

Special Topics in Menopause Therapy

Treatment of hot flashes in 2009

Hot Flashes

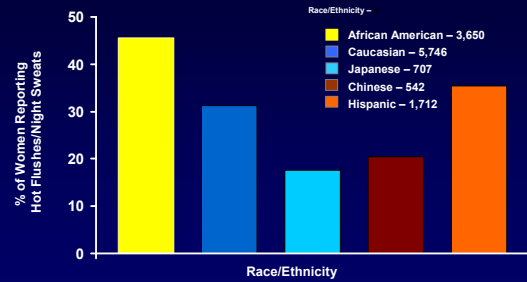
- Hot flashes are the most common symptom of perimenopause: 68%¹ to 93%² of women
- Result from a marked narrowing of the hypothalamic thermoregulatory set point
- Both norepinephrine and serotonin are involved in the regulation of temperature homeostasis in the hypothalamus

¹Freedman RR, In: Lobo RA, et al, eds. Menopause: Biology and Pathobiology, San Diego: Academic Press; 2000.
²Thompson B, et al. J Biosoc Sci. 1993;6:71-82.
³Kronenberg F. Ann NY Acad Sci. 1996;802:82-86.

Hot Flashes – Differential Diagnosis

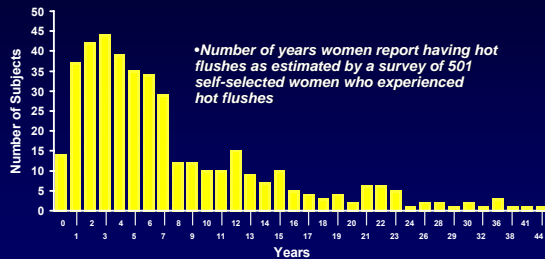
- Hyperthyroidism
- Pheochromocytoma
- Carcinoid
- Panic disorder
- Diabetes
- Side effects to medications
 - Antiestrogens
 - SERMS's
 - Beta blockers

SWAN Study: Reported Prevalence of Vasomotor Symptoms (Ages 40-55 Years; n = 12,357)



Gold EB, et al. Am J Epidemiol. 2000;152:463-73.

Hot Flashes May Continue Years After Menopause (Ages 29-82 Years)



Mean age of natural menopause was 48.5 years; mean age of surgical menopause was 43.7 years.

Kronenberg F. Ann NY Acad Sci. 1996;802:82-86.

Women's HOPE Study

Design

Methodology: prospective, randomized, double-blind, placebo-controlled, multicenter trial

Purpose: Investigate efficacy and safety of lower doses of CEE and CEE/MPA

Patients: 2673 healthy, postmenopausal women (40–65 years of age) with an intact uterus

Outcomes: vasomotor symptoms, vaginal atrophy, bleeding profile, endometrial hyperplasia, metabolic profile, and bone mineral density

Ulian WK, et al. Fertil Steril. 2001;75:1065-79.

Women's HOPE Study

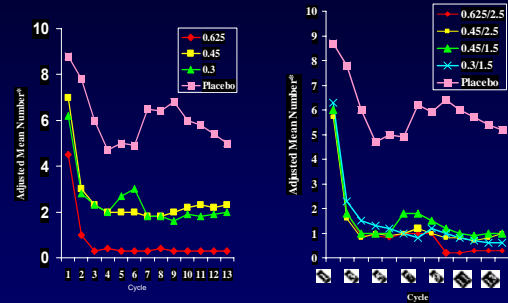
Demographic and Baseline Characteristics

	Total (n = 2673) Mean ± SD
Age (years)	53.3 ± 4.9
Age at menopause (years)	48.5 ± 4.3
Years since menopause	4.7 ± 4.2
Weight (kg)	65.5 ± 8.7
Body mass index (kg/m ²)	24.4 ± 2.8

No significant differences between 8 treatment groups were observed. Women were 88% Caucasian, 6% African American, 4% Hispanic, 2% Asian, and <1% Native American, Arabic, or "other."

Utian WH, et al. *Fertil Steril*. 2001;75:1065-75. Used with permission.

