MENOPAUSE

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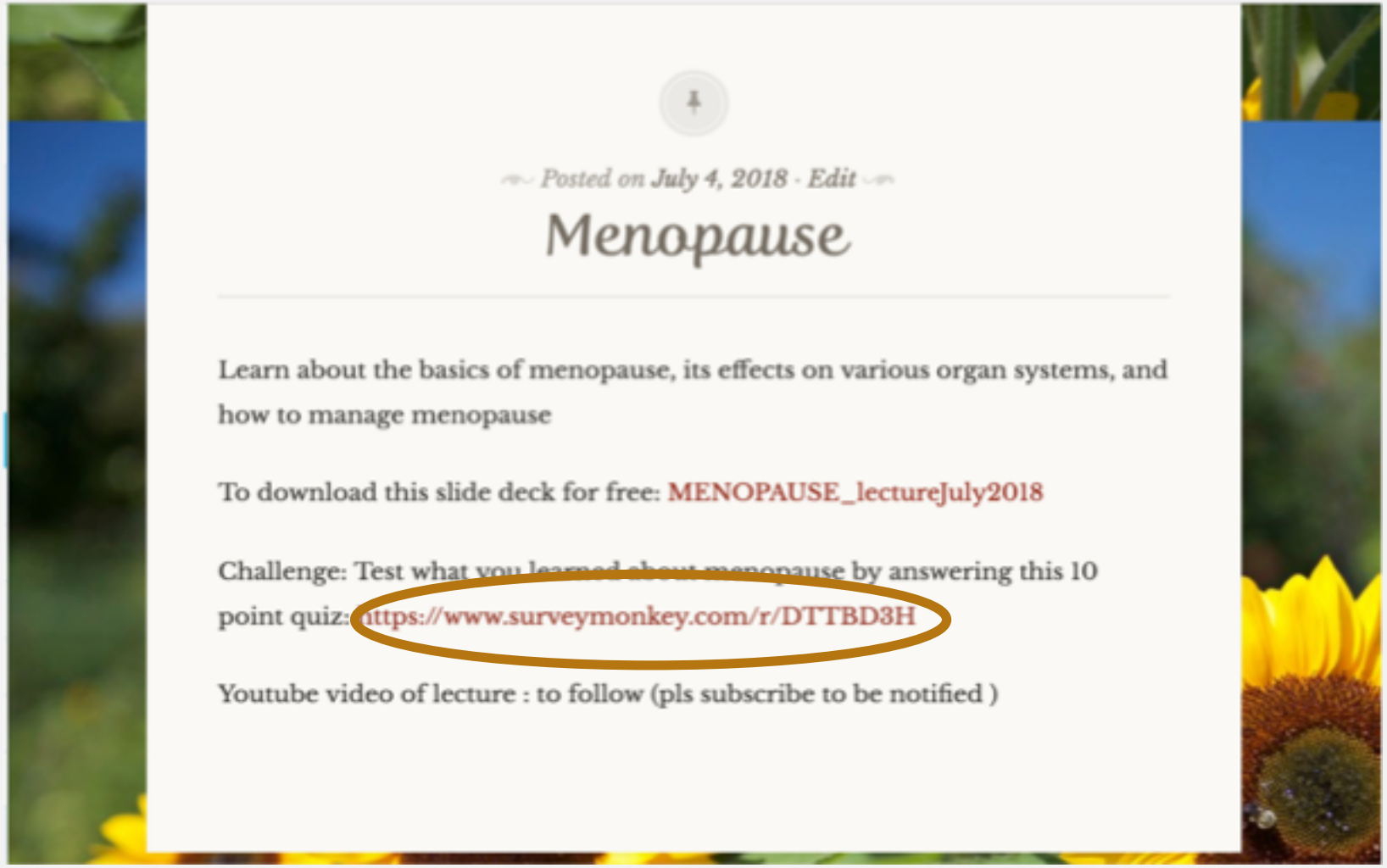
QUIZ



Posted on July 4, 2018 · Edit

Menopause

Learn about the basics of menopause, its effects on various organ systems, and how to manage menopause

To download this slide deck for free: MENOPAUSE_lectureJuly2018

Challenge: Test what you learned about menopause by answering this 10 point quiz: https://www.surveymonkey.com/r/DTTBD3H

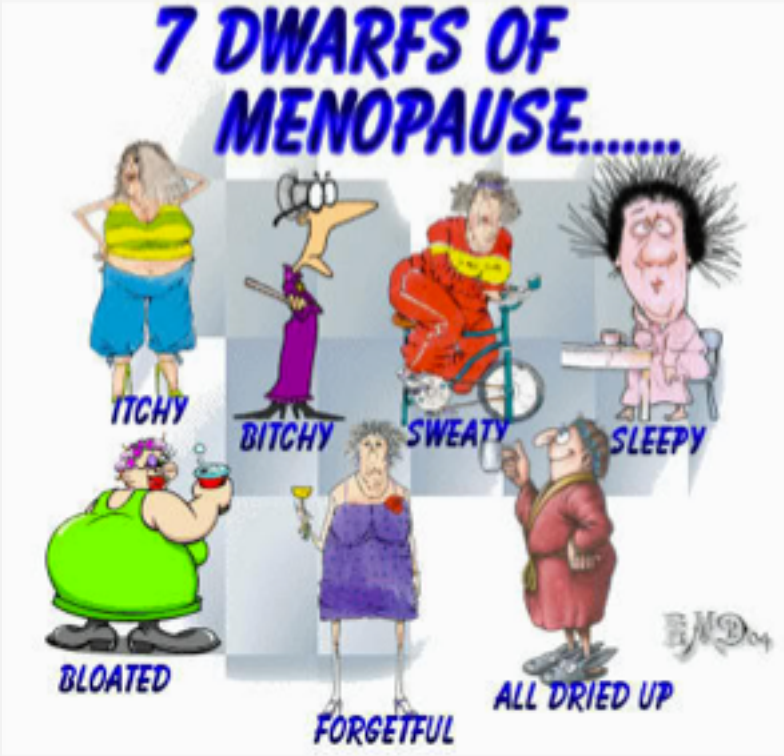
Youtube video of lecture : to follow (pls subscribe to be notified)

MAIN REFERENCES

- Comprehensive Gynecology 7th edition, 2017 (Lobo RA, Gershenson DM, Lentz GM, Valea FA *editors);* chapter 14, Menopause and Care of the Mature Woman ; pp 258-291
- North American Menopause Society (NAMS) position statements and menopause lecture deck

OUTLINE

1. Definition of terms
2. Symptomatology
3. Effects of menopause on various organ systems
4. Treatment



WHAT IS MENOPAUSE ?

- Menopause is a normal, natural event, defined as the final menstrual period (FMP), confirmed after **1 year** of no menstrual bleeding
- Represents the permanent cessation of menses resulting from loss of ovarian follicular function, usually due to aging

North American Menopause Society 2012

WHEN IS MENOPAUSE?

- Naturally (spontaneously) average **age 51**
- Prematurely from medical intervention
  (eg, total hysterectomy with bilateral oophorectomy, chemotherapy, radiotherapy)
- At any time from impaired ovarian function (genetic causes)

North American Menopause Society 2012

MEAN AGE OF ONSET

- Western countries: 51- 52
- Asian = 42.1 – 49.5
- Filipinas: 47- 48

Age of menopause is a genetically programmed event;
Other factors that may affect age of menopause:

- Ethnicity
- General health status
- Parity
- smoking

1. Palacios et al. Age of Menopause and Impact of Climacteric Symptoms by Geographical Region. Climacteric Journal Vol.13 2010.
2. Ramoso-Jalbuena, Climacteric Filipino Women: A Preliminary Survey in the Philippines. Maturitas – European Journal of Climacteric Medicine Oct;19(3):183-90. 1994
3. Calimbas K, Meceren-Medina A. Assessement of Climacteric Symptoms among Filipino Women ages 40 years and above seen at a Tertiary Hospital in Metro Manila
4. The changes during menopause as perceive by women in Dumaguete City and relationship to their self-concept and coping mechanism

MENOPAUSE

- the initial endocrinologic change signaling the onset of menopause is **decreased AMH and ovarian inhibin-B production** accompanied by an increase in FSH.

