Female sexual dysfunction is associated with personal distress and includes female sexual interest and arousal disorder (including former hypoactive sexual desire disorder), female orgasmic disorder, genitopelvic pain and penetration disorder, and substance- or medication-induced sexual dysfunction. These disorders are remarkably common among women, with an estimated prevalence of 20–40%. It is our responsibility as obstetrician–gynecologists to identify risk factors and screen for female sexual dysfunction. Appropriate screening allows for further exploration into sexual function and dysfunction and, ultimately, determination of associated distress. Treatment often involves addressing the underlying issue through therapy or medical management. For female sexual interest and arousal disorder, treatment generally includes cognitive behavioral therapy, often with a mindfulness focus, and consideration of pharmaceutical management. Female orgasmic disorder is treated with education and awareness, as well as therapy. Evaluation for underlying etiology is particularly critical for genitopelvic pain and penetration disorder to allow treatment of an underlying condition. Finally, substance- or medication-induced sexual dysfunction is best managed by cessation of the implicated substance and consideration of adjunctive therapy if dysfunction is related to antidepressants.

Female sexual dysfunction is often overlooked in clinical practice; however, there are effective medical and psychological options for management. 

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health issues in recent years, with Committee Opinion No. 706 published in 2017, providing an overview on approach to sexual health in the clinic, and, subsequently, Practice Bulletin No. 213, published July 2019, which provides an excellent review of female sexual dysfunction.\textsuperscript{4,5} We will work to build off of these existing resources and provide further details on therapeutic management in this Clinical Expert Series article.

**BACKGROUND**

**Models of Sexual Response**

Human sexual response is a highly individual and emotional process. Historically, sexual response has been defined by a series of models to describe the physiologic changes seen during the course of arousal and response. The Masters and Johnson Model delineated four phases of sexual response, including excitement, plateau, orgasm, and resolution. This approach was then modified by Kaplan to include desire before excitement and orgasm. However, subsequent studies found that these models were predominantly based on male sexual response, that not all women experienced desire, and that many women experienced overlapping of the phases in a less linear progression.\textsuperscript{6,7} In 2003, Basson et al\textsuperscript{6} advocated for expansion and revision of the definition of sexual response and dysfunction in women. It is now recognized that, rather than progressing in a linear sequence from desire to arousal to orgasm and resolution, these phases may overlap and the sequence may vary.\textsuperscript{7,8} It is generally understood that, despite the biological foundation of sexual health, sexual functioning is experienced in a far more complex context, with influences of environment and relationships.\textsuperscript{1,8}

**Physiology**

The physiology of female sexual desire and arousal is complex and multifactorial. It is thought to involve a combination of parasympathetic and sympathetic stimulation, as well as sex hormones and environmental and psychological factors.

Sexual arousal begins in the central nervous system, mediated by the medial preoptic, anterior hypothalamic region, and other related limbic-hippocampal structures.\textsuperscript{9} Sexual arousal and erotic stimulation lead to release of vasodilators, nitric oxide and vasointestinal polypeptide, from both parasympathetic and sympathetic nerves.\textsuperscript{8} Acetylcholine is similarly released, which blocks vasoconstrictive mechanisms and leads to additional release of nitric oxide.\textsuperscript{8} The release of these neurotransmitters leads to vaginal vasocongestion and relaxation of vaginal smooth muscle, allowing expansion, and dilation of the arterioles increases transudation of interstitial fluid, promoting lubrication.\textsuperscript{8,10}

Estrogens play a critical role in female sexual response and function. Estrogen is thought to affect cells throughout the nervous system, with vasoprotective and vasodilatory effects.\textsuperscript{9} Decrease in estrogen leads to thinning of the vaginal mucosal epithelium and atrophy of the smooth muscle. Thus, with the decline in estrogen during menopause, either natural or surgical, changes in sexual function are common. There are some studies evaluating the role of estrogen levels and vasocongestion that suggest the relationship is more complex and that low estrogen may make postmenopausal women more vulnerable to sexual dysfunction, but is not entirely causative.\textsuperscript{8,11} Testosterone is similarly thought to play a role in female sexual arousal and function; however, low serum levels have not been demonstrated to be associated with decreased sexual interest or arousal.\textsuperscript{12} Testosterone and dopamine supplementation have been found to improve response, suggesting some role for these pathways.\textsuperscript{13,14}

**APPROACH TO SEXUAL HEALTH IN THE CLINIC**

The American College of Obstetricians and Gynecologists published Committee Opinion No. 706 in July 2017, recommending:

- Clinical conversations should acknowledge the contributions of sexuality, relationships, and sexual behavior to overall health.
- Ob-gyns should focus on the positive aspects of sexuality, not only the disease processes.
- Discussions of sexual health and aging within the framework of well-woman care should include the evolution of sexual health issues across a lifespan.\textsuperscript{4}

Sexual health is a critical aspect of self-identity and is influenced by biology, psychology, culture, environment, and relationships, among other factors. Sexual health develops and changes with a patient through the lifespan and can be affected by life events, including medical intervention, reproductive experiences, relationships, and normal physiologic changes and, thus, must be re-evaluated routinely as part of well-woman care.\textsuperscript{4}

Comprehensive sexual health care is best approached as an open dialogue, starting with a sexual history focusing on positive aspects of sexuality, as well as identifying opportunities for risk reduction and possible areas of distress. Questions are best asked in an open-ended format using gender-neutral terminology.\textsuperscript{4} Specific questions regarding desire, arousal, and
orgasm may help delineate potential areas of dysfunction, though it is considered dysfunctional only if the patient finds it distressing. It is the responsibility of the ob-gyn to normalize and validate the range of “complex normal experiences.” However, when a point of distress is identified, further exploration may allow for diagnosis and treatment.

