CE 3.1 CONTACT HOURS Rx 3.1 CONTACT HOURS

Pharmacologic therapy for female sexual dysfunction

Abstract: Female sexual dysfunction (FSD) is a common health issue that can have significant negative effects on overall well-being and quality of life. The primary purpose of this article is to review commonly noted pharmacologic therapies for FSD. The pathophysiology, clinical evaluation, and selected nonpharmacologic therapies are also briefly addressed as well as recommendations for practice.

By Christine Bradway, PhD, RN, FAAN, and Joseph Boullata, Pharm D, RPh, BCNSP

Female sexual health is a complex, multidimensional, individual experience that changes as women age. Multiple variables interact and affect female sexual health, including personal relationships, psychosocial factors, physiologic changes associated with aging as well as pathologic changes associated with disease, and pharmacologic influences on health and disease.[1] While at least one author argues that female sexual dysfunction (FSD) is a phenomenon created by the pharmaceutical and medical community to further the development of drug therapy approaches to treatment, others support the notion that a range of disorders that comprise FSD can be classified and defined.[2-6] The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR [text revised]; DSM-V), based on the most traditional, linear model of the female sexual response cycle, is primarily focused on the emotional and psychological factors associated with FSD.[3,4,7]

Distinct categories, such as those described by the DSM-IV-TR and DSM-V, are useful as a starting point; however, from a clinical standpoint, it is likely that women may present with one primary disorder and, in addition, also experience a cluster of symptoms suggestive of two or more coexisting conditions.[1] Furthermore, as understanding of the female sexual response cycle evolves, an alternate classification system has been proposed that reflects a more cyclical, holistic response model that addresses the complexity of the female sexual experience, and incorporates the concepts of intimacy-based motivation and personal distress as a diagnostic criterion.[8,9]

Although FSD is common, it is challenging to determine exact prevalence because investigators use different definitions (for example, distress, dysfunction, and difficulty) and a wide variety of validated and nonvalidated instruments to collect data; describe heterogeneous populations including pre-, peri-, and postmenopausal women affected by different categories of FSD; include women with and without coexisting conditions that overlap and may affect the presentation of FSD (for example, natural or surgical menopause, depression, and other comorbid health conditions); and may or may not include a clinical/physical exam to determine specific characteristics associated with subjective complaints.[8,10-14] Thus, the documented prevalence of sexual problems varies widely (9% to 43%).[11] FSD is described as occurring most often "around middle-age."[8] For example, one cross-sectional prevalence study of 31,581 American women (including those who

Keywords: female sexual arousal disorder, female sexual dysfunction, pharmacotherapy, systematic review

sought care for FSD and those who had not) documented decreased sexual desire, arousal, and orgasm in 14.8% for women between ages 45 and 64, compared with 8.9% of those age 65 and over and 10.8% for those between ages 18 through 44.[15] Specific prevalence rates for individual categories of FSD also vary; most sources agree that female sexual desire disorders are the most common followed by female sexual arousal disorder (FSAD) and/or female orgasmic disorder (FOD).[12,14,16,17]

FSD negatively affects health-related quality of life (HRQoL), including self-esteem, mood, and relationships with sexual partners, and overall well-being.[18-20] Numerous health conditions (diabetes, hypertension, arthritis, and obesity) in addition to pharmacologic therapies (certain antihypertensive medications, selective serotonin reuptake inhibitors [SSRIs]) commonly prescribed in clinical practice have the potential to negatively impact women's sexual responsiveness and satisfaction.[21-24] Therefore, it is important that clinicians have an understanding of the evaluation and treatment of FSD. The primary purpose of this article is to review the most commonly discussed options for the pharmacologic treatment of FSD. The pathophysiology, evaluation, and nonpharmacologic therapies will also be briefly reviewed as well as recommendations for practice.

Although not completely understood, several sex hormones and neurotransmitters affect sexual function and can lead to FSD.

Search methods

A literature search focused on research articles related to pharmacologic treatment of FSD. Initially, three online databases were included: Cumulative Index of Nursing and Allied Health Literature, Medline, and PubMed. Keywords female sexual dysfunction, pharmacotherapy, and FSAD were used to identify articles published in English between 2008 and 2013 and focused on humans. From these citations, additional keywords sildenafil, hormone therapy, bupropion, and androgens were searched to identify articles specifically focused on some of the more common pharmacologic therapies. Finally, the topic was further explored by searching the Scopus and Joanna Briggs Institute databases and by adding references cited in primary review and research articles. This expanded the database, as selected publications prior to 2008 were also then identified and included because of their importance to the topic. The total number of citations reached over 1,000, primarily from medicine and pharmacology sources. This initial reference list was narrowed by focusing primarily on the population most affected by FSD (peri- and postmenopausal women) living in the community (not hospitalized or living in a long-term care facility), and those that included primary content regarding pharmacologic options for treatment of FSD not associated with a specific disease, such as cancer. This resulted in 40 evidence-based articles focused on the pharmacologic treatment of FSD that comprise the research citations included in this paper.

Pathophysiology

"Normal" female sexual function is complex and involves psychological and relational components as well as physiologic factors, including androgen function and the central and peripheral nervous systems.[12,14] Although not completely understood, several sex hormones and neurotransmitters affect sexual function and can lead to FSD. These include estrogen (impacting sexual arousal and sexual desire) and testosterone (affecting sexual desire); dehydroepiandrosterone ([DHEA], inconclusive understanding of impact on sexual function); norepinephrine, serotonin (affecting sexual arousal); dopamine (affecting sexual desire and arousal); and nitric oxide (possibly affecting clitoral vasocongestion).[12,14] For peri- and postmenopausal women, the roles of circulating androgens (most important estrogen and testosterone) and accompanying hormonal decreases that occur with age and menopause are the primary factors affecting female sexual function. For example, declining estrogen levels lead to vaginal epithelial thinning, reduced vasocongestion, and lubrication during sexual arousal, which result in sexual pain/dyspareunia.[8] Similarly, age-associated decreases in testosterone (which may begin as early as age 20) are thought to negatively affect sexual desire and, in turn, lead to decreased sexual activity.[8]

Clinical evaluation

Because FSD is multifactorial, the evaluation varies based on the clinical setting as well as other factors, such as time constraints, patient preference, and available referral sources and treatment options.[12] In general, the history may begin with an open-ended question, such as "Do you have any concerns about your sexual functioning?"[25] It can go on to address primary etiologies of FSD, including hormonal/endocrine (menopause and/or thyroid disorders), musculogenic (pelvic floor muscle hyper- or hypotonicity), neurogenic (spinal cord injury, stroke, and/or diabetes),

psychogenic (relationship issues and chronic or recent-onset mental health disorders), vasculogenic (atherosclerosis to genital tissues and/or trauma), anatomic (pelvic organ prolapse and/or surgical procedures), and medication-related (chemotherapy, antihypertensive agents, and/or serotonergic antidepressants) factors.[5,10,12,14,26]

