Female Sexual Dysfunction

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Editor-in-Chief, Sexual Medicine Reviews
Editor Emeritus, The Journal of Sexual Medicine
Editor Emeritus, International Journal of Impotence Research
Thank you for this honor

dr.irwingoldstein@gmail.com
“There exist fundamental rights for the individual, including the right to sexual health and a capacity to enjoy and control sexual and reproductive behaviour in accordance with a social personal ethic—freedom from fear, shame, guilt, false beliefs and other factors inhibiting sexual response and impairing sexual relationships—freedom from organic disorders, disease and deficiencies that interfere with sexual and reproductive function.”

World Health Organization, 1994, 1999
ISSWSH is a multidisciplinary, academic, and scientific organization founded in 2000 whose purposes are:

- To provide opportunities for communication among scholars, researchers, and practitioners about women's sexual function and sexual experience
- To support the highest standards of ethics and professionalism in research, education, and clinical practice of women's sexuality, and
- To provide the public with accurate information about women's sexuality and sexual health.

Questions: info@isswsh.org

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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

Female Sexual Dysfunction Classification

Sexual Aversion Disorder
Hypoactive Sexual Desire Disorder
Sexual Desire Disorders
Sexual Arousal Disorder
FEMALE SEXUAL DYSFUNCTION
Orgasmic Disorder
Dyspareunia
Vaginismus
Non-coital Pain Disorder
Sexual Pain Disorders

→ Genital
→ Subjective
→ Combined Genital Subjective
→ Persistent Genital Arousal

Who has more sexual dysfunction – men or women?
### Prevalence of Male and Female Sexual Dysfunction - National Health and Social Life Survey (1994)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experience pain during sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex not pleasureable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unable to achieve orgasm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lacked interest in sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety about performance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Climax too early</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men unable to keep erection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women have trouble lubricating</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*From: Laumann et al. (1994)*
Is female sexual dysfunction exclusively psychologic or exclusively biologic?
Female Sexual Dysfunction

Bio Musculoskeletal Psychosocial

- **Physiological**
  - Neurological problems
  - Cardiovascular disease
  - Cancer
  - Urogenital disorders
  - Medications
  - Fatigue
  - Hormonal loss or abnormality

- **Musculoskeletal**
  - High Tone Pelvic Floor Dysfunction
  - Low Back Pain
  - Post-Abdominal or Pelvic Surgery
  - Orthopedic Conditions
  - Urinary Incontinence
  - Pelvic Organ Prolapse
  - Low Tone Pelvic Floor Dysfunction

- **Sociocultural Influences**
  - Inadequate education
  - Conflict with religious, personal, or family values
  - Societal taboos

- **Interpersonal Relationships**
  - Partner performance and technique
  - Lack of partner
  - Relationship quality and conflict
  - Lack of privacy

- **Psychological**
  - Depression/anxiety
  - Prior sexual or physical abuse
  - Stress
  - Alcohol/substance abuse

Sexual Dysfunction
What is the most common FSD - HSDD?
# Prevalence of Female Sexual Dysfunction (PRESIDE)

<table>
<thead>
<tr>
<th>Sexual Complaint</th>
<th>Sexual Problem</th>
<th>Sexual Problem Plus Distress</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desire</td>
<td>38.7%</td>
<td>10.0%</td>
</tr>
<tr>
<td>Arousal</td>
<td>26.1%</td>
<td>5.4%</td>
</tr>
<tr>
<td>Orgasm</td>
<td>20.5%</td>
<td>4.7%</td>
</tr>
<tr>
<td>Any Dysfunction</td>
<td>44.2%</td>
<td>12.0%</td>
</tr>
</tbody>
</table>

Low desire was the most common of the three sexual problems among women of all ages.

PRESIDE = Prevalence of Female Sexual Problems Associated with Distress and Determinants of Treatment Seeking

**Management of HSDD**

<table>
<thead>
<tr>
<th>What is it called when:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Having sex is not on your radar</td>
</tr>
<tr>
<td>• You love your partner and you perform duty or mercy sex</td>
</tr>
<tr>
<td>• When you would do anything else but have sex</td>
</tr>
<tr>
<td>• When you go to sleep early or stay up late to avoid sex</td>
</tr>
<tr>
<td>• When you used to be interested in sex used to initiate sex and now do not and this bothers you</td>
</tr>
<tr>
<td>• When a switch went off that made having sex a chore</td>
</tr>
<tr>
<td>• When you find other things to do to avoid having sex</td>
</tr>
<tr>
<td>• You lost your femininity</td>
</tr>
</tbody>
</table>
Acquired vs. Generalized HSSD

Nature of Onset

**Acquired**
Sexual dysfunction that **not** limited to certain types of stimulation, situations, or partners

**Lifelong**
Sexual dysfunction that **has** been present since the onset of sexual functioning

Context

**Generalized**
Sexual dysfunction that **not** limited to certain types of stimulation, situations, or partners

**Situational**
Sexual dysfunction that is **limited** to certain types of stimulation, situations, or partners

Acquired vs. Generalized HSSD

Nature of Onset

Acquired
Sexual dysfunction that develops only after a period of normal functioning

Lifelong
Sexual dysfunction that has been present since the onset of sexual functioning

Context

Generalized
Sexual dysfunction that is not limited to certain types of stimulation, situations, or partners

Situational
Sexual dysfunction that is limited to certain types of stimulation, situations, or partners

Can women with HSDD improve their female sexual function?
FDA News Release

FDA approves first treatment for sexual desire disorder

Addyi approved to treat premenopausal women

For Immediate Release August 18, 2015

The U.S. Food and Drug Administration today approved Addyi (flibanserin) to treat acquired, generalized hypoactive sexual desire disorder (HSDD) in premenopausal women. Prior to Addyi's approval, there were no FDA-approved treatments for sexual desire disorders in men or women.

"Today's approval provides women distressed by their low sexual desire with an approved treatment option," said Janet Woodcock, M.D., director of the FDA's Center for Drug Evaluation and Research (CDER). "The FDA strives to protect and advance the health of women, and we are committed to supporting the development of safe and effective treatments for female sexual dysfunction."
I cannot believe the difference now that I am near the end of my second month of flibanserin! I am actually INITIATING sex! It is so amazing as I have not initiated in at least 20 years, maybe longer. I orgasm faster and more intensely And I lubricate as soon as I am aroused, which is amazing. It used to take a while for that to happen when we had intercourse, which was maybe once a month. Last week, on vacation we had intercourse four times. In a normal week, I supplied my husband with an orgasm, about twice, but normally did not have intercourse. That is not happening at all anymore. Flibanserin is making me so happy! S
Flibanserin continues to increase efficacy as time passes. That first month, I knew not to expect much, had decided it was probably mostly placebo. Now, after a little more than three months, I am absolutely certain the flibanserin effects are real and have value for me and for “us.” More able to feel pleasure in being touched? check; Orgasm easier? check; Dramatic increase in overall sexual interest? Check?; Generally more easygoing? check; Find it easier to let go of anger? check; Happier marriage; check check check check check check check!!!!!! I am shocked at the changes. T
HSDD Rx may engage both psychosocial and biological strategies (psychosocial/interpersonal and biological factors impact each other).

