THE PERIMENOPAUSAL & MENOPAUSAL PATIENT - UPDATES

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We will be using interactive media: Participants can join at slido.com with #968557

Financial Disclosures

- I have nothing to disclose

Objectives

- At the end of this presentation, the attendee will be able to:
  - Define perimenopause, menopause, and postmenopause
  - Explain the physiologic changes that occur during perimenopause, menopause, and postmenopause
  - Explain the signs and symptoms of perimenopause, menopause, and postmenopause
  - Name evidence based treatment option for the signs and symptoms of perimenopause, menopause, and postmenopause
  - Understand other health risks that could present themselves during menopause and postmenopause.

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How long before menopause does perimenopause usually start?

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Definitions

- Perimenopause
  - Also referred to as menopausal transition/menopause transition
  - Used to be called The climacteric
  - the time of physiologic change around the decline in ovarian function
  - After the reproductive years but before menopause
- Menopause
  - Permanent cessation of menses without any other obvious pathological or physiological cause
  - Retrospectively as 12 months of amenorrhea
- Postmenopause
  - span of life after menopause

Harlow SD, Gass M, Hall JE, et al. STRAW + 10 Collaborative Group. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. J Clin Endocrinol Metab 2012;97:1159–68
Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. JAMA 2013;310:1353–68

The Stages of Reproductive Aging Workshop +10 staging system for reproductive aging in females

Menarche — FMP (0)

Stage	−5	−4	−3b	−3a	−2	−1	+1a	+1b	+1c	+2
Terminology	REPRODUCTIVE				MENOPAUSAL TRANSITION		POSTMENOPAUSE			
	Early	Peak	Late		Early	Late	Early			Late
					Perimenopause					
Duration	Variable				Variable	1-3 years	2 years (1+1)		3-6 years	Remaining lifespan
PRINCIPAL CRITERIA										
Menstrual cycle	Variable to regular	Regular	Regular	Subtle changes in flow/ strength	Variable length: Persistent ≥7-day difference in length of consecutive cycles	Interval of amenorrhea of ≥60 days				
SUPPORTIVE CRITERIA										
Endocrine FSH AMH Inhibin B			 Low Low	 Variable* Low Low	 ↑ Variable* Low Low	 ↑ >25 international units/L¶ Low Low	 ↑ Variable Low Low		 Stabilizes Very low Very low	
Antral follicle count			Low	Low	Low	**Low**	Very low		Very low	
DESCRIPTIVE CHARACTERISTICS										
Symptoms						Vasomotor symptoms likely	Vasomotor symptoms most likely			Increasing symptoms of urogenital atrophy

FMP: final menstrual period; FSH: follicle-stimulating hormone; AMH: anti-müllerian hormone; Arrow: elevated.

* Blood draw on cycle days 2 to 5.

¶ Approximate expected level based on assays using current international pituitary standard.

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True or False?

Elevated FSH is the only way to diagnose Menopause.

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Physiology

- Perimenopuase
  - the time of waning ovarian function associated with menstrual irregularity and vasomotor symptoms
  - Diagnose based on symptoms NOT labs
    - measurements of serum FSH during the late menopausal transition are not routinely recommended, because of their variability
- Menopause
  - menstrual changes that reflect ovarian follicular depletion and subsequent changes in ovarian hormone production (low estrogen and high FSH)
- postmenopause

Casper MD, Robert. Clinical manifestations and diagnosis of menopause. In: *UpToDate*, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on July 1, 2021.)

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Which hormones have the most significant change during menopause?

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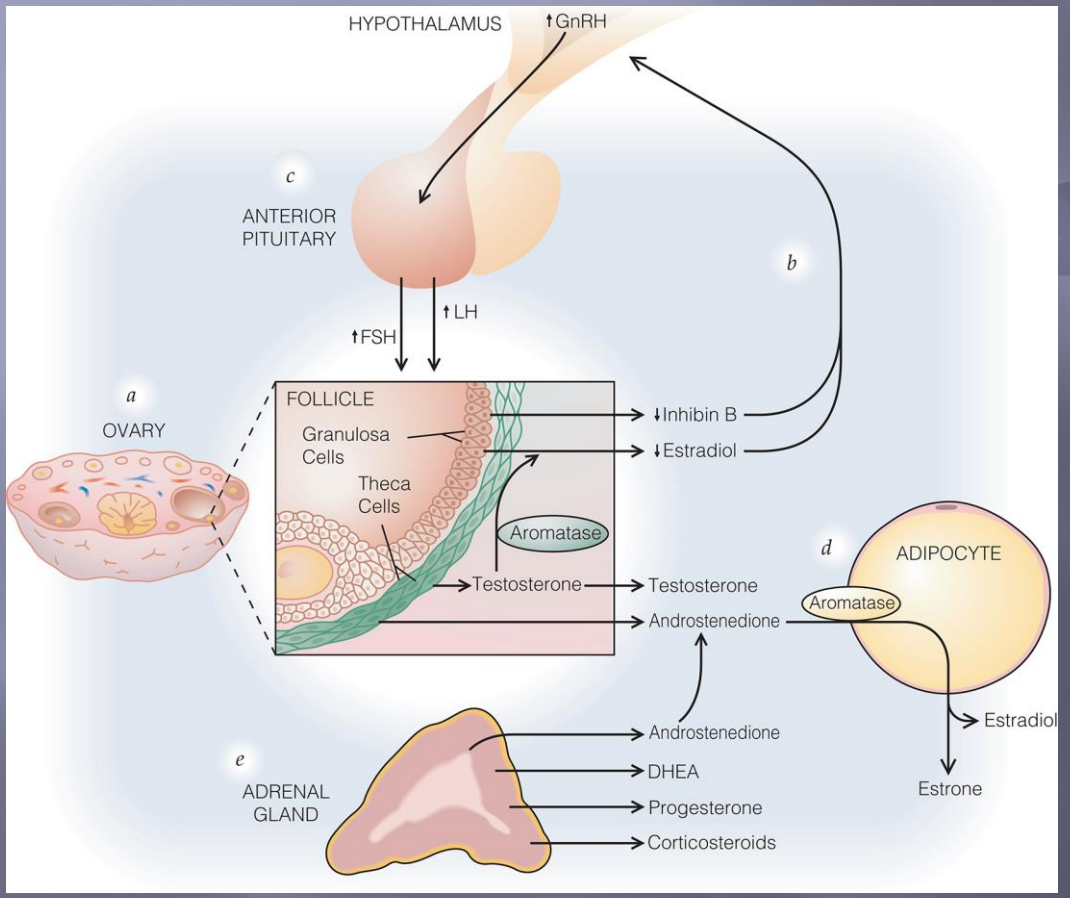
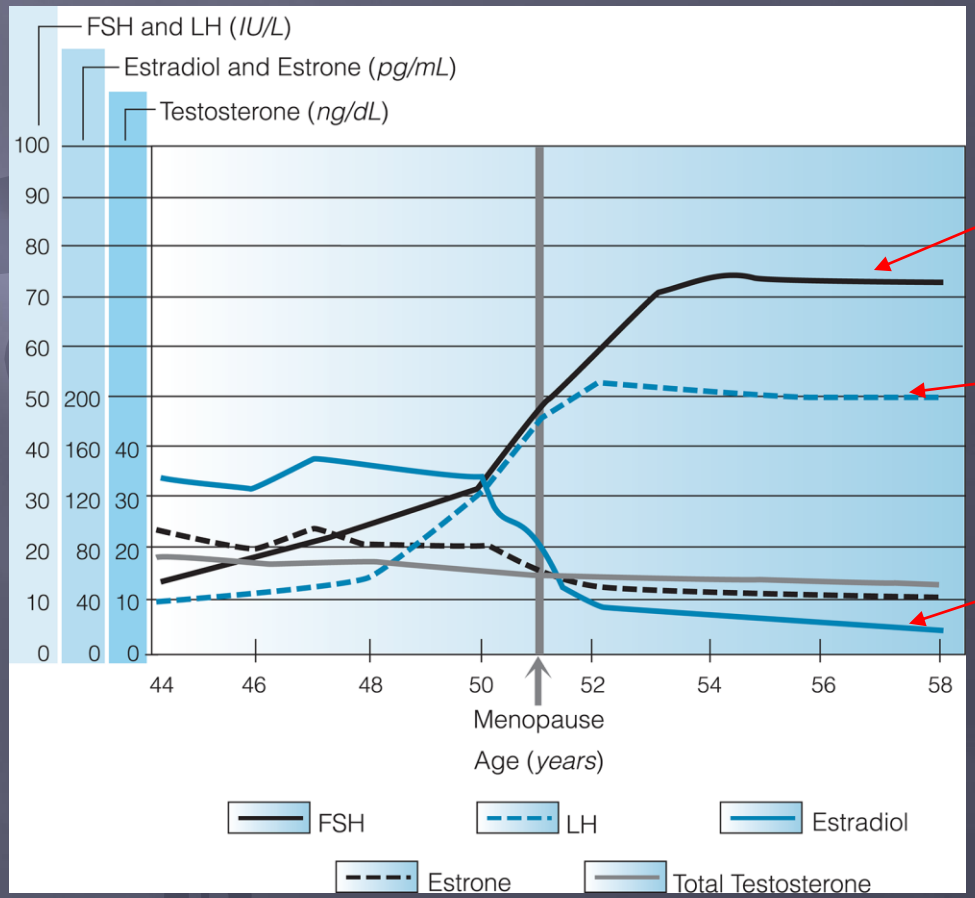
Hormonal Changes





