# MANAGEMENT OF HYPOACTIVE SEXUAL DESIRE DISORDER IN WOMEN: AWARENESS AND TREATMENTS


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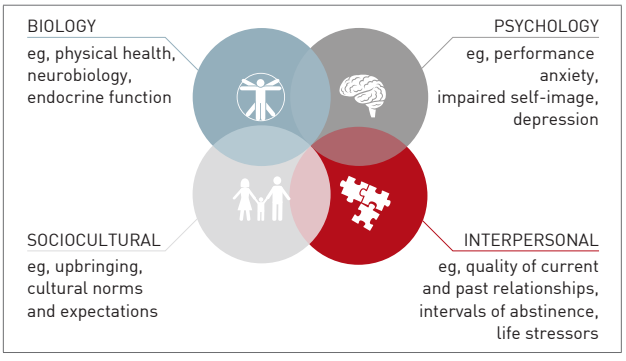
# Diagnosis of Hypoactive Sexual Desire Disorder

**Atlanta** – Hypoactive Sexual Desire Disorder (HSDD) is a condition that is estimated to affect 7% to 10% of the global population of women. Recently, there has been an evolution in thought with respect to the definition of HSDD and its classification and nomenclature. Recent revisions distinguish HSDD from other disorders of female sexual dysfunction such as female genital arousal disorder (FGAD).

## Introduction

Sexual desire and sexual response are complex, involving biological, psychological, sociocultural, and interpersonal elements (Figure 1).[1] As such, there have been various estimates of the prevalence of hypoactive sexual desire disorder (HSDD). Initial epidemiological research did not necessarily ensure that patients who reported low sexual desire also expressed distress; more recent prevalence figures do reflect the presence of this chief symptom of HSDD. There are several nomenclatures available to describe HSDD, a condition that is estimated to affect about 10% of adult women.[2]

**FIGURE 1 |** Biopsychosocial Model of Sexual Response




Adapted from Althof SE et al. *J Sex Med.* 2005 Nov;2(6):793-800; Rosen RC et al. *Obstet Gynecol Clin North Am.* 2006; 334: 515-26.

There has been an evolution in thought with regards to the definition of HSDD. It is now recognized by ISSWSH that HSDD differs from other disorders of female sexual dysfunction such as female genital arousal disorder (FGAD).

## Non-ISSWSH Classifications of HSDD

The Diagnostic and Statistical Manual of Mental Disorders (DSM) system, a classification system of the American Psychiatric Association, in its fourth classification system (DSM-IV), provides for broad sexual complaint in specific phases, such as desire or genital arousal, as well as distress not due to any known condition or substance. As an example, a woman who is post-partum and expressing a decreased sexual desire, for example, would not be diagnosed with HSDD. Rather, her decreased desire would be attributed to being post-partum.[3] The conditions that were included in this nomenclature are HSDD and female sexual arousal disorder (FSAD).

In a subsequent classification system, under the DSM-V, interest and arousal plus distress were combined under a single heading. The DSM-V combined the diagnoses of HSDD and FSAD into female sexual interest/arousal disorder (FSIAD).

The DSM-V also created a list of symptoms and required that patients have these symptoms 70% of the time in order to fit a diagnosis of HSDD. These criteria would overlook patients who have more mild or moderate degrees of HSDD, according to Dr. Anita Clayton, Chair, David C. Wilson, Professor, Psychiatry and Neurobehavioral Sciences, University of Virginia Health System, Charlottesville, Virginia.

In terms of diagnosis, "it is less useful," said Dr. Clayton. "It makes the severity criteria moot because the classification would make everyone have severe HSDD, so it makes the diagnosis very restrictive."

Limitations of the DSM-V provided an impetus for ISSWSH to create an expert consensus panel review to develop a system of diagnostic classification that would distinguish normal sexual variants from sexual function and develop nomenclature on desire disorders, arousal disorders, and orgasm disorders.

The emerging nomenclature with International Classification of Diseases (ICD)-11, which clinicians in the US use for billing codes, represents an advance

**FIGURE 2 |** Different Classifications for HSDD: DSM-V and ICD-11

| Diagnostic and Statistical Manual of Mental Disorders (DSM) -V | International Classification of Diseases (ICD)-11 |
|---|---|
| Interest and arousal plus distress were combined under a single heading - FSIAD | Represents an advance from DSM-V for classification of HSDD |
| Created a list of symptoms and required that patients have these symptoms 70% of the time to fit a HSDD diagnosis | Separates sexual conditions from mental health and obstetric-gynecologic disorders |
| Severity criteria are debatable because under the classification list, many would have severe HSDD | Outlines that HSDD is a disorder that can be experienced by both men and women |

because it separates sexual conditions from mental health and obstetric-gynecologic disorders. "Sexual conditions are in a separate section in ICD-11," said Dr. Clayton. Of note and different from the DSM-V, ICD-11 outlines that HSDD is a disorder that can be experienced by both men and women (Figure 2).[4]

## Outcomes from ISSWSH Expert Consensus Panel Review

As mentioned previously, ISSWSH created an expert consensus panel to review existing nomenclatures and to develop a new nomenclature for HSDD, amongst other objectives.

"The prior nomenclature was developed by the DSM, which means that it was for the mental health community, and we thought we had to develop something that would work for all of us," said Sue Goldstein CCRC, AASECT-CSC, IF, of Alvarado Hospital's Sexual Medicine Program, San Diego, California.

*"The prior nomenclature was developed by the DSM, which means that it was for the mental health community, and we thought we had to develop something that would work for all of us."*

Dr. Sharon Parish, Professor of Medicine, Clinical Psychiatry, Weill Cornell Medicine, New York, noted the fourth International Consultation on Sexual Medicine in 2015, from which a consensus statement aimed at refining the definitions of sexual dysfunctions in women and men emerged. ICSM 4 defined HSDD as "persistent or recurrent deficiency or absence of sexual/erotic thoughts or fantasies and desire for sexual activity."[5]

The ISSWSH nomenclature clearly differentiates between HSDD and FSAD, denoting that the former indicates a lack of motivation for sex and lack of desire coupled with distress while FSAD impairs genital response coupled with distress.[6] In contrast to HSDD, FGAD denotes an inability to develop and maintain genital arousal.[6]

One of the apparent ways in which HSDD and FGAD differ is in how the diagnosis of each condition is reached. HSDD is arrived at through an interview with the patient and tools like the Decreased Sexual Desire Screener (DSDS), which detects generalized and acquired HSDD in women, can be employed (Figure 3).[7]

FGAD is diagnosed through physical examination given questionnaires have not yet been validated for this new diagnosis, noted Dr. Andrew Goldstein, Director of the Centers for Vulvovaginal Disorders in Washington, DC and New York, NY and Clinical Professor at the George Washington University School of Medicine in Washington, DC.

As Dr. Clayton noted, an advance in ICD-11 is a separate chapter on sexual health that separates desire and arousal into distinct dysfunctions, according to Dr. Parish.

