Medication for Female Sexual Dysfunction - where are we?

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Sexological Clinic Copenhagen, Denmark
Disclosures

• Eli Lilly - lecturer
• Boehringer – advisory board
• Pfizer - lecturer, advisory board
• Sandoz – advisory board
• Apricus BioScience – advisory board
• Emotional Brain – advisory board
Prevalence of FSD: Preside study

Biopsychosocial Model of Female Sexual Response

Biology (e.g., physical health, neurobiology, endocrine function)

Psychology (e.g., performance anxiety, depression)

Sociocultural (e.g., upbringing, cultural norms and expectations)

Interpersonal (e.g., quality of current and past relationships, intervals of abstinence, life stressors, finances)

Central effects

- Estrogen
- Testosterone
- 5-HT_{2+3} (serotonin)
- Opioids
- Progesterone
- Norepinephrine
- 5-HT_{2+3} (serotonin)
- Dopamine
- Prolactin
- Melanocortins
- Oxytocin

Desire
Subjective excitement
Orgasm
Peripheral effects of neurotransmitters and hormones on sexual functioning

- **Testosterone**
- **Estrogens**
- **Cholinergic stimulation**
- **NO**
- **5-HT\(_{2+3}\)** (serotonin)
- **Testosterone**
- **Estrogens**
- **Norepinephrine**

**Erectile tissue**

**Blood flow**

**Sensation**
Sexual response – an interaction between brain and genitals

**Efferent signals from brain** activate arousal changes in genitalia

**Afferent signals from genitalia** feed information to brain to activate further efferent output - Positive or negative
Etiology of HSDD: Imbalance Between Excitation/Inhibition

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

- **Inhibition**
  - Serotonin
  - Opioids
  - Endocannabinoids
  - Relationship conflict
  - Negative Stress
  - Negative beliefs about Sex
  - Experience/behavior

With thanks to Dr. S. Kingsberg

Where do we come from with pharmacological treatment?

• Estrogens (local and/or systemic)
  - Improve lubrication, decrease atrophy symptoms (local and systemic)
  - Some studies small increase in desire and enjoyment (systemic)

• Testosterone
  - Improvement in sexual desire, satisfying sexual events, satisfaction and decrease in distress

• Tibolone
  - Estrogenic and androgenic effects of its metabolites
  - Effect on menopausal symptoms and desire, satisfying sexual events, arousal, sexual initiative

Sildenafil and sexual response in women

• Sildenafil enhanced genital blood flow in open-label studies in healthy females and in females with arousal problems but without convincing effects on subjective sexual arousal.

  Kaplan et al Urology 53, 1999
  Berman et al J Sex Marital Ther 27, 2001
  Laan et al J Women Health Gend Based Med 11, 2002

• Inconsistent results on improved sexual responses by sildenafil in randomized controlled studies of females with FSAD.

  Basson et al J WOmen Health Gend Based Med 11, 2002
  Basson and Brotto BJOG 110, 2003
  Berman et al J Urol 170, 2003
Flibanserin (Addyi®)

Approved in 2015 in USA for HSDD in premenopausal women
What is Desire in the brain?

- Balance between excitatory activity driven by DA (desire) and NE (arousal) and inhibitory activity driven by 5-HT (satiety) is necessary for a healthy sexual response.

- This balance may be disrupted in sexual dysfunction.

- By selectively modulating these neurotransmitters in a regionally specific way, flibanserin may act to re-balance these systems in HSDD women.

Pfaus JG. J Sex Med. 2009;6:1506-33
Flibanserin®

• A 5-HT1A serotonin receptor agonist and a 5-HT2A serotonin receptor antagonist

• In animals shown to reduce the 5-HT2A and increase noradrenaline and dopamine in the prefrontal cortex

Thorp et al. BJOG 2014;121;1328-32
### Table A

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Flibanserin</th>
<th>Placebo</th>
<th>Mean difference</th>
<th>Mean difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thorp J 2012</td>
<td>1.9</td>
<td>5.96</td>
<td>1.1</td>
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<tr>
<td>DeRogatis LR 2012</td>
<td>1.6</td>
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<td>Katz M 2013</td>
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<td>Simon JA 2014</td>
<td>2.1</td>
<td>2.67</td>
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<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>1695</td>
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</table>

Heterogeneity: χ² = 4.83, df = 3 (P = 0.18); I² = 38%
Test for overall effect: Z = 5.30 (P < 0.00001)

### Table B

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Flibanserin</th>
<th>Placebo</th>
<th>Mean difference</th>
<th>Mean difference</th>
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<tbody>
<tr>
<td>DeRogatis LR 2012</td>
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<td>Thorp J 2012</td>
<td>8.5</td>
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<td>Total (95% CI)</td>
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Heterogeneity: χ² = 0.08, df = 1 (P = 0.78); I² = 0%
Test for overall effect: Z = 2.20 (P = 0.03)

