Clinical Updates – His, Hers and Ours

Men's Health

Kelly A. Lempicki, PharmD, BCPS

This speaker has no actual or potential conflict of interest in relation to this presentation.

Objectives

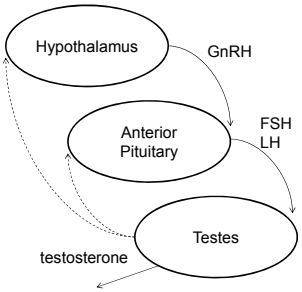
- Pharmacists
  - Review the condition of low-testosterone
  - Describe therapies available for the treatment of low-testosterone
  - Identify current "hot topics" in men's health
- Technicians
  - Explain the condition of low-testosterone and its associated signs and symptoms
  - Recognize medications that are used to treat low-testosterone

Meet Mr. T

- 67 yo man reports decreased libido and hot flushes for several months
  - Also c/o decreased energy and muscle strength and increased body fat
- PMH: HTN, hyperlipidemia
- Medications: lisinopril, simvastatin
- (-) tobacco, (+) EtOH – 1 glass wine daily
- No regular activity since retiring 2 years ago
- DRE WNL
- Labs
  - CBC, LFTs, BMP, PSA - normal
  - Testosterone 230 ng/dl, repeat 220 ng/dl

What is Low-Testosterone?

- Hypogonadism
  - Clinical syndrome resulting from subphysiologic testosterone levels caused by disruption of the hypothalamic-pituitary-gonadal (HPG) axis



1. Bhasin S, et al. *J Clin Endocrinol Metab* 2010;95:2536-2559.

Diagnosis

- Two components
  - Consistent signs and symptoms of androgen deficiency
  - Consistently low serum testosterone levels

1. Bhasin S, et al. *J Clin Endocrinol Metab* 2010;95:2536-2559.
2. Dohle GR, et al. *Guidelines on male hypogonadism* 2012.

Androgen Deficiency S/Sx

- Delayed puberty
- ↓ sexual desire (libido) and activity
- ↓ spontaneous erections
- Breast discomfort, gynecomastia
- ↓ body hair or need for shaving
- Small (<5 ml) or shrinking testes
- Infertility
- ↓ BMD, low trauma fracture, height loss
- Hot flushes, sweats

1. Bhasin S, et al. *J Clin Endocrinol Metab* 2010;95:2536-2559.
2. Dohle GR, et al. *Guidelines on male hypogonadism* 2012.

Less Specific S/Sx

- ↓ energy, motivation, initiative, self-confidence
- Depressed mood
- Poor concentration and memory
- Sleep disturbances (↑ sleepiness)
- Mild anemia
- ↓ muscle mass and strength
- ↑ body fat, ↑ BMI
- ↓ physical or work performance

1. Bhasin S, et al. *J Clin Endocrinol Metab* 2010;95:2536-2559.
2. Dohle GR, et al. *Guidelines on male hypogonadism* 2012.

Which of Mr. T's symptoms are more specific for androgen deficiency?

1. Hot flushes
2. Decreased energy
3. Decreased muscle strength
4. Increased body fat

Testosterone Level

- Specific cut-offs for low testosterone have not been established
  - Generally less than 280-300 ng/dl
- Recommend checking *at least two* total testosterone levels
  - Morning level
  - Not acutely ill

1. Bhasin S, et al. *J Clin Endocrinol Metab* 2010;95:2536-2559.
2. Dohle GR, et al. *Guidelines on male hypogonadism* 2012.

When to Use Testosterone Therapy

- Treatment with testosterone is recommended when:
  - The patient has symptoms of androgen deficiency

    AND
  - The testosterone level is consistently low

1. Bhasin S, et al. *J Clin Endocrinol Metab* 2010;95:2536-2559.
2. Dohle GR, et al. *Guidelines on male hypogonadism* 2012.

When to Avoid Testosterone Therapy

- Prostate cancer
- Breast cancer
- Unevaluated prostate nodule or induration
- PSA >4 ng/ml
  - >3 ng/ml if at high risk for prostate cancer (African American, 1st degree relative with prostate cancer)
- Hematocrit >50%
- Uncontrolled heart failure or sleep apnea
- Male infertility
- Severe lower urinary tract symptoms due to BPH

1. Bhasin S, et al. *J Clin Endocrinol Metab* 2010;95:2536-2559.
2. Dohle GR, et al. *Guidelines on male hypogonadism* 2012.

Would Mr. T be an appropriate candidate for testosterone therapy?

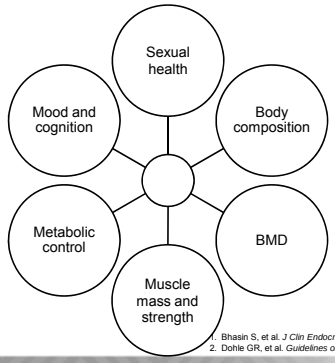
1. Yes
2. No

Goals of Therapy

- Improve quality of life and sense of well-being
- Improve sexual function
- Improve BMD
- Increase testosterone to a level that is mid-normal for young healthy men

1. Bhasin S, et al. *J Clin Endocrinol Metab* 2010;95:2536-2559.
2. Dohle GR, et al. *Guidelines on male hypogonadism* 2012.

