



Pharmacologic therapeutic options for sexual dysfunction

Claire S. Burton^a and Kavita Mishra^b

Purpose of review

Sexual problems are reported by up to 45% of individuals assigned female at birth. Although sexual function is a complex biopsychosocial construct, there are a number of pharmacologic treatment options aimed at addressing the changing vaginal hormonal milieu in postmenopausal individuals and moderating the excitatory and inhibitory aspects of the central nervous system in those with hypoactive sexual desire disorder.

Recent findings

The last decade has seen an increase in the number and type of pharmacologic treatment options for dysfunction primarily associated with menopause and hypoactive sexual desire disorder. Recent publications and systematic reviews have strengthened the safety data of existing FDA-approved medications as well as off-label therapies.

Summary

Pharmacologic treatment with local estrogen and testosterone replacement in postmenopausal individuals and with centrally-acting therapies such as flibanserin, bremelanotide, and testosterone in premenopausal individuals assigned female at birth are safe and can be used to improve sexual desire and sexual satisfaction.

Keywords

dyspareunia, female sexual dysfunction, menopause, testosterone

INTRODUCTION

Sexual dysfunction (SD) is a broad term for a diverse set of symptoms and syndromes that impact sexual function and satisfaction. In general, sexual function is multifactorial with biologic, psychologic, and sociologic factors all playing an integral role. Despite this, there has been increased attention to the understanding the biologic components of sexual dysfunction, which has led to the advent of medical and pharmacologic therapies.

The authors acknowledge that the literature on sexual dysfunction in individuals assigned female at birth (AFAB) is commonly referred to as female sexual dysfunction. For the purposes of this review, we will use SD in place of the female sexual dysfunction to refer to sexual function and dissatisfaction symptoms in those AFAB or of female biologic sex.

In a survey of a nationally representative sample of 31 500 adult individuals AFAB, 44% reported any sexual problem, with the most common being low desire in 39%, and 12% reported associated distress [1]. This is likely an underestimation of the true incidence, as 63% of patients presenting to a female

urology practice reported any element of SD [2]. Because SD in AFAB individuals commonly occurs with other disorders frequently encountered by the urogynecologist, clinicians should be comfortable with the assessment and management of the biologic components of SD.

This review will focus on both hormonal and nonhormonal pharmacologic treatments of SD associated with genitourinary syndrome of menopause (GSM) and hypoactive sexual desire disorder (HSDD) (Table 1). Diagnosis and pathophysiology are beyond the scope of this review and will only be briefly mentioned.

^aDepartment of Urology and ^bDepartment of Obstetrics & Gynecology, Stanford University, Stanford, California, USA

Correspondence to Claire S. Burton, MD, Urology – 5656, 453 Quarry Rd, Palo Alto, CA 94304, USA. Tel: +1 650 725 5746; fax: +1 650 498 5346;

e-mail: csburton@stanford.edu

Curr Opin Obstet Gynecol 2022, 32:000–000

DOI:10.1097/GCO.0000000000000821

KEY POINTS

- Sexual dysfunction is common in both pre and postmenopausal individuals and has been associated with significant impact on quality of life.
- In postmenopausal individuals, nonhormonal treatment such as vaginal moisturizers can be effective for mild to moderate symptoms, whereas hormonal treatment with vaginal estrogen is often required for improvement in more severe symptoms.
- Premenopausal individuals with hypoactive sexual desire disorder may benefit from either FDA approved medication (flibanserin or bremelanotide) or transdermal testosterone.

GENITOURINARY SYNDROME OF MENOPAUSE

Genitourinary syndrome of menopause (GSM) refers to symptoms associated with low estrogen states. While most commonly associated with menopause, low estrogen states can also be found in individuals who have had surgical menopause, hypothalamic amenorrhea, are lactating, have a history of chronic oral contraceptive use, who are undergoing hormonal treatment for breast cancer or sex dysphoria, who have a history of pelvic radiotherapy, or have undergone chemotherapy. An estimated 27–84% of postmenopausal individuals will experience GSM, which can present with a wide array of symptoms including vaginal dryness, burning, or irritation, dyspareunia, decreased sexual

desire and arousal, and urinary symptoms [3,4[■],5]. GSM also has a significant impact on quality of life, with 75% reporting that their symptoms negatively impact their lives [6]. Although vasomotor symptoms (VMS) tend to improve with time, GSM is often progressive and requires ongoing management [4[■]].

