Talking with Your Patients About Hypoactive Sexual Desire Disorder and Advances in its Treatment

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Faculty Disclosures

Dr. Kingsberg has the following disclosures:

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Objectives

- Define hypoactive sexual desire disorder (HSDD)
- Address barriers that inhibit the appropriate diagnosis and management of HSDD
- Identify the screening tools that allow for diagnosis of HSDD
- Identify current therapeutic modalities to manage HSDD

Talking with Your Patients About Hypoactive Sexual Desire Disorder and Advances in its Treatment
Hypoactive Sexual Desire Disorder (HSDD)

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Hypoactive Sexual Desire Disorder (HSDD): DSM-IV

- Persistent or recurrent deficiency or absence of sexual thoughts, fantasies and/or desire for, or receptivity to, sexual activity
  - Accompanied by clinically significant personal distress or interpersonal difficulties
  - Not otherwise accounted for by another medical disorder, drug/medication, or psychiatric condition

ISSWSH Consensus Nomenclature for HSDD

Any of the following for >6 months:

- Lack of motivation for sexual activity manifested by either:
  - Reduced or absent spontaneous desire (sexual thoughts, fantasies)
  - Reduced or absent responsive desire to erotic cues and stimulation or inability to maintain desire
- Loss of desire to initiate or participate, including behavioral responses such as avoidance, not secondary to a sexual pain disorder

Clinically significant personal distress that includes frustration, grief, incompetence, loss, sorrow, or worry

ISSWSH = International Society for the Study of Women’s Sexual Health

Biopsychosocial Model of Female Sexual Response

- Biology (e.g., physical health, neurobiology, endocrine function)
- Psychology (e.g., performance anxiety, depression)
- Sociocultural (e.g., upbringing, cultural norms and expectations)
- Interpersonal (e.g., quality of current and past relationships, intervals of abstinence, life stressors, finances)
Prevalence of FSD: PRESIDE

- **OBJECTIVES:** Estimate the prevalence of self-reported sexual problems (any, desire, arousal, and orgasm), the prevalence of problems accompanied by personal distress, and describe related correlates
- **POPULATION:** 31,581 US female respondents ≥18 years of age from 50,002 households
- **RESULTS:** Response rate was 63% (n=31,581/50,002)


Low Sexual Desire Negatively Affects Self-image and Partner Relationships

Online Survey: Premenopausal women with self-described low sexual desire (n=306)

Affect your personal life?

- Body image: 69%
- Self-confidence: 51%
- Self-worth: 33%

Affect relationship with your partner?

- Less communication: 67%
- Less pleasant: 35%
- Worry partner will cheat: 35%

Kingsberg SA. J Women’s Health 2014;23(10):817-23.
Etiology of HSDD Imbalance Between Excitation/Inhibition

- Dopamine
- Oxytocin
- Melanocortin
- Vasopressin
- Norepinephrine

Physiological/ Organic

- Serotonin
- Opioids
- Endocannabinoids

Psychosocial/ Interpersonal

- Relationship conflict
- Negative Stress
- Negative beliefs about Sex
- Experience/behavior

EXCITATION INHIBITION


PET Scan Changes in Neural Activity in Response to Erotic Video

Women with HSDD have weaker activation in cerebral cortex in right hemisphere
Possibly representing muted response to sexual cues
Women with HSDD have less deactivation in left hemisphere possibly representing inability to deactivate higher order processing and perpetuates inhibitory neural pathways

Evaluating Sexual Desire: Are Patients Asking? Are Ob/Gyns Asking?


Are Patient’s Asking?

3,239 women with self-reported sexual problems of desire, arousal, and/or orgasm.
Reporting of HSDD

- 80% of women with self reported HSDD did not mention it to a health care provider
- 50% reported that discomfort or embarrassment contributed to their unwillingness to seek treatment


Are Physicians Asking?

