been reformulated as a subcutaneous injection. In a recently completed phase 2B clinical trial, bremelanotide in 1.25- and 1.75-mg doses significantly increased sexual arousal, sexual desire, and the number of sexually satisfying events, and decreased associated distress in premenopausal women with HSDD. In the phase 2B trial that has yet to be published,[177] bremelanotide showed a statistically significant increase in the number of SSEs versus placebo (mean [SE] increase in SSEs, 0.8 [2.9] for 1.75 mg ($P = 0.0215$) and 0.7 [2.4] for 1.25/1.75 mg pooled ($P = 0.0180$) vs 0.2 [2.3] for placebo) and a statistically significant decrease in distress as measured by the Female Sexual Distress Scale-Desire, Arousal, Orgasm (FSDS-DAO) compared with placebo.

Lybrido and Lybridos are combination sublingual drugs that are under development for the treatment of HSDD.[178-180]

Lybrido[179] is designed for women whose HSDD is caused by overactivation of sexual inhibitory mechanisms and combines testosterone with a phosphodiesterase inhibitor (PDE5). PDE5 inhibitors cause an increase in physiologic genital response. Although clinical trials of sildenafil versus placebo conducted in women with sexual arousal disorder (FSAD) showed no significant differences (perhaps due in part to FSAD being the primary diagnosis in not quite 50% of women),[181] the combination therapy is theorized to work differently and in a different population of women. The testosterone-induced increase in sexual motivation facilitates a peripheral response via PDE5 inhibition. The increased peripheral response provides, in turn, a potent sexual cue to the more sexually sensitive brain, creating a positive feedback loop that further increases sexual motivation, desire, and sexual responsiveness.

Lybridos[180] combines testosterone with buspirone and is designed for women with HSDD who also have sexual inhibition. Short-term treatment with a 5-HT_{1A} agonist might decrease serotonergic inhibitory control in the prefrontal cortex and therefore might inhibit the inhibition of sexual responses in certain women with HSDD. In Lybridos, the pharmacologic effects of the 5-HT_{1A} agonist coincide with the sexual motivational window induced by testosterone administration.

Investigational treatments of depression and/or antidepressant-induced sexual dysfunction

Extended-release gepirone is an investigational drug for the treatment of depression and sexual dysfunction. Similar to flibanserin, it has a 5-HT_{1A} mechanism of action (but does not affect other serotonin receptors), has been shown in phase 2 clinical trials to have a prosexual effect at daily dosing of 40 to 80 mg, and has improved HSDD in women diagnosed with depression.[182]

Although not an investigational drug or a drug that is indicated for the treatment of sexual dysfunction, sustained-released bupropion is an antidepressant that has been shown to have a moderate prosexual effect and is often used to treat the sexual adverse effects of SSRIs. It blocks the uptake of dopamine and norepinephrine and has been found to significantly improve sexual arousal and orgasm, but not sexual desire alone, in nondepressed women.[29]

As described earlier, clinical trials have not shown sildenafil to be more effective than placebo in treating women with a spectrum of sexual disorders.[181] However, a small randomized controlled trial demonstrated that sildenafil (adjustable dose, 50 or 100 mg) was significantly more effective than placebo in reducing SSRI/serotonin-norepinephrine reuptake inhibitor–induced sexual dysfunction.[183]

Other hormone treatments

DHEA is a prohormone of testosterone that is available as an over-the-counter supplement in tablets of 25 to 50 mg. Clinical trials using DHEA in a transdermal vaginal approach for the treatment of HSDD and vaginal atrophy and for the prevention of osteoporosis are now being conducted.[184]

CONCLUSIONS

Hypoactive sexual desire, categorized either as HSDD (as per the DSM-IV-TR)[12] or as FSIAD (as per the DSM 5),[11] is a highly prevalent medical condition that negatively impacts women's sexual lives and overall quality of life. Yet, the condition remains underdiagnosed by clinicians and has few treatment options. However, several factors are converging to create a palpable shift toward greater attention and awareness. The inclusion of hypoactive sexual desire as a topic for a *Menopause* invited review is evidence of this swing. Greater societal acceptance of women's entitlement to healthy sexual function has helped this shift, although many postmenopausal women continue to hold the belief that society disapproves of their sexuality.[185]

The continued pursuit of pharmacologic agents to treat the physiologic component of hypoactive desire is certainly one of the stronger forces influencing greater attention by researchers and clinicians. Even the FDA has weighed in on this shift by including female sexual dysfunction as a disease area deserving focus. Furthermore, several pharmacologic agents targeting hypoactive sexual desire are in phase 2 or phase 3 development. Despite this positive momentum, if clinicians do not address the sexual concerns of women, then those women with hypoactive sexual desire who would otherwise want to be evaluated and treated will remain invisible and untreated. Some of the major barriers to HCPs addressing the sexual concerns of women are their lack of knowledge of the condition, their discomfort in addressing the topic, and their confusion over treatment within a biopsychosocial model. The value of this review will be determined by its effectiveness in removing those barriers.

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