The current standard of care for HSDD:

**Nonmedical approaches**

- Counseling,
- psychotherapy,
- cognitive behavioral therapy (CBT)

**Prescription Medications**

- FDA-approved – *flibanserin*
- Off-label: testosterone, bupropion, buspirone

Current treatments for HSDD and their hypothetical mechanisms of action. All treatment modalities are hypothesized to modify the functional neural pathways through experiential stimuli, steroid hormone action, and/or modulation of neurotransmitter levels.
How is HSDD Diagnosed?
# Management of HSDD

## Recognizing HSDD in the Clinic: Decreased Sexual Desire Screener (DSDS)

### Decreased Sexual Desire Screener (DSDS)

**Dear Patient,**

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:
   - An operation, depression, injuries, or other medical condition  □ Yes  □ No
   - Medication, drugs or alcohol you are currently taking  □ Yes  □ No
   - Pregnancy, recent childbirth, menopausal symptoms  □ Yes  □ No
   - Other sexual issues you may be having (pain, decreased arousal or orgasm)  □ Yes  □ No
   - Your partner’s sexual problems  □ Yes  □ No
   - Dissatisfaction with your relationship or partner  □ Yes  □ No
   - Stress or fatigue  □ Yes  □ No

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

Management of HSDD

Recognizing HSDD in the Clinic: Decreased Sexual Desire Screener (DSDS)

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   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.

Management of HSDD

Recognizing HSDD in the Clinic: Decreased Sexual Desire Screener (DSDS)

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<td>G. Stress or fatigue</td>
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When complete, please give this form back to your clinician.


- Specifically designed to screen for acquired, generalized HSDD
- Intended for use in practicing clinicians with little to no experience in recognizing HSDD
- Patient must answer Yes to questions 1-4 and No to all rule-outs assessed by question 5 to screen positive for HSDD
- Validated in 263 women in 27 centers across the US and Canada
- When compared with standard diagnostic interview, DSDS had α:
  - **Sensitivity** of 83.6% (138/165 screened as having HSDD by both measures)
  - **Specificity** of 87.8% (86/98 screened as not having HSDD by both measures)
Is Hypoactive Sexual Desire Disorder (HSDD) MAGIC or a NETWORK problem?
HSDD is NOT MAGIC
HSDD is HARDWARE

Gert Holstege, Center for Uroneurology, UMCG, Groningen, The Netherlands

2/25/16 Charleston SC, ISSWSH Annual Meeting
Excitatory Pathways for Sexual Function

Excitatory systems

Dopamine (DA) +

Noradrenaline (NA) +

ENDOCRINE, AUTONOMIC, REGULATION, MOTIVATION, SEXUAL DESIRE, REWARD, ATTENTION, MOVEMENT

SEXUAL AROUSAL

“medial pre-optic area” (mPOA) is a general neural switch that controls sympathetic and parasympathetic blood flow in the presence of sexual cues

Response to visual erotica

Excitatory Pathways for Sexual Function

Excitatory systems

**Melanocortins**

**Oxytocin**

**Action of melanocortins in the mPOA**

*DESIRE, AROUSAL*

*AROUSAL, BONDING*

---

Inhibitory systems

- Opioids
- Serotonin (5-HT)

Proopiomelanocortin (POMC) system:

PLEASURE, REWARD

SATIETY

Women With No History of Sexual Dysfunction (NHSD) versus Women With Hypoactive Sexual Desire Disorder (HSDD): A Functional Magnetic Resonance Imaging Study

Less Right sided Brain Activating Area in Women with HSDD

Brain activation and de-activation caused by erotic movies is lower in HSDD- than in non-HSDD-volunteers

Gert Holstege¹, H.K. Huynh², Antoon Willemsen², Caroline Beers³, Erna Lont³, Ellen Laan³, Rudi Dierckx², Monique Jansen³, Michael Sand³, and Willibrord Weijmar Schultz³

¹Center for Uroonology, UMCG, Groningen, The Netherlands;
²Dept. Nuclear Medicine UMCG, Groningen, The Netherlands;
³Dept. Sexology, AMC Amsterdam, The Netherlands;
⁴Dept. Gynaecology UMCG, Groningen, The Netherlands;
⁵Boehringer-Ingelheim, Alkmaar, The Netherlands
Less Pre-optic Area Brain Activating Area in Women with HSDD
Less Periaqueductal Gray Brain Activating Area in Women with HSDD

Visual sexual stimuli activate the periaqueductal gray and medial preoptic area in healthy women, but not in women with hypoactive sexual desire disorder

Gert Holstegel1,2, Hieu K. Huynh3, Sue Goldstein4, Monique Jansen5, Ellen Laan6, Antoon Willemsen7, and Wilbrord Weijmar Schultz7

1Asia Pacific Centre for Neuro modulation, The University of Queensland, Brisbane Qld 4072, Australia;
3Innience Foundation Haven, The Netherlands;
5CCRC, IF Clinical Research Manager, SDSM Sexuality Educator, San Diego, USA;
6Boehringer-Ingelheim Pharma Inc., Allmaar, The Netherlands;
7Dept. of Sexology and Psychosomatic Obstetrics and Gynecology, Academic Med. Ctr., Amsterdam, The Netherlands;
8Obstetrics and Gynecology, Univ. Med. Ctr. Groningen, The Netherlands

Watching high erotic versus neutral movies

Preoptic area

Periaqueductal Gray

[Images of brain scans showing activations in different areas for NHSD and HSDD]
Periaqueductal gray (PAG)

caudal ventromedial medullary tegmentum
rostral ventromedial medullary tegmentum
subreticular nucleus
respiratory cell groups in the lateral medulla
pelvic organ and pelvic floor stimulating centers
nucleus retroambigus
pelvic parasympathetic and pelvic floor motoneurons
larynx, pharynx, soft palate, internal intercostal, abdominal and pelvic floor motoneurons

diffuse excitation and inhibition of all somatic and autonomic motoneurons

nociception control
cardiovascular control
respiration
defecation
parturition
vaginal lubrication
vaginal vasocongestion
localization
respiration
crying
daughter

level-setting systems

specific emotional motor systems

Less Pre-optic Area Brain Activating Area in Women with HSDD

Less Periaqueductal Gray Brain Activating Area in Women with HSDD

Visual sexual stimuli activate the periaqueductal gray and medial preoptic area in healthy women, but not in women with hyposexual arousal disorder

Watching high erotic versus neutral movies

Preoptic area

NHSD
HSDD

Periaqueductal Gray

NHSD
HSDD

Vaginal vasocongestion
Vaginal lubrication
Vaginal vasocongestion
Vaginal lubrication