Several self-report and interview-based instruments are available to augment history-taking. Most have been used primarily for research purposes, but at least two have been suggested as useful in a clinical, primary care settings.[12,27] The Brief Sexual Symptom Checklist was developed by an international committee of experts for use in primary care as a screening tool and to augment a more comprehensive sexual assessment.[25] No psychometric data regarding reliability, validity, or the target age of the population (pre- versus postmenopausal) have been published, and two versions of the checklist ("men's" and "women's") were developed. The women's version includes four questions regarding satisfaction with sexual function, determination of specific sexual problems, and the woman's interest in discussing sexual issues with a healthcare provider. The Decreased Sexual Desire Screener is a psychometrically sensitive and specific, five-item questionnaire that can be used to diagnose hypoactive sexual desire disorder (HSDD) in both pre- and postmenopausal women.[28] Women respond "yes" or "no" to four questions regarding sexual desire. These include the following:

- In the past, was your level of sexual desire or interest good and satisfying to you?
- Has there been a decrease in your level of sexual desire or interest?
- Are you bothered by your decreased level of sexual desire or interest?
- Would you like your level of sexual desire or interest to increase?[28]

Responses are then reviewed by the clinician and followed by additional evaluation as necessary.

Key elements of the physical exam include the following: vital signs, neurologic, cardiovascular, and thyroid assessments; peripheral pulses and lower extremity vibratory sensation; and a complete genital exam, including assessment of secondary sexual characteristics, pelvic organ prolapse, hyper- or hypotonicity of pelvic floor muscles, pelvic/perineal pain or tenderness, body hair, and fat distribution.[12,25] Additional diagnostic lab tests may be included and should be based on findings from the history and/or physical exam. For example, determination of thyroid function, hormone levels in postmenopausal women, fasting blood glucose, cholesterol, and lipid levels may provide the clinician with additional important information to rule in or rule out other conditions impacting sexual function.[12,25]

Nonpharmacologic therapies

Nonpharmacologic therapies play an important role in the care of women experiencing FSD. At least one expert notes that without consideration of the psychosocial aspects of FSD and use of counseling as needed, pharmacologic therapy alone will not be successful.[10] Counseling may include the following: providing information and addressing specific issues, such as intimacy, physical health, cultural norms, cognitive behavioral therapy, and couples therapy.[8,19,29] Use of the PLISSIT (Permission, Limited Information, Specific Suggestions, Intensive Therapy) model[30] has also been suggested as an assessment and counseling model that can be used in a variety of settings, including primary care, to help patients gain insight with regard to their sexual feelings and desired sexual response.[26]

Healthy lifestyle habits include minimizing alcohol intake, as overindulgence can blunt sexual responsiveness; smoking cessation, as smoking restricts blood flow to sexual organs and decreases sexual arousal; and keeping physically active, which increases stamina and elevates mood.[31] Following a Mediterranean-style diet may also be helpful. A recent study included 595 (mean age of 58) women with type 2 diabetes mellitus (DM) who completed a food-frequency questionnaire and self-report measures of sexual function to examine the relationship between consumption of a Mediterranean diet and sexual function.[32] In this population, those with greater adherence to a Mediterranean diet were also associated with an overall lower prevalence of FSD and a significantly ($P = 0.04$) higher degree of sexual satisfaction than those less adherent to a Mediterranean diet.[32] Physiotherapy may also be helpful, particularly for sexual pain disorders,[33] and includes instruction and use of specific devices to enhance sexual satisfaction and lubrication (for example, vibrator or dilator), biofeedback, and massage. Additional complementary therapies that may be considered include mindfulness meditation, acupuncture, and yoga.[31]

Pharmacologic therapies

Pharmacologic therapies for FSD vary widely; in some cases, specific medications are prescribed or have been investigated for more than one of the DSM-IV-TR[3] categories of FSD. For example, although not approved by the U.S. FDA, tibolone has been noted to be helpful for women experiencing sexual pain disorders/vulvovaginal atrophy (VVA)/dyspareunia and has also been investigated as a treatment for general sexual function, sexual satisfaction, and frequency of sexual activity.[34,35] In addition, some studies address FSD, but not in terms of a specific category. In general, the pharmacologic therapies most often associated with one or more categories of FSD are arranged by the FSD

category they are most commonly associated with and are discussed in the section that follows. (See *Current and in-development pharmacologic therapies for FSD.*)

Sexual desire disorders

Testosterone preparations are the most commonly mentioned pharmacologic therapies for the treatment of sexual desire disorders and, in particular, HSDD. Although bupropion has been studied as a possible treatment for several of the FSD categories, it is included here, as HSDD is one of the primary categories mentioned in terms of use of this medication.

Testosterone. In women and men, androgens are thought to influence sexual desire, and as women age, androgen levels decline.[36] Although not approved for FSD by the U.S. FDA, transdermal testosterone preparations (gel, patch, nasal spray, [with or without concomitant estrogen use]) are the most frequently investigated therapies for menopausal (surgical, natural) women reporting FSD/HSDD. Several randomized, double-blind, placebo-controlled trials have found a transdermal testosterone patch safe, well-tolerated, and effective at 300 mcg/day (150 mcg/day was not found to be effective, and the 450 mcg/day was no better than 300 mcg/day) in improving sexual desire and frequency of satisfying sexual activity in surgically menopausal women also receiving estrogen therapy.[37-39]

Transdermal testosterone therapy has also been studied, to a lesser extent, in naturally occurring menopausal and premenopausal women. In a well-designed, randomized, placebo-controlled, double-blind study (the INTIMATE NM 1 study) of 483 (mean age = 54) naturally menopausal women also receiving estrogen replacement therapy, a transdermal testosterone patch (releasing 300 mcg/day) was compared with placebo.[40] Those receiving testosterone noted significantly improved sexual desire ($P = 0.0001$) and decreased personal distress ($P = 0.0001$) compared to

Current and in-development pharmacologic therapies for FSD[1,34,35,37-43,45,46,49,51,53-67,69,71-76,78,83,84,86*]