Benefits of Testosterone Therapy



1. Bhasin S, et al. *J Clin Endocrinol Metab* 2010;95:2536-2559.
2. Dohle GR, et al. *Guidelines on male hypogonadism* 2012.

Adverse Effects

- Erythrocytosis
- Oily skin, acne
- Growth of prostate cancer
- ↓ spermatogenesis and fertility
- Potential for abuse/dependence
  - Schedule III
- Cardiovascular events?

1. Bhasin S, et al. *J Clin Endocrinol Metab* 2010;95:2536-2559.
2. Dohle GR, et al. *Guidelines on male hypogonadism* 2012.

Available Products

- Transdermal
  - Gel (AndroGel, Fortesta, Testim)
  - Solution (Axiron)
  - Patch (Androderm)
- Injectable
  - Cypionate (Depo-Testosterone)
  - Enanthate (Delatestryl)
- Implantable pellet (Testopel)
- Buccal bioadhesive tablet (Striant)

Testosterone Gel

- Directions
  - Apply once daily in the morning to clean, dry, intact skin

Product	Application Site
AndroGel	Shoulders, upper arms, abdomen
Fortesta	Thighs
Testim	Shoulders, upper arms

1. Bhasin S, et al. *J Clin Endocrinol Metab* 2010;95:2536-2559.
3. Lexicomp 2014

Testosterone Gel

- Adverse effects
  - Skin irritation
  - **Boxed warning**: transfer through skin-to-skin contact
    - Cover application site with clothes
    - Wash hands with soap and water after application

1. Bhasin S, et al. *J Clin Endocrinol Metab* 2010;95:2536-2559.
3. Lexicomp 2014

Testosterone Solution

- Directions
  - Apply to the axilla at the same time each morning
    - 1 pump per application
- Adverse effects
  - Skin irritation
  - **Boxed warning**: transfer through skin-to-skin contact
    - Cover application site with clothes
    - Wash hands with soap and water after application

1. Bhasin S, et al. *J Clin Endocrinol Metab* 2010;95:2536-2559.
3. Lexicomp 2014

Testosterone Patch

- Directions
  - Apply every evening to clean, dry skin
    - Back, abdomen, upper arms, thighs
      - Areas without prolonged pressure
    - Rotate sites daily
      - Allow 7 days before returning to a site again
- Adverse effects
  - Skin irritation
    - May apply topical hydrocortisone cream after removal or triamcinolone 0.1% cream under the patch

1. Bhasin S, et al. *J Clin Endocrinol Metab* 2010;95:2536-2559.
3. Lexicomp 2014

Injectable Testosterone

- Directions
  - Inject IM every 1-4 weeks
    - Gluteal muscle
- Adverse effects
  - Peaks and troughs in testosterone levels
    - Fluctuations in mood or libido
  - Pain at injection site
  - Excessive erythrocytosis (especially in elderly)
  - Cough

1. Bhasin S, et al. *J Clin Endocrinol Metab* 2010;95:2536-2559.
3. Lexicomp 2014

Testosterone Pellet

- Directions
  - Implant subcutaneously every 3-6 months
  - Requires surgical incision for insertion
- Adverse effects
  - Infection
  - Expulsion of pellet

1. Bhasin S, et al. *J Clin Endocrinol Metab* 2010;95:2536-2559.
3. Lexicomp 2014

Buccal Testosterone

- Directions
  - Apply to the gum above the incisor tooth every 12 hours
- Adverse effects
  - Taste alteration
  - Gum irritation

1. Bhasin S, et al. *J Clin Endocrinol Metab* 2010;95:2536-2559.
3. Lexicomp 2014

Which testosterone product would you recommend for Mr. T?

1. Gel
2. Patch
3. Implantable pellet
4. Buccal tablet

Monitoring

	Baseline	3 months	6 months	12 months	Annually
Symptoms	X	X	X	X	X
Testosterone level	X	X	X	X	X
Hematocrit		X	X	X	X
DRE/PSA	X	X	X	X	X

- BMD – every 1-2 years (if abnormal at baseline)

1. Bhasin S, et al. *J Clin Endocrinol Metab* 2010;95:2536-2559.
3. Lexicomp 2014

Timing of Testosterone Level

- Gel
  - AndroGel, Testim - √ in the morning after 14 days of use
  - Fortesta - √ 2 hrs after application, after 14 days of use
- Solution
  - √ 2-8 hrs after application, after 14 days of use
- Patch
  - √ 3-12 hrs after application, after ~ 14 days of use

1. Bhasin S, et al. *J Clin Endocrinol Metab* 2010;95:2536-2559.
3. Lexicomp 2014

Timing of Testosterone Level

- Injection
  - √ midway between injections
- Implantable pellet
  - √ at the end of the dosing interval
- Buccal bioadhesive tablet
  - √ immediately before or after application

1. Bhasin S, et al. *J Clin Endocrinol Metab* 2010;95:2536-2559.
3. Lexicomp 2014

Testosterone Controversy

- Is testosterone therapy associated with an increased risk of cardiovascular events?

