Learning Objectives

1. Discuss the epidemiology and pathophysiology associated with hypoactive sexual desire disorder
2. Describe the diagnostic criteria associated with hypoactive sexual desire disorder
3. Discuss the current treatment therapies available for hypoactive sexual desire disorder
4. Evaluate the current literature available for flibanserin and formulate a treatment strategy for hypoactive sexual desire disorder
Female Sexual Dysfunction

1. Definition as per *Diagnostic and Statistical Manual of Mental Disorder, 4th edition, text revision* (DSM-IV-TR): Generally characterized as any sexual complaint or problem resulting from disorders of desire, arousal, orgasm, or sexual pain that causes marked distress or interpersonal difficulty [1-3]

2. DSM-IV Female Sexual Dysfunction (FSD) Diagnosis[2, 4, 5]
   a. Hypoactive Sexual Desire Disorder (HSDD)
      i. Persistent/recurrent absence or deficiency of sexual desire or receptivity to sexual activity that causes marked distress or interpersonal difficulty
      ii. Not caused by a co-existing medical or psychiatric disorder (i.e. depression, mood disorders), medication, or a problem within a relationship
      iii. Most common sexual dysfunctional syndrome in women
   b. Female arousal disorder
      i. Inability to complete sexual activity with adequate lubrication
      ii. Affects roughly 5% of U.S. women
   c. Female orgasmic disorder
      i. Persistent/recurrent absence or delay of orgasm after a normal excitement phase
      ii. Affects 3.4-5.8% of U.S. women
   d. Sexual pain disorders
      i. Vaginismus
         1. Recurrent or persistent involuntary spasm of the muscles of the outer one-third of the vagina
         2. Affects 1-6% of U.S. women
      ii. Dyspareunia
         1. Recurrent or persistent genital pain associated with sex and not caused exclusively by lack of lubrication or by vaginismus
         2. Common among postmenopausal women; affects roughly 8-22% of U.S. women


<table>
<thead>
<tr>
<th>Table 1: DSM-IV versus DSM-V Female Sexual Dysfunction Diagnosis[6]</th>
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<tbody>
<tr>
<td><strong>DSM-IV TR</strong></td>
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<tr>
<td>Hypoactive sexual desire disorder</td>
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<tr>
<td>Female arousal disorder</td>
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<td>Female orgasmic disorder</td>
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<tr>
<td>Dyspareunia</td>
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<td>Vaginismus</td>
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Hypoactive Sexual Desire Disorder

1. History[4-6]
   b. No longer a stand-alone diagnosis in recent 2013 DSM-V guidelines
   c. The American College of Obstetricians and Gynecologists (ACOG) continues to recognize HSDD as its own disorder
2. Epidemiology\(^{7-9}\)
   a. Varying data
   b. Prevalence ranges from 26.7% in premenopausal women and 52.4% in naturally menopausal women, according to a representative sample taken in the U.S.
   c. Approximately 10% of 31,000 women polled in the U.S. (ages 18-102 years old) reported low sexual desire with related personal distress
   d. Young, premenopausal women
      i. Can be linked to patients experiencing:
         1. Dysfunctional interpersonal relationships
         2. Chronic diseases such as depression or gynecological disorders
         3. Medication use
   e. Women aged 40-60 years old
      i. Disorder peaks in this age range and in women who have undergone surgical menopause
      ii. Can be linked to patients experiencing:
         1. Chronic diseases such as depression
         2. Endocrine problems and adrenal insufficiency
         3. Medication use
      iii. Usually diagnosed as an isolated event
   f. Ethnicities
      i. Highest rates of low sexual desire are reported in Chinese women followed by Japanese, Caucasian, African-American, and Hispanic women, respectively
3. Potential Risks: Commonly Multifactorial\(^{7,10}\)
   a. Medical conditions
      i. Hypothyroidism, cardiovascular disease, diabetes mellitus, chronic rheumatic diseases, and urinary incontinence
      ii. Malignant gynecological diseases - endometriosis and chronic pelvic inflammatory disease
      iii. Menopausal symptoms - vaginal dryness and dyspareunia
   b. Medication related
      i. Antidepressants, ACE-inhibitors, anxiolytics, nonselective \(\beta\)-blockers, and illicit substances
   c. Psychological or interpersonal factors
      i. Anxiety involving intercourse, poor self-esteem, stress, and relationship issues
   d. Female reproductive events/hormone changes
      i. Decreasing testosterone and estrogen levels
      ii. Menstrual cycles, hormonal contraceptives, postpartum states, lactation, oophorectomy, hysterectomy, perimenopausal state, postmenopausal state
4. Classification\(^{7,11}\)
   a. Generalized versus situational
      i. Generalized indicates dysfunction is not limited to certain types of stimulation, situations, or partners
      ii. Situational indicates a lack of desire with current partner
   b. Acquired versus lifelong
      i. Acquired indicates the onset beginning after a period of normal function
      ii. Lifelong infers the person has always had low or no desire

\[\text{Figure 1: Another study showing different results}^{[1]}\]
HSDD Pathophysiology

1. Role of Neurotransmitters\textsuperscript{[12, 13]}
   a. Serotonin (5-HT) - increased in HSDD
      i. Exerts inhibitory effect on sexual function
      ii. Released right after climax

   b. Dopamine (DA) - decreased in HSDD
      i. Elevated levels in brain increases focused attention
         1. Causes each spouse to intensely focus on each other and exclude other surroundings
      ii. Increased dopamine levels associated with increased sexual desire

   c. Norepinephrine (NE) - decreased in HSDD
      i. Generates exhilaration and increased energy
      ii. Studies indicate blood levels increase when anticipating intercourse

Figure 2: Serotonin's regulatory role in both depression and sexual function\textsuperscript{[14]}

HSDD Diagnosis

1. 2013 American Psychiatric Association (APA) Guidelines\textsuperscript{[6]}
   a. Sexual problem must
      i. Be recurrent or persistent
      ii. Cause personal distress or interpersonal difficulty
      iii. Not be due to a different diagnosis
      iv. Not be caused by a medication

\begin{table}[h]
\centering
\begin{tabular}{|c|}
\hline
\textbf{Table 2: HSDD Diagnosis Criterion}\textsuperscript{[7]} \\
Lack of sexual interest or arousal for $\geq 6$ months causing distress \\
+ \\
\hline
At least 4 of the following: \\
\begin{itemize}
\item Absent or reduced sexual activity \\
\item Absent or reduced sexual thoughts \\
\item No initiation of sexual activity \\
\item Absent or reduced sexual excitement during sexual activity \\
\item Desire is not triggered by sexual stimulus \\
\item Absent or reduced genital and/or nongenital changes \\
\end{itemize}
\hline
\end{tabular}
\end{table}
2. Determine if HSDD is caused by:
   a. Physiological effects of a medication → a substance-induced sexual dysfunction
   b. Medical condition → general medical condition-induced sexual dysfunction
3. Differentiate between classifications
   a. Generalized versus situational
   b. Acquired versus lifelong
4. Validated Questionnaires[15]
   a. Decreased Sexual Desire Screener (DSDS)
      i. 5 questions, self-administered
      ii. Assesses for generalized acquired HSDD
   b. Female Sexual Function Index (FSFI)
      i. 19 questions, self-administered
      ii. All dimensions of female sexual function, including sexual satisfaction
   c. Sexual Interest and Desire Inventory-Female (SIDI-F)
      i. 13 items, clinician administered
      ii. Severity of HSDD
   d. Brief Hypoactive Sexual Desire Disorder Screener
      i. 4 questions, self-administered
      ii. HSDD in postmenopausal women
   e. Female Sexual Distress Scale-Revised (FSDS-R)
      i. 13 questions, self-administered
      ii. Distress associated with female sexual dysfunction