Uterus
Vagina

Pelvic nerve
Pelvic or intramural autonomic ganglion

Sacral spinal cord
Pelvic or intramural autonomic ganglion

Pelvic organ and pelvic floor stimulating centers

Preoptic area

Pelvic Organ Stimulating Center
Less Left sided Brain Deactivating Area in Women with HSDD (Multi-Task Area)
More Brain Deactivating Area in Women with HSDD (Medial Orbito-frontal Cortex)

Brain activation and de-activation caused by erotic movies is lower in HSDD- than in non-HSDD-volunteers

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⁴Dept. Gynaecology UMCG, Groningen, The Netherlands;
⁵Boehringer Ingelheim, Hanover, Germany;
⁶UMCG, Groningen, The Netherlands
More Brain Deactivating Area in Women with HSDD (Medial Orbito-frontal Cortex)
In NHSD - Visual Cortex – Medial Orbito-frontal Area - POSITIVE –
Deactivation of Multi-Task Area Left side of Brain

In HSDD - Visual Cortex – Medial Orbito-frontal Area - NEGATIVE
– NO Deactivation of Multi-Task Area Left side of Brain

Less Left sided Brain Deactivating Area in Women with HSDD (Multi-Task Area)
More Brain Deactivating Area in Women with
NHSD (Medial Orbito-frontal Cortex)
How Does A Central Agent Change the Network in HSDD?
Flibanserin Modulates Serotonin Through Post-Synaptic 5-HT$_{1A}$ and 5-HT$_{2A}$ Receptors

- In vitro binding studies show that Addyi has high affinity for serotonin 5-HT$_{1A}$ and 5-HT$_{2A}$ receptors$^1$

- In vitro binding studies show that Addyi functions as a postsynaptic 5-HT$_{1A}$ agonist and 5-HT$_{2A}$ antagonist$^1$

- In vitro binding studies also show that Addyi moderately blocks 5-HT$_{2B}$, 5-HT$_{2C}$ receptors and is a partial agonist of dopamine D$_4$.$^1$


Hypothesis: Over Time Flibanserin Prevents Negative Post-Synaptic 5-HT$_{1A}$ & 5-HT$_{2A}$ Receptors Effects in the Medial Orbito-frontal Area Allowing Deactivation of the Multi-Task Left-sided Brain Area

Effect of acute administration of vehicle or flibanserin (15 or 45 mg/kg, arrow) on 5-HT levels in:

*P < 0.05 in comparison with vehicle, 15 mg/kg flibanserin-administered group

#P < 0.05 in comparison with vehicle, 45 mg/kg flibanserin-administered group

&P < 0.05, 45 mg/kg flibanserin in comparison with 15 mg/kg flibanserin-administered group

Flibanserin - Mechanism of Action

Allers et al J Sex Med 2010; 7: 1757
Effect of acute administration of vehicle or flibanserin (15 or 45mg/kg, arrow) on norepinephrine (NE) levels in:

- *P < 0.05 in comparison with vehicle, 15 mg/kg flibanserin-administered group
- #P < 0.05 in comparison with vehicle, 45 mg/kg flibanserin-administered group

Flibanserin Regional Selectivity: Effects on Dopamine, Norepinephrine, and Serotonin

After acute administration, there are regional selectivities of Flibanserin in the PFC, Nacc, mPOA - for DO, NE, 5 HT

- PFC – Flibanserin
- NAcc – Flibanserin
- mPOA – Flibanserin

mPOA, medial preoptic area of the hypothalamus; NAcc, nucleus accumbens; PFC, prefrontal cortex.
Effect of acute administration of vehicle or flibanserin (15 or 45 mg/kg, arrow) on dopamine (DA) levels in:

#P < 0.05 in comparison with vehicle, 45 mg/kg flibanserin-administered group
&P < 0.05, 45 mg/kg flibanserin in comparison with 15 mg/kg flibanserin-administered group
Neuroplasticity - brain plasticity, - umbrella term describing lasting change to the brain - research showed many aspects of the brain remain changeable (or "plastic") even into adulthood.

Flibanserin: a brief history...

- 1992:
  - Evidence that primary effects of SSRIs can be reproduced by 1 of 15 known 5-HT receptors: 5-HT1a
  - Blier and deMontigny (McGill) suggest that blockade of the 5-HT2a receptor would result in enhanced effectiveness of a 5HT1a agonist
  - BI initiates drug discovery for a combined 5-HT1a agonist/5-HT2a antagonist, produces BIMT-17 (flibanserin)

Neuroplasticity in HSDD

<table>
<thead>
<tr>
<th>Neuroplasticity in HSDD</th>
<th>Generalized Acquired HSDD for YEARS</th>
<th>Prolonged Treatment of Generalized Acquired HSDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHSD</td>
<td>RIGHT</td>
<td>RIGHT</td>
</tr>
<tr>
<td>LEFT</td>
<td>RIGHT</td>
<td>LEFT</td>
</tr>
</tbody>
</table>

Baseline Means about 3.5 days/month

PoC Trials Pooled - Sexual Thoughts Days per Month, Mean Change From Baseline

![Graph showing FSBQ Frequency Sexual Thoughts Mean Change from Baseline](image)

<table>
<thead>
<tr>
<th>FSBQ Frequency Thoughts Mean Change from Baseline</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANCOVA comparing treatment against placebo, controlling for Center &amp; Baseline</td>
<td>0.03</td>
</tr>
</tbody>
</table>

LS Means are adjusted for Center and Baseline
Neuroplasticity in HSDD

Neuroplasticity - brain plasticity, an umbrella term describing lasting change to the brain - research showed many aspects of the brain remain changeable (or "plastic") even into adulthood.

NHSD

Generalized Acquired HSDD for YEARS

Prolonged Treatment of Generalized Acquired HSDD

How Does a Central Agent Work on Glutamate in the Brain?
dual regulation of glutamate by serotonin

5HT$_{1A}$

Activate

Serotonin

$\text{HO}$

$\text{NH}_2$

5HT$_{2A}$

Activate

AC $\rightarrow$ G$_i$

Decrease Glutamate

↓ cAMP

(High Desire) High DA & NE

↓

Increase Glutamate

↑ IP$_3$

Low DA & NE (Low Desire)

Glutamate neuron activity may be elevated in HSDD

Preferential stimulation of 2A receptors

5-HT 2A (activation)

Increased Glutamate Release

LOW DESIRE

LOW DA & NE
Dual Activity of Flibanserin (MSAA)

How do other Central Agents and Sex Therapy affect HSDD?
WE ARE TRYING TO DEVELOP AN ISSWSH EXPERT CONSENSUS PANEL FOR “Process of Care for HSDD Management for the Primary Care Setting”

