SEXUAL HEALTH AFTER MENOPAUSE: The gynecologist’s perspective

Linda S. Mihalov, MD, FACOG
Virginia Mason Medical Center
Certified Menopause Practitioner
North American Menopause Society
Objectives

• Review sexual response cycle and impact of menopausal hormonal changes
• Review strategies for satisfying sexual function
• Review safety and efficacy of medications including estrogen and testosterone
World Health Organization

Technical Consultation on Sexual Health, January 2002:

“Sexual health is a state of physical, emotional, mental and social well-being in relation to sexuality; it is not merely the absence of disease, dysfunction or infirmity. Sexual health requires a positive and respectful approach to sexuality and sexual relationships, as well as the possibility of having pleasurable and safe sexual experiences free of coercion, discrimination and violence.”
“Sexuality is a central aspect of being human throughout life and encompasses sex, gender identities and roles, sexual orientation, eroticism, pleasure, intimacy and reproduction. Sexuality is experienced and expressed in thoughts, fantasies, desires, beliefs, attitudes, values, behavior, practices, roles and relationships. While sexuality can include all of these dimensions, not all of them are always experienced or expressed. Sexuality is influenced by the interaction of biological, psychological, social, economic, political, cultural, ethical, legal, historical, religious and spiritual factors.”
Age at Menopause has Remained Constant While Life Expectancy Has Increased (in USA)

Age at Menopause has remained constant while life expectancy has increased (in USA).

1/3 of life spent in menopause.
Key Points

NAMS 2012 Hormone Therapy Position Statement
FEMALE SEXUAL RESPONSE
Traditional sexual response cycle of Masters and Johnson

Basson, Obstetrics and Gynecology 2001;98:350-3
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FEMALE SEXUAL RESPONSE CYCLE

- Emotional Intimacy
  - motivates the sexually neutral woman
to find/be responsive to
- Sexual Stimuli
  - psychological and biological factors govern "arousability"

- "Spontaneous" Sexual Drive "Hunger"

- Emotional and Physical Satisfaction

- Arousal & Sexual Desire

- Sexual Arousal
Mean Steroid Levels in Women (pg/ml)

<table>
<thead>
<tr>
<th></th>
<th>Reproductive Age</th>
<th>Natural Menopause</th>
<th>Surgical Menopause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol</td>
<td>150</td>
<td>10-15</td>
<td>10</td>
</tr>
<tr>
<td>Testosterone</td>
<td>400</td>
<td>290</td>
<td>110</td>
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<tr>
<td>Androstenedione</td>
<td>1900</td>
<td>1000</td>
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</tr>
<tr>
<td>DHEA</td>
<td>5000</td>
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<td>DHEAS</td>
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UROGENITAL ATROPHY
## Presenting genital symptoms and physical signs of vaginal atrophy

### Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dryness</td>
<td>Burning leukorrhea</td>
</tr>
<tr>
<td>Itching</td>
<td>Vulvar pruritus</td>
</tr>
<tr>
<td>Burning</td>
<td>Feeling of pressure</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>Yellow malodorous discharge</td>
</tr>
</tbody>
</table>

### Signs on physical exam

<table>
<thead>
<tr>
<th>Sign</th>
<th>Sign</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pale, smooth, or shiny vaginal epithelium</td>
<td>Pelvic organ prolapse</td>
</tr>
<tr>
<td>Loss of elasticity or turgor of skin</td>
<td>Rectocele</td>
</tr>
<tr>
<td>Sparsity of pubic hair</td>
<td>Vulvar dermatoses</td>
</tr>
<tr>
<td>Dryness of labia</td>
<td>Vulvar lesions</td>
</tr>
<tr>
<td>Fusion of labia minora</td>
<td>Vulvar patch erythema</td>
</tr>
<tr>
<td>Introital stenosis</td>
<td>Petechiae of epithelium</td>
</tr>
<tr>
<td>Friable, unrugated epithelium</td>
<td></td>
</tr>
</tbody>
</table>
Atrophic Vaginitis: Clinical Evaluation

- **Evaluation**
  - Examination of urogenital tissues for signs of atrophy or inflammation
  - Simple pH test (elevated in vaginitis)
  - Vaginal cytology

