From Bench to Bedside to Beltway: What’s Next in the Treatment of Female Sexual Dysfunction

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Where Have We Come From?

- Historically female sexual health defined by cultural norms and given little attention

- In the 1800s it was discovered that female orgasm was irrelevant to conception

- 2014: Women’s sexual health is considered a *human rights issue* by the World Health Organization (WHO) and is recognized as an *integral part of overall health*
Human Sexual Response: Classic Models

- Excitement
- Plateau
- Orgasm
- Resolution

Linear Progression

Female Sexual Response Cycle: Basson

- Emotional Intimacy
- Emotional and Physical Satisfaction
- Spontaneous Sexual Drive
- Arousal and Sexual Desire
- Sexual Arousal
- Sexual Stimuli

Biologic
Psychological
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)


The Dual Control Model: Interpersonal/psychological

Stimulation
- Intimacy
- Shared values
- Romance

Inhibition
- Relationship conflict
- Negative Stress
- Negative beliefs about sex

John Bancroft
The Dual Control Model: Physiological

Stimulation

- DOPAMINE
- OXYTOCIN
- MELANOCORTIN
- NOREPINEPHRINE

Inhibition

- SEROTONIN
- OPIOIDS
- ENDOCANNABINOIDS
- PROLACTIN

John Bancroft
# Female Sexual Dysfunction: DSM-IV-TR Codes and Definitions

<table>
<thead>
<tr>
<th>Sexual desire disorders</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoactive sexual desire disorder</td>
<td>302.71 or 799.81</td>
<td>Absence or deficiency of sexual interest and/or desire</td>
</tr>
<tr>
<td>Sexual aversion disorder</td>
<td>302.79</td>
<td>Aversion to and avoidance of genital contact with a sexual partner</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sexual arousal disorders</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sexual arousal disorder</td>
<td>302.72</td>
<td>Inability to attain or maintain adequate lubrication-swelling response of sexual excitement</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Orgasmic disorders</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female orgasmic disorder</td>
<td>302.73</td>
<td>Delay in or absence of orgasm after a normal sexual excitement phase</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pain disorders</th>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspareunia</td>
<td>302.76 or 625.0</td>
<td>Genital pain associated with sexual intercourse</td>
</tr>
<tr>
<td>Vaginismus</td>
<td>306.51 or 625.1</td>
<td>Involuntary contraction of the perineal muscles preventing vaginal penetration</td>
</tr>
</tbody>
</table>

# Female Sexual Disorders: DSM 5

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Code</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female Orgasmic Disorder</td>
<td>302.73</td>
<td>Presence of either of the following on all or almost all (75%-100%) occasions of sexual activity:</td>
</tr>
<tr>
<td></td>
<td>(F52.31)</td>
<td>1. Marked delay in, marked infrequency of, or absence of orgasm.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Markedly reduced intensity of orgasmic sensations.</td>
</tr>
<tr>
<td>Female Sexual Interest/Arousal</td>
<td>302.72</td>
<td>Lack of, or significantly reduced, sexual interest/arousal as manifested by 3 of the following:</td>
</tr>
<tr>
<td>disorder</td>
<td>(F52.22)</td>
<td>1. Absent/reduced interest in sexual activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Absent/reduced sexual/erotic thoughts or fantasies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. No/reduced initiation of sexual activity and unreceptive to partner's attempts to initiate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Absent/reduced sexual excitement/pleasure during sexual activity in almost all or all (75%-100%) sexual encounters</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. Absent/reduced sexual interest/arousal in response to any internal or external sexual/erotic cues (written, verbal, visual)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6. Absent/reduced genital or nongenital sensations during sexual activity in almost all or all (75%-100%) sexual encounters</td>
</tr>
</tbody>
</table>

Symptoms persisted a minimum of 6 months and not better explained by a nonsexual mental disorder or consequence of severe relationship distress or other significant stressors and not due to effects of substance/medication or other medical condition.
## Female Sexual Disorders: DSM 5

| Genito-Pelvic Pain/Penetration Disorder | 302.76 (F52.6) | Persistent or recurrent difficulties with 1 or more of the following:
|                                           |                | 1. Vaginal penetration during intercourse
|                                           |                | 2. Marked vulvovaginal or pelvic pain during intercourse or penetration attempts
|                                           |                | 3. Marked fear or anxiety about vulvovaginal or pelvic pain in anticipation of, during, or as a result of vaginal penetration
|                                           |                | 4. Marked tensing or tightening of the pelvic floor muscles during attempted vaginal penetration.

