Data and Women’s Preferences Should Inform the Treatment of Hypoactive Sexual Desire Disorder: The Case for Pharmacologic Agents

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Disclosures

Sheryl A. Kingsberg, PhD, is a consultant, investigator or on a scientific advisory board for Emotional Brain, Valeant, Endoceutics, Novo Nordisk, Palatin Technologies, Pfizer, Shionogi, Materna, Nuelle, Bayer, TherapeuticsMD, Viveve and Acerus Pharmaceuticals.

Sources of Evidence for Physiological Mechanisms Modulating Sexual Desire

- Neurobiology
- Flibanserin RCTs
- Women with HSDD treated with flibanserin

Biopsychosocial Model of Female Sexual Response

Sexual Dysfunction: Definition & Diagnosis

1987 (DSM-III-R)
Frequency + Sexual Dysfunction
Persistently or recurrently deficient or absent sexual fantasies and desire for sexual activity

2000 (DSM-IV-TR)
Frequency + Sexual Dysfunction + Distress
Persistently or recurrently deficient or absent sexual fantasies and desire for sexual activity with marked distress or interpersonal difficulty; not otherwise accounted for by a general medical or psychiatric condition

2013 (DSM-5)
Frequency + Distress + Frequency + Duration
Lack of sexual interest/arousal as manifested by a preset number of indicators (with/without a specified frequency) with clinically significant distress, and has persisted ≥ 6 months; not otherwise accounted for by a general medical or psychiatric condition

HSDD = hypoactive sexual desire disorder
FSIAD = female sexual interest/arousal disorder

Hypoadic Sexual Desire Disorder (HSDD) (DSM IV)
- Persistent or recurrent deficiency or absence of sexual thoughts, fantasies and/or desire for sexual activity
  - Causes marked personal distress or interpersonal difficulties
  - Not better accounted for by another primary disorder, drug/medication, or general medical condition

DSM-5 (2013): Changes To Nomenclature & Diagnosis
- Female hypoactive desire dysfunction and female arousal dysfunction were merged into a single syndrome
- Increased precision: includes a preset number of indicators (with/without a specified frequency) and a minimum duration of 6 months to differentiate "disorder" from "transient dysfunction"

Female Sexual Interest/Arousal disorder (DSM 5)
Lack of, or significantly reduced, sexual interest/arousal as manifested by 3 of:
1. Absent/reduced interest in sexual activity
2. Absent/reduced sexual/erotic thoughts or fantasies
3. No/reduced initiation of sexual activity and unreceptive to partner’s attempts to initiate
4. Absent/reduced sexual excitement/pleasure during sexual activity in almost all or all (75%-100%) sexual encounters
5. Absent/reduced sexual interest/arousal in response to any internal or external sexual/erotic cues (written, verbal, visual)
6. Absent/reduced genital or nongenital sensations during sexual activity in almost all or all (75%-100%) sexual encounters
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 Sexual Problems Associated with Distress (PRESIDE)

<table>
<thead>
<tr>
<th>Age-stratified Prevalence</th>
<th>Desire 2868/28,447</th>
<th>Arousal 1556/28,461</th>
<th>Orgasm 1315/27,854</th>
<th>Any 3456/28,403</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-44</td>
<td>8.9</td>
<td>3.3</td>
<td>3.4</td>
<td>10.8</td>
</tr>
<tr>
<td>45-64</td>
<td>12.3</td>
<td>7.5</td>
<td>5.7</td>
<td>14.8</td>
</tr>
<tr>
<td>65 or older</td>
<td>7.4</td>
<td>6.0</td>
<td>5.8</td>
<td>8.9</td>
</tr>
</tbody>
</table>


PET Scan Changes in Neural Activity in Response to Erotic Video

Women with HSDD have weaker activation in cerebral cortex in Rt 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


Key Regions in Brain Regulating Sexual Desire

- Prefrontal cortex
- Locus coeruleus
- Medial preoptic area (mPOA)
- Paraventricular nucleus
- Reward and attention processing centers of the ventral tegmental area and nucleus accumbens

Reward Center Circuitry

Etiology of HSDD: Imbalance Between Excitation/Inhibition

- Dopamine
- Oxytocin
- Melanocortin
- Vasopressin
- Norepinephrine

Physiological/Organic

- Serotonin
- Opioids
- Endocannabinoids

Psychosocial/Interpersonal

- Intimacy
- Shared values
- Romance
- Experience/behavior

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

Excitatory and Inhibitory Pathways Regulating Sexual Response

How does this translate into pharmacologic treatment options?