Mean Number of Hot Flashes Per Day Over 13 Cycles



*Adjusted for baseline Mean hot flashes at baseline = 12.3 (range 11.3-13.8) Source: Utian WH, Fertil Steril, 2001

Low dose HT

Lower doses of estrogen and progestin

- Relieve vasomotor symptoms and prevent vaginal atrophy
- Are associated with a reduced incidence of endometrial bleeding, especially in the early months of therapy
- Provide effective endometrial protection
- Prevent early postmenopausal bone loss

Since 2002, many pharmaceutical companies have released lower dose regimens

“Doctor, do you prescribe bioidenticals?”

- Salivary levels?
 - Inaccurate and unreliable
 - No data available regarding given levels/given response
- Compounds themselves
 - Lack of FDA control
 - Lack of consistency and quality control
 - No safer than prescription meds
- ACOG and NAMS position statements on-line
- Is there an alternative for this patient?
 - Estradiol +/- oral micronized progesterone?

WHAT ELSE IS THERE?

ALTERNATIVE THERAPIES FOR MENOPAUSAL SYMPTOMS

Alternative Treatments for Menopausal Symptoms

- Phytoestrogens
 - Soy, red clover
- Black cohosh
- Dong quai, chinese herbs
- Vitamin E
- Ginseng
- Wild yam extract, progesterone cream
- Evening primrose oil
- Alternative prescription medications

Problems with Complementary and Alternative Medicines

- Standardization/purification of preparation
- Unknown mechanism of action
- Underreporting of adverse events
- Unknown drug interactions

Problems with Interpreting Existing Studies

- Varying doses/preparations
- Lack of placebo controls
- Small trial arms

Phytoestrogens

- Lignans
 - Whole grains, flaxseed, fruits, vegetables, rye, millet, legumes
- Isoflavones
 - Soy, clover, beans, alfalfa
- Coumestans
 - Sunflower seeds, bean sprouts

Soy

- Daidzein
- Genistein
- Glycitein

Soy

Design	n	Soy Source Isoflavone Dose	Results (% fewer hot flashes from baseline)	Comments
Murkies (1995)	14-wk RCT	58 Flour 45 g/d	Soy: 40% Wheat: 25% ($P<0.001$)	
Albertazzi (1998)	12-wk RCT, PL	104 Protein (isolated) 76 mg/d	Soy: 45% PL: 30% ($P<0.001$)	50% withdrew due to GI AEs
Washburn (1999)	3x6-wk RCT, C-O, PL	51 Protein 34 mg/d		Only severity was reduced ($P<0.0001$)
Scambia (2000)	12-wk RCT, PL	39 Tablets (extract) 50 mg/d	Soy: 45% PL: 25% ($P<0.01$)	At 4 wk, CEE added; both groups improved after CEE added
Upmalis (2000)	12-wk RCT, PL	177 Tablets (extract) 50 mg/d	Soy: 28% PL: 19% ($P=0.03$)	
Han (2002)	4-mo RCT, PL	82 Capsules 100 mg/d	Soy: 27% PL: 9% ($P<0.01$)	Low placebo effect

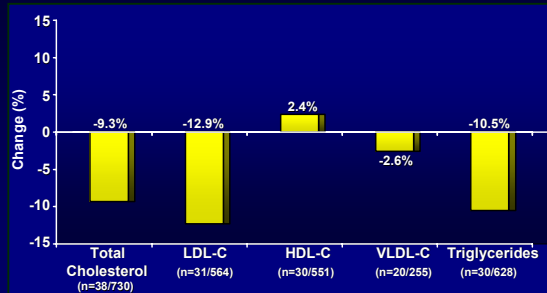
OL=open-label; RCT=randomized controlled trial; PL=placebo; NBTP=no better than placebo.