![Vaginal biopsy specimen showing atrophic changes](image1)

![Vaginal biopsy specimen from the same patient after local estrogen therapy](image2)

- **Local estrogen therapy actually reverses vaginal atrophy**
  - Promotes cell growth and maturation
  - Enhances blood flow and reduces pH

Images from Lila Nachtigall, MD.
KEEPING SEX COMFORTABLE
Frequency of sexual activity

- 52 women, mean age 57, married, not on hormones
- Sexually active women had intercourse at least 3 times a month and had less vaginal atrophy and higher levels of androgens
- Sexually inactive women had intercourse less than 3 times/mo and more atrophy
- Masturbation may be helpful in lieu of intercourse

Leiblum, et al., *JAMA* 1983
Non-Rx therapies for vaginal dryness

- Vaginal moisturizers effective; also produce low pH to guard against infection
- Vaginal lubricants ease penetration
- Avoid use of petroleum-based products
- Douches may worsen condition; antihistamines may have drying effect
- Continued sexual activity and/or stimulation may benefit vaginal health
Choosing a lubricant

• Latex-safe: water-based and silicone-based, not oil-based
• Glycerin may be irritating or promote yeast infections
• Nonoxynol-9 may be irritating
• Thick vs thin consistency

www.babeland.com
Water-based lubricants

- Liquid Silk: moisturizer-like consistency, no glycerin, long-lasting
- Maximus: long-lasting
- Pjur Woman Aqua: liquid and gel forms
- Astroglide: widely available, contains glycerin
- O’My: natural, glycerin, hemp oil

www.babeland.com
Silicone-based lubricants

- Pjur Eros
- Pjur Woman Bodyglide: gel and liquid forms

www.babeland.com
www.pjur.com
## Vaginal moisturizers

### Table 2. Over-the-counter vaginal moisturizers

<table>
<thead>
<tr>
<th>Product</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astroglide</td>
<td>BioFilm Inc., Vista, CA</td>
</tr>
<tr>
<td>K-Y Jelly</td>
<td>Johnson &amp; Johnson Merck, Fort Washington, PA</td>
</tr>
<tr>
<td>K-Y Plus</td>
<td>Johnson and Johnson Merck, Fort Washington, PA</td>
</tr>
<tr>
<td>Replens</td>
<td>LDS Consumer Products Inc., Cedar Rapids, IA</td>
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<tr>
<td>Silken Secret</td>
<td>BioFilm Inc., Vista, CA</td>
</tr>
<tr>
<td>Summer's Eve Lubricating Jelly</td>
<td>C.B. Fleet Co. Inc., Lynchburg, VA</td>
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<tr>
<td>Vagisil Intimate Moisturizer</td>
<td>Combe Inc., White Plains, NY</td>
</tr>
<tr>
<td>VCF Personal Lubricant</td>
<td>Apothecus Pharmaceuticals Corp., Oyster Bay, NY</td>
</tr>
<tr>
<td>Wet Light</td>
<td>Trigg Laboratories, Valencia, CA</td>
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</table>
### All Lubricants

**browse:** sexual well-being  |  lubricants

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Size</th>
<th>Savings</th>
<th>Price</th>
<th>Buy</th>
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<tbody>
<tr>
<td><strong>Aqua Lube</strong></td>
<td>4 fl oz</td>
<td></td>
<td>$10.49</td>
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<tr>
<td>Advanced Formula Gel Personal</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lubricant, with PCA natural moisture factors</td>
<td></td>
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<tr>
<td>in stock</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Aqua Lube</strong></td>
<td>2 fl oz</td>
<td>save 13%</td>
<td>$6.49</td>
<td></td>
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<tr>
<td>Personal Lubricant, Water Based</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>in stock</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Show products in brand:**  
- All Brands

**Sort by:**  
- A-Z

**Top brands:** Pre-Seed  |  K-Y  |  Astroglide  |  Aqua Lube

- New AVEENO® Continuous Radiance® Moisturizing Lotion

- We always ship in our plain, everyday packaging.
Local estrogen products

- Estradiol vaginal ring (Estring)
- Estradiol vaginal tablets (Vagifem)
- Estrogen vaginal cream
  - Estradiol
  - Conjugated estrogens
Estradiol ring (Estring)