• HSDD is a maladaptation of the brain where the PFC loses excitatory control over the reward/motivation structures of the brain (limbic system).
• This maladaptation is represented by the dysregulation of DA, NE and 5-HT.
• Correcting this imbalance in the PFC is the biological foundation to correcting the maladaptation.
• Similar maladaptation in depression/anxiety (chronic stress alters architecture of neurons changing synaptic interaction)
  – differing in type and magnitude of dysregulation

Reward Processing: Impaired Reward Circuitry Pathways

• Consequence of the inhibitory and excitatory imbalance: HSDD and Depression
• Constructs and key features of depression and HSDD
  – Anhedonia: The loss of interest in or reduced pleasure from rewarding activities
  • Consummatory: Reduced ability to respond to pleasurable rewards
  • Motivational: Reduced ability to seek out pleasurable rewards
  – Avolition: The loss of motivation to seek out rewarding activities
  – Experience-based neuroplasticity—link between behavior and cellular (neuronal circuits), synaptic or molecular mechanisms


Drugs Approved or In Development for Low Desire:

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Drug Category</th>
<th>Pharma Sponsor</th>
<th>Current Developmental Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flibanserin 100 mg PO qhs at bedtime</td>
<td>Non-hormonal CNS agent</td>
<td>Sprout Pharmaceuticals</td>
<td>Approved 8/2015 for HSDD in premenopausal women, available 10/17/15</td>
</tr>
<tr>
<td>Bremelanotide subq injection melancortin receptor modulator</td>
<td>Melanocortin receptor modulator</td>
<td>Palatin Technologies</td>
<td>Phase III completed for HSDD/FSIAD</td>
</tr>
<tr>
<td>Lybridos (on demand oral tablet) buspirone + testosterone</td>
<td></td>
<td>Emotional Brain</td>
<td>Phase II completed for HSDD</td>
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<tr>
<td>Lybrido (on demand oral tablet) eledelstat + testosterone</td>
<td></td>
<td>Emotional Brain</td>
<td>Phase II completed for HSDD</td>
</tr>
</tbody>
</table>

Kingsberg SA, Clayton A, Flaxa J. CNS Drugs, 2015
Flibanserin

- Mixed post-synaptic 5HT₁A agonist and 5HT₂A antagonist.
  - 5HT₁A agonists could have pro-sexual effects.
  - 5HT₂A antagonists could have pro-sexual effects.
- Has activity at dopamine D₄ receptors as well as moderate affinity for 5HT₂B and 5HT₂C receptors.
- Thought to produce region-specific elevations in dopamine and norepinephrine which offset inhibitory serotonergic activity = increased desire pathways.
- Serotonin may have a role in low desire by acting as a sexual satiety signal

Study Design

Three 24-week randomized, double-blind, placebo-controlled trials

**CO-PRIMARY ENDPOINTS** (Mean change from baseline at Week 24)
- No. of monthly SSEs (satisfying sexual events)
- Sexual desire
  - Monthly sexual desire score via eDiary (Studies 1 & 2)
  - Desire domain of the Female Sexual Function Index (FSFI-D) (Study 3)

**SECONDARY ENDPOINTS** (Mean change from baseline at Week 24)
- FSFI-D (Studies 1 & 2)
- Distress related to sexual desire
  - [Question 13 of Female Sexual Distress Scale – Revised (FSDS-R)]

<table>
<thead>
<tr>
<th>STUDY</th>
<th>TREATMENT</th>
<th>POPULATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIOLET</td>
<td>Flibanserin (50mg, 100mg); N = 585 Placebo; N = 295</td>
<td></td>
</tr>
<tr>
<td>DARY</td>
<td>Flibanserin (50mg, 100mg); N = 1183 Placebo; N = 398</td>
<td></td>
</tr>
<tr>
<td>BEGONIA</td>
<td>Flibanserin (100 mg); N = 542 Placebo; N = 545</td>
<td></td>
</tr>
</tbody>
</table>

Mechanism of Action

Serotonin may have a role in low desire by acting as a sexual satiety signal.
CO-PRIMARY ENDPOINT: Satisfying Sexual Events (SSEs)

Studies 1, 2 & 3

Number of monthly* SSEs

- Women indicated daily if they had experienced a sexual event.
- If a sexual event occurred, the SSE primary endpoint was measured by the eDiary question: “Was the sex satisfying for you?”
- Standardized to a 28 day period:
  \[ \text{Total monthly count of SSEs} = 28 \times \left( \frac{\text{sum of the number of SSE entered}}{\text{sum of number of days entered}} \right) \]

Studies 1, 2 & 3


RESULTS:

<table>
<thead>
<tr>
<th>Study 1 Study 2 Study 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flibanserin 1.6* 1.8* 2.5**</td>
</tr>
<tr>
<td>Vehicle 0.0 0.5 1.0</td>
</tr>
</tbody>
</table>

Mean Change from Baseline at Week 24

Flibanserin showed a statistically significant improvement in the mean change from baseline at week 24 in number of monthly SSEs in all 3 pivotal studies.