An initial approach to a patient with possible sexual dysfunction is reviewed in ACOG Practice Bulletin No. 213, “Female Sexual Dysfunction,” and includes comprehensive history, physical examination, and diagnosis based on Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria. Additionally, a physician or advanced practice health care professional may use a model developed by psychologist Jack Annon in 1974, known as the PLISSIT model. PLISSIT stands for permission, limited information, specific suggestions, and intensive therapy. It suggests starting by asking for permission to discuss sexual issues if a concern is raised, then offering targeted information or education, then specific suggestions for how to address the problem, and, finally, consideration for more intensive therapy should it be indicated. The PLISSIT model will be discussed further in the section on treatment of female orgasmic dysfunction.

**RISK FACTORS FOR SEXUAL DYSFUNCTION**

The etiology of sexual dysfunction is complex and multifactorial. Medical and psychiatric conditions, medications, fatigue and stress, age and menopausal status, and relationship and environmental factors may all play a role (Box 1).

Medical comorbidities, specifically gynecologic conditions, may affect sexual function. Sexual function can be affected by pregnancy and the postpartum period. This is thought to be multifactorial, with both hormonal and anatomic changes after delivery, as well as the difficulty of caring for a newborn. According to a review by Leeman et al, postpartum sexual dysfunction affects 40–80% of women. Although results have been inconsistent, sexual health after delivery does not seem to be affected by mode of delivery (reviewed by Leeman, et al). Infertility similarly affects intimacy, with 43–90% of women with infertility reporting sexual dysfunction. Gynecologic conditions, including pelvic organ prolapse, endometriosis, and gynecologic cancers, can also affect sexual health and play a role in sexual dysfunction. There has been some question regarding the effect of hysterectomy on sexual health; however, a narrative review of 10 studies, performed by Danesh et al, in 2015, found that the majority of studies demonstrated an improvement in sexual functioning after hysterectomy, particularly for benign conditions. The writers reinforce the importance of preoperative counseling on the possible effect of hysterectomy on sexual health, though any dysfunction generally improves with time. Other medical conditions, including obesity, hypertension, and neurologic disease, have also been demonstrated to affect sexual health.

The PRESIDE study found that depression and anxiety are associated with increased risk for sexual dysfunction. Some would argue that mental health is, in fact, the most important risk factor for sexual dysfunction. Unfortunately, the medications used to treat these conditions, including benzodiazepines, selective serotonin reuptake inhibitors (SSRIs), and mood stabilizers, are known for their adverse effect on sexual arousal and ability to achieve orgasm. Care should be taken to identify the effect of mental health on sexual function and optimization of both psychological and pharmacotherapy for these patients.

Age and menopause are difficult to differentiate as potential risk factors, but the PRESIDE study found

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**Box 1. Common Etiologies and Risk Factors for Female Sexual Dysfunction**

- Anxiety disorder
- Diabetes
- Depression
- Female genital mutilation
- Genitourinary syndrome of menopause
- History of sexual abuse
- Hypertension
- Hysterectomy
- Intimate partner violence
- Medications (psychotropic medications [selective serotonin reuptake inhibitors], antihypertensives, histamine blockers, hormonal medications)
- Negative sexual attitudes
- Neurologic disease
- Personality traits of perfectionism and self-dislike
- Postpartum period
  - Breastfeeding
  - Obstetric trauma
- Premature ovarian failure
- Psychologic sequelae of gynecologic cancer and breast cancer
- Relationship discord
- Stress—emotional or environmental
- Stress urinary incontinence
- Substance use disorder

that the highest rates of sexual dysfunction were in the 45–64-year age group. Vaginal atrophy and dyspareunia have been found to increase after menopause, understandably related to decreased estrogen. The PRESIDE study looked specifically at natural menopause compared with surgical menopause and found that decreased arousal and difficulty with orgasm were worse after surgical menopause than natural menopause. Thus, age and both surgical and natural menopause should be considered risk factors for sexual dysfunction.

Finally, relationships and environment have a critical influence on sexual health. Multiple studies have demonstrated that dissatisfaction with a partner and lack of emotional well-being were associated with sexual dysfunction, leading to distress in the patient. Additionally, a history of childhood sexual abuse or adult sexual assault increase the risk of sexual dysfunction. This may present with dyspareunia; difficulties with interest, arousal, or orgasm; or avoidance of sex. Although rates of sexual dysfunction are higher among women with sexual abuse, it is critical to not assume that all women with sexual dysfunction have an abuse history. However, given the increased risk of sexual dysfunction in survivors, eliciting a trauma history is a crucial step in the effort to better understand the underlying etiology of the sexual dysfunction.