Comprehensive Gynecology 7th edition, 2017 (Lobo RA, Gershenson DM, Lentz GM, Valea FA *editors);* chapter 14, Menopause and Care of the Mature Woman ; pp 258-291

MENOPAUSE: An Estrogen Deficiency State

Age, years	Early		Intermediate			Late	
	40	45	50	55	60	65	70+
Hot flushes							
Sweating							
Insomnia							
Menstrual irregularity							
Psychological symptoms							
Vaginal atrophy							
Dyspareunia							
Skin atrophy							
Urge-stress incontinence							
Osteoporosis							
Atherosclerosis							
Coronary heart disease							
Cardiovascular disease							
Alzheimer's disease							

Reduced quality of life

Modified from Speroff L, et al. In: Mitchell C, ed 6. Clinical Gynecologic Endocrinology and Infertility. 6th ed. Lippincott Williams & Wilkins; 1999:643-724. van der Mooren MJ, Kenemans P. Drugs. 2004;64(8):821-36.

TERMINOLOGY: PERIMENOPAUSE

- The time around menopause, also called "the menopause transition"
- The most symptomatic phase for women

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PERIMENOPAUSE

- Clinical treatment of women in the perimenopause should address three general areas of concern:
  - (1) irregular bleeding
  - (2) symptoms of early menopause, such as hot flushes
  - (3) the inability to conceive.

- **short-term use of an oral contraceptive (usually 20 mcg ethinyl estradiol)

North American Menopause Society 2012

TERMINOLOGY: INDUCED MENOPAUSE

- Cessation of menstruation that follows bilateral oophorectomy (with or without hysterectomy) or chemotherapy or pelvic radiation therapy;
- also called iatrogenic menopause

North American Menopause Society 2012

PREMATURE OVARIAN FAILURE (POF)

Premature ovarian failure (or ***premature ovarian insufficiency*** (POI)), is defined as hypergonadotropic ovarian failure occurring prior to **age 40**

Table 14-2 Possible Causes of Premature Ovarian Failure

Genetic
Enzymatic
Immune
Gonadotropin defects
Ovarian insults
Idiopathic

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MANAGEMENT OF PREMATURE OVARIAN INSUFFICIENCY

- screening for autoimmune disorders and a karyotype
- Transvaginal ultrasound may be useful for assessing the size of the ovaries and the degree of follicular development
- Screen carefully for thyroid, adrenal, and other autoimmune disorders.
- Treatment of all cases usually consists of estrogen replacement.
- If fertility is a concern, the most efficacious treatment is oocyte donation. A spontaneous pregnancy rate as high as 5% has been suggested.

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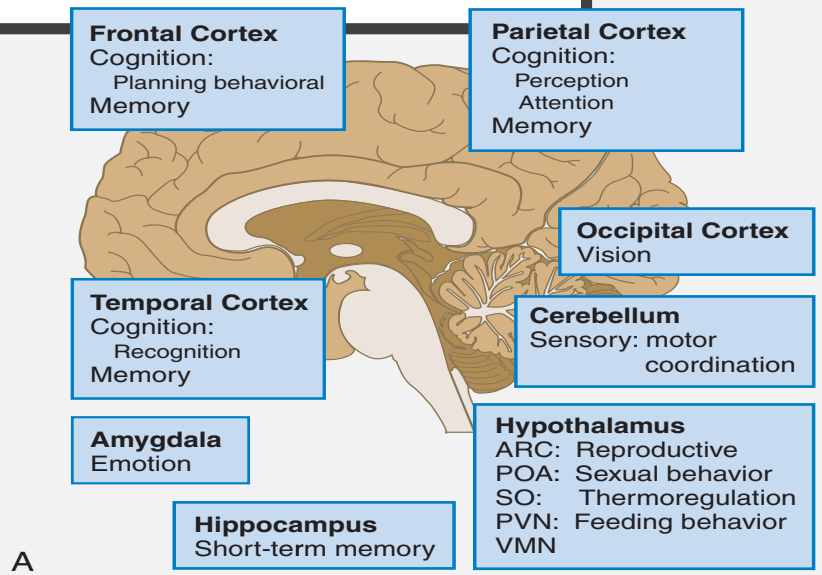
EFFECTS OF MENOPAUSE ON VARIOUS ORGAN SYSTEMS

1. CENTRAL NERVOUS SYSTEM

- the brain is an active site for estrogen action as well as estrogen formation.
- Estrogen activity in the brain is mediated via estrogen receptor (ER) α and ER β.



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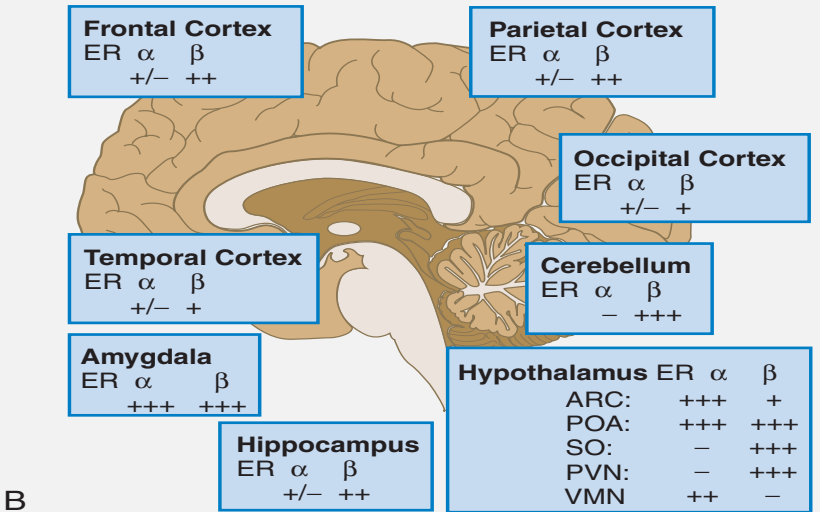

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CENTRAL NERVOUS SYSTEM: VASOMOTOR SYMPTOMS

- hallmark feature of declining estrogen status in the brain is the "hot flush" /"hot flash" or "vasomotor episode"
- The **"hot flash"** usually refers to the acute sensation of heat
- The **"hot flush"** or vasomotor episode includes changes in the early perception of this event and other skin changes (including diaphoresis).
- Hot flushes usually occur for 2 years after the onset of menopause but can persist for 10 or more years. (The severity of hot flushes decreases with time)

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CENTRAL NERVOUS SYSTEM: VASOMOTOR SYMPTOMS

- The **fall in estrogen** levels precipitate the vasomotor symptoms.
- hot flushes are due to thermoregulatory disruption with a much narrower temperature range between sweating and shivering.
- The difference in temperature at which shivering occurs, and when sweating occurs, termed the *thermoneutral zone*, is wide in asymptomatic women → this zone is substantially more narrowed in symptomatic women, explaining their vulnerability to vasomotor symptoms

