Female Anorgasmia: From “No” to “Go!”

Alexander W. Pastuszak, MD, PhD
Assistant Professor
Center for Reproductive Medicine
Division of Male Reproductive Medicine and Surgery
Scott Department of Urology
Baylor College of Medicine
Disclosures

• Endo – speaker, consultant, advisor
• Boston Scientific / AMS – consultant
• Woven Health – founder, CMO
Objectives

• Understand what delayed ejaculation (DE) and anorgasmia are

• Review the anatomy and physiology relevant to these conditions

• Review what is known about the causes of DE and anorgasmia

• Discuss management of DE and anorgasmia
Definitions

Delayed Ejaculation (DE) / Anorgasmia

- The persistent or recurrent delay, difficulty, or absence of orgasm after sufficient sexual stimulation that causes personal distress

Intravaginal Ejaculatory Latency Time (IELT)
- Normal (median) → 5.4 minutes (0.55-44.1 minutes)
- DE → mean IELT + 2 SD = 25 minutes
- Incidence → 2-11%
  - Depends in part on definition used

Ejaculation

Separate event from erection!
Thus, can occur in the ABSENCE of erection!

Sensory input - glans (S2-4)

Emission
Sympathetic input (T12-L1)
Periurethral muscle contraction
Vas deferens contraction
SV, prostate contraction
Bladder neck contraction
Bulbocavernosus / spongiosus contraction

Projectile ejaculation

Expulsion
Somatic input (S1-3)

Supraspinal centers
Higher brain centers
Pons:
Nucleus paragigantocellularis (NPGi)

Sympathetic centers (~T12-L1) emission
Lumbar spinothalamic (LSt) cells (L3-L4 in rats)
spinal generator of ejaculation
Somatom (expulsion) and parasympathetic (secretion) centers (S1-S3)
Somatic inputs from genital areas

Motor supply to the bulbospongiosus muscle

Dorsal nerve of penis

Neurochemistry

Sexual Response Areas of the Brain
- Pons
  - Nucleus paragigantocellularis

Neurochemicals
- *Norepinephrine, serotonin*:
  - Inhibit libido, erectile response, ability to climax
- *Dopamine* - promotes the above
- *Prolactin* – involved in the refractory period

**SSRIs** - increase serotonin / norepi & cause sexual dysfunction!
- Anorgasmia is most common symptom
Neurochemistry of Sexual Function

Human Central Mechanisms: Insights from Clinical Drug Trials

Serotonin

Dopamine

Prolactin

Oxytocin

Melanocortins

 Desire

Arousal and/or Subjective Excitement

Orgasm

Norepinephrine

(+)

(-)

(+)

(+)

Oxytocin & Vasopressin:
- genital reflexes?
- socio-sexual behaviors?

Different receptor subtypes and their pre- vs. post-synaptic distribution can mediate opposing effects on sexual function.

N. Kim, Institute for Sexual Medicine. 2013
Normal Hormonal Function

Testosterone
• AR ubiquitous → including pelvic floor
• High T – PE; Low T = DE in some men
  • T levels vary in men with DE

Thyroid Hormone
• Similar to T levels in effect → high thyroid = PE; low thyroid = DE

Prolactin
• May be surrogate of serotonergic activity
• High Prl → low T and PE
• Suppressed during orgasm → spikes after

Oxytocin
• Surges during ejaculation, orgasm, and detumescence
• Increases ejaculation, paternal nurturing, sexual desire, and long-term romantic bonds
Causes of Anorgasmia

IELT Determinants:

- Genetics
- Neurophysiology
- Behaviors
- Psychosocial variables
- Cultural influences

Somatic Considerations:

- Aging – decreased orgasm intensity
- Neurologic disorders (i.e. MS, DM)
- Endocrine disorders (i.e. low T, high Prl, thyroid)
- Medications

Table 1. Medications Associated With Ejaculatory Dysfunction

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Clomipramine</th>
<th>Fluoxetine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam</td>
<td>Desmethylimipramine</td>
<td>Mesoridazine</td>
</tr>
<tr>
<td>Aminocaproic acid</td>
<td>Fluvoxamine</td>
<td>Methadone</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Guanadrel</td>
<td>Metyldopa</td>
</tr>
<tr>
<td>Amoxapine</td>
<td>Guanethidine</td>
<td>Naproxen</td>
</tr>
<tr>
<td>Baclofen</td>
<td>Haloperidol</td>
<td>Nortriptyline</td>
</tr>
<tr>
<td>Bethanidine</td>
<td>Haloperidol</td>
<td>Pargyline</td>
</tr>
<tr>
<td>Butaperazine</td>
<td>Hexamethonium</td>
<td>Paroxetine</td>
</tr>
<tr>
<td>Chloridazepoxide</td>
<td>Imipramine</td>
<td>Perphenazine</td>
</tr>
<tr>
<td>Chlorimipramine</td>
<td>Iproniazid</td>
<td>Phenothiazine</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Isocarboxazid</td>
<td>Phenoxybenzamine</td>
</tr>
<tr>
<td>Chlorprothixene</td>
<td>Lorazepam</td>
<td>Phentolamine</td>
</tr>
</tbody>
</table>

SSRIs = selective serotonin reuptake inhibitors.