Drug	Mechanism of action	Indication: Potential or current	U.S. FDA approved
Bremelanotide	Melanocortin 4 receptor agonist	Postmenopausal FSAD	No; not available and not approved in the United States
Bupropion	Norepinephrine reuptake inhibitor/nicotinic acetylcholine receptor antagonist	HSDD; FSAD; FOD SSRI-induced FSD	No; not approved; is available in the United States but not for this indication
DHEA	"pre-androgen"	FSD; postmenopausal VVA/dyspareunia	No; not approved; is available in the United States but not for this indication
Estrogen: Systemic	Reverse systemic effects of low postmenopausal hormone levels	FSAD; HSDD	No; not approved; is available in the United States but not for this indication
Estrogen: Topical/vaginal	Reverse local effects of low postmenopausal hormone levels	Postmenopausal VVA/dyspareunia	Yes; approved and available in the United States
Ospemifene	Selective estrogen receptor modulator	Postmenopausal VVA/dyspareunia	Yes; approved and available in the United States
Sildenafil	PDE 5 inhibitor	FSAD; FOD; SRI-induced FSD	No; not approved; is available in the United States but not for this indication
Testosterone: Transdermal	Androgen receptor agonist	Female desire disorders; HSDD	No; not approved; is available in the United States but not for this indication
Tibolone	Androgen receptor agonist	Postmenopausal VVA/dyspareunia	No; not approved and not available in the United States

Key to abbreviations: U.S. FDA = United States Food and Drug Administration; VVA = vulvovaginal atrophy; FSAD = female sexual arousal disorder; FOD = female orgasmic disorder; HSDD = hypoactive sexual desire disorder; SRI = serotonin reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor

* References used as research/evidence of pharmacologic therapy for FSD

those receiving placebo. Similarly, in a well-designed, randomized, double-blind, placebo-controlled study of 261 premenopausal women between 35 and 46 with low testosterone levels and subjective reports of decreased satisfying sexual activity, varied doses of transdermal testosterone delivered by metered-dose nasal spray) were administered over a 16-week period.[41] Women receiving the middle strength dose (one 90 microliter spray/day) were significantly more likely to note increased satisfying sexual activity than those receiving placebo ($P = 0.04$); however, none of the doses achieved statistical significance when participants completed validated sexual function and sexual satisfaction questionnaires.[41] No serious adverse reactions have been identified in any of these studies[37-41]; however, all were of relatively short duration (4 to 24 weeks), a significant limitation in terms of addressing long-term safety issues, such as adverse reactions on the cardiovascular system, stimulation of breast and endometrial tissue, particularly in terms of achieving U.S. FDA approval.[42] To address these concerns, a prospective, 5-year, Phase III clinical trial comparing a daily dose of 1% testosterone gel versus an equal weight of placebo gel is currently underway (the BioSante LibiGel Safety Study [BLISS]).[43] The primary purpose of the BLISS study is to evaluate the long-term effects of the product on cardiovascular risk, breast cancer, and general safety. To date, more than 3,600 postmenopausal women (natural and oophorectomized), most at the "higher end" of the cardiovascular risk continuum (67.9% with diabetes, 64.7% with dyslipidemia, and 53.3% taking antihypertensive agents) have been enrolled in the study.[43] Results are forthcoming and will add important information to the evidence base regarding the use of this product.

"Normal" female sexual function is complex and involves psychological and relational components as well as physiologic factors.

Bupropion. Bupropion is classified as an aminoketone antidepressant and acts via dual inhibition of norepinephrine and dopamine reuptake.[44] The drug is U.S. FDA-indicated for the treatment of major depressive disorder as well as for use in smoking cessation and has also been studied for its potential effects in FSD. In one small study, 51 pre- and postmenopausal, nondepressed women (mean age = 42) with HSDD (almost 30% of the subjects also had a diagnosis of FSAD) participated in an 8-week, single-blind, open-label trial of 150 mg twice daily bupropion. The study was limited by the small sample size (underpowered) and the lack of a parallel placebo-control group; however, at the end of the treatment trial, 39% of the women subjectively rated their sexual satisfaction as having increased, and significant increases in interest in sexual activity, sexual arousal, and sexual fantasy were also identified.[45] A subsequent double-blind, placebo-controlled trial of 66 nondepressed women (mean age = 36) with HSDD were randomized to receive either study drug (in an escalating dose, average daily dose = 389 mg) or placebo over a 112-day trial period.[46] Statistically significant increases between drug and placebo ($P = 0.05$) were identified in sexual arousal and orgasm completion using one reliable and valid measure (the Changes in Sexual Function Questionnaire) but were not found on a second measure (the Brief Index of Sexual Functioning in Women).[46-48] This study was limited by a small sample size and fairly large attrition rate (for example, at day 112, 41 subjects [62%] remained in the trial) as well as by lack of significant findings on all measures included in the study.

In addition to these studies of bupropion as a treatment for HSDD and FSAD, one small study (N = 30, median age = 31) examined the effect of bupropion on orgasmic dysfunction in nondepressed women (N = 20) and men (N = 10).[49] This single-blind, sequential treatment order (3 weeks placebo, followed by 3 weeks bupropion 150 mg/day, followed by 3 weeks bupropion 300 mg/day) study was limited by the small sample size as well as the occurrence of a fairly strong placebo effect; however, women reported significant improvements in overall sexual satisfaction and orgasmic intensity compared to placebo occurred in both the 150 mg/day and 300 mg/day arms of the study.

Because sexual dysfunction is a common adverse drug event (ADE) associated with use of SSRIs, a recent randomized controlled clinical trial examined the use of bupropion 150 mg twice daily (N = 109) versus placebo (N = 109) in a group of premenopausal women (mean age = 34) with major depressive disorder who developed a new diagnosis of FSD after initiating outpatient treatment with an SSRI.[50-51] By adding bupropion 150 mg twice daily as an adjunctive therapy, sexual desire ($P = 0.001$), arousal ($P = 0.01$), lubrication ($P = 0.001$), orgasm ($P = 0.001$), and satisfaction ($P = 0.001$) all significantly improved compared to placebo. This study has important clinical implications, as sexual dysfunction is a potential adverse reaction associated with antidepressant use.[50]

Despite the trends toward positive findings and the clinical significance of using bupropion as a primary or adjunctive therapy for treating FSD, the drug is not U.S. FDA

approved for this disorder. In one expert review article, Clayton suggests that clinicians consider choosing bupropion as an antidepressant for women who are also experiencing either comorbid HSDD or an orgasmic dysfunction, with the understanding that FSD would not be the primary indication for use of the drug, but it may have a positive effect on these "secondary" health issues.[44]

FSAD

In this section, two medications are reviewed: bremelanotide and sildenafil. Bupropion and systemic estrogen therapies have also been suggested as possible treatments for FSAD; these drugs are reviewed in the sections devoted to sexual desire disorders and sexual pain disorders.