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**Treatment Options for HSDD**

| Table 3: Approaching Treatment for Premenopausal Versus Postmenopausal Women[10] |
|-----------------------------------------------|-----------------------------------------------|
| Premenopausal Women | Postmenopausal women |
| • Postpartum or lactating women | • Assess for hormone deficiency |
| o Treat any mood disorder | o Estrogen deficiency |
| o Educate about hormonal changes | i. Begin with replacement estrogen |
| ▪ Consider estrogen vaginal cream | o Androgen deficiency |
| i. Begin with replacement androgen |
| ii. Consider replacement with androgen |
| • Treat any medical problem possibly negatively impacting desire |
| • Medications possibly negatively impacting sexual desire |
| o Consider switching to other medications with fewer sexual side effects or add an antidote medication |
| ▪ Bupropion, sildenafil, flibanserin (premenopausal) |

**Figure 4: Possible HSDD Treatments**
1. Treatment Categories[7,16-18]
   a. Lifestyle assessment and behavioral modifications
      i. Smoking cessation, avoid alcohol abuse and/or illicit drug abuse
      ii. Exercise on a daily basis
      iii. Proper nutrition
      iv. Sleep hygiene techniques
      v. Stress relief techniques
      vi. Social and partnership skills
         1. Regular acts of kindness and affectionate behaviors
         2. Patient and partner’s ability to communicate intimate desires with each other
   b. Psychotherapy[14, 18]: efficacy has not been demonstrated in randomized, controlled trials
      i. Marriage counseling/couple’s therapist
      ii. Psychotherapy[14, 18]: efficacy has not been demonstrated in randomized, controlled trials
         1. Dual sex therapy
            a. Shown success in treatment of desire disorders
            b. Involves psychological and physiological aspects of sexual functioning
            c. Treatment applicable when there is a dysfunctional person in a relationship
            d. Treatment is short-term and behaviorally oriented
            e. Most effective when sexual dysfunction exists apart from other psychopathology
      2. Cognitive behavioral therapy (CBT)
         a. Can be used to treat sexual desire disorders
         b. Revolves around premise that activating events cause negative automatic thoughts leading to disturbed negative feelings and dysfunctional behaviors
         c. Study in 2001 evaluated CBT for women with HSDD[18]
            i. Involved 74 couples in a 12 week program with 2 hour group sessions
            ii. Used the following techniques: psychosexual education, sensate focus, communication skills, positive reinforcement, cognitive restructuring, and sexual fantasies training
            iii. Post-therapy 74% of women considered themselves cured
      3. Analytical oriented sex therapy
         a. One of the most effective treatment modalities which combines sex therapy with psychodynamic and psychoanalytic therapy
         b. Conducted over a longer period of time than usual therapy and allows learning or relearning of sexual satisfaction under the realities of the couple’s daily life
         c. Optimal in treating desire disorders due to developmental and identity issues
   c. Complementary and alternative agents[7]
      i. Efficacy and safety unproven (largely untested)
      ii. Unregulated products and dosages
      iii. Risk of multiple drug interactions
   d. Non-FDA approved pharmacologic options[7,11,19]
      i. Androgen products: testosterone[19]
         1. MOA → Thought to be involved with sexual arousal, genital sensation, libido, and orgasm
            2. Commonly prescribed off-label for HSDD in postmenopausal women against American Endocrine Society and FDA recommendations due to safety concerns associated with hormonal therapy
            3. Studies show questionable efficacy in premenopausal women
            4. Some benefit has been seen with testosterone supplementation in menopausal and postmenopausal females with HSDD; however conflicting evidence has raised debate regarding testosterones’ clinical efficacy in this population
ii. Phosphodiesterase-5 (PDE-5) inhibitor: sildenafil[20]
   1. MOA $\rightarrow$ improves blood flow to genital tissue
      a. PDE-5 inhibitor enhancement of nitric oxide-cyclic guanosine
         monophosphate in nonadrenergic-noncholinergic signaling for women
         seems similar to men
   2. In 2008, a study showed sildenafil demonstrated a significant reduction in adverse
      sexual effects of antidepressants (SSRIs and SNRIs) in premenopausal women

iii. Melanocortin receptor agonist: bremelanotide[21, 22]
   1. MOA $\rightarrow$ involves activating endogenous melanocortin hormone pathways involved
      in sexual arousal response
   2. Currently being studied in subcutaneous formulation which appears to have less
      effect on blood pressure

iv. Psychotropic agents: Bupropion
   1. MOA $\rightarrow$ inhibits dopamine and norepinephrine reuptake; might have a role in pro-
      sexual effects
   2. Studies show that it may increase the frequency of sexual arousal and desire, but
      there is a lack of efficacy and safety data

e. FDA approved pharmacological options
   i. Psychotropic agent
      1. Flibanserin

<table>
<thead>
<tr>
<th>Flibanserin</th>
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<tbody>
<tr>
<td><img src="image" alt="Flibanserin Structural Formula" /></td>
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<tr>
<td>Figure 5: Flibanserin Structural Formula[23]</td>
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</tbody>
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1. Origin[5, 24, 25]
   a. Originally studied as an antidepressant
      i. Failed to show efficacy in phase-2 trials
      ii. Did show potential to increase female sex drive in a post-hoc analysis

2. MOA $\rightarrow$ Exact mechanism unknown[5, 26, 27]
   a. Thought to increase DA and NE activity and reduce 5-HT activity in CNS
      i. 5-HT1A agonist and 5-HT2A antagonist
      ii. 5-HT1A ultimately reduces the release of 5-HT
      iii. Decrease in 5-HT is associated with facilitation of sexual behavior
   b. Moderate antagonist at 5-HT2B, 5-HT2C, and dopamine D4 receptors

3. Flibanserin's Role in HSDD
   a. Mechanism unknown, but predicted to work via enhancing dopaminergic and noradrenergic
      activity in PFC while reducing serotonin release
   b. Believed to restore control in PFC over motivation/rewards and generate sexual desire

4. Pharmacokinetics
   a. 100 mg flibanserin daily at bedtime in premenopausal women
      i. Median Tmax: 45 minutes (to 4 hours)
      ii. $T_1/2$: 11 hours
      iii. Cmax is dose-proportional from 100 – 250 mg

5. Adverse Effects
   a. CNS depression, dizziness, somnolence, nausea, fatigue, insomnia, dry mouth, syncope, hypotension

6. Contraindications
   a. Moderate to strong CYP3A4 inhibitors
      i. Fluconazole, clarithromycin
   b. Alcohol
1. Flibanserin Timeline

- **June 2010**
  - FDA votes unanimously that the benefits of flibanserin from Boehringer Ingelheim did not outweigh side effects (fatigue, depression, fainting spells) after first two phase 3 trials

- **Dec 2013**
  - After acquiring rights, Sprout Pharmaceuticals files an appeal with FDA to reconsider rejection of flibanserin
  - FDA again rejects flibanserin after third phase 3 trial

