The Biopsychosocial Perspective: Pharmacologic Treatment Possibilities

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Disclosures
• No financial disclosures to share

The Neurobiology of Female Sexual Function

Female sexual function appears to be modulated by specific neurotransmitters, brain structures, and neurohormones

- Dopamine
- Serotonin
- Epinephrine
- Norepinephrine
- Basal ganglia
- Amygdala
- Insular cortex
- Caudate nucleus
- Hypothalamus
- Spinal cord
- Pituitary
- Hippocampus
- Ventral tegmental area

- Estrogen
- Testosterone
- Oxytocin
- Endogenous opioids
- Pheromones

Neuroimaging studies comparing premenopausal women with and without HSDD reveals differences in brain activity patterns when shown erotic stimuli.a,b,c,d

- For women with HSDD their prefrontal cortex is unable to deactivate, frustrating their ability to feel sexual desire.
- The prefrontal cortex is responsible for executive functions such as coordination of tasks, problem solving and information analysis.

Images supplied courtesy of Gert Holstege MD PhD
**Role of Steroid Hormones**

- Estradiol
  - maintains vaginal lubrication, blood flow to clitoris, urethra and vagina
  - Produced in granulosa cells of the ovary in premenopausal women
  - Estrone, estriol present have lower numbers and less affinity for receptors
- Postmenopause
  - estrogen deficient state
  - Produced by precursors dehydroepiandosterone (DHEA), dehydroepiandosterone sulphate(DHEAS) and androstenedion (A4) in the adrenal glands and ovary

**Role of Steroid Hormones**

- Testosterone and DHT are most potent and almost entirely bound by albumin and SHBG
  - Remaining 1-2% of total is freely circulating and available to estrogen and testosterone sensitive tissues (including brain and skin)
- SHBG synthesized in the liver
  - Estrogen increases, testosterone decreases synthesis
- Affected by medication via first pass metabolism

**Role of Steroid Hormones**

- Prohormones: DHEAS, DHEA, A4 converted into testosterone (T) and dihydrotestosterone (DHT)
- Ovary via the theca cells produces 25% of T, 50% of A, and 20% of DHEA
- Adrenal Gland produces 25% of T, 50% of A, 50% of DHEA and 100% of DHEAS
  - Remaining 30% of DHEA is peripheral conversion of DHEAS
- Testosterone is also produced in the central nervous system starting from cholesterol
  - Implications for treatment

**Sex Hormone-Binding Globulin**

- SHBG is the carrier protein for estrogen and testosterone
  - SHBG-bound fraction is unavailable for biological activity
- Production regulated by estrogen-testosterone balance
  - Estrogen stimulates SHBG production by the liver
  - Testosterone decreases SHBG synthesis

CNS Effects of Hormones on Female Sexual Function

Role of Neurotransmitters/Signaling Molecules

- Exact central neuroendocrine mechanism remains unclear
- Involved areas of the brain: brain stem, hypothalamus, forebrain (amygdala)
- Excitatory factors
  - Estrogen, testosterone, melanocortin, oxytocin, dopamine and norepinephrine
- Inhibitory Factors
  - Serotonin, prolactin, endogenous opioids
- The Balance is...“the sexual tipping point.”

Perlman MA. The sexual tipping point. J Sex Med 2009

Physiology of Sexual Function

Role of Neuroendocrine Molecules

- On the cellular level it is nitric oxide (NO), vasoactive peptide (VIP) and acetylcholine (ACh) that interact for sexual arousal
- Based upon penile erection and animal studies
  - Sexual stimulation releases NO from vascular epithelium
  - Stimulates guanylate cyclase to guanosine triphosphate into guanosine monophosphate (cGMP)
  - Stimulates smooth muscle relaxation in the penile arteries and corpora cavernosum causing increased blood flow

Berman JR et al. World J Urol 2002

*slide adapted from website herdesire.net
Physiology of Sexual Function
Peripheral Tissues: effects of neurotransmitters and hormones

Role of Neuroendocrine System

- Drive is triggered in the hypothalamus and activates the dopamine system
- System is activated early, norepinephrine is released, sexual excitation increases and desire to continue sexual activity continues
- Heart rate, blood pressure increase suggesting the activation of the noradrenergic system
- Neurobiology of the orgasm is unknown although includes the mesolimbic dopamine pathway, pudendal, pelvic and hypogastric nerves
- Orgasm occurs with the release of contracting agents oxytocin and serotonin in the tissue
- Leads to rhythmic contractions of levator plate, uterus, vagina
- Resolution varies

How does this translate into pharmacologic treatment options?
Biological Approaches for Low Desire

