Financial Disclosures

• None
The Menopause Solution

A DOCTOR’S GUIDE TO:

- relieving hot flashes
- enjoying better sex
- sleeping well
- controlling your weight
- and being happy!

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DIRECTOR OF THE MAYO CLINIC WOMEN’S HEALTH CLINIC
AND OFFICE OF WOMEN’S HEALTH
Objectives

• Identify sexual function changes associated with aging and with menopause

• Explain the female sexual response cycle and biopsychosocial model of female sexual dysfunction

• Describe management strategies for treatment of biological and psychosocial etiologies of sexual dysfunction

• Determine when to refer
Hormonal Changes with Menopause

- Progesterone
- Estrogen
- Testosterone

Pre Menopause | Menopause | Post Menopause

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Sexual dysfunction and distress

Shifren et al, Obstet Gynecol 2008; 112:970
Sexual dysfunction and distress

Shifren et al, Obstet Gynecol 2008; 112:970
Sexual dysfunction and distress

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Menopause vs. Aging

- **Arousal**
  - Lack of breast-size increase w/stimulation
  - Clitoral shrinkage - ↓ perfusion/↓ engorgement
- **Vaginal changes**
  - Delayed or absent vaginal lubrication
  - Decreased vaginal elasticity
  - Thinning of vaginal mucosa
  - Decreased tactile sensation

Menopause vs. Aging

• Orgasm
  • Increased time from arousal to orgasm
  • Decreased intensity
  • Fewer uterine contractions

• Desire/Drive
  • Decreased spontaneous sex drive
What does this mean for women?

• Importance of sexuality remains relatively constant
• Sexual desire declines
• Pain with intercourse increases
• Frequency of sexual activity remains relatively constant despite reports of dryness/discomfort
  • Women continue to have sex, even if it’s painful!
What is the impact?

- Disappointment
- Sense of loss
- Loss of sexual well-being can lead to:
  - Depression
  - Dissatisfaction
  - Relationship discord and stress

Does this get better with age?

- We don’t know
- But... likely to remain sexually active if:
  - Partner available
  - No depression
  - Local vaginal estrogen therapy
  - Moderate alcohol intake
- Predict sexual activity 68%
How do we address sexual dysfunction concerns?
Female Sexual Response Cycle: Intimacy – based model

- Emotional and physical satisfaction
- Arousal and sexual desire
- Sexual arousal
- Spontaneous sexual drive
- Sexual stimuli
- Emotional intimacy

Seeking out and being receptive to

Biological
Psychological

Biopsychosocial Model

- Physiological
- Psych/emotional
- Interpersonal relationships
- Sociocultural influences
Biopsychosocial Model

- Medications
- Hormones
- Genitourinary syndrome of menopause (GSM)
- Aging
- Illness
- Fatigue
Biopsychosocial Model

- Medications
- Hormones
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Balance Between Excitatory and Inhibitory Factors

- Serotonin
- Prolactin
- Endogenous opioids

- Sex Steroids
- Norepinephrine
- Dopamine
- Melanocortin
- Oxytocin

Antidepressant-induced Sexual Dysfunction

- SSRI/SNRI
  - Likely a class effect related to impact on serotonin (5-HT)
    - Suspends vasocongestion
    - Decreased arousal and orgasm
    - Decreases nitric oxide function
    - Decreased genital sensation
  - Genetic differences
  - Gender differences

## Relative Frequency of Sexual Dysfunction by Drug

<table>
<thead>
<tr>
<th>Drug</th>
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<th>Sexual arousal</th>
<th>Orgasm</th>
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Treatment of Antidepressant-induced Sexual Dysfunction

- Behavioral strategies
  - Wait-5-10% improve, but takes 4-6 months
  - Regular planned sexual activity 3X/week
  - Vibrator for more intense stimulation
  - Psychotherapy
  - Exercise
    - 20 min 3x/week (immediately prior to sex)
    - Improved sexual desire
    - Improved global sexual function for those with sexual dysfunction at baseline

Treatment of Antidepressant-induced Sexual Dysfunction

- Pharmacologic strategies
  - Lower dose or discontinue if not needed
  - Switch to (or start) drug w/ fewer sexual SE
  - Drug holiday on weekends
    - May lead to discontinuation symptoms
  - Augmentation
    - Bupropion XL150-300 mg
    - PDE5 Inhibitors: for arousal, not libido
    - Testosterone
      - 300 mcg patch 2X/week for 12 weeks
      - Increased 4 wk SSE 2.5 to 4.7

Biopsychosocial Model

- Medications
- Hormones
- Genitourinary syndrome of menopause (GSM)
- Aging
- Illness
- Fatigue
Genitourinary Syndrome of Menopause (GSM)

- Loss of labial/vulvar fullness
- Pallor of urethral/vaginal epithelium
- Decreased vaginal moisture/fissures
- Pain with palpation
Genitourinary Syndrome of Menopause: Scope of the Problem

- Affects up to 50% of PM women
  - 32 million women suffer from GSM!
  - Only 7% currently treated w/ rx treatments
- GSM progresses w/o treatment
- 10% of women on lower-dose systemic MHT regimens continue to have vaginal sx

