

# Menopause - Symptoms and Treatments

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# Objectives

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- Review the symptoms of menopause
- Review the WHI information
- Review the treatments for menopausal symptoms

# Menopause

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*“There is nothing to compare with the almost sudden decay of the organs of reproduction which marks the middle age of woman.”*

Barnes 1873

Term menopause first invented in 1821 by French MD Gardanne

# Menopause

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- WHO definition:
  - “Permanent cessation of menstruation resulting from loss of ovarian follicular activity”
- STRAW: Stages of Reproductive Aging Workshop
  - “The anchor point that is defined after 12 months of amenorrhea following the final menstrual period, which reflects a near complete but natural diminution of ovarian function”
- CAMS: Council of Affiliated Menopause Societies
  - “Occurs after 12 months of amenorrhea for which there is no other obvious pathologic or physiologic cause”

# Long Term Effects

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- Cessation of reproductive capacities
- Increase risk for CHD
- Osteoporosis
- Dementia

# What do women expect?

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- Seattle Midlife Women's Health Study of 508 women between the ages of 35-55:
  - 22% expected no change
  - 21% had negative expectations
  - 24% uncertain
  - 19% positive; 13% mixed
  - Women were unaware of the health risks associated with menopause

*Woods NF et.al. Anticipating menopause: observations from the Seattle Midlife Women's Health Study. Menopause 1999;6:167-173.*

Over 5700 books on topic

# Basic Facts

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- Generally occurs between 45-55
  - average age of 51 yrs
  - < 10% reach menopause before 46
- Factors leading to earlier menopause
  - Genetic predisposition to the age of onset
    - A woman has a 5% chance of entering menopause before age 46, however if she has a first – degree relative who entered menopause before 46 her risk goes up to 25%
  - shorter cycles
  - smokers - avg 2 years earlier
  - Low BMI
  - Nulliparity
  - Lack of OCP use
- With increasing life expectancy women can expect to spend at least 1/3 of their life in an estrogen deficient state

# Premature Menopause

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- Defined as menopause before age 40
- 1% of women
- Etiology:
  - Familial – 10% of cases
  - Chemotherapy or radiation therapy
  - Genetic mutations – ex: Turner's syndrome, mutation of FMR1 gene (fragile x)
  - Autoimmune destruction

# Symptoms

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- In order of frequency:
  - Vasomotor symptoms
  - Mood disturbances
    - But major depression is not more common during menopause
  - Sleep disturbances
  - Sexual dysfunction
  - Vaginal Dryness

# Cultural Variation in Experiences

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US about 75% experience hot flashes

Japan about 12% report hot flashes

Survey of Nigerian women: 30% reported hot flashes

# Natural History of Reproductive Cycle

# Straw: Stages of Reproductive Aging Workshop

								Final Menstrual Period (FMP)	
								0	
<i>Stages:</i>	-5	-4	-3	-2	-1	+1	+2		
<i>Terminology:</i>	<b>Reproductive</b>			<b>Menopausal Transition</b>		<b>Postmenopause</b>			
	Early	Peak	Late	Early	Late*	Early*	Late		
				<b>Perimenopause</b>					
<i>Duration of Stage:</i>	variable			variable		(a) 1 yr	(b) 4 yrs	until demise	
<i>Menstrual Cycles:</i>	variable to regular	regular		variable cycle length (>7 days different from normal)	intervals of amenorrhea (>42 days)	A men x 12 mos	none		
<i>Endocrine:</i>	normal FSH		↑ FSH	↑ FSH		↑ FSH			

*\*Stages most likely to be characterized by vasomotor symptoms*

# Perimenopause

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- Stages -2 (early) and -1 (late) on the STRAW
- Onset about 3 to 5 years before the FMP
- Wide fluctuations of hormones
  - FSH and Estrogen levels fluctuate
  - Estrogen levels can be higher than during peak reproductive years
- Ovulatory and anovulatory cycles with variable cycle length and periods of amenorrhea
  - 10% of women will have cessation of menses without prior irregularity