NON-HORMONAL THERAPY

Moisturizers and lubricants

First-line therapy for GSM as recommended by the North American Menopause Society (NAMS) includes moisturizers and vaginal lubricants [4[■]]. Lubricants are often used at the time of intercourse, whereas vaginal moisturizers are longer acting and designed to be used regularly. Vaginal moisturizers rehydrate the vaginal lining by serving as an emollient that is absorbed into the skin. The benefits of vaginal moisturizers often last 2–3 days. Beyond enhancing vaginal moisture, some, such as Replens, have also been found to lower the pH, restoring it to premenopausal acidity [7,8]. Moisturizers can be used in place of hormonal therapy or as an adjunct to vaginal estrogen, frequently used on alternating days.

In a randomized trial of 172 postmenopausal individuals with vaginal dryness randomized to receive either a hormone-free vaginal moisturizer or vaginal estriol (0.1%) cream, the nonhormonal moisturizer was found to be noninferior to vaginal estriol for symptom improvement in women with mild to moderate symptoms [9[■]]. Though earlier

Table 1. Summary of pharmacologic treatment options for sexual dysfunction in pre and postmenopausal individuals

Therapy	FDA approved vs. off-label	Indications	Dosing	Monitoring
Postmenopausal individuals				
Moisturizers	Over the counter	GSM	Per vagina PRN (usually 2–3×/week; see product labeling)	None
Vaginal estrogen	FDA approved	GSM	0.5–1 g per vagina daily × 2 weeks then twice weekly	None
Vaginal DHEA (prasterone)	FDA approved	GSM	6.5 mg per vagina daily	None
Ospemifene (SERM)	FDA approved	GSM	50 mg oral daily	None
Vaginal testosterone	Investigational	GSM	0.1% per vagina daily	None
Transdermal testosterone	Off-label	HSDD	300 mcg patch or 0.5 ml of 1% gel transdermal daily, titrate to symptoms	Free and total T at 3–6 weeks, level < ULN for premenopausal women
Premenopausal individuals				
Bremelanotide	FDA approved	HSDD	1.75 mg subcutaneous INJ PRN (no more than 1 dose/24 h, 8 doses per month)	None
Flibanserin	FDA approved	HSDD	100 mg oral daily	None

GSM, genitourinary syndrome of menopause; HSDD, hypoactive sexual desire disorder.

systematic review found that vaginal estrogen was superior to moisturizers in patients with more than one symptom [10], this study adds support for the use of vaginal moisturizers for mild to moderate GSM. Both hyaluronic acid and polycarbophil-based polymers are used as active ingredients in vaginal moisturizers [11]. In a randomized trial comparing hyaluronic acid to polycarbophil moisturizers use in 53 individuals, symptoms improved in both groups with no significant difference between the two [12]

TOPICAL HORMONE THERAPY

Vaginal estrogen

Vaginal estrogen remains the mainstay of treatment for GSM. Formulations include 17- β -estradiol cream or ring, conjugated equine estrogen cream, and estradiol vaginal tablets or gel capsules. Low dose vaginal estrogen is sufficient for the treatment of symptoms of GSM and numerous studies have demonstrated no change in systemic estrogen levels above normal postmenopausal levels [13,14]. A 2016 Cochrane review found that there was no difference between preparations of vaginal estrogen for improvement of symptoms of GSM, though they concluded that the evidence for vaginal estrogen over placebo for vulvovaginal atrophy was of low quality [13]. In a more recent systematic review of the efficacy and safety of vaginal estrogen, vaginal estrogen was superior to placebo for all objective and subjective endpoints of GSM [3].

Vaginal estrogen is generally applied daily for two weeks followed by administration 2–3 times per week. The estradiol ring is changed every 3 months but may be challenging to maintain for women with pelvic organ prolapse. Although it may take several months to achieve maximal benefit, improvements in dyspareunia may be seen even within the first 2 weeks of treatment [15].

Vaginal estrogen is generally considered to be safe, even in individuals with a history of breast cancer [16,17[†]]. The American College of Obstetrics & Gynecology consensus statement on vaginal estrogen in individuals with breast cancer, including those currently on tamoxifen or aromatase inhibitors, notes that vaginal estrogen may be used if nonhormonal vaginal moisturizers are insufficient and the patient undergoes shared decision making with their providers [17[†]]. Though vaginal estrogen use has been associated with a thicker endometrial lining, there is no clear association with endometrial cancer [13]. Lastly, while systemic estrogen use has been associated with dementia, there has been no link between vaginal estrogen and dementia in population-based studies [18].