**Process**

1. IDENTIFICATION OF HYPOACTIVE SEXUAL DESIRE DISORDER

2. PATIENT (AND PARTNER) ASSESSMENT AND EDUCATION

3. MODIFY REVERSIBLE CAUSES

4. FIRST LINE THERAPY – SEX THERAPY

4. FIRST LINE THERAPY – CNS AGENTS

5. ADJUNCTIVE THERAPIES

**Action**

Psychosocial History, Medical History, DSDS, Physical examination, Lab tests

Review findings, HSDD Education, Referral needs

Change medications, lifestyle modification, diet, exercise

**Outcome**

HSDD diagnosis confirmed, additional testing

Patient and partner needs and preferences determined, referral as needed

Follow-up and Assessment, Referral as needed

4. FIRST LINE THERAPY – HORMONE TREATMENT
Treatment

- Psychological therapy (mindfulness, sensate focus, CBT)
- Experience/behavior
- Testosterone

Hypothetical Mechanisms of Action

- Trophic (neuroplastic) and functional effects
- Androgenic action

Decreased activation of PFC, increased activation of mPOA, VTA, and NAcc

- 5HT2A receptor antagonist
- 5HT1A receptor partial agonist
- Presynaptic DA receptor antagonist
- Reuptake inhibitor for NE & DA
HSDD is NOT MAGIC

HSDD is HARDWARE

Gert Holstege, Center for Uroneurology, UMCG, Groningen, The Netherlands

2/25/16 Charleston SC, ISSWSH Annual Meeting
A variety of psychotherapeutic techniques have been suggested for the treatment of HSDD: i) basic counseling, ii) body-centered therapy, iii) couples therapy, and iv) cognitive behavioral therapy (CBT).

Cognitive behavioral therapy (CBT) - targeted program focusing on communication skills, sexual skills, as well as intimacy issues and performance anxiety (typically consists of 10-12 sessions)

McCabe et al found CBT to be effective in 44.4% of women:

- Most likely to be effective in women with anorgasmia and sexual arousal disorder
- Least effective in women who experienced a lack of sexual interest

• 54% still reported a lack of sexual interest posttherapy

Testosterone for HSDD

- Double blind placebo controlled studies investigating testosterone therapy for treatment of HSDD were conducted in postmenopausal women (both naturally occurring and surgically induced)\(^1\)-\(^5\)
  - Efficacy established but lack of long-term safety data (median study duration ~6 months)

- Few studies in premenopausal women with HSDD and in those reporting low or diminished sexual function\(^5\)-\(^8\)
  - Efficacy in some only for arousal while other showed increases in sexual interest, activity, and the number of satisfying sexual events (SSEs)

Consistent Efficacy of Transdermal Testosterone Patches (Intrinsa™) in 4 different Clinical Trials

Satisfying Sexual Activity (events/4weeks)

Sexual Desire (PFSD score)

Sexual Distress (PDS score)

* Adjusted & capped data
Effects of Sex Steroid Hormones in the Brain

Serotonin

Testosterone (in MPOA)

(+)

Aromatase

Estradiol (classical effects)

(-)

(-)

Prolactin

Melanocortins

Dopamine

(+)

(+)

Gonadotropin Secretion
Copulatory Behavior
Injury Repsonse
(nerve growth)

Norepinephrine

Desire

Arousal and/or Subjective Excitement
How do you diagnose low testosterone in a woman?
9 Blood Tests: Testosterone, SHBG, Dihydrotestosterone, Estradiol, Progesterone, LH, FSH, TSH, prolactin

- Total testosterone, SHBG, calculated free testosterone (ng/dl)
- DHT (ng/dl)
- Peri/post-menopausal Estradiol (pg/ml)
- Peri/post-menopausal Progesterone (ng/ml)
- TSH (mIU/L)
- LH/FSH (mIU/ml)
- Prolactin (ng/ml)

Use free testosterone calculator (0.6 - 0.8)

Suspicious in lower tertile

Aim for 35 - 50 pg/ml

Aim for 1 ng/ml

Suspicious > 3.0

Range established

Range established

Blood tests at baseline and every three months

9 Blood Tests: Testosterone, SHBG, Dihydrotestosterone, Estradiol, Progesterone, LH, FSH, TSH, prolactin

- Total testosterone, SHBG, calculated free testosterone (ng/dl)
- DHT (ng/dl)
- Use free testosterone calculator (0.6 - 0.8)
- Suspicious in lower tertile

- CAG repeat Androgen receptor
- 2D4D ratio
- $3^\alpha$-dihol-G & ADT-G
- Short repeat length
- Low ratio
- Normal levels
GOAL

Calculated free testosterone
= 0.6 – 0.8 ng/dl
Serum androgen levels in healthy premenopausal women with and without sexual dysfunction: Part A. Serum androgen levels in women aged 20-49 years with no complaints of sexual dysfunction.

Center for Sexual Function, Lahey Clinic Northshore, One Essex Center Drive, Peabody, MA 01960, USA. andre.t.guay@lahey.org

Abstract
Androgen insufficiency is a recognized cause of sexual dysfunction in men and women. Age-related decrements in adrenal and gonadal androgen levels also occur naturally in both sexes. At present, it is unclear if a woman’s low serum androgen level is a reflection of the expected normal age-related decline or indicative of an underlying androgen-deficient state. We studied premenopausal women with no complaints of sexual dysfunction to help define a normal female androgen profile. In all, 60 healthy, normally menstruating women, ages 20-49 y, were studied. The Abbreviated Sexual Function Questionnaire was administered along with a detailed interview. Radioimmunoassay measurements of morning serum testosterone (T), free testosterone (fT), dehydroepiandrosterone-sulfate (DHEAS), sex hormone-binding globulin (SHBG), and free androgen index (FAI) were measured during days 8-15 of the menstrual cycle. In women 20-49 y old without complaints of sexual dysfunction, serum androgen levels exhibit a progressive stepwise decline. Comparing values obtained in women age 20-29 y to those obtained in women 40-49 y, specific hormone decrements were DHEAS 195.6-140.4 microg/dl, serum T 51.5-33.7 ng/dl, fT 1.51-1.03 pg/ml. SHBG did not change significantly in women in this age group. The FAI reflected the age-related decrease in female androgen levels. The framework for the development of a female androgen profile in women with no complaints of sexual dysfunction has been established, and an age-related decrease in testosterone and its adrenal precursor, DHEAS, has been demonstrated. The FAI mirrors these decreases and its usefulness in clinical practice is confirmed. A precipitous decline in all androgens occurs after the decade of the 20s, yet SHBG does not show a significant change throughout the premenopausal years.
### Hormonal Levels In Healthy Premenopausal Women

<table>
<thead>
<tr>
<th>Age</th>
<th>20-29 (n=17)</th>
<th>30-39 (n=23)</th>
<th>40-49 (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHEAS ug/dL</td>
<td>176.9-214.3</td>
<td>139.0-170.8</td>
<td>124.7-156.1</td>
</tr>
<tr>
<td>SHBG nmol/L</td>
<td>43.6-58.6</td>
<td>44.6-52.4</td>
<td>47.0-58.4</td>
</tr>
<tr>
<td>Total T ng/dL</td>
<td>45.5-57.5</td>
<td>27.6-39.8</td>
<td>27.0-38.6</td>
</tr>
<tr>
<td>Free Androgen Index (FAI)</td>
<td>3.72-4.96</td>
<td>2.04-2.96</td>
<td>1.98-2.94</td>
</tr>
<tr>
<td>Calculated Free T picomol/L</td>
<td>21.5-27.2</td>
<td>13.4-19.5</td>
<td>12.4-17.8</td>
</tr>
<tr>
<td>Calculated Free T ng/dl</td>
<td>0.6 - 0.8</td>
<td>0.4 - 0.6</td>
<td>0.4 - 0.6</td>
</tr>
</tbody>
</table>

---

*Int J Impot Res. 2004 Apr;16(2):112-20.*

Serum androgen levels in healthy premenopausal women with and without sexual dysfunction: Part A. Serum androgen levels in women aged 20-49 years with no complaints of sexual dysfunction.