Adverse events associated with testosterone administration[4]

The Testosterone in Older Men with Mobility Limitations (TOM) Trial

Basaria 2010

Design	Randomized, double-blind, placebo-controlled trial
Subjects	Men ≥ 65 yo with low testosterone and limitations in mobility (n=209)
Intervention	100 mg testosterone gel vs placebo applied once daily x 6 months
Results	Cardiovascular-related events: 23 (testosterone) vs 5 (placebo) [OR 5.4; 95% CI 2.0-14.9]
	Atherosclerosis-related events: 7 (testosterone) vs 1 (placebo) [OR 7.2; 95% CI 0.9-59.7]

Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels[5]

Vigen 2013

Design	Retrospective cohort study in the Veterans Affairs system
Subjects	Men who underwent coronary angiography and had a total testosterone level < 300 ng/dl (n=8709)
Cohorts	Men prescribed testosterone therapy vs men with no prescription
Primary end point	Time to all-cause mortality or hospitalization for MI or ischemic stroke

Vigen 2013

Results	Testosterone group (n=1223): 67 died, 23 MIs, 33 strokes
	No testosterone group (n=7486): 681 died, 420 MIs, 486 strokes
	Testosterone use was associated with an increased risk of all-cause mortality, MI, and stroke HR 1.29; 95% CI 1.05-1.58; p=0.02

Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men[6]

Finkle 2014

Design	Retrospective cohort study
Cohorts	Men with a first prescription for testosterone (n=55,593) vs men with a first prescription for a PDE5 inhibitor (n=167,279)
Outcome	Incidence of acute MI in the 90 days post-prescription compared to the 1 year pre-prescription

Finkle 2014

Results	Pre- vs post-prescription: 193 vs 65 events
	Rate ratio post/pre: 1.36; 95% CI 1.03-1.81

	Age < 65 years (n=48,539)		**Age ≥ 65 years (n=7,054)**	
Rate ratio (post/pre) (95% CI)	1.17 (0.84-1.63)		2.19 (1.27-3.77)	
	Heart Disease (n=4,006)	**No Heart Disease (n=44,533)**	**Heart Disease (n=2,047)**	**No Heart Disease (n=5,057)**
	2.9 (1.49-5.62)	0.90 (0.61-1.34)	2.16 (0.92-5.10)	2.21 (1.09-4.46)

Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials[7]

Xu 2013

Design	Meta-analysis
Study selection	Randomized, placebo-controlled trials which reported cardiovascular-related events by study arm (n=27)
Results	Included 2,994 men who experienced 180 cardiovascular-related events
	Testosterone therapy was associated with an increased risk of cardiovascular-related events OR 1.54; 95% CI 1.09-2.18

FDA Statement

- Released 1/31/14
- Evaluating data about risk of death, MI, and stroke associated with testosterone therapy
  - No final conclusion or recommendation yet
- Patients should discuss concerns with health care professionals
- Health care professionals should consider risks vs benefits of testosterone therapy

8. Food and Drug Administration 2014

How would you respond to Mr. T's question about the safety of testosterone therapy?

1. Advise Mr. T to contact his doctor
2. Discuss the recent safety literature with Mr. T so he can make an informed decision
3. Encourage Mr. T to continue testosterone since the safety concerns do not apply to him

Summary

- Hypogonadism is diagnosed based on consistent symptoms of androgen deficiency and consistently low testosterone levels
- Testosterone therapy is available in many dosage forms
- Evidence suggesting an association between testosterone therapy and cardiovascular events continues to grow

References

1. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in adult men with androgen deficiency syndromes: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2010;95:2536-2559.
2. Dohle GR, Arver S, Bettochi C, et al. *Guidelines on male hypogonadism*. Arnhem, The Netherlands: European Association of Urology; 2012.
3. Testosterone. Lexi-Drugs. Lexicomp. Available at: www.lexi.com. Accessed March 3, 2014.
4. Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. *N Engl J Med*. 2010;363(2):109-122.

References

5. Vigen R, O'Donnell CI, Baron AE, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA*. 2013;310(17):1829-1836.
6. Finkle WD, Greenland S, Ridgeway GK, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. *PLoS ONE*. 2014;9(1):e85805.
7. Xu L, Freeman G, Cowling BJ, Schooling CM. Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. *BMC Med*. 2013;11:108.
8. Food and Drug Administration. FDA evaluating risk of stroke, heart attack and death with FDA-approved testosterone products. Available at: http://www.fda.gov/drugs/drugsafety/ucm383904.htm. Accessed March 3, 2014.