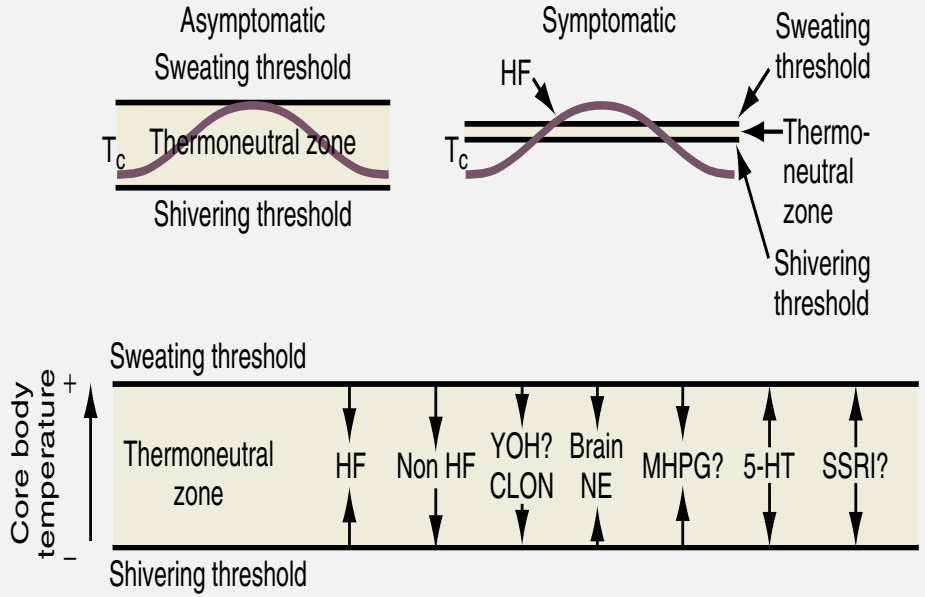
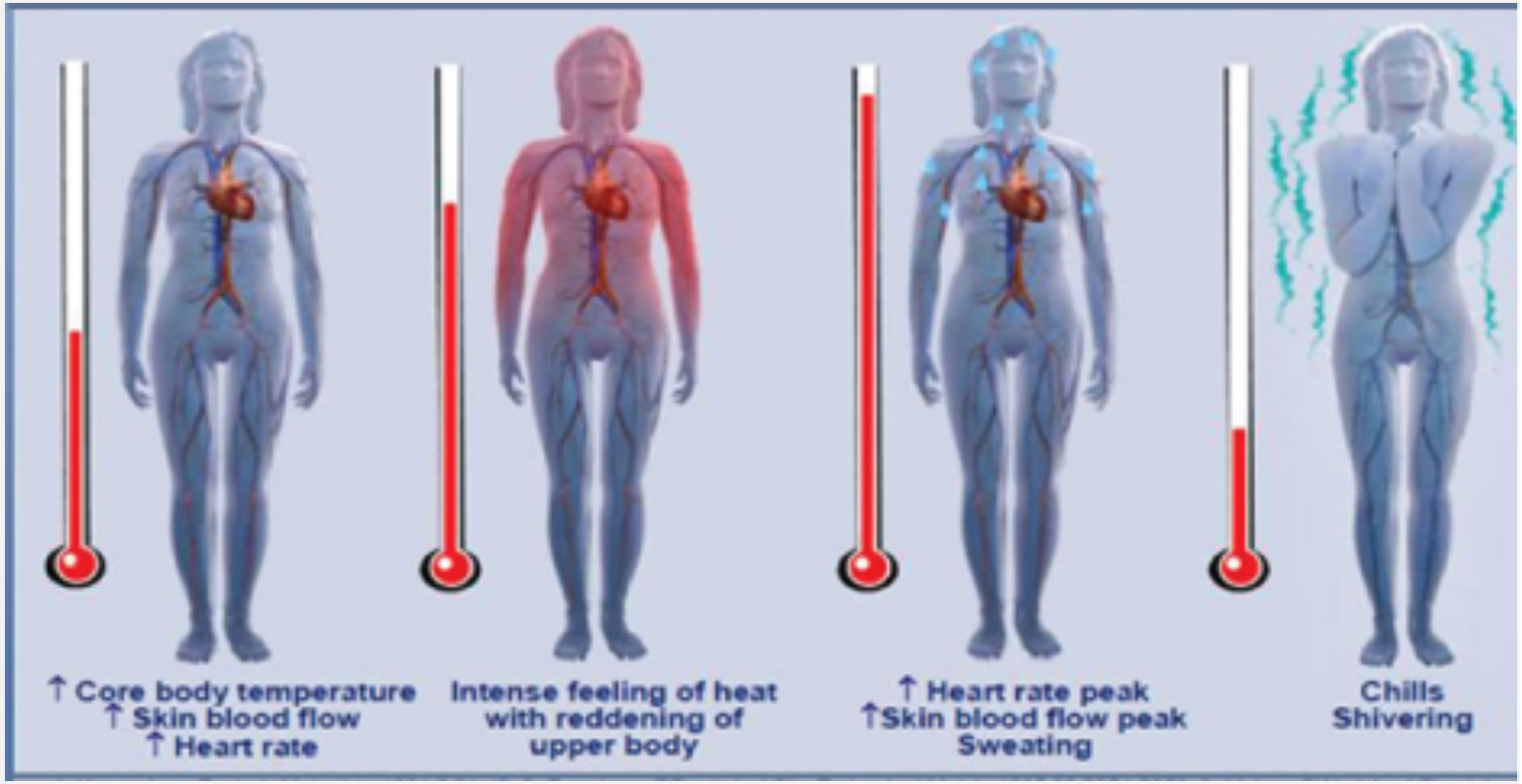


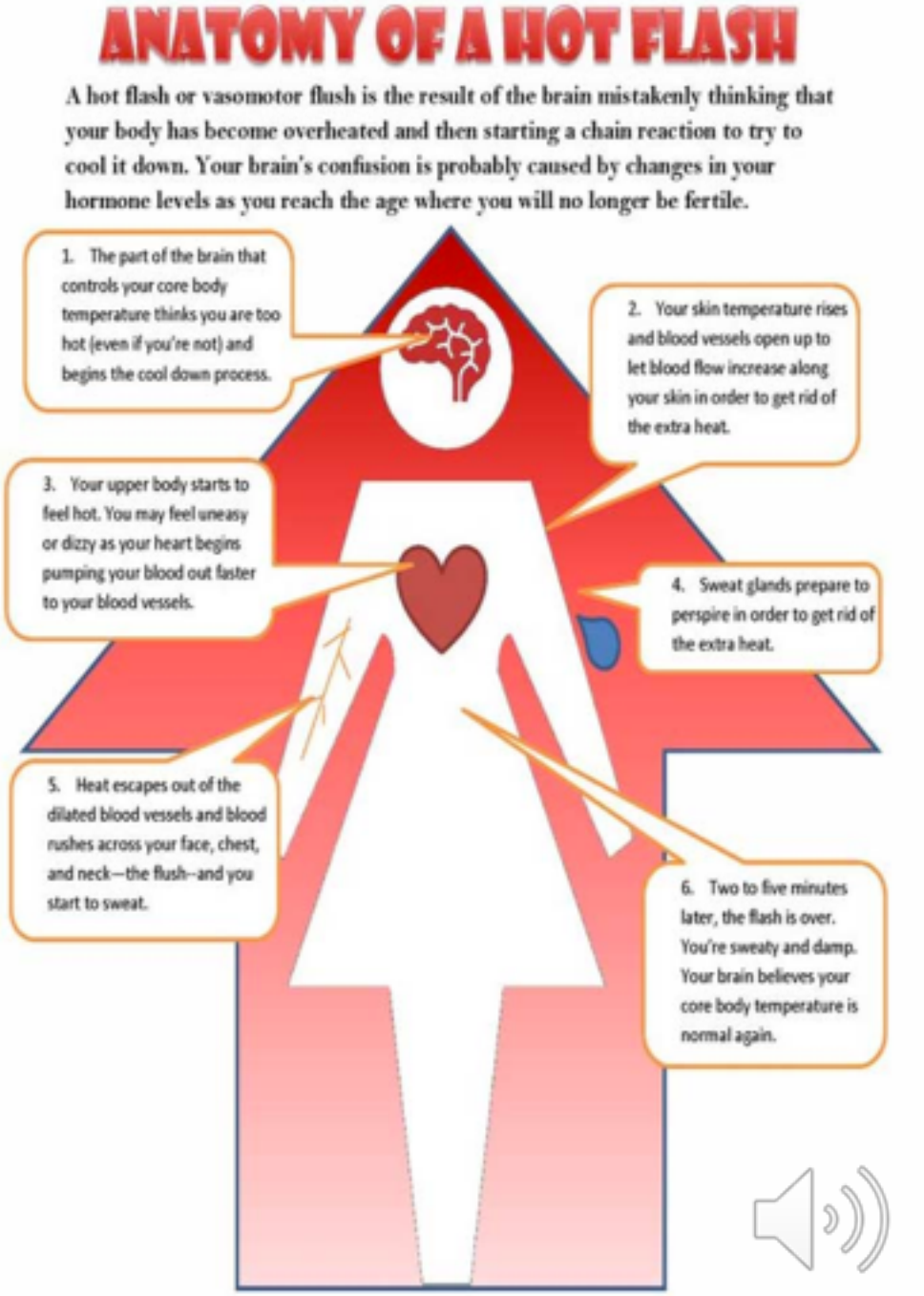
Figure 14.17 Narrowing of the thermoregulatory zone in symptomatic women. *HF,* Hot flush. (Data from Freedman RR: Menopausal hot flashes. In: Lobo RA, ed. *Treatment of the Postmenopausal Woman.* 4th ed. New York: Academic Press; 2007:187-198.)