FIG. 2. Correlation of various methods for measuring free T

Miller, K. K. et al. J Clin Endocrinol Metab 2004;89:525-533
Calculated free testosterone calculator: http://www.issam.ch/freetesto.htm

These calculated parameters more accurately reflect the level of bioactive testosterone than does the sole measurement of total serum testosterone. Testosterone and dihydrotestosterone (DHT) circulate in plasma unbound (free approximately 2 - 3%) bound to specific plasma proteins (sex hormone-binding globulin SHBG) and weakly bound to nonspecific proteins such as albumin. The SHBG-bound fraction is biologically inactive because of the high binding affinity of SHBG for testosterone. Free testosterone measures the free fraction, bioavailable testosterone includes free plus weakly bound to albumin.

**Albumin** 4.3 g/dL

**SHBG**

**Testosterone**

**Free Testosterone**

**Bioavailable Testosterone**

Disclaimer: Results from this calculator should NOT be solely relied upon in making (or refraining from making) any decision in any case/circumstances without the prior consultation of experts or professional persons. No responsibility whatsoever is assumed for its correctness or suitability for any given purpose.

WARNING! The calculated free and bioavailable testosterone are reliable in most clinical situations, but should not be relied upon in situations with potential massive interference by steroids binding to SHBG; e.g. in women during pregnancy, in men during treatment inducing high levels of DHT (e.g. transdermal DHT, oral testosterone) or mesterolon

This calculator was developed at the Hormonology department, University Hospital of Ghent, Belgium. If you have suggestions to improve this calculator, or for further questions or help contact us Dr. Tom Fiers or Prof. Dr. J.M. Kaufman
Free & Bioavailable Testosterone calculator

These calculated parameters more accurately reflect the level of bioactive testosterone than does the sole measurement of total serum testosterone. Testosterone and dihydrotestosterone (DHT) circulate in plasma unbound (free approximately 2 - 3%) bound to specific plasma proteins (sex hormone-binding globulin SHBG) and weakly bound to nonspecific proteins such as albumin. The SHBG-bound fraction is biologically inactive because of the high binding affinity of SHBG for testosterone. Free testosterone measures the free fraction, bioavailable testosterone includes free plus weakly bound to albumin.

<table>
<thead>
<tr>
<th>Albumin</th>
<th>4.3</th>
<th>g/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHBG</td>
<td>25</td>
<td>nmol/L</td>
</tr>
<tr>
<td>Testosterone</td>
<td>40</td>
<td>ng/dL</td>
</tr>
</tbody>
</table>

**Free Testosterone**

0.838 ng/dL = 2.1%

**Bioavailable Testosterone**

19.7 ng/dL = 49.1%

Normal calculated free testosterone is 0.6 - 0.8 ng/dl

Disclaimer: Results from this calculator should NOT be solely relied upon in making (or refraining from making) any decision in any case/ circumstances without the prior consultation of experts or professional persons. No responsibility whatsoever is assumed for its correctness or suitability for any given purpose.

WARNING! The calculated free and bioavailable testosterone are reliable in most clinical situations, but should not be relied upon in situations with potential massive interference by steroids binding to SHBG; e.g. in women during pregnancy, in men during treatment inducing high levels of DHT (e.g. transdermal DHT, oral testosterone) or mesterolon

Calculated free testosterone calculator: http://www.issam.ch/freetesto.htm
For women with suspected androgen deficiency

**Free & Bioavailable Testosterone calculator**

These calculated parameters more accurately reflect the level of bioactive testosterone than does the sole measurement of total serum testosterone. Testosterone and dihydrotestosterone (DHT) circulate in plasma unbound (free approximately 2 - 3%) bound to specific plasma proteins (sex hormone-binding globulin SHBG) and weakly bound to nonspecific proteins such as albumin. The SHBG-bound fraction is biologically inactive because of the high binding affinity of SHBG for testosterone. Free testosterone measures the free fraction, bioavailable testosterone includes free plus weakly bound to albumin.

### Calculated Results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (g/dL)</td>
<td>4.3</td>
</tr>
<tr>
<td>SHBG (nmol/L)</td>
<td>168</td>
</tr>
<tr>
<td>Testosterone (ng/dL)</td>
<td>40</td>
</tr>
<tr>
<td>Free Testosterone</td>
<td>0.21 ng/dL = 0.526%</td>
</tr>
<tr>
<td>Bioavailable Testosterone</td>
<td>4.93 ng/dL = 12.3%</td>
</tr>
</tbody>
</table>

**Normal calculated free testosterone is 0.6 - 0.8 ng/dl**

Disclaimer: Results from this calculator should NOT be solely relied upon in making (or refraining from making) any decision in any case/circumstances without the prior consultation of experts or professional persons. No responsibility whatsoever is assumed for its correctness or suitability for any given purpose.

WARNING! The calculated free and bioavailable testosterone are reliable in most clinical situations, but should not be relied upon in situations with potential massive interference by steroids binding to SHBG; e.g. in women during pregnancy, in men during treatment inducing high levels of DHT (e.g. transdermal DHT, oral testosterone) or mesterolon

Calculated free testosterone calculator: [http://www.issam.ch/freetesto.htm](http://www.issam.ch/freetesto.htm)
SHBG = 25 nmol/L

SHBG = 168 nmol/L
Assessment of Hormone Status

Glans Clitoris – Testosterone

Labia Minora – Estradiol

Urethral Glans/Meatus – Estradiol/Testosterone

Minor Vestibular Glands – Testosterone and Estradiol

Vagina – Estradiol

Peri-Urethral Tissue - Testosterone

Vulvoscopy
Three Testosterone-Dependent Organs in the Vestibule

Glans clitoris
Minor Vestibular Glands
Peri-urethral tissue – G-spot
Testosterone Therapy

Use FDA-approved testosterone at 10% of male dose

1. Daily transdermal gel - 1/10th tube daily to calf/thigh
   Daily transdermal solution (0.3 ml daily underarm)
2. Weekly IM injections - 0.1 ml - 50 mg/ml testosterone enanthate/cypionate - into vastus lateralis muscle – anterolateral mid-thigh; 27 gauge needle; 1 ml syringe
3. 4-6 month subcutaneous testosterone pellet
GOAL:
Calculated free testosterone = 0.6 – 0.8 ng/dl