**FIGURE 3 |** Decreased Sexual Desire Screener (DSDS)

| | | Yes | No |
|---|---|---|---|
| 1. | In the past, was your level of sexual desire or interest good and satisfying to you? | ☐ | ☐ |
| 2. | Has there been a decrease in your level of sexual desire or interest? | ☐ | ☐ |
| 3. | Are you bothered by your decreased level of sexual desire or interest? | ☐ | ☐ |
| 4. | Would you like your level of sexual desire or interest to increase? | ☐ | ☐ |
| 5. | Please check all the factors that you feel may be contributing to your current decrease in sexual desire or interest: | | |
| | A. An operation, depression, injuries, or other medical condition | ☐ | ☐ |
| | B. Medications, drugs or alcohol you are currently taking | ☐ | ☐ |
| | C. Pregnancy, recent childbirth, menopausal symptoms | ☐ | ☐ |
| | D. Other sexual issues you may be having (pain, decreased arousal or orgasm) | ☐ | ☐ |
| | E. Your partner's sexual problems | ☐ | ☐ |
| | F. Dissatisfaction with your relationship or partner | ☐ | ☐ |
| | G. Stress or fatigue | ☐ | ☐ |

### Analyzing DSDS Answers

- If the patient answers "**NO**" to any of the questions **1-4**, then she does not qualify for the diagnosis of generalized acquired HSDD.
- If the patient answers "**YES**" to all of the questions **1-4**, and your review confirms "**NO**" answers to all of the factors in question **5**, then she does qualify for the diagnosis of generalized acquired HSDD.
- If the patient answers "**YES**" to all of the questions **1-4** and "**YES**" to any of the factors in question 5, then decide if the answers to question 5 indicate a primary diagnosis other than generalized acquired HSDD. Comorbid conditions such as arousal or orgasmic disorder do not rule out a concurrent diagnosis of HSDD.

Adapted from Althof SE et al. *J Sex Med.* 2005 Nov;2(6):793-800; Rosen RC et al. *Obstet Gynecol Clin North Am.* 2006; 334: 515-26.

"The separation of the two (arousal and disorder) was based on the clinical principle and similar biologic evidence used by the ICSM and ISSWSH nomenclature processes," said Dr. Parish, adding that the ICD-11 chapter on sexual health allows HSDD to be applied to either men or women.[4]

## Diagnosing HSDD Using the ISSWSH Nomenclature

The ISSWSH recommends that clinicians pose open-ended questions to arrive at a diagnosis of HSDD. Dr. Clayton stressed that clinicians need not gather intimate details of sexual activity in a patient interview. The PLISSIT technique (Permission, Limited Information, Specific Suggestions, Intensive Therapy) can be used to identify sexual concerns and initiate non-pharmacological management.[8]

The diagnosis of HSDD is arrived at mainly through clinical presentation; there are no laboratory values that can lead to a diagnosis of HSDD. It is critical for clinicians to take a sexual and reproductive history and assess if there has been sexual trauma, which may be a source of diminished desire.

It is also critical to evaluate if decreased desire is specific to the current relationship or if it is generalizable to potentially all partners. Similarly, there is a temporal aspect to sexual desire. Diminished desire may be situational and owing to daily life stressors. As an example, it may be that taking a vacation increases desire, said Dr. Clayton.[6]

Duration of symptoms has become more important to arriving at a diagnosis of HSDD. "The data support having this problem for three months or longer," said Dr. Clayton.

The significance that a patient attaches to sex in her life is also a factor in evaluating the presence of HSDD, according to Dr. Clayton.

"You want to know where people prioritize sex in their lives," said Dr. Clayton. "You want to know where they prioritized sex when they used to have a satisfactory sex life and where the priority for sex is now, that they don't have a satisfactory sex life."

Loss of desire to initiate sexual activity as well as an avoidant behaviour, such as not going to bed at the same time with a partner on an ongoing basis and/or staying up late to work, is an illustration of behaviour that would be consistent with an HSDD diagnosis, according to Dr. Clayton. Similarly, a woman might avoid kissing her partner as it may signal receptivity to sexual activity.

Dr. Parish stressed that sexual desire is not specifically event-related and that fact should be considered in the diagnosis and the management of HSDD.[6]

## Patient Input in an HSDD Diagnosis

Indeed, an important criterion for women with acquired HSDD is that they have known a stage in their life where they had sustained sexual desire and are aware they no longer have sustained sexual desire, according to Dr. James G Pfaus, Professor of Psychology, Concordia University, Montreal, Quebec.

*"HSDD as a whole should be rated by the person affected as mild, moderate, or severe. Give the person the chance to be part of the diagnosis."*

"By definition, these women have experienced healthy, adequate desire and are distressed to have lost it," said Dr. Pfaus. "HSDD as a whole should be rated by the person affected as mild, moderate, or severe. Give the person the chance to be part of the diagnosis."[6]

The motivations behind sexual desire should be considered, whether sexual desire is a wish to participate in sexual activity with a goal of physical pleasure, emotional intimacy, or other reasons. Desire can be attached to reward and desire can diminish overtime with diminishing sexual reward over time.

## Ruling Out Other Causes of Low Sexual Desire

Citing data from a meta-analysis, Dr. Clayton highlighted the bi-directional relationship that exists between depression and sexual dysfunction where the presence of depression increases the risk of sexual dysfunction and, conversely, the presence of sexual dysfunction greatly increases the risk of depression.[9]

Taking a detailed sexual history is key in a general assessment of a patient, since past sexual experience can influence a desire for sex. A myriad of other factors can contribute to decreased desire that is causing distress including physiologic co-morbidities like thyroid disease and urinary incontinence and psychiatric conditions like anxiety and depression, as well as the use of medications or substances of abuse.[10]

Women who have pain disorders would not be regarded as having HSDD. The diminished desire and/or avoidance of sex would be a consequence of the pain experienced during sex, explained Dr. Clayton.

Part of the process in arriving at a diagnosis of HSDD in a pre-menopausal woman is ruling out sexual dysfunction in the partner. There can be instances where women report having diminished

desire to compensate for sexual dysfunction, such as erectile dysfunction, on the part of her partner.

"There is an impact on the woman where she accommodates to that," explained Dr. Clayton. "She may report it as her own sexual dysfunction."

## Conclusion

According to the ISSWSH expert panel, the recent distinction between HSDD and FGAD as two discrete clinical entities, both of which are diagnoses of female sexual dysfunction, respond to a multi-disciplinary need for practical definitions that will serve various communities in healthcare including clinicians, researchers, and regulatory agencies. "This definition (of FGAD) completely excludes the central issue such as subjective arousal that was controversial and convoluted in prior definitions of FSAD. In so doing, it strengthens both the new definition of FGAD as well as the definition of HSDD," said Dr. Goldstein. ●

