Hypoactive Sexual Desire Disorder (HSDD)

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Professor of Clinical Medicine

Conflict Of Interest Disclosure Statement

• Advisory board: AMAG, Allergan, Valeant Pharmaceuticals
• Speaker: AMAG, Pfizer and Valeant Pharmaceuticals
• Writing support: Allergen, Pfizer Pharmaceuticals
Objectives

• Describe epidemiology, associated features, and indications for psychological treatment and pharmacotherapy for HSDD.

• Explain mechanism of action, efficacy, safety, and treatment considerations for flibanserin, a centrally acting, oral daily FDA approved medication for generalized, acquired HSDD in premenopausal women.

• Discuss efficacy and safety of testosterone therapy for HSDD in late reproductive age and postmenopausal women.

• Review published Clinical Guidelines and Position Statements regarding testosterone therapy for women, and discuss practical considerations and applications regarding off-label, evidenced-based testosterone therapy.

• Discuss drugs in development for HSDD and future directions.

The Sexual Response Cycle

Modified by Kaplan (1974) and Georgiadis et al. (2012)

Hypoactive Sexual Desire Dysfunction (HSDD): DSM IV-TR, ICSM (clinical principle)

• 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


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

### Classification: DSM-IV-TR vs. DSM-5

<table>
<thead>
<tr>
<th>Defined by Onset</th>
<th>Defined by Context</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifelong</td>
<td>Generalized</td>
<td>Clinically significant distress &amp; persistence</td>
</tr>
<tr>
<td>Present since onset of sexual functioning</td>
<td>Not limited to certain types of stimulation, situations, or partners</td>
<td>Subtypes: Psychogenic, organic, mixed, unknown etiology</td>
</tr>
<tr>
<td>Acquired</td>
<td>Situational</td>
<td>Duration &amp; frequency (6 months, &gt; 75% of encounters)</td>
</tr>
<tr>
<td>Develops after period of “normal” functioning</td>
<td>Limited to certain types of stimulation, situations or partners</td>
<td>Severity: mild, moderate, severe</td>
</tr>
</tbody>
</table>

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders 2000;4

### Female Sexual Response Cycle: Circular Model

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

Hypoactive Sexual Desire Disorder (HSDD)

**Sexual desire is a construct that is not specifically event-related.**

*Grade B: level of evidence 2-3*

Manifests as *any* of the following for a minimum of six months:

- Lack of motivation for sexual activity as manifested by either:
  - Reduced or absent spontaneous desire (sexual thoughts or fantasies)
  - Reduced or absent responsive desire to erotic cues and stimulation or inability to maintain desire or interest through sexual activity
- Loss of desire to initiate or participate in sexual activity, including behavioral responses such as avoidance of situations that could lead to sexual activity, that is not secondary to sexual pain disorders
- AND is combined with clinically significant personal distress that includes frustration, grief, incompetence, loss, sadness, sorrow, or worry


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**Case Scenario – Premenopausal ♀ with HSDD**

- **Julia – age 41, seeks treatment for Hypoactive Sexual Desire Disorder (HSDD)**

**SEXUAL HISTORY**

- Distressing low sexual desire for 5+ years
- Low or no initiation, frequency once monthly or less
- Motivation is not endogenous drive
- Rare masturbation
- Normal arousal & orgasm, no sexual pain
- Husband Geoffrey age 46, normal sexual function
- Individual and couples therapy have not improved sex life
Case Scenario – Premenopausal ♀ HSDD (2)

- Marriage as solid and supportive
- Alcohol use, 1-2 glasses of wine, 3-4 nights/week
- Work related social events - alcohol is “part of the job”
- OCPs since age 16, discontinued 3 years ago due to low sex drive, nl menses
- Depression since age 18, intermittent use of SSRIs
- Currently on venlafaxine (SNRI) 75 mg daily for 3 years
- Physical exam: general & pelvic normal
- Lab: nl TSH, prolactin, FT4, calculated free testosterone 0.4 (nl 0.6-0.8), SHBG 95
  (http://www.issam.ch/freetesto.htm)

Treatment Strategy?