Comprehensive Gynecology 7th edition, 2017 (Lobo RA, Gershenson DM, Lentz GM, Valea FA *editors);* chapter 14, Menopause and Care of the Mature Woman ; pp 258-291

HOT FLUSH PHYSIOLOGY ILLUSTRATION



North American Menopause Society 2012



CENTRAL NERVOUS SYSTEM: VASOMOTOR SYMPTOMS

- One of the primary complaints of women with hot flushes is sleep disruption.
- They may awaken several times during the night and require a change of bedding and clothes because of diaphoresis.
- This disturbed sleep often leads to fatigue and irritability during the day. The frequency of awakenings and hot flushes is reduced appreciably with estrogen treatment

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CENTRAL NERVOUS SYSTEM: COGNITIVE CHANGES

- Cognitive decline in postmenopausal women is related to aging as well as to estrogen deficiency.
- Verbal memory appears to be enhanced with estrogen
- Dementia increases as women age, and the most common form of dementia is Alzheimer's disease (AD).

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CENTRAL NERVOUS SYSTEM: COGNITIVE CHANGES

- Estrogen has a role in enhancing neurotransmitter function, which is deficient in women with AD.
- Estrogen use after menopause appears to decrease the likelihood of developing or delaying the onset of AD
- However, once a woman is affected by AD, estrogen is unlikely to provide any benefit.

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CENTRAL NERVOUS SYSTEM: MOOD DISORDERS

- Feelings of upset, loss of control, irritability, fatigue, and blue moods (dysphoria) at midlife may be caused by fluctuating hormone levels

  that perturb neural systems transiently
- Women with a history of premenstrual syndrome, significant stress, sexual dysfunction, physical inactivity, or hot flashes are more vulnerable to depressive symptoms

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CENTRAL NERVOUS SYSTEM: MOOD DISORDERS

- The most predictive factor for depression at midlife and beyond is prior history of clinical depression
- Relaxation and stress reduction techniques, antidepressants, and counseling or psychotherapy are options to consider in symptom management

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CENTRAL NERVOUS SYSTEM: COGNITIVE CHANGES AND MOOD DISORDERS

- early treatment with estrogen in younger women at the onset of menopause *may* be beneficial for cognition and mood. Later treatment (e.g., after age 65, or > 10 years after onset of menopause) has no benefit and may even be detrimental

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CENTRAL NERVOUS SYSTEM: COGNITIVE CHANGES

- There is NO benefit of estrogen or estrogen/progestogen, or even a worsening of cognition in women initiating hormonal therapy **after age 65**.
- This suggests that *timing of initiation of hormone therapy is critical*
- The early exposure to estrogen decreased the possibility of brain damage from free radicals and also promoted maintenance of neuronal and synaptic activity.

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2. COLLAGEN AND OTHER TISSUES

- Estrogen has a positive effect on collagen, which is an important component of bone and skin and serves as a major support tissue for the structures of the pelvis and urinary system.
- Estrogen therapy generally improves collagen content after menopause and improves skin thickness substantially after about 2 years of treatment

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COLLAGEN AND OTHER TISSUES: URINARY SYMPTOMS

- Reductions in collagen support and atrophy of the vaginal and urethral mucosa have been implicated
- urinary incontinence, overactive bladder (OAB)
- Mild incontinence in early perimenopause tends to decline in the first 5 years after menopause
- Weight loss for overweight women is effective
- Kegel exercises can cure more than 50% of cases of stress incontinence when performed regularly

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COLLAGEN AND OTHER TISSUES: URINARY SYMPTOMS

- Estrogen has also been shown to decrease the incidence of recurrence of urinary tract infections.
- Estrogen may restore bladder control in older women
- Estrogen may improve urge and other irritative urinary symptoms.

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3. VULVOVAGINAL ATROPHY

- Vulvovaginal complaints are often associated with estrogen deficiency.
- With this change, an increase in sexual complaints also occurs (eg dyspareunia)
- Estrogen deficiency results in a thin, paler vaginal mucosa.
- The moisture content is low, the pH increases (usually greater than 5), and the mucosa may exhibit inflammation and small petechiae.

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VULVOVAGINAL ATROPHY

- Unlike vasomotor symptoms, which abate over time, vaginal atrophy is typically progressive and unlikely to resolve on its own
- Treatments include: regular sexual activity, lubricants and moisturizers, and local vaginal estrogen

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4. BONES

- Estrogen deficiency can cause bone loss.
- Loss of **trabecular bone** (spine) is greater with estrogen deficiency than is loss of **cortical bone (**long bones)
- Postmenopausal bone loss leading to osteoporosis is a substantial health care problem
- Attainment of peak bone mass in the late second decade is key to ensuring that the subsequent loss of bone mass with aging and estrogen deficiency does not lead to early osteoporosis.

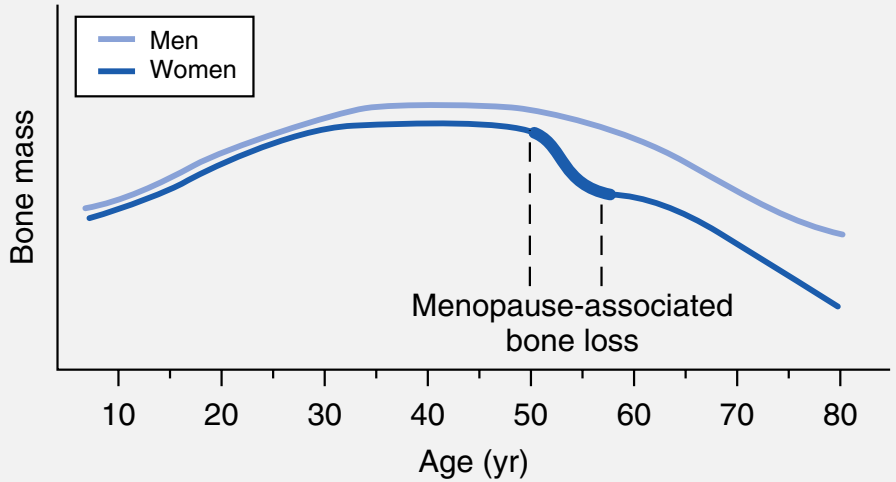


Figure 14.20 Bone mass by age and sex. (Modified from Finkelstein JS: Osteoporosis. In: Goldman L, Bennet JC, eds. *Cecil Textbook of Medicine.* 21st ed. Philadelphia: Saunders;1999:1366-1373; Riggs BL, Melton LJ III. Involutional osteoporosis. *N Engl J Med.* 1986;314:1676.)