1 - 2% testosterone gels/solution (back of calf, underarm)
Female dose: (10% of male dose)

Injections (thigh)
Testosterone enanthate or cypionate
(50 mg/ml) – 0.1 ml = 5 mg/week

Testosterone pellet implants 75 mg
Subcutaneous insertion of 1 pellets every 4 – 6 months
How do other Central Agents and Sex Therapy affect HSDD?
Bupropion for HSDD

Antidepressant also approved to aid in smoking cessation

Classified as a norepinephrine-dopamine reuptake inhibitor (NDRI)

Inhibits dopamine transporter (DAT) and norepinephrine transporter (NET)

Investigated in several clinical trials for the treatment of HSDD

Bupropion improved sexual function (as measured by CSFQ and BISF-W)

Wellbutrin (bupropion hydrochloride) [prescribing information]. Research Triangle Park, NC; GlaxoSmithKline; revised 7/2014.


Buspirone for HSDD

Classified as a serotonin 5-HT1A partial agonist
Greater presynaptic than postsynaptic effects, resulting in a reduction in serotonergic tone

Post hoc analysis of add-on buspirone to a selective serotonin reuptake inhibitors (SSRI) for the treatment of depression showed improvement in SSRI-induced sexual dysfunction

- 58% of subjects treated with buspirone reported an improvement in sexual function, compared with 30% treated with placebo
Bupropion SR for HSDD in Premenopausal Women

Arousal Scores

Orgasm Completion Scores

Desire scores were higher for bupropion vs placebo, but not statistically significant

CSFQ: Changes in Sexual Functioning Questionnaire

Average bupropion dose at Day 112 = 389 mg

How do other Central Agents and Sex Therapy affect HSDD?
Flibanserin is currently the only FDA-approved treatment for generalized, acquired HSDD in pre-menopausal women in the US.

- Flibanserin is dosed at 100 mg at bedtime.
- Flibanserin is a non-hormonal, centrally acting postsynaptic 5-HT$_{1A}$ receptor agonist and a 5-HT$_{2A}$ receptor antagonist (a multifunctional serotonin agonist and antagonist (MSAA)).
- Flibanserin use results in a decrease in serotonin activity and an increase in dopamine and norepinephrine activity.

Consistency of Efficacy Endpoints in all Flibanserin Pivotal Studies

**SSEs**

- Study 147
- Monthly Frequency, Mean ± SE
- Placebo vs Flibanserin 100 mg qhs

**FSFI-Desire**

- Study 71
- LS Mean ± SE
- Placebo vs Flibanserin 100 mg qhs

**FSDS-R13 (Distress)**

- Study 75
- Monthly Frequency, Mean ± SE
- Placebo vs Flibanserin 100 mg qhs

* p < 0.05; ** p < 0.01
LS=least squares.

46 to 60 Percent of Patients Responded to Flibanserin

**Placebo**

- SSE: 34.0%
- FSFI-Desire Study 147 (FAS, LOCF): 39.0%
- FSDS-R13 (Distress): 48.0%

**Flibanserin**

- SSE: 46.4%
- FSFI-Desire Study 147 (FAS, LOCF): 50.6%
- FSDS-R13 (Distress): 59.7%

*p < 0.0001 for Placebo vs. Flibanserin*

*p = 0.0002 for Placebo vs. Flibanserin*

*p = 0.0001 for Placebo vs. Flibanserin*

*Responder defined as ≥minimally improved, much improved or very much improved*

Data on file: Sprout Pharmaceuticals, Inc.
Flibanserin Magnitude of Response

Responder defined as improved, much improved or very much improved

SSEs

Week 24 Change from Baseline in

<table>
<thead>
<tr>
<th>Week 24 Change</th>
<th>Placebo</th>
<th>Flibanserin 100 mg qhs FAS</th>
<th>Flibanserin 100 mg qhs responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 525</td>
<td>1.5</td>
<td>2.5</td>
<td>5.7</td>
</tr>
<tr>
<td>n = 506</td>
<td>0.7</td>
<td>1.0</td>
<td>2.0</td>
</tr>
<tr>
<td>n = 302</td>
<td>-0.7</td>
<td>-1.0</td>
<td>-1.8</td>
</tr>
</tbody>
</table>

FSFI-D

<table>
<thead>
<tr>
<th>Week 24 Change</th>
<th>Placebo</th>
<th>Flibanserin 100 mg qhs FAS</th>
<th>Flibanserin 100 mg qhs responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 525</td>
<td>0.7</td>
<td>1.0</td>
<td>2.0</td>
</tr>
<tr>
<td>n = 506</td>
<td>-0.7</td>
<td>-1.0</td>
<td>-1.8</td>
</tr>
</tbody>
</table>

FSDS-R13

<table>
<thead>
<tr>
<th>Week 24 Change</th>
<th>Placebo</th>
<th>Flibanserin 100 mg qhs FAS</th>
<th>Flibanserin 100 mg qhs responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 525</td>
<td>0.0</td>
<td>-0.7</td>
<td>-1.0</td>
</tr>
<tr>
<td>n = 506</td>
<td>-0.5</td>
<td>-1.0</td>
<td>-1.8</td>
</tr>
</tbody>
</table>

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.
Return of Desire in Responders

1. Over the past 4 weeks, how often did you feel sexual desire or interest?

<table>
<thead>
<tr>
<th></th>
<th>Almost never or never</th>
<th>A few times (less than half the time)</th>
<th>Sometimes (about half the time)</th>
<th>Most times (more than half the time)</th>
<th>Almost always or always</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flibanserin 100 mg (FAS)</td>
<td>Baseline 1.6</td>
<td>Flibanserin all subjects 2.4</td>
<td>Flibanserin Responders 3.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flibanserin 100 mg (Responders)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.0</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>Very low or none at all</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
<th>Very High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flibanserin 100 mg (FAS and Responder Populations, LOCF)</td>
<td>Baseline 1.6</td>
<td>Flibanserin all subjects 2.4</td>
<td>Flibanserin Responders 3.1</td>
<td>4.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Study on File: Sprout Pharmaceuticals</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Postmenopausal Flibanserin Study: Mean Change from Baseline Across Key Endpoints at Week 24

Primary endpoints

- **SSEs**
  - Placebo: 0.6
  - Flibanserin 100 mg: 1.0
  - *P = 0.0040*

- **FSFI-Desire**
  - Placebo: 0.4
  - Flibanserin 100 mg: 0.7
  - *P < 0.0001*

Secondary endpoint

- **FSDS-R Item 13**
  - Placebo: -0.6
  - Flibanserin 100 mg qhs: -0.8
  - *P = 0.0083*

What are the Clinical Side Effect Data with a Central Agent?
CNS drugs have similar adverse event (AEs) profiles

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

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

Flibanserin Prescribing Information, 2015.