10-20 fold
Increase in FSH

3 to 5 fold
Increase in LH

Estradiol levels
Fall below 50 pg/mL

Hormonal changes Summarized

- overall changes in reproductive steroid hormones after menopause
  - shift from physiologic importance of circulating hormone concentrations to intracrine concentrations and function
  - Negligible estradiol production by the ovary
  - shift from the ovary to the adrenal gland as the primary source of steroid hormone precursors
  - Emergence of estrone as the dominant circulating estrogen
  - Continued testosterone production by the ovarian stroma
  - An overall increase in the ratio of androgens to estrogens
  - A decrease in circulating progesterone levels resulting from anovulation; production from cholesterol continues at low levels in local tissues.

Signs & Symptoms of Perimenopause

- Anovulation
  - Enometrial thickening
- Cycles irregular and heavier
- Intermenstrual bleeding
- Genitourinary atrophy (mild/asymptomatic)
- Breast tenderness
- Bone resorption exceeds formation (loss of bone mass)
- Theory that estrogen given before atherosclerosis occurs may decrease heart disease
- Decrease libido

Signs & Symptoms of Perimenopause

- Adipose deposition increases centrally and decreases peripherally
- Changes in coagulation factors begins
- Integument changes begin
- Joint, tendon, and muscle changes begin
- Uterine fibroids typically grow

Signs & Symptoms of Perimenopause

- Vasomotor symptoms (hot flashes and night sweats)
  - 80% of white women experience hot flashes and/or night sweats
  - a strong sensation of warmth accompanied by flushing, a prickling sensation of the skin, and perspiration that seems to move from the trunk toward the head before it dissipates
  - Hormonal fluctuations have a dramatic impact on the central nervous system
    - thermoregulatory dysfunction
    - initiated by the hypothalamus in response to hormonal fluctuations
    - “thermoregulatory null zone” is decreased
    - To be susceptible to hot flashes, a woman needs to have been exposed to reproductive levels of estrogen and then experience estrogen withdrawal

Rossmanith WG, Ruebberdt W. What causes hot flushes? The neuroendocrine origin of vasomotor symptoms in the menopause. Gynecol Endocrinol 2009;25:303–14.
Dennerstein L, Dudley EC, Hopper JL, et al. A prospective population-based study of menopausal symptoms. Obstet Gynecol 2000;96:351–8

Signs & Symptoms of Perimenopause

- Depression
  - Fluctuations in FSH, LH, and estradiol
- Changes in sleep
  - CNS decreases in estrogen, and allopregnanolone
- Forgetfullness & difficulty concentrating
  - have been associated with changes in reproductive hormone levels during the menopausal transition but this finding has not been consistently demonstrated
- Dementia and parkinsonism
  - may also be influenced by chronic hypoestrogenism

Freeman EW, Sammel MD, Lin H, Nelson DB. Associations of hormones and menopausal status with depressed mood in women with no history of depression. Arch Gen Psychiatry 2006;63:375–82
Pluchino N, Luisi M, Lenzi E, et al. Progesterone and progestins: effects on brain, allopregnanolone and beta-endorphin. J Steroid Biochem Mol Biol 2006;102:205–13
Woods NF, Smith-Dijulio K, Percival DB, et al. Symptoms during the menopausal transition and early postmenopause and their relation to endocrine levels over time: observations from the Seattle Midlife Women's Health Study. J Womens Health (Larchmt) 2007;16:667–77
Rocca WA, Grossardt BR, Maraganore DM. The long-term effects of oophorectomy on cognitive and motor aging are age dependent. Neu-rodegener Dis 2008;5:257–60