CO-PRIMARY ENDPOINT: Sexual Desire

STUDIES 1 & 2

- Monthly Sexual Desire Score
- Daily record via eDiary

FSFI-D Desire

\[ \text{FSFI-D} = \left[ \frac{Q1 + Q2}{2} \right] \times 0.6 \]

Range: 1.2 - 6

STUDY 3

- Desire domain of the Female Sexual Function Index (FSFI-D)

Monthly Sexual Desire Score = 28 day sum


RESULTS:

<table>
<thead>
<tr>
<th>Study 1 Study 2 Study 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flibanserin 9.1† 8.3†</td>
</tr>
<tr>
<td>Vehicle 0.0 2.0 4.0 6.0</td>
</tr>
</tbody>
</table>

Mean Change from Baseline at Week 24

Flibanserin did not show a statistically significant improvement in desire using an eDiary, but did using the validated FSFI-D instrument in Study 3.

Notes:
- *P < 0.01 versus PBO
- **P < 0.0001 versus PBO
RESULTS:
FSFI- Desire (Secondary)

Mean Change from Baseline at Week 24

- Flibanserin showed a consistent improvement in sexual desire across all 3 studies using the validated FSFI-D instrument.

Study 1 Study 2 Study 3
f 0.9* 0.9* 0.9*
Vehicle

1. P-value not reported for secondary endpoints because the trials failed on the eDiary co-primary efficacy endpoint.

SECONDARY ENDPOINT:
Female Sexual Distress

STUDIES 1, 2 & 3

- Question 13 of Female Sexual Distress Scale - Revised (FSDS-R)
  - Assessed over a 7-day recall period

How often do you feel bothered by low sexual desire?

<table>
<thead>
<tr>
<th>Always</th>
<th>Frequently</th>
<th>Occasionally</th>
<th>Rarely</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

31. How often do you feel bothered by low sexual desire?

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).

**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)

**Mean Change from Baseline in Key Endpoints by Visit**
Postmenopausal Women Study 130 (FAS, LOCF)

<table>
<thead>
<tr>
<th>Week</th>
<th>FSFI-Desire</th>
<th>FSDS-R13</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>SSEs</strong></td>
<td><strong>FSFI-Desire</strong></td>
</tr>
<tr>
<td>0</td>
<td></td>
<td><strong>SSEs</strong></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td><strong>SSEs</strong></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td><strong>SSEs</strong></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td><strong>SSEs</strong></td>
</tr>
<tr>
<td>16</td>
<td></td>
<td><strong>SSEs</strong></td>
</tr>
<tr>
<td>20</td>
<td></td>
<td><strong>SSEs</strong></td>
</tr>
<tr>
<td>24</td>
<td></td>
<td><strong>SSEs</strong></td>
</tr>
</tbody>
</table>

**PGI-I Anchored Responder Analysis**

Responders, % ± 95% CI

<table>
<thead>
<tr>
<th>Study</th>
<th>SSEs FSFI-Desire</th>
<th>FSDS-R13 SSEs FSFI-Desire</th>
</tr>
</thead>
<tbody>
<tr>
<td>147</td>
<td></td>
<td></td>
</tr>
<tr>
<td>71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Responder rates were higher in subjects receiving flibanserin compared to placebo across all three studies on all three major efficacy measures.
1. Over the past 4 weeks, how often did you feel sexual desire or interest?

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almost never or never</td>
<td>1</td>
</tr>
<tr>
<td>A few times (less than half the time)</td>
<td>2</td>
</tr>
<tr>
<td>Sometimes (about half the time)</td>
<td>3</td>
</tr>
<tr>
<td>Most times (more than half the time)</td>
<td>4</td>
</tr>
</tbody>
</table>

2. Over the past 4 weeks, how would you rate your level (degree) of sexual desire or interest?

<table>
<thead>
<tr>
<th>Level</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low or none at all</td>
<td>1</td>
</tr>
<tr>
<td>Low</td>
<td>2</td>
</tr>
<tr>
<td>Moderate</td>
<td>3</td>
</tr>
<tr>
<td>High</td>
<td>4</td>
</tr>
<tr>
<td>Very high</td>
<td>5</td>
</tr>
</tbody>
</table>

FSFI-Desire Domain
Study 147 (Flibanserin FAS and Responder Populations, LOCF)

FAS=full analysis set.