- Increase androgens (locally(DHEA) and systemically)
- Increase dopamine
- Increase norepinephrine
- Modulate serotonin
- Melanocortins
- PDE-5 Inhibitor

Drugs In Development or Approved for Low Desire:

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Drug Category</th>
<th>Pharma Sponsor</th>
<th>Current Developmental Status</th>
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<tbody>
<tr>
<td>Flibanserin</td>
<td>Non-hormonal</td>
<td>Sprout Pharmaceuticals</td>
<td>Approved 8/2015 for HSDD in premenopausal women, available 10/17/15</td>
</tr>
<tr>
<td>Lybrido (on demand oral tablet)</td>
<td>Sildenafil +</td>
<td>Emotional Brain</td>
<td>Phase II completed for HSDD</td>
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<tr>
<td>Lybridos (on demand oral tablet)</td>
<td>testosterone</td>
<td>Emotional Brain</td>
<td>Phase II in progress for HSDD</td>
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<tr>
<td>DHEA Vaginal Ovules</td>
<td>Androgenic</td>
<td>EndoCeutics, Inc.</td>
<td>In Phase III completed for VVA in postmenopausal women (future investigation for HSDD)</td>
</tr>
<tr>
<td>Bremelanotide (PT-141) subq</td>
<td>melanocortin receptor modulator</td>
<td>Palatin Technologies</td>
<td>Phase III underway for HSDD/FSIAD</td>
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<tr>
<td>Extended release daily oral</td>
<td>bupropion and</td>
<td>SR-I Biopharma</td>
<td>Phase III set to begin</td>
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<tr>
<td>buspirone and bupropion</td>
<td>trazodone</td>
<td></td>
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</tbody>
</table>

Sexual Desire: Excitatory and Inhibitory Pathways

- Estrogen
- Testosterone
- Oxytocin
- Melanocortins

Biological Approaches

- Increase androgens (locally(DHEA) and systemically)
- Increase dopamine
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- PDE-5 Inhibitor
Testosterone for Low Desire

Adapted from Clayton A, Hamilton D. Psychiatr Clin N Am. 2010;33:323-338

Slide adapted from herdesire.net.

Desire
Subjective Excitement
Orgasm

5-HT
Estrogen
Prolactin
Oxytocin

Testosterone
Progesterone
Melanocortins
Dopamine (DA)
5-HT
Norepinephrine (NE)

Published Randomized Studies Demonstrating Efficacy of Testosterone in Postmenopausal Women

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

NM= naturally menopausal
SM= surgically menopausal

Published Randomized Studies

Off-Label Testosterone Options for Low Desire

- Testosterone transdermal patches
- Testosterone gels and patches approved for men
- Compounded 1% testosterone cream or gel for women
- Oral methyltestosterone (MT)
- Testosterone enanthate injections
- Subcutaneous pellets
- Sublingual testosterone

Davis & Braunstein: Summary of Efficacy & Safety

- Randomized, double-blind placebo controlled studies have established efficacy of transdermal patch for relieving symptoms of HSDD in naturally and surgically menopausal women with and without concomitant estrogen or estrogen/progesterone therapy
- Main side effects: increased hair growth and acne
- Available safety data, although not conclusive, were reassuring with respect to cardiovascular, breast, and endometrial outcomes
- Interim data from a long-term phase III safety trial of testosterone gel demonstrate a continued low rate of cardiovascular events and breast cancer in postmenopausal women at increased cardiovascular risk

**Biological Approaches**

- Increase androgens (locally (DHEA) and systemically)
- Increase dopamine
- Increase norepinephrine
- Modulate serotonin
- Melanocortins
- PDE-5 Inhibitor

**Drugs Known to Increase Dopamine**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Indication</th>
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<tbody>
<tr>
<td>Bromocriptine (Parlodel)</td>
<td>Hyperprolactinemia/Parkinson’s disease/Restless leg syndrome</td>
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<tr>
<td>Cabergolin (Dostinex)</td>
<td>Hyperprolactinemia/Parkinson’s disease/Restless leg syndrome, Parkinson’s disease/Parkinson’s disease/Restless leg syndrome</td>
</tr>
<tr>
<td>Pramipexole (Mirapex and Sifrol)</td>
<td>Parkinson’s disease/Restless leg syndrome</td>
</tr>
<tr>
<td>Quinagolide (Norprolac)</td>
<td>Parkinson’s disease / Restless leg syndrome</td>
</tr>
<tr>
<td>Ropinirole (Requip)</td>
<td>Parkinson’s disease / Restless leg syndrome</td>
</tr>
<tr>
<td>Rotigotine (Neupro)</td>
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<th>Pharma Sponsor</th>
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<tbody>
<tr>
<td>Transdermal testosterone patch (Intrinsa®)</td>
<td>Testosterone</td>
<td>Warner Chilcott</td>
<td>FDA NDA withdrawn, US, off the market EU</td>
</tr>
<tr>
<td>Bromocriptine (Parlodel)</td>
<td>Non-hormonal</td>
<td>Sprout Pharmaceuticals</td>
<td>Approved 8/2015 for HSDD in premenopausal women, available 10/17/15</td>
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<td>Cabergolin (Dostinex)</td>
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<td>DHEA Vaginal Ovules (Prasterone)</td>
<td>Androgenic Precursor for VVA</td>
<td>EndoCeutics, Inc.</td>
<td>Bayer Phase 3 completed for VVA in postmenopausal women; future investigation for HSDD</td>
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<tr>
<td>Bremelanotide (PT-141) subq injection (PL6983)</td>
<td>Melanocortin receptor modulator</td>
<td>Palatin Technologies</td>
<td>Phase III underway for HSDD/FSIAD</td>
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Bupropion