Soy

Design	n	Soy Source Isoflavone Dose	Results (% fewer hot flashes from baseline)	Comments
Dalais (1998)	2x12-wk RCT, C-O	52 Bread 53 mg/d	Soy: 22% Linseed: 41% Wheat: 51%	
Queila (2000)	2x4-wk RCT, C-O, PL	177 Tablets 150 mg/d	Soy: 35% PL: 38%	68% were on tamoxifen
Kotsopoulos (2000)	3-mo RCT, PL	94 Beverage 118 mg/d	NBTP	20% withdrew due to GI AEs
St Germain (2001)	24-wk RCT, PL	91 Protein 80 mg/d	Soy: 49% PL: 44%	
Knight (2001)	12-wk RCT, PL	24 Beverage 134 mg/d	Soy: 43% PL: 20%	25% withdrew due to GI AEs
Van Patten (2002)	12-wk RCT, PL	157 Beverage 90 mg/d	Soy: 30% PL: 40%	GI AEs with soy
Burke (2003)	2-y RCT, PL	211 Protein 42 or 58 mg/d	58 mg/d: 59% 42 mg/d: 42% PL: 77%	
Nikander (2003)	3-mo RCT, C-O, PL	56 Tablets 114 mg/d	NBTP	

OL=open-label; RCT=randomized controlled trial; PL=placebo; NBTP=no better than placebo.

Effects of Soy Protein Intake on Serum Lipids: Meta-Analysis



N values=number of studies/patients.
Anderson JW, et al. *N Engl J Med.* 1995;333:276-282.

Other Effects of Soy

- Endometrium
 - 3 studies, no effect
 - 1 study, 5 years, increased risk of endometrial hyperplasia
- Vaginal dryness
 - 2 studies positive
 - 7 studies no effect
- CNS-SOPHIA study*
 - Favorable effect on verbal memory
- Bone
 - 3 studies favorable, but all only 6 months
- Breast: ?

*Kritz-Silverstein D, et al. *Menopause.* 2003;10:196-202.

Red Clover

- Genistein
- Daidzein
- Formononetin
- Biochanin A

Red Clover

Design	n	Isoflavone Dose (mg/d)	Results (% fewer hot flashes from baseline)
Van de Weijer (2002) 12-wk RCT, PL	30	80	80 mg/d: 60% PL: 16% (P<0.01)
Knight (1999) 12-wk RCT, PL	37	40 160	160 mg/d: 34% 40 mg/d: 29% PL: 35%
Baber (1999) 12-wk RCT, C-O, PL	51	40	40 mg/d: 20% PL: 17%
Tice (2003) 12-wk RCT, PL	252	57 82	82 mg/d: 41% 57 mg/d: 34% PL: 36%

RCT=randomized controlled trial; C-O=cross-over; PL=placebo;
NBTP=no better than placebo.

Black Cohosh (*Cimicifuga racemosa*)

- Black snakeroot, bugbane, rattleroot, snake root, rattle weed, rattle top, black root
- Commission E
 - Premenstrual discomfort, dysmenorrhea, menopausal neurovegetative ailments
- Remifemin
 - Ethanol extract of the rhizome of the plant

Black Cohosh

- Mechanism of action
 - Via estrogen receptors
 - Central activity mediated by dopaminergic or serotonin receptors

Black Cohosh

Design	n	Treatment	Results	Comments
Warncke (1985)	3-mo OL	60 BC 80 mg/d CEE 0.625 mg/d Diazepam 2 mg/d	Significant improvement in all groups	No statistics reported
Stroll (1987)	3-mo RCT, PL	80 BC 80 mg/d CEE 0.625 mg/d	Significant improvement with BC	No estrogen effect
Lehmann (1988)	6-mo OL	60 Estriol 1 mg/d CEE 1.25 mg/d Estrogen/gestogen BC 80 mg/d	Significant improvement in all groups	
Liske (2002)	6-mo RCT	152 BC 39 and 127 mg/d	Both doses showed equal effect	
Jacobson (2001)	2-mo RCT, PL	85 BC 40 mg/d	NBTP (except less sweating)	69% on tamoxifen 19% withdrew

OL=open-label; RCT=randomized controlled trial; BC=black cohosh; PL=placebo; NBTP=no better than placebo.

Black Cohosh

- 400 postmenopausal women
- 12 months
- Followed with endometrial biopsies and endometrial thickness on transvaginal ultrasound
- Endometrial safety demonstrated by both biopsies and ultrasound criteria

Wuttke, et al. *Menopause* 2006;13(4): 687-691.