Bremelanotide (P-141). Bremelanotide is a melanocortin agonist and a synthetic peptide analogue of alpha-melanocyte-stimulating hormone, alpha-MSH.[52] Initially, intranasal bremelanotide was tested in male subjects experiencing erectile dysfunction (ED) and female subjects diagnosed with FSAD.[1,53,54] Despite promising results in women and men, significant concerns with the adverse reaction of increased BP led to the discontinuation of further clinical trials for intranasal bremelanotide as a first-line treatment for ED and FSAD. Currently, a subcutaneous preparation is under development for the treatment of FSAD in premenopausal women. Ongoing Phase IIB clinical trials are in progress and are promising in terms of limited exposure to the drug via this method of administration and, in turn, fewer adverse reactions, including increase in BP.[52,55] Results of the most recent randomized, double-blind, placebo-controlled, parallel-group clinical trial of three fixed-dose levels were presented in early 2013. In this study, premenopausal women (N = 297, mean age = 37) diagnosed with HSDD and/or FSAD self-administered subcutaneous bremelanotide at home on an as-needed basis.[55] Results suggest that for women with FSD, subcutaneous bremelanotide was effective in decreasing sexual distress, and increasing arousal and desire, versus those treated with placebo. The drug was generally well-tolerated, and no significant differences in BP between those receiving the drug versus those receiving placebo were identified (2% of the sample for both those receiving the drug and those receiving placebo).[55]

Dyspareunia associated with VVA may limit a woman's interest, desire, or responses to sexual activity.

Phosphodiesterase type 5 (PDE-5) inhibitors. Sildenafil, vardenafil, and tadalafil have been used successfully for a number of years to treat male ED. These drugs work by inhibiting PDE-5 and enhancing nitric oxide cyclic guanosine monophosphate (cGMP) pathway, thereby, improving penile engorgement and erection. Because genital engorgement is also one of the physiologic responses to sexual stimulation in women, and as a result of the effectiveness of PDE-5 inhibitors in men, a number of investigators have examined the use of sildenafil in women suffering from FSAD.[56-60] None of the PDE-5 inhibitors are currently U.S. FDA approved for the treatment of FSD.

Sildenafil has been studied as a standard treatment option for women affected by FSAD.[57,59] In an early study, Berman and colleagues enrolled 202 postmenopausal women with a primary diagnosis of FSAD[57]; in addition, 112 of the study's subjects also had a concomitant diagnosis of HSDD. During the treatment phase of the study, subjects were given sildenafil 50 mg to be taken approximately 1 hour before sexual intercourse; the dose could be adjusted to 25 mg or 100 mg once during the treatment phase if needed. Women without HSDD experienced significant improvements in arousal-sensation ($P < 0.001$), arousal-lubrication ($P = 0.003$), and orgasm ($P = 0.01$) with sildenafil as compared to placebo. However, these same subjects did not experience any significant improvements in sexual desire, sexual enjoyment, or decreased pain, and for women with concomitant HSDD, no significant improvements in any outcome measures were identified.[57] More recently, Leddy and colleagues performed a double-blind, placebo-controlled crossover study of clitoral engorgement responses (measured by noncontrast magnetic resonance imaging) after administering 100 mg of sildenafil versus placebo followed by audiovisual sexual stimulation.[59] This was a small study (N = 19 premenopausal women with FSAD), sildenafil did not augment the genital response in women with FSAD, and no differences in clitoral engorgement were identified between the sildenafil and placebo treatments. Overall, because these two studies as well as earlier studies of sildenafil as a treatment for FSAD have a number of limitations (such as small sample sizes and inconsistent use of measurement instruments) and have yielded inconclusive results, there is currently no support for the use of sildenafil as a general treatment for FSAD.[19,57,59,61,62] In addition, in contrast to male ED, primary FSAD does not appear to be a disorder of vulvovaginal/genital engorgement.[59]

Others have examined sildenafil in women with FSD that occurs in association with a neurodegenerative disorder

or as an ADE associated with selective and nonselective serotonin reuptake inhibitors (SRIs). Sildenafil may be beneficial for these subgroups of women affected by FSD.[19,63] An early pilot study showed improvements in subjective and objective measures (genital arousal) of sexual function in women with spinal cord injury[64]; unfortunately, a follow-up randomized controlled trial (RCT) in 52 multinational (North America, Europe, Australia, South Africa) pre- and postmenopausal women (mean age = 37) with FSAD as a result of spinal cord injury failed to achieve statistical significance between the sildenafil and placebo-treated subjects.[56] In another study, nonobese (mean body mass index = 25 kg/m^2), premenopausal women with type 1 DM (N = 32; mean age = 33), and FSAD participated in a double-blind crossover, placebo-controlled study to determine if oral sildenafil would improve genital arousal.[58] Women randomly assigned to sildenafil took 100 mg of the drug 1 hour prior to sexual intercourse–no more than once daily–over an 8-week period. In this group of women with type 1 DM, subjective experiences of arousal ($P < 0.01$) and orgasm ($P < 0.05$) were improved over placebo as well as clitoral blood flow (measured by Doppler ultrasound; $P < 0.05$). Finally, for women who experience FSAD as an ADE associate with SRI antidepressant use, 49 premenopausal subjects experiencing FSAD and diagnosed with major depressive disorder and currently treated with a selective and nonselective SRI were studied by randomly assigning them to either placebo or a flexible dose of sildenafil (50 mg to 100 mg) before sexual activity.[60] For this population, women in the sildenafil group had a higher mean improvement in orgasm ($P = 0.01$) and significantly better ability to achieve orgasm ($P = 0.01$) than those in the placebo group.[60]

FOD

Both sildenafil and bupropion have been studied for the treatment of FOD and are reviewed in sections above. No additional pharmacologic therapies are commonly suggested for FOD.

Sexual pain disorders

Limited data exist to support pharmacologic treatment of vaginismus; therefore, VVA/dyspareunia is the primary focus of this section.[19] In addition to over-the-counter (OTC) use of a water-soluble lubricant, several prescription preparations also may be helpful for treatment of VVA/dyspareunia including topical and systemic estrogen therapy, ospemifene, and tibolone. Some authors also mention DHEA as a possible treatment for VVA/dyspareunia; therefore, information on DHEA is also included in this section.