## References

1. Althof SE, Leiblum SR, Chevret-Measson M, et al. Psychological and interpersonal dimension of sexual function and dysfunction. *J Sex Med.* 2005 Nov;2(6):793-800.
2. Goldstein I, Kim NN, Clayton AH, et al. Hypoactive Sexual Desire Disorder: International Society for the Study of Women's Sexual Health (ISSWSH) Expert Consensus Panel Review. *Mayo Clin Proc.* 2017 Jan;92(1):114-128.
3. DeJudicibus MA, McCabe MP. Psychological factors and the sexuality of pregnant and postpartum women. *The Journal of Sex Research.* 2002 May;39(2):94-103.
4. Reed GM, Drescher J, Krueger RB, et al. *World Psychiatry.* 2016 Oct;15(3):205-221.
5. McCabe MP, Sharlip ID, Atalla E, et al. Definitions of Sexual Dysfunctions in Women and Men: A Consensus Statement from the Fourth International Consultation on Sexual Medicine 2015. *J Sex Med.* 2016 Feb;13(2):135-43.
6. Parish SJ, Goldstein AT, Goldstein SW, et al. Toward a More Evidence-Based Nosology and Nomenclature for Female Sexual Dysfunctions-Part II. *J Sex Med.* 2016 Dec;13(12)1888-1906.
7. Clayton AH, Goldfischer ER, Goldstein I, Derogatis L, Lewis-D'Agostino DJ, Pyke R. Validation of the decreased sexual desire screener (DSDS) *J Sex Med.* 2009 Mar;6(3):730-8
8. Frank JE, Mistretta P, Will J. Diagnosis and treatment of female sexual dysfunction. *Am Fam Physician.* 2008 Mar 1;77(5):635-42.
9. Atlantis E, Sullivan T. Bidirectional association between depression and sexual dysfunction: a systematic review and meta-analysis. *J Sex Med.* 2012 Jun;9(6):1497-507.
10. McCabe MP, Sharlip ID, Lewis R, et al. Risk Factors for Sexual Dysfunction Among Women and Men: A Consensus Statement From the Fourth International Consultation on Sexual Medicine 2015. *J Sex Med.* 2016 Feb;13(2):153-67

Guest Editor

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# Treatments – Psychology

Data presented at the
*International Society for the Study of Women's Sexual Health (ISSWSH) Annual Meeting*
February 23-26, 2017, Atlanta, Georgia
and reviewed by Dr. Lori Brotto, Vancouver, BC

**Atlanta** – Hypoactive Sexual Desire Disorder is a condition that is estimated to affect 10% of adult women.[1] Psychological treatments like cognitive behavioral therapy and mindfulness can be employed to treat these women. Clinicians need to recognize cultural or religious factors that influence the patient, as well as mental health conditions that may need to be addressed in women who present with reduced sexual desire.

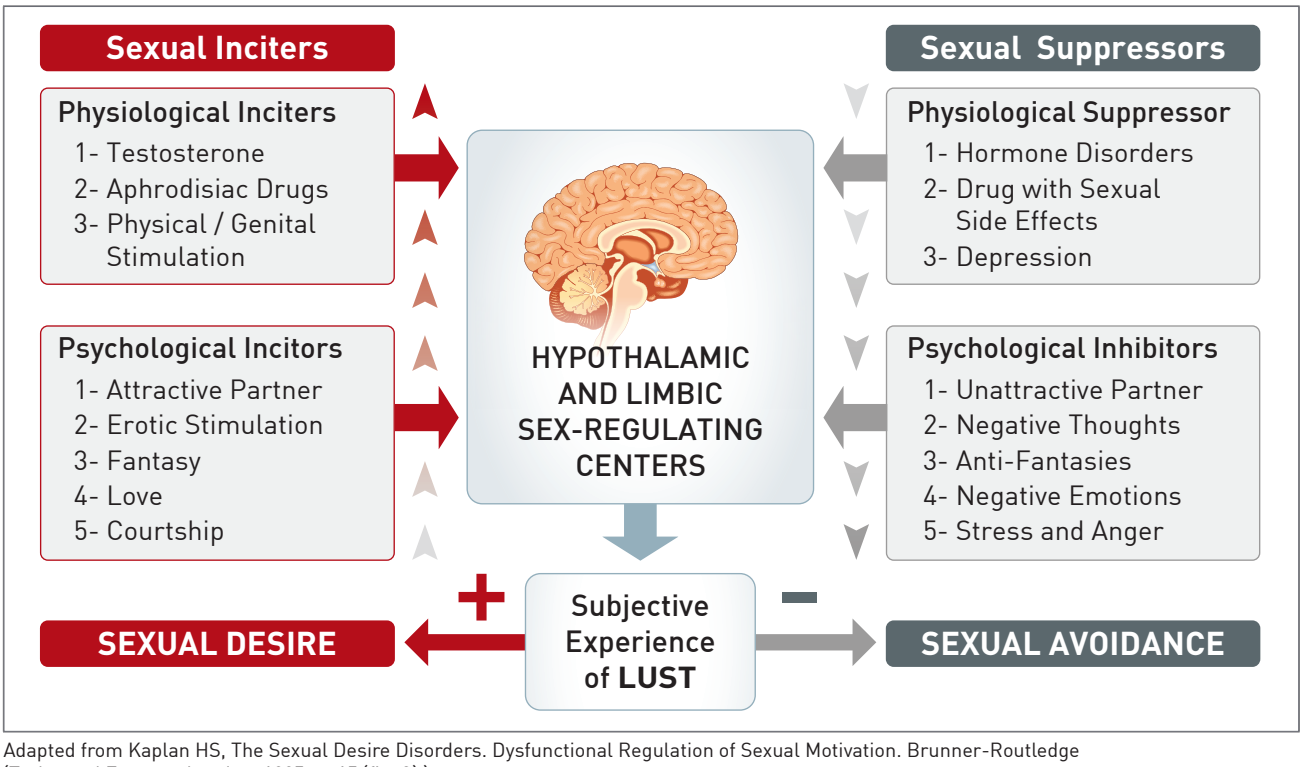
## Introduction

As mentioned in Chapter 1, a complex interplay of biopsychosocial and cultural factors influence sexual desire.[2] Although the Diagnostic and statistical manual of mental disorders (DSM-5) replaced hypoactive sexual desire disorder (HSDD) with sexual interest/arousal disorder (SIAD) in 2013,[3] there are no validated instruments available to make a diagnosis of SIAD at the present time. A diagnosis of HSDD can be made using a variety of instruments. The Decreased Sexual Desire Screener,[4] which can identify generalized and acquired HSDD in women, is a validated tool to detect persistent loss of sexual desire marked by personal distress.

## The Impact of Low Desire

Diminished sexual desire is the most frequent sexual complaint that women have.[6,1] There is no one cause for reduced sexual desire. Research suggests that sexual response, and by extension sexual problems, can arise from an imbalance of excitatory and inhibitory neurobiological pathways regulating the sexual response in mammals, known as the Dual Control Model.[7] Helen Singer Kaplan, a pioneer in the field of sex therapy, depicted this as sexual inciters and sexual suppressors (Figure 1). Dr. Michael Perelman, Co-director, Human Sexuality Program, Clinical Emeritus Professor of Psychiatry, Reproductive Medicine

**FIGURE 1 |** Dual Control Elements of Human Sexual Motivation: A Psychosomatic Model




Adapted from Kaplan HS, The Sexual Desire Disorders. Dysfunctional Regulation of Sexual Motivation. Brunner-Routledge (Taylor and Frances, London, 1995: p. 15 (fig. 2) )

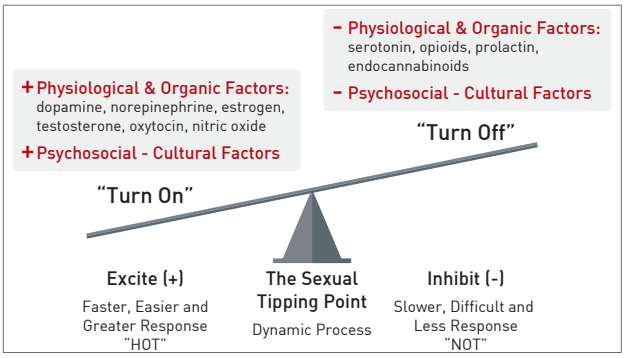
Some of the challenges that clinicians face when making a diagnosis of HSDD or SIAD can include separating other commonly co-occurring conditions (such as stress, anxiety, or depression from reduced desire[5]) or identifying life experiences (such as past sexual trauma, or pinpointing cultural beliefs) that can affect sexual desire.[5] It may be necessary to treat co-occurring conditions to effectively improve women's low or absent sexual desire. Often, psychological interventions, such as cognitive behavioral therapy (CBT) or mindfulness-based therapy can be implemented to address both long-standing reduced sexual desire that causes personal distress or a fairly new phenomenon of decreased sexual desire that causes personal distress, as well as these psychological comorbidities.