Referral to sex therapist (CBT, mindfulness)  
Bupropion Off label testosterone (male or compounded)

Bremelanotide when available  
FDA-approved Flibanserin

Awaiting published CLINICAL GUIDELINES OR INDICATIONS FOR PHARMACOTHERAPY FOR HSDD
Biopsychosocial Model of Female Sexual Response

Integrated Model of Sexual Dysfunction
Contributors to Desire Problems™

- Biological: Neurotransmitters, Sex Hormones, Illness, Fatigue
- Expectation of negative outcome: Past history of disappointing sex
- Lack of appropriate stimuli: Lack of privacy, Safety, Emotional rapport, Cultural beliefs
- Interpersonal: Trauma (sexual, physical, medical), Negative emotions (anxiety, fear, shame, guilt)
- Intrapersonal development history: Past history of disappointing sex
- Contextual: Trauma (sexual, physical, medical), Negative emotions (anxiety, fear, shame, guilt)

Created by: Sandra Leiblum, PhD.

Processing of Sexual Cues and Stimuli Impacted by Multiple Factors

Cognitive Component: Integration of Signals
- Motor Imagery
- Appraisal
- Attention
- Motivational & Emotional
- Autonomic & Endocrine

Sexual Stimulation

Inhibition / Devaluation / Withholding

Sexual Desire & Appetitive & Consummatory Behavior
The Dual Control Model

Physiological and Organic Issues

−

Physiological and Organic Issues

Sexual Tipping Point®

Variable and Dynamic Process

Inhibition

Excitation

Etiology of HSDD: Imbalance Between Excitation/Inhibition

- Dopamine
- Oxytocin
- Melanocortin
- Vasopressin
- Norepinephrine
- Intimacy
- Shared values
- Romance
- Experience/behavior

Physiological/Organic

Physiological and Organic Issues

Psychosocial/Interpersonal

- Serotonin
- Opioids
- Endocannabinoids
- Relationship conflict
- Negative stress
- Negative beliefs about sex
- Experience/behavior

Neurotransmitter/Central Regulation of Desire/Arousal


Key Regions in Brain Regulating Sexual Desire

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

Slide courtesy of Jim Pfaus
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


Arnow et al. (2009) Neuroscience, 158, 484-502
Most Prevalent Female Sexual Dysfunction (FSD) is HSDD: Affecting 1 in 10 Women

Prevalence of Female Sexual Problems Associated With Distress

Population: 31,581 US female responders ≥18 years of age from 50,002 households


Decreased Sexual Desire With Distress

Prevalence of Sexual Problems Associated With Sexually Related Personal Distress

N=31,581 women

Sexual pain not measured in this survey

Shifren JL et al. Obstet Gynecol. 2008;112(5);970-978.
HSDD and Personal Distress: WISHeS Study

• Low desire associated with psychological, emotional distress and lower sexual, relationship satisfaction
• >80% of women with HSDD concerned, unhappy, letting partner down
• Dissatisfaction
  • 11 times more likely dissatisfied with sex lives
  • 2.5 times more likely dissatisfied with relationship


Impact of Low Sexual Desire on Quality of Life

Does your level of sexual desire affect other aspects of your personal life?

How does your level of sexual desire affect your relationship with your partner?
Prevalence of Sexual Dysfunction: Role of Depression

<table>
<thead>
<tr>
<th>SEXUAL COMPLAINT</th>
<th>SEXUAL PROBLEM</th>
<th>PROBLEM PLUS DISTRESS</th>
<th>FSD WITHOUT DEPRESSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desire</td>
<td>38.7%</td>
<td>10%</td>
<td>6.3 – 8.8%</td>
</tr>
<tr>
<td>Arousal</td>
<td>26.1%</td>
<td>5.4%</td>
<td>3.3 – 4.7%</td>
</tr>
<tr>
<td>Orgasm</td>
<td>20.5%</td>
<td>4.7%</td>
<td>2.8 – 4.1%</td>
</tr>
<tr>
<td>Any Dysfunction</td>
<td>44.2%</td>
<td>12%</td>
<td>7.6 – 10.7%</td>
</tr>
</tbody>
</table>

N=31,581. Definition of depression: Self-reported depressive sx’s + AD use; AD use without current depressive sx’s; Depressive symptoms without AD use


Diagnosing HSDD in the Clinic

Decreased Sexual Desire Screener (DSDS)

Please answer each of the following questions:

1. In the past was your level of sexual desire or interest good and satisfying to you? □ Yes □ No
2. Has there been a decrease in your level of sexual desire or interest? □ Yes □ No
3. Are you bothered by your decreased level of sexual desire or interest? □ Yes □ No
4. Would you like your level of sexual desire or interest to increase? □ Yes □ No
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 □ Yes □ No
   B. Medication, drugs or alcohol you are currently taking □ Yes □ No
   C. Pregnancy, recent childbirth, menopausal symptoms □ Yes □ No
   D. Other sexual issues you may be having (pain, decreased arousal or orgasm) □ Yes □ No
   E. Your partner’s sexual problems □ Yes □ No
   F. Dissatisfaction with your relationship or partner □ Yes □ No
   G. Stress or fatigue □ Yes □ No

When complete, please give this form back to your clinician.