Estrogen. Both local and systemic estrogen preparations have been studied for the treatment of VVA and dyspareunia associated with age-related menopausal decreases in circulating estrogen. In addition, estrogen therapy has also been studied as a treatment for FSAD. Women experiencing VVA commonly report symptoms such as vaginal dryness, irritation, decreased lubrication, itching, and dyspareunia. Although the distinct effect on the multiple aspects of FSD is not completely understood, in one study, women with VVA were found to be 3.84 times more likely to also experience FSD (95% CI, 2.99 to 4.94) than women without VVA[8,12,65]; therefore, a relationship between VVA and FSD has been proposed. Moreover, dyspareunia associated with VVA may limit a woman's interest, desire, or responses to sexual activity.[65]

Local estrogen therapy. Local estrogen therapy in the form of a cream, tablet, or silicone ring is considered a first-line pharmacologic option for reversing/managing VVA and reducing dyspareunia.[5,10,19] For example, a recent review suggests that ultra-low-dose estradiol vaginal tablets (10 mcg) are safe and highly effective in reversing VVA.[66] Intravaginal estrogen cream (0.625 mg conjugated equine estrogen [CEE]/1 g vaginal cream) inserted once daily for 3 months has also been found to improve sexual function and decreases vaginal dryness and dyspareunia ($P < 0.05$) in postmenopausal women.[67] Although few additional studies exist regarding the use of local estrogen therapies, in practice, topical estrogen is often prescribed, is generally well-received and tolerated by patients, and for women without other indications for use of systemic estrogen therapy, is more appropriate, and provides even better symptom relief of VVA than systemic therapies.[19,68-70]

Systemic estrogen therapy. Although oral and transdermal estrogen preparations are also effective in treating postmenopausal VVA, concerns regarding systemic absorption and decreased effectiveness as compared with local estrogen therapies suggest that systemic estrogen therapy should not be a first-line treatment for VVA.[5,26,71] Systemic estrogen therapy has, however, been examined in a few studies as a treatment for FSAD with mixed results. Currently, no evidence-based protocols exist for using systemic estrogen therapy as a primary treatment for FSD.[27,72-74] The effects of oral estrogen and progestin (varied doses; 0.625 mg or 1.25 mg CEE/5 mg medroxyprogesterone acetate) on sexual function were investigated in 48 naturally perimenopausal (no menses for at least 6 months) women (age range: 47 to 57); in this early study, all treatment groups experienced an increase ($P < 0.05$) in sexual desire and sexual arousal during the time they were receiving estrogen/progestin therapy compared to the period when they were receiving placebo.[73]

Transdermal preparations of estradiol have also been examined. One double-blind, placebo-controlled study examined the effect of transdermal estrogen therapy (50 mcg/24 hours) on HRQoL and sexual function in postmenopausal women (N = 223; mean age = 52).[72,74] Women were randomized to either treatment (transdermal estradiol patch, changed twice weekly) or placebo (patch, changed twice weekly) over a 12-week period. Those in the treatment group noted significant improvements in overall HRQoL ($P = 0.0003$) as well as in sexual problems ($P < 0.0001$; for example, frequency of sexual activity, sexual fantasies, degree of enjoyment), and sexual dysfunction ($P = 0.01$); frequency of orgasm and sexual arousal were not improved with estradiol therapy.[72,74]

Ospemifene. In February 2013, ospemifene, a selective estrogen receptor modulator (SERM), was approved by the U.S. FDA as a treatment for postmenopausal women experiencing moderate-to-severe dyspareunia as a result of VVA. Because SERMs act by targeting specific tissues but do not pose the same risks and safety concerns as orally administered estrogen and other forms of hormone therapy, interest in their use for the treatment of postmenopausal VVA and dyspareunia has increased in recent years. At least two phase III clinical trials have found the drug safe and effective for postmenopausal women with VVA.[75,76] In the most recent and largest double-blind, parallel group clinical trial, 605 women (ages 40 to 80) diagnosed with VVA and self-reporting dyspareunia were randomized to receive either 60 mg of oral ospemifene once/day versus placebo.[76] In this study, dyspareunia was significantly decreased as compared with placebo ($P < 0.0001$).[76] Common adverse reactions include hot flushes/flashes, vaginal discharge, muscle spasms, genital discharge, and excessive sweating. A boxed warning is included with the drug to alert providers and patients that because the drug acts like estrogen on vaginal tissues, it can stimulate the lining of the uterus, and postmenopausal women who experience any vaginal bleeding should contact their healthcare provider for additional evaluation. Thrombotic (0.72/1,000 women) and hemorrhagic strokes (1.45/1,000 women) have also been documented; however, the U.S. FDA notes that these rates are low in comparison with traditional estrogen therapy.[77]

Healthcare providers in both primary and specialty care settings are likely to encounter women experiencing one or more types of FSD.

Tibolone. Tibolone is classified as a synthetic steroid hormone with estrogenic and androgenic properties and has been prescribed for the treatment of postmenopausal symptoms and as a treatment for preventing osteoporosis in countries around the world, including Europe, Australia, and Asia-Pacific for more than 20 years.[35,78,79] The drug has also been associated with improved sexual function in postmenopausal women.[8,34,35] In an early study, tibolone resulted in improvements in sexual satisfaction, frequency of sexual activity, and sexual enjoyment as compared with women who received a combination of estradiol/norethisterone acetate to treat symptoms of FSD.[34] More recently, Nijland and colleagues randomized 403 naturally postmenopausal women (N = 293 who completed the entire 24-week study) with FSD to receive either 2.5 mg of tibolone or transdermal estradiol (E_2; 50 mcg)/norethisterone acetate (NETA; 140 mcg) to compare the efficacy on sexual function between these two drug regimes.[35] No statistically significant differences were found between the two regimes; both improved overall sexual function. Adverse reactions were comparable between the two groups; however, serious ADEs, including cerebral hemorrhage/death (one woman in the tibolone group) and a hypertensive crisis requiring hospitalization (one woman in the E_2/NETA group) occurred.[35] Although the drug has been reviewed, it was determined to be "not approvable" by the U.S. FDA as a treatment for menopausal symptoms, and in June 2006, the pharmaceutical company Organon withdrew their application for U.S. FDA approval of tibolone for U.S. women.[80] Possible cardiovascular ADEs and a lack of large-scale RCTs have been cited as a primary reasons for the lack of U.S. FDA approval.[81]

DHEA. DHEA is an unlicensed, OTC dietary supplement ingredient that can be purchased in many countries worldwide. DHEA is classified as a "prohormone" or "preandrogen" because it can be converted into both testosterone and estrogen (biologically active steroids) via the androgenic pathway. Additionally, because both men and women experience age-associated changes in DHEA levels, a role for its use in treating numerous age-related health conditions, including sexual dysfunction, has been hypothesized.[8,14,82] Although a specific, evidence-based role for its use in the treatment of FSD is unclear, authors of several recent reviews continue to mention the supplement.[8,14,19,27] One double-blind, placebo-controlled study examined women diagnosed with adrenal insufficiency and low levels of DHEA (N = 24; mean age = 42) and identified improvements in frequency of sexual thoughts ($P = 0.006$), sexual interest ($P = 0.002$), and mental ($P = 0.009$) and physical ($P = 0.02$) aspects of sexu-

ality in the DHEA versus the placebo group.[83] Other, less-rigorous studies consistently found no benefit in using DHEA for the treatment of FSD in women without adrenal insufficiency.[84,85] More recently, however, at least one FSD expert has suggested that topical vaginal administration of DHEA remains a promising area for additional research, and a recent Phase III RCT of DHEA (N = 114 postmenopausal women without adrenal insufficiency) found that severity scores for dyspareunia decreased significantly after 12 weeks of treatment for women using intravaginal DHEA as compared with those receiving placebo.[10,86]

