Etiology of hypoactive sexual desire disorder and implications for treatment: 4 case scenarios

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Intended audience: This continuing education (CE) activity has been designed to meet the educational needs of nurse practitioners and other healthcare providers who provide primary care for women.

CE approval period: Now through April 30, 2022

Estimated time to complete this activity: 1 hour

CE approval hours: 1.0 contact hour of CE credit, including 0.25 contact hours of pharmacology content

Goal statement: To apply one's knowledge about the etiology of hypoactive sexual desire disorder (HSDD) in order to select an appropriate therapeutic approach for each woman in whom the disorder is diagnosed.

Needs assessment: About 10% of women—a substantial proportion of a healthcare provider's (HCP's) patient population—experience HSDD. The underlying cause of HSDD in a given case may be a simple physiologic one, although in most cases, it is multifactorial. HCPs need to ascertain the likely cause(s) of each woman's loss of sexual desire and design a treatment plan best suited for her.

Educational objectives: At the conclusion of this educational activity, participants should be able to:

1. Identify patients whose symptoms are suggestive of HSDD.
2. Ascertain physiologic, sociocultural, psychological, and interpersonal factors that might be relevant in each case of suspected HSDD.
3. Diagnose HSDD and consider which nonpharmacologic and/or pharmacologic approaches might be optimal in each case.

Accreditation statement: This activity has been evaluated and approved by the Continuing Education Approval Program of the National Association of Nurse Practitioners in Women's Health (NPWH), and has been approved for 1.0 contact hour of CE credit, including 0.25 contact hours of pharmacology content.

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Commercial support: This activity is supported by an educational grant from AMAG Pharmaceuticals, Inc.

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In this discussion, the etiology and management of hypoactive sexual desire disorder (HSDD) are succinctly reviewed. Four case studies follow that illustrate the methods of diagnosing and managing HSDD.

Key words: hypoactive sexual desire disorder, HSDD, psychological approaches, OTC supplements, flibanserin, bremelanotide

Hypoactive sexual desire disorder (HSDD) is the most prevalent female sexual health problem.[1] Studies have shown, and experts have concluded, that about 10% of women experience HSDD. These women constitute a substantial proportion of the patient population of healthcare providers (HCPs).[1–3]

HSDD is defined as the presence of either of the following for at least 6 months:

- Lack of motivation for sexual activity, as manifested by either reduced or absent spontaneous desire (sexual thoughts or fantasies) or reduced or absent responsive desire to erotic cues and stimulation or inability to maintain desire or interest through sexual activity; or
- Loss of desire to initiate or participate in sexual activity including behavioral responses such as avoidance of situations that could lead to sexual activity (ie, not secondary to a sexual pain disorder).[4*]

Both of these sexual problems are accompanied by clinically significant personal distress manifested by a sense of frustration, grief, incompetence, loss, sadness, sorrow, or worry.[4]

Etiology

The underlying cause of HSDD in a given case may be a simple physiologic one. An example would be that of a woman who has been using a selective serotonin reuptake inhibitor (SSRI) for years that has diminished her sexual desire and ability to respond, resulting in distress about a part of her life that was once highly pleasurable. In most cases, however, the cause of HSDD is multifactorial. According to a biopsychosocial model and other similar models, female sexual response, whether normal or abnormal, is influenced by a wide range of determinants *(Box)*.[6–8]

The etiology of HSDD can be thought of as an imbalance between excitatory factors and inhibitory factors.[9–11] Certain chemicals and hormones (eg, dopamine, oxytocin, melanocortin, vasopressin, norepinephrine) can increase a

*Although many experts prefer to use the hypoactive sexual desire disorder and HSDD nomenclature, as used in this article, DSM-5 no longer includes the term hypoactive sexual desire disorder.[2,5] Instead, disorders pertaining to low sexual desire and female arousal disorder are merged into one term: female sexual interest and arousal disorder (FSIAD). This merging into one term is not widely endorsed in the sexual health community, however, and most published research to date on distressing low sexual desire has used the term HSDD instead of the term FSIAD.