and Urology, Weill Cornell Medicine, New York, has depicted this imbalance in the Sexual Tipping Point® model,[8] which puts forth that positive physical and mental factors increase sexual response while negative physical and mental factors inhibit sexual response. Speaking at an instructional course on psychological approaches to female sexual dysfunction at this year's ISSWSH, Dr. Perelman has suggested that an integrated method can address the etiology and management of female sexual dysfunction (Figure 2).[8]

Diminished desire can affect a woman's sense of self, according to Dr. Sheryl Kingsberg, Chief, Division of Behavioral Medicine, Department of Obstetrics and Gynecology, University Hospitals Cleveland Medical Center, Ohio. "Women who have

a loss of desire are much more negative in many aspects of their lives," explained Dr. Kingsberg. "HSDD has a downstream effect on how women see themselves."

**FIGURE 2 |** The Sexual Tipping Point: Excitation vs. Inhibition




Adapted from Perelman, MA. *J Sex Med.* 2006 Nov;3(6):1004-12. Perelman, MA. *J Sex Med.* 2009 Mar;6(3):629-31. Pfaus JG. *J Sex Med.* 2009 Jun;6(6):1506-1533.

Indeed, findings from a survey that Dr. Kingsberg conducted support the contention that HSDD has "a reach far outside the bedroom". The survey, based on 450 women aged 20 to 60, found more than 70% of women attributed negative impacts on body image and self-confidence.[9] Interestingly, respondents to the survey did not view distressing reduced sexual desire as a medical condition that could be treated and did not report their reduced sexual desire to their healthcare providers.[9]

The findings from the survey also suggest that healthcare providers may need to introduce the topic of sexual functioning and sexual desire in their interaction with their patients, since patients may not raise the topic of their decreased desire without being prompted to do so. The PLISSIT model outlines possible ideas for office-based counseling and education, and suggests that primary care physicians with even limited training in sexual health should, at a minimum, give their patients permission to discuss sexual concerns, and provide *limited information* such as accurate information about the nature of sexual response and common predictors of sexual problems.[10]

Of note, there is scant literature examining the frequency of HSDD in women in same-sex relationships or women seeking same-sex intimate interactions. There is also the possibility that with psychotherapy, a woman may come to realize that she is no longer attracted to men and that she has sexual desire and attraction for other women, noted Dr. Althof.

There remains a need for exploration of psychological treatments within the framework of clinical studies to provide robust data on the efficacy of psychological interventions and to identify predictors of success that will permit clinicians to better match specific psychological therapies to the needs of women seeking treatment for low or absent sexual desire.

*"HSDD has a downstream effect on how women see themselves."*

## The Patient Interview

It is paramount that clinicians conduct a thorough patient interview to try and identify all the possible factors that may be contributing to decreased desire *or* to evaluate whether diminished desire has given rise to other conditions, including poor body image and decreased self-confidence.

By asking a series of focused questions and taking a quick sex status,[11] a healthcare provider can determine what factors are affecting sexual desire, according to Dr. Perelman. He spoke recently at ISSWSH about the value of taking a sex status, noting one of the key components of taking a sex status is asking about a patient's last sexual experience and aspects of that experience.

At this year's ISSWSH, Dr. Perelman gave an example of an interaction with a patient in which deep-seated cultural beliefs can affect a woman's sexual desire. If a woman is ultra-Orthodox Jewish, for instance, a psychotherapist may have to reach out to a religious authority, such as a rabbi, who would grant permission for a couple to be exposed to sources of eroticism in an effort to stimulate desire and have the couple enjoy a mutually-satisfying sexual experience.

Among the many different physical contributors to low sexual desire is pelvic floor dysfunction. For example, a woman's pelvic floor tightness associated with a fear of penetration may lead her to eventually lose desire for sex[12] and, in such cases, pelvic floor physiotherapy to address the pelvic floor tone, combined with psychosocial approaches to address the anxiety, may be necessary in order to improve the woman's sexual desire.

Depression is a very common condition, and research has found considerable comorbidity between reduced desire and major depressive disorder.[13] Each condition can ultimately worsen the other. Furthermore, there may be a negative impact of anti-depressant medication on sexual response.[13] It is vital that clinicians keep the relationship between depression and sexual function top of mind when assessing a woman presenting with low or absent sexual desire. Mindfulness has been an approach that has demonstrated success in treating depressed mood in women with low sexual interest.[14]

The patient interview may serve as an opportunity to investigate relationship dynamics and how they are affecting sexual desire and sexual functioning in a way that brief screeners cannot. Reduced sexual desire can be the result of an unsatisfying relationship or decreased sexual desire can result in partner avoidance in addition to hostility and antagonism in a relationship. Communication skills training may be a helpful strategy to improve intimacy and may prove to have a positive impact on sexual desire.

## Sex Therapy

Several types of psychological interventions can be initiated to address low or absent sexual desire, noted Dr. Stanley Althof, Professor Emeritus of Psychology in the Department of Psychiatry at Case Western Reserve University School of Medicine in Cleveland, Ohio, and Executive Director of the Center for Marital and Sexual Health of South Florida in West Palm Beach, Florida, addressing attendees at an instructional course on psychological approaches to female sexual dysfunction at this year's ISSWSH. One of the most long-standing psychological approaches is sex therapy, which targets issues such as sexual desire, arousal, orgasm, and pain. It can be conducted on an individual basis, between a couple, or in a group setting, and typically lasts for a finite amount of time (e.g., three months with weekly sessions). Sex therapy can consist of exercises such as sensate focus, which includes non-demand sensual touching designed to enhance sexual desire in a gradual manner and decrease the avoidance of sexual activity.[15]

"Sensate focus is a way of having couples touch each other and give each other feedback about what is pleasurable and what is not," explained Dr. Althof, in an interview following the instructional course. "They can engage in this practice at home. The idea is to not focus on intercourse but to have a woman not feel anxiety about sex."