Recommendations for practice

Based on this review, recommendations for the assessment and treatment of FSD include the following:

- Acknowledgement that multiple, coexisting factors affect female sexual health.
- Sexual function should be addressed in women of all ages during annual and periodic health visits.
- Screening instruments may be used to augment the health history.[25,28]
- Approach the management and treatment of FSD holistically, and include both nonpharmacologic and pharmacologic therapies based on the health assessment, individual patient preference and needs, and the healthcare provider's expertise/ability to initiate specific therapeutic options.
- Nonpharmacologic therapies should be considered as treatment options; however, further research is necessary.
- Further research regarding the evidence base for numerous pharmacologic therapies is necessary.
- Transdermal testosterone may be useful for women experiencing sexual desire disorders; however, it is not currently U.S. FDA approved for these indications.
- Consider bupropion as a primary antidepressant choice in women diagnosed with depression who also report concomitant FSD.[44] Bupropion may be useful in the treatment of HSDD, FSAD, and FOD; however, it is not U.S. FDA approved for any of these disorders.
- Continue to examine results of ongoing clinical trials/approval for subcutaneous bremelanotide as a potential treatment for FSAD, sildenafil as a treatment for FSAD that occurs in association with a neurodegenerative disorder or as an ADE associated with SSRI use, and new pharmacologic options for treatment of FOD.
- Consider pharmacologic therapy for treatment of postmenopausal VVA/dyspareunia, including local estrogen therapy as a first-line treatment. Oral ospemifene (60 mg/day) may also be an option.
  - In the United States, tibolone is not an option for treatment of postmenopausal VVA/dyspareunia.
  - Continue to monitor the evidence/approval of topical DHEA as a treatment for postmenopausal VVA/dyspareunia.

Moving forward

FSD is a complex health issue affecting women worldwide, and healthcare providers in both primary and specialty care settings are likely to encounter women experiencing one or more types of FSD. Evaluation and management of FSD should be holistic, and nonpharmacologic and pharmacologic therapies are important to consider on an individual basis, taking into account the provider's expertise and current approval status as well as patient preference. NP

REFERENCES

1. Diamond LE, Earle DC, Heiman JR, Rosen RC, Perelman MA, Harning R. An effect on the subjective sexual response in premenopausal women with sexual arousal disorder by bremelanotide (PT-141), a melanocortin receptor agonist. *J Sex Med.* 2006;3(4):628-638.
2. Moynihan R. The making of a disease: female sexual dysfunction. *BMJ.* 2003;326(7379):45-47.
3. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed. Washington, DC: American Psychiatric Publishing, Inc.; 2003.
4. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 5th ed. Washington, DC: American Psychiatric Publishing, Inc.; 2013.
5. Basson R. Women's sexual function and dysfunction: current uncertainties, future directions. *Int J Impot Res.* 2008;20(5):466-478.
6. World Health Organization. World Health Organization international statistical classifications of diseases and related health problems (ICD-10). Geneva 1992.
7. Masters WH, Johnson VE. *Human Sexual Response*. Boston, MA: Little, Brown; 1966.
8. Al-Azzawi F, Bitzer J, Brandenburg U, et al. Therapeutic options for postmenopausal female sexual dysfunction. *Climacteric.* 2010;13(2):103-120.
9. Basson R, Berman J, Burnett A, et al. Report of the international consensus development conference on female sexual dysfunction: definitions and classifications. *J Urol.* 2000;163(3):888-893.
10. Basson R. Pharmacotherapy for women's sexual dysfunction. *Expert Opin Pharmacother.* 2009;10(10):1631-1648.
11. Davis SR, Nijland EA. Pharmacological therapy for female sexual dysfunction: has progress been made? *Drugs.* 2008;68(3):259-264.
12. Frank JE, Mistretta P, Will J. Diagnosis and treatment of female sexual dysfunction. *Am Fam Physician.* 2008;77(5):635-642.
13. Hayes RD, Dennerstein L, Bennett CM, Fairley CK. What is the "true" prevalence of female sexual dysfunctions and does the way we assess these conditions have an impact? *J Sex Med.* 2008;5(4):777-787.
14. Simon JA. Low sexual desire—is it all in her head? Pathophysiology, diagnosis, and treatment of hypoactive sexual desire disorder. *Postgrad Med.* 2010;122(6):128-136.
15. Shifren JL, Monz BU, Russo PA, Segreti A, Johannes CB. Sexual problems and distress in United States women: prevalence and correlates. *Obstet Gynecol.* 2008;112(5):970-978.
16. Boston University School of Medicine and Epidemiology of FSD. 2013. http://www.bumc.bu.edu/sexualmedicine/physicianinformation/epidemiology-of-fsd/.
17. Jordan R, Hallam TJ, Molinoff P, Spana C. Developing treatments for female sexual dysfunction. *Clin Pharmacol Ther.* 2011;89(1):137-141.
18. Biddle AK, West SL, D'Aloisio AA, Wheeler SB, Borisov NN, Thorp J. Hypoactive sexual desire disorder in postmenopausal women: quality of life and health burden. *Value Health.* 2009;12(5):763-772.
19. Fooladi E, Davis SR. An update on the pharmacological management of female sexual dysfunction. *Expert Opin Pharmacother.* 2012;13(15):2131-2142.