HSDD: Physical, Medical and Medication Factors

**Medical & Psychiatric Conditions**
- Depression
- Urinary Incontinence
- Neurological Disease
- Cancer
- Genitourinary Syndrome of Menopause
- AIDS
  - Hypothyroidism/Hyperthyroidism
  - Hypothalamic amenorrhea
  - Primary ovarian insufficiency
  - Adrenal Insufficiency
  - Hypopituitarism
  - Pituitary tumors
  - Hypoprolactinemia
  - Following oophorectomy
  - Diabetes
  - Obesity
  - Metabolic Syndrome

**Psychosocial Factors**
- Relationship conflict
- Partner sexual dysfunction
- Fatigue and stress
- Mood disorder
- Poor body image

**Sexual Factors**
- Inadequate stimulation
- Poor attention focus on stimulation
- Poor sexual context
- Pain or diminished arousal

**Medications**
- Psychopharmacologic
  - Antidepressants
  - Antipsychotics
  - Barbiturates
  - Benzodiazepines
  - Hypnotics
- Hormones
  - Oral contraceptives
  - Gonadotropin releasing agonists and analogs
  - Anti-androgens (eg, spironolactone)
  - Anti-estrogens
  - Other
  - Cholesterol-lowering agents
  - Beta-blockers
  - Chemotherapeutics

**Substances of Abuse**
- Legal
- Controlled
- Illegal


**HSDD PROCESS OF CARE**

Ask/Permission to Discuss:
Are you sexually active? What sexual concerns do you have?

- Yes
  - Low sexual interest/desire
  - DSOS and/or Focused Hx
    - Acquired, Generalized HSDD
      - Focused Medical Assessment
        - HSDD with potentially modifiable factors
          - Education
            - Modification
        - HSDD without modifiable factors
          - Education
    - Acquired, Situational low sexual interest/desire
      - Education/ Counseling/ Referral
  - No FSD
    - Other FSD
    - Referral

- No
  - HSDD with potentially modifiable factors
    - Education
    - Modification
    - HSDD without (remaining) modifiable factors
      - Education

Pre-menopausal
- Sex Therapy / CNS agents

Peri-menopause (late reproductive yrs)
- Sex Therapy / CNS Agents / Androgens

Post-menopausal
- PreTx labs
Identification of Psychological Factors Contributing to HSDD Helps Determine Appropriate Intervention

<table>
<thead>
<tr>
<th>Psychological Factor</th>
<th>Recommended Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression/anxiety</td>
<td>Pharmacotherapy/cognitive behavioral therapy</td>
</tr>
<tr>
<td>Poor self/body image</td>
<td>Psychotherapy</td>
</tr>
<tr>
<td>Stress/distraction</td>
<td>Cognitive behavioral therapy</td>
</tr>
<tr>
<td>History of abuse (physical, sexual, emotional)</td>
<td>Psychotherapy</td>
</tr>
<tr>
<td>Substance abuse</td>
<td>Psychotherapy</td>
</tr>
<tr>
<td>Self-imposed pressure for sex</td>
<td>Office-based counseling or refer for cognitive behavioral therapy</td>
</tr>
<tr>
<td>Religious, personal, cultural or family values, beliefs and taboos</td>
<td>Office-based counseling or refer for cognitive behavioral therapy</td>
</tr>
<tr>
<td>Relationship factors</td>
<td>Office-based counseling or refer for individual/couples therapy</td>
</tr>
<tr>
<td>Lifestyle factors (e.g., fatigue, sleep deprivation)</td>
<td>Office-based counseling</td>
</tr>
<tr>
<td>Sexual factors (e.g., inadequate stimulation)</td>
<td>Office-based counseling</td>
</tr>
</tbody>
</table>


Psychotherapy Trials for HSDD

- Mindfulness Meditation Training and CBT trials all small with waitlist or uncontrolled—no placebo
- 3 CBT trials and 2 MMT trials superior to wait-list control¹
  - Insufficient data to conclude efficacy due to
    - Lack of hierarchy of endpoints and preplanned primary endpoints
    - Lack of randomization
    - Lack of adequate control/placebo
- Nocebo Effect: A negative placebo effect
  - Waiting list may be a nocebo condition in psychotherapy trials²

What are the FDA Recognized Measures to Assess HSDD in Clinical Trials?