Box. Biopsychosocial model of female sexual response[6–8]

Physiologic factors
Physical health
Neurotransmitter effects
Endocrine function
Illness

Psychological factors
Performance anxiety
Depression

Sociological factors
Upbringing
Cultural norms/expectations

Contextual factors
Insufficient privacy
Safety
Emotional support

Lack of appropriate stimuli
Inadequate physical stimulation
Partner dysfunction

Interpersonal factors
Relationship discord
Lack of emotional intimacy

Interpersonal development history
Sexual, physical, or medical trauma
Distressful emotions: fear, shame, guilt

Expectation of an adverse outcome
Having a history of disappointing sex

woman's desire, arousal, and ability to have an orgasm, whereas others (eg, serotonin, opioids, endocannabinoids) do the opposite. Similarly, certain psychosocial or interpersonal factors (eg, intimacy, shared values, romance, certain experiences and/or behaviors) can heighten a woman's sexual desire and response, whereas others (eg, relationship conflict, negative stress, negative beliefs about sex, certain experiences and/or behaviors) do the reverse.

To expand on the effects of the neurotransmitters, agents such as opioids and SSRIs inhibit dopamine in the medial preoptic area (mPOA) and the prefrontal cortex, respectively, of the brain.[11] As a consequence, women who use these agents on a long-term basis may lose the beneficial effects of dopamine, which has a direct impact on the endocrine system, autonomic regulation, motivation, desire, and reward. Dopamine release in the mPOA is a general neural switch that controls sympathetic and parasympathetic blood flow in the presence of sexual cues, which then triggers sexual response. As to certain other neurotransmitters and hormones, norepinephrine enhances attention, movement, and arousal; melanocortins stimulate desire and arousal; and oxytocin promotes arousal and bonding. Scientists have recently discovered that melanocortin-stimulating hormone latches on to a receptor, causing an increased release of dopamine, which in turn can enhance a woman's receptivity to sexual cues.[12]

Sexual history taking, screening, and treatment

Readers are directed to an article[B] in the December 2019 issue of this journal that covers sexual history taking, screening, and treatment for HSDD.[13] The column "Focus on sexual health"[C] in the June 2018 issue also describes the process of care for HSDD developed by the International Society for the Study of Women's Sexual Health and includes their useful algorithm for evaluating, diagnosing, and treating female patients with distressing low sexual desire.[14]

Treatment options for HSDD

Treatment for HSDD includes nonpharmacologic options, such as psychological approaches and use of over-the-counter (OTC) supplements, and pharmacologic options.

Psychological approaches

The various psychological approaches to the treatment of HSDD address some common themes. These include relationship conflict, major life stressors, boredom, discrepant desire levels between partners, cultural/religious prohibitions and guilt, and subclinical depression, anxiety, and/or body image problems.

Sex counseling/therapy.

This approach is used for women whose chief complaint is a sexual problem. Therapy is problem focused and considers where the patient (or couple) is right now and where she, or they, want to be. Although the stated goal of sex therapy is to correct a sexual problem, this therapy may also facilitate communication between partners. Sex therapy typically includes brief, solution-focused sessions aimed at altering dysfunctional emotions, behaviors, and cognitions.

Psychotherapy.

Goals of psychotherapy are to initiate cognitive restructuring, resolve past problems that interfere with sexual function, regain confidence in one's sexual performance, reconnect to one's sensual self, surmount barriers to intimacy, resolve interpersonal issues that cause/maintain HSDD, increase communication, and minimize or prevent relapse.

Mindfulness-based therapy.

This Eastern-based therapy has been shown to be effective in improving desire.[15] A woman is encouraged to think about how her body is responding, how everything feels to her, and how her partner is responding to her.[16,17] Mindfulness may enhance sexual desire by brightening one's mood, easing anxiety, increasing self-compassion, and reducing distraction.[16]

Sensate focus.
This approach, developed by Masters and Johnson in the late 1960s, entails a series of progressive sexual exercises for individuals or couples with three main goals: to decrease avoidance/anxiety, to increase awareness of one's own and one's partner's experiences and needs, and to improve sexual function.[18] Current use of sensate focus is less formulaic and more individualized.[19]

Efficacy of these approaches.
Few randomized trials have evaluated the efficacy of these various psychotherapies. Three trials of cognitive-behavioral therapy and two trials of mindfulness-based therapy demonstrated their superiority over wait-list control status.[20] Data are insufficient, however, to establish efficacy because of multiple weaknesses in the designs of these trials, including the use of waiting-list status as a placebo condition. Nevertheless, psychotherapy in its various forms, alone or with medication therapy, is considered a useful approach for women with distressing low desire.