- 2mg ring replaced every 3 months
- Delivers 7.5 mcg estradiol daily, of which ~10% is systemically absorbed
- Serum levels not increased above postmenopausal level
- Do not confuse with Femring, a vaginal ring which delivers a systemic dose of estradiol
Estradiol tablets (Vagifem)

- 10 mcg tablets, daily for the first 14 days, then twice weekly for maintenance
- Steady state serum level similar to normal postmenopausal level
- If distal vaginal symptoms are prominent, tablets may be inserted into the outer third of the vagina
Vagifem® vs Premarin® Vaginal Cream: Systemic Absorption

*P < 0.001 (the Fisher exact test).
Vagifem® vs Premarin® Vaginal Cream: Endometrial Biopsy Results

*Baseline for endometrial biopsy results was defined as the screening visit. Premarin® Vaginal Cream package insert, April 2004.
Estrogen creams

• Useful externally for vulvar symptoms
• Vaginal use may achieve levels similar to systemic administration
• Unopposed use may induce hyperplasia at higher doses
• Systemic levels unpredictable
Choosing vaginal ET

- Low-dose, local, prescription vaginal ET products FDA-approved for treating vaginal atrophy include:
  - estradiol vaginal cream (Estrace Vaginal Cream)
  - CE vaginal cream (Premarin Vaginal Cream)
  - estradiol vaginal ring (Estring)
  - estradiol hemihydrate vaginal tablet (Vagifem)

- All are equally effective at doses recommended in labeling

- Choice depends on clinical experience and patient preference

Estring vs. Vagifem

- Randomized controlled trial comparing Estring and Vagifem for 12mos
- No difference in efficacy or endometrial thickness
- Fewer patients with bleeding in Estring group (0 vs 6%)

Weisberg, Ayton, et.al. Climacteric 2005; 8, 83
Vaginal estrogen

• 19 trials with 4162 women
• Cream, ring, tablets improved atrophy compared to placebo and non-hormonal gel
• Patient preference for ring
• Some evidence of endometrial overstimulation or side effects with cream

Suckling, et al, *Cochrane Database of Systematic Reviews* 2006
Need for endometrial surveillance

There are insufficient data to recommend annual endometrial surveillance in asymptomatic women using low-dose, local vaginal ET.

Closer surveillance may be required if a woman is:

- at high risk for endometrial cancer
- using a greater dose of vaginal ET
- having symptoms such as spotting, breakthrough bleeding

Endometrial Safety of Vaginal Estrogen

• Randomized double-blind placebo-controlled trial
• 52 wks of treatment with 10 mcg estradiol
• Endometrial biopsies evaluated
• No increased risk of endometrial hyperplasia or carcinoma

Low-dose local ET may improve sexual satisfaction by improving lubrication and increasing blood flow and sensation in vaginal tissue.

HT is not recommended as the sole treatment of other sexual function problems (e.g., diminished libido).

Systemic or vaginal estrogen?

Although all estrogen and estrogen/progestin combination products are approved for treatment of urogenital atrophy, ACOG and NAMS Position Statements on menopausal hormone therapy both state that for treatment of urogenital symptoms alone, local estrogen therapy should be considered.
HT & Vaginal Symptoms

- ET is most effective treatment of moderate to severe symptoms of vulvar and vaginal atrophy
- Many systemic HT and local vaginal ET products are available for treating one or both of these symptoms

HT & Urinary Tract Health

- Local ET may benefit some women with overactive bladder
- Only vaginal ET is effective for urinary tract infection
- Systemic ET may worsen or provoke stress incontinence
- Ultralow-dose transdermal ET has no effect on incontinence

“There is now a critical mass of data—including data from preplanned as well as post hoc subgroup analyses of the WHI—to support a “unifying hypothesis” that age or time since menopause may importantly influence the benefit-risk ratio associated with HT, especially with respect to coronary disease outcomes, and that the method of administration, dose, formulation and duration of use of exogenous hormones may also be relevant.”