- 53 primary care physicians completed questionnaire about their experience asking about low libido
  - 86.3% had not screened for low libido
  - 90% had not diagnosed low libido
    - 53% felt not confident at all
    - 38% little confidence

Are Ob-Gyns Asking?

- 63% Routinely Ask About Sexual Activities
- 40% Routinely Ask About “Problems”
- 13.8% Ask About Pleasure During Sexual Activity
- Females doctors twice as likely to ask

*1,154 practicing U.S. ob/gyns (53% male; mean age 48 years) was surveyed regarding their practices of communication with patients about sex

Physician-Based Barriers

- Lack of Training-Inadequate Knowledge of Solutions
- Lack of awareness of associated co-morbidities
- HCP embarrassment
- Fear of embarrassing patient
- “Improving quality of life” not a high priority
- Time constraints
- Underestimation of prevalence
- Consider other issues as higher priorities

References:
### Validated Tools to Assess FSD

<table>
<thead>
<tr>
<th>Validated Tool</th>
<th>Assessment Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased Sexual Desire Screener (DSDS)(^1)</td>
<td>Brief diagnostic tool for Hypoactive Sexual Desire Disorder (HSDD)</td>
</tr>
<tr>
<td>Female Sexual Function Index (FSFI)(^2,3)(^*)</td>
<td>Desire, arousal, orgasm, and pain</td>
</tr>
<tr>
<td>Female Sexual Distress Scale-Revised (FSDS-R)(^4)</td>
<td>Distress</td>
</tr>
</tbody>
</table>

\(^*\)FSFI questionnaire and scoring key available at: [www.fsfi-questionnaire.com](http://www.fsfi-questionnaire.com)

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Types of Interventions

- Psychotherapy/counseling
- Pharmacologic therapies
- Combined therapy
- Treatment determined by etiology


Psychotherapy Goals and Techniques

1. Lessen performance anxiety
2. Cognitive restructuring
3. (Re)gain confidence in their sexual performance
4. Redirect focus from performance to sensuality and pleasure
5. Surmount barriers to intimacy
6. Resolve interpersonal issues that cause/maintain HSDD
7. Improve communication skills
8. Predict in order to prevent relapse
FDA-Approved Pharmacologic Options for Generalized, Acquired Hypoactive Sexual Desire Disorder (HSDD)

Flibanserin  
Bremelanotide

David J. Portman, MD  
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Department of Obstetrics and Gynecology  
Founder and CEO, Sermonix Pharmaceuticals  
Columbus, OH

Neurotransmitters and Central Regulation of Desire/Arousal

Flibanserin: FDA approved for Generalized, Acquired Pre-Menopausal HSDD August 2015

- Once nightly oral medication
- Mixed post-synaptic 5HT1A agonist and 5HT2A antagonist
  - 5HT1A agonists could have pro-sexual effects
  - 5HT2A antagonists could have pro-sexual effects
- Activity at dopamine D4 receptors
- Thought to produce region-specific elevations in dopamine and norepinephrine which offset inhibitory serotonergic activity
- Flibanserin is believed to work on brain function by enhancing excitatory elements and lessening the inhibitory response to sexual cues

Excitatory and Inhibitory Effects of Neurotransmitters and Hormones on Sexual Desire

Pro-inflammatory cytokines

Prolactin
SEROTONIN
Opioids

Inhibitory

DESIRE

Estrogen
Progesterone
Melanocortin
DOPAMINE
Testosterone

Excitatory
Flibanserin Increased Sexual Desire on Daily eDiary vs. Placebo

While subjects responding to Flibanserin showed an increase in sexual desire as measured by the eDiary, the difference did not reach statistical significance.