**TYPES OF SEXUAL DYSFUNCTION**

According to the DSM-5, female sexual dysfunction includes four primary diagnoses: female sexual interest and arousal disorder (includes former hypoactive sexual desire disorder), female orgasmic disorder, genitopelvic pain and penetration disorder, and substance- or medication-induced sexual dysfunction. When making any of these diagnoses, the following factors should be considered in the course of evaluation: partner factors (partners health or sexual problems), relationship factors (poor communication, discrepancies in desire for sexual activity), individual vulnerability factors (poor body image, history of sexual or emotional abuse), psychiatric comorbidity (depression, anxiety) or stressors (job loss, bereavement), cultural and religious factors (inhibitions related to prohibitions against sexual activity, attitudes toward sexuality), and medical factors.

**Female Sexual Interest and Arousal Disorder**

Female sexual interest and arousal disorder is a broad category of female sexual dysfunction that is characterized by a lack of interest in sexual activity or difficulty with arousal. This was previously defined as two separate groups in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition: desire and interest*. Given that they often present as two distinct diagnoses and it is easier to specify treatment, some groups prefer to maintain these definitions.

When considering female sexual interest and arousal disorder, women may report absent or reduced interest in sexual activity or erotic thoughts. They may also note a reluctance to initiate sexual activity and lack of response to initiation from a partner. When considering the arousal side of the spectrum, women may experience reduced or absent sexual excitement or pleasure, or even sensation, during sexual activities. The DSM suggests that these features should be present 75–100% of the time to make the diagnosis. It may be specified whether it takes place in specific contexts (situational) or if it is generalized across all sexual encounters. To give a patient a diagnosis of sexual interest and arousal disorder, the lack of desire or arousal must be accompanied by distress. It is important to remember that there are a variety of ways this disorder may present; a woman may be distressed by a persistent lack of interest in sexual activity, or, despite a desire for sexual activity, she may not be able to become sexually excited. For the sake of this review, we will use the terminology *female sexual interest and arousal disorder*, as defined by the DSM-5, though the DSM-5 uses the diagnosis *female sexual interest/arousal disorder*, understanding that a patient may fall on either the arousal or interest end of the spectrum.

Fluctuations in sexual interest and arousal can be a normal response to changes in a woman’s life, particularly with stress, fatigue, environmental changes, or new medical diagnoses. To meet criteria for female sexual interest and arousal disorder, the symptoms must cause distress and be present for at least 6 months.

Female sexual interest and arousal disorder is often associated with difficulties achieving orgasm and pain with sexual activity. Other associated issues in women with sexual interest and arousal disorder include body dysmorphia, impaired intimate relationships, and low self-worth.

Female sexual interest and arousal disorder is the most common cause of female sexual dysfunction and is often the most difficult to treat. The etiologies of sexual interest and arousal disorder are varied, and the diagnosis may be made only after organic or medical causes are excluded (medication-induced, poorly controlled diabetes, and neuropathy, among others). Other etiologies of female sexual interest and arousal disorder include history of sexual abuse and...
Finally, environmental factors, psychiatric diagnoses, mainly major depressive disorder, has also been associated with sexual interest and arousal disorder.20 Environmental factors, including relationship stress, history of sexual abuse, and partner sexual functioning, are important possible etiologies to consider.

The exact prevalence of female sexual interest and arousal disorder is unknown, but the PRESIDE data suggest that low desire was seen in 38.7% of respondents and low arousal was reported in 26.1%; sexually related personal distress was reported in 22.8% of respondents. They found that rates of reported sexual dysfunction increased with age, but associated sexual distress was most common in younger and middle-aged women.9

**Female Orgasmic Disorder**

Female orgasmic disorder occurs in women when orgasm or significant sexual pleasure is not achieved despite significant stimulation. This is clinically different from female sexual interest and arousal disorder in that women have the desire and are able to be aroused but are unable to achieve climax or attain orgasm. It may also present as a markedly reduced intensity of orgasm. To meet formal criteria, these features must be present with all or almost all (75–100%) sexual encounters, persist for 6 months, and cause significant distress to the patient.1

The etiologies of orgasmic disorder are multifactorial. It is important to first evaluate for medical conditions or substances or medications that may lead to difficulty with orgasm, because iatrogenic causes are thought to play the biggest role. The use of SSRIs is known to delay or inhibit orgasms in women.23 Concomitant medical conditions including diabetes, hypertension, or other chronic illnesses may lead to difficulty with orgasm. Nerve damage from radical hysterectomy or other nerve injuries can affect ability to achieve orgasm. Illicit drug use including alcohol and chronic opioid use may also play a role. Once these conditions are ruled out, interpersonal context must be evaluated, including relationship distress, intimate partner violence, or other significant stressors. Although the effect on sexual health and ability or orgasm may be substantial, a patient would not technically meet criteria for female orgasmic disorder if there is an acute exacerbating factor. Finally, it is important to evaluate whether the patient’s sexual stimulation is sufficient, because many women require clitoral stimulation to achieve orgasm; if she is able to achieve orgasm by clitoral stimulation alone, it would not be a true orgasmic disorder. If none of the above conditions are met, the patient is considered to have a true orgasmic disorder, though, even if there is a clear etiology for the orgasmic disorder, the sexual dysfunction must still be addressed.