Signs & Symptoms of Postmenopause

- Amenorrhea
- Vagina, vulva, and base of bladder become thin and friable
- GU atrophy is progressive and can become severe
  - Dryness, pruritis, dyspareunia, postcoital spotting, dysuria, frequency, incontinence
  - Referred to as “genitourinary syndrome of menopause”
- Majority of breast tissue replaced by adipose
  - Mammographic density declines
- Bone mass loss 3-5% per year in first few years and then 1-2%
  - Spine, hip, bone, distal radius earlier (trabecular bone) and then cortical bone
- Balance
  - Impaired balance may be a central effect of reduced estrogen

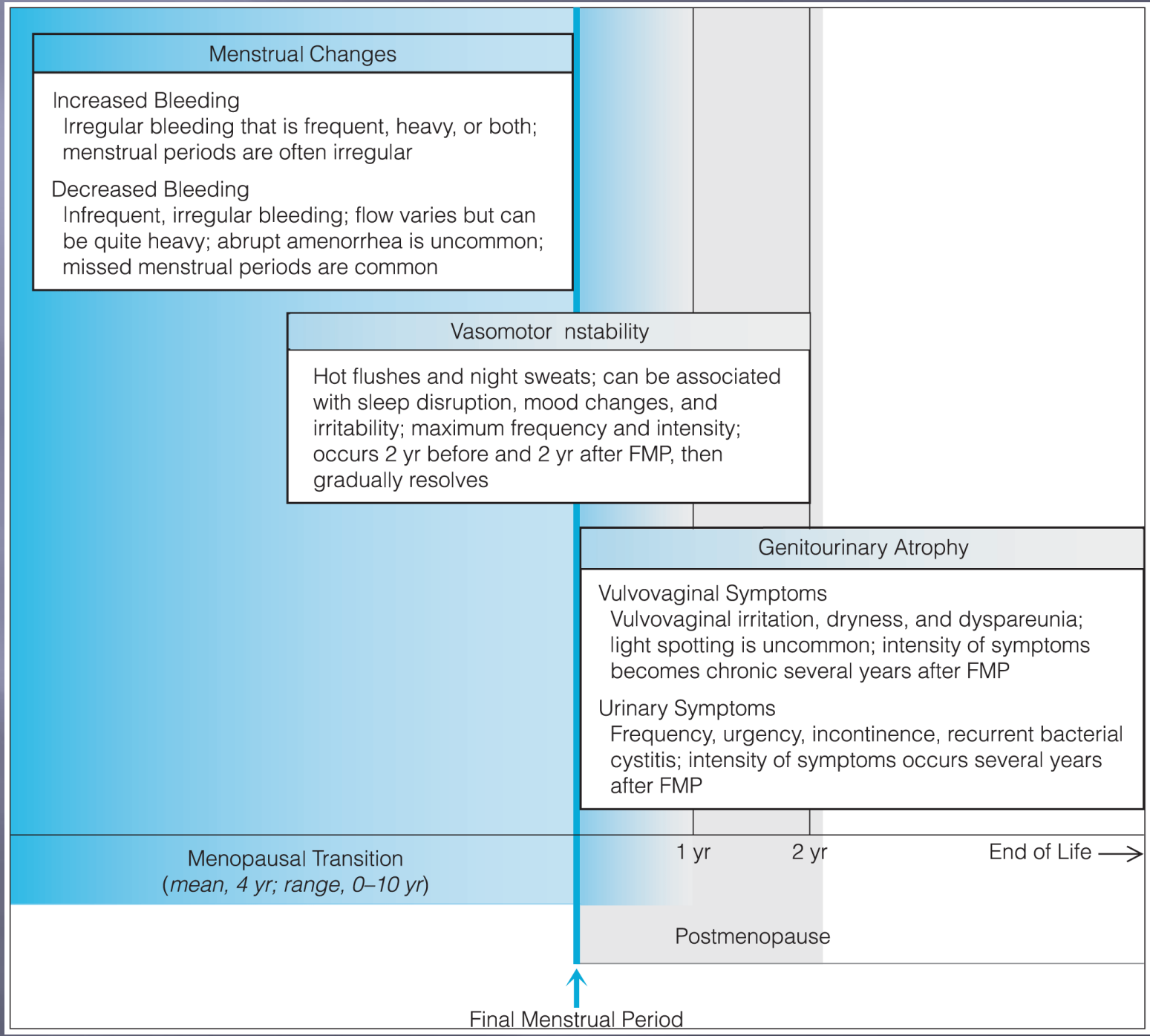
Dalal PK, Agarwal M. Postmenopausal syndrome. Indian J Psychiatry. 2015;57(Suppl 2):S222-S232. doi:10.4103/0019-5545.161483

Signs & Symptoms of Postmenopause

- LDL and apolipoprotein B increase
  - Risk of CV progressively worsens with age
- CNS symptoms begin to improve
  - Vasomotor, mood, sleep, cognition, libido
- Increase in visceral and central adiposity
  - Average 1 lb per year over 5 years
  - Increase insulin resistance
  - In nonobese women ghrelin appears in increase
- Complex changes in coag factors increases coagulation

Signs & Symptoms of Postmenopause

- Dermal collagen production declines
  - Wrinkles and dryness
  - Slower wound healing
- Muscle aches and pain, Osteoarthritis, muscle mass decreases
- Diminished lung function and more respiratory symptoms
  - FEV1 and FVC are lower
- Uterine fibroids typically regress
- Decreased libido
  - Decreased testosterone and estrogen levels play a role


Menstrual Changes
Increased Bleeding
Irregular bleeding that is frequent, heavy, or both; menstrual periods are often irregular
Decreased Bleeding
Infrequent, irregular bleeding; flow varies but can be quite heavy; abrupt amenorrhea is uncommon; missed menstrual periods are common
Vasomotor nstability
Hot flushes and night sweats; can be associated with sleep disruption, mood changes, and irritability; maximum frequency and intensity; occurs 2 yr before and 2 yr after FMP, then gradually resolves
Genitourinary Atrophy
Vulvovaginal Symptoms
Vulvovaginal irritation, dryness, and dyspareunia; light spotting is uncommon; intensity of symptoms becomes chronic several years after FMP
Urinary Symptoms
Frequency, urgency, incontinence, recurrent bacterial cystitis; intensity of symptoms occurs several years after FMP
Menopausal Transition
(mean, 4 yr; range, 0–10 yr)
1 yr
2 yr
End of Life
Postmenopause
Final Menstrual Period

Differential Diagnosis

- Don’t forget to rule out common diagnoses and do not always blame perimenopause or menopause!
  - Always rule out pregnancy!!!!!!
  - Ie heavy frequent bleeding with cycle <21 days and intermenstrual bleeding deserves endometrial biopsy
  - r/o hypothyroidism and other conditions for amenorrhea if weight gain, hair loss, lethargy are present
  - r/o Grave’s disease and carcinoid for hot flashes if anxiety, diarrhea, abd cramping, etc are present
  - r/o lymphoma for Night sweats if weight loss, fever, masses etc are present
  - Etc…..