Allison and Manson
The Good News

• Local Estrogen treatment highly effective and well tolerated
• Minimal systemic absorption
• Can be used by women at risk for breast cancer, including survivors
• Progestin opposition not required
Transdermal hormone therapy

- Better absorption in some patients
- Avoids first-pass liver metabolism
- Does not raise triglycerides
- Does not raise SHBG, which would result in lower free testosterone levels
- Lower risk of thromboembolism
- Patch drawbacks: poor adherence, skin reactions, adhesive residue
Effect of ERT on T levels

- ERT can effect the total and free testosterone
  - oral estrogen: ↑ SHBG 184%
    ↓ total T 5%, ↓ free T 57%
  - transdermal estradiol: ↑ SHBG 7%
    ↓ total T 7%, ↓ free T 12%
HT & Quality of Life

- Although HT is not approved for enhancing QOL, HT can improve health-related QOL in symptomatic women.

- Unclear if HT improves health-related QOL in asymptomatic women.

HT & Osteoporosis

- HT reduced the risk for fracture (e.g., hip, spine, nonspine) in postmenopausal women in the Women’s Health Initiative (WHI) who were not selected on basis of osteoporosis

- Many systemic HT products are approved for preventing postmenopausal osteoporosis

- No HT product is approved for treating osteoporosis

(cont’d)
HT & Osteoporosis (cont’d)

- Extended use of HT is option for women at high risk of osteoporotic fracture when alternate therapies aren’t appropriate
- Risks of long-term HT use should be considered
- Benefits of HT on bone mass dissipate quickly after discontinuation

HT & Coronary Heart Disease

- ET may reduce CHD and coronary artery risk when initiated in younger and more recently postmenopausal women without a uterus.

- HT is currently not recommended for coronary protection in women of any age.

HT & Stroke

Both ET and EPT appear to increase ischemic stroke risk and have no effect on hemorrhagic stroke risk

HT & Venous Thromboembolism

- Oral HT increases the risk of VTE in postmenopausal women
- VTE risk emerges soon after HT initiation (1-2 y) and decreases over time
- Lower VTE risk with either EPT or ET in women before age 60
- Possible lower VTE risk with transdermal and lower oral HT doses. No RCT evidence

HT & Diabetes Mellitus

- HT reduces new-onset DM, although no HT product approved for prevention.

- Inadequate evidence to recommend HT for sole or primary indication for DM prevention in peri- or postmenopausal women.

HT & Endometrial Cancer

- Unopposed systemic ET in postmenopausal women with an intact uterus is associated with increased endometrial cancer risk related to dose and duration of use.

- HT not recommended with history of endometrial cancer history.

HT & Breast Cancer

- Diagnosis of breast cancer increases with EPT use beyond 3-5 years
- Unclear whether EPT risk differs between continuous and sequential progestogen
- EPT and to a lesser extent ET increase breast cell proliferation, breast pain, and mammographic density

HT & Breast Cancer (cont’d)

- EPT may impede diagnostic interpretation of mammograms
- Breast cancer diagnosis dissipated 3 years post EPT cessation
- Breast cancer mortality higher in women assigned to EPT compared to placebo
- Women starting EPT shortly after menopause experience increased breast cancer risk, but those with a gap time greater than 5 years do not

HT & Breast Cancer (cont’d)

- ET arm of WHI showed no increased cancer risk after mean 7.1 years on study

- ET and EPT use in breast cancer survivors may increase recurrence risk

HT & Total Mortality

- HT may reduce total mortality when initiated soon after menopause
- Both ET and EPT may reduce total mortality by 30% when initiated in women younger than age 60

Class vs Specific Product

Effect

- All estrogens share some common features but may have unique properties as well
- Same is true for progestogens
- Without RCTs, data for one agent should be generalized to all agents within same hormonal family
- More research required

Progestogen Indication

- Primary menopause-related indication for progestogen use is endometrial protection from systemic ET.
- Adequate progestogen recommended for women with an intact uterus using systemic ET.
- Progestogen generally not indicated with low-dose local ET for vaginal atrophy.
Dose & Route of Administration

- Therapeutic goal is lowest effective estrogen dose consistent with individual treatment goals, benefits, and risks, plus appropriate progestogen dose for women with a uterus.