- **Feb 2014**
  - FDA requests more studies; door is open for approval if studies indicate safety
  - Flibanserin is resubmitted to FDA following a lobbying blitz by politicians, women's groups, and consumer advocates

- **June 2015**
  - FDA raises concerns again in a review that comes 2 days before a meeting with external advisors
  - Advisory panel votes 18-6 to approve flibanserin for premenopausal HSDD

- **July 2015**
  - Critics in FDA’s Office of New Drugs express concern over flibanserin efficacy when safety profile is not yet fully approved

- **Aug 2015**
  - FDA approves flibanserin with a Black Box warning and a risk strategy (REMS)
  - Valeant Pharmaceuticals buys Sprout; flibanserin on market as of 4th quarter of 2015

*Figure 6: Timeline to Flibanserin FDA Approval* [28]

2. Flibanserin Trials in Premenopausal women
   a. Non-pivotal phase-3 special studies
      i. ROSE
         1. Part 1: long-term safety
         2. Part 2: withdrawal effects
      ii. SUNFLOWER
         1. Longest and largest trial observing flibanserin in women with HSDD
         2. Primary end points were adverse effects seen in previous trials
         3. Included women who had received flibanserin in a previous placebo-controlled trial
   b. Pivotal phase-3 supportive efficacy trials
      i. DAISY, VIOLET, BEGONIA
### Table 4: Flibanserin Trials in Premenopausal Women[5, 7, 29-33]

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Drug</th>
<th>Control</th>
<th>End Points</th>
</tr>
</thead>
</table>
| ROSE (2011): Goldfishe et al, multicenter, North America, 48-wk trial | Open-label, flexible-dose study for 24 wk, followed by an additional 24-wk randomized, double-blind, placebo-controlled trial | Open-label: all on flib (n=749); Flexible-flib dosing: 50 mg qhs, 50 mg BID, 100 mg qhs (n=163) | Placebo (n=170) | Δ from baseline to randomization
SSE: 2.6 (0.2)
eDiary desire score: 13.2 (0.6)
Δ from randomization to study end
SSE: flib -1.4 (0.3), placebo -2.3 (0.3) p<0.01
eDiary desire score: flib -4.9 (1.1), placebo -8.2 (1.1) p< 0.05 |
| DAISY (2012): Thorp et al, multicenter, North America, 24-wk trial | 4-wk baseline phase followed by 24-wk randomized, double-blind, placebo-controlled trial | Flib 25 mg bid, 50 mg bid, 100 mg qhs (n=1,183) | Placebo (n=398) | Mean Δ SSEs/mo, baseline to wk 24
Flib 25 mg BID 1.4 (p= 0.29 vs placebo)
Flib 50 mg BID 1.4 (p= 0.20 vs placebo)
Flib 100 mg daily 1.9 (p< 0.01 vs placebo)
Placebo 1.1
Mean Δ sexual desire score, baseline to wk 24
Flib 25 mg BID 7.9 (p= 0.28 vs placebo)
Flib 50 mg BID 8.8 (p= 0.06 vs placebo)
Flib 100 mg daily 8.5 (p= 0.12 vs placebo)
Placebo 6.8 |
| VIOLET (2012): DeRogatis et al, multicenter, North America, 24-wk trial | 4-wk baseline phase followed by 24-wk randomized, double-blind, placebo-controlled trial | Flib 50 mg qhs, 100 mg qhs (n=585) | Placebo (n=295) | Mean Δ SSEs/mo, baseline to wk 24
Flib 50 mg daily 1.4 (p< 0.05 vs placebo)
Flib 100 mg daily 1.6 (p< 0.01 vs placebo)
Placebo 0.8
Mean Δ sexual desire score, baseline to wk 24
Flib 50 mg daily 8.2 (p= 0.25 vs placebo)
Flib 100 mg daily 9.1 (p= 0.07 vs placebo)
Placebo 6.9 |
| SUNFLOWER (2012): Jayne et al, multicenter, North America, 52-wk trial | 52-wk, uncontrolled, open-label, extension study | Flexible-dose flib: 50-100 mg qhs or 25 or 50 mg bid (n=1,723) | Placebo (n=1,705) | Somnolence, sedation, fatigue, dizziness, nausea, and vomiting reported by 1.5, 1.6, 7.6, 6.9, 6.3, and 1.4% patients, respectively
Overall reported AEs 1,282 women (74.4%)
Discontinuation due to AEs
185 women (10.7%)
Reported serious AEs 20 women (1.2%) |
| BEGONIA (2013) Katz et al, multicenter, North America, 24-wk trial | 4-wk baseline phase followed by 24-wk randomized, double blind, placebo-controlled trial | Flib 100 mg qhs (n=542) | Placebo (n=545) | Mean Δ in SSEs, baseline to study end
Flib 2.5 (4.6) vs placebo 1.5 (4.6) p< 0.001
Mean Δ in FSFI desire domain, baseline to study end
Flib 1.0 (0.1) vs placebo 0.7 (0.1) p< 0.001 |
| SNOWDROP (2014) Simon et al, multicenter, North America, 24-wk trial | 4-wk baseline phase followed by 24-wk randomized, double-blind, placebo-controlled trial | Flib 100 mg qhs (n= 468) | Placebo (n= 481) | Mean Δ in SSEs, baseline to study end
Flib 1.0 (0.1) vs placebo 0.6 (0.1) p= 0.004
Mean Δ in FSFI desire domain, baseline to study end
Flib 0.7 (0.1) vs placebo 0.4 (0.1) p< 0.001 |