GSM Treatment

- Replacing vaginal estrogen in post-menopausal women
  - increases pelvic blood flow
  - increases lubrication, elasticity
  - protects against clitoral fibrosis
  - increases genital tactile perception and sensation
  - reduces vaginal pH, risk of UTI
- Long term use possible (no serious AEs)
- Progestogen not needed
# Vaginal Estrogens Available for Postmenopausal Use in the US

<table>
<thead>
<tr>
<th>Composition</th>
<th>Name</th>
<th>Dosing</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vaginal cream</strong></td>
<td>Estrace®</td>
<td>Initial 0.5-1 g/d for 1-2 wk Maintenance: 0.5-1 g/d (0.1 mg active ingredient/g) 0.5-1.0 g (0.625 mg active ingredient/g) 3x weekly</td>
<td>Premarin® is also indicated for dyspareunia</td>
</tr>
<tr>
<td>Estradiol</td>
<td>Premarin®</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjugated estrogens</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Vaginal ring</strong></td>
<td>Estring®</td>
<td>Device containing 2 mg releases 7.5 μg/d for 90 d</td>
<td></td>
</tr>
<tr>
<td>Estradiol acetate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vaginal tablet</strong></td>
<td>Vagifem®</td>
<td>Initial: 1 tablet/d for 2 wk Maintenance: 1 tablet twice/ wk (tablet 10.3 μg of estradiol hemihydrate equivalent to 10 μg of estradiol)</td>
<td>The 10 mcg dose is the only available formulation of the drug available in the US</td>
</tr>
<tr>
<td>Estradiol hemihydrate</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. www.eMPR.com.
REJOICE trial of low dose estradiol gel cap

• Investigational study of 4mcg, 10 mcg and 25 mcg applicator-free bioadhesive solubilized 17β-estradiol softgel capsule
  • Given daily for 2 weeks, then 2X weekly
  • Rapidly treats symptoms of GSM/VVA
    • Improved dyspareunia at all doses in 2 weeks
    • Improved vaginal dryness in 2 weeks (10 and 25 mcg; 4 mcg in 6 weeks)
  • Negligible to low systemic absorption
  • Easy insertion/no mess

Simon JA Abstract NAMS 2016 meeting
Ospemifene: SERM for GSM

• Favorable effect on vagina
  • antagonistic to EM and breast
• Effective for dyspareunia and dryness
• Safety data (52 wks)
  • no endometrial hyperplasia or carcinoma
  • no VTE
• Adverse effects
  • hot flashes 7.2% with 60 mg dose vs 2% with placebo

Fractional CO2 laser (vaginal erbium laser)

• Laser treatment of vulvar and vaginal tissues to improve vaginal health in women with genitourinary syndrome of menopause (GSM)

• Criteria for clearance of devices less stringent than for drug approval
  • Not specifically indicated for treatment of VVA/GSM
Fractional CO2 laser (vaginal erbium laser)

- Laser system: MonaLisa Touch (Cynosure) marketed for treatment of vaginal dryness
- Three 5-10 minute procedures 6 weeks apart
- No anesthesia
- Some patients report improvements after 1-3 treatments
- Claim: stimulates collagen like plastic surgery procedures for the face

Courtesy of OBG Management
Educational use
Fractional CO2 laser (vaginal erbium laser)-the evidence

- Pathology specimens from 8 women
  - Remodeling of connective tissues
  - No surrounding damage

- 12 week study of 50 postmenopausal women with VVA
  - 3 treatments improved most bothersome symptom

- 12 week study of 77 women with VVA
  - Improvements in sexual function scores (FSFI)
  - No sham control or control for hormone treatment
  - Selection bias (women distressed and motivated for treatment)

Fractional CO2 laser (vaginal erbium laser)-the evidence

- Pilot 30 women (ave age 58 yrs) with GSM
  - 3 treatments 6 weeks apart; 27 completed tx
  - Assessed 3 months after last treatment
    - Improvement in visual analog scale for dryness, burning, pain, itching, dyspareunia
    - Improved Vaginal Health Index (p<0.001)
    - Improved Female Sexual Function Index (p<0.001)
    - Improvement in comfortable dilator size 25/30 at 3 months
    - 26/27 (96%) reported being satisfied or extremely satisfied
Fractional CO2 laser (vaginal erbium laser)

• Limitations
  • Short follow up, uncertainties about:
    • Duration of effect
    • Potential long-term complications
  • Lack of sham-controlled trials and comparison with estrogen
  • Costly ($1800-$3000 or more for 3 treatments), not covered by insurance

Physical Therapy

• Increase awareness and proprioception of pelvic floor muscles
• Improve muscle relaxation
• Normalize muscle tone
• Increase elasticity at the vaginal opening
• Desensitize painful areas
• Decrease fear of penetration
What About Androgen Therapy in Women?

• Several RCTs demonstrate transdermal testosterone significantly improves
  • Sexual desire
  • Arousal
  • Orgasm frequency
  • Sexual satisfaction

*In women with low sexual desire (naturally or surgically menopausal, w/ or w/o E)
Who should be considered for testosterone treatment?