- Lower doses have fewer side effects and may have more favorable benefit-risk ratio than standard doses but lower doses not been tested in long-term trials.

(NAMS position statement. Menopause 2012. (cont’d))
Dose & Route of Administration (cont’d)

- All routes of administration of ET can effectively treat menopausal symptoms
- Nonoral routes may offer both advantages and disadvantages compared with oral route (but no RCT outcomes)
- Transdermal ET may be associated with lower risk of DVT, stroke, and MI
- Multiple progestogen options for endometrial protection

Duration of Use

- With EPT, increased risk of breast cancer incidence and mortality with 3-5 years of use.
- With ET, no increase of breast cancer with early postmenopausal use; decrease found after hiatus in estrogen exposure.
- With ET, potential CAD and CHD benefits with early use.
- Initial increase in CHD risk when EPT is initiated further from menopause.

Duration of Use (cont’d)

Extending EPT use is acceptable for:

- Women who request it and are well aware of potential risks and benefits
- Prevention of further osteoporosis-related fracture and bone loss when alternate therapies are not appropriate or cause unacceptable adverse effects

Discontinuation

After 3 years of EPT discontinuation:
- Rate of cardiovascular events, fractures, and colon cancer same as placebo group
- Increase in rate of all cancers and mortality from breast cancer

After 3 years of ET discontinuation:
- No increase in CHD, DVT, stroke, hip fracture, colorectal cancer, or total mortality
- Decrease in breast cancer persisted

(cont’d)
Discontinuation (cont’d)

- HRs for all-cause mortality neutral for both
- 50% chance of vasomotor symptoms recurring when HT discontinued
- Symptom recurrence similar whether tapered or abruptly discontinued
- Decision to continue HT should be individualized

Conclusions & Recommendations

- Individualization is key in decision to use HT and should incorporate the woman’s health and QOL priorities as well as her personal risk factors for VTE, CHD, stroke, and breast cancer.
Conclusions & Recommendations (cont’d)

- Duration of use recommendations differ for EPT and ET:
  - For EPT, duration is limited by the increased risk of breast cancer and breast cancer mortality associated with 3-5 years of use.
  - For ET, more favorable benefit-risk profile during mean of 7 years of use and 4 years of follow-up, a finding that allows more flexibility in duration of use.
Conclusions & Recommendations (cont’d)

- ET is most effective treatment for vulvar and vaginal atrophy; low-dose local vaginal ET advised when only vaginal symptoms are present.

- Women with premature or early menopause can use HT until median age of menopause (51 y); longer duration can be considered for symptom management.

Conclusions & Recommendations (cont’d)

- Although ET did not increase breast cancer risk in WHI, there is lack of safety data for breast cancer survivors, and one RCT reported higher increase in recurrence rates.

- Both transdermal and low-dose oral estrogen associated with lower risks of VTE and stroke but RCT evidence not yet available.
What Are Bio-identicals?

- Not a scientific term, and no uniform definition in any medical dictionary
- Molecularly very similar or identical to endogenous hormones; plant-derived from soybean or yam
- “Individualized exact doses” to replicate homeostatic hormone levels of Estrogen, Progesterone, Testosterone
- Dosage is adjusted according to salivary or blood hormone levels, unlike commercial HR which is adjusted based on symptom relief
- Purported anti-aging, sexual vibrancy and energizing effects are similar to structure/function claims made for dietary supplements rather than disease treatment/prevention claims made for drugs
“Bioidentical hormones”

- Pharmaceutically produced estradiol and progesterone are bio-identical
- There is no scientific evidence to support use of salivary hormone testing to customize hormone treatment
- There is no evidence to support a different risk-benefit profile for compounded hormones
- Little regulatory oversight of compounded products
Bioidentical Hormone Therapy (BHT)

- Many well-tested, government-approved, brand-name HT products contain hormones chemically identical to those made by ovaries.

- "BHT" usually refers to custom-compounded formulations.