- Norepinephrine and dopamine reuptake inhibitor, prescribed for depression and smoking cessation
- Results in an increase of these neurotransmitters and downstream effects
- Prosexual side effects used to treat sexual side effects of SSRIs

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Bupropion for Low Desire

Adapted from Clayton A, Hamilton D. Psychiatr Clin N Am. 2010;33:323-338
Slide adapted from herdesire.net.

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SP-1 Biopharma

- IND was filed in early 2012 and a single-patient pilot study of Lorexs (aka SIP-104) completed.
- The name Lorexs is derived from orgasm and ecstasy
- Lorexs combines two FDA-approved antidepressants in a slow-release formulation.
- Lorexs is a combination of Trazodone (Desyrel®) and Bupropion (Wellbutrin®)
- Three Phase III trials with 900 patients will occur in 2015.

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Biological Approaches

- Increase androgens (locally(DHEA) and systemically)
- Increase dopamine
- Increase norepinephrine
- Modulate serotonin
- Melanocortins
- PDE-5 Inhibitor
Norepinephrine for Low Desire

Adapted from Clayton A, Hamilton D. Psychiatr Clin N Am. 2010;33:323-338
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Biological Approaches

- Increase androgens (locally(DHEA) and systemically)
- Increase dopamine
- Increase norepinephrine
- Modulate serotonin
- Melanocortins
- PDE-5 Inhibitor

Serotonin

- Serotonin may have a role in low desire by acting as a sexual satiety signal.
- Serotonergic agents (e.g. SSRIs) inhibit desire, arousal, and orgasm in the brain and in the tissue.

Norepinephrine Increasing Agents

- Medications for ADHD and Depression
- Variety of classes
  - Amphetamine stimulants: Adderall, Dexedrine, Dextrostat, Vyvanse
  - Methylphenidate stimulants: Ritalin, Methylin, Concerta
  - Nonstimulants: Straterra
  - Antidepressants: Wellbutrin, Tofranil, Pamelor
- Benefits: improved focus, concentration, vigilance, presence, increase drive
- Side effects: sleep disturbance, anxiety, increased BP, elevated heart rate, headaches, appetite changes/weight loss, suicidal thoughts, decrease drive
Serotonin Receptors

- $\text{5-HT}_{1A}$ agonist (prosexual)
- $\text{5-HT}_{2A}$ antagonist (prosexual)
- $\text{5-HT}_{2A}$ agonist (Antidepressant; Anti-sexual)
- $\text{5-HT}_{2B}$ agonist (Cardiovascular; Heart valves)
- $\text{5-HT}_{2C}$ agonist (Satiety; Weight Loss)

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### Flibanserin

- Mixed post-synaptic $\text{5-HT}_{1A}$ agonist and $\text{5-HT}_{2A}$ antagonist.
  - $\text{5-HT}_{1A}$ agonists could have pro-sexual effects.
  - $\text{5-HT}_{2A}$ antagonists could have pro-sexual effects.
- Has activity at dopamine $D_4$ receptors as well as moderate affinity for $\text{5-HT}_{4B}$ and $\text{5HT}_{3C}$ receptors.
- Originally studied for depression and precise mechanism for HSDD is unknown
- Thought to produce region-specific elevations in dopamine and norepinephrine which offset inhibitory serotonergic activity = increased desire pathways.