flib= flibanserin
Δ= change
SSEs= satisfying sexual events

<table>
<thead>
<tr>
<th>Objectives</th>
<th>To analyze the efficacy and tolerability of flibanserin in the treatment of premenopausal women with HSDD</th>
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<tbody>
<tr>
<td><strong>Design</strong></td>
<td><strong>Inclusions</strong></td>
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<tr>
<td></td>
<td>• 1,584 women randomized in a double-blind, placebo-controlled trial conducted at 77 center in U.S. and Canada</td>
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<td>• Included a 4-week baseline period followed by a 24-week treatment period</td>
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<td><strong>Exclusions</strong></td>
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<tr>
<td></td>
<td>• Clinically relevant conditions that might interfere with trial</td>
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<tr>
<td></td>
<td>• Sexual dysfunctions other than HSDD, arousal disorder, or orgasmic disorder</td>
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<td>• Psychiatric disorder that could impact sexual function</td>
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<td></td>
<td>• Major Depressive Disorder within previous 6 months</td>
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<td>• Score ≥14 on Beck Depression Inventory II</td>
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<td>• Use of sex hormones other than contraceptives</td>
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<td></td>
<td>• Any medication that may affect sexual function within previous 4 weeks</td>
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<tr>
<td></td>
<td>• Gynecological disorder</td>
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<td>• Partner with inadequately treated sexual dysfunction</td>
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<td><strong>Population</strong></td>
<td><strong>Inclusions</strong></td>
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<tr>
<td></td>
<td>• Women ≥18 years old</td>
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<td>• Premenopausal</td>
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<td></td>
<td>• Diagnosed with generalized, acquired HSDD for ≥24 weeks</td>
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<td>• FSDS-R score ≥15</td>
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<td>• A rating on the receptivity item of the Sexual Interest and Desire Inventory-Female of 0 or 1</td>
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<td>• In stable, heterosexual relationship for ≥1 year with sexually functional partner</td>
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<td>• Compliant with use of eDiary o ≤5 days of missing data during the 4-week baseline period</td>
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<td><strong>Exclusions</strong></td>
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<td>• Partner with inadequately treated sexual dysfunction</td>
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<tr>
<td><strong>Interventions</strong></td>
<td><strong>Randomized for 24 weeks with:</strong></td>
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<tr>
<td></td>
<td>• Flibanserin 25 mg twice daily</td>
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<td>• Flibanserin 50 mg twice daily (uptitrated from 50 mg once daily at week 2)</td>
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<td>• Flibanserin 100 mg daily at bedtime (uptitrated from 50 mg once daily at week 2)</td>
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<td>• Placebo</td>
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<tr>
<td><strong>Endpoints</strong></td>
<td><strong>Two co-primary:</strong> Change from baseline (weeks -4-0) to study end (weeks 21-24) in number of satisfying sexual events (SSE) and in sexual desire score, both measured using an eDiary</td>
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<td><strong>Secondary:</strong> Change in:</td>
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<td>• Female Sexual Distress Scale-Revised (FSDS-R) total score and item 13 score (distress due to low sexual desire)</td>
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<td>• Female Sexual Function Index (FSFI) total and desire domain scores</td>
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<td>• Patient’s Global Impression of Improvement (PGI-I) and Patient Benefit Evaluation (PBE) scores</td>
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<td></td>
<td><strong>Safety:</strong> Evaluation of AEs, clinical laboratory parameters (sex hormones, hematology, biochemistry, and urinalysis), vital signs, physical findings, and ECG data</td>
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<tr>
<td><strong>Statistics</strong></td>
<td><strong>Sample size of 304 participants per treatment group calculated a 90% power at the two-sided α=0.0167 level of significance to detect a meaningful difference between flibanserin and placebo</strong></td>
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<td>• Frequency counts of SSE were analyzed using the Wilcoxon Rand-Sum test (two-sided test, overall α=0.05)</td>
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<tr>
<td><strong>Results</strong></td>
<td><strong>Patients:</strong></td>
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<td></td>
<td>• 1,584 women were randomized to receive placebo (n= 399), flibanserin 25 mg bid (n= 396) flibanserin 50 mg bid (n= 393), or flibanserin 100 mg qhs (n= 396)</td>
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<td>• 1,071 women completed the trial (n = 287 [72.1%] placebo, n = 274 [69.2%] flibanserin 25 mg bid, n = 259 [66.1%] flibanserin 50 mg, n = 251 [63.5%] flibanserin 100 mg qhs)</td>
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<td></td>
<td><strong>Baseline characteristics</strong></td>
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<td>• Mean age: 35.5 years</td>
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<td>• Majority of the women were Caucasian (86.2%) and married (79.1%)</td>
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<td>• Average patient had been in current relationship for ~10.7 years and had suffered from HSDD for ~5 years</td>
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Watkins | 10
<table>
<thead>
<tr>
<th>Co-primary endpoints</th>
<th>Flib 25 mg BID (n=396)</th>
<th>Flib 50 mg BID (n=393)</th>
<th>Flib 100 mg qhs (n=396)</th>
<th>Placebo (n=398)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSEs</td>
<td>From baseline</td>
<td>From baseline</td>
<td>MeanΔ: 1.9 (0.3) (p&lt;0.01 vs placebo)</td>
<td>MeanΔ: 1.1 (0.2) %Δ: 71.6% effect size: 0.3</td>
</tr>
<tr>
<td></td>
<td>MeanΔ: 1.4 (0.2) (p=0.20 vs placebo, NS)</td>
<td>MeanΔ: 1.4 (0.2) (p=0.20 vs placebo, NS)</td>
<td>%Δ: 50.3</td>
<td>%Δ: 42.2</td>
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<tr>
<td></td>
<td>%Δ: 46.2</td>
<td>%Δ: 50.3</td>
<td>%Δ: 71.6%</td>
<td>%Δ: 42.2</td>
</tr>
<tr>
<td>eDiary sexual desire score</td>
<td>MeanΔ: 7.9 (0.8) (p= 0.28 vs placebo, NS)</td>
<td>MeanΔ: 8.5 (0.8) (p= 0.12 vs placebo, NS)</td>
<td>MeanΔ: 8.5 (0.8)</td>
<td>MeanΔ: 6.8 (0.8) %Δ: 68.2 effect size: 0.2</td>
</tr>
<tr>
<td></td>
<td>%Δ: 68.0</td>
<td>%Δ: 71.8</td>
<td>%Δ: 68.2</td>
<td>%Δ: 66.6</td>
</tr>
<tr>
<td>Secondary endpoints</td>
<td>Flib 25 mg BID (n=396)</td>
<td>Flib 50 mg BID (n=393)</td>
<td>Flib 100 mg qhs (n=396)</td>
<td>Placebo (n=398)</td>
</tr>
<tr>
<td>FSFI desire domain score</td>
<td>MeanΔ: 0.8 (0.1) (p&lt; 0.01 vs placebo)</td>
<td>MeanΔ: 0.8 (0.1) (p&lt; 0.01 vs placebo)</td>
<td>MeanΔ: 0.9 (0.1) (p&lt; 0.0001 vs placebo)</td>
<td>MeanΔ: 0.6 (0.1)</td>
</tr>
<tr>
<td>FSFI total score</td>
<td>MeanΔ: 3.9 (0.3) (p&lt; 0.01 vs placebo)</td>
<td>MeanΔ: 3.8 (0.3) (p&lt; 0.01 vs placebo)</td>
<td>MeanΔ: 4.1 (0.3) (p&lt; 0.01 vs placebo)</td>
<td>MeanΔ: 2.6 (0.3)</td>
</tr>
<tr>
<td>FSDS-R item 13 score (lower score= less distress)</td>
<td>MeanΔ: -0.6 (0.1) (p&lt; 0.05 vs placebo)</td>
<td>MeanΔ: -7.0 (0.1) (p&lt; 0.05 vs placebo)</td>
<td>MeanΔ: -7.0 (0.1) (p&lt; 0.001 vs placebo)</td>
<td>MeanΔ: -0.5 (0.1)</td>
</tr>
<tr>
<td>FSDS-R total score</td>
<td>MeanΔ: -6.5 (0.5) (p&lt; 0.05 vs placebo)</td>
<td>MeanΔ: -7.1 (0.5) (p&lt; 0.01 vs placebo)</td>
<td>MeanΔ: -7.8 (0.5) (p&lt; 0.001 vs placebo)</td>
<td>MeanΔ: -5.2 (0.5)</td>
</tr>
<tr>
<td>PGI-I</td>
<td>35.9% (p= 0.06 vs placebo)</td>
<td>44.1% (p&lt; 0.0001 vs placebo)</td>
<td>47.0%</td>
<td>44.1%</td>
</tr>
<tr>
<td>PBE</td>
<td>30.5% (p&lt; 0.05 vs placebo)</td>
<td>36.4% (p&lt; 0.001 vs placebo)</td>
<td>41.9% (p&lt; 0.0001 vs placebo)</td>
<td>24.2%</td>
</tr>
<tr>
<td>Safety endpoints</td>
<td>Flib 25 mg BID (n=396)</td>
<td>Flib 50 mg BID (n=393)</td>
<td>Flib 100 mg qhs (n=396)</td>
<td>Placebo (n=398)</td>
</tr>
<tr>
<td>Total with any AE</td>
<td>241 (60.9)</td>
<td>283 (72.2)</td>
<td>274 (72.2)</td>
<td>234 (58.8)</td>
</tr>
<tr>
<td>Infections/infestations</td>
<td>95 (24.0)</td>
<td>99 (25.3)</td>
<td>96 (24.3)</td>
<td>93 (23.4)</td>
</tr>
<tr>
<td>Nervous System disorders</td>
<td>85 (21.5)</td>
<td>42 (36.2)</td>
<td>131 (33.2)</td>
<td>64 (16.1)</td>
</tr>
<tr>
<td>GI disorders</td>
<td>52 (13.1)</td>
<td>81 (20.7)</td>
<td>91 (23.0)</td>
<td>46 (11.6)</td>
</tr>
<tr>
<td>General disorders</td>
<td>37 (9.3)</td>
<td>69 (17.6)</td>
<td>65 (16.5)</td>
<td>37 (9.3)</td>
</tr>
</tbody>
</table>