Vaginal androgen therapy

Vaginal prasterone (DHEA)

Androgens are important in sexual health, and testosterone has been implicated in desire, arousal, genital blood flow, vaginal lengthening, and lubrication in AFAB individuals [19,20]. Testosterone is produced equally by the adrenals and ovaries, and as individuals enter menopause their testosterone levels are approximately 50% of premenopausal levels [19]. Additionally, androgen receptors are present in female genital tissue. Dehydroepiandrosterone (DHEA) is produced physiologically by the adrenal glands, subsequently metabolized to androgens (androstenedione and testosterone) and then further aromatized to estrogens (estrone, estradiol) [21[†],22]. Vaginally administered DHEA 6.5 mg (prasterone, FDA approved in 2016) is converted locally in vaginal tissues to testosterone, dihydrotestosterone (DHT), and estradiol. Similarly to vaginal estrogen, systemic levels of estrogen and androgens do not rise with vaginal DHEA and it appears to be safe in individuals with breast cancer [22,23]. Vaginal DHEA has also been found to improve both objective and subjective symptoms of GSM along with improvement in sexual function [24]. A 2018 systematic review of three randomized trials found significant improvement in vaginal dryness but no difference in rates of dyspareunia with DHEA vs. placebo [25]. Vaginal DHEA is an alternative treatment for the 12–15% of individuals with persistent symptoms despite estrogen use [13].

Vaginal testosterone

Though not FDA approved in the United States, vaginal testosterone therapy (0.1%) can be compounded for use in GSM. In a systematic review, vaginal testosterone was similar to vaginal estrogen in effect on sexual function [25]. In two small trials of vaginal testosterone in individuals with breast cancer, vaginal testosterone improved dyspareunia and vaginal dryness [26,27]. Because of limited available data, the NAMS does not recommend vaginal testosterone for the treatment of GSM [4[†]].

SYSTEMIC HORMONE THERAPY

Systemic estrogen/progesterone

Individuals with both GSM and VMS may opt for systemic hormone replacement therapy, with either estrogen alone (after hysterectomy) or combination estrogen/progesterone. In a systematic review of three studies comparing systemic hormone therapy and vaginal estrogen there was no difference in subjective (urinary urgency, vaginal dryness, dyspareunia) or

objective (vaginal maturation, pH) markers of GSM, though there were higher rates of adverse events in the systemic estrogen group [3].

It should be noted however, that systemic therapy may not provide sufficient resolution of GSM symptoms. In that case, it is advisable to combine both vaginal and systemic estrogens. If systemic estrogen therapy is used, the lowest possible dose for resolution of symptoms should be administered [4[■]]. Additionally, as VMS symptoms tend to improve with time, women may be able to discontinue systemic hormone use and transition to vaginal estrogen, which carries far fewer adverse effects.

Ospemifene

Ospemifene, FDA approved since 2013, is a selective estrogen receptor agonist/antagonist, and is the only oral therapy specifically approved for the treatment of GSM. Daily administration of 60 mg of oral ospemifene in randomized trials was shown to improve dyspareunia, vaginal maturation, and vaginal pH [28–30]. In a 52-week efficacy and safety study of 180 individuals there were no cases of VTE, endometrial hyperplasia, or cancer [31]. Despite this, the label contains warnings for use in AFAB individuals with estrogen-dependent neoplasia, a history of venous thromboembolism, or myocardial infarction. Ospemifene has not been adequately studied in breast cancer to support its use, though national insurance database claims research has suggested that it may be protective against breast cancer [32]. Although not FDA approved for osteoporosis, there is also evidence that ospemifene has positive effects on bone density [31]. Ospemifene remains an excellent option for those who cannot tolerate vaginal estrogen.

Although there is overlap between GSM and disorders of desire and arousal, the following section will address therapeutic options beyond hormonal replacement as described above. Pharmacologic management may be considered in premenopausal individuals with normal estrogen states or in postmenopausal individuals with persistent bothersome symptoms.

HYPOACTIVE SEXUAL DESIRE DISORDER AND FEMALE SEXUAL AROUSAL DISORDER

Hypoactive sexual desire disorder (HSDD) was classified in the DSM-IV as a decrease or absent spontaneous sexual desire, response to erotic cues, or inability to maintain desire throughout sexual activity, or a loss of previously present desire that is associated with distress [33]. Controversially, in

the DSM-V this diagnosis was combined with female sexual arousal disorder (FSAD), and has been merged into a new diagnosis titled female sexual interest/arousal disorder (FSIAD) [34]. Because the literature on pharmacologic therapies continues to differentiate between HSDD and FSAD, they will continue to be referred to separately in this review. Development to date has been primarily aimed at the centrally acting excitatory (dopamine, noradrenaline, melanocortin) and inhibitory (serotonin, endocannabinoid, opioid) receptors to augment the sexual desire response [35]. Although our understanding of the neurochemical basis for HSDD is poor, the prevailing hypothesis is that an interplay between the serotonergic system and other neurochemical pathways leads to increased inhibition or decreased excitation, and pharmaceutical development has been aimed at these pathways [36].