Prevalence of orgasmic difficulties varies from 10 to 40%, but this does not take into account presence of distress. The PRESIDE study found that 20% of women surveyed reported orgasm difficulties, and more than 5% of women reported distress related to orgasm dysfunction.3

**Genitopelvic Pain and Penetration Disorder**

Genitopelvic pain and penetration disorder encompasses the symptoms of dyspareunia and vaginismus.27 It is characterized by persistent difficulty with vaginal intercourse or penetration, vulvovaginal or pelvic pain during intercourse or penetration attempts, fear or anxiety about pain in anticipation of intercourse, and marked tensing or tightening of pelvic floor during attempted penetration. A patient requires only one of these four components to make a diagnosis of genitopelvic pain and penetration disorder, because only one of these symptoms is often sufficient to cause significant distress.1 Similar to other female sexual disorders, to meet criteria for the diagnosis, these symptoms must be present for at least 6 months and cause significant distress.1

Genitopelvic pain and penetration disorder includes intercourse as well as any vaginal penetration, including gynecologic examinations and tampon insertion. Vulvovaginal or pelvic pain during intercourse should be evaluated thoroughly, because it may be elicited on examination. It may be more specifically characterized as deep or superficial or by the type of pain (i.e., shooting or burning). Fear or anxiety in anticipation of intercourse is often reported by women with a history of pain during intercourse and may lead to avoidance. In other cases, there is no history of pain, but the fear of pain still leads to avoidance, and the disorder behaves more like a phobia. Finally, tensing of the pelvic floor is often a reflexive spasm of the pelvic muscles in response to attempted penetration.1

Genitopelvic pain and penetration disorder is often associated with female sexual interest or arousal disorder, though not always. Patients may demonstrate avoidance patterns similar to phobias, including
avoidance of gynecologic examination. It is not uncommon that, despite having symptoms for many years, women may present for care only when trying to conceive. Although the exact prevalence of genitopelvic pain and penetration disorder is unknown, 15% of women report recurrent pain during intercourse.1

Genitopelvic pain and penetration disorder is very difficult to treat, because the etiologic cause is usually multifactorial and difficult to isolate. Common reasons for pain during intercourse include organic causes such as endometriosis, vaginitis, menopause causing vaginal dryness, malignancy, and infection.26 A history of gynecologic cancer may increase risk for genitopelvic pain and penetration disorder, because postsurgical and posttreatment changes may cause new potential sources of pain. Anatomic variations including septate uterus should also be considered in the differential diagnosis. Other factors include psychological or environmental conditions, including depression and past sexual trauma or early childhood sexual abuse.

In many cases, genitopelvic pain and penetration disorder will be associated with an underlying medical condition, such as lichen sclerosis, endometriosis, vulvovaginal atrophy, or pelvic inflammatory disease. Wright et al encourage taking a systematic approach to diagnosis and to consider etiologies in three categories: irritative, anatomic, and infectious.27 Irritative etiologies include vaginal dryness, atrophic vaginitis, vulvar dermatoses, and vulvodynia and vestibulitis. Anatomic etiologies include endometriosis, leiomyomas, pelvic organ prolapse, malignancy, and postsurgery and treatment scarring. Infectious etiologies can include sexually transmitted infections, pelvic inflammatory disease, and vulvovaginal candidiasis.27 In some cases, treatment of the underlying condition will lead to improvement in the genitopelvic pain and penetration disorder. The key to distinguishing the etiology of this disorder is taking a thorough history to determine the aggravating symptoms and assessing the quality of sexual activity that elicits pain; then the appropriate workup for potential irritative, anatomic, or infectious causes can guide treatment.

Substance- or Medication-Induced Sexual Dysfunction

According to the DSM, substance- or medication-induced sexual dysfunction is a clinically significant disturbance in sexual function, with evidence from evaluation of the patient that the symptoms developed during or soon after intoxication with the substance or initiation of a given medication.1 The involved substance or medication must be capable of causing the noted sequelae. The changes in sexual function should demonstrate a temporal relationship with the causative agent; for example, symptoms start with initiation of medication and improve with dose reduction or cessation. If symptoms persist for at least 1 month after cessation or withdrawal, a non–substance- or medication-induced sexual disorder should be considered.

Many substances can cause sexual dysfunction, including alcohol, cocaine, anxiolytics, sedatives, and opioids. Similarly, withdrawal from these substances can affect sexual function. The medications that are most likely to cause sexual dysfunction are antidepressants [particularly SSRIs] and antipsychotics, and there are some data for oral contraceptives. Selective serotonin reuptake inhibitors are particularly associated with difficulty with orgasm, the prevalence depending on the specific medication, though it is estimated that 22–58% of women using antidepressants will suffer sexual side effects.6 Time from initiation of the medication to start of side effects may be as rapid as 8 days. For some, the dysfunction will resolve after 6 months of use. Approximately 50% of patients taking antipsychotics will report adverse sexual side effects, including inhibited desire and decreased lubrication.

TREATMENT OF SEXUAL DYSFUNCTION

Female Sexual Interest and Arousal Disorder

Management of female sexual interest and arousal disorder is guided by the history and generally includes both psychological intervention and consideration of pharmaceutical intervention.