## **During late perimenopause (-1) and early menopause (+1) women**

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- Hot flashes/flushes begin
- Sleep disturbances including early morning awakenings
- Pts may c/o of dizziness, palpitations, and in some cases vertigo
- Increased Irritability
- Vaginal Dryness

# Diagnosis of Menopause

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- Clinical Diagnosis: absence of menses for 12 months
- Lab: used when only clinical diagnosis in doubt
  - FSH  $\geq$  40IU (represents 2SD above peak FSH seen periovulatory peak)
    - Studies show can have FSH  $>$  40 and ovulatory cycles
  - If on OC than FSH  $\geq$  30 two weeks after a pill-free interval
  - Estradiol ( $<$ 20 pg/ml)

# Case # 1

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- 60 yo WF calls your office in a panic. She has heard about the dangers of hormone replacement and wants to discuss stopping her Prempro<sup>R</sup>.
- What other questions would you ask her regarding the HRT?

# Question

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- What did the WHI tell us about the risk of developing the following in women on combination HRT?
  - Heart disease
  - Breast cancer
  - Colon Cancer
  - Dementia
  - Osteoporosis

# WHI Summary

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- Multi-center double-blind, placebo-controlled trial
- Enrolled 16,608 women with intact uterus and 10,739 without b/w ages of 50-79
- Randomized to estrogen/medroxyprogesterone acetate vs placebo or estrogen only arm –vs- placebo
- Goal – look at effect of HRT on decreasing cardiovascular events

# WHI Combination Arm

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- 24% overall increase in the risk of CHD
  - 6 more heart attacks annually per 10,000 women using E+P
  - 81% increased risk of CHD in the first year after starting E+P
  - Subgroup analysis shows increasing risk with increasing age and increasing number of years since menopause
  - Increased risk began in first year of using HRT

# WHI Combination Arm:

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- **24% Increased risk of breast cancer**
  - 8 additional cases of breast cancer for every 10,000 women over one year
  - Risk increased after 3 years of use
- **31% increase in the risk for stroke**
  - Excess of 7 strokes for every 10,000 women over one year

## WHI cont:

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- WHI memory study included 4500 women over 65 followed over a 4-year period:
- **Dementia risk in the E+P group was 2x placebo**
  - An additional 23 cases per 10,000 per year among women taking combination therapy
  - Most of the dementia
    - Probable Alzheimer's disease
    - Vascular dementia ranking second

# Combination Arm Benefits

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- Decreased risk of colon cancer
  - HR 0.56
- Decreased risk of osteoporotic fractures
  - HR 0.65 vertebrae and wrist
  - HR 0.67 hip

# WHI Estrogen Only Arm

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- Increased stroke risk
  - HR 1.39 vs placebo
- Increased VTE risk
  - HR 1.33
- Trend toward slightly lower rate of breast cancer;  $p=.06$
- Decreased osteoporotic fracture risk
- No difference in rate of colorectal cancers
- No increase in cardiovascular events
  - Suggestion of protective effect in women 50-59

# Limitations of WHI

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- Data should not be extrapolated to women who are on HRT at a young age due to premature ovarian failure
- AA women accounted for only 6.8% of patients in the WHI
  - WHI found no effect of race on CV or Breast Cancer outcomes

# Ovarian Cancer Risk

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- Studies suggest an increased risk of ovarian cancer in women taking HRT - most recent JAMA 2009
- current users of hormones had incidence rate ratios for all ovarian cancers of 1.38. The risk declined with years since last use
- risk did not differ significantly with different hormone therapies or duration of use
- approximates 1 extra ovarian cancer for roughly 8300 women taking hormone therapy each year

# Million Women Study

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- Retrospective Cohort Study in the UK
- Involved 1,804,100 women between ages of 50-64 recruited between 1996-2001
- Designed to look at specific types of HRT and Breast Cancer risk
  - Current use associated with increased risk with both combination and estrogen only therapy
    - Combination higher - 2x vs 1.3
    - Increased risk with increased duration - 10 years of use led to 19 cases per 1000 users of combination HRT
  - Risk not influenced by dose and type of preparation
- Confirmed WHI for women on combination therapy

Beral, V. Lancet.2003 Aug 9;362(9382):419-427.