Evidence Base Treatment

- Treatment strategies
  1. Identify stage of reproductive phase
  2. Identify symptoms for which treatment is desired
  3. Identify medical conditions that might influence management options
  4. Use shared decision making and informed consent
  5. Use lowest risk strategies that adequately address symptom(s)

Nonhormonal Therapy

- Vasomotor Symptoms
  - more effective than and appear similarly effective as at least low-dose estrogen therapy
    - SNRIs
      - venlafaxine and desvenlafaxine
    - SSRIs
      - citalopram, escitalopram, paroxetine
    - gabapentin
  - Less evidence to support effectiveness
    - clonidine
    - Vitamin E

Rapkin AJ. Vasomotor symptoms in menopause: physiologic condition and central nervous system approaches to treatment. Am J Obstet Gynecol 2007;196:97–106.
Butt DA, Lock M, Lewis JE, et al. Gabapentin for the treatment of menopausal hot flashes: a randomized controlled trial. Menopause 2008;15:310–8.
Joffe H, Guthrie KA, LaCroix AZ, et al. Low-dose estradiol and the serotonin-norepinephrine reuptake inhibitor venlafaxine for vasomotor symptoms: a randomized clinical trial. JAMA Intern Med 2014;174:1058–66.
Reddy SY, Warner H, Guttuso T Jr, et al. Gabapentin, estrogen, and placebo for treating hot flushes: a randomized controlled trial. Obstet Gynecol 2006;108:41–8.

Nonhormonal Therapy

- Vasomotor Symptoms
  - No significant improvement over placebo
    - Phytoestrogens (including dietary soy)
    - Black cohosh
      - Associated with cases of hepatic failure
    - Red clover extract
    - Dong quadi, Evening primrose oil, Siberian ginseng
    - Omega-3 fatty acids
  - Not studied in clinical trials
    - Valerian, Motherwort, chasteberry

Barton DL, Loprinzi CL, Quella SK, et al. Prospective evaluation of vitamin E for hot flashes in breast cancer survivors. J Clin Oncol 1998;16:495–500.
Newton KM, Reed S, Uchiyama S, et al. A cross-sectional study of equol producer status and self-reported vasomotor symptoms. Meno-pause 2015;22:489–95
Newton KM, Reed S, LaCroix AZ, et al. Treatment of vasomotor symptoms of menopause with black cohosh, multibotanicals, soy, hor-mone therapy, or placebo. Ann Intern Med 2006;145:1–11
Joy D, Joy J, Duane P. Black cohosh: a cause of abnormal postmenopausal liver function tests. Climacteric 2008;11:84–8
Pinn G. Herbs used in obstetrics and gynaecology. Aust Fam Physician 2001;30:351–6.
Cohen LS, Joffe H, Guthrie KA, et al. Efficacy of omega-3 for vasomotor symptoms treatment: a randomized controlled trial. Menopause 2014;21:347–54

Nonhormonal Therapy

- Vasomotor Symptoms
  - Behavioral modification may diminish the severity of hot flashes.
  - Paced respiration, mindfulness-based stress reduction, and clinical hypnosis have been evaluated, but the evidence is too weak to recommend unequivocally
  - Exercise and yoga have not been shown to decrease the frequency or severity of vasomotor symptoms
  - Acupuncture is of unproven benefit
  - Stellate ganglion block has been suggested to be of benefit in small studies

Mann E, Smith MJ, Hellier J, et al. Cognitive behavioural treatment for women who have menopausal symptoms after breast cancer treatment (MENOS 1): a randomised trial. Lancet Oncol 2012;13:309–18.
Carpenter JS, Burns DS, Wu J, et al. Paced respiration for vasomotor and other menopausal symptoms: a randomized, controlled trial. J Gen Intern Med 2013;28:193–200.
Carmody JF, Crawford S, Salmoirago-Blotcher E, et al. Mindfulness training for coping with hot flashes: results of a randomized trial. Menopause 2011;18:611–20
Elkins GR, Fisher WI, Johnson AK, et al. Clinical hypnosis in the treatment of postmenopausal hot flashes: a randomized controlled trial. Menopause 2013;20:291–8.
Sternfeld B, Guthrie KA, Ensrud KE, et al. Efficacy of exercise for menopausal symptoms: a randomized controlled trial. Menopause 2014;21:330–8
Newton KM, Reed SD, Guthrie KA, et al. Efficacy of yoga for vasomotor symptoms: a randomized controlled trial. Menopause 2014;21:339–46
Dodin S, Blanchet C, Marc I, et al. Acupuncture for menopausal hot flushes. Cochrane Database Syst Rev 2013;7:CD007410
Walega DR, Rubin LH, Banuvar S, et al. Effects of stellate ganglion block on vasomotor symptoms: findings from a randomized con-trolled clinical trial in postmenopausal women. Menopause 2014;21:801–14

Nonhormonal Therapy

- Mood
  - Antidepressants
- Sleep
  - SSRIs, gabapentin, short-term zolpidem, low-dose trazodone, CBT
- Hyposexual desire disorder
  - flibanserin 100 mg
- Quality of life
  - Improved with taking SSRIs for vasomotor symptoms and women practicing yoga

Caan B, LaCroix AZ, Joffe H, et al. Effects of estrogen and venlafaxine on menopause-related quality of life in healthy postmenopausal women with hot flashes: a placebo-controlled randomized trial. Menopause 2015;22:607–15.
LaCroix AZ, Freeman EW, Larson J, et al. Effects of escitalopram on menopause-specific quality of life and pain in healthy menopausal women with hot flashes: a randomized controlled trial. Maturitas 2012;73:361–8
Reed SD, Guthrie KA, Newton KM, et al. Menopausal quality of life: RCT of yoga, exercise, and omega-3 supplements. Am J Obstet Gy-necol 2014;210:244 e1–11.