Clinical Updates – His, Hers and Ours
Men's Health
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0121-0000-14-021-L01-P
0121-0000-14-021-L01-T

Learning Assessment Questions

1. Which of the following potential symptoms of hypogonadism is more specific for androgen deficiency?
    a. Decreased libido
    b. Decreased muscle strength
    c. Increased body fat
    d. Increased sleepiness

2. Which of the following testosterone products is administered twice daily?
    a. Buccal tablet
    b. Implantable pellet
    c. Patch
    d. Solution

3. Which statement most accurately describes the findings of recent literature evaluating the association between testosterone therapy and cardiovascular events?
    a. Testosterone therapy does not impact the risk of cardiovascular events
    b. Testosterone therapy increases the risk of cardiovascular events in older men and decreases the risk in younger men
    c. Testosterone therapy is associated with a decreased risk of cardiovascular events
    d. Testosterone therapy is associated with an increased risk of cardiovascular events

Clinical Updates – His, Hers and Ours

Women's Health

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Conflicts

- I have no conflicts of interest to disclose.

ICHP 2014 Spring Meeting: Taking Bold Steps for Patient Care

Objectives

- **Pharmacists**
  - Identify current topics in post-menopausal women's health
  - Describe new pharmacologic agents for use in post-menopausal women's health-related disease states
- **Technicians**
  - Identify current topics in post-menopausal women's health
  - Recognize medications that are used in post-menopausal women's health and relate them to their respective disease states.

ICHP 2014 Spring Meeting: Taking Bold Steps for Patient Care

Abbreviations

- ET = Estrogen therapy
- HT = Hormone therapy
- EAA = Estrogen Agonist/Antagonist
- SERM = Selective estrogen receptor modulator
- UTI = Urinary tract infection
- TAH = Total abdominal hysterectomy
- BSO = Bilateral salpinoophorectomy
- CAD = Coronary artery disease
- MI = Myocardial infarction
- CVA = Cerebrovascular accident
- DVT = Deep vein thrombosis
- Wk = Week
- MOA = Mechanism of action
- ADR = Adverse Drug Reaction

ICHP 2014 Spring Meeting: Taking Bold Steps for Patient Care

Case

- A 50 yoF is at the pharmacy and states her doctor said she is post-menopausal. She starts getting teary-eyed and says that she doesn't need her Ovcon-35 anymore. She states she doesn't feel any different and asks what are symptoms of menopause.
- What are the most common symptoms of menopause?

A. Vasomotor symptoms
B. Insomnia
C. Vaginal dryness
D. Irritability

Which of the above symptoms will not get better with time?

ICHP 2014 Spring Meeting: Taking Bold Steps for Patient Care

Definitions

- **Menopause** is the loss of ovarian function leading to a state of permanent amenorrhea
  - Occurs after 12 consecutive months of amenorrhea
  - TAH vs. TAH/BSO
- **Perimenopause** is the transition period to nonreproductive life characterized by irregular menses

ICHP 2014 Spring Meeting: Taking Bold Steps for Patient Care

Menopausal symptoms

- Vasomotor
  - Hot flushes/sweating
- Insomnia/fatigue
- Irritability
- Forgetfulness and ↓ concentration
- Osteoporosis
- Atherosclerosis
- Urogenital atrophy
  - Vaginal dryness
  - Dysparenia
  - Decreased libido
  - Increased risk for UTI
  - Urinary incontinence
- Dry Skin
- Dysfunctional uterine bleeding during perimenopause

Menopause

Estrogen (ET) and Estrogen plus Progestin (HT or E+P)

- Indications
  - Moderate to severe symptoms associated with menopause
  - Moderate to severe vulvar and vaginal atrophy associated with menopause
  - Prevention of postmenopausal osteoporosis

Menopause Symptoms

- Vasomotor: systemic therapy
  - Cochrane Review of 24 trials (3,329 pt)
    - HT decreased frequency by 75% and severity
- Urogenital symptoms: Estrogens (any route)
  - Urogenital atrophy, Vaginal dryness, Dyspareunia
- ↓ risk of UTI
  - Only local estrogen

ACOG Obstet Gynecol 2014;123:202-16.
USPTFS. Ann Pharmacother 2012;157;1-11.
Cochrane Database Syst Rev 2004;4:CD002978

Benefits

- Osteoporosis prevention
- Quality of life
  - Mood stability
  - Fatigue
  - Insomnia

ACOG Obstet Gynecol 2014;123:202-16.
USPTFS. Ann Pharmacother 2012;157;1-11.
Cochrane Database Syst Rev 2004;4:CD002978

Risks

- Cardiovascular risk
  - HT primary prevention (WHI)
    - No overall increase in CV events or death
    - Absolute risk: 7 per 10,000 person-years
  - HT secondary prevention (HERS)
    - ↑ risk MI in 1st year
  - ET primary prevention (WHI-ET)
    - No overall increase in CV events or death
- Consider age and time since menopause

Anderson et al. jAMA 2004;291:1701-12.
Manson et al. N Engl J Med 2007;356:2591-602.
Manson et al. JAMA 2013;310:1353-68.
Hulley et al. JAMA 1998;280:605-13.
Grady JAMA 2002;288:49-57.
Writing group WHI. JAMA 2002:288;321-33.