Over-the-counter supplements
A number of products have been tested and found effective in certain groups of women.

Oral supplements.
The daily multivitamin ArginMax contains L-arginine, ginseng, gingko, and damiana. Unlike some prescription medications on the market, it can be used by premenopausal, perimenopausal, or postmenopausal women. A double-blind, placebo-controlled study showed that premenopausal women on this daily multivitamin, versus those on placebo, reported significant improvement in their level of sexual desire, frequency of sexual desire and sexual intercourse, and satisfaction with their overall sex life.[21] Among perimenopausal women, those taking the multivitamin fared better than those on placebo in terms of frequency of intercourse, satisfaction with their sexual relationship, and vaginal dryness. Postmenopausal women receiving it, versus those receiving placebo, primarily showed an increased level of sexual desire.

The oral supplement Stronvivo contains L-arginine, L-citrulline, L-carnitine, magnesium, and zinc. In studies of premenopausal and postmenopausal women, use of the supplement resulted in significant improvements compared with baseline in all areas of sexual functioning, including desire, arousal, lubrication, orgasm, and mood.[22]

Another oral supplement is Ristela, which has been available in the United States since 2019 (and has been studied for more than 7 years in Europe). It contains pine bark extract, L-arginine, L-citrulline, and rose hips extract (PACR). Placebo-controlled studies have shown that PACR significantly improved sexual function across all domains in women of late reproductive age, perimenopausal women, and postmenopausal women.[23–25] PACR was well tolerated and caused no unwanted effects. This supplement is contraindicated in women using prescription anticoagulants.

Topical supplements.
A medical cannabis product, Pleasure, contains liquid coconut oil, tetrahydrocannabinol (THC), and other cannabinoids. Women apply 4 to 8 sprays directly onto the clitoris and labia and inside the vagina. Consumer studies are limited, but the manufacturer reports that it produces a warming sensation, mild pain relief, and increased arousal, desire, and ease of orgasm. Women who reside in states in which THC-containing products are illegal can use Awaken, which contains cannabidiol (CBD) and kava kava root.

The topical botanical preparation Zestra contains borage seed oil, evening primrose oil, angelica root, and coleus extracts. It is designed to enhance arousal and orgasm after application to the clitoris and labia (but causes a burning sensation if applied to the introitus). Double-blind, placebo-controlled studies have shown that both women with desire/interest/arousal/orgasm disorders and those with normal sexual functioning experienced improved desire, arousal, and orgasm with its use.[26]

Pharmacologic options
Two agents, flibanserin and bremelanotide (BMT), are US Food and Drug Administration (FDA)–approved to treat HSDD in premenopausal women. Bupropion is prescribed off label for this indication.

Flibanserin.
This agent is believed to act mainly on serotonin receptors in the brain. Serotonin may have a role in low desire by acting as a sexual satiety signal. Flibanserin may also produce region-specific elevations in dopamine and norepinephrine, which offset inhibitory serotonergic activity, thereby increasing desire pathways.

Efficacy and safety of flibanserin (100 mg orally at bedtime) were established in three 24-week, randomized, double-blind, placebo-controlled trials: DAISY, VIOLET, and BEGONIA.[27–29] All study participants were premenopausal (mean age, 36 years) and had HSDD for a mean duration of 5 years. In all of the trials, women taking flibanserin, versus those taking placebo, experienced greater sexual desire,

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which translated into a significantly higher number of sexually satisfying events—defined as sexual intercourse, oral sex, masturbation, or genital stimulation by the partner the woman reported as gratifying, fulfilling, satisfactory, and/or successful, irrespective of whether she had an orgasm. In addition, flibanserin recipients, versus placebo recipients, experienced a greater decrease in distress related to low sexual desire. The most common side effects of flibanserin were dizziness, somnolence, and nausea.