Psychological Approach

Cognitive behavioral therapy is a critical part of the treatment of female sexual interest and arousal disorder. Cognitive behavioral therapy can assist patients in identifying and modifying factors that contribute to or exacerbate sexual dysfunction. This could include examining maladaptive thoughts, unreasonable expectations, behaviors that reduce interest or trust in the relationship, or insufficient stimuli while simultaneously working to improve the emotional closeness of the couple.8 The focus of this is on the development and natural evolution of sexual activity rather than a focus on intercourse and orgasm.28 Patients are taught to not focus on end results of sexual desire, but rather on activities that achieve intimacy and pleasure with their partner. Though there are minimal data to support these techniques, Trudel et al29 published a study in 2001 evaluating a short-term cognitive behavioral therapy
approach to women with hypoactive sexual desire disorder [as defined at the time] and found a significant improvement in symptoms and subsequent improvement in behavioral, cognitive, and marital functioning. Mindfulness is also an appropriate technique in this realm. Sex therapy can also take it one step further with sensate focus techniques, which focus on being present during intimate exchanges and eventual progression toward sexual touch. Psychotherapy is used when the drivers of female sexual interest and arousal disorder seem to be more deeply rooted conflicts with self-image or sexual trauma.

**Pharmaceutical Approach**

Hormonal therapy has been used historically for sexual interest and arousal dysfunction in women. There have been a series of placebo-controlled trials evaluating transdermal testosterone in women with surgically induced menopause, and each of the studies found a moderate increase in satisfying sexual activity and sexual desire and response, as well as significant reductions in distress. The majority of studies have been completed in naturally postmenopausal women simultaneously taking estrogen supplementation, though others have focused on postmenopausal women taking only testosterone, both of which found a moderate improvement in number of satisfying sexual episodes over the course of a month. In 2017, Achilli et al published a systematic review and meta-analysis of seven randomized controlled trials on the use of transdermal testosterone, with a standardized dose of 300 micrograms compared with placebo, in more than 3,000 postmenopausal women. They found short-term efficacy, with improvement in the number of sexually satisfying experiences, sexual activity, number of orgasms, and sexual desire, and a significant reduction in personal distress, in both naturally and surgically menopausal women. The meta-analysis found no significant difference in the rate of adverse effects, though they did find increased incidence of acne and increased hair growth among patients using transdermal testosterone. However, safety and efficacy data are limited, because most studies evaluated use for only 6 months.

The Endocrine Society published a clinical practice guideline recommending transdermal testosterone for short-term use in postmenopausal patients with female sexual interest and arousal disorder. They recommend counseling regarding unknown risks of long-term use and continuous monitoring for evidence of androgen excess. Given only modest improvement seen in the existing literature and limited data regarding long-term side effects, testosterone is not currently approved by the U.S Food and Drug Administration (FDA) for treatment of women with sexual dysfunction. Furthermore, the physiologic transdermal dosing evaluated in the majority of these studies is not available in the United States and thus requires compounding. The Global Consensus Position statement from multiple societies does caution regarding compounding and the risk of supraphysiologic doses of testosterone, as well as testosterone administered through pellets. For premenopausal women with female sexual interest and arousal disorder, there are isolated studies evaluating the role of transdermal testosterone; however, the evidence is considered insufficient to recommend testosterone-based treatment.

When considering nonhormonal interventions, bupropion, a dopamine and norepinephrine agonist, has been studied for treatment of female sexual interest and arousal disorder. In 2004, Seagraves et al published a randomized, double-blind, placebo-controlled trial of 66 nondepressed patients and found that bupropion had a significant effect on increasing measures of sexual arousal, orgasm completion, and sexual satisfaction. In 2019, a phase II/I A study was published to evaluate dose tolerability for a new pharmaceutical, a combination of the stimulating and excitatory dopamine–norepinephrine reuptake inhibitor bupropion and the sedating and inhibitory serotonergic agonist–antagonist trazodone. It was an open-label, active control study that found that most patients both tolerated and responded to the moderate dose of the combination drug, paving the way for phase III evaluation. Based on these studies, off-label use of bupropion remains a key nonhormonal option for the management of female sexual interest and arousal disorder.

Sildenafil citrate, a potent selective inhibitor of phosphodiesterase 5, has been shown to enhance genital blood flow and vaginal and clitoral vasocongestion. Several studies have evaluated its potential as an off-label agent to treat female sexual interest and arousal dysfunction, with varying results. An early study looking at sexual dysfunction in postmenopausal women did identify an improvement in vaginal lubrication and clitoral sensitivity; however, it did not find an overall improvement in function. A subsequent study by Berman et al focused specifically on female sexual arousal disorder, independent of evidence of dysfunction in sexual interest, and found through a double-blind, placebo controlled approach that sildenafil lead to improvement on the Female Intervention Efficacy Index, thus demonstrating an immediate improved outcome in patients with arousal-specific dysfunction. A more recent study
focused specifically on women with antidepressant-associated sexual dysfunction, which will be discussed further under treatment for substance- or medication-induced sexual dysfunction.43

For a review of all off-label pharmaceuticals available to treat sexual interest and arousal dysfunction, please see Table 1.