NON-HORMONAL THERAPY

Flibanserin

Flibanserin (Addyi[®]) was FDA approved in 2015 for the treatment of HSDD in premenopausal individuals. Flibanserin acts as a multifunctional serotonin agonist and antagonist, which ultimately leads to an increase in dopamine and norepinephrine in the prefrontal cortex and an overall decrease in inhibitory serotonin [37]. It is taken as a 100 mg tablet nightly. In a pooled analysis of 2465 premenopausal individuals from three pivotal multicenter randomized clinical trials, there was an average increase of one sexually satisfying event (SSE) per month over placebo (2.1 vs. 1.1), and a significant increase in the level of sexual desire and reduction of sexual desire-related distress compared to placebo [38]. Yet, a meta-analysis and systematic review of eight studies including 5914 patients found a pooled mean difference of only 0.5 SSE per month and minimal to no difference in the global impression of change among all-comers [39].

Though not approved for postmenopausal individuals, one randomized trial and one open label continuation arm have both demonstrated safety and efficacy [40]. There appears to be less efficacy in postmenopausal individuals, with approximately 40% in the postmenopausal group considered to be responders compared to 50% in the premenopausal group [40,41[■]].

The most common reported side effects are dizziness, somnolence, nausea, and headache [38–40]. Upon initial approval, the FDA included a black box warning against alcohol use while taking the medication due to concerns for hypotension and somnolence, though this was revised in 2019 after

numerous postmarket studies demonstrated safety. Currently, there remains a black box warning to avoid alcohol consumption within two hours of taking the medication. Flibanserin is safe to use with SSRI and SNRIs. It is metabolized by cytochrome p450, so prescribers should exercise caution in patients taking other CYP450 inhibitors as they may be at increased risk of somnolence and hypotension [42]. Patients who do not notice improvement after 8 weeks should discontinue the medication.

There remains a dearth of information on the effectiveness of the medication in nonwhite individuals, individuals who have undergone surgical menopause, and transgender and gender diverse people. Additionally, there has been no study on the safety of the medication in pregnant or breastfeeding individuals, so its use in these populations is not recommended.

Bremelanotide

Bremelanotide (Vyleesi[®]) is the second FDA-approved medication (approved in 2019) for HSDD in premenopausal individuals [43]. It is a melanocortin receptor agonist, with affinity for MC4R in presynaptic neurons of the hypothalamus, which activates the release of dopamine and enhances the excitatory pathways in arousal and desire [36]. It is administered subcutaneously approximately 45 min prior to intercourse, and can be used once per 24 h up to 8 times per month. In analysis of the two pivotal phase 3 clinical trials comparing 1267 individuals AFAB receiving bremelanotide to placebo, significant durable improvements were seen in sexual desire, decreased distress, and number of sexually satisfying events [41[¶]]. In the 52-week open label extension, durability of effect was seen in the treatment group as well as a significant improvement in the cross-over group who was initially given placebo [38]. Similarly to flibanserin, about 50–60% of study participants reported a clinically meaningful response [38,44]. Although the clinical benefit may be modest, qualitative analysis of exit interviews with subjects showed meaningful benefits in their relationship with their partner [44].

Most commonly reported side effects include nausea in 40%, flushing in 20% and headache in 12% of individuals [38]. Unlike flibanserin, there is no black box warning related to alcohol usage and no significant interactions with other medications [45].

Although there are no studies to date investigating the combined usage of flibanserin, bremelanotide and testosterone, their mechanisms of action are each distinct and there is no theoretical reason why they cannot be combined.

Other nonhormonal agents

Bupropion, currently approved as an antidepressant and smoking cessation aid, has shown efficacy in several studies as a treatment for HSDD in both pre- and postmenopausal women [46,47]. A recently published meta-analysis found a dose-dependent improvement in sexual desire, with 300 mg dosing having a stronger effect than 150 mg [48]. Buspirone, another antidepressant, and trazodone, which is pharmacologically similar to flibanserin, have also been described as having some benefit in the treatment of HSDD [49,50]. These may be attractive options for individuals with concurrent depression and HSDD.