## Cognitive Behavioral Therapy (CBT)

One of the objectives of CBT is to pinpoint behavior and thoughts (cognitions) that are contributing to decreased sexual desire, and eliciting negative emotions which further drive the unhelpful behaviors and maladaptive thoughts (Figure 3). A core aspect of CBT involves using a journal or diary to track negative sex-related encounters, and identify the specific thoughts the woman experienced in that situation. Then, using a technique called cognitive restructuring, she is invited to evaluate the evidence for and against that thought, and to consider revising it to a more accurate and adaptive thought. As a result of adjusting maladaptive thoughts, CBT predicts that behavior and emotions improve as a result. CBT can also include an educational component, and involves informing a woman, or both a woman and her sexual partner, about using adequate erotic and physical stimulation to heighten sexual desire

**FIGURE 3 |** A Sample of the Reasons/motivations provided for why Humans have Sex

| POSITIVE reasons for sex | NEGATIVE reasons for sex |
|---|---|
| 1. I feel attracted to the person. | 1. I feel embarrassed, ashamed and inadequate. |
| 2. I want to experience physical pleasure. | 2. I can't satisfy my partner, so I won't try. |
| 3. It feels good. | 3. It's all my partner's fault. |
| 4. I want to show my affection for my partner. | 4. If we kiss, my partner might expect sex. |
| 5. I want to express my love. | 5. My partner might leave me. |
| 6. I feel sexually aroused and want the release. | 6. This would not happen with someone else. |
| 7. I feel horny. | 7. I'm not a real woman anymore. |
| 8. It's fun. | |
| 9. I am in love. | |
| 10. I love being swept up by the moment. | |
| 11. I wanted to please my partner. | |
| 12. I want the closeness/intimacy. | |
| 13. I want the pure pleasure. | |
| 14. I want an orgasm. | |
| 15. This is exciting. | |
| 16. I wanted to feel connected to the person. | |
| 17. The person's physical appearance turned me on. | |
| 18. Love this setting. | |
| 19. This person really desires me. | |
| 20. This person makes me feel sexy. | |

Adapted from Meston, CM and Buss, DM. *Arch Sex Behav.* 2007 Aug;36(4):477-507.

and arousal. From a CBT perspective, when the feelings of sexual arousal improve, then associated thoughts and behaviors are also affected.

## Mindfulness

Because of the widespread prevalence of cognitive distraction during sexual activity, as well as the vast number of negative and judgmental thoughts that women have about themselves and about sex, mindfulness has arisen as a possible strategy to improve sexual desire. Mindfulness is defined as present moment, non-judgmental, awareness.[16] Mindfulness aims to teach the woman skills in remaining focused on a particular target, such as bodily sensations, the breath, and sounds, and to notice but not get caught up in the contents of negative thoughts. There is evidence that mindfulness can strengthen the connection between genital and subjective arousal and therefore improve sexual arousal concordance.[17] A number of studies found four sessions of group mindfulness-based therapy to improve sexual desire.[18] More recently, however, experts have turned exclusively to 8-session group mindfulness programs, as they simulate the standardized protocols used for individuals with chronic pain, anxiety, and depression. One study found this 8-session group mindfulness-based program, which included mindfulness exercises conducted at home, produced improvements in sexual desire, overall sexual function, and sex-related distress, regardless of the duration of decreased desire.[14]

One of the benefits that has been observed through using mindfulness is potential improvements in the regulation of attention, emotion, and self-awareness. Indeed, there is evidence suggesting that the practice of mindfulness can lead to neuroplastic alterations in the structure and function of the brain areas that are linked to the regulation of attention, emotion, and self-awareness.[18]

"There can be a high level of distractibility," explained Dr. Althof, speaking in an interview at this year's ISSWSH. "A woman may be pre-occupied with her work, may be thinking about taking care of her kids or a sick parent, and may be thinking about all the things she has scheduled in her life."

Dr. Kingsberg said many women with HSDD are aware that sexual activity can offer pleasure but no longer have a motivation to seek out this pleasure on an ongoing basis. "There is a lack of wanting," she said, agreeing with Dr. Althof that CBT and/or mindfulness can assist women to focus on what is relevant to a sexual encounter and ignore elements that distract from sexual interaction.

Part of a therapeutic recommendation may include requesting that a partner avoid making any demands for sexual intercourse, so that a woman does not feel ongoing pressure to have regular intercourse in daily life, explained Dr. Althof.

## The Widespread Application of CBT and Mindfulness

Psychological treatments such as CBT and mindfulness are appropriate for women who have decreased desire that is causing them distress after specific medical therapy.[2]

The feasibility of mindfulness-based programs to improve sexual desire and decrease sexual desire, amongst other outcomes, in women with cervical and endometrial cancer has been studied. Brief sessions involving a combination of education, CBT, and mindfulness were found to be able to achieve those outcomes.[19] Online, unidirectional adaptations of these programs similarly offer benefit for women cancer survivors in terms of decreasing sex-related distress and improving mood and sexual function.[20] A systematic review of the medical literature supports psychological interventions to address sexual difficulties subsequent to cancer treatment.[21]

## Conclusion

Psychotherapy and specific strategies such as mindfulness and CBT have been studied in various populations of women who have expressed reduced sexual desire causing personal distress with outcomes showing varying degrees of success, including significant improvements in sexual desire and sexual response. An advantage of a psychological treatment approach is that it does not pose a risk of adverse events, and is often far more cost-effective to the approved sexual pharmaceuticals to treat low desire. Psychological treatments can be initiated across populations of women who have low desire regardless of the etiology of those concerns. Moreover, they can simultaneously address and improve other common psychological comorbidities such as stress, anxiety, low mood, and body image concerns. ●

## References

1. Mitchell KR, Mercer CH, Ploubidis GB, Jones KG, et al. Sexual function in Britain: findings from the third National Survey of Sexual Attitudes and Lifestyles (Natsal-3). *Lancet.* 2013 Nov 30;382(9907):1817-29.
2. Brotto L, Atallah S, Johnson-Agbakwu C, et al. Psychological and interpersonal dimensions of sexual function and dysfunction. *J Sex Med.* 2016 Apr;13(3):538-71
3. American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Washington, DC. Author.
4. Clayton AH, Goldfischer ER, Goldstein I, Derogatis L, Lewis-D'Agostino DJ, Pyke R. Validation of the decreased sexual desire screener (DSDS). *J Sex Med.* 2009 Mar;6(3):730-8.
5. McCabe MP, Sharlip ID, Lewis R, et al. Risk factors for Sexual Dysfunction Among Women and Men: A Consensus Statement from the Fourth International Consultation on Sexual Medicine 2015. *J Sex Med.* 2016 Feb:13 (2):153-167.
6. Shifren JL, Monz BU, Russo PA, Segreti A, Johannes CB. Sexual problems and distress in United States women: prevalence and correlates. *Obstet Gynecol.* 2008 Nov;112(5):970-8.
7. Bancroft J, Graham CA, Janssen E, Sanders SA. The dual control model: current status and future directions. *J Sex Res.* 2009 Mar-Jun;46(2-3):121-42.
8. Perelman MA. The sexual tipping point: a mind/body model for sexual medicine. *J Sex Med.* 2009 Mar;6(3):629-32.
9. Kingsberg SA. Attitudinal survey of women living with low sexual desire. *J Women's Health (Larchmt).* 2014 Oct;23(10):817-23.
10. Annon JS. The PLISSIT Model: A Proposed Conceptual Scheme for the Behavioral Treatment of Sexual Problems. *J Sex Ed & Ther.* 1976;2(1):1-15.
11. Perelman MA. Sex coaching for physicians: combination treatment for patient and partner. *Int J Impot Res.* 2003 Oct; 15 Suppl 5: S67-74.
12. Li-Yun-Fong RJ, Larouche M, Hyakutake M, et al. Is Pelvic Floor Dysfunction an Independent Threat to Sexual Function? A Cross-Sectional Study in Women with Pelvic Floor Dysfunction. *J Sex Med.* 2017 Feb;14(2):226-237.
13. Atlantis E, Sullivan T. Bidirectional association between depression and sexual dysfunction: a systematic review and meta-analysis. *J Sex Med.* 2012 Jun;9(6):1497-507.
14. Paterson LQ, Handy AB, Brotto LA. A pilot study of Eight-Session Mindfulness-Based Cognitive Therapy Adapted for Women's Sexual Interest/Arousal Disorder. *J Sex Res.* 2016 Aug 15:1-12.
15. Althof SE. Sex therapy and combined (sex and medical) therapy. *J Sex Med.* 2011 Jun;8(6):1827-8.
16. Bishop SR, Lau M, Shapiro S, et al. Mindfulness: A proposed operational definition. *Clinical Psychology Science and Practice.* 2004;11(3):230-241.
17. Brotto LA, Chivers ML, Millman RD, Albert A. Mindfulness-Based Sex Therapy Improves Genital-Subjective Arousal Concordance in Women With Sexual Desire. *Arch Sex Behav.* 2016 Nov;45(8):1907-1921.
18. Brotto LA, Goldmeier D. Mindfulness Interventions for Treating Sexual Dysfunctions: The Gentle Science of Finding Focus in a Multitask World. *J Sex Med.* 2015 Aug;12(8):1687-9.
19. Brotto LA, Heiman JR, Goff B, et al. A psychoeducational intervention for sexual dysfunction in women with gynecologic cancer. *Arch Sex Behav.* 2008 Apr;37(2):317-29.
20. Brotto LA, Dunkley CR, Breckon E, et al. Integrating Quantitative and Qualitative Methods to Evaluate an Online Psychoeducational Program for Sexual Difficulties in Colorectal and Gynecologic Cancer Survivors. *J Sex Marital Ther.* 2016 Sep 3:1-18.
21. Brotto LA, Yule M, Breckon E. Psychological interventions for the sexual sequelae of cancer: a review of the literature. *J Cancer Surviv.* 2010 Dec;4(4):346-60.