Black Cohosh

- NIH-funded trials currently underway
 - Columbia University
 - Effect of black cohosh on hot flashes, bone metabolism, cognitive function
 - University of Illinois at Chicago
 - 1-year, double-blind placebo-controlled study comparing hormone therapy, black cohosh, and red clover

Dong Quai

- Chinese herb used for disorders of menstruation including menopausal symptoms
- Hirata (1997)
 - Design
 - 24-week RCT
 - 71 women
 - Results
 - No better than placebo for symptoms, endometrial thickness, vaginal maturation
 - Side effects
 - Potentiates effects of Warfarin
 - Contains psoralens (photosensitizing)

Hirata JD, et al. *Fertil Steril*. 1997;68:981-986.

Chinese Medicinal Herbs

- Davis (2001)
 - Design
 - 12-week RCT
 - 78 women (age range: 52-58 years)
 - Combination of 12 herbs
 - Results
 - No significant effect on symptoms over placebo
 - 23/78 withdrew due to taste intolerance

Davis SR, et al. *Med J Aust*. 2001;174:68-71.

Formula of Chinese Herbs Used

- *Rehmannia glutinosa* (Shu Di Huang)
- *Cornus officinalis* (Shan Zhu Yu)
- *Dioscorea opposita* (Shan Yao)
- *Allisma orientalis* (Ze Xie)
- *Paeonia suffruticosa* (Dan Pi)
- *Poria cocos* (Fu Shen)
- *Citrus reticulata* (Chen Pi)
- *Lycium chinensis* (Di Gu Pi)
- *Albizia julibrissin* (He Huan Pi)
- *Zizyphu jujuba* (Suan Zao Ren)
- *Eclipta prostrata* (Han Lian Cao)
- *Ligustrum Lucidum* (Nu Zhen Zi)

Davis SR, et al. *Med J Aust*. 2001;174:68-71.

Chinese Medicinal Herbs

- **Davis (2001)**
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Davis SR, et al. *Med J Aust.* 2001;174:68-71.

Vitamin E

- **Barton (1998)**
 - Design
 - 12-week RCT, cross-over design
 - 125 breast-cancer survivors
 - Results
 - 22% fewer hot flashes with placebo
 - **25% fewer hot flashes with Vitamin E**
 - $P < 0.05$, but only 1 hot flash/day less than placebo

Barton DL, et al. *J Clin Oncol.* 1998;16:495-500.

Ginseng

- Root of a perennial herb native to China, Russia, Korea
- **Wiklund (1999)**
 - Design
 - 16-week RCT
 - 384 women
 - Results
 - **No significant effect on hot flashes over placebo**
 - Safety concern
 - Insomnia, hypertension

Wiklund IK, et al. *Int J Clin Pharmacol Res.* 1999;19:89-99.

Wild Yam Cream

- Contain steroidal saponins including diosgenin which has been claimed to influence endogenous steroidogenesis
- **Komesaroff (2001)**
 - Design
 - 3-month RCT, crossover design
 - 50 women (age range: 45-60 years)
 - Results
 - **No significant effect on hot flashes over placebo**
 - 27/50 withdrew, majority due to no symptom relief

Komesaroff PA, et al. *Climacteric.* 2001;4:144-150.

Progesterone Cream

	Design	n	Treatment	Results	Comments
Komesaroff (2001)	3-mo RCT, C-O, PL	23	1 tsp bid Biogest	NBTP for symptoms	No sig. \uparrow in serum or salivary PR levels 54% withdrew
Wren (2003)	3-mo RCT, PL	80	32 mg/d	NBTP for symptoms	Serum PR 0.11-0.31 ng/mL ($P=0.000$)
Leonetti (1999)	12-mo RCT, PL	102	20 mg/d	PR vs PL: 83% vs 19% better	Low PL response Fewer PL patients with symptoms at baseline
Cooper (1998)	33-d RCT, C-O, PL	20	10 d cream (1 tsp bid); 5 d oral PR (300 mg/d)	PR level (nmol/L) Cream: 2.9 Oral: 9.5	Insufficient levels to protect endometrium or conserve bone
Wren (1998)	12-wk RCT	27	Cream at luteal phase (16, 32, 64 mg/d)	No \uparrow serum PR, no conversion to secretory endometrium	All patients had 17- β estradiol patch
Lewis (2002)	2-mo RCT, PL	24	20 mg/d 40 mg/d	Minimal \uparrow in plasma + RBC levels; marked \uparrow in salivary levels	Salivary levels not recommended

C-O=cross-over; PL=placebo; PR=progesterone;
NBTP=no better than placebo.