20. Davison SL, Bell RJ, LaChina M, Holden SL, Davis SR. The relationship between self-reported sexual satisfaction and general well-being in women. *J Sex Med.* 2009;6(10):2690-2697.
21. Min LJ, Drury V, Taylor B. The experiences of and meaning for women living and coping with type 2 diabetes: a systematic review of qualitative evidence. *The JBI Library of Systematic Reviews.* 2012;10:2998-3047.
22. Lindau ST, Schumm LP, Laumann EO, Levinson W, O'Muircheartaigh CA, Waite LJ. A study of sexuality and health among older adults in the United States. *N Engl J Med.* 2007;357(8):762-774.
23. Pace G, Silvestri V, Gualá L, Vicentini C. Body mass index, urinary incontinence, and female sexual dysfunction: how they affect female postmenopausal health. *Menopause.* 2009;16(6):1188-1192.
24. Williams VS, Baldwin DS, Hogue SL, Fehnel SE, Hollis KA, Edin HM. Estimating the prevalence and impact of antidepressant-induced sexual dysfunction in 2 European countries: a cross-sectional patient survey. *J Clin Psychiatry.* 2006;67(2):204-210.
25. Hatzichristou D, Rosen RC, Broderick G, et al. Clinical evaluation and management strategy for sexual dysfunction in men and women. *J Sex Med.* 2004;1(1):49-57.
26. Janeway M, Baum M, Smith R. Sexual dysfunction in older women. *Clin Geriatr.* 2012;20(11):16-20.
27. Palacios S. Hypoactive Sexual Desire Disorder and current pharmacotherapeutic options in women. *Womens Health (Lond Engl).* 2011;7(1):95-107.
28. Clayton AH, Goldfischer ER, Goldstein I, Derogatis L, Lewis-D'Agostino DJ, Pyke R. Validation of the decreased sexual desire screener (DSDS): a brief diagnostic instrument for generalized acquired female hypoactive sexual desire disorder (HSDD). *J Sex Med.* 2009;6(3):730-738.
29. McCabe MP. Evaluation of a cognitive behavior therapy program for people with sexual dysfunction. *J Sex Marital Ther.* 2001;27(3):259-271.
30. Annon JS. *Behavioral Treatment of Sexual Problems:Brief Therapy*. Hagerstown, MS: Harper & Row; 1976.
31. Mayo Clinic Staff. Female Sexual Dysfunction. 2012. http://www.mayoclinic.com/health/female-sexual-dysfunction/DS00701/METHOD=print.
32. Giugliano F, Maiorino MI, Di Palo C, et al. Adherence to Mediterranean diet and sexual function in women with type 2 diabetes. *J Sex Med.* 2010;7(5):1883-1890.
33. Rosenbaum TY. Physiotherapy treatment of sexual pain disorders. *J Sex Marital Ther.* 2005;31(4):329-340.
34. Nathorst-Böös J, Hammar M. Effect on sexual life—a comparison between tibolone and a continuous estradiol-norethisterone acetate regimen. *Maturitas.* 1997;26(1):15-20.
35. Nijland EA, Weijmar Schultz WC, Nathorst-Böös J, et al. Tibolone and transdermal E2/NETA for the treatment of female sexual dysfunction in naturally menopausal women: results of a randomized active-controlled trial. *J Sex Med.* 2008;5(3):646-656.
36. Davison SL, Davis SR. Androgenic hormones and aging—the link with female sexual function. *Horm Behav.* 2011;59(5):745-753.
37. Braunstein GD, Sundwall DA, Katz M, et al. Safety and efficacy of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial. *Arch Intern Med.* 2005;165(14):1582-1589.
38. Buster JE, Kingsberg SA, Aguirre O, et al. Testosterone patch for low sexual desire in surgically menopausal women: a randomized trial. *Obstet Gynecol.* 2005;105(5 Pt 1):944-952.
39. Davis SR, van der Mooren MJ, van Lunsen RH, et al. Efficacy and safety of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial. *Menopause.* 2006;13(3):387-396.
40. Shifren JL, Davis SR, Moreau M, et al. Testosterone patch for the treatment of hypoactive sexual desire disorder in naturally menopausal women: results from the INTIMATE NM1 Study. *Menopause.* 2006;13(5):770-779.
41. Davis S, Papalia MA, Norman RJ, et al. Safety and efficacy of a testosterone metered-dose transdermal spray for treating decreased sexual satisfaction in premenopausal women: a randomized trial. *Ann Intern Med.* 2008;148(8):569-577.
42. Braunstein GD. Safety of testosterone treatment in postmenopausal women. *Fertil Steril.* 2007;88(1):1-17.
43. White WB, Grady D, Giudice LC, Berry SM, Zborowski J, Snabes MC. A cardiovascular safety study of LibiGel (testosterone gel) in postmenopausal women with elevated cardiovascular risk and hypoactive sexual desire disorder. *Am Heart J.* 2012;163(1):27-32.
44. Clayton AH. Extended-release bupropion: an antidepressant with a broad spectrum of therapeutic activity? *Expert Opin Pharmacother.* 2007;8(4):457-466.
45. Segraves RT, Croft H, Kavoussi R, et al. Bupropion sustained release (SR) for the treatment of hypoactive sexual desire disorder (HSDD) in nondepressed women. *J Sex Marital Ther.* 2001;27(3):303-316.
46. Segraves RT, Clayton A, Croft H, Wolf A, Warnock J. Bupropion sustained release for the treatment of hypoactive sexual desire disorder in premenopausal women. *J Clin Psychopharmacol.* 2004;24(3):339-342.
47. Clayton AH, Montejo AL. Major depressive disorder, antidepressants, and sexual dysfunction. *J Clin Psychiatry.* 2006;67(suppl 6):33-37.
48. Mazer NA, Leiblum SR, Rosen RC. The brief index of sexual functioning for women (BISF-W): a new scoring algorithm and comparison of normative and surgically menopausal populations. *Menopause.* 2000;7(5):350-363.
49. Modell JG, May RS, Katholi CR. Effect of bupropion-SR on orgasmic dysfunction in nondepressed subjects: a pilot study. *J Sex Marital Ther.* 2000;26(3):231-240.
50. Clayton AH, Montejo AL. Major depressive disorder, antidepressants, and sexual dysfunction. *J Clin Psychiatry.* 2006;67(suppl 6):33-37.
51. Safarinejad MR. Reversal of SSRI-induced female sexual dysfunction by adjunctive bupropion in menstruating women: a double-blind, placebo-controlled and randomized study. *J Psychopharmacol.* 2011;25(3):370-378.
52. Palatin Technologies I. Bremelanotide for female sexual dysfunction. 2013. www.palatin.com/products/bremelanotide.asp.
53. Diamond LE, Earle DC, Rosen RC, Willett MS, Molinoff PB. Double-blind, placebo-controlled evaluation of the safety, pharmacokinetic properties and pharmacodynamic effects of intranasal PT-141, a melanocortin receptor agonist, in healthy males and patients with mild-to-moderate erectile dysfunction. *Int J Impot Res.* 2004;16(1):51-59.
54. Rosen RC, Diamond LE, Earle DC, Shadiack AM, Molinoff PB. Evaluation of the safety, pharmacokinetics and pharmacodynamic effects of subcutaneously administered PT-141, a melanocortin receptor agonist, in healthy male subjects and in patients with an inadequate response to Viagra. *Int J Impot Res.* 2004;16(2):135-142.
55. Jordan R, Edelson J, Greenberg S, et al. Efficacy of subcutaneous bremelanotide self-administered at home by premenopausal women with female sexual dysfunction: a placebo-controlled dose-ranging study [poster presentation]. International Society for the Study of Women's Sexual Health, New Orleans, LA. Feb 28-March 3, 2013.
56. Alexander MS, Rosen RC, Steinberg S, Symonds T, Haughie S, Hultling C. Sildenafil in women with sexual arousal disorder following spinal cord injury. *Spinal Cord.* 2011;49(2):273-279.
57. Berman JR, Berman LA, Toler SM, Gill J, Haughie S, Sildenafil Study Group. Safety and efficacy of sildenafil citrate for the treatment of female sexual arousal disorder: a double-blind, placebo controlled study. *J Urol.* 2003;170(6 Pt 1):2333-2338.
58. Caruso S, Rugolo S, Agnello C, Intelisano G, Di Mari L, Cianci A. Sildenafil improves sexual functioning in premenopausal women with type 1 diabetes who are affected by sexual arousal disorder: a double-blind, crossover, placebo-controlled pilot study. *Fertil Steril.* 2006;85(5):1496-1501.
59. Leddy LS, Yang CC, Stuckey BG, et al. Influence of sildenafil on genital engorgement in women with female sexual arousal disorder. *J Sex Med.* 2012;9(10):2693-2697.
60. Nurnberg HG, Hensley PL, Heiman JR, Croft HA, Debattista C, Paine S. Sildenafil treatment of women with antidepressant-associated sexual dysfunction: a randomized controlled trial. *JAMA.* 2008;300(4):395-404.
61. Basson R, McInnes R, Smith MD, Hodgson G, Koppiker N. Efficacy and safety of sildenafil citrate in women with sexual dysfunction associated with female sexual arousal disorder. *J Womens Health Gend Based Med.* 2002;11(4):367-377.
62. Kaplan SA, Reis RB, Kohn IJ, et al. Safety and efficacy of sildenafil in postmenopausal women with sexual dysfunction. *Urology.* 1999;53(3):481-486.
63. Brown DA, Kyle JA, Ferrill MJ. Assessing the clinical efficacy of sildenafil for the treatment of female sexual dysfunction. *Ann Pharmacother.* 2009;43(7):1275-1285.
64. Sipski ML, Rosen RC, Alexander CJ, Hamer RM. Sildenafil effects on sexual and cardiovascular responses in women with spinal cord injury. *Urology.* 2000;55(6):812-815.
65. Levine KB, Williams RE, Hartmann KE. Vulvovaginal atrophy is strongly associated with female sexual dysfunction among sexually active postmenopausal women. *Menopause.* 2008;15(4 Pt 1):661-666.
66. Chollet JA. Efficacy and safety of ultra-low-dose Vagifem (10 mcg). *Patient Prefer Adherence.* 2011;5:571-574.
67. Long CY, Liu CM, Hsu SC, Wu CH, Wang CL, Tsai EM. A randomized comparative study of the effects of oral and topical estrogen therapy on the vaginal vascularization and sexual function in hysterectomized postmenopausal women. *Menopause.* 2006;13(5):737-743.