Watkins | 11
In premenopausal women with HSDD, flibanserin 100 mg qhs was well tolerated and associated with statistically significant improvements in SSE, sexual desire (FSFI desire domain, not eDiary score), sexual function, and a decrease in sexual distress versus placebo.

**Pros**
- Randomized, double-blind, placebo-controlled, multicenter
- Increased internal validity due to appropriate exclusion criteria
  - Medications or comorbidities that could interfere with results
  - Relationship problems
- 4-week baseline to compare 24-wks of therapy or placebo
- Included effect sizes

**Cons**
- Decreased external validity to other ethnicities as the majority of women were Caucasian
  - Sexuality greatly impacted by certain cultures
- Decreased external validity to non-heterosexual women
- SSEs is a behavioral outcome, not criteria of HSDD (i.e. cognitive event)
- Women may not recognize desire in a 24-hour period (daily diary)
- Subjective endpoints
- 24-weeks not effective in showing long-term remission or recurrence
- Missing data

**Take Home**
- Efficacy for the eDiary desire score component of co-primary endpoint was not seen
- Ruled out flibanserin 25 and 50 mg bid doses
- Nightly doses better tolerated than doses taken during daytime
- Really small effect sizes, meaning small clinically meaningful difference compared to placebo

**Authors’ Conclusions**
- In premenopausal women with HSDD, flibanserin 100 mg qhs was well tolerated and associated with statistically significant improvements in SSE, sexual desire (FSFI desire domain, not eDiary score), sexual function, and a decrease in sexual distress versus placebo.

**Critique**
- Randomized, double-blind, placebo-controlled, multicenter
- Increased internal validity due to appropriate exclusion criteria
  - Medications or comorbidities that could interfere with results
  - Relationship problems
- 4-week baseline to compare 24-wks of therapy or placebo
- Included effect sizes

**Pros**
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- Efficacy for the eDiary desire score component of co-primary endpoint was not seen
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- Nightly doses better tolerated than doses taken during daytime
- Really small effect sizes, meaning small clinically meaningful difference compared to placebo


<table>
<thead>
<tr>
<th>Objectives</th>
<th>To evaluate the efficacy and tolerability of flibanserin in the treatment of premenopausal women with HSDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>• 880 women randomized in a double-blind, placebo-controlled trial conducted at 54 centers in U.S. and Canada</td>
</tr>
<tr>
<td></td>
<td>• Included a 4-week baseline period followed by a 24-week treatment period</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>North American premenopausal women with HSDD</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Inclusions</th>
<th>Exclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premenopausal women ≥18 years old</td>
<td>Clinically relevant conditions that might interfere with trial</td>
</tr>
<tr>
<td>Diagnosed with generalized, acquired HSDD for ≥24 weeks</td>
<td>Sexual dysfunctions other than HSDD, arousal disorder, or orgasmic disorder</td>
</tr>
<tr>
<td>Presence of other sexual dysfunctions of lesser concern and later onset than her HSDD</td>
<td>Any other psychiatric disorder that could impact sexual function</td>
</tr>
<tr>
<td>Female Sexual Distress Scale-Revised (FSDS-R) score ≥15</td>
<td>Major Depressive Disorder</td>
</tr>
<tr>
<td>A rating on the receptivity item of the Sexual Interest and Desire Inventory-Female of 0 or 1</td>
<td>Score ≥14 on Beck Depression Inventory II</td>
</tr>
<tr>
<td>In stable, heterosexual relationship for ≥1 year with sexually functional partner</td>
<td>Use of sex hormones other than contraceptives</td>
</tr>
<tr>
<td>Compliant with use of eDiary</td>
<td>Any medication that may affect sexual function within previous 4 weeks</td>
</tr>
<tr>
<td>≤5 days of missing data during the 4-week baseline period</td>
<td>Psychotherapeutic treatment within previous 12 weeks or experienced major life stress or relationship discord that could interfere with sexual activity</td>
</tr>
</tbody>
</table>

**Exclusions**
- Premenopausal women ≥18 years old
- Diagnosed with generalized, acquired HSDD for ≥24 weeks
- Presence of other sexual dysfunctions of lesser concern and later onset than her HSDD
- Female Sexual Distress Scale-Revised (FSDS-R) score ≥15
- A rating on the receptivity item of the Sexual Interest and Desire Inventory-Female of 0 or 1
- In stable, heterosexual relationship for ≥1 year with sexually functional partner
- Compliant with use of eDiary
  - ≤5 days of missing data during the 4-week baseline period
- Clinically relevant conditions that might interfere with trial
- Sexual dysfunctions other than HSDD, arousal disorder, or orgasmic disorder
- Any other psychiatric disorder that could impact sexual function
- Major Depressive Disorder
- Score ≥14 on Beck Depression Inventory II
- Use of sex hormones other than contraceptives
- Any medication that may affect sexual function within previous 4 weeks
- Psychotherapeutic treatment within previous 12 weeks or experienced major life stress or relationship discord that could interfere with sexual activity
- Gynecological disorder
- Partner with inadequately treated sexual dysfunction

Infections and infestations: upper respiratory tract infection, nasopharyngitis; Nervous system disorders: somnolence, dizziness, headache; GI disorders: nausea; General disorders: fatigue

**Notes:**
- Flib= flibanserin, qhs= at bedtime, Δ= change, NS= not significant, AE= adverse event
**Interventions**  
Randomized for 24 weeks with:  
- Flibanserin 50 mg daily at bedtime  
- Flibanserin 100 mg daily at bedtime  
- Placebo

**Endpoints**  
**Primary:** Change from baseline (weeks -4-0) to study end (weeks 21-24) in number of satisfying sexual events (SSE) and in sexual desire score, both measured using an eDiary  
**Secondary:** Change in:  
- FSDS-R total score and item 13 score (distress due to low sexual desire)  
- FSFI total and desire domain scores  
- PGI-I and PBE scores  
Measured at baseline and clinic visits during week 4, 8, 16, and 24

**Safety:** Evaluation of AEs, clinical laboratory parameters (sex hormones, hematology, biochemistry, and urinalysis), vital signs (blood pressure and pulse rate), physical findings, and ECG data

**Statistics**  
- Sample size of 279 participants per treatment group calculated a 90% power at the two-sided \( \alpha = 0.05 \) level of significance  
- Frequency counts of SSE were analyzed using the Wilcoxon Rank-Sum test (two-sided test, overall \( \alpha = 0.05 \))