Treatment Approaches

General Approaches:
- Psychotherapy
- Sex Therapy
- Pharmacotherapy

Psychological & Sexual Therapy

When Should I See a Sex Therapist?
• No organic cause of DE
• Psychosexual factors suspected

General Principles
• Involve patient’s partner
  • Set expectations
  • Educate on sexual response cycle
  • Improve communication between partners
Sex Therapy - Approaches

Theories of Psychological DE and Treatment

- Insufficient Stimulation
  - PVS
  - Sex Technique Training
  - Cognitive Arousal

- Psychic Conflict
  - Masturbation Retraining
  - Psychotherapy

- Idiosyncratic Masturbation
  - Revision of Fantasy
  - Psychotherapy

- Desire Disorder
  - Psychotherapy

There is NO MEDICATION FOR DE that is currently approved by the U.S. FDA

Pharmacotherapies

• There are no clinical trials demonstrating efficacy
• Studies are small, underpowered, retrospective, and not controlled
• Disparities in outcomes likely reflect different populations

<table>
<thead>
<tr>
<th>Cabergoline</th>
<th>Bupropion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxytocin</td>
<td>Cyproheptadine</td>
</tr>
<tr>
<td>Buspirone</td>
<td>Pseudoephedrine</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>Midodrine</td>
</tr>
<tr>
<td>Yohimbine</td>
<td>Amantadine</td>
</tr>
<tr>
<td>Apomorphine</td>
<td>Bethanechol</td>
</tr>
<tr>
<td>Loratadine</td>
<td>Reboxitine</td>
</tr>
</tbody>
</table>
Pharmacotherapy

Central effects of neurotransmitters and hormones on sexual functioning

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

Bupropion
Apomorphine
Amantadine
Cabergoline
Oxytocin

Buspirone
Ephedrine
Pseudoephedrine
Midodrine
Pharmacotherapy – General Principles

- DE with concurrent ED should be treated with PDE5 inhibitors
- Penile vibratory stimulation can be helpful → 72% success with 3 x 1 minute rest / application cycles
- Most helpful drug effect → switch to bupropion from SSRI
- Cabergoline is another top choice for medical management
## Treatment of SSRI-Induced DE

- Use when SSRI is likely cause of DE
- Can also switch to different SSRI in same class
- DE treatment with meds up to 70% effective

<table>
<thead>
<tr>
<th>Drug</th>
<th>PRN Dosage</th>
<th>Daily Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyproheptadine</td>
<td>4-12 mg (3-4h prior to sex)</td>
<td>--</td>
</tr>
<tr>
<td>Bethanechol</td>
<td>20 mg (1-2 hours prior to sex)</td>
<td>--</td>
</tr>
<tr>
<td>Amantadine</td>
<td>100-400 mg (for 2 days prior to sex)</td>
<td>75-100 mg BID / TID</td>
</tr>
<tr>
<td><strong>Bupropion</strong></td>
<td>--</td>
<td>75 mg BID / TID</td>
</tr>
<tr>
<td>Buspirone</td>
<td>--</td>
<td>5-15 mg VID</td>
</tr>
<tr>
<td>Loratadine</td>
<td>--</td>
<td>10 mg Daily</td>
</tr>
</tbody>
</table>