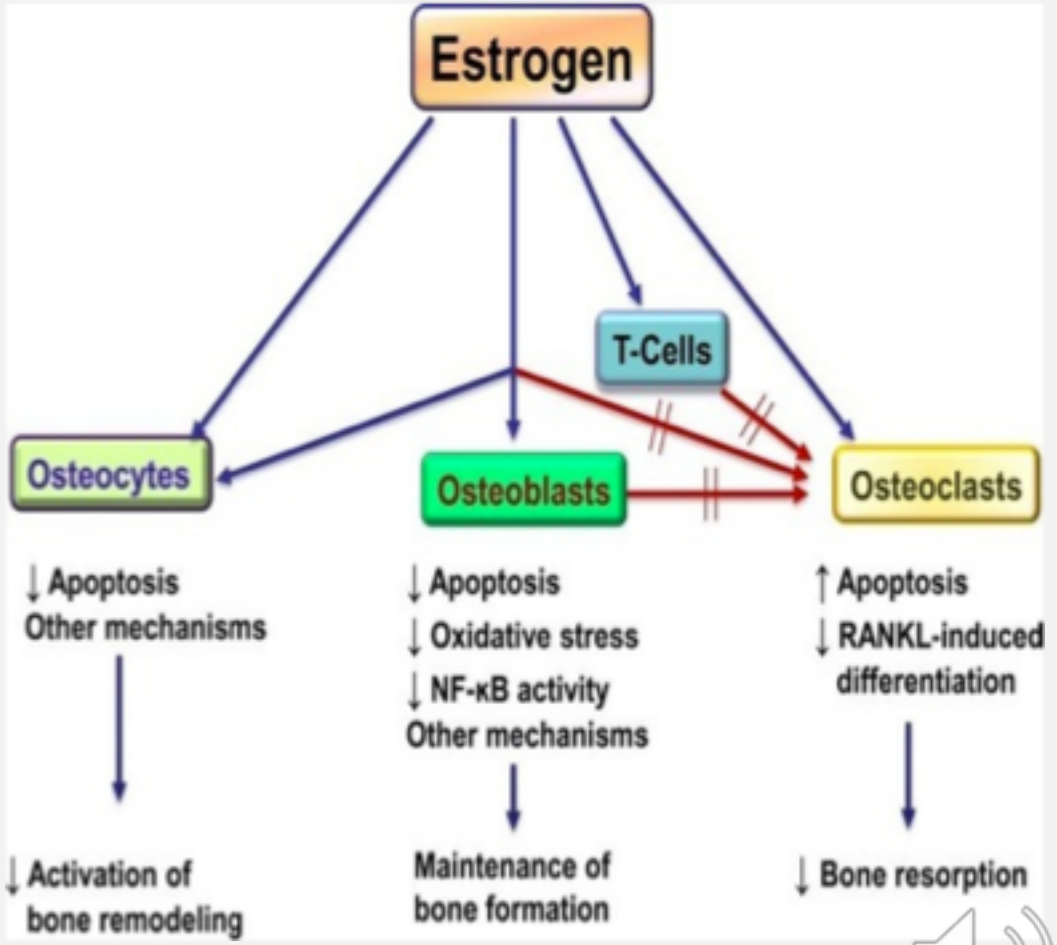
Comprehensive Gynecology 7th edition, 2017 (Lobo RA, Gershenson DM, Lentz GM, Valea FA *editors);* chapter 14, Menopause and Care of the Mature Woman ; pp 258-291

OSTEOPOROSIS

- Defined as compromised bone strength
- Serious health threat for aging postmenopausal women by increasing risk of fracture
- Definitions based on BMD results:
  - Normal: T-score greater than or equal to –1.0
  - Low bone mass (**osteopenia**): T-score between –1.0 and –2.5
  - **Osteoporosis:** T-score less than or equal to –2.5

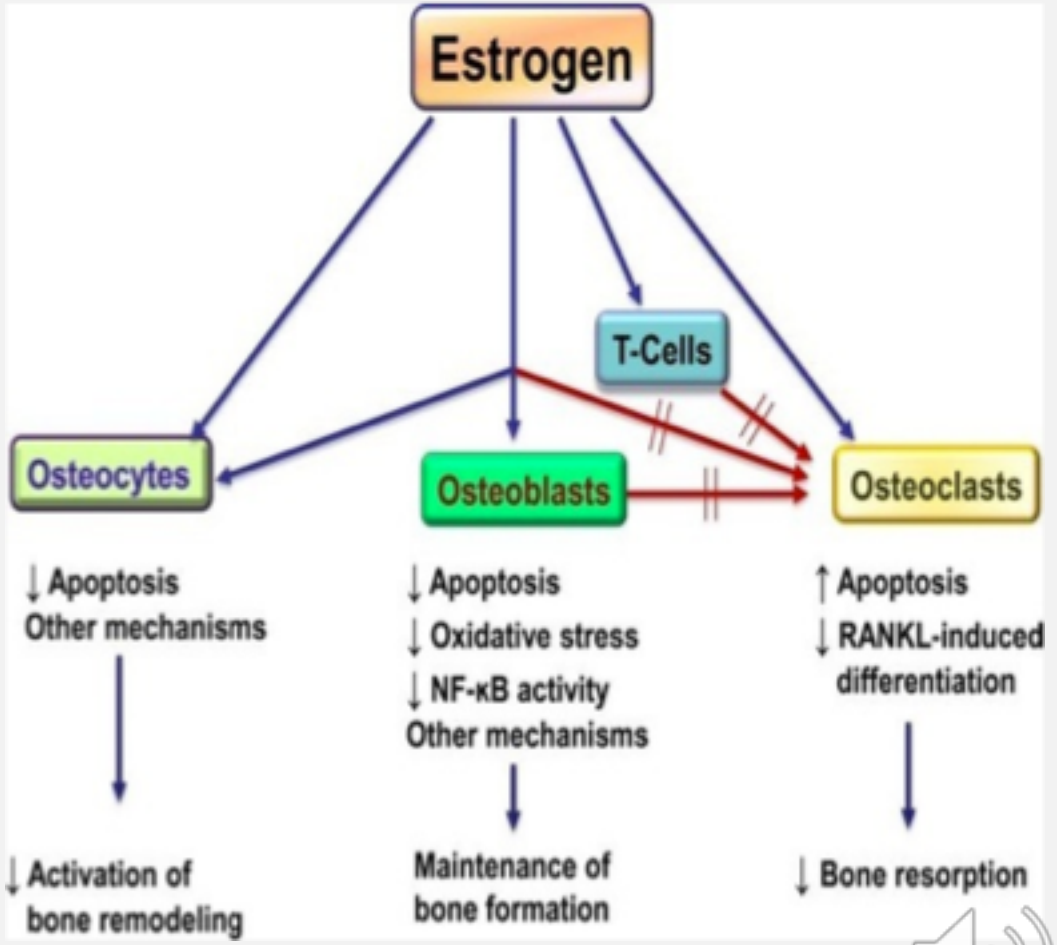
OSTEOPOROSIS: ROLE OF ESTROGEN?

- Estrogen receptors are present in osteoblasts, osteoclasts, and osteocytes.
- Estrogen suppress bone turnover and maintain a certain rate of bone formation.
- Bone is remodeled in functional units, called *bone multicenter units* (BMUs), where resorption and formation should be in balance. Multiple sites of bone go through this turnover process over time.



BONES: OSTEOPOROSIS

- Estrogen decreases osteoclasts by increasing apoptosis thus reducing their life span.
- Estrogen antagonizes glucocorticoid-induced osteoblast apoptosis.
- Estrogen deficiency increases the activities of remodeling units, prolongs resorption, and shortens the phase of bone formation. It also increases osteoclast recruitment in BMUs, thus resorption outstrips formation.



OSTEOPOROSIS: HOW TO DIAGNOSE?

- Bone mass can be detected by a variety of radiographic methods
- **Dual-energy x-ray absorptiometry (DEXA)** scans have become the standard of care for detection of **osteopenia** and **osteoporosis**.
- By convention, the **T score** is used to reflect the number of standard deviations of bone loss from the peak bone mass of a young adult.
- Osteopenia is defined by a T score of –1 to –2.5 standard deviations;
- Osteoporosis is defined as greater than 2.5 standard deviations.

Table 14.2 Techniques for the Detection of Bone Mass

Technique	Anatomic Site of Interest	Precision in Vivo (%)	Examination and Analysis Time (min)	Estimated Effective Dose Equivalent (uSv)
Conventional radiographs	Spine, hip	NA	<5	2000
	2000			
Radiogrammetry	Hand	1-3	5-10	<1
Radiographic absorptiometry	Hand	1-2	5-10	<1
Single x-ray absorptiometry	Forearm, heel	1-2	5-10	<1
Dual x-ray absorptiometry	Spine, hip, forearm, total body	1-3	5-20	1-10
Quantitative computed tomography	Spine, forearm, hip	2-4	10-15	50-100
Quantitative ultrasound	Heel, hand, lower leg	1-3	5-10	None

Modified from van Kuijk C, Genant HK. Detection of osteopenia. In: Lobo RA, ed. *Treatment of the Postmenopausal Woman: Basic and Clinical Aspects.* 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 1999:287-292.
NA, Not applicable.

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OSTEOPOROSIS: HOW TO MONITOR RESPONSE TO TREATMENT?