Hormone Therapy

- Initiating HT
  - Effective
  - Risks are age, dose, and formulation dependent and vary by ET and estrogen + progesterone therapy (EPT)
  - Use lowest dose for shortest duration
  - Use tissue targeted therapies whenever possible

Cutson, T., & Meuleman, E. (2000). Managing MenopausePerimenopausal contraception: A practice-based approach. American Family Physician, 61(5), 1391–1400. Retrieved from https://www.aafp.org/afp/2000/0301/p1391.html

Hill, A., & Hill, S. (2016). Hormone Therapy and Other Treatments for Symptoms of Menopause. *American Family Physician*, *94*(11), 884–889. Retrieved from https://www.aafp.org/afp/2016/1201/p884.html

Hormone Therapy

- General principles
  - Do not initiate HT for disease prevention (primary or secondary)
  - Do not initiate over age 60
  - Estrogen alone, progesterone alone, and estrogen plus progesterone are all effective in diminishing symptoms
  - Among symptomatic women younger than 60 years without a uterus, the benefits of estrogen alone outweigh the risks in the majority of women
  - Women with a uterus require progesterone, but the risks with EPT are greater than with ET
  - Use the lowest dose possible to achieve an effect, thereby decreasing risk

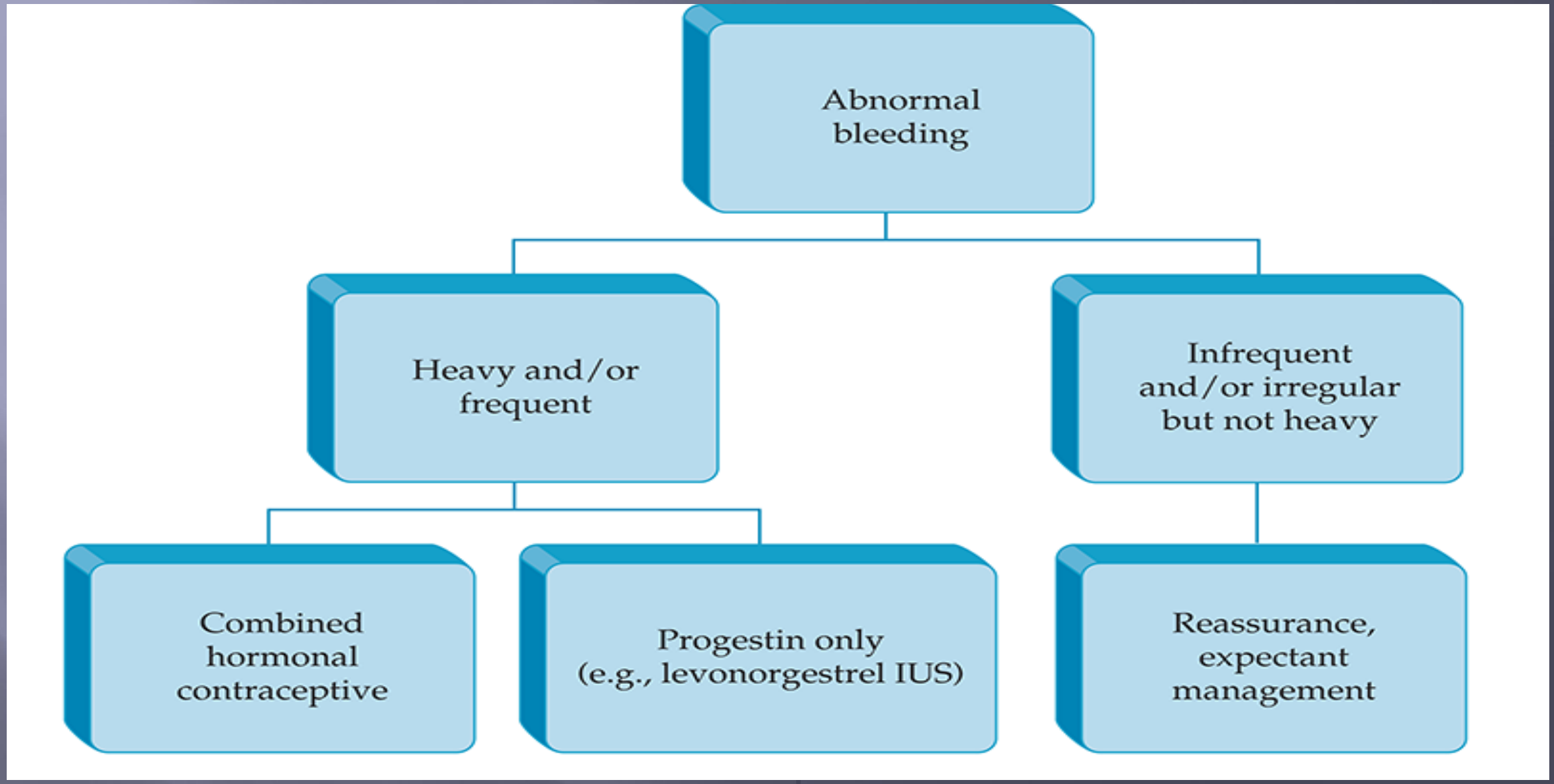
Hormone Therapy

- Reevaluate **at least** annually
  - instruct to refrain from taking HT 1 to 2 weeks before the annual assessment to allow the physician and the patient to evaluate the current severity of symptoms
- Up to 10% of women experience lifelong bothersome symptoms
- Women who choose to stop HT may prefer a slow taper, ranging from 3 to 6 months, for successful cessation
  - data do not support tapering over abrupt cessation in most circumstances
- Classified as standard, low and ultralow dose
- Systemic administration of estrogen can be achieved orally, transdermally (in the form of patch, gel, cream, or spray), or transvaginally (vaginal ring)

Aslan E, Bagis T, Kilicdag EB, et al. How best is to discontinue postmenopausal hormone therapy: immediate or tapered? Maturitas 2007;56:78–83