Evening Primrose Oil

- **Chenoy (1994)**
 - Design
 - 6-month RCT
 - 56 women
 - Results
 - **Placebo was significantly more effective than active arm**

Chenoy R, et al. *Br Med J.* 1994;308:501-503.

Clonidine

- Centrally acting alpha-adrenergic agonist
- Pandya (2000)
 - Design
 - 8-week RCT
 - 194 breast cancer survivors on tamoxifen
 - Clonidine 0.1 mg/day vs placebo
 - Results
 - 24% fewer hot flashes with placebo
 - 38% fewer hot flashes with clonidine ($P<0.006$)
 - But, only 1 less hot flash per day with clonidine
 - Many side effects
 - Insomnia, dry mouth, constipation, postural hypotension

Pandya KJ, et al. *Ann Intern Med.* 2000;132:788-793.

Oxybutynin

- Sexton (2007)
 - Design
 - Retrospective chart review
 - 52 patients
 - Results
 - 70% of patients showed a partial or excellent response
 - Randomized control trial is planned

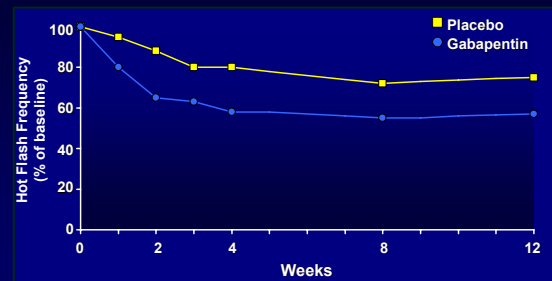
Sexton, et al. *Menopause.* 2007;14(5):505-509.

Gabapentin

- Gamma-aminobutyric acid analogue
- Guttuso (2003)
 - Design
 - 12-week RCT
 - 59 women (age range: 49-56 years)
 - gabapentin 900 mg/d vs placebo
 - Results
 - 29% fewer hot flashes with placebo
 - 45% fewer hot flashes with gabapentin ($P=0.02$)
 - 13% withdrew from active treatment arm due to adverse events (somnolence, rash, nausea)
 - Placebo group was younger, more raloxifene
 - Side effects – fatigue, dizziness, peripheral edema

Guttuso T, et al. *Obstet Gynecol.* 2003;101:337-345.

Gabapentin and Hot Flash Frequency



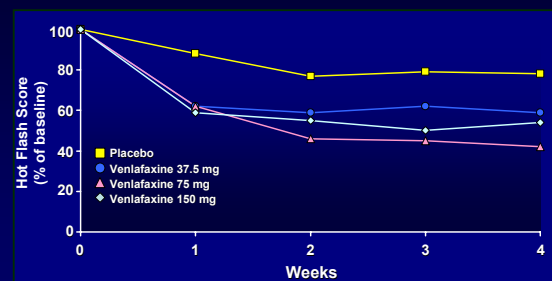
Guttuso T, et al. *Obstet Gynecol.* 2003;101:337-345.

Venlafaxine

- Affects serotonin and norepinephrine reuptake
- Loprinzi (2000)
 - Design
 - 4-week RCT
 - 191 breast cancer survivors
 - venlafaxine XR vs placebo
 - Results
 - 27% fewer hot flashes with placebo
 - 37% fewer hot flashes with 37.5 mg/d ($P=0.008$)
 - 61% fewer hot flashes with 75 mg/d ($P<0.0001$)
 - 61% fewer hot flashes with 150 mg/d ($P<0.0001$)

Loprinzi CL, et al. *Lancet.* 2000;345:2059-2063.