Sildenafil, a PDE-5 inhibitor, has been shown to increase vaginal and clitoral blood flow [51]. In a large randomized trial of sildenafil 100 mg per day vs. placebo in individuals with HSDD, FSAD, or female orgasmic disorder, there was no difference in vaginal lubrication or sensation, sexual desire, or satisfaction [52]. In a randomized trial of 202 postmenopausal individuals, sildenafil 25–100 mg daily did lead to an improvement in genital sensation and satisfaction with intercourse in individuals with FSAD without HSDD [53].

HORMONAL THERAPY

Transdermal testosterone

In 2019, 12 international societies authored the Global Consensus Statement on the use of Testosterone Therapy for Women to standardize recommendations for its use in postmenopausal individuals [54]. Additionally, in 2021 the International Society for the Study of Women's Sexual Health (ISSWSH) published a practice guideline for the use of testosterone in AFAB individuals with HSDD [21[¶]].

Though there is no established link between HSDD and testosterone levels, transdermal testosterone has been used off-label in postmenopausal individuals to increase sexual desire [54]. Because testosterone is produced equally by the adrenal glands and ovaries, AFAB individuals undergoing bilateral oophorectomy have an acute decline in their testosterone levels [21[¶]]. In naturally menopausal individuals, testosterone decline occurs with age and is likely related to ovarian functional decline. Older studies demonstrated benefit of oral or intramuscular testosterone in combination with estrogen replacement [55], but these preparations made dosing difficult and patients likely received supraphysiologic doses. A meta-analysis of 36 RCTs of all preparations of systemic testosterone in over 8000 postmenopausal individuals found that testosterone significantly increased sexual desire, pleasure, arousal, and orgasm

and reduced distress compared to placebo or estrogen \pm progesterone [56]. This study also reaffirmed that nonoral administration was preferred due to significant rises in cholesterol and triglycerides in orally-administered testosterone.

The transdermal route (300 mcg/day patch or 5 mg/0.5 ml gel) allows for more accurate dosing, with a goal of achieving premenopausal testosterone levels. In a systematic review of transdermal testosterone, both surgically and naturally postmenopausal women with HSDD, with and without adjuvant estrogen replacement had an increase in the number of SSEs, orgasms, and desire vs. placebo [57].

The most common side effects are androgenic, including hirsutism and acne. In short-term safety trials of transdermal testosterone, metabolic markers, renal, and liver function tests were similar to controls and longer-term studies similarly demonstrated no increased adverse events [56,58]. Testosterone can be prescribed as the FDA-approved male-formulation products (at one-tenth the dose), and it is recommended to monitor free and total testosterone levels after 3–6 weeks of therapy to ensure that the value is not above the upper limit of the normal range for premenopausal AFAB individuals (approx. 40 ng/dl) [21*,54]. Because testosterone is currently off-label for AFAB individuals, informed consent should be obtained.

CONCLUSION

SD is common, with multiple forms and etiologies. Many individuals never seek care or even discuss their concerns with a clinician, leading to both under-diagnosis and undertreatment of the disease. Despite this, we know that SD has a significant impact on quality of life. Therefore, it is incumbent upon clinicians to discuss sexual activity to both recognize and manage the disease. At this time, there are many hormonal and nonhormonal treatment options for AFAB individuals with SD that are well tolerated and efficacious and do not require extensive monitoring, with recent publications further highlighting their safety. Both urologists and gynecologists should consider this within their scope of practice, as referrals to sexual medicine specialists may not be immediately available in the majority of geographic areas [59].

Additionally, pharmacologic therapy only addresses one element of the complex biopsychosocial triad that governs sexual satisfaction. Referral to adjunct and supportive care from pelvic floor physical therapists, psychologists or psychiatrists, and sexual health therapists are also often required for maximum benefit. Sexual health is important to