68. Al-Baghdadi O, Ewies AA. Topical estrogen therapy in the management of postmenopausal vaginal atrophy: an up-to-date overview. *Climacteric.* 2009;12(2):91-105.
69. Nappi RE, Albani F, Chiovato L, Polatti F. Local estrogens for quality of life and sexuality in postmenopausal women with cardiovascular disease. *Climacteric.* 2009;12(suppl 1):112-116.
70. North American Menopause Society. The role of local vaginal estrogen for treatment of vaginal atrophy in postmenopausal women: 2007 position statement of The North American Menopause Society. *Menopause.* 2007;14(3 Pt 1):355-369; quiz 370-371.
71. Archer DF, Pickar JH, MacAllister DC, Warren MP. Transdermal estradiol gel for the treatment of symptomatic postmenopausal women. *Menopause.* 2012;19(6):622-629.
72. Nathorst-Böös J, Wiklund I, Mattsson LA, Sandin K, von Schoultz B. Is sexual life influenced by transdermal estrogen therapy? A double blind placebo controlled study in postmenopausal women. *Acta Obstet Gynecol Scand.* 1993;72(8):656-660.
73. Sherwin BB. The impact of different doses of estrogen and progestin on mood and sexual behavior in postmenopausal women. *J Clin Endocrinol Metab.* 1991;72(2):336-343.
74. Wiklund I, Karlberg J, Mattsson LA. Quality of life of postmenopausal women on a regimen of transdermal estradiol therapy: a double-blind placebo-controlled study. *Am J Obstet Gynecol.* 1993;168(3 Pt 1):824-830.
75. Bachmann GA, Komi JO, Ospemifene Study Group. Ospemifene effectively treats vulvovaginal atrophy in postmenopausal women: results from a pivotal phase 3 study. *Menopause.* 2010;17(3):480-486.
76. Portman DJ, Bachmann GA, Simon JA, Ospemifene Study Group. Ospemifene, a novel selective estrogen receptor modulator for treating dyspareunia associated with postmenopausal vulvar and vaginal atrophy. *Menopause.* 2013;20(6):623-630.
77. U.S. Food and Drug Administration. FDA approves Osphena for postmenopausal women experiencing pain during sex. 2013. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm341128.htm.
78. Morris EP, Wilson PO, Robinson J, Rymer JM. Long term effects of tibolone on the genital tract in postmenopausal women. *Br J Obstet Gynaecol.* 1999;106(9):954-959.
79. Weinblatt V. Nutrition and tibolone. 2011. http://www.livestrong.com/article/549029-nutrition-tibolone/.
80. Oganon. FDA says tibolone not approvable as a menopause treatment in the U.S. 2066. http://www.drugs.com/nda/tibolone.
81. Robb-Nicholson Cnd. What's the latest on tibolone, the estrogen alternative? http://www.health.harvard.edu/newsweek/Whats_the_latest_on_tibolone.htm.
82. Palacios S. Androgens and female sexual function. *Maturitas.* 2007;57(1):61-65.
83. Arlt W, Callies F, van Vlijmen JC, et al. Dehydroepiandrosterone replacement in women with adrenal insufficiency. *N Engl J Med.* 1999;341(14):1013-1020.
84. Kritz-Silverstein D, von Mühlen D, Laughlin GA, Bettencourt R. Effects of dehydroepiandrosterone supplementation on cognitive function and quality of life: the DHEA and Well-Ness (DAWN) Trial. *J Am Geriatr Soc.* 2008;56(7):1292-1298.
85. Panjari M, Davis SR. DHEA therapy for women: effect on sexual function and wellbeing. *Hum Reprod Update.* 2007;13(3):239-248.
86. Labrie F, Archer DF, Bouchard C, et al. Intravaginal dehydroepiandrosterone (prasterone), a highly efficient treatment of dyspareunia. *Climacteric.* 2011;14(2):282-288.

Christine Bradway is an Associate Professor of Gerontological Nursing at University of Pennsylvania, Philadelphia, Pa. Joseph Boullata is a Professor of Pharmacology & Therapeutics at University of Pennsylvania, Philadelphia, Pa.

The authors and planners have confirmed that they have financial relationships related to this article: Bradway—Direct Supply Inc. and Health Resources and Services Administration (HRSA)

DOI-10.1097/01.NPR.0000440641.32261.7c