- Biochemical assays are also available to assess bone resorption and formation in both blood and urine
- serum markers appear to be most useful for assessing changes
- **useful as markers of the effectiveness of treatment**

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Table 14.3 Bone Turnover Markers

Marker	Specimen
Bone Resorption Markers	
Cross-linked N-telopeptide of type I collagen (NTX)	Urine, serum
Cross-linked C-telopeptide of type I collagen (CTX)	Urine (αα and ββ forms) Serum (ββ form)
MMP-generated telopeptide of type I collagen (ICTP or CTX-MMP)	Serum
Deoxypyridinoline, free and peptide bound (fDPD, DPD)	Urine, serum
Pyridinoline, free and peptide bound (fPYD, PYD)	Urine serum
Hydroxyproline (OHP)	Urine
Glycosyl hydroxylysine (GylHyl)	Urine, serum
Helical peptide (HelP)	Urine
Tartrate resistant acid phosphatase 5b isoform specific for osteoclasts (TRACP 5b)	Serum, plasma
Cathepsin K (Cath K)	Urine, serum
Osteocalcin fragments (uOC)	Urine
Bone Formation Markers	
Osteocalcin (OC)	Serum
Procollagen type I C-terminal propeptide (PICP)	Serum
Procollagen type I N-terminal propeptide (PINP)	Serum
Bone-specific alkaline phosphatase (bone ALP)	Serum

OSTEOPOROSIS RISK FACTORS

Risk factors for osteoporotic fracture used in FRAX

10-year calculator (www.shef.ac.uk/FRAX/tool.jsp)

- Advanced age (ages 50-90)
- Parental history of fragility fracture
- Female sex
- Current tobacco smoking
- Weight
- Long-term use of glucocorticoids
- Height
- Rheumatoid arthritis
- Low femoral neck BMD
- Prior fragility fracture
- Alcohol intake ≥3 units daily*
- smoking
- Other causes of secondary osteoporosis

*1 glass of beer (285 ml), 1 measure of spirits (30 ml), 1 medium-sized glass of wine (120 ml), or 1 aperitif (60 ml)

NAMS, 2012

5. CARDIOVASCULAR EFFECTS

- Women have a very low incidence of cardiovascular disease (CVD) prior to menopause, but after menopause, the risk increases significantly.
- Coronary artery disease is the leading cause of death in women: lifetime risk of death is 31% in postmenopausal women versus a 3% risk of dying of breast cancer.
- Premature ovarian failure constitutes a significant risk: increased risk of myocardial infarction (2-3fold), and oophorectomy before age 35 increases the risk 7-fold

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WHY ARE MENOPAUSAL WOMEN AT RISK FOR CARDIOVASCULAR DISEASE ?

- There is an accelerated rise in total cholesterol in postmenopausal women.
- This increase in total cholesterol is explained by increases in levels of low-density lipoprotein cholesterol (LDL-C).
- The oxidation of LDL-C is also enhanced, as are levels of very low density lipoproteins and lipoprotein (a).
- High-density lipoprotein choesterol (HDL-C) levels trend downward with time, but these changes are small and inconsistent relative to the increases in LDL-C.

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WHY ARE MENOPAUSAL WOMEN AT RISK FOR CARDIOVASCULAR DISEASE ?

- Blood flow in all vascular beds decreases after menopause; prostacyclin production decreases, endothelin levels increase, and vasomotor responses to acetylcholine are constrictive, reflecting reduced nitric oxide synthetase activity.
- Most of these latter changes are due primarily to the fairly rapid reduction in estrogen levels

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CARDIOVASCULAR EFFECTS

- With estrogen, all these parameters improve, and coronary arterial responses to acetylcholine are dilatory with a commensurate increase in blood flow.
- Overall, the direct vascular effects of estrogen are viewed to be as important, or more important, than the changes in lipid and lipoproteins after menopause.

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CARDIOVASCULAR EFFECTS: ESTROGEN THERAPY

- the beneficial arterial effects of estrogen may only be seen in younger (stage B1) postmenopausal women.
- Women with significant atherosclerosis or risk factors do not respond well to this treatment because of coronary plaque burden, which prevents estrogen action.
- *Estrogen has NO protective effect in women with established coronary disease.*

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CARDIOVASCULAR EFFECTS; ESTROGEN THERAPY

- Hormone therapy may lead to plaque destabilization and thrombosis in some women with established (although possibly silent) coronary disease.
- The molecular mechanisms for this may be due to estrogen up-regulating matrix metalloproteinase-9 and inhibiting its natural inhibitor within the mural area of the plaque;
- the resultant disruption of the gelatinous covering then leads to thrombosis.

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TIMING HYPOTHESIS

- *early intervention shows benefit* and *late intervention* with hormonal therapy is *possibly harmful* for the cardiovascular (CV) system.
- while younger women benefit, older women do not and may endure harm.
- HT may lead to plaque destabilization and thrombosis in some women with established (although possibly silent) coronary disease.

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7. CANCER

- Menopause is not associated with increased cancer risk
- But because cancer rates increase with age, screen for the following cancers regularly:
  - Breast cancer: mammogram every 2 years, ages 50-74 (USPSTF)
  - Colorectal cancer: colonoscopy (every 10 y) or fecal occult blood test, sigmoidoscopy, or barium enema (every 5 y) beginning at age 50
  - Endometrial cancer: evaluation of any postmenopausal bleeding with pelvic ultrasound and/or endometrial biopsy
  - Ovarian cancer: no satisfactory screening tests, but timely evaluation needed if presenting with bloating, pelvic pain, or urinary urgency

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7. CANCER

- Cervical cancer:
  - Pap test every 3 years (or every 5 years if combined with HPV test) after a normal report 3 years in a row for women ages 50-64
  - Screening not necessary ≥age 65 with 3 or more normal Pap tests in a row, no abnormal Pap in past 10 years, or 2 or more negative HPV tests in past 10 years

Comprehensive Gynecology 7th edition, 2017 (Lobo RA, Gershenson DM, Lentz GM, Valea FA *editors);* chapter 14, Menopause and Care of the Mature Woman ; pp 258-291

TREATMENT FOR MENOPAUSE

INITIAL MANAGEMENT OF A MENOPAUSAL WOMAN

1. Lifestyle Modification
    a. Smoking cessation
    b. Limit alcohol intake
2. "Common Sense" Solution
    a. Comfortable clothing
    b. Adequate Hydration
3. Increase physical activity – can improve mood, lowers stress and improves body image
4. Weight loss – improves VMS

Zain A, Al-Safi, Santoro N. Menopausal hormone therapy and menopausal symptoms. Fertility and Sterility Vol 101 No. 4

HORMONE THERAPY

Hormone therapy (HT) is the *recommended first-line pharmacologic therapy* for treating menopausal symptoms. HT encompasses both estrogen-alone and estrogen-progestogen therapies.

- *Estrogen therapy (ET):* Unopposed estrogen is prescribed both a) systemically for women who do not have a uterus, and b) locally in very low doses for any woman with vaginal symptoms
- *Estrogen-progestogen therapy (EPT):* Progesterone is added to ET to protect women with a *uterus against endometrial cancer*, which can be caused by estrogen alone

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HORMONE THERAPY

- Hormone therapy involves taking *estrogen in doses high enough to raise the level of estrogen in the blood in order to treat hot flashes and other symptoms.*
- Because estrogen stimulates the lining of the uterus, women with a uterus need to take progesterone to protect the uterus.
- Women without a uterus can take estrogen alone.
- If patient only has vaginal dryness → low doses of estrogen placed directly into the vagina.
  - These low doses generally do not raise blood estrogen levels above postmenopause levels and do not treat hot flashes.
  - No need to take a progestogen when using only low doses of estrogen in the vagina.