all individuals and clinicians should become familiar with the available treatment options.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Shifren JL, Monz BU, Russo PA, *et al.* Sexual problems and distress in united states women: prevalence and correlates. *Obstet Gynecol* 2008; 112:970–978.
 2. Elsamra S, Nazmy M, Shin D, *et al.* Female sexual dysfunction in urological patients: findings from a major metropolitan area in the USA. *BJU Int* 2010; 106:524–526.
 3. Biehl C, Plotsker O, Mirkin S. A systematic review of the efficacy and safety of vaginal estrogen products for the treatment of genitourinary syndrome of menopause. *Menopause* 2019; 26:431–453.
 4. Faubion SS, Kingsberg SA, Clark AL, *et al.* The 2020 genitourinary syndrome of menopause position statement of the North American Menopause Society. *Menopause* 2020; 27:976–992.
- This update to the 2013 NAMS guidelines thoroughly discusses evaluation, diagnosis, and pharmacologic and nonpharmacologic treatment options for GSM.
5. Palma F, Volpe A, Villa P, Cagnacci A. Vaginal atrophy of women in postmenopause. Results from a multicentric observational study: the AGATA study. *Maturitas* 2016; 83:40–44.
 6. Kingsberg SA, Wysocki S, Magnus L, Krychman ML. Vulvar and vaginal atrophy in postmenopausal women: findings from the REVIVE (REal Women's Views of Treatment Options for Menopausal Vaginal ChangEs) survey. *J Sex Med* 2013; 10:1790–1799.
 7. Bachmann G. Vaginal dryness in menopausal women: clinical characteristics and nonhormonal treatment. *Clin Pract Sex* 1991; 7:25–32.
 8. De Seta F, Caruso S, Di Lorenzo G, *et al.* Efficacy and safety of a new vaginal gel for the treatment of symptoms associated with vulvovaginal atrophy in postmenopausal women: a double-blind randomized placebo-controlled study. *Maturitas* 2021; 147:34–40.
 9. Garcia de Arriba S, Grüntkemeier L, Häuser M, *et al.* Vaginal hormone-free moisturising cream is not inferior to an estriol cream for treating symptoms of vulvovaginal atrophy: prospective, randomised study. *PLoS One* 2022; 17:e0266633.
- This randomized clinical trial comparing vaginal estrogen to vaginal moisturizers shows that moisturizers are noninferior in resolution of GSM symptoms for women with mild to moderate symptoms.
10. Rahn DD, Carberry C, Sanses TV, *et al.* Vaginal estrogen for genitourinary syndrome of menopause: a systematic review. *Obs Gynecol* 2014; 124:1147–1156.
 11. Hirschberg AL, Bitzer J, Cano A, *et al.* Topical estrogens and nonhormonal preparations for postmenopausal vulvovaginal atrophy: an EMAS clinical guide. *Maturitas* 2021; 148:55–61.
 12. Cagnacci A, Barattini DF, Casolati E, *et al.* Polycarbophil vaginal moisturizing gel versus hyaluronic acid gel in women affected by vaginal dryness in late menopausal transition: a prospective randomized trial. *Eur J Obstet Gynecol Reprod Biol* 2022; 270:239–245.
 13. Lethaby A, Ayeleke RO, Roberts H. Local oestrogen for vaginal atrophy in postmenopausal women. *Cochrane Database Syst Rev* 2016; 2016:.
 14. Pérez-López FR, Phillips N, Vieira-Baptista P, *et al.* Management of postmenopausal vulvovaginal atrophy: recommendations of the International Society for the Study of Vulvovaginal Disease. *Gynecol Endocrinol* 2021; 37:746–752.
 15. Cuerva MJ, González SP, Lazaro-Carrasco De La Fuente J, *et al.* Effect of oestriol gel on dyspareunia in postmenopausal women in 2 weeks of treatment: a pilot study. *J Obstet Gynaecol (Lahore)* 2022; 1–3; Epub ahead of print.