**Results**  
**Patients:**  
- 880 women were randomized to receive placebo (n= 295, 33.5%), flibanserin 50 mg (n= 295, 33.5%), or flibanserin 100 mg (n=290, 33.0%)  
- 217 women discontinued prematurely (61 [20.7%] placebo, 65 [22.0%] flibanserin 50 mg, 91 [31.4%] flibanserin 100 mg)

**Baseline characteristics**  
- Mean age: 35.8 years  
- Majority of the women were Caucasian (79.6%) and married (77.2%)  
- Average patient had been in current relationship for 10.6 years and had suffered from HSDD for ~5 years

<table>
<thead>
<tr>
<th>Co-primary endpoints</th>
<th>Flib 50 mg (n= 295)</th>
<th>Flib 100 mg (n= 290)</th>
<th>Placebo (n= 295)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SSEs</strong></td>
<td>From baseline MeanΔ: 1.4 (0.21) (p &lt; 0.05 vs placebo) %Δ: 52.3</td>
<td>From baseline MeanΔ: 1.6 (0.23) (p&lt; 0.01 vs placebo) %Δ: 52.1</td>
<td>From baseline MeanΔ: 0.8 (0.20) %Δ: 30.2</td>
</tr>
<tr>
<td>eDiary sexual desire score</td>
<td>From baseline MeanΔ: 8.2 (0.9) (p= 0.26 vs placebo) %Δ from baseline: 70.9</td>
<td>From baseline MeanΔ: 9.1 (1.0) (p= 0.07 vs placebo) %Δ from baseline: 65.6</td>
<td>From baseline MeanΔ: 6.9 (0.9); %Δ from baseline: 55.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary endpoints</th>
<th>Flib 50 mg (n= 295)</th>
<th>Flib 100 mg (n= 290)</th>
<th>Placebo (n= 295)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FSFI desire domain score</strong></td>
<td>From baseline MeanΔ: 0.8 (0.1) (p&lt; 0.05 vs placebo)</td>
<td>From baseline MeanΔ: 0.9 (0.1) (p&lt; 0.0001 vs placebo)</td>
<td>From baseline MeanΔ: 0.5 (0.1)</td>
</tr>
<tr>
<td><strong>FSFI total score</strong></td>
<td>From baseline MeanΔ: 3.9 (0.4) (p&lt; 0.01 vs placebo)</td>
<td>From baseline MeanΔ: 5.0 (0.4) (p&lt; 0.0001 vs placebo)</td>
<td>From baseline MeanΔ: 2.4 (0.4)</td>
</tr>
<tr>
<td><strong>FSDS-R item 13 score</strong></td>
<td>From baseline MeanΔ: -0.6 (0.1) (p= 0.11 vs placebo)</td>
<td>From baseline MeanΔ: -0.8 (0.1) (p&lt; 0.001 vs placebo)</td>
<td>From baseline MeanΔ: -0.5 (0.1)</td>
</tr>
<tr>
<td><strong>FSDS-R total score</strong></td>
<td>From baseline MeanΔ: -6.1 (0.7) (p= 0.16 vs placebo)</td>
<td>From baseline MeanΔ: -8.9 (0.7) (p&lt; 0.0001 vs placebo)</td>
<td>From baseline MeanΔ: -4.9 (0.7)</td>
</tr>
<tr>
<td><strong>PGI-I</strong></td>
<td>39.6% (p&lt; 0.05 vs placebo)</td>
<td>50% (p&lt; 0.05 vs placebo)</td>
<td>30.3%</td>
</tr>
</tbody>
</table>

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Table 7: Katz M et al, Efficacy of Flibanserin in Women with Hypoactive Sexual Desire Disorder: Results from the BEGONIA Trial. International Society for Sexual Medicine, 2013. 10: p. 1807-1815.[32]

<table>
<thead>
<tr>
<th>Objectives</th>
<th>To investigate the efficacy and safety of premenopausal women with HSDD taking flibanserin 100 mg at bedtime for a treatment period of 24 weeks</th>
</tr>
</thead>
</table>
| Design     | • 1,090 women randomized in a multicenter, double-blind, placebo-controlled trial  
• Included a 4-week baseline period followed by a 24-week treatment period |
| Population | North American premenopausal women with HSDD |

<table>
<thead>
<tr>
<th>Inclusions</th>
<th>Exclusions</th>
</tr>
</thead>
</table>
| • Premenopausal women ≥18 years old  
• Diagnosed with generalized, acquired HSDD for ≥24 weeks  
• Presence of other sexual dysfunctions of lesser concern and later onset than her HSDD  
• FSDS-R score ≥15 | **Sexual dysfunctions other than HSDD, arousal disorder, or orgasmic disorder**  
• Any other psychiatric disorder that could impact sexual function  
• Major Depressive Disorder within previous 6 months |

<table>
<thead>
<tr>
<th>Safety endpoints</th>
<th>Flib 50 mg</th>
<th>Flib 100 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total with any AE</td>
<td>192 (65.1)</td>
<td>193 (66.6)</td>
<td>175 (59.3)</td>
</tr>
<tr>
<td>Infections/infestations</td>
<td>90 (30.5)</td>
<td>72 (24.8)</td>
<td>74 (25.1)</td>
</tr>
<tr>
<td>Nervous System disorders</td>
<td>62 (21.0)</td>
<td>86 (29.7)</td>
<td>48 (16.3)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>22 (7.5)</td>
<td>50 (17.2)</td>
<td>34 (11.5)</td>
</tr>
<tr>
<td>GI disorders</td>
<td>52 (17.6)</td>
<td>56 (20.0)</td>
<td>33 (11.2)</td>
</tr>
<tr>
<td>General disorders</td>
<td>26 (8.8)</td>
<td>37.2 (12.8)</td>
<td>19 (6.4)</td>
</tr>
</tbody>
</table>

**Author’s Conclusions**

• Flibanserin 50 mg and 100 mg daily at bedtime is well tolerated in premenopausal women with HSDD. The doses were associated with statistically significant improvements in SSE, sexual desire (FSFI desire domain score but not eDiary desire score) and overall sexual function, and reduction of sexual distress when compared to placebo.

**Critique**

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
</table>
| • Randomized, double-blind, placebo-controlled, multicenter  
• Increased internal validity due to appropriate exclusion criteria  
  o Medications or comorbidities that could interfere with results  
  o Relationship problems  
• 4-week baseline to compare 24-wks of therapy or placebo | • Decreased external validity to other ethnicities as the majority of women were Caucasian  
  o Sexuality greatly impacted by certain cultures  
• Decreased external validity to non-heterosexual women  
• SSEs is a behavioral outcome, not criteria of HSDD (i.e. cognitive event)  
• Women may not recognize desire in a 24-hour period (daily diary)  
• Subjective endpoints  
• 24-weeks not effective in showing long-term remission or recurrence  
• No effect sizes provided  
• Missing data |

**Take Home**

• Efficacy for the eDiary desire score component of co-primary endpoint was not seen  
• Flibanserin 50 mg and 100 mg bedtime doses shown to have statistically significant increases in SSEs
## Interventions

- Flibanserin 100 mg once daily qhs
- Placebo

## Endpoints

**Two co-primary:** Change from baseline (week 0) to week 24 in FSFI desire domain score and in number of SSE standardized to a 28-day period

**Secondary:**

- Change from baseline to week 24 in: FSDS-R total score and item 13 score (distress due to low sexual desire)
- PGI-I score and Patient Benefit Evaluation (PBE) at week 24