The flibanserin dosage is 100 mg daily at bedtime. It may take up to 4 weeks for effects of the medication to occur and 8 to 12 weeks for the full effect to occur. If a woman experiences no benefits after that time, the medication is not going to work for her and it can be discontinued. If she drinks one or two alcoholic beverages, she should wait at least 2 hours before taking her flibanserin dose for the day.[30] If she has three or more drinks, she should skip the dose that night. If she misses a dose, she should take the next dose at bedtime the next evening. Flibanserin is contraindicated in women taking moderate/strong CYP3A4 inhibitors and in those with hepatic impairment.

Bremelanotide.

BMT is a recently approved novel cyclic 7-amino acid melanocortin-receptor agonist, with high affinity for the type-4 melanocortin receptor, which is believed to be important for sexual function.[31] It is administered via an auto injector on an as-desired basis.

Efficacy and safety of BMT for HSDD were established by the RECONNECT trial.[32] Unlike the studies of flibanserin, BMT studies included women who were not heterosexual in addition to those who were heterosexual. From baseline to end of study, BMT users, relative to placebo users, experienced significant increases in sexual desire and significant reductions in distress related to low sexual desire. In both trials, BMT was associated with significant improvements in arousal, lubrication, and orgasm. BMT users experienced more nausea, flushing, and headache than did placebo users, but these adverse events were generally mild or moderate in intensity. Women who completed the core phase of the RECONNECT trial could enroll in a 52-week open-label extension.[33] Overall, they experienced sustained improvement in their HSDD symptoms. The most common treatment-emergent adverse events were nausea, flushing, and headache.

The BMT dose, administered into the abdomen or thigh with a small auto injector, is 1.75 mg/0.3 mL. Women should use no more than 1 dose per 24 hours and no more than 8 doses per month. The product does not need to be refrigerated. Although some women may hesitate to use an auto injector, 4 of 5 women who used the product reported having no trouble with it.[34]

Bupropion.

This norepinephrine–dopamine reuptake inhibitor, which is FDA approved to treat major depressive disorder and to promote smoking cessation, is believed to work by acting centrally on both dopaminergic and norepinephrine systems, with no serotonergic action.[35] Study results have indicated that bupropion is effective in treating HSDD, including HSDD secondary to SSRI use.[35–37] As a result, this agent is used off label to treat HSDD. Results of one study have suggested that use of bupropion should be coupled with psychotherapy.[38] Downsides of bupropion use are its dose-dependent risk of lowering the seizure threshold and its side-effect profile: agitation, insomnia, anxiety, mania, psychosis, weight loss, and hypertension.[39,40]

Testosterone.

Of note, the presentation at the NPWH annual conference in Savannah, Georgia, in October 2019, on which this article is based, focused primarily on the treatment of HSDD in premenopausal women. Testosterone is also commonly used off label to treat HSDD, although it is suggested for use only in postmenopausal women with HSDD and low testosterone.[41] Therefore, further discussion of testosterone for premenopausal women with HSDD is outside the scope of this article.

Four case scenarios

Sarah

Sarah, age 42 years, has been married for 18 years and has two teenage children. She works full time as a teacher and likes to run, read, and knit. She is comfortable discussing sexual concerns. She recalls having a stronger sex drive early in her relationship with her husband but reports a gradual decline in her desire over the years, which causes her distress. She also experiences decreased arousal and slightly weaker orgasms. She describes her marriage as good, with open communication. She is busy with her job, her church activities, and her children's school activities. The couple tries to make time for intimacy 3 to 4 times per month, typically on Saturday nights. This negotiated frequency suits them both, but Sarah has difficulty getting in the mood and feels as though she needs "a little jump start."

Her health history includes hypothyroidism, for which she is taking levothyroxine. She has had a bilateral tubal ligation (BTL) and has regular menses. She is well groomed and well spoken, with appropriate affect. She has no thyroid enlargement or nodules. Her vulvovaginal and pelvic exam findings are unremarkable. After reflecting on possible therapeutic options for Sarah, her HCP thinks Sarah is an ideal candidate for BMT. Sarah agrees to try it and reports that she is doing well with it at a 3-month follow-up visit.