Symptoms persisted a minimum of 6 months and not better explained by a nonsexual mental disorder or consequence of severe relationship distress or other significant stressors and not due to effects of substance/medication or other medical condition
HSDD/FSIAD DIAGNOSIS Exclusions

- Women with a relationship problem - a dysfunctional, unsatisfying or abusive relationship
- Discrepancy in level of desire but woman is satisfied with her own level of desire
- Low desire is secondary to depressive illness, another medical condition, or a medication that reduces sexual desire
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.

**NOT DETERMINED:** Whether low desire with sexually related personal distress was primary or secondary to another illness; pain was not assessed.

**POPULATION:** 31,581 US female respondents ≥18 years of age from 50,002 households.

**RESULTS:** Response rate was 63% (n=31,581 / 50,002)

**Prevalence of Female Sexual Problems Associated With Distress**

<table>
<thead>
<tr>
<th>Sexual Problems</th>
<th>Distressing Sexual Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desire</td>
<td>37.7%</td>
</tr>
<tr>
<td>Arousal</td>
<td>25.3%</td>
</tr>
<tr>
<td>Orgasm</td>
<td>21.1%</td>
</tr>
<tr>
<td>Any</td>
<td>43.1%</td>
</tr>
</tbody>
</table>

US Women (‘)
Impact on QOL and Relationships

- HSDD is associated with significant quality of life burden, distress, marital dissatisfaction, and difficulties maintaining stable sexual relationships.¹

  - 8 to 10 times more likely than women with normal desire to report (often or always) feeling unhappy, disappointed, upset, frustrated, sad, ashamed, bitter, low self-esteem and feeling like sexual failures.¹

- Women with HSDD have higher QOL burdens on SF 12 (general health impact) similar to those of people with chronic conditions such as diabetes and back pain,² at 2x rate of general population³

What are the Components of Desire?

**DRIVE:**
Biological component based on neuroendocrine mechanisms

**COGNITIVE:**
Reflects expectations, beliefs and values

**MOTIVATION:**
Willingness to engage in sexual activity
Current Treatment of HSDD

- **Sex/Behavioral Therapy**
  - Paucity of randomized controlled trials evaluating sex therapy\(^1,2\)
  - Uncontrolled studies of psychological techniques report variable outcomes\(^3,4\)

- **Pharmacologic Therapy**
  - There are no approved drug options for HSDD/FSIAD
  - Testosterone (2 million off-label prescriptions written in the USA in 2006-2007\(^5\)) and bupropion used off-label

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Pharmacologic Treatments For The Bedside That Are Stuck On the Beltway

- Flibanserin
- Bremelanotide
- Librido/Libridos
Flibanserin: Structure/Mechanism of Action

- Flibanserin is a non-hormonal 5-HT\textsubscript{1A} receptor agonist and 5-HT2A antagonist increasing dopamine activity and reducing serotonin activity.

Phase 3 Results:
flibanserin 100mg qhs increases SSE

statistically significant separation from placebo in 4-8 weeks.

All data represent mean change from baseline for satisfying sexual events (SSE), standardized for a one month period. Treatment comparison by visit using Wilcoxon rank sum test (*p < 0.05 between treatment groups).
flibanserin 100mg qhs improves sexual desire

statistically significant separation from placebo at 4 weeks

All data represent change from baseline of least squares (LS) means. Treatment comparison by visit using ANCOVA (*p < 0.05 between treatment groups).

FSFI-SD maximum score = 10
flibanserin 100mg qhs reduces distress associated with low sexual desire

25% reduction in distress associated with low desire

All data represent change from baseline of least squares (LS) means. Treatment comparison by visit using ANCOVA (*p < 0.05 between treatment groups).

reduction in score = improvement
FSDS-R13 (0=never;4=always)
PGI of Improvement:
PGI-I Very Much/Much/Minimally Improved

How is your condition today – meaning decreased sexual desire and feeling bothered by it – compared with when you started study medication?