# Postmenopausal Flibanserin Study: Summary of Adverse Events

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo (N = 480)</th>
<th>Flibanserin (N = 467)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse events</td>
<td>51.7% (248)</td>
<td>63.4% (296)</td>
</tr>
<tr>
<td>Investigator-defined drug-related adverse events</td>
<td>12.7% (61)</td>
<td>29.8% (139)</td>
</tr>
<tr>
<td>Adverse events leading to discontinuation</td>
<td>3.5% (17)</td>
<td>8.1% (38)</td>
</tr>
<tr>
<td>Severe adverse events</td>
<td>3.5% (17)</td>
<td>6.0% (28)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>0.8% (4)</td>
<td>1.7% (8)</td>
</tr>
<tr>
<td><strong>Most frequent adverse events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>3.1% (15)</td>
<td>9.9% (46)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>1.5% (7)</td>
<td>8.8% (41)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3.5% (17)</td>
<td>7.5% (33)</td>
</tr>
<tr>
<td>Headache</td>
<td>4.8% (23)</td>
<td>6.0% (28)</td>
</tr>
</tbody>
</table>

*Reported by 5% or more of women in either group (treated set).*
Safety was established in clinical trials where the most common adverse events (AEs) in terms of placebo-corrected rates of occurrence in premenopausal women were dizziness (9.2%), somnolence (8.3%), nausea (6.5%), and fatigue (3.7%).

- It should be noted these types of AEs are common with CNS-active medications that influence serotonin.

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

- The discontinuation rate due to AEs was 13% in patients treated with flibanserin 100 mg and 6% in patients treated with placebo.

- A dedicated driving study demonstrated that flibanserin had no negative impact on next-day cognitive function nor on driving performance - these results are reassuring with respect to the sedating effects of flibanserin.

Clinically significant hypotension and syncope with co-administration of a CYP3A4 inhibitor and concomitant alcohol use

<table>
<thead>
<tr>
<th>Population</th>
<th>Total incidence of any hypotension- or syncope-related event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 3 target (any dose)</td>
<td>0.4% (16/3,973)</td>
</tr>
<tr>
<td>Phase 1 flibanserin alone (any dose)</td>
<td>0.5% (6/1,235)</td>
</tr>
<tr>
<td>Phase 1 combination with a moderate or strong CYP3A4 inhibitor</td>
<td>6.5% (4/62)</td>
</tr>
<tr>
<td>Phase 1 combination with alcohol</td>
<td>40% (10/25)</td>
</tr>
</tbody>
</table>
Alcohol Interaction Study

In the alcohol interaction study, in which excessive exposure to alcohol was observed to synergize with the side effects of fibanserin when given in the morning, there was demonstrated increased frequency and severity of sedation, hypotension and syncope which resolved in all cases with lying down/Trendelenburg position.

As a result of this study, fibanserin has a boxed warning highlighting the increased risks of “serious hypotension and syncope” with concomitant use of alcohol.
Alcohol and Flibanserin in Clinical Trials

• In the clinical trials leading to approval, alcohol was not restricted and 58% (n=898) of women treated with flibanserin 100 mg reported “social drinking” at study entry.

• While alcohol consumption was not monitored during the trials, rates of syncope and pre-syncope (including hypotension) remained low in the flibanserin group (0.8% in drinkers and 0.2% in nondrinkers) versus the placebo group (0.3% in drinkers and 0.2% in nondrinkers).

• In comparison, hypotension and syncope are reported to have an annual incidence of 6% in the general population, and account for 1-3% of ER visits and hospitalizations.

Boxed Warning

WARNING: HYPOTENSION AND SYNCOPE IN CERTAIN SETTINGS

Contraindicated With Alcohol
The use of flibanserin and alcohol increases the risk of severe hypotension and syncope. Therefore, alcohol use is contraindicated in patients taking flibanserin. Before prescribing flibanserin, assess the likelihood of the patient abstaining from alcohol, taking into account the patient's current and past drinking behavior, and other pertinent social and medical history. Because of the increased risk of hypotension and syncope due to an interaction with alcohol, flibanserin is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the flibanserin REMS Program.

Contraindicated With Strong or Moderate CYP3A4 Inhibitors
The concomitant use of flibanserin and moderate or strong CYP3A4 inhibitors increases flibanserin concentrations, which can cause severe hypotension and syncope. Therefore the use of moderate or strong CYP3A4 inhibitors is contraindicated in patients taking flibanserin.

Contraindicated in Patients With Hepatic Impairment
The use of flibanserin in patients with hepatic impairment increases flibanserin concentrations, which can cause severe hypotension and syncope. Therefore, flibanserin is contraindicated in patients with hepatic impairment.
Flibanserin is contraindicated:
  With use of alcohol.
  With concomitant use with moderate or strong CYP3A4 inhibitors.
  In women with hepatic impairment.

Summary of Warnings and Precautions
Hypotension and Syncope due to an interaction with alcohol. An interaction between flibanserin and alcohol increases the risk of severe hypotension and syncope.
Alcohol use is contraindicated.
Before prescribing flibanserin, the healthcare provider should assess the likelihood of the woman abstaining from alcohol use.
<table>
<thead>
<tr>
<th>CNS DRUG</th>
<th>CONCOMITANT USE OF ALCOHOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flibanserin</td>
<td>Use of ADDYI and alcohol increases the risk of severe hypotension and syncope; therefore, alcohol use is contraindicated. Before prescribing ADDYI, assess the likelihood of the patient abstaining from alcohol. Counsel patients prescribed ADDYI about the importance of abstaining from alcohol.</td>
</tr>
<tr>
<td>Buspirone</td>
<td>“While formal studies of the interaction of buspirone with alcohol indicate that buspirone does not increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use of alcohol and buspirone.”</td>
</tr>
</tbody>
</table>
| Bupropion  | “In postmarketing experience, there have been rare reports of adverse neuropsychiatric events or reduced alcohol tolerance in patients who were drinking alcohol during treatment with WELLBUTRIN. The consumption of alcohol during treatment with WELLBUTRIN should be minimized or avoided.”
   “Do not take Wellbutrin if you drink a lot of alcohol and abruptly stop drinking…”
   Limit or avoid using alcohol during treatment with WELLBUTRIN. If you usually drink a lot of alcohol, talk with your healthcare provider before suddenly stopping. If you suddenly stop drinking alcohol, you may increase your risk of having seizures.” |
<table>
<thead>
<tr>
<th>CNS DRUG</th>
<th>CONCOMITANT USE OF ALCOHOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duloxetine (Cymbalta)</td>
<td>Although Cymbalta does not increase the impairment of mental and motor skills caused by alcohol, use of Cymbalta concomitantly with heavy alcohol intake may be associated with severe liver injury. For this reason, Cymbalta should not be prescribed for patients with substantial alcohol use.”</td>
</tr>
<tr>
<td>Fluoxetine (Prozac)</td>
<td>Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs, or alcohol.</td>
</tr>
<tr>
<td>Paroxetine: (Paxil)</td>
<td>Although PAXIL has not been shown to increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking PAXIL.</td>
</tr>
<tr>
<td>Sertraline (Zoloft)</td>
<td>Although ZOLOFT did not potentiate the cognitive and psychomotor effects of alcohol in experiments with normal subjects, the concomitant use of ZOLOFT and alcohol is not recommended.</td>
</tr>
<tr>
<td>Vortioxetine: (Brintellix)</td>
<td>Tell your healthcare provider if you drink alcohol. Avoid drinking alcohol while taking BRINTELLIX.</td>
</tr>
</tbody>
</table>
What is the relationship with SSRI/SNRI and flibanserin?