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HORMONE THERAPY

- Chronic unopposed endometrial exposure to estrogen increases the risk for endometrial hyperplasia or cancer.
- Progestogen prevents endometrial overgrowth and the increased risk of endometrial cancer during ET use.
- Progestins commonly used include MPA, norethindrone acetate, and native progesterone.
- Women with an intact uterus using systemic ET should receive adequate progestogen unless they are taking CEE combined with bazedoxifene.10

Comprehensive Gynecology 7th edition, 2017 (Lobo RA, Gershenson D Lentz GM, Valea FA *editors);* chapter 14, Menopause and Care of the Mature Woman ; pp 258-291

INDICATIONS FOR HORMONE REPLACEMENT THERAPY (HRT)
(FDA-APPROVED INDICATIONS)

1. Vasomotor Symptoms (VMS)
   - HRT as first line therapy
2. Prevention of bone loss
   - Decreases risk of fracture
3. Premature ovarian insufficiency (POI) or those had early surgical menopause
4. Genitourinary symptoms of menopause (GSM)
   - HRT in the form of locally placed-estrogen

HRT OPTIONS

I. VMS with intact uterus
   1. CEE (*Premarin*®)
   2. Estradiol Valerate (*Progynova*®)
   - Both once daily continuously **AND ADD** MPA (Provera®) 10 mg/tab once daily on day 10-12 days
   3. Estradiol hemihydrate (1mg/tab) + Drosperinone (2) mg (Angeliq®) – once daily continuously

II. VMS without uterus
   1. CEE (*Premarin*®)
   2. Estradiol Valerate (*Progynova*®)
   - Both once daily

HRT OPTIONS

Genito-urinary syptoms of Menopause (GSM)

1. Estradiol vaginal tablet (Vagifem®) - 10 mg/tab

- 1 tablet per vagina 1x/day for 2 weeks then 1 tablet 2x/week

2. Estriol cream (Ovestin®) - 0.5 mg / day

- 0.5 mg once a day for 21 days then 7 days off

FOR GSM

- **Vaginal Estrogen**
  - Cream (CEE 0.5gm 2-3x/week; Estriol 1mg 2-3x/week
  - Tablet (Estradiol) – 10ug, 2x/week
  - Tablet (Estriol + Lactobacillus) – 30ug
  - Ring (Estradiol)
- **SERM** – Ospemifene 60mg PO

Menopausal hormone therapy preparations.

Preparation	Starting dose	Comments
Estrogen		
Oral		
17 β-Estradiol	0.5 mg/d	1 tablet/d
Ethinyl estradiol	2.5 mcg/d	1 tablet/d
Conjugated estrogen	0.3 mg/d–0.45 mg/d	1 tablet/d
Transdermal		
17 β-estradiol patch	0.014mg/d–0.0375 mg/d	1 patch twice/wk
17 β-estradiol gel	0.25 mg/d or 0.75 mg/d	0.25 g gel daily 1.25 g gel daily
17 β-estradiol spray	1.53 mg/d	1spray daily
17 β-estradiol emulsion	8.7 mg/d	2 foil-laminated pouches/d
Vaginal		
17 β-estradiol vaginal cream	0.2 mg (2 g of cream)/d	2 g–4 g daily for 2 wk, then taper to maintenance dose of 1 g 1 to 3 times/wk
Conjugated estrogen vaginal cream	0.3125 mg (0.5 g of cream)/d	0.5 g daily for 21 d on and 7 d off or twice/wk
17 β-estradiol vaginal tablet	10 mcg/d	1 tablet/d for 2 wk, then 1 tablet twice/wk
17 β-estradiol vaginal ring	2 mg/ring (7.5 mcg/d) or 12.4 mg/ring (50 mcg/d)	1 ring/90 d
Progestogen		
Oral		
Medroxyprgosesterone acetate	1.5 mg/d–2.5 mg/d	Daily in combination preparations or 14 d/mo; 1.5 mg with 0.3 mg of conjugated estrogen combination
Norethindrone acetate	0.1 mg/d	Daily in combination preparations or 14 d/mo
Drospirenone	0.25 mg/d	Daily
Micronized progesterone	100 mg/d–200 mg/d	100 mg/d continuously or 200 mg/d for 12 d/mo
Transdermal		
Norethindrone acetate	0.14 mg/d	1 patch twice/wk
Levonorgestril	0.015 mg/d	1 patch/wk

Al-Safi. Menopausal symptoms and hormone therapy. Fertil Steril 2014.

Menopausal hormone therapy preparations.

Preparation	Starting dose	Comments
Estrogen		
Oral		
17 β-Estradiol	0.5 mg/d	1 tablet/d
Ethinyl estradiol	2.5 mcg/d	1 tablet/d
Conjugated estrogen	0.3 mg/d–0.45 mg/d	1 tablet/d → Premarin®
Transdermal		
17 β-estradiol patch	0.014mg/d–0.0375 mg/d	1 patch twice/wk
17 β-estradiol gel	0.25 mg/d or 0.75 mg/d	0.25 g gel daily → Oestrodose® 1.25 g gel daily
17 β-estradiol spray	1.53 mg/d	1spray daily
17 β-estradiol emulsion	8.7 mg/d	2 foil-laminated pouches/d
Vaginal		
17 β-estradiol vaginal cream	0.2 mg (2 g of cream)/d	2 g–4 g daily for 2 wk, then taper to maintenance dose of 1 g 1 to 3 times/wk
Conjugated estrogen vaginal cream	0.3125 mg (0.5 g of cream)/d	0.5 g daily for 21 d on and 7 d off or twice/wk
17 β-estradiol vaginal tablet	10 mcg/d → Vagifem®	1 tablet/d for 2 wk, then 1 tablet twice/wk
17 β-estradiol vaginal ring	2 mg/ring (7.5 mcg/d) or 12.4 mg/ring (50 mcg/d)	1 ring/90 d
Progestogen		
Oral		
Medroxyprgosesterone acetate	1.5 mg/d–2.5 mg/d → Provera®	Daily in combination preparations or 14 d/mo; 1.5 mg with 0.3 mg of conjugated estrogen combination
Norethindrone acetate	0.1 mg/d	Daily in combination preparations or 14 d/mo
Drospirenone	0.25 mg/d	Daily
Micronized progesterone	100 mg/d–200 mg/d → Utrogestan®	100 mg/d continuously or 200 mg/d for 12 d/mo
Transdermal		
Norethindrone acetate	0.14 mg/d	1 patch twice/wk
Levonorgestril	0.015 mg/d	1 patch/wk

Al-Safi. Menopausal symptoms and hormone therapy. Fertil Steril 2014.

ESTROGEN REGIMEN

- **Standard dose**:
  - CEE 0.625mg
  - Estradiol Valerate 2mg
  - Transdermal Estrogen 0.05mg
  - 5ug EE daily
- **Low dose**:
  - CEE 0.3mg
  - Estradiol Valerate 1mg per day

- **Ultra Low dose**:
  - 0.5mg 17beta Estradiol and 2.5mg Dydrogesterone PO
  - Transdermal Estrogen 0.014mg/day
  - Oral Estradiol 0.25mg/day

1. RCT – placebo controlled *(Stevenson; Maturitas 2010)* 0.5mg E + 2.5mg Dydrogesterone vs 1mg E with 5 mg Dydrogesterone vs placebo 313 healthy PMW, 54 years old average, 52 weeks: Significant reduction in VMS
2. RCT: CHOICE *(Panay. Climacteric 2007)* 0.5 mg E+ 0.1mg or 0.25mg NETA577 PMW, 55.5 years old ave, 24 weeks: well tolerated, good bleeding control, no VTE

OTHER MHT PREPARATIONS

- **Combination E /P:**
  - Oral
  - Transdermal
  - CEE + MPA
  - Estradiol + Norethindrone / Drospirenone
- **Tibolone**
- **TSEC** – tissue selective estrogen complex
  - CEE + Bazedoxifene
  - Ospemifene – for GSM
- **Testosterone?**
- **Vaginal Estrogen**
  - Cream (CEE / Estriol)
  - Tablet (Estradiol)
  - Ring (Estradiol)

LOCALLY AVAILABLE HRT

1. CEE *(Premarin®)* - 0.3, 0.625 mg/tab
2. Estradiol Valerate *(Progynova®)* – 2mg/tab
3. Medroxyprogesterone acetate *(Provera ®)* – 10 mg/tab
4. Estradiol hemihydrate (1mg/tab) + Drosperinone (2) mg *(Angeliq®)*
5. Estradiol vaginal tablet (Vagifem®) - 10 mg/tab
6. Estriol cream (Ovestin®) - 0.5 mg / day

SIDE EFFECTS OF HRT

- Breast tenderness
- Vaginal bleeding
- Nausea and vomiting
- Headache
- Weight changes
- Rash and pruritus
- Cholecystitis

Zain A, Al-Safi, Santoro N. Menopausal hormone therapy and menopausal symptoms. Fertility and Sterility Vol 101 No. 4

CONTRAINDICATIONS & PRECAUTIONS TO MHT

CIRCUMSTANCES WHERE MHT SHOULD NOT BE USED

- Unexplained vaginal bleeding
- Stroke, TIA, MI, PE, VTE
- Breast or endometrial cancer
- Active liver disease

EXERCISE CAUTION IN WOMEN WITH

- Diabetes
- Hypertriglyceridemia
- Active gallbladder disease
- Increased risk of breast cancer or CVD
- Migraine with aura