Venlafaxine and Hot Flash Score



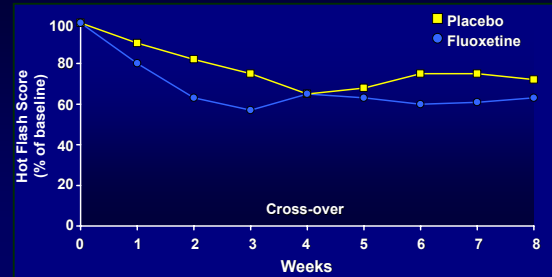
Loprinzi CL, et al. *Lancet.* 2000;345:2059-2063.

Fluoxetine

- Loprinzi (2002)
 - Design
 - 8-week RCT, cross-over design
 - 81 breast cancer survivors
 - Results
 - 36% fewer hot flashes with placebo
 - 50% fewer hot flashes with 20 mg/d fluoxetine ($P=0.02$)

Loprinzi CL, et al. *J Clin Oncol.* 2002;20:578-583.

Fluoxetine and Hot Flash Score



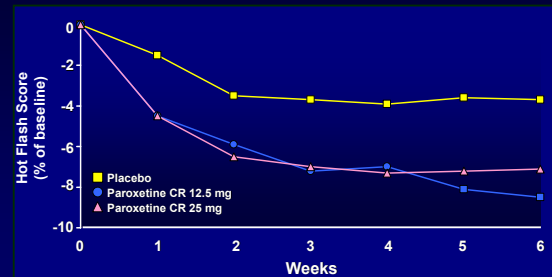
Loprinzi CL, et al. *J Clin Oncol.* 2002;20:578-583.

Paroxetine

- Stearns (2003)
 - Design
 - 6-week RCT
 - 165 women
 - Results
 - 38% fewer hot flashes with placebo
 - 63% fewer hot flashes with 12.5 mg/d ($P<0.001$)
 - 65% fewer hot flashes with 25 mg/d ($P<0.001$)

Stearns V, et al. *JAMA.* 2003;289:2827-2834.

Paroxetine and Hot Flash Score



Stearns V, et al. *JAMA.* 2003;289:2827-2834.

Sertraline

- Grady (2007)
 - No benefit after 6 weeks of treatment
- Gordon (2006)
 - Design
 - 10-week RCT, crossover design
 - 87 women
 - Results
 - 5 fewer hot flashes per week while on sertraline

Grady, et al. *Obstetrics and Gynecology.* 2007;109(4):823-829.
Gordon, et al., *Menopause.* 2006;13(4):568-575

Citalopram

- Kalay (2007)
 - Design
 - 8-week RCT
 - 100 women
 - Dose started at 10 mg/day, increase to 20 mg/day after week 1
 - Results
 - 13% fewer hot flashes with placebo
 - 37% fewer hot flashes with 20 mg/d ($P<0.01$)

Kalay, et al. *Menopause.* 2007;14(2):223-229.

Side Effects of SSRI's, SNRI's

- Dry mouth
- Nausea
- Insomnia
- Fatigue
- Sexual dysfunction
- Gastrointestinal disturbances
- Weight gain

Summary

- Soy/isoflavones
 - Possible modest benefit
- Black cohosh
 - Probably modest benefit safety beyond 6 months unclear
- No effect
 - Dong quai
 - Chinese medicinal herbs
 - Vitamin E
 - Ginseng
 - Wild yam extract/progesterone cream
 - Evening primrose oil

Summary

- Clonidine 0.1 mg/d
 - Modest effect
- Gabapentin 900 mg/d
 - 45% reduction
- Venlafaxine XR 37.5-75 mg/d
 - 61% reduction
- Fluoxetine 20 mg/d
 - 50% reduction
- Paroxetine CR 12.5 mg/d
 - 63% reduction
- Citalopram 10-20 mg/d
 - 37% reduction
- Sertraline 50-100 mg/d - ?? benefit
- Tibolone

The Seven Dwarves of Menopause



Itchy, Bitchy, Sweaty, Sleepy, Bloated, Forgetful, & Psycho!