Guest Editor

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# Treatments – Pharmacology

**Atlanta** – Hypoactive sexual desire disorder (HSDD) is estimated to affect about one in every 10 adult women[1]. Several promising pharmacotherapies for HSDD are currently in clinical trials as adjuncts to traditional sex therapy. These include hormonal treatments and agents that target the central nervous system (CNS) to increase sexual excitation or decrease sexual inhibition in specific centers of the brain that are crucial for sexual desire. These novel pharmacological agents are new tools in a more comprehensive and patient-oriented approach to the treatment of HSDD.

## Introduction

A comprehensive clinical intake interview, along with instruments such as the Decreased Sexual Desire Screener,[2] are key in identifying HSDD, a condition that can be treated with psychological interventions, with pharmacological interventions, or with a combination of both. Recently, novel agents are emerging that respond to the neurobiology and mechanisms that lie behind decreased desire. Specifically, therapies that target the CNS and areas of the brain such as the pre-frontal cortex, the locus coeruleus, ventral tegmental area, and medial preoptic area of the hypothalamus, have demonstrated efficacy in the clinical trial setting and at least one therapy that acts on the CNS, flibanserin has been approved by the US Food and Drug Administration and is currently under review at Health Canada.[3] Bremelanotide and others still under investigation, all of which act on the CNS and modulate pathways in the brain crucial for sexual desire, are expected to be available in the future for both pre- and post-menopausal women. This will create more choice and a greater ability for clinicians to tailor their strategies to meet the individual needs of all women with HSDD.

## History of Pharmacotherapy Use in HSDD

In the absence of any pharmacotherapy indicated to treat HSDD, clinicians have had to use off-label therapies that are not indicated for the treatment of HSDD such as testosterone, a hormonal treatment that has offered benefits but also raised concerns about long-term safety, though to a lesser extent with transdermal delivery.[4] Buspirone, a 5-$HT_{1A}$ partial agonist indicated to treat generalized anxiety disorder, has found some success in the management of HSDD[5], as has bupropion[6], a norepinephrine-dopamine reuptake inhibitor used to treat depression and prescribed for smoking cessation. Both of these off-label therapies are acting on the CNS but neither alone has been studied specifically for the purpose of treating HSDD. Furthermore, there are no safety data specific to the use of bupropion and buspirone in the management of women who have HSDD.

## The Basis for CNS-acting Therapies to Treat HSDD

The dilemma of decreased desire is a "network problem" in the brain, according to Dr. Irwin Goldstein, Clinical Professor of Surgery, University of California at San Diego School of Medicine, Director, Sexual Medicine, Alvarado Hospital-San Diego, and Director, San Diego Sexual Medicine, California.

The pathways involved in sexual desire feature key excitatory neurotransmitters that are integral to the excitatory systems in the brain including dopamine, melanocortins, oxytocin, vasopressin, and norepinephrine. These transmitters act on neural pathways in the hypothalamus, limbic system, and cortex. In contrast to sexual excitation, the key neurotransmitters involved in the pathways of sexual inhibition include opioids and serotonin (5-HT). The inhibitory systems can dull the excitatory systems so that sexual excitation in response to competent sexual stimuli fails to be activated.[1]

"We are dealing with poorly-excited and/or highly-inhibited women," explained Dr. Goldstein, describing patients who have HSDD. "What allows you to be excited is not activated, and what allows you to be inhibited is activated too much. It is a network problem (in the brain) and we can manipulate it to our advantage and help some of our patients."

Images of the brains of women with HSDD and those of healthy controls clearly differ, as evidenced by images captured with functional magnetic resonance imaging in one investigation.[7] Women with no history of sexual dysfunction were compared to women with HSDD in terms of their responses to viewing erotic videos, sports, and relaxing images. Women with HSDD had greater activation in the medial frontal gyrus, right inferior front gyrus, and bilateral putamen. Investigators concluded there were differences between women without and those with HSDD in encoding arousal stimuli, retrieval of past erotic experiences, or both.[7]

"In women who do not have pathology, their brains light up when exposed to sexual stimuli," said Dr. Goldstein. "Women (with HSDD) will not have things light up (in the brain) at appropriate times."

Furthermore, in another study, where women with HSDD were exposed to two different levels of erotic film segments (high and low) and neutral movies, investigators found women with HSDD experienced diminished left-sided de-activation in the area of the brain that deals with multi-tasking coupled with less right-sided brain activation or more brain de-activation in the medial orbito-frontal cortex.[8]

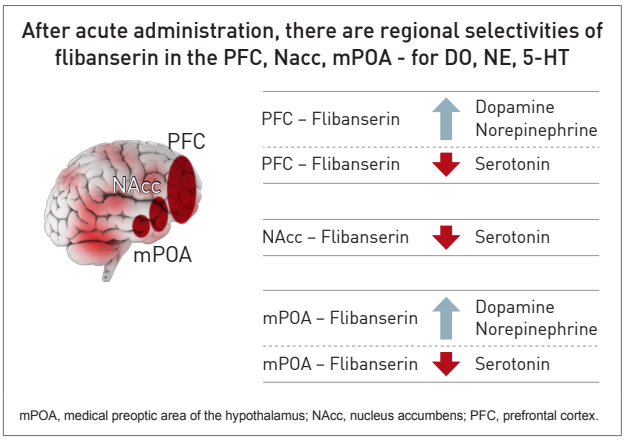
"Sex is about turning off the multi-task areas in the brain," said Dr. Goldstein. "You have to be able to de-activate the things that compete in the brain. You can't be thinking about the laundry, getting food ready, the children, and finances."