16. Crandall CJ, Hovey KM, Andrews CA, *et al.* Breast cancer, endometrial cancer, and cardiovascular events in participants who used vaginal estrogen in the women's health initiative observational study. *Menopause* 2018; 25:11–20.
 17. Treatment of urogenital symptoms in individuals with a history of estrogen-dependent breast cancer: clinical consensus. *Obstet Gynecol* 2021; 138:950–960.
- ACOG consensus guideline statement on the management of GSM in women with or with a history of breast cancer discusses both nonhormonal and all hormonal treatment options.
18. Pourhadi N, Mørch LS, Holm EA, *et al.* Vaginal estrogen and association with dementia: a nationwide population-based study. *Alzheimers Dement* 2022; 18:625–634.
 19. Simon JA, Goldstein I, Kim NN, *et al.* The role of androgens in the treatment of genitourinary syndrome of menopause (GSM): International Society for the Study of Women's Sexual Health (ISSWSH) expert consensus panel review. *Menopause* 2018; 25:837–847.
 20. Ingram CF, Payne KS, Messori M, Scovell JM. Testosterone therapy and other treatment modalities for female sexual dysfunction. *Curr Opin Urol* 2020; 30:309–316.
 21. Parish SJ, Simon JA, Davis SR, *et al.* International Society for the Study of Women's Sexual Health Clinical Practice Guideline for the use of systemic testosterone for hypoactive sexual desire disorder in women. *J Womens Health (Larchmt)* 2021; 30:474–491.
- This guideline for use of testosterone therapy in HSDD reviews in depth the rationale, administration, and monitoring of testosterone administration.
22. Stute P, Bertschy S, Birkhaeuser M, *et al.* Swiss consensus on the role of DHEA in the management of genitourinary syndrome of menopause. *Climacteric* 2022; 25:246–256.
 23. Labrie F, Martel C. A low dose (6.5 mg) of intravaginal DHEA permits a strictly local action while maintaining all serum estrogens or androgens as well as their metabolites within normal values. *Horm Mol Biol Clin Investig* 2017; 29:39–60.
 24. Labrie F, Derogatis L, Archer DF, *et al.* Effect of intravaginal prasterone on sexual dysfunction in postmenopausal women with vulvovaginal atrophy. *J Sex Med* 2015; 12:2401–2412.
 25. Pitsouni E, Grigoriadis T, Douskos A, *et al.* Efficacy of vaginal therapies alternative to vaginal estrogens on sexual function and orgasm of menopausal women: a systematic review and meta-analysis of randomized controlled trials. *Eur J Obstet Gynecol Reprod Biol* 2018; 229:45–56.
 26. Witherby S, Johnson J, Demers L, *et al.* Topical testosterone for breast cancer patients with vaginal atrophy related to aromatase inhibitors: a phase I/II study. *Oncologist* 2011; 16:424.
 27. Melisko ME, Goldman ME, Hwang J, *et al.* Vaginal testosterone cream vs estradiol vaginal ring for vaginal dryness or decreased libido in women receiving aromatase inhibitors for early-stage breast cancer: a randomized clinical trial. *JAMA Oncol* 2017; 3:313–319.
 28. Pingarron C, de Lafuente P, Ierullo AM, *et al.* Ospemifene in clinical practice for vulvo-vaginal atrophy: results at 3 months of follow-up of use. *Gynecol Endocrinol* 2021; 37:562–566.
 29. Di Donato V, schiavi MC, iacobelli V, *et al.* Ospemifene for the treatment of vulvar and vaginal atrophy: a meta-analysis of randomized trials. Part I. Evaluation of efficacy. *Maturitas* 2019; 121:86–92.
 30. Simon JA, Lin VH, Radovich C, Bachmann GA. One-year long-term safety extension study of ospemifene for the treatment of vulvar and vaginal atrophy in postmenopausal women with a uterus. *Menopause* 2013; 20:418–427.
 31. Simon JA, Altomare C, Cort S, *et al.* Overall safety of ospemifene in postmenopausal women from placebo-controlled phase 2 and 3 trials. *J Womens Health* 2018; 27:14–23.
 32. Cai B, Simon J, Villa P, *et al.* No increase in incidence or risk of recurrence of breast cancer in ospemifene-treated patients with vulvovaginal atrophy (VVA). *Maturitas* 2020; 142:38–44.
 33. Brotto LA. The DSM diagnostic criteria for hypoactive sexual desire disorder in women. *Arch Sex Behav* 2010; 39:221–239.
 34. O'loughlin JL, Basson R, Brotto LA. Women with hypoactive sexual desire disorder versus sexual interest/arousal disorder: an empirical test of raising the bar. *J Sex Res* 2018; 55:734–746.
 35. Nappi RE, Tiranini L, Martini E, *et al.* Medical treatment of female sexual dysfunction. *Urol Clin North Am* 2022; 49:299–307.
 36. Pfau JG, Sadiq A, Spana C, Clayton AH. The neurobiology of bremelanotide for the treatment of hypoactive sexual desire disorder in premenopausal women. *CNS Spectrums* 2022; 27:281–289.