- Custom BHT may combine several hormones and use nonstandard routes of administration.

- Use of compounded BHT and salivary hormone testing are not recommended.

(NAMS position statement. Menopause 2012.)
Bioidentical Hormone Therapy (cont’d)

- BHT is not tested for efficacy, safety, batch standardization, or purity
- FDA says compounding pharmacies make false and misleading claims about safety and effectiveness of BHT
- BHT should include package inserts explaining benefits & risks just like government-approved HT products
- Compounded HT should only be used by women allergic to ingredients in approved products

The Problems with BHT

• No tested in good clinical trials, and no endometrial safety data
• “Natural” does not really equal “safer”
• No clinician or patient package inserts documenting safety/efficacy, and no black box warnings
• No uniform manufacturing standards. In one study 25% of compounded products tested failed quality control testing vs. 2% of commercially manufactured drug products
• No formal review of accuracy of advertised claims

This is A LOT of “Nots”. Will it even matter to those determined to take these products?
Supports FDA regulation and oversight of all hormones, regardless of chemical structure or method of manufacture. This should include:
- surveys for purity and dosage accuracy
- mandatory reporting by drug manufacturers of adverse events
- a registry of adverse events related to the use of hormone preparations
- inclusion of uniform information for patients, such as warnings and precautions, in packaging of hormone products
Management of postmenopausal symptoms in breast cancer survivors

• Vaginal moisturizers first, then vaginal estrogen if needed
• Avoid testosterone since it is aromatized to estrogen
• No evidence for value of phytoestrogens
• One small study urged caution with vaginal estrogen in women on aromatase inhibitors

Bruno and Feeney, *Seminars in Oncology*, Dec. 2006
Vaginal atrophy in cancer patients

- For women treated for non-hormone-dependent cancer, management is similar to that for women without a cancer history.
- For women with a history of hormone-dependent cancer, management recommendations are dependent upon each woman’s preference in consultation with her oncologist.

Impact of Age on Free Testosterone Levels

Female Sexual Dysfunction (FSD)*

- Hypoactive sexual desire disorder
- Arousal Disorder
- Orgasmic Disorder
- Painful sexual function

*Diagnosed only if the woman experiences personal distress

Sexual Function Health Council of the American Foundation for Urologic Disease
Hypoactive Sexual Desire Disorder (HSDD)

Medical Causes
- Androgen insufficiency
- Thyroid disease
- Metabolic/nutritional disorders
- Depression
- Immunologic disorders
- Fatigue from medical disorders

Other Causes
- Medications
- Tension/stress
- Relationship difficulties
- Intra- or interpersonal issues
- Substance abuse
Princeton Consensus Statement: Female Androgen Insufficiency

- A pattern of clinical symptoms with decreased bioavailable testosterone due to age or secondary cause
- Androgen insufficiency should only be diagnosed in women who are adequately estrogenized because of the strong association of estrogen levels and sexual function

Princeton Consensus Statement on Female Androgen Insufficiency (FAI): Symptoms

- Diminished sense of well-being
- Persistent, unexplained fatigue
- Sexual function changes – decreased libido, sexual receptivity, and pleasure
- Bone loss
- Decreased muscle strength
- Changes in cognition or memory

Female Androgen Insufficiency (FAI) - Laboratory Aspects

Unresolved at Princeton Conference*:

• No agreed upon cut-off level for normal range of T

• Problems with assay standardization; total T, free T or bioavailable T?

Establishing a Diagnosis of Hypoactive Sexual Desire Disorder (HSDD)

Persistent or recurrent deficiency or absence of sexual fantasies, thoughts, and/or desire for, or receptivity to, sexual activity*

Yes

Plus Personal Distress

Hypoactive sexual desire Disorder (HSDD)

No

No desire disorder

Current Management of HSDD

- No approved pharmaceutical therapies
- Off-label use of testosterone products:
  - Doses are too high
    - Leading to virilizing side effects
    - Significant decrease of high density lipoprotein (HDL)
    - Potential for other serious side effects
  - Compounding leads to variations in dose
- Herbals and Nutraceuticals
  - Lack of valid safety and efficacy data for herbals/nutraceuticals
Current Pharmacologic Management of HSDD