### Table C

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Flibanserin</th>
<th>Placebo</th>
<th>Mean difference</th>
<th>Mean difference</th>
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<tr>
<td>DeRogatis LR 2012</td>
<td>0.9</td>
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<td>Thorp J 2012</td>
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<td>1.99</td>
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<tr>
<td>Katz M 2013</td>
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<td>Simon JA 2014</td>
<td>0.7</td>
<td>2.16</td>
<td>0.4</td>
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<tr>
<td>Total (95% CI)</td>
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<td>1695</td>
<td></td>
</tr>
</tbody>
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Heterogeneity: χ² = 0.38, df = 3 (P = 0.95); I² = 0%
Test for overall effect: Z = 4.60 (P < 0.00001)

### Table D

<table>
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<tr>
<th>Study or subgroup</th>
<th>Flibanserin</th>
<th>Placebo</th>
<th>Mean difference</th>
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<td>Thorp J 2012</td>
<td>4.1</td>
<td>5.96</td>
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<td>DeRogatis LR 2012</td>
<td>5</td>
<td>6.81</td>
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<td>Katz M 2013</td>
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<td>4.5</td>
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<td>Simon JA 2014</td>
<td>4.2</td>
<td>8.65</td>
<td>2.7</td>
<td>8.77</td>
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<tr>
<td>Total (95% CI)</td>
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<td>1695</td>
<td></td>
</tr>
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</table>

Heterogeneity: χ² = 2.78, df = 3 (P = 0.43); I² = 0%
Test for overall effect: Z = 7.48 (P < 0.00001)

### Sexual Distress

#### Patient Global Impression Improvement

#### Patient Benefit Evaluation

Mean Change from Baseline in Key Endpoints in Postmenopausal women

- **SSEs**
- **FSFI-Desire**
- **FSDS-R13 (Distress)**

*Mean Change from Baseline ± SE*

- Placebo
- Flibanserin 100 mg qhs

*\(p<0.05\); **\(p<0.01\).

With thanks to Dr. S. Kingsberg

Flibanserin (Addyi®)

• Central acting – not acting on the peripheral
• Increasing desire
• Major adverse events: dizziness, sleepiness and nausea
• First FDA approved drug to treat Hypoactive Sexual Desire Disorder in premeopausal women in the US
Bremelanotide

- Bremelanotide completed Phase 3 trials
- First-in-class melanocortin receptor 4 agonist
  - a synthetic peptide analog of the naturally occurring hormone alpha-MSH (melanocyte-stimulating hormone).
- Originally developed as an intranasal formulation; the current subcutaneous administration provides an improved tolerability profile
- On-demand use with rapid onset of activity and well-tolerated
- Evaluated in 31 clinical studies, in over 2,500 people, showing efficacy in both HSDD and ED

With thanks to Dr. S. Kingsberg
Bremelanotide

- RCT study on 327 premenopausal women
- Diagnosed with HSDD and/or FSAD
- 4 weeks single blind placebo control run-in period
- 12 weeks double blind placebo or BMT
- On demand, subcutaneous dosing as desired
- 45 minutes before sexual activity

Clayton et al. Women’s Health 2016;12:325
Lybridos/lybridio
**Lybrido**

- Sublingual testosterone (0.5 mg) and sildenafil (50 mg)
- Women with low desire (HSDD), low sexual motivation and insensitivity to sexual cues
- Increase sensitivity to external and internal sexual cues and the physiological sexual response

**Lybridos**

- Sublingual testosterone (0.5 mg) and 5-HT1A receptor agonist (buspirone 10 mg)
- Women with HSDD induced by dysfunctional sexual inhibition mechanism
- Increase sexual motivation and inhibit overactive sexual inhibition

Bloemers J et al. JSM. 2013:10:791
Effect of T+PDE-5 inhibitor relative to placebo on the subjective indices of subjective evaluation. Significant effect of drug vs. Placebo and between groups.
Effect of T+5-HT1A relative to placebo on subjective indices of the week diaries.
# Drugs Approved or In Development for Low Desire

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

With thanks to Dr. S. Kingsberg
Conclusion

• Several central acting agents for treatment of FSD are under development and Flibanserin has been launched August 2015
• The results are promising in clinical trials
• Are we ready for this treatment modality of FSD?
World Meeting on Sexual Medicine

20th Congress of the European Society for Sexual Medicine
21st World Meeting of the International Society for Sexual Medicine

February 28 - March 3, 2018
Lisbon, Portugal

Jointly organized by:
European Society for Sexual Medicine
www.eossm.org
International Society for Sexual Medicine
www.issm.info

See you in Lisbon!
www.issmossm2018.org
Medical side effects
General health
Comorbidities
Hormonal factors
Age/aging
Menopause
Family
Careers
Partner?
Culture
Self-image
Depression
Anxiety
PSYCHO
SOCIAL
BIO
REGION
JSM Family
Common Adverse Events in ≥1% of Premenopausal Women

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

bid = twice daily; qhs = once every evening.
MedDRA version used for reporting: 11.1.
Includes Trials 511.70, 511.71, 511.75, 511.77, and 511.147.
Lybrido, Lybridos – PKPD

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

T = 0.5 mg, Buspiron = 10 mg, Sildenafil = 50 mg

Testosterone

Sildenafil/5HT$_{1A}$ra

Pharmacokinetic curve of T

Pharmacokinetic and -dynamic curve of Sildenafil and buspirone

Time (hrs)