 37. Invernizzi RW, Sacchetti G, Parini S, *et al.* Flibanserin, a potential antidepressant drug, lowers 5-HT and raises dopamine and noradrenaline in the rat prefrontal cortex dialysate: role of 5-HT1A receptors. *Br J Pharmacol* 2003; 139:1281–1288.
 38. Simon JA, Thorp J, Millheiser L. Flibanserin for premenopausal hypoactive sexual desire disorder: pooled analysis of clinical trials. *J Womens Health* 2019; 28:769–777.
 39. Jaspers L, Feys F, Bramer WM, *et al.* Efficacy and safety of flibanserin for the treatment of hypoactive sexual desire disorder in women: a systematic review and meta-analysis. *JAMA Intern Med* 2016; 176:453–462.
 40. Simon JA, Kingsberg SA, Shumel B, *et al.* Efficacy and safety of flibanserin in postmenopausal women with hypoactive sexual desire disorder: results of the SNOWDROP trial. *Menopause* 2014; 21:633–640.
 41. Simon JA, Kingsberg SA, Portman D, *et al.* Prespecified and integrated subgroup analyses from the RECONNECT phase 3 studies of bremelanotide. *J Womens Health* 2022; 31:391–400.
- A subgroup analysis of subjects in the two pivotal RCTs for bremelanotide demonstrated that bremelanotide is effective treatment for HSDD across multiple subgroups, but may be less effective in individuals on hormonal contraception.
42. Clayton AH, Brown L, Kim NN. Evaluation of safety for flibanserin. *Expert Opin Drug Saf* 2020; 19:1–8.
 43. Dhillon S, Keam SJ. Bremelanotide: first approval. *Drugs* 2019; 79:1599–1606.
 44. Koochaki P, Revicki D, Wilson H, *et al.* The patient experience of premenopausal women treated with bremelanotide for hypoactive sexual desire disorder: RECONNECT exit study results. *J Womens Health* 2021; 30:587–595.
 45. Mayer D, Lynch SE. Bremelanotide: new drug approved for treating hypoactive sexual desire disorder. *Ann Pharmacother* 2020; 54:684–690.
 46. Taylor Segraves R, 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; 27:303–316.
 47. Safarinejad MR, Hosseini SY, Asgari MA, *et al.* A randomized, double-blind, placebo-controlled study of the efficacy and safety of bupropion for treating hypoactive sexual desire disorder in ovulating women. *BJU Int* 2010; 106:832–839.
 48. Razali NA, Sidi H, Choy CL, *et al.* The role of bupropion in the treatment of women with sexual desire disorder: a systematic review and meta-analysis. *Curr Neuropharmacol* 2022; 20:1941–1955.
 49. Landén M, Eriksson E, Agren H, Fahlén T. Effect of buspirone on sexual dysfunction in depressed patients treated with selective serotonin reuptake inhibitors. *J Clin Psychopharmacol* 1999; 19:268–271.
 50. Pyke RE. Trazodone in sexual medicine: underused and overdosed? *Sex Med Rev* 2020; 8:206–216.
 51. Cavalcanti AL, Bagnoli VR, Fonseca AM, *et al.* Effect of sildenafil on clitoral blood flow and sexual response in postmenopausal women with orgasmic dysfunction. *Int J Gynecol Obstet* 2008; 102:115–119.
 52. Basson R, McInnes R, Smith MD, *et al.* Efficacy and safety of sildenafil citrate in women with sexual dysfunction associated with female sexual arousal disorder. *J Womens Health Gend Based Med* 2002; 11:367–377.
 53. Berman JR, Berman LA, Toler SM, *et al.* Safety and efficacy of sildenafil citrate for the treatment of female sexual arousal disorder: a double-blind, placebo controlled study. *J Urol* 2003; 170:2333–2338.
 54. Davis SR, Baber AR, Panay N, *et al.* Global consensus position statement on the use of testosterone therapy for women. *J Sex Med J Clin Endocrinol Metab* 2019; 104:4660–4666.
 55. Lobo RA, Rosen RC, Yang HM, *et al.* Comparative effects of oral esterified estrogens with and without methyltestosterone on endocrine profiles and dimensions of sexual function in postmenopausal women with hypoactive sexual desire. *Fertil Steril* 2003; 79:1341–1352.
 56. Islam RM, Bell RJ, Green S, *et al.* Safety and efficacy of testosterone for women: a systematic review and meta-analysis of randomised controlled trial data. *Lancet Diabetes Endocrinol* 2019; 7:754–766.
 57. Achilli C, Pundir J, Ramanathan P, *et al.* Efficacy and safety of transdermal testosterone in postmenopausal women with hypoactive sexual desire disorder: a systematic review and meta-analysis. *Fertil Steril* 2017; 107:475–482; e15.
 58. Nachtigall L, Casson P, Lucas J, *et al.* Safety and tolerability of testosterone patch therapy for up to 4 years in surgically menopausal women receiving oral or transdermal oestrogen. *Gynecol Endocrinol* 2011; 27:39–48.
 59. Kingsberg SA, Schaffir J, Faught BM, *et al.* Female sexual health: barriers to optimal outcomes and a roadmap for improved patient-clinician communications. *J Womens Health (Larchmt)* 2019; 28:432–443.