• Off-label use of testosterone products:
  ▪ Patches (Androderm® Transdermal Systems)
    • 2.5-5 mg per day
  ▪ Gels (Androgel®, Testim®)
    • 50, 75, or 100 mg per day (1% cream with 10% absorption)
  ▪ Creams (compounded) – varied doses
  ▪ Injections (Delatestryl® Injection) – 200 mg/ml
  ▪ Oral mucoadhesive (Striant® Buccal System) 30 mg
  ▪ Methyltestosterone (Estratest® tablets, Testred® capsules, Virilon® capsules)
    • 1.25 – 10 mg per day
Testosterone products for women

The role of testosterone therapy in postmenopausal women: NAMS position statement, *Menopause, 2005*

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Product name, developer</th>
<th>Trial status</th>
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<tbody>
<tr>
<td>Oral methyltestosterone (plus esterified estrogens)</td>
<td>Estratest, Solvay Pharmaceuticals, Inc.</td>
<td>Phase 2/3</td>
</tr>
<tr>
<td>Testosterone cream</td>
<td>Androsorb, Novavax, Inc.</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Testosterone gel</td>
<td>Tostrelle, Cellegy Pharmaceuticals, Inc.</td>
<td>Phase 2/3</td>
</tr>
<tr>
<td>Testosterone gel (plus estrogen)</td>
<td>Libigel, Biosante Pharmaceuticals</td>
<td>Phase 2/3</td>
</tr>
<tr>
<td>Testosterone patch</td>
<td>Intrinsa, Procter &amp; Gamble Pharmaceuticals</td>
<td>Phase 3</td>
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<tr>
<td>Testosterone spray (metered-dose transdermal system)</td>
<td>Testosterone, MDTS, Vivus, Inc.</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Vaginal ring</td>
<td>[No product name], Warner Chilcott</td>
<td>Phase 2</td>
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</tbody>
</table>
Increases in Total Satisfying Sexual Activity at 24 Weeks

INTIMATE SM 1

% increase from baseline: 33% 74%
p = 0.0003

INTIMATE SM 2

% increase from baseline: 23% 51%
p = 0.001

Placebo
TTP

Increase in Desire at 24 Weeks

INTIMATE SM 1

p=0.0006

INTIMATE SM 2

p=0.0006

% increase from baseline

Placebo

TTP

29%

56%

18%

49%
Conclusions

• The 300 mcg/day T patch significantly increased satisfying sexual activity and desire in oophorectomized women with HSDD.
• The T patch was also well tolerated.
Study Design and Population

- Randomized, double-blind, parallel-group, placebo-controlled, multi-center
- 24-week treatment period
- Patch applied twice weekly
  - Placebo, Testosterone 300 mcg/day
  - Estrogen (oral only)
- Healthy naturally menopausal women with low sexual desire causing distress
- 40-70 years old
- Stable relationship with partner
- Stable dose of oral estrogen with or without progestin for ≥3 months
Overall Conclusion

- In naturally menopausal women with low sexual desire, the testosterone patch
  - Significantly improved sexual function
    - \( \uparrow \) Activity
    - \( \uparrow \) Desire
    - \( \downarrow \) Distress
  - Was safe and well tolerated
Potential Risks

- ↑ cardiovascular risk
- Affect lipid and carbohydrate metabolism
- Weight distribution
- Secondary male characteristics
- ↑ breast cancer risk?
NAMS position statement

-No T level has been clearly linked to a syndrome of hypoandrogenism
-Lab assays are not accurate at low levels in postmenopausal women
-Labs should be used only to monitor for supraphysiologic levels during therapy, not to diagnose insufficiency
-Salivary testing not reliable

Menopause 2005
If T treatment is used:

- Baseline lipids and LFTs
- Transdermal may be preferred over oral due to avoidance of first-pass hepatic effects
- Caution with compounded products due to inconsistent dosing
- Insufficient data re: efficacy and safety beyond 6mos

*Menopause 2005*
## Off-Label Uses of Drugs for Investigational Treatment of Sexual Dysfunction