- Endocrine society guideline
  - PM women with diagnosis of HSDD
  - Not “routinely” recommended for those with low androgen states including POI, early oophorectomy
  - Lack of safety and efficacy data

Endocrine Society Guideline for Androgens in Women

• No clearly defined androgen deficiency state in women
  • Recommends against routinely measuring T for dx as levels and symptoms not correlated
• 3-6 month trial for postmenopausal women with HSDD requesting a trial
Endocrine Society guideline for Androgens in Women

• Use and monitoring
  • Use a transdermal formulation “if available”
    • Do not use a formulation for men
  • Check baseline level and in 3-6 weeks, then every 6 months
  • Monitor for signs of androgen excess
  • Aim for mid-normal premenopausal level
  • Stop if no response in 6 months
  • No safety data beyond 2 years

Androgen Treatment Options

• 1% testosterone in vanicream in metered dose dispenser (dispensing volume is 0.25 mg/click)
• Buccal troches, pellets, IM injections
• Oral (methyl-testosterone or testosterone undecanoate)
• Intrinsa patch in Europe-pharma company voluntarily withdrew its product license 10/2012 due to “commercial reasons”
• Androfemel1% cream available in Australia
• In development: transdermal metered dose spray, transdermal gel, intranasal gel
Flibanserin

• Mixed post-synaptic $5\text{HT}_{1A}$ agonist and $5\text{HT}_{2A}$ antagonist-exact mechanism unknown

• FDA-approved for generalized HSDD in premenopausal women not caused by:
  • Medical or psychiatric condition
  • Relationship problems
  • Effects of a medication/drug

• 100mg PO daily at bedtime

• REMS program and certification to prescribe/dispense

Efficacy of Flibanserin in Three Phase 3 Trials*

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Mean baseline</th>
<th>Improvement over baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Satisfying sexual events</td>
<td>2–3/mo</td>
<td>0.5–1.0/mo (median)</td>
</tr>
<tr>
<td>FSFI desire (range, 1.2–6.0)</td>
<td>1.8–1.9</td>
<td>0.3–0.4</td>
</tr>
<tr>
<td>Daily desire (range, 0–84)</td>
<td>10–12</td>
<td>1.7–2.3</td>
</tr>
<tr>
<td>Distress (range, 0–4)</td>
<td>3.2–3.4</td>
<td>0.3–0.4</td>
</tr>
</tbody>
</table>

*Improvement data represent least-square means, unless otherwise noted. The improvement in daily desire was not statistically significant. FSFI denotes Female Sexual Function Index. For the FSFI and daily desire scales, the higher the number, the greater the sexual desire. For the distress scale, the higher the number, the greater the distress.

Joffe, H. FDA approval of flibanserin-treating hypoactive sexual desire disorder. NEJM 374(2): 101-104
## 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>
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Flibanserin

- Alcohol study
  - Participants (23/25 men) 100 mg flibanserin in am with 2 alcoholic drinks
  - Some required intervention for hypotension
  - Phase 3 trials not regulating alcohol documented no increase in syncope
  - 0.4% flibanserin; 0.2% placebo
- Snowdrop trial showed effectiveness in postmenopausal women

Biopsychosocial Model

- Medications
- Hormones
- Genitourinary syndrome of menopause (GSM)
- Aging
- Illness
- Fatigue
Biopsychosocial Model

- Anxiety
- Depression
- Hx of sexual abuse/trauma
- Poor body image
- Substance abuse
- Distraction
- Sandwich generation
Biopsychosocial Model

- Discord
- No emotional intimacy
- Partner dysfunction
- Inadequate stimulation
- Lack of privacy
Biopsychosocial Model

- Limited sex education
- Conflict with religious, personal, or family values
- Societal taboos
Take Home Messages

• Maintaining sexual function is important to midlife women

• Low sexual desire has a multifactorial etiology (biopsychosocial model)

• Assess the multiple factors
  • Treat GSM and antidepressant-related side effects

• Refer everything else
THANK YOU!

Any questions?

faubion.stephanie@mayo.edu
Bibliotherapy

• Tired Woman’s Guide to Passionate Sex by Mintz
• Reclaiming Your Sexual Self by Hall
• Pleasure: A Woman’s Guide to Getting the Sex You Want, Need and Deserve by Hutcherson
• Getting the Sex you Want: A Women’s guide to Becoming Proud, Passionate and Pleased in Bed by Leiblum & Sachs
• The Heart of Desire by Resnick
Sex Therapy Referrals

• American Association of Sex Educators, Counselors, and Therapists (AASECT)
• Society for Sex Therapy and Research (SSTAR)
• International Society of the Study of Women’s Health (ISSWSH)
Pelvic/Genital Pain Referrals

- American Physical Therapy Association (APTA)
    - Choose “Women’s Health” as the expertise
- International Pelvic Pain Society (IPPS)
  - http://www.pelvicpain.org/providers/find_provider.aspx
- www.vaginismus.com
- National Vulvodynia Association (NVA)
  - www.nva.org
Menopause Resource

• North American Menopause Society (NAMS)
  http://www.menopause.org/