• Female Sexual Function Index (FSFI)
• Female Sexual Distress Scale-Revised (FSDS-R)
  • Item 13: distress related to low sexual desire
• Satisfying Sexual Events (SSEs)

Female Sexual Function Index (FSFI)

• Developed and validated as a “brief self-report measure of female sexual arousal and other relevant domains of sexual functioning in women”
• Full scale consists of 19 questions, 6 domains over 4 weeks
  – Desire (2 questions)
  – Arousal (4 questions)
  – Lubrication (4 questions)
  – Orgasm (3 questions)
  – Satisfaction (3 questions)
  – Pain (3 questions)
• Female sexual dysfunction (FSD) = score <26.5
• Limitation: physiologic, genital aspects; current function
• www.fsfiquestionnaire.com

Flibanserin

- Classified as a multifunctional serotonin agonist and antagonist (MSAA)
- Mixed post-synaptic 5HT\textsubscript{1A} agonist and 5HT\textsubscript{2A} antagonist
  - Exact mechanism unknown
  - 5HT\textsubscript{1A} agonists 5HT\textsubscript{2A} antagonists may have pro-sexual effects
- Activity at dopamine D\textsubscript{4} receptors and moderate affinity for 5HT\textsubscript{2B} and 5HT\textsubscript{2C} receptors
- Region-specific elevations in dopamine and norepinephrine offset inhibitory serotonergic activity resulting in increased desire pathways

Flibanserin

- FDA-approved for acquired, generalized HSDD in premenopausal women not caused by:
  - Medical or psychiatric condition
  - Relationship problems
  - Effects of a medication/drug
- 100 mg PO daily at bedtime
- REMS program: certification to prescribe (for pharmacies to dispense)
- Warnings:
  - Hypotension and syncope due to interaction with alcohol
  - Avoid in patients with liver impairment or on CYP3A4 inhibitors


Flibanserin Clinical Program:
Inclusion Criteria/Baseline Characteristics

- Premenopausal women : Mean Age 36
- HSDD per DSM-IV-TR criteria, generalized acquired type
- HSDD duration ≥24 weeks
- Comorbid secondary FSAD and/or FOD, only if HSDD commenced prior, and of more importance as assessed by the patient
- In a stable, monogamous relationship for at least one year, with a sexually functional partner who was present for at least ½ the time
- Willingness to try to engage in sexual activity at least 1/Mo

<table>
<thead>
<tr>
<th>Baseline Characteristic, Mean (SD)</th>
<th>Placebo (n=536)</th>
<th>Flibanserin 100 mg qhs (n=532)</th>
<th>Cut-Off Scores (Score Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time in relationship, years</td>
<td>10.8 (7.2)</td>
<td>11.1 (7.5)</td>
<td>1</td>
</tr>
<tr>
<td>Duration of HSDD, months</td>
<td>49.5 (44.7)</td>
<td>49.2 (42.5)</td>
<td>6</td>
</tr>
<tr>
<td>SSE, per month</td>
<td>2.7 (2.9)</td>
<td>2.5 (2.5)</td>
<td>N/A (0–+++))</td>
</tr>
</tbody>
</table>

Sprout Report: Sprout Briefing Document, June 2015 Flibanserin Advisory Committee
Flibanserin Trials: Satisfying Sexual Events

Statistically significant separation from placebo in 4-8 weeks (*p < 0.05)


Flibanserin Improves Sexual Desire (FSFI)

Statistically significant separation from placebo at 4 weeks (p < 0.05)

Flibanserin Reduces Distressing Low Sexual Desire (FSDS-R)

25% reduction in distress associated with low desire (p < 0.05)