Mackenzie

Mackenzie is a 23-year-old full-time student who has been in a long-term monogamous relationship for the past 5 years. She has been taking combination oral contraceptives (COCs) for the past 6 years. She reports that she previously had a strong sex drive, with normal arousal, lubrication, and orgasm. Four years ago, however, she began to experience vaginal dryness, loss of sex drive, and difficulty achieving orgasm. These symptoms have gradually worsened, causing her great distress. She has no sexual interest outside the relationship and reports no relationship discord.

Her health history includes heavy menses, which have improved with COC use. She is well groomed, with appropriate affect, but she is timid, anxious, tearful, and uncomfortable when discussing sexual concerns. Her physical exam findings are unremarkable. Her pelvic exam shows moderate, generalized vulvovaginal mucosal dryness but no significant tenderness. Her HCP ordered a testosterone panel to see whether the results might suggest that Mackenzie's long-term COC use might be affecting her desire for sex. (Of note, her HCP could have made this suggestion about switching from a COC to an intrauterine device [IUD] without ordering a testosterone panel first.) Mackenzie is found to have low levels of testosterone and dihydrotestosterone and an elevated level of sex hormone–binding globulin (SHBG), a common effect of long-term COC use. Mackenzie's HCP suggests that she stop taking the pill, which could be causing her HSDD, and replace it with an IUD. It is the estrogen in the COC that causes the SHBG rise. Within several months of switching from her COC to an IUD, Mackenzie's HSDD symptoms have improved.

Karen

For Karen, age 31 years, HSDD developed after giving birth to her first child and worsened 2 years later, after having her second child. She reports that she has never had a strong sex drive, although she was more receptive to sexual activity years ago. She states that her husband is highly frustrated with and unsupportive of her, and she questions his fidelity to her.

Her health history includes irritable bowel syndrome (for which she is currently on no medications because she has had no flares since prior to her pregnancy) and vaginal dryness associated with breastfeeding (treated with twice-weekly application of estradiol cream). She is well groomed but looks fatigued. She expresses great frustration about her husband's lack of understanding about her having to care for two young children and about their frequent arguments regarding sex. Her physical, vulvovaginal, and pelvic exam findings are unremarkable. She has a well-healed episiotomy site. Her HCP recommends marriage counseling as the first step, with bupropion considered as a possible pharmacotherapeutic intervention for Karen if needed. Currently, Karen and her husband are still undergoing marriage counseling.

The case scenarios illustrate that sometimes taking a woman off an offending medication is just as effective as prescribing a medication to relieve HSDD symptoms.

Marissa

Marissa, age 36 years, has undergone a BTL, is bisexual, and is in a long-term open relationship. She and her partner participate in swingers parties. She relates having always had a high sex drive, even higher than that of her past male partners. She noticed that her desire began to wane a few years ago, however, and now she thinks of sex only once a week or so and is distressed about it. In fact, she says that she feels "like an old lady."

Her health history includes depression and HSDD. She has taken various antidepressants for years, most recently, fluoxetine for the past 3 years. She is well groomed but has a flat affect and inhibited verbal communication. Her physical, vulvovaginal, and pelvic exam findings are unremarkable. Because Marissa wants to feel "ready all the time" and is likely to want to have sex more than 8 times per month, her HCP recommends flibanserin and also believes that psychotherapy might be helpful for her HSDD. Marissa has been using flibanserin for several months and reports great improvement in her sex drive.

Conclusion

The advent of the 2020s brings many therapeutic options for women with HSDD. Nondrug options include psychological approaches and OTC supplements, among others. At this point in time, two prescription medications, flibanserin and bremelanotide, are FDA approved for premenopausal women with HSDD. One antidepressant, bupropion, is used off label to treat this disorder. The case scenarios illustrate that sometimes taking a woman off an offending medication is just as effective as prescribing a medication to relieve HSDD symptoms. In every case, the therapeutic approach should be individualized. ●

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Web resources

A. npwh.org/courses/home/details/1464
B. npwomenshealthcare.com/hypoactive-sexual-desire-disorder-how-do-you-identify-it-and-treat-it/
C. npwomenshealthcare.com/implementation-hsdd-clinical-practice/