Flibanserin Increased Sexual Desire on FSFI-D vs. Placebo


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Flibanserin Showed a Decrease in Distress vs. Placebo Across All 3 Studies

![Graph showing mean change from baseline to week 24 across three studies](image)

- Study 1
  - Flibanserin: -0.8
  - Placebo: -0.8
- Study 2
  - Flibanserin: -1.0
  - Placebo: -0.8

* P < 0.0001
† P-value not reported for secondary endpoints in study 1 and 2 because the trials failed to meet the eDiary co-primary efficacy endpoint


Flibanserin Adverse Reactions

- The majority of these adverse reactions began within the first 14 days of treatment

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Flibanserin (n=1543)</th>
<th>Placebo (n=1536)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>11.4%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>11.2%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Nausea</td>
<td>10.4%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9.2%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4.9%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>2.4%</td>
<td>1.0%</td>
</tr>
</tbody>
</table>

- Adverse reactions leading to discontinuation of hypoactive sexual desire disorder patients receiving Flibanserin 100 mg at bedtime and at a higher incidence than placebo-treated patients were: dizziness, nausea, insomnia, somnolence, and anxiety

- Discontinuation rate due to adverse reactions was 13% for Flibanserin 100 mg and 6% for placebo
Prescribing Flibanserin

- Continuous bedtime dosing
- Boxed warning for:
  - Hypotension, syncope in certain settings:
    - Alcohol within 2 hours of dosing and contraindicated with moderate or strong CYP3A4 inhibitors, hepatic impairment
- REMS program—Pharmacy and prescriber certification
- Labeling changes August 2019
  - FDA removed alcohol contraindication
  - Remains a warning and precaution

FDA-Approved Pharmacologic Options for Hypoactive Sexual Desire Disorder (HSDD)

Bremelanotide
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Bremelanotide (BMT): Approved for Premenopausal HSDD June 2019

- Novel cyclic 7-amino acid melanocortin-receptor agonist, with high affinity for the type-4 melanocortin receptor, an analog of α-melanocyte-stimulating hormone (MSH)

- BMT is delivered via an auto-injector on an “as needed” basis 45 minutes before sexual activity
- BMT demonstrated significant efficacy vs. placebo in measures in increasing sexual desire and decreasing distress


BMT MOA: Potential to Modulate Brain Pathways Involved in Sexual Desire


- Bremelanotide (BMT): an investigational, novel cyclic 7-amino acid melanocortin-receptor-4-agonist (MC4R)¹
- BMT (Vyleesi™) acts on the physiological and neurobiological components of female sexual function
  - Potential to modulate brain pathways involved in sexual desire and arousal in women with HSDD²
Excitatory and Inhibitory Effects of Neurotransmitters and Hormones on Sexual Desire

Prolactin
Serotonin
Opioids

Inhibitory

DESIRE

Estrogen
Progesterone
MELANOCORTIN
DOPAMINE
Testosterone

Excitatory

Excitatory and Inhibitory Effects of Neurotransmitters and Hormones on Sexual Desire

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The RECONNECT Study

Placebo-controlled, phase 3 studies of BMT administered as-desired for the treatment of HSDD

- Healthy, premenopausal, nonpregnant women, ≥18 years of age, currently in a stable (≥6 months) relationship
- Diagnosed with HSDD (with/without decreased arousal) for ≥6 months
- Experienced “normal” sexual function in the past for ≥2 years
- Willing to engage in sexual activities ≥1X/month during the study
- Had ALL of the following at screening:
  - Patient Health Questionnaire-9 total score <10 and a score of 0 on question 9
  - Female Sexual Function Index (FSFI) total score ≤26 (if diagnosed with HSDD with/without symptoms of decreased arousal) OR
  - FSFI desire domain (FSFI-D) score ≤5 (if diagnosed with HSDD without decreased arousal) regardless of total FSFI score
  - Female Sexual Distress Scale-Desire/Arousal/Orgasm (FSDS-DAO) total score >18

Efficacy of Bremelanotide for HSDD in Women: RECONNECT Open-Label Extension Phase Results [8Q]
Clayton, Anita H., MD; Kingsberg, Sheryl A., PhD; Simon, James A., MD, CCD, NCMP, IF; Jordan, Robert; Lucas, Johna, MD Obstetrics 
& Gynecology: May 2018 - Volume 131 - Issue - p 1865
doi: 10.1097/AOG.0000000000003221.21767.0a