North American Menopause Society. The 2017hormone therapy position statement of the North America Menopause Society. Menopause (New York, NY). 2017 Mar;19(3):25

CHOOSING THE APPROPRIATE PREPARATION

Presence of other medical conditions / risks:

- ✓ Increased triglycerides
- ✓ Diabetes mellitus
- ✓ Risks for breast CA
- ✓ Increased mammographic density
- ✓ Family history of VTE

Strategies:

- ✓ Avoid first pass effect: go transdermal E
- ✓ Choose progestin with safer metabolic profile
- ✓ Ultra low dose preparations

ENDOMETRIAL PROTECTION

Women with uterus

- Systemic E + Progestogen
- CEE with Bazedoxifene

Low dose Vaginal ET

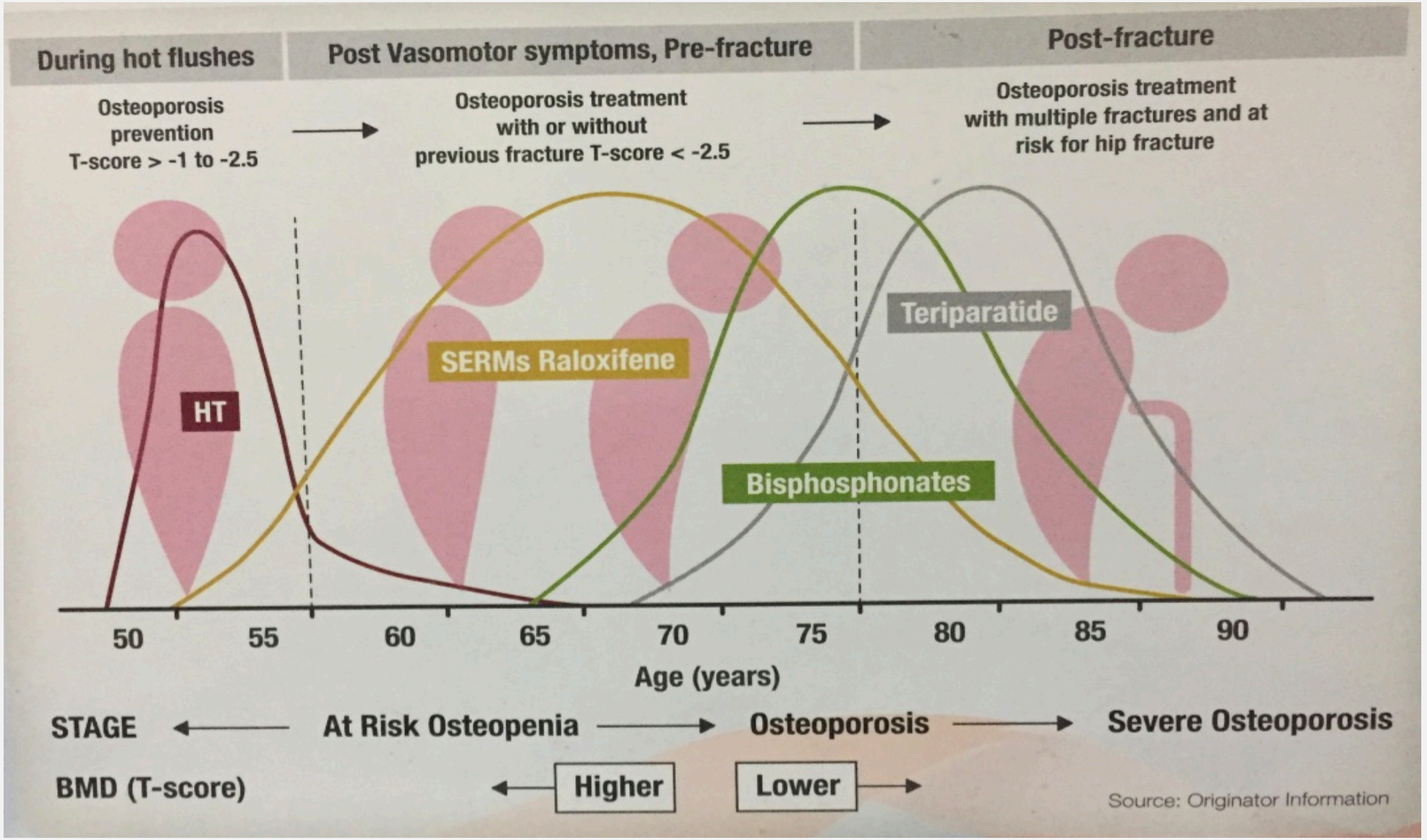
- Progesterone not recommended
- Endometrial evaluation needed if vaginal bleeding occurs

North American Menopause Society. The 2017 hormone therapy position statement of the North American Menopause Society. Menopause (New York, NY). 2017 Mar;19(3):257.

OSTEOPOROSIS MANAGEMENT

- In addition to lifestyle changes, osteoporosis drug therapy is recommended for:
  - Postmenopausal women who have had vertebral or hip fracture
  - Postmenopausal women with T-scores ≤−2.5 at the lumbar spine, femoral neck, or total hip
  - Postmenopausal women with T-scores from −1.0 to −2.5 and 10-year FRAX risk of major osteoporotic fracture of at least 20% or of hip fracture of at least 3%

Treatment for osteoporosis



OSTEOPOROSIS: TREATMENT

- Estrogen has been shown to reduce the risk of osteoporosis as well as to reduce osteoporotic fractures.
- Selective estrogen receptor modulators (SERMs) such as raloxifene, droloxifene, and tamoxifen have all been shown to decrease bone resorption.
- Tibolone has also been shown to be an effective treatment for osteoporosis.
  - Tibolone has SERM-like properties, but it is not specifically a SERM because it has mixed estrogenic, antiestrogenic, androgenic, and progestogenic properties.

Comprehensive Gynecology 7th edition, 2017 (Lobo RA, Gershenson DM, Lentz GM, Valea FA *editors);* chapter 14, Menopause and Care of the Mature Woman ; pp 258-291

OSTEOPOROSIS: TREATMENT

- Bisphosphonates (etidronate, alendronate, risedronate, ibandronate, and zoledronic acid).
  - May cause osteonecrosis of the jaw, fractures of long bones such as the femur, with long term use
- Calcitonin (50 IU subcutaneous injections daily, or 200 IU intranasally) has been shown to inhibit bone resorption.

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OSTEOPOROSIS: TREATMENT

- Fluoride increases bone density. Lowdose (50 mcg daily) of slow-release sodium fluoride does not seem to cause adverse effects (gastritis) and has efficacy in preventing vertebral fractures.
- Parathyroid hormone (PTH) is an effective agent to increase bone mass in women with significant osteoporosis (Teriparatide 20 mcg needs to be injected subcutaneously on a daily basis for no longer than 18 months.)

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OSTEOPOROSIS: TREATMENT

- Adjunctive measures for prevention of osteoporosis include:
  - Calcium: 1500 mg daily
  - Vitamin D: 400 to 800 IU
  - Exercise beneficial for building muscle and bone mass and for reducing falls.
- Calcium with vitamin D treatment has been shown to increase bone only in older individuals. This will not prevent bone loss in younger women at the onset of menopause.
- These modalities alone are not thought to be effective for the treatment of osteoporosis.

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ALTERNATIVES TO HORMONE THERAPY

- Nonhormonal prescription drugs (off-label use):
  - Antidepressant
    - SSRIs: fluoxetine, paroxetine, escitalopram
    - SNRIs: venlafaxine and desvenlafaxine
  - Hypnotic
    - Eszopiclone
  - Anticonvulsant
    - Gabapentin
  - Antihypertensive
    - Clonidine
  - Neuropathic pain drug
    - Pregabalin

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ALTERNATIVES TO HORMONE THERAPY

- Complementary & Alternative Medicine
  - Soy isoflavones
  - Traditional Chinese medicine
  - Herbs
    - Black cohosh
    - Cranberry
    - St. John's wort
    - Valerian
    - Vitex
- Over-the-counter hormones (dietary supplements)
  - Topical progesterone
  - Melatonin

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Thank you!

youtube channel: Ina Irabon

www.wordpress.com: Doc Ina OB Gyne