Reduction in score = improvement


Efficacy Endpoints
Phase 3 Pivotal Studies

<table>
<thead>
<tr>
<th>Study 147</th>
<th>Study 71</th>
<th>Study 75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flibanserin 100 mg qhs</td>
<td>Flibanserin 100 mg qhs</td>
<td>Flibanserin 100 mg qhs</td>
</tr>
<tr>
<td>SSE</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>eDiary Desire</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>FSFI-Desire</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>FSDS-R13 (Distress)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>FSFI-Total Score</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>FSDS-R Total Score</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

**Efficacy of Flibanserin in Three Phase 3 Trials**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Mean baseline</th>
<th>Improvement over baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Satisfying sexual events</td>
<td>2–3/mo</td>
<td>0.5–1.0/mo (median)</td>
</tr>
<tr>
<td>FSFI desire (range, 1.2–6.0)</td>
<td>1.8–1.9</td>
<td>0.3–0.4</td>
</tr>
<tr>
<td>Daily desire (range, 0–84)</td>
<td>10–12</td>
<td>1.7–2.3</td>
</tr>
<tr>
<td>Distress (range, 0–4)</td>
<td>3.2–3.4</td>
<td>0.3–0.4</td>
</tr>
</tbody>
</table>

*Improvement data represent least-square means, unless otherwise noted. Improvement in daily desire was not statistically significant. FSFI denotes Female Sexual Function Index. For the FSFI and daily desire scales, the higher the number, the greater the sexual desire. For the distress scale, the higher the number, the greater the distress.

Joffe et al. NEJM 2016;374(2):101-104.

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**Flibanserin: Magnitude of Response**

*Responder defined as much improved or very much improved*

Flibanserin 100 mg qhs FAS
Flibanserin 100 mg qhs responders

FAS = full analysis set; FSDS-R13 = Female Sexual Distress Scale-Revised Item 13; FSFI-D = Female Sexual Function Index-Desire domain; SSE = satisfying sexual event; PGI-I = Patient Global Impression of Improvement

Data on file: Sprout Pharmaceuticals, Inc.
Clinical Relevance
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?

Common Adverse Events in ≥1%

<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>

Adverse Events and Discontinuation

- Hypotension was observed in 0.2% of patients taking flibanserin compared to 0.1% of subjects taking placebo.

- Syncope occurred in 0.4% on flibanserin compared to 0.2% on placebo.

- Discontinuation rates due to adverse effects for women taking 100 mg/day 13.4 vs.10.1% for placebo, 11.4 vs 3.4% & 9.6 vs. 3.7%.

CNS Drugs Have Similar Adverse Event (Aes) Profiles

<table>
<thead>
<tr>
<th>Flibanserin</th>
<th>Bupropion</th>
<th>Buspirone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>11.4%</td>
<td>13.5%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>11.2%</td>
<td>Agitation 9.7%</td>
</tr>
<tr>
<td>Nausea</td>
<td>10.4%</td>
<td>Dry Mouth 9.2%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9.2%</td>
<td>Constipation 8.7%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4.9%</td>
<td>Excessive sweating 7.7%</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>2.4%</td>
<td>Dizziness 6.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nausea/vomiting 1.0%</td>
</tr>
</tbody>
</table>

Most AEs were transient or episodic, mild to moderate in severity, and mitigated by bedtime dosing

Flibanserin Prescribing Information, 2015.
Flibanserin, Depression, SSRI/SNRIs

Division Summary, phase 3 placebo-controlled trials

SS/NRIs

- Depression more common among flibanserin treated subjects than placebo; incidence is dose-proportional...no signal of suicidality
- Flibanserin did not exacerbate depression or anxiety in patients taking SSRI or SNRI medication.
- Combination of flibanserin with SS/NRI exacerbated dizziness and insomnia (in dedicated SSRI study).
- Adverse events exacerbated by concomitant use of flibanserin with an SS/NRI were anxiety, somnolence, fatigue, insomnia, and dizziness (pivotal trial).

Findings should not preclude concomitant use but consideration should be given...