<table>
<thead>
<tr>
<th>Type of Sexual Dysfunction</th>
<th>Drug</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual desire/interest disorder, subjective and combined arousal disorders</td>
<td>Bupropion (a dopamine and norepinephrine agonist)</td>
<td>In one small, four-month study, nondepressed, premenopausal women showed increased arousability and sexual response but not initial desire.</td>
</tr>
<tr>
<td>Testosterone (plus estrogen)</td>
<td></td>
<td>In six-month randomized trials, women had improved “total satisfying sexual activity” and improved measures of desire and response, as reported on questionnaires. No long-term safety data or data on women lacking estrogen are available.</td>
</tr>
<tr>
<td>Dehydroepiandrosterone (a precursor of estradiol and testosterone)</td>
<td></td>
<td>Data from trials involving women with adrenal insufficiency are conflicting. A study of perimenopausal women with reduced feelings of well-being and low level of desire showed no benefit.</td>
</tr>
<tr>
<td>Tibolone (an estrogenic, progestogenic, androgenic steroid)</td>
<td></td>
<td>Data from small trials of postmenopausal women show improved sexual function, as compared with those receiving placebo or a regimen of 17β-estradiol (1 mg daily) plus norethindrone (1 mg daily). The drug has not been studied in women with diagnosed sexual dysfunction and is associated with a possible increased risk of breast cancer.</td>
</tr>
<tr>
<td>Phosphodiesterase inhibitors (sildenafil, tadalafil, vardenafil)</td>
<td></td>
<td>In large multicenter trials involving pre- and postmenopausal women, no benefit from sildenafil was reported.</td>
</tr>
<tr>
<td>Yohimbine (a centrally acting noradrenergic agent) plus arginine (a precursor of nitric oxide)</td>
<td></td>
<td>In one randomized, controlled crossover laboratory study of 24 women, yohimbine (6 mg) plus arginine (6 g) increased vaginal congestion, but not subjective arousal, in response to an erotic film.</td>
</tr>
<tr>
<td>Ephedrine (agonist of α- and β-adrenergic receptors)</td>
<td></td>
<td>In one randomized, controlled crossover laboratory study of 20 women, ephedrine (50 mg) increased vaginal congestion, but not subjective arousal, in response to an erotic film.</td>
</tr>
<tr>
<td>Genital arousal disorder despite estrogen-replete status</td>
<td>Phosphodiesterase inhibitors (sildenafil, tadalafil, vardenafil)</td>
<td>In one laboratory randomized trial, it was shown that only some women given a diagnosis of genital arousal disorder have demonstrably reduced genital congestion, and they alone showed evidence of benefit. It was not possible clinically to distinguish this subgroup. In one randomized study of neurogenic genital arousal disorder from multiple sclerosis, treatment with sildenafil led to increased lubrication.</td>
</tr>
</tbody>
</table>

* Only drugs for which at least one randomized trial has been published are listed.
† All agents act by increasing levels of cyclic guanosine monophosphate (generated by nitric oxide).

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Painful Sexual Function

Dyspareunia
  Recurrent or persistent genital pain associated with sexual intercourse

Vaginismus
  Overcontraction of the muscles of the outer 1/3 of the vagina when penetration is attempted

Noncoital Sexual Pain Disorder
  Recurrent or persistent genital pain associated with noncoital sexual stimulation
Dyspareunia

- Vaginal/Vulvar health
  - Estrogen lack
  - Infection
  - Vulvar vestibulitis
  - Interstitial cystitis
  - Vulvar dystrophies
  - Endometriosis
  - Posterior fourchette tears
  - FSAD
  - Anatomic changes
  - Prolonged intercourse
Vaginismus

- Absence of physical findings
- Associated with a fear of vaginal entry
- May stem from
  - Psychologic or physical stress
  - Protective response to repeated painful procedures
  - Protective response to dyspareunia
Keys to satisfying postmenopausal sex….

• Maintain an overall healthy lifestyle including exercise
• Keep at it
• Use lubrication
• Use vaginal estrogen if needed
• Share sexual response cycle information with partner
• Stay tuned for information about testosterone….
REFERENCES AND RESOURCES

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