# Summary of Recommendations for HRT

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- Hormone replacement therapy should not be used for chronic disease prevention in post-menopausal women
- Primary indication for use of HRT in women is for management of post-menopausal symptoms
  - In healthy women the absolute risk for an adverse event is extremely low so therapy should not be withheld from patient's with severe symptoms
  - Therapy should be used for shortest duration possible at the lowest dose possible

# Case Follow Up

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- On review of the patients medical history you note she has a history of HTN, DM, and CAD.
- You agree she should stop the HRT due to concern for side effects
- How would you counsel this patient regarding discontinuing the hormone replacement therapy?

# How to stop HRT

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- No studies on the best way to wean though abruptly stopping can cause worsening symptoms in some patients
  - JAMA study: 8405 women who had participated in WHI combined arm told to abruptly stop medication
    - 55% of pt's reported mod-severe recurrent symptoms
- Options include:
  - Slow taper - Decreasing the pill one dose per week
  - Decreasing the dose of estrogen in the pill

# Case Follow Up

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- The same patient returns to clinic 3 months later. She has been tapered off her HRT and is now complaining of worsening hot flashes and sweats occurring 15 times per day and interfering with her sleep.
- What other treatment options are available to treat hot flashes?

# Vasomotor Symptoms

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- Begins 1-2 years before menopause
- Prevalence peaks in the first year following LMP
- Symptom duration: 6 months to 5 years
  - 50-75% of women will have cessation within 5 years
  - 10% of women have symptoms > 15 years after menopause

# Definition

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- Sudden sensation of heat on the upper chest and face followed by feeling cold
- Occurs several times per day
- Lasts from 2-4 minutes
- Can have profuse sweating and palpitations
- 15% of the cases the hot flashes are severe

# Treatment of Hot Flashes

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- Estrogen is most effective
- Other Agents include
  - SSRI and SSNRI
  - Gabapentine
  - Clonidine
  - Progestins
  - Herbals
  - Acupuncture

# SSNRI's

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- Efficacy of venlafaxine has been shown in RCT
- 221 women (+ Breast Cancer)
- 4 weeks
- Venlafaxine 75mg/day decreased hot flash score by 61%
  - dose of 37.5 mg / day decreased score by 37%
  - Dose above 75 mg not more effective with more side effects
- Responses occurred within days

*Loprinzi CL, et.al. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. Lancet 2000;356:2059-*

# SSRI: Paroxetine (Paxil CR ®)

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- Randomized, double-blind placebo controlled trial
- 165 postmenopausal women for 6 weeks (7% had history of breast cancer but not under treatment)
- Treatment Group
  - 12.5 mg had 62.2% decrease by week 6
  - 25 mg/day had 64.6% decrease by week 6
  - Placebo 37.8% decrease
  - Some effect seen in week one

*Stearns V et.al. Paroxetine controlled release in the treatment of menopausal hot flashes: a randomized controlled trial. JAMA 2003;289:2827-*

# Fluoxetine (Prozac ®)

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- Double blind, randomized, cross over method
- 81 women with a history of breast cancer
- 4 weeks per group
- 20 mg/d
- Hot flash scores (frequency x average severity) decreased 50% in the fluoxetine arm versus 36% in the placebo arm

*Loprinzi CL, et. al. Phase III evaluation of fluoxetine treatment of hot flashes. J Clin Oncol 2002 Mar 15;20(6):1578-83.*

# Other SSRI's

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- Sertraline (Zoloft):
  - Found to be no more effective than placebo in two randomized controlled trials of breast cancer survivors
- Citalopram (Celexa)
  - Preliminary studies showed good results with standard dosing

# Summary of Anti-depressants

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- No head to head trials comparing these drugs versus HRT
- Effexor usually first line
- Women generally respond immediately (not like treating depression)
- SSRI's good too ( except zoloft)