Common Adverse Events in ≥1% of Premenopausal Women

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Placebo N = 1905 N (%)</th>
<th>Flibanserin 100 mg qhs N = 1543 N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>41 (2.2)</td>
<td>176 (11.4)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>77 (3.7)</td>
<td>181 (11.9)</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>Anorexia</td>
<td>17 (0.9)</td>
<td>28 (1.8)</td>
</tr>
<tr>
<td>Constipation</td>
<td>9 (0.5)</td>
<td>26 (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>26 (1.7)</td>
</tr>
<tr>
<td>Vertigo</td>
<td>4 (0.3)</td>
<td>16 (1.0)</td>
</tr>
</tbody>
</table>

University Hospitals
MacGready Women’s Hospital
(Back of One)

Bremelanotide
- Bremelanotide completed Phase 3 trials
- First-in-class melanocortin receptor 4 agonist
- A synthetic peptide analog of the naturally occurring hormone alpha-MSH (melanocyte-stimulating hormone).
- Originally developed as an intranasal formulation; the current subcutaneous administration provides an improved tolerability profile
- On-demand use with rapid onset of activity and well-tolerated
- Evaluated in 31 clinical studies, in over 2,500 people, showing efficacy in both HSDD and ED
- Completed a large Phase 2B trial in HSDD, FSAD and HSDD/FSAD Mixed patients with subcutaneous (pre-filled syringes) formulation
**Study 54 Clinical Data**

- The results of 327 premenopausal patients analyzed shows clinically meaningful and statistically significant effects for BMT vs. placebo.
- Robust efficacy in all clinically key endpoints at all the 1.75 and some of the 1.25: FSFI total score, FSDS-DAO total score and SSEs.
- Improves multiple domains of sexual function (FSFI).
- Decreases distress associated with sexual dysfunction (FSDS-DAO).
- Influences downstream behavior with an increase in SSEs.
- 1.75 mg dose analysis also demonstrated clinically meaningful and statistical significance:
  - SSE improvement from baseline to end-of-study: 1.8 to 2.6 (p=0.021)
  - FSFI total score mean change vs. placebo: 4.56 vs. 1.88 (p=0.0021)
  - FSDS-DAO total score mean change vs. placebo: -13.1 vs. -6.8 (p=0.013)

---

**Satisfying Sexual Events (SSEs)**

- The mean absolute number of SSEs for the screening month (no-treatment month) and the baseline month (placebo month) ranged from 0.7 to 0.8 and 1.5 to 1.9, respectively.

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**FSFI: Desire & Arousal Domain Scores**

- The mean change from baseline for the Desire domain was statistically significant for all doses compared to placebo.
- The mean change from baseline for the Arousal domain was not statistically significant for all doses compared to placebo.
The mean absolute FSDS-DAO Score for the screening month (no-treatment month) and the baseline month (placebo month) ranged from 38.9 to 41.7 and 30.5 to 33.3, respectively. Total score can range from 0 to 60. The higher the score the greater the distress associated with sexual dysfunction.

Lybrido and Lybridos

- Testosterone/Sildenafil (Lybrido): increases the brain’s response to sexual cues and enhances genital sexual response
- Testosterone/Buspirone (Lybridos): increases the brain’s response to sexual cues and reduces the inhibitory response to sexual cues.
- Based on the concept of HYPERactive INHIBITORY response, HYPOactive EXCITATORY response or combination of both

Lybrido and Lybridos - PKPD

Lybrido and lybridos have a unique release profile. Testosterone is released directly and sildenafil (lybrido) or buspirone (lybridos) are release 2.5 hrs later so that the effects of the separate components coincide.

T=5 mg, Buspirone=10 mg, Sildenafil=50 mg

Pharmacokinetic curve of T

Pharmacokinetic curve of Sildenafil

Pharmacokinetic and dynamic curve of Sildenafil and Buspirone

Sublingual route

Oral route

Testosterone

Sildenafil/SHTIR

Thank You!

Sheryl.Kingsberg@UHhospitals.org