**Safety:** Evaluation of AEs, clinical laboratory parameters (testosterone, prolactin, hematology, biochemistry, and urinalysis), vital signs (blood pressure and pulse rate), suicide ideation (C-SSRS), and physical examinations

## Statistics

- Based on the co-primary endpoint of standardized SSE as a continuous outcome, 420 subjects per treatment arm at week 0 were required to achieve ≥90% power to detect a difference between treatments
  - Allowed for a drop-out rate of 7% before the first complete month of SSE data collection (baseline period)

## Results

### Patients:

- 1,090 women were randomized to receive fribanserin (n= 543) or placebo (n= 547)
- 3 women were not treated and 233 women discontinued prematurely (134 [24.7%] fribanserin and 99 [18.2%] placebo)

### Baseline characteristics similar in both groups

- Mean age: 36.5 years
- Majority of the women were Caucasian (73.9%)
- Average patient had been in current relationship for 11 years and had suffered from HSDD for ~4 years

<table>
<thead>
<tr>
<th>Co-primary endpoints</th>
<th>Flib 100 mg (n= 542)</th>
<th>Placebo (n= 545)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSFI desire domain score</td>
<td>1.0 (0.1)</td>
<td>0.7 (0.1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Standardized SSE</td>
<td>2.5 (4.6)</td>
<td>1.5 (4.5)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary endpoints</th>
<th>Flib 100 mg (n= 542)</th>
<th>Placebo (n= 545)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSDS-R item 13 score</td>
<td>-1.0 (0.1)</td>
<td>2.0 (0.1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>FSDS-R total score</td>
<td>-9.4 (0.6)</td>
<td>-6.1 (0.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>FSFI total score</td>
<td>5.3 (0.3)</td>
<td>3.5 (0.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PGI-I score</td>
<td>3.2</td>
<td>3.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PBE</td>
<td>219 (44.7%)</td>
<td>174 (34.8%)</td>
<td>= 0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Safety endpoints</th>
<th>Flib 100 mg (n= 542)</th>
<th>Placebo (n= 545)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>337 (62.2)</td>
<td>275 (50.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Investigator-defined drug-related AEs</td>
<td>198 (36.5)</td>
<td>86 (15.8)</td>
<td>NS</td>
</tr>
<tr>
<td>AEs leading to discontinuation</td>
<td>52 (9.6)</td>
<td>20 (3.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Serious AEs*</td>
<td>4 (0.7)</td>
<td>2 (0.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Severe AEs**</td>
<td>25 (4.2)</td>
<td>19 (3.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Condition</td>
<td>Placebo Mean (SD)</td>
<td>Flibanserin Mean (SD)</td>
<td>p-Value</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-------------------</td>
<td>-----------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Somnolence</td>
<td>78 (14.4)</td>
<td>19 (3.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Dizziness</td>
<td>56 (10.3)</td>
<td>6 (1.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Nausea</td>
<td>41 (7.6)</td>
<td>12 (2.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Fatigue</td>
<td>31 (5.7)</td>
<td>18 (3.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>28 (5.2)</td>
<td>13 (2.4)</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Author’s Conclusions**
- Flibanserin 100 mg qhs has the potential to improve sexual desire and sexual function and reduce distress related to loss of sexual desire in premenopausal women with HSDD
- No significant safety concerns associated with 24-week treatment

**Critique**
- Randomized, double-blind, placebo-controlled, multicenter
- Increased internal validity due to appropriate exclusion criteria
  - Medications or comorbidities that could interfere with results
  - Relationship problems
- 4-week baseline to compare 24-wks of therapy or placebo
- Included effect sizes
- Decreased external validity to other ethnicities as the majority of women were Caucasian
  - Sexuality greatly impacted by certain cultures
- Decreased external validity to non-heterosexual women
- SSEs is a behavioral outcome, not criteria of HSDD (i.e. cognitive event)
- Women may not recognize desire in a 24-hour period (daily diary)
- Subjective endpoints
- 24-weeks not effective in showing long-term remission or recurrence
- Measured desire primary endpoint differently than the previous phase-3 trials
- Missing data

**Take Home**
- Efficacy is seen in flibanserin 100 mg qhs in terms of SSEs and sexual desire
- Distress shown as statistically significant, but is secondary endpoint
- Small effect sizes, which can be interpreted as less clinically meaningful difference compared to placebo

*AEs that resulted in death, were immediately life threatening, resulted in persistent or significant disability, required prolonged hospitalization, or were deemed serious for other reasons
**AEs that were incapacitating or caused inability to work or undertake usual activity

---

**Flibanserin Approval Controversy**

1. Concerns Precluding Approval of Flibanserin in 2015 FDA Summary Review [24, 35-37]
   a. Undetermined if numerically small treatment differences outweighed the risks; Overall flibanserin:
      i. Increased SSEs by 0.5-1.0 events per month
      ii. Increased sexual desire by 0.3-0.4 points (1.2-6.0 scale)
      iii. Decreased distress by 0.3-0.4 points (0-4 point scale)
      iv. Meaningful benefits were seen in only 10% more women taking flibanserin versus placebo
   b. Shifting efficacy endpoints and the use of patient-reported outcome measure
      i. First application to FDA used a daily diary to rate the participant’s most intense desire as the primary endpoint
      ii. Second application utilized the FSFI desire subscale
         1. 4-week recall of frequency and intensity of desire
         2. FSFI used in third phase-3 trial as the co-primary efficacy endpoint and in the two previous phase-3 trials as a secondary endpoint
      iii. Patient-reported outcomes are increasingly prioritized in research
         1. Better suited for gathering multidimensional and more subjective data than eDiary
         2. HSDD is defined by two subjective measures

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c. Concerns over how providers would identify appropriate patients for flibanserin, taking into account the change in DSM diagnostic criteria
   i. Patients can be diagnosed with FSIAD if they have low sexual desire disorder, an arousal disorder, or a combination of both
   ii. Allows for diagnosis of women whose symptoms overlap between desire and arousal disorders

d. Clinically significant interaction with alcohol causing hypotension and syncope
   i. Alcohol was not prospectively assessed in the phase-3 trials
   ii. Alcohol interaction study enrolled mostly men and did not assess typical alcohol or flibanserin use
      1. Required participants to drink alcohol within 10 minutes following flibanserin dosed in the morning
      2. Resulted in concerning cases of hypotension and pre-syncpe/syncope
   iii. Designated population is prone to drinking alcohol

e. Increased exposures to flibanserin with moderate and strong CYP3A4 inhibitors
   i. Causing clinically significant hypotension in some patients

f. Events of CNS depression, some of which appeared temporally associated with accidental injury
   i. Concerns for residual next-day impairment after bedtime dosing negatively affecting activities requiring alertness, such as driving
   ii. A safety study showed absence of next-day driving impairment
      1. Compared flibanserin’s adverse event profile with other marketed products
      2. Possibly misleading as FDA product reviews are not fundamentally comparative in nature

2. Marginal efficacy with substantial safety concerns\cite{35}
   a. Use of Risk Evaluation Mitigation Strategies (REMS) program\cite{38}
      i. Includes elements to assure safe use
         1. Certification of both pharmacist and physician to ensure healthcare providers and patients are well-informed of risks
         2. Informed consent via Patient-Provider Agreement Form to document patient understands the risks of treatment specifically with alcohol contraindication when counseling patient for the first time
      ii. Limited data regarding core components of the REMS program in terms of their measurement and success