![Bar chart showing improvement rates for Flibanserin 100 qhs and Placebo at Week 24 FAS, LOCF.](chart.png)

- **Flibanserin 100 qhs**
  - Week 24: 47.0%
- **Placebo**
  - Week 24: 30.3%

Adjusted p-values:
* p < 0.05
** p < 0.01
*** p < 0.001
**** p < 0.0001
Common Adverse Events in ≥1% of Premenopausal Women

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Placebo N = 1905</th>
<th>Flibanserin 100 mg qhs N = 1543</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>41 (2.2)</td>
<td>176 (11.4)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>59 (3.1)</td>
<td>173 (11.2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>71 (3.7)</td>
<td>161 (10.4)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>95 (5.0)</td>
<td>142 (9.2)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>46 (2.4)</td>
<td>75 (4.9)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>17 (0.9)</td>
<td>37 (2.4)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>17 (0.9)</td>
<td>28 (1.8)</td>
</tr>
<tr>
<td>Constipation</td>
<td>9 (0.5)</td>
<td>25 (1.6)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>15 (0.8)</td>
<td>23 (1.5)</td>
</tr>
<tr>
<td>Sedation</td>
<td>3 (0.2)</td>
<td>20 (1.3)</td>
</tr>
<tr>
<td>Vertigo</td>
<td>6 (0.3)</td>
<td>16 (1.0)</td>
</tr>
</tbody>
</table>

bid = twice daily; qhs = once every evening.
MedDRA version used for reporting: 11.1.
Includes Trials 511.70, 511.71, 511.75, 511.77, and 511.147.
<table>
<thead>
<tr>
<th>AE comparison with commonly prescribed drugs (&gt;5%)</th>
</tr>
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<tbody>
<tr>
<td><img src="" alt="Table" /></td>
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</tbody>
</table>

lower than flib by ≥1.5 – higher than flib by ≥1.5 – within 1.5
flibanserin studies underway

- A pharmacogenomic screening study on CYP enzymes – 2C9 & 2C19
- Enzymes responsible for 10-15% of flibanserin metabolism
- Driving study to confirm no next day impairment
- Somnolence incidence 9.8% in clinicals
- Agency focused on this issue with all drugs post Ambien/Lunesta dosage changes
Bremelanotide (BMT) is a novel cyclic melanocortin peptide that acts as a melanocortin-receptor-4 agonist, with potential downstream effects on brain pathways involved in sexual response.

- Novel mechanism of action activating endogenous pathways involved in sexual response
- On-demand/as-needed treatment
Overall Efficacy Outcomes

**SSEs Per Month**

- Placebo
- 0.75 mg
- 1.25 mg
- 1.75 mg

**FSFI Total Score**

- Placebo
- 0.75 mg
- 1.25 mg
- 1.75 mg

**FSDS-DAO Total Score**

*P<0.05
**P<0.01
***P<0.001
Change in FSFI Desire & Arousal Domain Scores

**P<0.01
Change in FSDS-DAO Desire & Arousal Item Scores

**Desire**

![Bar graph showing change in FSDS-DAO Desire scores from Placebo to 1.25 mg.](image)

- Placebo: -0.6
- 1.25 mg: -1.0

**Arousal**

![Bar graph showing change in FSDS-DAO Arousal scores from Placebo to 1.25 mg.](image)

- Placebo: -0.4
- 1.25 mg: -1.0

*P<0.05, **P<0.01
Change in FSDS-DAO Total Score, by Primary Diagnosis

Mixed HSDD/FSAD

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo N=65</td>
<td>-1.0</td>
</tr>
<tr>
<td>0.75 mg N=65</td>
<td>-2.0</td>
</tr>
<tr>
<td>1.25 mg N=54</td>
<td>-3.0</td>
</tr>
<tr>
<td>1.75 mg N=57</td>
<td>-4.0</td>
</tr>
</tbody>
</table>

**P<0.01

Note: The FSAD-only sub-group had insufficient numbers to analyze.

HSDD Only

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo N=23</td>
<td>-1.0</td>
</tr>
<tr>
<td>0.75 mg N=19</td>
<td>-2.0</td>
</tr>
<tr>
<td>1.25 mg N=18</td>
<td>-3.0</td>
</tr>
<tr>
<td>1.75 mg N=15</td>
<td>-4.0</td>
</tr>
</tbody>
</table>
Safety/Adverse Events

- the most common AE types were nausea, flushing, and headache.
“It is incredible to me that any woman should consider the fight for full equality won. It has just begun. There is hardly a field, economic or political, in which the natural and unaccustomed policy is not to ignore women...Unless women are prepared to fight politically they must be content to be ignored politically.”

(Alice Paul, 1920)
FDA is hosting a Patient-Focused Drug Development Public Meeting and Scientific Workshop on Female Sexual Dysfunction (FSD) on October 27-28, 2014.

The goal of the meeting is to hear patient perspectives on a) symptoms of FSD that matter most to them and b) current approaches to treating FSD

Date: Monday, October 27, 2014

Time: 12:00 PM to 5:00 PM (Eastern)

Location: FDA White Oak Campus
10903 New Hampshire Avenue
Silver Spring, MD