Flibanserin, a 5-hydroxytryptamine (5-HT) modulator, specifically a 5-HT<sub>1A</sub> agonist and 5-HT<sub>2A</sub> antagonist, was the first pharmaceutical approved by the FDA for hypoactive sexual desire disorder, the sexual interest component of female sexual interest and arousal disorder.44 In 2019, Simon et al<sup>45</sup> published a pooled analysis that evaluated flibanserin 100 mg once daily at bedtime compared with placebo in premenopausal women with hypoactive sexual desire disorder, which was evaluated across three multicenter studies. The primary tools for evaluation were the number of satisfying sexual events over 28 days, the Female Sexual Function Index-Desire Domain score, and a modified Female Sexual Distress Scale score. The analysis ultimately included 2,465 women with a mean age of 36 years and a mean duration of hypoactive sexual desire disorder of 56 months. The mean number of satisfying sexual events over 28 days was 2.1 with flibanserin compared with 1.2 with placebo ($P<0.001$). The change in Female Sexual Function Index-Desire Domain and Female Sexual Distress Scale scores was also significantly improved with flibanserin.<sup>45</sup> Adverse events were evaluated, with somnolence and dizziness in 12% and 10% of participants, respectively. The authors concluded that flibanserin was well tolerated, improved sexual desire, and reduced sexual distress associated with hypoactive sexual desire disorder in premenopausal women.<sup>45</sup> A recent evaluation of safety for flibanserin with a focus on sedation- and hypotension-related side effects, confirms that flibanserin is well tolerated and effective.<sup>44</sup> There had been concern about the possible influence of alcohol on flibanserin side effects, particularly hypotension; however, a subsequent study found no appreciable dose response between flibanserin and alcohol.46 Thus, the FDA changed their recommendation to update the box warning regarding alcohol and instead caution that care must be taken with alcohol but that it does not need to be avoided entirely. Specifically, they recommend delaying taking flibanserin for 2 hours after last alcohol consumption and delay further alcohol consumption after flibanserin until the next morning.<sup>47</sup>

Bremelanotide (Vyleesi) is a melanocortin 4 receptor agonist and was the second pharmaceutical to be approved by the FDA for treatment of the sexual interest component of female sexual interest or arousal dysfunction.<sup>48</sup> Bremelanotide is a subcutaneous auto-injection, administered into the thigh or abdomen 45 minutes before sexual activity. Dosing can be repeated every 24 hours, but it should not be used more than eight times in 1 month.<sup>49</sup> The RE-CONNECT studies evaluated bremelanotide as a subcutaneous injection. These two phase-III trials included premenopausal patients with reported hypoactive sexual desire disorder, the majority of whom also experienced decreased arousal. Both studies showed improvement in primary endpoints: Female Sexual Function Index-Desire Domain score, indicating greater increase in desire, and Female Sexual Distress Scale score, indicating improvement in sexual distress.<sup>50</sup> Bremelanotide was also associated with statistically significant improvement in the sexual satisfaction, lubrication, orgasm, and arousal domains.<sup>50</sup> Although the number of satisfying sexual events was not significant in either trial, they were higher in the bremelanotide group, raising the question of true clinical benefit.<sup>48,50</sup> Most adverse effects were mild or moderate, most commonly nausea, facial flushing, or headache. Adverse effects were responsible for 18% of participants discontinuing or interrupting treatment.<sup>48</sup>

### Table 1. Off-Label Pharmaceuticals for Female Sexual Interest and Arousal Disorder

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism</th>
<th>Dose</th>
<th>Side Effects</th>
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<tbody>
<tr>
<td>Testosterone&lt;sup&gt;14,30,32–35&lt;/sup&gt;</td>
<td>Androgen, stimulation of neurotransmitters to increase libido</td>
<td>150 micrograms/d or 300 micrograms/d transdermal patch (not available in the United States)</td>
<td>Hair growth, acne (though not seen in all studies)</td>
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<tr>
<td>Bupropion&lt;sup&gt;*&lt;/sup&gt;,&lt;sup&gt;38–40&lt;/sup&gt;</td>
<td>Dopamine and norepinephrine agonist</td>
<td>150 mg daily, increased to 300 mg daily OR 150 mg twice daily</td>
<td>Anxiety, irritability, headache, seizures</td>
</tr>
<tr>
<td>Sildenafil citrate&lt;sup&gt;7,41–43&lt;/sup&gt;</td>
<td>Phosphodiesterase 5 inhibitor, increases genital blood flow and vaginal and clitoral vasocongestion</td>
<td>50 mg or 100 mg tablets, 1 h before sexual encounter</td>
<td>Headache, flushing, nausea; contraindicated in patients taking nitrate therapy</td>
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<sup>*</sup> Particular benefit when concern for selective serotonin reuptake inhibitor–induced sexual dysfunction.

<sup>1</sup> Particular benefit with selective serotonin reuptake inhibitor–induced sexual dysfunction and sexual arousal disorder.
A subsequent long-term safety and efficacy analysis of 272 patients was performed, which found no new safety concerns and confirmed sustained response to the intervention.\(^5\)

For a review of FDA-approved pharmaceuticals available to treat sexual interest and arousal dysfunction in women, please see Table 2.

**Female Orgasmic Disorder**

Female orgasmic disorder is defined as either primary, when a patient has never had an orgasm, or secondary, when she has had an orgasm in the past but currently has not had an orgasm for approximately 6 months and it causes her distress.\(^1\) Primary female orgasm disorder may be related to childhood exposures or trauma and thus may be best addressed by psychotherapy.\(^27\) Primary female orgasm disorder may also be related to an underlying medical condition, such as neurologic injury, in which case the underlying medical condition needs to be addressed. Finally, primary female orgasm disorder may be idiopathic, which is more difficult to treat. Secondary female orgasmic dysfunction may be caused by psychosocial changes (eg, new relationship conflict, body image), new underlying medical conditions including neurologic or vascular disorders, and medications including SSRIs. If the change in sexual function is preceded by the start of a new medication or an acute interpersonal stressor, the diagnosis of female orgasmic disorder is ruled out; however, symptoms may still require attention.\(^52\)