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### Drugs In Development or Approved for HSDD:

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<tr>
<td>Lybrido (on demand oral tablet)</td>
<td>serotonergic antidepressant</td>
<td>Emotional Brain</td>
<td>Phase II completed for HSDD</td>
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<td>Lybrido (on demand oral tablet)</td>
<td>buspirome + testosterone</td>
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<tr>
<td>DHEA Vaginal Ovules (Prasterone)</td>
<td>Androgenic Precursor for VVA</td>
<td>EndoCeutics, Inc</td>
<td>Phase II completed for VVA in postmenopausal women; future investigation for HSDD</td>
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<tr>
<td>Bremelanotide (PT-141)</td>
<td>melanocortin receptor modulator</td>
<td>Palatin</td>
<td>Phase II underway for HSDD/FSAD</td>
</tr>
<tr>
<td>Extended release daily oral buspirome and trazodone (Libexin™)</td>
<td></td>
<td>SP-1 Biopharma</td>
<td>Phase II set to begin</td>
</tr>
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### Flibanserin

- Submitted to FDA February 2015
- Advisory Committee Hearing June 4, 2015
- Approved August 18, 2015
- Available October 17, 2015
- 100mg PO qhs statistically improved sexually satisfying events, desire, and distress when compared with placebo
- Warning: hypotension and syncope due to interaction with alcohol, patients with liver impairment or use with CYP3A4 inhibitors
- Only available through a restricted program
**Flibanserin for Low Desire**

- Testosterone
- Progesterone
- Melanocortins
- 5-HT
- Dopamine (DA)
- Norepinephrine (NE)
- Oxytocin
- Estrogen
- Prolactin
- Oxytocin

**Other Serotonin Modulators with Potential**

- **Buspirone** (Buspar)
  - Anxiolytic psychotropic drug for generalized anxiety disorder (GAD).
  - It is a weak 5-HT1A partial agonist.
  - Appears to produce some oxytocin stimulation, and can partially antagonize the sexual side effects of SSRIs.

- **Trazodone** (Desyrel, Oleptro, etc.)
  - Antidepressant of the serotonin antagonist and reuptake inhibitor (SARI) class.
  - Anxiolytic and sleep-inducing (hypnotic) effects.
  - Psychosexual side effects in women, including increased libido, priapism of the clitoris, and spontaneous orgasms.
  - A 5-HT2A receptor antagonist, and a moderate 5-HT1A partial agonist.

- **Vilazodone** (Viibryd)
  - SSRI for major depressive disorder.
  - A 5-HT1A partial agonist.

**Biological Approaches**

- Increase androgens (locally (DHEA) and systemically)
- Increase dopamine
- Increase norepinephrine
- Modulate serotonin
- Melanocortins
- PDE-5 Inhibitor

**PDE5 inhibitors**

- Alone, no change in desire
- If patient complains of slow or no arousal, vaginal estrogen and/or 25-50mg of Sildenafil one hour before intercourse maybe beneficial
- Many increase clitoral vasocongestion
- Newer data supports the use of PDE5 inhibitors with women who suffer from SSRI induced orgasmic complaints of increased latency or decreased intensity or anorgasmia
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<td>DHEA Vaginal Ovules (Pharmacia)</td>
<td>Androgenic Precursor for VVA</td>
<td>Bayer</td>
<td>Phase III completed for VVA in postmenopausal women; future investigation for HSDD</td>
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<tr>
<td>Bremelanotide (PT-141) subq injection (PL6983)</td>
<td>Melanocortin receptor modulator</td>
<td>Palatin Technologies</td>
<td>Phase II completed for FSAD; Phase III underway for HSDD/FSIAD</td>
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<td>Extended release daily oral buspirone and bupropion (Lybridos)</td>
<td></td>
<td>SP-1 Biopharma</td>
<td>Phase II set to begin</td>
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</table>

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

Lybrido/Lybridsos for Low Desire:

Biological Approaches

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<td>Phase II completed for VVA in postmenopausal women/dose investigation for HSDD</td>
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<td>Bremelanotide (PT-141)</td>
<td>melanocortin receptor modulator</td>
<td>Palatin Technologies</td>
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<td>buspirone and bupropion</td>
<td>JH-1 Biopharma</td>
<td>Phase II set to begin</td>
</tr>
</tbody>
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Bremelanotide

- A melanocortin agonist and first-in-class
- Activates endogenous pathway that stimulates attention and desire
- On-demand use with rapid onset of activity and well-tolerated
- Phase 2B studies showed that the 1.75mg dose to be most effective and is currently undergoing Phase 3 trials.

Bremelanotide for Low Desire

*slide adapted from website herdesire.net
Sexual Desire: Excitatory and Inhibitory Pathways


Inhibitory

- Estrogen
- Testosterone
- Lorexys
- Bupropion SR
- Flibanserin
- Lybrido/Lybridos
- Bremelanotide

Excitatory

- Dopamine
- Norepinephrine
- Oxytocin
- Melanocortins
- 5-HT
- Prolactin
- Endocannabinoids
- Opioids

Thank you for your kind attention!

- Roya.Rezaee@uhhospitals.org