Risks

- Cerebrovascular risk
  - HT (WHI)
    - Absolute risk of 8 per 10,000 person-years
  - ET (WHI-ET)
    - Absolute risk of 12 per 10,000 person-years

Hulley et al. JAMA 1998;280:605-13.
Grady JAMA 2002;288:49-57.
Writing group for the women's health initiative investigators. JAMA 2002:288;321-33.
Anderson et al. jAMA 2004;291:1701-12.

Risks

- Thromboembolism
- Breast cancer
  - HT (WHI):
    - Non-significant ↑ 15% with use <5 years of use
    - Significant ↑54% with ≥ 5 years of use
  - ET: ↑ after 10–15 years of use
- Endometrial cancer
  - Role of Progestogens

Hulley et al. JAMA 1998;280:605-13.
Grady JAMA 2002;288:49-57.
Writing group for the women's health initiative investigators. JAMA 2002:288;321-33.
Anderson et al. jAMA 2004;291:1701-12.

Risks

- Gallbladder dysfunction
- Cognitive decline (WHIMS)
  - HT: ↑ risk for dementia in women ≥65 years
- Ovarian cancer
  - ET/HT: Meta-analysis, case-control, and cohort trials
  - 1 RCT did not show increased risk.

Shumaker et al. JAMA 2003;289:2651-62.
NAMS Menopause 2012; Menopause 2012;19:257-71.

Case

- A 54yoF is complaining of intolerable hot flashes. She states it's embarrassing at work to sweat so much that she needs to change clothes or being unable to concentrate during a meeting because of them. She wakes up a couple times a night from them, too. She said her primary care doctor refused to give her hormones because he doesn't want the liability. She wants to know what she should ask her Ob/Gyn to prescribe. Last menstrual period 13 months ago. PMH: hypertension, DVT (10 years ago on contraceptives), obesity. What is the best recommendation?

A. 17-B estradiol patch
B. Ospemifene
C. Conjugated equine estrogens + bazedoxifene
D. Paroxetine

CEE + Bazedoxifene

- Conjugated equine estrogens (CEE) 0.45mg + bazedoxifene 20mg (Duavee®) daily
- Estrogen + Estrogen agonist/antagonist (EAA)
- Indications
  - Treatment of moderate to severe vasomotor symptoms
  - Prevention of osteoporosis

Duavee Package Insert. Pfizer, 2013.

CEE + Bazedoxifene

- Contraindications
  - Undiagnosed abnormal uterine bleeding
  - Breast cancer
  - Known/Suspected estrogen dependent noeplasia
  - Thromboembolism, thrombophilias
  - Hypersensivity
  - Hepatic impairment or disease
  - Pregnancy or lactation

Duavee Package Insert. Pfizer, 2013.

CEE + Bazedoxifene

Randomized, Controlled, Double-blind, Multi-center Trial
-Postmenopausal females
-Experiencing mod/sev vasomotor symptoms

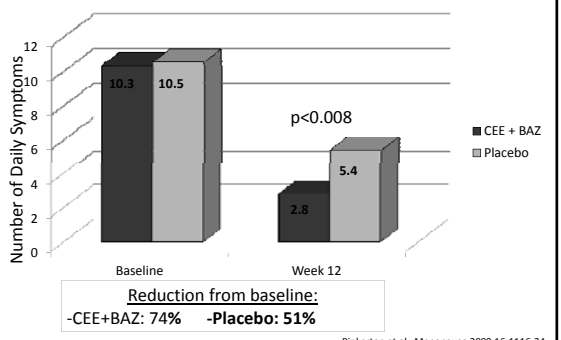
Daily Vasomotor Symptoms Severity
(0 = None, 1= Mild, 2=Moderate, 3=Severe)
(# of Mild x1) + (# of Moderate x2) + (# of Severe x3) = Score

CEE + Baz x 12weeks (n=122)	Placebo x 12 weeks (n=63)

- **Baseline Severity: 2.3**
- **Baseline Frequency: 10.4 Moderate-Severe Symptoms per day**

Pinkerton et al. Menopause 2009;16:1116-24.

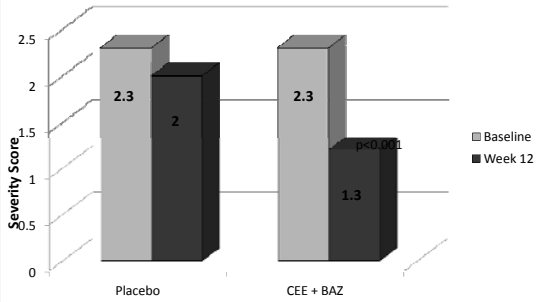
Vasomotor Frequency



Reduction from baseline:
-CEE+BAZ: 74% **-Placebo: 51%**

Pinkerton et al. Menopause 2009;16:1116-24.

Severity of Vasomotor Symptoms



Symptoms at week 12

Pinkerton et al. Menopause 2009;16:1116-24.