<table>
<thead>
<tr>
<th>Preferred Term, n (%)</th>
<th>SSRI/SNRI + Placebo</th>
<th>SSRI/SNRI + flibanserin 100 mg qhs</th>
<th>Rate Difference, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total AEs</td>
<td>27 (71.1)</td>
<td>40 (55.6)</td>
<td>-15.5</td>
</tr>
<tr>
<td>Anxiety</td>
<td>2 (5.3)</td>
<td>2 (2.8)</td>
<td>-2.5</td>
</tr>
<tr>
<td>Depressive symptom</td>
<td>0</td>
<td>1 (1.4)</td>
<td>1.4</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>2 (2.8)</td>
<td>2.8</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1 (2.6)</td>
<td>3 (4.2)</td>
<td>1.6</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (5.3)</td>
<td>0</td>
<td>-5.3</td>
</tr>
<tr>
<td>Somnolence</td>
<td>3 (7.9)</td>
<td>1 (1.4)</td>
<td>-6.5</td>
</tr>
<tr>
<td>Blood Pressure increase</td>
<td>1 (2.6)</td>
<td>0</td>
<td>-2.6</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Treatment with flibanserin did not increase the prevalence of depression or suicidality when compared with placebo

What is the relationship with oral contraceptives and flibanserin?

Oral contraceptives (OC) are classified as weak CYP3A4 inhibitors.

Concomitant use of flibanserin and OC (30 mcg ethinyl estradiol/150 mcg levonorgestrel) may increase risk of AEs.

Co-administration with OC resulted in a slight increase in prevalence of dizziness, somnolence, and fatigue when compared with flibanserin treatment alone.

Meta-analysis results from phase 1 studies showed exposure to flibanserin was slightly increased when co-administered with OC.

- 1.4-fold increase in AUC and 1.3-fold increase in $C_{\text{max}}$. 

Are There Post-Approval Clinical Experience Data?
Dr. Goldstein, I have been using Addi for just over two months now and I must say that I have noticed a change in my attitude toward my sex life. While we have been enjoying our sexual relations for a long time now, I now find myself thinking about sex and looking forward to it even on days that we are not having sex. Before Addi I really didn't think about it until it was time to do it, where now I'm ready anytime. I also have a more overall sense of well being and happiness. In simple terms, I just feel better and enjoy sex more since I've been taking Addi which makes for a more fulfilling life. Thank you so much for making Addi part of our life. B
Dear Dr. G, Up to date with Addyi. My 3rd month taking Addyi has shown the greatest changes (started about week 7). Increased desire—(all the time). Increased arousal, instant & increased lubrication. Orgasms—powerful, last longer. I didn't know this level was possible to reach. Reach orgasm faster. I'm close to orgasm just thinking about sex, honestly it's wild. I met a new man recently, have not consummated the relationship yet but soon. Will update. L Xo
Objectives:

The first FDA approved medication for women with hypoactive sexual desire disorder (HSDD), flibanserin (Addyi), was available by prescription as of October 2015. Our center has over 120 patients prescribed flibanserin. Pivotal clinical trials show a 40-60% response rate. Our aim was to retrospectively review the personal reflections of those who responded favorably to flibanserin for use in HSDD.

Material and Methods:

Patients currently prescribed flibanserin were asked via email to provide testimonial paragraphs concerning their experiences on flibanserin. Responses were collected and later examined for responsivity to flibanserin, and to themes with regards to response time to the drug, short-term improvements, longer-term changes, and other general observations. Testimonials from 32 responders were analyzed.
Conclusions:

Our experiences with responders to flibanserin for HSDD have shown us that for some women, the drug is life-changing in multiple dimensions.

We have observed positive changes in women that are both sexual and non-sexual, resulting in more sexual satisfaction and overall happiness.
Patient Testimonial

...... 1 out of 4 women will be abused in her lifetime and 1 out of 10 will suffer lingering and often debilitating after effects of sexual traumas. If flibanserin is a drug that helps my brain have the capability of differentiating and accepting a renewed possibility of sexual pleasure vs emotional abuse and sexual debasement, then women like me now have hope; better, we have a potentially life-giving solution for the silent, soul-withering belief that our sexual selves should remain safer buried once and for all! With flibanserin's help, you have not only reignited my sexual self, you have established a fresh platform for more cocreative sexual pleasure and joy...this round safely, playfully and sensually on my terms! In other words, I have my life force back!! G

Courtesy I Goldstein MD
Objectives: As of October 2015 women with hypoactive sexual desire disorder (HSDD) have an FDA approved prescription medication available for treatment, flibanserin (Addyi). Pivotal clinical trials show a 40–60% response rate. With more than 135 of our patients prescribed flibanserin for HSDD, we retrospectively reviewed the personal reflections of those who responded favorably. We analyzed the subset who also had either a history of resolved sexual pain a history of sexually based post-traumatic stress disorder (PTSD).

Material and Methods: Patients currently prescribed flibanserin were asked to share their experiences with the medication by email in an attempt to follow their progress. Responses were collected and later examined for responsivity to flibanserin, and for themes with regard to response time to the drug, short-term improvements, longer-term changes, and other general observations. Testimonials from 42 respondents were analyzed including 7 (17%) who had either history of sexual pain that had been resolved or sexual-based PTSD.
Conclusions: Responder experiences have shown us that for some women, use of flibanserin for HSDD is life changing in multiple dimensions. The improvement in desire in women with resolved sexual pain and sexual PTSD has not been previously reported. Both sexual and non-sexual positive changes have been observed in this population of women, resulting in their increased sexual satisfaction and overall happiness.

Summary: The improvement in desire as well of other positive changes in women with HSDD with and without resolved sexual pain and sexual PTSD has resulted in increased sexual satisfaction and overall happiness.
“There exist fundamental rights for the individual, including the right to sexual health and a capacity to enjoy and control sexual and reproductive behaviour in accordance with a social personal ethic—freedom from fear, shame, guilt, false beliefs and other factors inhibiting sexual response and impairing sexual relationships—freedom from organic disorders, disease and deficiencies that interfere with sexual and reproductive function.”

*World Health Organization, 1994, 1999*