Clinical interviewing is a critical aspect of evaluation for orgasmic disorders, including characterization of nature, onset, and chronicity of difficulty with orgasms.\(^52\) Wright and O’Connor\(^27\) recommend use of the PLISSIT model—permission, limited information, specific suggestions, intensive therapy. Permission includes conversation with the patient regarding normalization of sexual behaviors. Limited information is available regarding behaviors that could improve sexual arousal, as well as evaluation of possible medications or underlying conditions that may affect ability to achieve orgasm. Specific suggestions include lubricants, specific positions, and modifications to sexual encounters that may assist in ability to achieve orgasm. Finally, intensive therapy includes referral to a sex therapist to further evaluate and treat possible sources of the dysfunction, including tools to decrease anxiety around sex and the use of sensate focus exercises, depending on the needs of the couple.\(^27\) Women who have never had an orgasm in any context tend to be younger and have less experience with sexual activity. This is in contrast to women with acquired anorgasmia, for whom it is critical to determine the context of the change, including medical, psychological, and relational factors.\(^52\)

Treatment of female orgasmic dysfunction is predominantly cognitive and behavioral, along with psychoanalytic therapy. Education is a key component of intervention for female orgasmic disorder. This includes education about anatomy and physiology, variations in sexual response, and forms of stimulation used to reach orgasm.\(^52\) Directed masturbation, which includes a series of exercises focused on self-awareness and exploration, is intended to improve comfort with the erotic areas of the body.\(^52\) Sensate focus, as described for female sexual interest and arousal disorder, is also used for female orgasmic disorder. Additionally, a single-arm, prospective study has evaluated the use of vibratory stimulation for women with arousal and orgasmic disorders and demonstrated increased lubrication, orgasm, and genital sensation after 3 months of use in the majority of patients.\(^53\) Thus, the use of vibrators may be considered in conjunction with cognitive therapeutic support and more directive sexual therapy techniques such as directed masturbation and sensate focus.

**Genitopelvic Pain and Penetration Disorder**

Treatment of genitopelvic pain and penetration disorder is dependent on the underlying etiology, if one is identified. Genitourinary syndrome of menopause

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**Table 2. U.S. Food and Drug Administration–Approved Pharmaceuticals for Female Sexual Interest and Arousal Disorder**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism</th>
<th>Dose</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flibanserin(^45) (Addyi)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-HT(<em>{1A}) agonist, 5-HT(</em>{2A}) antagonist</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100-mg nighttime oral dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension (possibly exacerbated with alcohol), fatigue, dry mouth, nausea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bremelanotide(^50,51) (Vyleesi)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanocortin 3 and 4 receptor agonist</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.75-mg subcutaneous injection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, bradycardia, nausea, flushing, headache, injection site reactions</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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affects more than 50% of midlife and older women and is the most common cause of genitopelvic pain and penetration disorder in postmenopausal women.\textsuperscript{54} Previously known as vulvovaginal atrophy, genitourinary syndrome of menopause is considered to be more medically accurate and all-encompassing of the genitourinary changes seen with menopause.\textsuperscript{54} Genitourinary syndrome of menopause is defined as “a collection of symptoms and signs associated with a decrease in estrogen and other sex steroids involving changes to the labia majora/minora, clitoris, vestibule/introitus, vagina, urethra and bladder...the syndrome may include but is not limited to genital symptoms of dryness, burning, and irritation; sexual symptoms of lack of lubrication, discomfort or pain, and impaired function; and urinary symptoms of urgency, dysuria and recurrent urinary tract infections.”\textsuperscript{54} Atrophic vaginitis may also be seen when bacterial overgrowth is noted in the setting of genitourinary syndrome of menopause.

Vulvovaginal atrophy may also be seen in postpartum women and in women taking antiestrogenic medication. Findings on physical examination including thinning of the vaginal mucosa, loss of labial fullness, and loss of vaginal rugae, or a vaginal pH of 4.5 or greater (if no infection), are consistent with atrophy.

Patients with genitourinary syndrome of menopause or other forms of vulvovaginal atrophy may be treated with vaginal moisturizers, such as Replens (Glycerin-Min Oil-Polycarbophil) or KY Liquebuds, and lubricants, such as KY or Pjur, all available over the-counter or online. Vaginal moisturizers and lubricants appear to be effective for many women and are recommended as the first line of therapy. Vaginal estrogen often serves as the second line. It is started at a low dose, with the intention to decrease systemic absorption. Vaginal estrogen may be delivered as estradiol (E2) tablets (10 micrograms E2), E2 ring (7.5 micrograms E2 daily, released over 90 days), E2 cream (100 micrograms E2/g of cream), or conjugated estrogen cream (0.625 mg conjugated estrogens/g of cream). For the E2 tablet and cream, a 2-week priming period is recommended, with daily followed by twice-weekly dosing. A randomized controlled trial evaluated vaginal moisturizers, vaginal estrogen, and placebo and found no difference between the three arms in reduction of vulvovaginal symptoms.\textsuperscript{55} However, there is some critique of this study, because the vaginal estrogen and moisturizer were dosed together and generally the nonhormonal approach is trialed before starting estrogen-based therapy. Additionally, the placebo gel may have had some therapeutic effect.