# Megestral acetate

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- Synthetic progestin
- Study of 97 women with breast cancer and 66 men with prostate cancer
- Randomized double blind placebo, cross-over
- 8 weeks total (4 treatment, 4 placebo)
- 20 mg BID shown to decrease hot flash frequency by 85%
- Effect seen at week 2 – 3
- High dose progestin therapy with IM injections also effective
- Side effects: N/V, constipation, depression, concerns over increased risk VTE, cardiovascular events

*Loprinzi CL, et.al. Megestrol acetate for the prevention of hot flashes. N engl J Med 1994;331:347*

# Clonidine

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- $\alpha$ -2 adrenergic agonist
- Has been shown in clinical trials in post-menopausal women, women on tamoxifen, and men with prostate cancer to relieve hot flashes
  - Generally 20% decrease in frequency/severity
- Can be given orally or transdermal
  - Dose range: 0.2 - 0.4 mg
- Consider as first line therapy in women with co-existent hypertension

# Gabapentin (Neurontin ®)

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- RCT in 59 women gabapentin at doses of 900 mg/day for 12 weeks
- Decreased hot flashes by 45% versus 29% for placebo
- Study in women with breast cancer also showed significant improvement over placebo
- Evening dose of 300 mg QHS also helpful for nighttime symptoms

# Tibolone (Livial ®)

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- Available in Europe and Australia
- Synthetic steroid metabolite w/ estrogenic, androgenic, and progestational effects
- 48 week study of 437 postmenopausal women
  - Tibolone found to be as effective as HRT in relieving symptoms of hot flashes
- Side effects - HA, wt gain, uterine bleeding

*Hammar M. A double-blind, randomised trial comparing the effects of tibolone and continuous combined hormone replacement therapy in postmenopausal women with menopausal symptoms. Br J Obstet Gynaecol 1998;105:904-911*

# Soy Products

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- Source of isoflavones which have both hormonal and nonhormonal properties
- Conflicting results of benefit
  - Review of 11 RCT of soy and isoflavone supplementation found no significant benefit in 7 of 11 studies
  - 4 that had positive effect showed a modest response (15% reduction over placebo)

*Kronenberg F et.al. Complementary and alternative medicine for menopausal symptoms: a review of randomized, controlled trials. Ann Intern Med 2002 ;137(10):805-13.*

# Red Clover

## *Trifolium pratense* L.

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Is a biennial or short-lived perennial **legume**

Flowers May-Sept

Habitat: roadsides, clearing, fields and meadows

# Red Clover cont:

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- Study published in JAMA in 2002
- 252 women assigned to receive red clover supplements versus placebo
- No clinically significant reduction of symptoms

*Tice JA. Et.al. Phytoestrogen supplements for the treatment of hot flashes: the isoflavone clover extract (ICE) study: a randomized controlled trial. JAMA 2003;290:207-*

## **Black Cohosh**(*Aristolochia serpentaria*).

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- A native of North America
- Grows freely in shady woods in Canada and the United States
- Other Names: Black Snake Root



# Black Cohosh

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- Most of the clinical trials looked at Remifemin (black cohosh product)
- Efficacy tied to levels of triterpene glycoside
- There have been 4 randomized studies but only 1 placebo controlled\*
  - 85 patients (59 on tamoxifen, 26 not on tamoxifen)
  - No significant difference between the two groups

*Jacobson JS et.al. Randomized trial of black cohosh for the treatment of hot flashes among women with a history of breast cancer. J Clin Oncol 2001;19:2739-45.*

# Dong quai

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- Touted to have estrogen like effect
  - Rat studies: increases uterine volume and weight in ovariectomized rats
- No studies show benefit for hot flash reduction
- Contains substances that have a coumarin-like effect
- Also contains safrole which is an oil with known carcinogenic potential