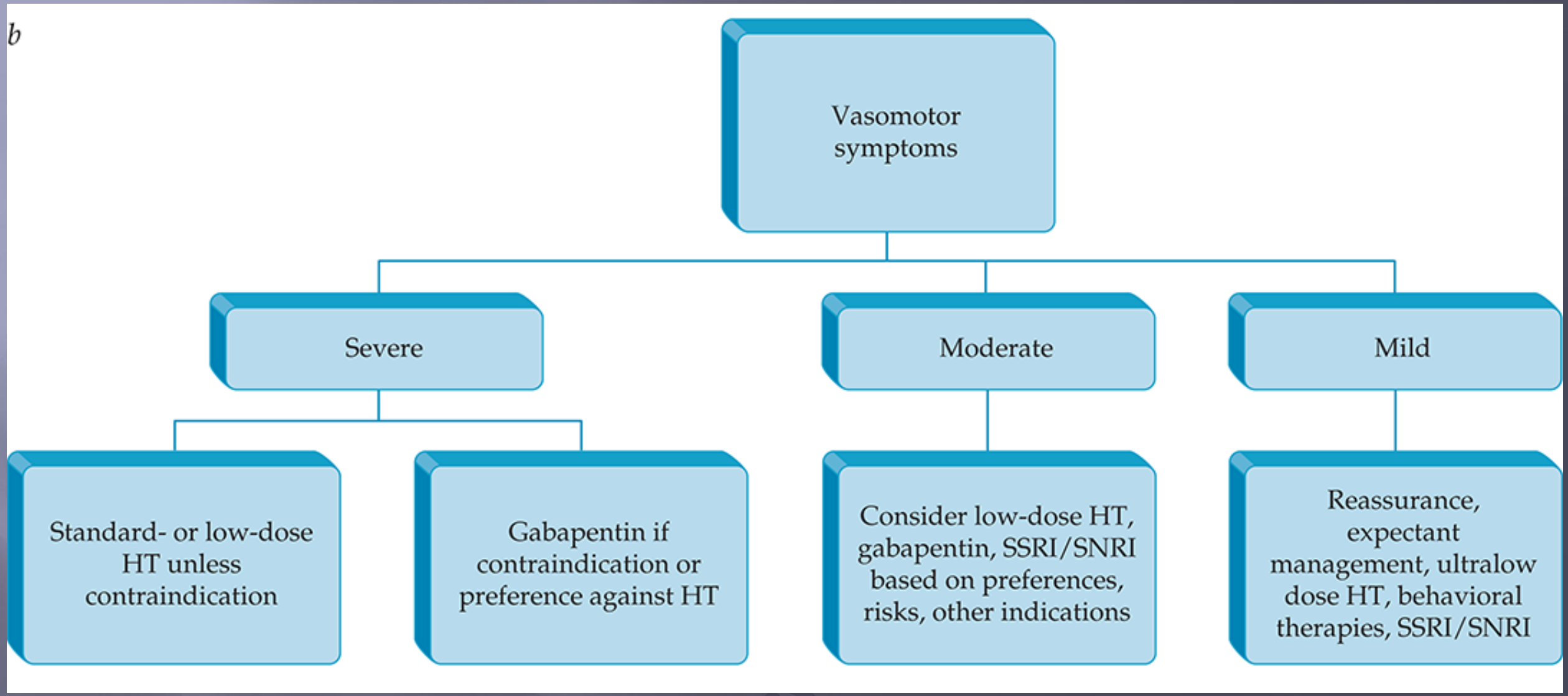
Symptom Specific Management

- Uterine bleeding
  - After appropriate evaluation
  - Low-dose COCs containing 10-20ug of ethinyl estradiol, POPs, pIUD
    - The overall risks of ethinyl estradiol at 10 µg/day are estimated to be greater than that of 0.625 mg/day of conjugated estrogen, but head-to-head trials comparing the clinical effects of the two estrogens do not exist.


Abnormal bleeding
Heavy and/or frequent
Infrequent and/or irregular but not heavy
Combined hormonal contraceptive
Progestin only (e.g., levonorgestrel IUS)
Reassurance, expectant management

Symptom Specific Management

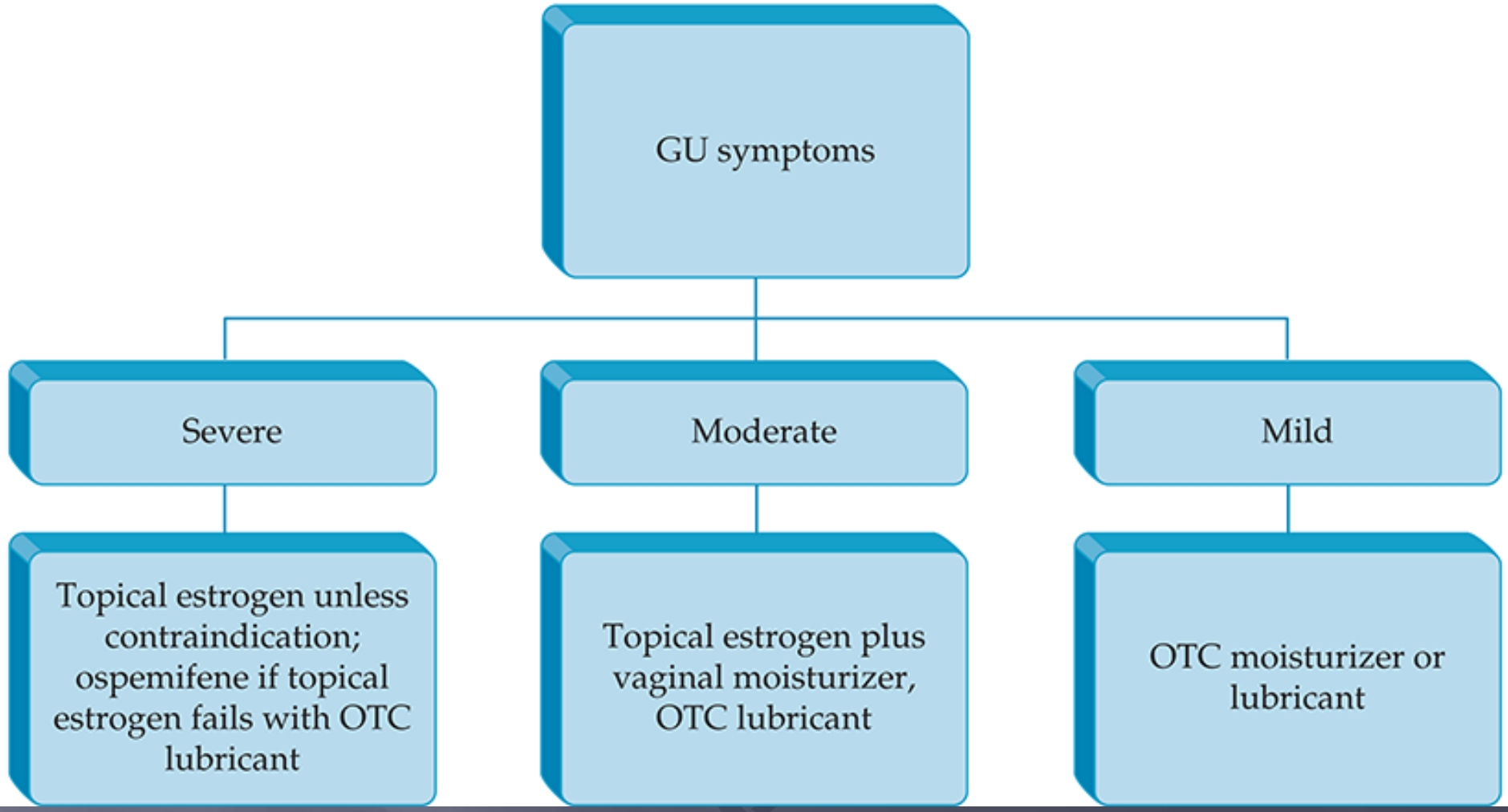
- Vasomotor Symptoms
  - If at risk for pregnancy in menopausal transition COCs or depot medoxyprogesterone
  - If predominately anovulatory cyclical HT is preferable if contraception is not needed
  - Continuous HT is 12 or more months amenorrhoriac
    - Can be associated with bothersome bleeding patterns if in menopausal transition
  - Progestin alone is effective for vasomotor symptoms65 but is rarely used due to potential concern for increased breast cancer risk.
  - the presence of new or worsened symptoms of depression, anxiety, insomnia, reduced libido, or musculoskeletal pain, in addition to typical vasomotor symptoms, may tip the scales toward a woman electing to try HT