Talking with Your Patients About Hypoactive Sexual Desire Disorder and Advances in its Treatment
Key Outcome Measures

- Co-primary Efficacy Endpoints
  - Change in the FSFI-D and FSDS-DAO Item 13 scores among women who completed the double-blind treatment phase of the RECONNECT study
- Responder Analysis Based On
  - Participants self-reporting a score of ≥5 (on a 7-point Likert scale) in response to question 3 on the General Assessment Questionnaire “To what degree do you think you benefited from taking the study drug?”
  - The proportion of participants meeting or exceeding the following predefined minimal clinically important differences (MCIDs)
    - FSFI-D score (MCID=0.6)
    - FSDS-DAO Item 13 score (MCID=-1.0)

Efficacy Results: FSFI-D

Compared with those taking placebo, women taking BMT had significantly increased scores on the desire domain of the FSFI at 6 months, indicating an increase in desire

Figure 2. Change in FSFI Desire Domain Score from Baseline to End of Core (Double-Blind) Phase

*P* values determined by unadjusted Wilcoxon rank-sum test. Error bars are standard error of the mean.
Efficacy Results: FSDS-DAO Item 13

Compared with those taking placebo, women using BMT had a significant reduction in their FSDS-DAO Item 13 score at 6 months, indicating a reduction in distress related to low sexual desire.

Figure 4. Change in FSDS-DAO Item 13 from Baseline to End of Core (Double-Blind) Phase

- Study 301: n = 274, -0.34, P < 0.0001
- Study 302: n = 190, -0.38, P = 0.0007
- Placebo: n = 219, -0.86

Values determined by unadjusted Wilcoxon rank-sum test. Error bars are standard error of the mean. FSDS-DAO, Female Sexual Distress Scale-Desire/Arousal/Orgasm.

Defined Anchor Analysis
Global Assessment Questionnaire Q3 for Co-Primary

“Compared with the start of the study (prior to taking the study drug), to what degree do you think you benefited from taking the study drug?”

<table>
<thead>
<tr>
<th>Very Much Worse</th>
<th>No Change</th>
<th>Very Much Better</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
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<tr>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
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</tr>
</tbody>
</table>

Responder defined as score of ≥5

Percent Responders Defined by a Score of ≥5 on GAQ Question #3

- Placebo: 35.6
- BMT 1.75 mg: 58.2

p < 0.0001

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Safety

- Bremelanotide: an on-demand auto-injector has a favorable safety profile
- Most AEs were mild or moderate in nature
  - Nausea, vomiting most common: 40%
  - 8% discontinued due to N/V
- TEAEs led to treatment discontinuation/interruption in approximately 18% of women taking bremelanotide (vs. 2% in placebo)
  - Most of the bremelanotide AEs causing withdrawal were gastrointestinal (11.1% in Study 301 and 7.6% in Study 302)
- Contraindication: uncontrolled hypertension or known CVD
- No interaction with alcohol

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Off-Label Therapy

- Testosterone
- Estrogen
- Bupropion
- PDE-5 Inhibitors

A 2017 systematic review and meta-analysis included 7 randomized controlled studies of transdermal testosterone (with or without concomitant estrogen therapy) that was composed of more than 3,000 postmenopausal women with HSDD.

- Postmenopausal women treated with the transdermal testosterone patch experienced significant increases in sexual desire, sexual activity, SSE, and orgasms and a significant decrease in personal distress compared with women in the placebo group.
- No testosterone product is approved in the U.S. for women

Conclusions

- HSDD is highly prevalent and presents a huge burden to the quality of life of women who suffer from this condition
- It is the responsibility of the HCP to initiate discussion of sexual concerns with all patients
- There are safe and effective treatments for HSDD.
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