# Vitamin E

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- Vitamin E is a fat-soluble vitamin that exists in eight different forms.
- Alpha-tocopherol is the most active form of vitamin E in humans
- First had been reported to treat menopausal symptoms in the 1940's

# Vitamin E

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- Placebo-controlled, randomized, crossover trial:
- Patients received 4 weeks of vitamin E 800 IU daily, then 4 weeks of an identical-appearing placebo
- Vitamin E was associated with a **minimal decrease** in hot flashes (one less hot flash per day than was seen with a placebo)
  - Unlikely to be of clinical benefit

*Barton DL Prospective evaluation of vitamin E for hot flashes in breast cancer survivors J Clin Oncol. 1998 Feb;16(2):495-500.*

# Ginseng: *Panax ginseng*

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- 384 women were randomized to receive ginseng versus placebo
- No significant improvement of vasomotor symptoms
- Treatment group reported a slightly improved quality of life

*Wiklund IK et. al. Effects of a standardized ginseng extract on quality of life and physiological parameters in symptomatic postmenopausal women: a double-blind, placebo-controlled trial. Swedish Alternative Medicine Group Int J Clin Pharmacol Res. 1999;19(3):89-99*

# Others

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- Wild Yam: *Dioscorea villosa*
  - Contain diosgenin which may be converted to progesterone
  - No improvement
- Evening primrose: no benefit
- Licorice: has glycyrrhizinic acid which has weak estrogenic effect but no studies support efficacy

# Acupuncture

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- Randomized controlled trial looking at electroacupuncture vs estrogen vs superficial needle insertion
- Mean # of flashes per 24 hrs:
  - Acupuncture - 7.3 decreased to 3.5
  - Superficial needle insertion - 8.1 decreased to 3.8
  - Estrogen - 8.4 decreased to 0.8
- Decrease persisted over 24 weeks of follow up

# Behavioral Modification

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- Avoid hot flash triggers
  - Down comforters, thermal blankets, hot spicy foods, alcohol, emotional and stressful situations, bright lights
- Wear layers, cool cotton clothing
- During the onset of a hot flash- paced respirations, drinking a cold beverage
- Studies have shown that behavior modification can reduce both the severity and frequency of hot flashes

# Summary

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- Mild vasomotor symptoms – behavioral modifications
- Moderate – severe symptoms – short term estrogen therapy
- CI to estrogen therapy, prolonged symptoms, side effects to estrogen therapy – SSRI, SNRI, gabapentin, clonidine

# Sexual Dysfunction

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- Painful intercourse

- Lack of estrogen leads to vaginal atrophy, decreased vaginal lubrication, decreased elasticity of vaginal wall
- Results in vaginal dryness and dyspareunia
- Affects 17-30% of postmenopausal women
- Vaginal dryness becomes increasingly more common throughout the menopausal transition

- Decreased libido / arousal

# Urinary Symptoms

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- Estrogen deficiency leads to atrophy of urethral epithelium and loss of compliance
  - Results in both stress and urge incontinence
  - Seen in 15-36% of postmenopausal women
- Estrogen deficiency leads to increased vaginal pH and altered vaginal flora
  - Increased rate of UTI

# Vaginal Estrogen

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- Effective for treatment of genitourinary symptoms and dyspareunia and vaginal dryness
  - safe to use due to lower levels of systemic absorption except in breast cancer patients
  - Selected vaginal preparations
    - Vaginal cream
      - Premarin - conjugated estrogen 1/8 applicator q day x 2 weeks then 2-3 x per week
    - Vaginal tablet - ex: vagifem; inserted 2 d/wk
    - Vaginal ring - estring - 0.0075 mcg /day - inserted q 90 days
- Vaginal moisturizers / lubricants also useful
  - Replens - OTC
    - Has been shown in clinical studies to relieve vaginal atrophy symptoms related to low estrogen levels
  - Use in breast cancer patients rather than estrogen

# Sleep Disturbance

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- Sleep disturbance seen in 35-60% of postmenopausal women
  - Hot flashes can lead to sleep disturbance
    - Most often occur at night and can occur hourly
  - Low estrogen levels related to decreased REM sleep
- Sleep disturbance can result in fatigue, irritability, depression, difficulty concentrating