CEE + Bazedoxifene

ADR	CEE + Bazedoxifene	Placebo
Nausea	8%	5%
Diarrhea	8%	5%
Dyspepsia	7%	6%
Upper abdominal pain	7%	5%
Muscle spasms	9%	6%
Neck pain	5%	4%
Dizziness	5%	3%
Oropharyngeal pain	7%	6%

Duavee Package Insert. Pfizer, 2013.

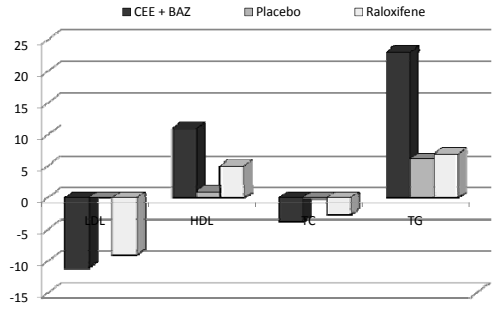
Other Effects

- Vasomotor Symptoms (up to 24 months)
  - Other studies decrease severity and frequency
- Vulvovaginal atrophy (12 weeks)
  - Improves cell lining, pH, symptoms, QOL
- Bone (at 24 months)
  - Prevent loss in women with normal bone density
  - No fracture data
- No difference
  - FBS, fasting insulin, c-reactive protein

Lindsay et al. Fertil Steril 2009;92:1045-52.

Lobo et al. Fertil Steril 2009;92:1025-38.
Kagan et al. Menopause 2010;17:281-9.

Cholesterol Changes



Lobo RA et al. Fertil Steril 2009;92:1025-38.

Serious Adverse Events

	CEE + BAZ	ET	HT
DVT	0.76 per 1000 pt years	0.7 per 1000 pt years	1.8 per 1000 pt years
CAD	CAD + Coronary insufficiency: 2.02 per 1000 MI: 1.56 per 1000	0.8 per 1000 pt years	0.5 per 1000 pt years
CVA	---	1.1 per 1000 pt years	0.8 per 1000 pt years

Lobo RA et al. Fertil Steril 2009;92:1025-38.
NAMS Menopause 2012; Menopause 2012;19:257-71.

Serious Adverse Events—2 years

- Vaginal bleeding
  - No difference vs. placebo and raloxifene
- Endometrial Protection
  - No difference vs. placebo endometrial events, cervical events, ovarian cysts, hyperplasia
- Breast
  - No difference vs. placebo in breast density

Pickar et al. Fertil Steril 2009;92:1018-24.
Archer Fertil Steril 2009;92:1039-44.
Harvey et al. Menopause 2012;20:138-45.

CEE + Bazedoxifene Summary

- Indication: vasomotor sx and osteoporosis prevention
  - Other options for osteoporosis prevention
  - Still need to have a uterus
  - ↓ frequency (50-80%) and severity
- Similar risks to HT
  - Alternative if intolerable ADR to HT

Case

- A 54yoF is complaining of intolerable hot flashes. She states it's embarrassing at work to sweat so much that she needs to change clothes or being unable to concentrate during a meeting because of them. She wakes up a couple times a night from them, too. She said her primary care doctor refused to give her hormones because he doesn't want the liability. She wants to know what she should ask her Ob/Gyn to prescribe. Last menstrual period 13 months ago. PMH: hypertension, DVT (10 years ago on contraceptives), obesity. What is the best recommendation? Is C correct?

A. 17-B estradiol patch
B. Ospemifene
~~C. Conjugated equine estrogens + bazedoxifene~~
D. Paroxetine

Paroxetine

- Paroxetine (Brisdelle™) 7.5 mg daily
- MOA: Selective Serotonin Receptor Antagonist
- Indication: moderate to severe vasomotor symptoms
- Contraindications:
  - MAO-I (within 14 days), thoridazine, pimozide
  - Hypersensitivity
  - Pregnancy

Brisdelle Package Insert. Noven, 2013.

Paroxetine

Randomized, placebo controlled
-Experiencing >7-8 mod/severe symptoms/day or 50-60/week
1° Outcome: Frequency and Severity of vasomotor symptoms

12 day Placebo, Single-blind run-in

12 Week Study		24 Week Study	
Paroxetine 7.5mg QHS (n=297)	Placebo (n=302)	Paroxetine 7.5mg QHS (n=285)	Placebo (n=285)

Simon JA et al. Menopause 2013;20:1027-35.

Methods

Calculations:

- Total weekly moderate and severe hot flashes at baseline = [(x on day 1 + x on day 2 … + x on day n) / (n-1)] x 7,
  - X = number of hot flashes
  - n = number of days in the run-in period
- Weekly hot flash score = $(2F_m + 3F_s) / (F_m + F_s)$
  - F_m and F_s = frequency of moderate and severe hot flashes during the study week

Baseline Mean Vasomotor: frequency 11.3/d and Severity 2.53

Simon JA et al. Menopause 2013;20:1027-35.