Phase 1 Alcohol Challenge Study

Study consisted of 5 single dose study periods; subjects received each of the 5 treatments

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Dosing Regimen</th>
<th>0.4 g/kg EtOH is equivalent to each of the following in a 70 kg (~154 lb) person:</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 subjects</td>
<td>A. 0.8 g/kg EtOH + flibanserin 100 mg</td>
<td>Two 12 oz cans of beer containing 5% alcohol content</td>
</tr>
<tr>
<td>(23 men, 2 women)</td>
<td>B. 0.8 g/kg EtOH + placebo</td>
<td>Two 5 oz glasses of wine containing 12% alcohol content</td>
</tr>
<tr>
<td>Mean age: 31 years (21-52)</td>
<td>C. 0.4 g/kg EtOH + flibanserin 100 mg</td>
<td>Two 1.5 oz shots of 80-proof spirit</td>
</tr>
<tr>
<td>Fasted for 10 hours</td>
<td>D. 0.4 g/kg EtOH + placebo</td>
<td></td>
</tr>
<tr>
<td>Ate a light breakfast</td>
<td>E. Flibanserin 100 mg</td>
<td></td>
</tr>
<tr>
<td>Administered study drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Given up to 10 minutes to ingest liquid solution (orange juice or ethanol [EtOH] + orange juice)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ClinicalTrials.gov. September 2017
Flibanserin and Alcohol

• Results
  • Participants took 100 mg flibanserin in morning and consumed 2 alcoholic drinks rapidly.
  • 17% required intervention for symptomatic hypotension
  • Orthostatic hypotension in 25% of subjects who consumed 100 mg of flibanserin and equivalent of 4 drinks
• Phase 3 trials not regulating alcohol documented no increase in syncope
  • No difference: 0.4% flibanserin; 0.2% placebo
  • Safety concerns raised by FDA, including hypotension/syncope rare to infrequent with proper bedtime dosing


Effects of Alcohol Administered with Flibanserin in Healthy Premenopausal Women

Subjects received each of the 5 treatments according to a randomized sequence:
- 0.4 g/kg ETOH (equivalent to):
- 0.8 g/kg ETOH (equivalent to):
- Orange Juice

Results:
- In this large, 7-treatment, 12-sequence, crossover study, administration of alcohol with flibanserin was not associated with an increased risk of hypotension and syncope
- 1 Subject in the ADDYI + 0.4 g/kg ETOH group experienced hypotension
- Adverse event profile for concomitant administration of mild (0.2 g/kg) or moderate (0.4 g/kg) quantities of ethanol with flibanserin was similar to that of flibanserin alone
- Increased drowsiness following administration of flibanserin (with or without ethanol) in this study supports the recommended (bedtime) dosing

Sicard, E; Effects of Alcohol Administered with Flibanserin on Dizziness, Syncope, and Hypotension in Healthy Premenopausal Women
Flibanserin Prescribing

• Due to alcohol interaction with flibanserin
  • Patients must abstain from alcohol
  • Prescribers evaluate patient’s ability to do this
• Contraindications:
  • Use of alcohol
  • Use of moderate or strong CYP-3A4 inhibitors
    • HIV drugs, antifungals, antibiotics (cipro, macrolides), diltiazem, verapamil, conivaptan, nefazodone
  • Hepatic impairment

Oral Contraceptives and Flibanserin

• Oral contraceptives (OC) are classified as weak CYP3A4 inhibitors
• Meta-analysis results from phase 1 studies showed exposure to flibanserin was slightly increased when co-administered with OC
• Concomitant use of flibanserin and OC (30 mcg ethinyl estradiol/150 mcg levonorgestrel) may increase risk of AEs
  • Dizziness, somnolence, and fatigue

Fluconazole and Flibanserin


Flibanserin-REMS program

- Must become a certified prescriber
  - Providers/pharmacies MUST participate in Risk Evaluation and Mitigation Strategy (REMS)
- To mitigate the increased risk of hypotension and syncope due to alcohol use
- To become a certified prescriber go to
  [www.AddyiREMS.com](http://www.AddyiREMS.com)
  - Read the prescribing information and complete training program
  - Complete an assessment
  - Enroll
Systemic Testosterone for Treatment of Low Libido

Randomized, placebo controlled trials consistently show benefits of transdermal testosterone vs. placebo for sexual desire and arousal, orgasm, pleasure, satisfaction, and pain.