# Treatment Options

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- medications
  - Trazodone
  - TCA's
  - Zaleplon (Sonata ®): nonbenzodiazepine
  - Clonidine or Gabapentin
    - Good option if having hot flashes
  - Hormone replacement therapy
    - 30% will report sleep improvement

# Insomnia Trx continued

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- Non pharmacologic therapy
  - Behavior modifications
  - Increasing physical activity
  - Adjusting light, noise, temperature

# Mood Disturbances

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- Conflicting evidence from studies analyzing relationship b/w menopause and mood disturbance
  - Observational studies have linked menopause with mood changes, anxiety, irritability
  - Studies have also shown estrogen at the time of menopause can be effective therapy for the treatment of depression in highly symptomatic individuals
- SSRI, SSNRI

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- NIH state of the Science Panel. NIH state of the science conference statement: Management of Menopause-related symptoms. *Ann Intern.Med.* 2005; 142: 1003-1013.

# Case 1

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- A 64 yo female presents to your clinic with a CC: of “feeling hot and sweaty”. She has been postmenopausal for about 10 years and at that time had terrible hot flashes, night sweats, and sleep disturbances. She had been symptom free for the past 5 years and wonders why she is again experiencing these symptoms.

# Case 1 cont:

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- PMHX: significant for HTN diagnosed 6 months ago
- PSHX: none
- Medications: Felodipine (Plendil ®) 10 mg po qd

What is your differential diagnosis?

## Secondary causes of hot flashes should be considered

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- Malignancy: e.g. lymphoma, medullary cancer of thyroid
- Medications
- Infections: e.g. TB, HIV
- Endocrine disorders: e.g. hyperthyroidism, pheochromocytoma
- Others: food additives, CVA

# Medications

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- Anti-migraine drugs
- Anti-hypertensive medications: b-blockers, calcium channel blockers
- GnRH agonists
- SERMS
- Others: NSAIDS, ASA, Niacin, etc

## Case 2

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A 54 yo female w/o a significant medical history presents to your clinic for a routine physical exam. She reports hot flashes since going through menopause one year ago. She also has stage I HTN trx with HCTZ and therefore decide to order a CMP.

## Case 2 cont:

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On the lab you note the following:

- ALT: 150 U/L
- AST: 130 U/L
- Alb: 3.0 g/dl
- Tp: 7.5 g/dl
- Rest of her labs are normal

## Case 2 cont:

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- You call her back to discuss her results.
- She has never had a blood transfusion and does not engage in high risk behavior.
- Her medications include:
  - Vitamin E
  - Vitamin C
  - Black Cohosh

## Case 2 cont:

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- Workup for her liver disease includes:
  - Neg: ANA
  - Hep C: NR
  - Hep B,A: negative
  - Iron, TIBC, Ferritin: normal
  - AFP: < 5

What is the likely culprit for her liver problem?

# Black Cohosh

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- Herbal remedies such as black cohosh have been reported in the literature to cause liver disease
- In the United States, the Food and Drug Administration (FDA) lists it as a "herb of undefined safety".

## Case 3

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- A 52 yo woman presents to your clinic for a routine health examination. Her medical history is significant for osteoarthritis. On ROS she tells you that she has felt anxious and unusually irritable over the last 6 months. In addition she has been having difficulty falling asleep at night. She continues to have **periods** however they have been **more irregular** over the past 1 year.
- How do you advise her?

# Mood Disorders

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- Trazodone: may be helpful for women with both mood and sleep disorder
- SSRI's
- Consider low dose estrogen / progesterone combination therapy

# Mood Disorders

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- Botanicals marketed for mood disorders
  - St John's Wort: 8 RCT showing modest benefit for treatment of mild to moderate depression. Induces P450. May interact with SSRI, TCA, anesthesia (can either inhibit or potentiate effects)
  - Ginseng
  - Kava kava: liver toxicity