*Andrology. 2015; 3: 626.*
## Treatment of DE – No SSRI

<table>
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<tr>
<th>Drug</th>
<th>PRN Dosage</th>
<th>Daily Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oxytocin</strong></td>
<td>24 IU intranasal / SL during sex</td>
<td>--</td>
</tr>
<tr>
<td><strong>Pseudoephedrine</strong></td>
<td>60-120 mg (120-150 min prior to sex)</td>
<td>--</td>
</tr>
<tr>
<td><strong>Ephedrine</strong></td>
<td>15-60mg (1 hour prior to sex)</td>
<td>--</td>
</tr>
<tr>
<td><strong>Midodrine</strong></td>
<td>5-40mg Daily (30-120 min prior to sex)</td>
<td>--</td>
</tr>
<tr>
<td><strong>Apomorphine</strong></td>
<td>0.5-1.5mg intranasal (20 min prior to sex)</td>
<td>--</td>
</tr>
<tr>
<td><strong>Yohimbine</strong></td>
<td>--</td>
<td>5.4 mg TID</td>
</tr>
<tr>
<td><strong>Cabergoline</strong></td>
<td>--</td>
<td>0.25-2 mg BIW</td>
</tr>
<tr>
<td><strong>Reboxetine</strong></td>
<td>--</td>
<td>4-8 mg</td>
</tr>
<tr>
<td><strong>Imipramine</strong></td>
<td>--</td>
<td>25-75 mg Daily</td>
</tr>
</tbody>
</table>
First Line Meds Used by SMSNA

- Cabergoline
- Bupropion
- Oxytocin
- Cyproheptadine
- Methylphenidate
- Yohimbine
- Buspirone
Medication Considerations

If patient is on SSRI

- Switch to **bupropion** 75 mg PO BID / TID
  - SUICIDALITY, chest pain, palpitations, blurred vision
- If cannot switch → **cyproheptadine** 4-12 mg 3-4 h before sex
  - Nausea, dizziness, urinary retention, photosensitivity,
- Next, try **loratadine** 10 mg QD
  - Drowsiness, fatigue, HA, dry mucous membranes, pharyngitis

If patient is NOT on SSRI

- Check prolactin levels
- Prolactin high / normal → **cabergoline** 0.25-2 mg BIW
  - Nausea, dizziness, fatigue, abdominal pain, anxiety
- Prolactin low / low normal → **oxytocin** 24 IU intranasal

Backup Agents

- **Yohimbine** 5.4 mg TID
  - Urinary retention, hyperglycemia, tachycardia, irritability, tremor, nausea, dizziness, HA, flushing, diaphoresis, HTN
Bupropion and Anorgasmia

• Used for SSRI-induced sexual dysfunction

Ashton & Rosen 1998:

• 47 men with SSRI-induced sexual dysfunction
• 75 vs. 150mg bupropion 1-2h prior to sex → 75mg TID × 2 weeks if not responding

RESULTS:

• 31/47 (66%) of patients had improvement
• 18/47 (38%) of patients improved with Prn use
• Side effects → discontinuation in 7/47 (15%)

Other studies have had mixed results
Fixed dose bupropion may work better than prn
Cyproheptadine and Anorgasmia

• Histamine, 5HT, and AChR antagonist
• Used for SSRI-induced sexual dysfunction

Ashton, Hamer & Rosen 1997:
• 596 patients on SSRI
• SSRI-associated sexual dysfunction in 97 (16%)
• 45 treated with yohimbine, amantadine, or cyproheptadine

RESULTS:
• Yohimbine more effective than amantadine or cyproheptadine

Only other studies are case reports
Partial response to cyproheptadine reported
Cabergoline and Anorgasmia

• D2 receptor agonist → lowers prolactin
• Decreases refractory period in men

Hollander et al. 2016:
• 131 men treated with cabergoline 0.5mg BIW for orgasmic disorder
• Duration and subjective treatment response noted

RESULTS:
• 87/131 (66%) reported improvement in orgasm
• 44/131 (34%) reported no change
• Not impacted by testosterone level / therapy, age, h/o prostatectomy

Oxytocin and Anorgasmia

• Oxytocin surges during orgasm in men
• Decreases ejaculatory latency in animals

Burri et al. 2008:
• DB, PC, balanced crossover study
• 10 healthy men treated with oxytocin 24 IU intranasal → washout period
• Examined oxytocin, catecholamine levels, sexual arousal

RESULTS:
• Increased oxytocin and catecholamine levels
• 8/10 men with increased sexual arousal
Yohimbine and Anorgasmia

• Used to treat ED and sexual dysfunction
• Acts on spinal cord adrenergic receptors to ejaculation
• Success with treatment of SSRI-induced DE

Adniyi et al. 2007:
• 29 men with orgasmic dysfunction
• Treated with 20 mg yohimbine to 50 mg if not effective

RESULTS:
• 19/29 (66%) men reached orgasm
• 3 needed PVS to reach orgasm
Summary

• Orgasmic function is dependent on interplay of numerous neurohormonal and physical factors
• Norepinephrine, serotonin, dopamine, and prolactin are the primary neurohormones involved
• DE/anorgasmia can be caused by many meds, in particular SSRIs
• Treatment should include psychosexual and medical therapy
• Medical therapies are poorly studied and not FDA approved
Thank you!
pastusza@bcm.edu