## Pharmacotherapies for HSDD

### *Flibanserin*

A therapy like flibanserin regulates activation of the prefrontal cortex so that it activates less and therefore does not permit multi-tasking of the brain and distractibility in a sexual encounter, explained Dr. Goldstein. "This is about networks in the brain," said Dr. Goldstein. "It is not about magic." (Figure 1)[9]

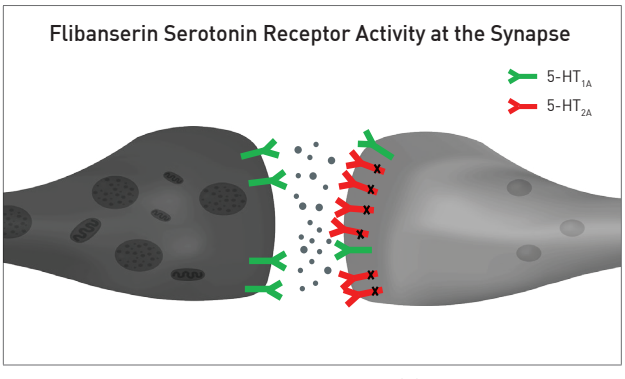
**FIGURE 1 |** Regional Selectivity: Effects on Dopamine, Norepinephrine and Serotonin




Adapted from Stahl SM, et al. *J Sex Med*. 2011;8:15–27

The mechanism of action of flibanserin in the treatment of HSDD is thought to begin with its actions on serotonin receptors in the brain. More specifically, this agent inhibits the release of serotonin by binding to 5-$HT_{1A}$ autoreceptors while simultaneously blocking the post-synaptic action of serotonin on 5-$HT_{2A}$ receptors (Figure 2).[10] Subsequently, these combined actions increase hypothalamic and mesolimbic dopamine transmission, while inhibiting serotonin's ability to activate sexual inhibition in the prefrontal cortex.

**FIGURE 2 |** Serotonin Receptor Binding in the Brain



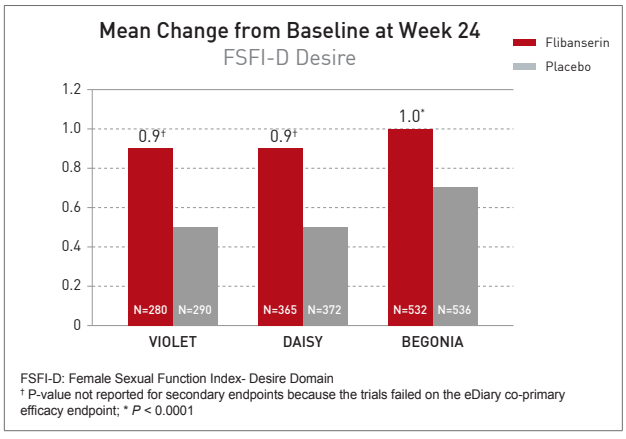

Adapted from Pfaus JG. *Cell*. 2015 Oct 22;163(3):533.

Three randomized, double-blind, placebo-controlled trials, known as DAISY, VIOLET and BEGONIA, enrolled premenopausal women and compared the efficacy and safety of flibanserin to placebo. Investigators concluded flibanserin was superior to placebo on numerous measures.[11, 12, 13]

In the DAISY study, 100mg of flibanserin, taken once daily, produced statistically significant improvements over placebo in satisfying sexual events (SSEs), sexual desire, as measured by the Female Sexual Function Index (FSFI) desire domain score, sexual function, and decreased sexual distress, as measured by Female Sexual Distress Scale-Revised (FSDS-R) total score and FSDS-R Item 13.[11]

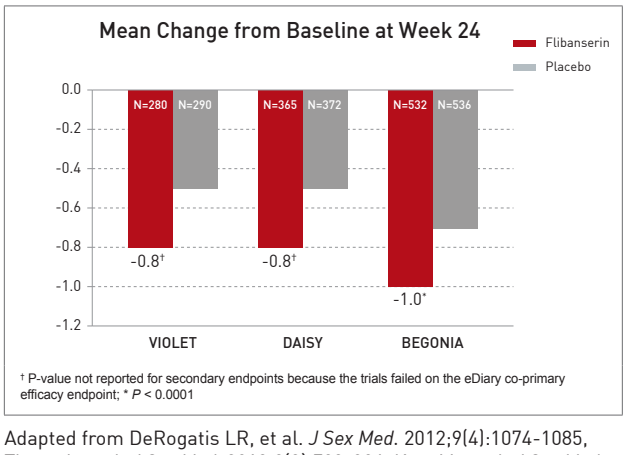
Similarly, in the VIOLET study, 100mg of flibanserin daily produced statistically significant increases in SSEs. FSFI desire domain and total scores increased in a statistically significant fashion, and FSDS-R and FSDS-R Item 13 fell in a statistically significant way.[12] Data from the BEGONIA trial were consistent with those from the other two studies: Compared to placebo, flibanserin produced significant improvements in the number of SSEs and sexual desire, as measured by FSFI desire domain score, and decreased distress associated with sexual dysfunction and low sexual desire, specifically on the FSDS-R total score and FSDS-R Item 13 (Figures 3 and 4).[13]

**FIGURE 3 |** VIOLET, DAISY and BEGONIA trials: Consistent Improvement in Sexual Desire




Adapted from DeRogatis LR, et al. *J Sex Med*. 2012;9(4):1074-1085, Thorp J, et al. *J Sex Med*. 2012;9(3):793-804, Katz M, et al. *J Sex Med*. 2013;10(7):1807-1815.

**FIGURE 4 |** VIOLET, DAISY and BEGONIA trials: Decrease in Distress




Adapted from DeRogatis LR, et al. *J Sex Med*. 2012;9(4):1074-1085, Thorp J, et al. *J Sex Med*. 2012;9(3):793-804, Katz M, et al. *J Sex Med*. 2013;10(7):1807-1815.

Flibanserin did not produce any major safety concerns, with documented adverse events including dizziness, nausea, insomnia, somnolence, and anxiety. It is important to note that alcohol is contraindicated with the use of flibanserin because of the risks of hypotension or syncope early in the treatment.

A post-hoc analysis of data originating from VIOLET, DAISY, and BEGONIA presented at ISSWSH found the rate of treatment response was 74.4% to 82.2% in premenopausal women with HSDD and that the median time to response was about two months.

"It suggests short-term treatment is adequate to know whether it will work or not in patients," said Dr. James A. Simon, CCD, NCMP, FACOG, Clinical Professor of Reproductive Endocrinology and Infertility, and Obstetrics and Gynecology at the George Washington University School of Medicine, Washington, DC, who presented the post-hoc analysis data at this year's ISSWSH. "Further, it is recommended that it be discontinued if the patient does not see improvement in her symptoms after eight weeks."

In the real-world setting, however, it would be at the discretion of the patient and the clinician that a patient remains on therapy beyond eight weeks if they are expectant of an onset of response to flibanserin, said Dr. Simon, responding to questions about the data and anecdotal evidence that women have experienced time to response beyond two months.

*Bremelanotide*

Another therapy targeting the CNS is bremelanotide, a melanocortin receptor 4-agonist that is administered subcutaneously with an auto-injector on an as-needed basis for HSDD treatment[14]. The RECONNECT study, which combined two Phase III, multi-center trials, looked at the efficacy and safety of bremelanotide as a treatment for premenopausal women with HSDD.