Baseline Mean Vasomotor: frequency 11.3/d and Severity 2.53

Mean Vasomotor sx per week	12 Weeks			24 Week s		
	Paroxetine	**Placebo**	**p-value**	Paroxetine	Placebo	p- value
Frequency (wk 4)	**-33.0**	**-23.5**	**<0.0001**	-28.9	-19.0	<0.0001
Composite score (wk 4)	**-0.09**	**-0.05**	**0.0048**	-0.09	-0.06	0.0452
Frequency (wk 12)	**-43.5**	**-37.3**	**0.009**	-37.2	-27.6	0.0001
Composite score (wk 12)	**-0.10**	**-0.5**	**0.2893**	-0.12	-0.07	0.0114

Effects sustained at 24 weeks

Simon JA et al. Menopause 2013;20:1027-35.

Adverse Events

- No difference in ADR
  - Mild-Moderate: 50.3% paroxetine vs. 46.7% placebo
  - Severe: 3.9% paroxetine vs. 3.1% placebo
  - Discontinuation: 4.4% paroxetine vs 3.6% placebo
- ADR >2% and twice as often as placebo
  - Nausea (paroxetine 3.8%, placebo 1.4%)
    - Fatigue (paroxetine 3.4%, placebo 1.5%)
    - Dizziness (paroxetine 2.0%, placebo 0.8%)

Simon JA et al. Menopause 2013;20:1027-35.

Off-label information

Paroxetine vs. Other Antidepressants

- Dosing
  - Subtherapeutic vs. therapeutic antidepressant
- Similar Efficacy in decreasing frequency
  - Paroxetine -50% vs. Venlafaxine -60% vs. other SSRI -50%
- Improved tolerability
- FDA indicated vs. off-label
- Cost

Case

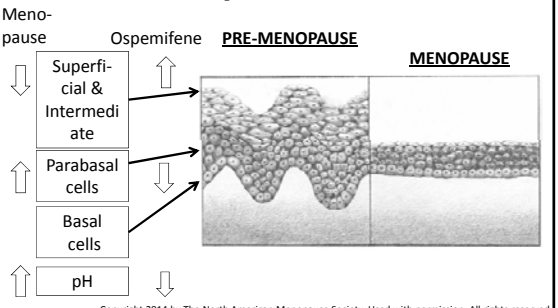
- A 62 yoF is complaining about vaginal dryness, itching all the time that also causes painful intercourse. She states the replens made her feel "leaky" sometimes. FH: CAD (father), breast cancer (sister). PSH: TAH (15 years age 2/2 fibroids). PMH: Hypertension, Hyperlipidemia, Osteoarthritis, diabetes type 2.
- What is the best recommendation?
  A. Estradiol vaginal cream
  B. Raloxifene
  C. Bremelanotide
  D. Ospemifene

Ospemiphene

- Ospemifene (Osphena®) 60mg daily with food
- Indication: moderate to severe dyspareunia
- MOA: EAA
- If pt has a uterus, still need a progestogen
- Contraindications
  - Undiagnosed vaginal bleeding
  - Pregnancy
  - Thromboembolism, MI, CVA
  - Estrogen dependent tumors

Ospemifene Package Insert. Shionogi, 2013.

Ospemifene



Ospemifene

Randomized, Controlled Trial
1: Safety and Efficacy of Ospemifene

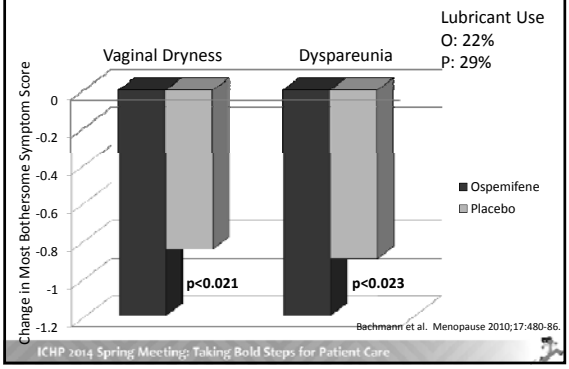
Ospemifene 60mg Qday x12 weeks (n=276)

Placebo x12 weeks (n=268)

Efficacy: Most Bothersome Symptom Score
(0 = None, 1= Mild, 2= Moderate, 3 = Severe)
- **Baseline Score for Vaginal Dryness: 2.4**
- **Baseline Score for Dyspareunia: 2.7**

Bachmann GA et al. Menopause 2010;17:480-86.

Ospemifene—12 weeks



Bachmann et al. Menopause 2010;17:480-86.

Ospemifene

Adverse Event	Ospemifene	Placebo
Vasomotor	7.5%	2.6%
Vaginal discharge Genital discharge	3.8% 1.3%	0.3% 0.1%
Muscle Spasms	3.2%	0.9%
Hyperhidrosis	1.6%	0.6%

Ospemifene Package Insert. Shionogi, 2013.