• Surgically postmenopausal women on E (A)
• Naturally postmenopausal women on E & P (A)
• Postmenopausal women on no other HT (A)
• Premenopausal women in late reproductive years (B)
• Treatment emergent SSRI/SNRI antidepressant induced SD (B)
• POF/POI with HSDD (expert opinion, clinical principle)
• No RCT data: Premenopausal women on COCs
• Lack of RCT data supporting use of systemic DHEA

Published Randomized Studies Demonstrating Efficacy of Testosterone (Patch) in Postmenopausal Women

<table>
<thead>
<tr>
<th>Study</th>
<th>Doses (mcg/d)</th>
<th>Subjects (n)</th>
<th>Estrogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shifren et al, 2000</td>
<td>150/300</td>
<td>SM (75)</td>
<td>+</td>
</tr>
<tr>
<td>Braunstein, et al 2005</td>
<td>150/300/450</td>
<td>SM (447)</td>
<td>+</td>
</tr>
<tr>
<td>Buster et al, 2005</td>
<td>300</td>
<td>SM (533)</td>
<td>+</td>
</tr>
<tr>
<td>Simon et al, 2005</td>
<td>300</td>
<td>SM (562)</td>
<td>+</td>
</tr>
<tr>
<td>Davis et al, 2006</td>
<td>300</td>
<td>SM (61)</td>
<td>+ (patch)</td>
</tr>
<tr>
<td>Davis et al, 2006</td>
<td>300</td>
<td>SM (76)</td>
<td>+ (aromatase inhibitors)</td>
</tr>
<tr>
<td>Shifren et al, 2006</td>
<td>300</td>
<td>NM (486)</td>
<td>+</td>
</tr>
<tr>
<td>Liu et al, 2008</td>
<td>300</td>
<td>NM (431)</td>
<td>+</td>
</tr>
<tr>
<td>Davis et al, 2008</td>
<td>150/300</td>
<td>NM/SM (814)</td>
<td>-</td>
</tr>
<tr>
<td>Panay et al, 2010</td>
<td>300</td>
<td>NM (272)</td>
<td>+/- groups</td>
</tr>
</tbody>
</table>

NM= naturally menopausal
SM= surgically menopausal

Summary of Efficacy & Safety

• **Randomized, double-blind placebo controlled studies have established efficacy of transdermal patch for relieving symptoms of HSDD in naturally and surgically menopausal women with and without concomitant estrogen or estrogen/progesterone therapy**

• Main side effects: increased hair growth and acne

• Available safety data, although not conclusive, were reassuring with respect to cardiovascular, breast, and endometrial outcomes.

• Long term safety data demonstrate no significant impact on intermediate metabolic endpoints and a low rate of cardiovascular events and breast cancer in postmenopausal women at increased cardiovascular risk.
  • No clinically relevant changes in lipids, liver function, hematology, carbohydrate metabolism
  • Small weight gain of 1.7 kg (p<0.05)
  • Small increase in blood pressure (<2 mm Hg) (p>0.05)
  • Rate of invasive breast cancer consistent with age appropriate expected rates

Khera M. Sex Med Rev 2015;3:137-144
Testosterone Therapy: Who to Treat

• Primary indication for testosterone therapy: treatment of persistent low libido that profoundly impairs quality of life
• Women late reproductive years and beyond who have experienced distinct change and are distressed
• Women with the following conditions & distressing loss of libido:
  • Surgical menopause
  • Premature ovarian failure
  • Adrenal insufficiency (including glucocorticosteroid)


Testosterone Therapy: 2009-2016

• ICSM 2009, 2015; ACOG Practice Bulletin 2011, reaffirmed 2017
• NAMS Recommendation for Clinical Care 2014, IMS 2016
• Decision to use T individualized, informed consent
• No pretreatment T level defines androgen deficiency
• Long term safety data lacking to support use > 6 months
• Current data do not support T in pre and peri-menopausal ♀
• Achieving physiological free T levels by transdermal delivery decreases adverse effects
• Relative contraindications: androgenic alopecia, seborrhea, acne, hirsuitism
• Contraindications: hyperlipidemia, liver dysfunction
• Contraindicated with or high risk: breast & endometrial cancer, CVD, veno-thrombotic events pending additional safety data

Clinical Guidelines - UpToDate

- Topical compounded 1 percent testosterone cream or gel (0.5 grams daily) applied daily (no regulation)
- Intrinsa 300 mg patch (2x/week) no longer in Europe (consistent blood levels)
- Transdermal patches and gels for men (supraphysiologic dosing, 1/10th dose; arms, legs, abdomen, risk to children)
- Oral: methyltestosterone, micronized testosterone (compounded), DHEA
- Intramuscular injections or implants (supra-physiologic dosing)