Vaginal estrogen is thought to have minimal systemic absorption and, thus, may be used in patients with a history of hormone-sensitive cancers if nonhormonal options are not effective, though this should be discussed with the patient’s oncologist before initiation.\textsuperscript{56,57} Topical aqueous lidocaine (4%, applied for 3 minutes before vaginal penetration) has been evaluated in postmenopausal women with hormone-sensitive breast cancer with good effect and serves as another nonhormonal option for control of genitourinary syndrome of menopause symptoms.\textsuperscript{58} Additionally, vaginal estrogen is considered safe in women with hereditary breast and ovarian cancer syndrome who have undergone risk-reducing salpingo-oophorectomy if nonhormonal options are not effective.

Intravaginal dehydroepiandrosterone (DHEA) has been studied both in preclinical and clinical settings on objective and subjective measures of vulvovaginal atrophy. A randomized, double-blind, placebo-controlled phase III trial evaluated vaginal DHEA (0.50%, 6.5 mg) compared with placebo and demonstrated improvement in both objective measures of vulvovaginal atrophy and decreased pain with sexual activity with vaginal DHEA.\textsuperscript{59} The only noted side effect was vaginal discharge, reported in 6% of participants.\textsuperscript{59}

Beyond vaginal therapy, ospemifene is a recently FDA-approved selective estrogen receptor modulator that is delivered orally (60 mg/d), functions as an estrogen agonist in the vagina, and has been found to be efficacious in treating vulvovaginal atrophy compared with placebo.\textsuperscript{60} The most frequently noted side effect was hot flushes at 6.0%.\textsuperscript{60} Given the agonistic effects on the endometrium, the FDA currently recommends using an opposing progestin when giving ospemifene if the patient still has a uterus, although this has not been evaluated in randomized trials.\textsuperscript{27}

Vulvar dermatoses can also cause genitopelvic pain and penetration disorder. A complete review of vulvar dermatoses is beyond the scope of this review, but three conditions to be familiar with are lichen sclerosis, lichen planus, and vulvodynia or vestibulitis. Lichen sclerosis is an inflammatory process that predominantly affects the labia, leading to discoloration and agglutination of the vulvovaginal tissue. Dyspareunia is often a later symptom, preceded by pain and pruritus. Lichen sclerosis can lead to fissuring and scarring, ultimately causing pain. Treatment with potent topical steroids improves symptoms and decreased progression of the disease.\textsuperscript{27,61} Lichen planus is another dermatosis caused by chronic irritation that can lead to stenosis of the vagina and dyspareunia. Patients will present with vulvar pain or pruritis...
and may have erythematous lesions or a reticular pattern on examination. Treatment includes avoidance of irritants and potent topical steroids. Finally, vulvodynia may be diagnosed if other vulvar etiologies are ruled out. It is often a sensitivity or burning, frequently noted at the vestibule or introitus, that can be diagnosed with directed cotton swab palpation. When localized to the vestibule, this may be considered vestibulitis. Vulvodynia and vestibulitis can be treated with topical lidocaine ointment (5%) applied before intercourse.27

Finally, a proper history, physical examination, and indicated testing should be performed to evaluate for other potential causes of genitopelvic pain and penetration disorder, including endometriosis, leiomyomas, prolapse, posttreatment scarring, new gynecologic malignancy, and infectious processes. If all of these causes are ruled out, the patient may be diagnosed with and treated for genitopelvic pain and penetration disorder. This often requires a multidisciplinary approach, with ob-gyns, psychologists, and pelvic floor physical therapists. Pelvic floor physical therapists may be able to assist with desensitization techniques and dilator exercises.27

Substance- or Medication-Induced Sexual Dysfunction

For substance- or medication-induced sexual dysfunction, cessation of the implicating agent should improve sexual function if it is definitively the underlying etiology. However, if a patient has a good response in mood to an antidepressant that is also causing sexual side effects, adjunctive therapy with sildenafil could be considered because it has been shown to have benefit.43 A prospective, randomized, double-blind, placebo-controlled clinical trial evaluated women who had improvement of their depressive symptoms on serotonin reuptake inhibitors but continued sexual dysfunction.43 Forty-nine patients were randomized to sildenafil or placebo before sexual activity; a reduction in sexual side effects was found in patients who received sildenafil.43 Given the mechanism and existing data, sildenafil may play a role in treatment for patients with either antidepressant–induced sexual dysfunction or specific sexual arousal dysfunction.43 Another option would be discussing transition to bupropion, given generally improved sexual functioning with this agent, though this requires a transition of antidepressant.

CONCLUSIONS

Female sexual dysfunction is a multifaceted medical problem that has a high prevalence. It is the responsibility of ob-gyns to screen women for sexual dysfunction. If sexual dysfunction is identified and confirmed to be distressing to the patient, a further evaluation into the etiology and exacerbating factors of the disorder is indicated. Psychotherapy is a cornerstone for treatment of female sexual interest and arousal and orgasmic disorders. In some scenarios, pharmacologic interventions may be indicated for female sexual interest and arousal disorder. When considering genitopelvic pain and penetration disorder, determination of the underlying etiology is paramount, followed by appropriate treatment. Referral to specialty centers as well as employing therapists trained in the management of sexual dysfunction are vital to the treatment of this spectrum of disorders.

REFERENCES


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- Differentiate female organic disorder, genitopelvic pain and penetration disorder, and substance- and medication-induced sexual dysfunction
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