b
Vasomotor symptoms
Severe
Moderate
Mild
Standard- or low-dose HT unless contraindication
Gabapentin if contraindication or preference against HT
Consider low-dose HT, gabapentin, SSRI/SNRI based on preferences, risks, other indications
Reassurance, expectant management, ultralow dose HT, behavioral therapies, SSRI/SNRI

Symptom Specific Management

- Genitourinary Syndrome of Menopause
  - usually improve within 2 weeks after initiation of ET and are controlled after 1 to 3 months of use
  - Administer topically with excellent local effect
  - Progestin not needed with vaginal formulations
  - Cessation results in return of symptoms

c


GU symptoms
Severe
Moderate
Mild
Topical estrogen unless contraindication; ospemifene if topical estrogen fails with OTC lubricant
Topical estrogen plus vaginal moisturizer, OTC lubricant
OTC moisturizer or lubricant

Symptom Specific Management

- Mood
  - ET may be beneficial but estrogen alone without an antidepressant does not appear sufficient to treat depression
- Sleep
  - estrogen is effective for most women with new-onset insomnia with hot flashes during the menopausal transition
- Cognition
  - Minimal effects and not recommended to improve cognitive skills
- Libido
  - Once psychosocial factors are eliminated as contributors, testosterone therapies have been shown, in some circumstances, to improve sexual function, frequency, desire, and psychological well-being

Shifren J, Braunstein GD, Simon JA, et al. Transdermal testosterone treatment in women with impaired sexual function after oophorecto-my. N Engl J Med 2000;343:682–8
Lobo RA, Rosen RC, Yang HM, et al. Comparative effects of oral esterified estrogens with and without methyltestosterone on endocrine profiles and dimensions of sexual function in postmenopausal women with hypoactive sexual desire. Fertil Steril 2003;79:1341–52

SORT: KEY RECOMMENDATIONS FOR PRACTICE

CLINICAL RECOMMENDATION	*EVIDENCE RATING*
Combined estrogen/progestogen therapy, but not estrogen alone, increases the risk of breast cancer after three to five years of use.	B
Systemic estrogen, alone or in combination with a progestogen, is the most effective therapy for menopausal hot flashes, and is approved by the U.S. Food and Drug Administration for this indication.	A
Because of the potential risks with long-term use of hormone therapy, clinicians should prescribe the lowest effective dosage for the shortest duration necessary to improve symptoms.	C
There is no high-quality, consistent evidence that black cohosh, botanical products, omega-3 fatty acid supplements, or lifestyle modification alleviates hot flashes.	B
The decision to continue combined hormone therapy for more than three to five years should be made after reviewing the risks, benefits, and symptoms with the patient.	C
Effective nonhormonal therapies for genitourinary syndrome of menopause include vaginal moisturizers and oral ospemifene (Osphena).	B

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-ori evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. F about the SORT evidence rating system, go to https://www.aafp.org/afpsort.

Risks and Benefits of HT

- Heart and Estrogen/Progestin Replacement Study [HERS]
  - no benefit of HRT for secondary prevention of cardiovascular events
    - HERS participants had established coronary heart disease
    - 25 percent of the women in the active treatment arm dropped out of this study

Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in post-menopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA 1998;280:605–13

Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. JAMA 2013;310:1353–68.

Women's Health Initiative [WHI]

- Prematurely halted trial of EPT in 2002
  - combined rates of adverse were 1% higher in the intervention group than in the control group and overshadowed the reduced risk of osteoporotic fractures and colon cancer
    - cardiovascular events
    - Stroke
    - Thromboembolism
    - breast cancer
  - no difference in overall or disease-specific mortality between the HT and placebo groups
- Prematurely halted trial of ET in 2004
  - Increased risk of stroke

Kronos Early Estrogen Prevention Study (KEEPS)

- main aim of the KEEPS was to assess atherosclerosis progression and cardiovascular risk factors after HT initiation
- No significant differences were found between the groups
- The study was underpowered for outcomes in a healthy population
- findings are reassuring for women ages 50 to 59 taking postmenopausal HT

HT Counseling

- Side effects
  - Breast tenderness
  - Breakthrough bleeding

HT Counseling

- Cardiovascular risk/benefit
  - Starting ET near the time of menopause may decrease cardiovascular risks
  - Transdermal carry lower risk of stroke, thromboembolism, elevation of bile acids, and hypertriglyceridemia than oral (observational studies)
    - Might also have more favorable effect on coagulation pathway and CRP
    - May maintain bone mineral density
  - Statins may attenuate the risk of VTE
  - women with metabolic syndrome at baseline who are treated with HT may be at heightened risk for coronary heart disease
  - Women with genetic or acquired risk of thrombophilia are at increased risk for VTE with ET use
    - this risk is increased with synthetic progestins but does not appear to be increased with micronized progesterone

Pai M, Evans NS, Shah SJ, et al. Statins in the prevention of venous thromboembolism: a meta-analysis of observational studies. Thromb Res 2011;128:422–30.