Ospemifene Risks

	Ospemifene	Placebo
DVT	1.45-2.12 per 1000	1.03-3.06 per 1000
Thromboembolic CVA	0.72 per 1000	1.04 per 1000
Hemorrhagic CVA	**1.45 per 1000**	0 per 1000
Endometrial thickening (≥5mm)	**60.1 per 1000**	21.1 per 1000
Endometrial Proliferation	**86.1**	13.3
Uterine Polyps	**5.9**	1.8

❖ Risk unknown with adding progestogen

Ospemifene Package Insert. Shionogi, 2013.

Case

- A 62 yoF is complaining about vaginal dryness, itching all the time that also causes painful intercourse. She states the replens made her feel "leaky" sometimes. FH: CAD (father), breast cancer (sister). PSH: TAH (15 years age 2/2 fibroids). PMH: HTN, Hyperlipidemia, OA, DM.
- What is the best recommendation?
  - A. Estradiol vaginal cream
  - B. Raloxifene
  - C. Bremelanotide
  - D. Ospemifene

Ospemifene Role

- Moderate to Severe dyspareunia
  - Significantly improved symptoms (mod/sev to none/mild)
- Generally well tolerated
- Same risks as systemic estrogen
- Still needs a progestogen
- Alternative to estrogen (topical, systemic)
  - No advantage, same risks

Who should receive ET/HT?

Do not use ET/HT

Vasomotor or UG Sx?

Yes

No

Any Contraindications?

Absolute	Relative
-Venous thromboembolism	-Uterine leiomyoma
-Known or suspected pregnancy	-History of migraines
-Undiagnosed vaginal bleeding	-Seizure disorder
-Suspected breast or endometrial cancer	-Hypertension
-Active liver disease	-FH of breast cancer
-CAD	
-CVA or TIA	

Yes. Do not use ET/HT

No. Consider ET/HT

Who should receive ET/HT?

No (CI)

Vasomotor: Antidepressants*, gabapentin, B-blockers, clonidine

Vaginal: Lubricating gels

Mild-Mod Non-estrogen alternatives

Mod-Severe ET/HT * Try to D/C by 5 years

Consider age and time since menopause

Step 1: Deciding on ET or HT/E+EAA

TAH or TAH/BSO?

Yes. Give ET

No. Give HT/E+EAA

Estrogen only

Estrogen + Progestogen (HT)

Estrogen + EAA

Step 2: Deciding a Route

Location of symptoms

Vasomotor Symptoms +UG?

UG Sx only?

Oral, Transdermal, Topical, Femring

Vaginal, Ospemifene (not Femring)

ADR due to po route? (GI intolerance, ↑TG)
Oral CI: ↑TG, liver disease, gallbladder disease
Choose non-oral route

Case

- A 54yoF is complaining of intolerable hot flashes. She states it's embarrassing at work to sweat so much that she needs to change clothes or being unable to concentrate during a meeting because of them. She wakes up a couple times a night from them, too. She said her primary care doctor refused to give her hormones because he doesn't want the liability. She wants to know what she should ask her Ob/Gyn to prescribe. Last menstrual period 13 months ago. PMH: hypertension, DVT (10 years ago on contraceptives), obesity. What is the best recommendation?

A. 17-B estradiol patch
B. Ospemifene
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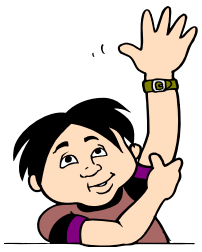
D. Paroxetine

Questions?



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9. Duavee Package Insert. Pfizer, 2013.
10. Brisdelle Package Insert. Noven, 2013.

ICHP 2014 Spring Meeting: Taking Bold Steps for Patient Care

Clinical Updates – His, Hers and Ours
Women's Health
Alicia Forinash, FCCP, BCPS, BCACP
0121-0000-14-021-L01-P
0121-0000-14-021-L01-T

Learning Assessment Questions

1. Which of the following is the best recommendation for treating vasomotor symptoms? Past medical history includes stroke (6 months ago).
    a. Ethinyl estradiol + drospirenone
    b. Conjugated equine estrogens + bazedoxifene
    c. Venlafaxine
    d. Paroxetine

2. Which new menopausal agent should you educate your patient on needing to take with food?
    a. Ospemifene
    b. Paroxetine
    c. Conjugated equine estrogens + bazedoxifene
    d. Bremelanotide

3. Which new product decreases the risk of endometrial hyperplasia in women who still have a uterus?
    a. Conjugated equine estrogens
    b. Bazedoxifene
    c. Ospemifene
    d. Paroxetine

4. Which new product is the best recommendation relieving symptoms in a patient only experiencing vulvovaginal atrophy? Past surgical history: total abdominal hysterectomy and bilateral salpingo-oopherectomy (TAH/BSO)
    a. Conjugated equine estrogens tablet
    b. Conjugated equine estrogens + Bazedoxifene tablet
    c. Ospemifene table
    d. Ospemifene tablet + medroxyprogesterone tablet

5. Which therapy helps prevent against osteoporosis?
    a. Ospemifene
    b. Paroxetine
    c. Conjugated equine estrogens + bazedoxifene
    d. Bremelanotide