Data from the two trials demonstrated that women who received bremelanotide compared to those given placebo, fared significantly better on endpoints such as the FSFI-Desire, $P<0.0001$ for both studies, and the Female Sexual Distress Scale-Desire-Arousal/Orgasm Item 13 scores, $P<0.0001$ for one study and $P=0.0007$ in the second study.

Patients also supplied their own impressions of their experiences with the injectable therapy. Patients were asked to respond to this question, using a 7-point Likert scale: "To what extent do you think you benefited from taking the study drug?" Responders were described as having a self-assessed benefit score of 5 or more. A total of 59% of subjects in the first trial were considered responders, and a total of 58% in the second trial were considered responders.

Secondary outcomes were also recorded in the two trials of the RECONNECT study. Dr. Leonard DeRogatis, Director of the Maryland Center for Sexual Health in Baltimore, Maryland, presented data on bremelanotide at ISSWSH, showing that it was linked to significant improvements in FSFI total, arousal, lubrication, orgasm, and satisfaction domain scores, all of which measured $P\leq0.01$.

## The Impact of Therapy in a Sample of Patients

A thematic analysis recently presented at ISSWSH of a small sample of women, both premenopausal and postmenopausal, who had been prescribed flibanserin indicated they experienced both sexual and non-sexual changes with the medication, according to Sue Goldstein CCRC, AASECT-CSC, IF, Manager of the Clinical Research Division and Educational Programming at San Diego Sexual Medicine, California.

Patients were not asked specific questions, but instead were asked what their experience had been with flibanserin. A total of 23 patients who had been on flibanserin found they experienced improvements in libido, orgasm intensity, as well as initiation of sexual activity and receptivity to sexual activity. Some respondents also identified non-sexual impacts on their lives such as feeling happy and feeling decreased stress and anxiety.

"While on the medication, they were feeling like sexual beings and feeling energetic," noted Goldstein, although she emphasized that the analysis had several limitations, including no specific study protocol and a small number of patients.

## HSDD Therapies under Investigation

Other agents are currently being investigated for the management of HSDD in premenopausal women, and are designed to be taken on an on-demand basis. These novel therapies include an agent whose active ingredients are testosterone and the phosphodiesterase inhibitor-5 sildenafil (which is used to treat erectile dysfunction in men).The testosterone component is designed to elevate brain sensitivity to sexual cues, with the sildenafil component designed to increase genital sexual arousal.[15] Another agent under study for HSDD contains testosterone and the 5-$HT_{1A}$ agonist buspirone[16]. It increases the brain's sensitivity to sexual cues through testosterone but suppresses inhibitory mechanisms in the prefrontal cortex via buspirone. Still another experimental therapy for HSDD is a combination of the anti-anxiety medication trazodone and the anti-depressant medication bupropion.[17] The combination is thought to make the movement between states of sexual excitation and inhibition more labile, giving the patient more ability to activate sexual excitation in appropriate and desired circumstances.

## Conclusion

For women with HSDD, there are reasons to be optimistic. Indeed, the therapeutic picture looks bright. There is now flibanserin, the commercial availability of bremelanotide is imminent, and other experimental therapies may become tools in the future for clinicians who treat HSDD. Therapies that target the CNS are offering novel strategies for managing HSDD. One of the issues moving forward with the ongoing exploration of pharmacotherapies to treat HSDD is ensuring that patients and clinicians have access to accurate information about mechanism and efficacy, along with more comprehensive treatment strategies, so that patients have the choices they need for the best therapeutic outcome. ●

## References

1. Goldstein I, Kim NN, Clayton AH, et al. Hypoactive Sexual Desire Disorder: International Society for the Study of Women's Sexual Health (ISSWSH) Expert Consensus Panel Review. *Mayo Clin* Proc. 2017 Jan;92(1):114-128
2. Clayton AH, Goldfischer ER, Goldstein I, Derogatis L, Lewis-D'Agostino DJ, Pyke R. Validation of the decreased sexual desire screener (DSDS). *J Sex Med.* 2009 Mar;6(3):730-8
3. Joffe HV, Chang C, Sewell C, et al. FDA Approval of Flibanserin—Treating Hypoactive Sexual Desire Disorder. *N Eng J Med.* 2016 Jan 14;374(2):101-4.
4. Braunstein GD, Sundwall DA, Katz M, et al. Safety and efficacy of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial. *Arch Intern Med.* 2005 Jul 25;165(14):1582-9.
5. Landen M, Eriksson E, Agren H, Fahlen T. Effect of buspirone on sexual dysfunction in depressed patients treated with selective serotonin reuptake inhibitors. *J Clin Psychopharmacol.* 1999 Jun;19(3):268-71.
6. Segraves RT, Clayton A, Croft H, Wolf A, Warnock J. Bupropion sustained release for the treatment of hypoactive sexual desire disorder in premenopausal women. *J Clin Psychopharmacol.* 2004 Jun;24(3):339-42.
7. Arnow BA, Millheiser L, Garrett A, et al. Women with hypoactive sexual desire disorder compared to normal females: a functional magnetic resonance imaging study. *Neuroscience.* 2009 Jan 23;158(2):484-502.
8. Huynh HK, Beers C, Willemsen A, et al. High-intensity erotic visual stimuli de-activate the primary visual cortex in women. *J Sex Med.* 2012 Jun;9(6):1579-87.
9. Stahl SM, Sommer B, Allers KA. Multifunctional pharmacology of flibanserin: possible mechanism of therapeutic action in hypoactive sexual desire disorder. *J Sex Med.* 2011 Jan;8(1):15-27.
10. Pfaus JG. Treatment for hypoactive sexual desire. *Cell.* 2015 Oct 22;163(3):533.
11. Thorp J, Simon J, Dattani D, et al. Treatment of hypoactive sexual desire disorder in premenopausal women: efficacy of flibanserin in the DAISY study. *J Sex Med.* 2012 Mar;9(3):793-804.
12. Derogatis LR, Komer L, Katz M, et al. Treatment of hypoactive sexual desire disorder in premenopausal women: efficacy of flibanserin in the VIOLET study. *J Sex Med.* 2012 Apr;9(4):1074-85.
13. Katz M, DeRogatis LR, Ackerman R, et al. Efficacy of flibanserin in women with hypoactive sexual desire disorder: results from the BEGONIA trial. *J Sex Med.* 2013 Jul;10(7):1807-15.
14. Clayton AH, Lucas J, DeRogatis LR, Jordan R. Phase I Randomized Placebo-Controlled, Double-Blind Study of the Safety and Tolerability of Bremelanotide Coadministered with Ethanol in Healthy Male and Female Participants. *Clin Ther.* 2017 Feb 9.
15. Bioemers J, van Rooij K, de Leede L, et al. Single dose sublingual testosterone and oral sildenafil vs. a dual route/dual release fixed dose combination tablet: a pharmacokinetic comparison. *Br J Clin Pharmacol.* 2016 Jun;81(6):1091-102.
16. van Rooij K, Poels S, Worst P, et al. Efficacy of testosterone combined with a PDE5 inhibitor and testosterone combined with a serotonin (1A) receptor agonist in women with SSRI-induced sexual dysfunction. A preliminary study. *Eur J Pharmacol.* 2015 Apr 15;753:246-51.
17. Farmer M, Yoon H, Goldstein I. Future Targets for Female Sexual Dysfunction. *J Sex Med.* 2016 Aug;13(8):1147-65.