HT Counseling

- Dementia—insufficient data
- Hip fracture—WHI decreased
- DM—WHI decreased
- Gallbladder—WHI increased
- Incontinence—WHI increased
- weight change—Cochrane review no evidence that HT results in weight change
- All-cause mortality—WHI lower all cause mortality

Health Risks

- Perimenopause
  - Endometrial hyperplasia and cancer due to high estrogen and progesterone balance (obese women are at increased risk in menopause transition and postmenopause)

Health Risks

- Postmenopause
  - Quality of life (due to all symptoms)
  - Breast cancer
  - Osteporosis
  - CV risks and events
  - Diabetes (if taking estrogen and progesterone)
  - Increased coagulation

Bisphosphonates for the treatment of osteoporosis

Bisphosphonate	Formulations	Dosing	Vertebral fracture reduction	Hip fracture reduction	Nonvertebral fracture reduction	Discontinuation of therapy (in selected patients*); after:
Alendronate	Oral¶	▪ 10 mg once daily, **or** ▪ 70 mg once weekly△	Yes	Yes	Yes	5 years
Risedronate	Oral, immediate release¶	▪ 5 mg once daily, **or** ▪ 35 mg once weekly, **or** ▪ 150 mg once monthly	Yes	Yes	Yes	5 years◇
	Oral, delayed-release (enteric-coated)§	▪ 35 mg once weekly				5 years◇
Zoledronic acid	Intravenous	▪ 5 mg once every 12 months	Yes	Yes	Yes	3 years
Ibandronate	Oral¶	▪ 150 mg once monthly	Yes	No	+/–	Limited data
	Intravenous	▪ 3 mg every 3 months				Limited data

Refer to UpToDate clinical topic reviews for detail on appropriate use of these agents. Dosing in this table is for adult patients with normal kidney function.

* For patients at low risk for fracture in the near future (eg, stable bone density, no previous vertebral or hip fractures), we suggest discontinuing therapy to reduce potential risks of long-term therapy, as there appears to be residual fracture benefit post-treatment.

¶ Most oral bisphosphonates should be taken alone on an empty stomach first thing in the morning with at least 240 mL (8 oz) of water. After administration, the patient should not have food, drink, medications, or supplements and should remain upright for at least one half-hour (alendronate, risedronate) or one hour (ibandronate).

△ The 70 mg dose is also available in an effervescent formulation (dissolved over at least 5 minutes in 4 oz of tap water) and an oral solution (follow administration with at least 2 oz of water).

◇ Based on indirect evidence from the alendronate extension trial.

§ The enteric-coated, delayed-release formulation is taken immediately after breakfast with 4 oz of water.

References:

1. *Black DM, Schwartz AV, Ensrud KE, et al. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): A randomized trial. JAMA 2006; 296:2927.*
2. *Black DM, Reid IR, Boonen S, et al. The effect of 3 versus 6 years of zoledronic acid treatment of osteoporosis: A randomized extension to the HORIZON-Pivotal Fracture Trial (PFT). J Bone Miner Res 2012; 27:243.*

Table 2 Selective Estrogen Receptor Modulators (SERMs) Used in Postmenopausal Women[64]

Characteristic	*Drug*			
	Tamoxifen	*Raloxifene*	*Bazedoxifene*	*Ospemifene*
Approval date and use (United States except where otherwise noted)	1977: Treatment metastatic breast cancer. 1990: Reduction in risk of breast cancer recurrence in node-negative cancer. 1998: Reduction of risk of primary or contralateral breast cancer.	1997: Prevention and treatment of osteoporosis in postmenopausal women. 2007: Reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis and in postmenopausal women at high risk for invasive breast cancer.	2009 (European Union): Monotherapy for osteoporosis prevention. 2013 (United States): In conjunction with CEE for women with uterus.	2013: Moderate to severe dyspareunia due to menopausal vulvar and vaginal atrophy
Beneficial effect (improves risk or alleviates symptom or effect)	Breast cancer (diagnosis, recurrence, and death); bone loss	Invasive breast cancer; bone mineral density; vertebral and nonvertebral fractures	Bone loss and bone turnover markers; vertebral fractures; endometrial hyperplasia; breast (reduces breast density on mammogram; no observed increase in adverse breast conditions)	Genitourinary atrophy and dyspareunia; possible reduction in bone turnover (based on animal studies); possible inhibitory effect on breast tumors (based on animal studies)
Adverse effect (worsens risk or causes symptom or effect)	Venous thromboembolism; endometrial hyperplasia and carcinoma; vasomotor symptoms; cataracts; leg cramps	Venous thromboembolism; fatal stroke in women at increased risk for stroke; vasomotor symptoms; leg cramps; cataracts (less than tamoxifen)	Venous thromboembolism	Arterial and venous thromboembolism; hypersensitivity, angioedema, rash; vaginal discharge; vasomotor symptoms
Neutral or mixed effect	Genitourinary	Genitourinary	Vasomotor symptoms	Breast; endometrium; vasomotor symptoms

CEE = conjugated equine estrogen.

Contraception

- COCPs (pills or vaginal ring)
  - safe in non-smokers up to the age of menopause
  - difficult to determine if menopause has occurred
    - irregular bleeding does not occur
    - vasomotor symptoms are rare
    - Measurement of FSH is unreliable
- POPs
  - more effective for women aged >40 years than for women who are younger
  - may cause poor cycle control, which may require investigation to exclude pathology in this age group
  - not licensed to protect the endometrium as part of menopausal hormone therapy

Bateson, D., & McNamee, K. (2017). Perimenopausal contraception: A practice-based approach. Australian Family Physician, 46(6), 372–377. Retrieved from https://www.racgp.org.au/afp/2017/june/perimenopausal-contraception-a-practice-based-approach/

Contraception

- Contraceptive implant
  - Few contraindications (breast cancer is notable exception)
  - May be associated with prolonged or frequent bleeding in approximately one in five women
  - threshold for investigation of troublesome bleeding to exclude cervical or endometrial pathology in women aged >40 years is lower than for women who are younger
  - Not licensed to protect endometrium
  - Amenorrhea cannot be used as indicator for menopause
- Depot medroxyprogesterone acetate
  - not used as first-line management in women aged >45 years, and not generally recommended beyond 50
    - Possible side effects on bone density and lipids

Contraception

- LNG-IUD
  - Women presenting with abnormal bleeding, including postcoital, intermenstrual or heavy menstrual bleeding, must always be investigated prior to insertion because of the risk of endometrial cancer and other pathology with increasing age, especially in the presence of additional risk factors such as obesity
  - Amenorrhea cannot be used as indicator for menopause
  - Can be used to protect endometrium in women using ET
- Cu-IUD
  - highly effective contraception without hormonal side effects or risks
  - Emergency contraception
  - Associated with heavier menstrual bleeding

Questions?

and

Thanks!