Available preparations for Postmenopausal Women not responding to nonpharmacological therapy
Not FDA approved
Long term safety data lacking

Off-Label Non-Hormonal Pharmacologic Therapy for HSDD

**Buproprion**
- Norepinephrine-dopamine reuptake inhibitor (NDRI)
  - Inhibits dopamine transporter and norepinephrine transporter
- Investigated in several clinical trials for the treatment of HSDD
  - Buproprion improved sexual function (as measured by CSFQ and BISF-W), but had no effect on frequency

**Buspirone**
- Presynaptic serotonin 5-HT_{1A} partial agonist
  - Greater presynaptic than postsynaptic effects, resulting in a reduction in serotonergic tone
- Post hoc analysis of add-on buspirone to selective serotonin reuptake inhibitors (SSRI) for the treatment of depression
  - 58% of subjects treated with buspirone reported an improvement in sexual function, compared with 30% treated with placebo

BISF-W, Brief Index of Sexual Functioning in Women; CSFQ - Changes in Sexual Functioning Questionnaire
### Drugs in Development for HSDD

<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>Lybrido (on demand oral tablet)</td>
<td>sildenafil + testosterone</td>
<td>Emotional Brain</td>
<td>Phase II completed for HSDD No activity in ClinTrials.gov</td>
</tr>
<tr>
<td>Lybridos (on demand oral tablet)</td>
<td>buspirone + testosterone</td>
<td>Emotional Brain</td>
<td>Phase II in completed for HSDD No activity in ClinTrials.gov</td>
</tr>
<tr>
<td>Bremelanotide (PT-141) subq injection (PL6983)</td>
<td>melanocortin receptor 4 agonist</td>
<td>AMAG Pharmaceuticals</td>
<td>Phase II B for FSAD completed Phase III completed for HSDD; extension ongoing. NDA planned 1Q19</td>
</tr>
<tr>
<td>Topical testosterone gel (Libigel)</td>
<td>testosterone</td>
<td>BioSante Pharmaceuticals</td>
<td>Phase III efficacy (failed) Phase III safety (stopped early)</td>
</tr>
<tr>
<td>Intransal testosterone gel (Tefina™)</td>
<td>testosterone</td>
<td>Trimel Pharmaceuticals</td>
<td>Phase II completed for anorgasmia No activity in ClinTrials.gov</td>
</tr>
<tr>
<td>Extended release daily oral bupropion and trazodone (Lorexys™)</td>
<td>bupropion and trazodone</td>
<td>SP-1 Biopharma</td>
<td>Phase II completed No activity in ClinTrials.gov</td>
</tr>
<tr>
<td>Transdermal sildenafil delivery system (SST 6007)</td>
<td>sildenafil</td>
<td>Strategic Science &amp; Technologies, LLC</td>
<td>Phase II for FSAD No activity in ClinTrials.gov</td>
</tr>
</tbody>
</table>

ClinTrials.Gov 9/17

### Key Points: HSDD Treatment Approaches

- HSDD is a prevalent condition affecting 1 in 10 women.
- Current standard of non-pharmacological care includes CBT, mindfulness, and psychotherapy; also office based counseling.
- Flibanserin is moderately effective for pre-menopausal women with generalized, acquired HSDD.
- Flibanserin must be prescribed in conjunction with the REMS and is contraindicated with strong CYP-3A4 inhibitors.
- Testosterone is effective for late reproductive and post-menopausal women with distressing low libido.
- Barriers exist related prescribing, patient eligibility and access.
- Drugs with combined CNS and peripheral mechanisms are in development.
ARS Question 1

Flibanserin, indicated for generalized acquired HSDD in premenopausal women, is contraindicated with all of the following except:
• a. Fluconazole
• b. Oral contraceptives
• c. Alcohol
• d. Clinically advanced hepatitis C
• e. SSRIs in patient with daytime sedation

ARS Question 2

Regarding testosterone therapy in women, which of the following is true:
 a. Testosterone is effective for both pre and postmenopausal women with HSDD.
 b. Main adverse events include increase rates of breast cancer.
 c. Pretreatment blood levels predict treatment response.
 d. Achieving physiological free T levels by transdermal delivery decreases adverse effects.
 e. Women receiving testosterone therapy should be prescribed 1/5th of the standard male dose.