3. Outdated 2000 FDA draft guidance on FSD clinical trial\cite{39,40}
   a. States the primary endpoint should be SSEs collected by daily diaries
      i. Low desire is only indirectly related to the number of sexual events, as they are often initiated by the partner of a woman with HSDD
         1. Women can experience desire in the absence of sexual activity or may take part in sexual activity for reasons other than desire
         2. A satisfying event does not necessarily motivate the woman to want another sexual encounter
         3. Many women have sex out of a feeling of obligation or love for their partner, not necessarily because of their own sense of desire
      ii. Recent evidence suggests recall periods of 1-4 weeks are more meaningful for assessing desire than a 24-hour eDiary
         1. Frequent diary entries keeps sexual activity on front of the mind, encouraging placebo effect
         2. Frequency and intensity of sexual desire collected on a daily basis may be conceptually irrelevant to HSDD

4. Other Influences\cite{35}
   a. Even the Score advocacy campaign
      i. Created via efforts of a consultant to flibanserin’s manufacturer
      ii. Formed to advocate for “gender equality” in access to treatments for sexual dysfunction
      iii. Promoted claim that men have 26 approved medication for sexual dysfunction and women have none
1. Claim rejected by FDA
   a. No approved product for low sexual desire in men
   b. The 26 medications include multiple formulations of testosterone
   b. Unmet medical need

Conclusions

1. Only one out of three phase-3 clinical trials met statistical significance in both primary outcomes, number of SSEs and FSFI desire score (differed from previous two phase-3 trials sexual desire co-primary endpoint)
   a. Trials showed minimal efficacy in terms of effect size, only increasing SSEs by 0.5-1.0 events per month
2. FDA guidance draft for women with FSD is outdated
   a. eDiary is suboptimal and allows for bias
   b. SSE measurement is not an accurate primary endpoint for HSDD
3. Flibanserin has a black box warning for hypotension and syncope with moderate to strong CYP3A4 inhibitors and alcohol
4. There is insufficient data to assess the alcohol interactions in women

Recommendations

1. Additional phase-3 trials with higher quality and larger samples are needed before implementing flibanserin into guidelines
   a. Utilize effect size
   b. Increase length of trials
   c. Include more diverse population
      i. FSAD, Comorbidities, medications, non-heterosexual women, balance variety of cultures, postmenopausal women and surgically-induced menopausal women
2. Update FDA FSD clinical trial guidance:
   a. Primary endpoints should include patient reported outcomes in the form of validated, self-administered questionnaires every 1-4 weeks
   b. Need to include components that directly define disorder: sexual desire and distress
3. Complete additional alcohol and driving studies using premenopausal women taking 100 mg of flibanserin orally at bedtime

References


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Appendix

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<thead>
<tr>
<th>Survey</th>
<th>Measurement</th>
<th>Questions</th>
<th>Scoring</th>
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<tbody>
<tr>
<td>Female Sexual Function Index (FSFI) (total score)</td>
<td>4-wk recall of all dimensions of female sexual function, including: desire, arousal, lubrication, orgasm, satisfaction, pain</td>
<td>19 questions, self-administered</td>
<td>• Each of the 6 domains scored from 0 or 1 (low function) to 5 (high function) • Total score is weighted, ranges from 2-36 • Score ≤26.55 is female sexual dysfunction</td>
</tr>
<tr>
<td>Female Sexual Function Index (FSFI) (desire domain score)</td>
<td>Specifically includes sexual desire or interest</td>
<td>2 questions, self-administered</td>
<td>• Each of the 6 domains scored from 1 (low function) to 5 (high function) • Weighted scores range from 1.2-6</td>
</tr>
<tr>
<td>Female Sexual Distress Scale-Revised (FSDS-R) (total score)</td>
<td>Distress associated with female sexual dysfunction</td>
<td>13 questions, self-administered</td>
<td>• Score ≥11 discriminates between women with FSD and no FSD • Scored 0 (never), 1 (rarely), 2 (occasionally), 3 (frequently), 4 (always)</td>
</tr>
<tr>
<td>Female Sexual Distress Scale-Revised (FSDS-R) (item 13)</td>
<td>Bothered by low sexual desire</td>
<td>1 of 13 FSDS-R questions, self-administered</td>
<td>• Scored 0 (never), 1 (rarely), 2 (occasionally), 3 (frequently), 4 (always)</td>
</tr>
<tr>
<td>Decreased Sexual Desire Screener (DSDS)</td>
<td>Assesses for generalized acquired HSDD</td>
<td>5 questions, self-administered</td>
<td>• Yes or no questions • Diagnosis of HSDD if ‘yes” is answered to all questions 1-4, and review confirms ‘no’ to all factors in question 5</td>
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Appendix B

eDiary Questions for SSEs (yes or no):
1. Did you have a sexual event?
   a. (sexual intercourse, oral sex, masturbation, genital stimulation by partner)
2. Was the sex satisfying for you?

eDiary Questions for desire scores:
1. Indicate your most intense level of sexual desire?
   a. No desire (0), low desire (1), moderate desire (2), strong desire (3)
FSFI Questions for Desire:
1. Over the past 4 weeks, how often did you feel sexual desire or interest?
   a. Almost always or always (5), most times (4), sometimes (3), a few times (2), almost never or never (1)
2. Over the past 4 weeks, how would you rate your level (degree) of sexual desire or interest?
   a. Very high (5), high (4), moderate (3), low (2), very low or none at all (1)
FSDS-R Question 13 for Distress:
1. How often did you feel bothered or distressed by low sexual desire over the past 4 weeks?
   a. Never (0), rarely (1), occasionally (2), frequently (3), always (4)
Patient’s Global Impression of Improvement (PGI-I):
1. How is your condition today compared to when you started the study medication?
   a. Very much improved (1), much improved (2), minimally improved (3), no change (4), minimally worse (5), much worse (6), very much worse (7)
Patient Benefit Evaluation (PBE) (yes or no):
1. Overall, do you believe you have experienced a meaningful benefit from the study medication?

Appendix C: Acronyms
HSDD- Hypoactive Sexual Desire Disorder
DSM- Diagnostic and Statistical Manual of Mental Disorder
FSD- Female Sexual Dysfunction
FSIAM- Female Sexual Interest/Arousal Disorder
ACOG- American College of Obstetricians and Gynecologists
5-HT- Serotonin
DA- Dopamine
NE- Norepinephrine
PFC- Prefrontal Cortex
APA- American Psychiatric Association
DSDS- Decreased Sexual Desire Screener
FSFI- Female Sexual Function Index
SIDP-F- Sexual Interest and Desire Inventory- Female
FSDS-R- Female Sexual Distressed Scale- Revised
CBT- Cognitive Behavioral Therapy
FDA- Food and Drug Association
MOA- Mechanism of Action
PDE-5- Phosphodiesterase-5 Inhibitor
SSRI- Selective Serotonin Reuptake Inhibitor
SNRI- Serotonin Norepinephrine Reuptake Inhibitor
CNS- Central Nervous System
REMS- Risk Evaluation Mitigation Strategies
Flib- Flibanserin
SSE- Satisfying Sexual Event
AE- Adverse Event
PGI-I- Patient Global Impression of Improvement
PBE- Patient Benefit Evaluation
eDiary- Electronic Diary
NS- Not significant