Symptoms of Perimenopause and Menopausal Hormone Therapy

SELF-STUDY
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Disclaimer

This module is intended to inform psychiatric providers about:

- Symptoms related to perimenopause
- Hormonal treatment options

BUT

- Does not train providers in prescribing menopausal hormone therapy (MHT).

Most psychiatric providers will refer to gynecologist or primary care colleagues to prescribe MHT, or seek specific training in prescribing MHT.

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Learning Objectives

1. What are the most common symptoms of perimenopause?
2. Which symptoms overlap with depression?
3. What data guide the administration of menopausal hormone therapy (MHT)?
4. How is evidence-based MHT administered?
5. What are some prescription alternatives to MHT for vasomotor symptoms?

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Review: The Menopausal Transition or Perimenopause

- The mean age of menopause (final menstrual period) in the US is 51.
- A woman is assessed as being in menopause one year after her final menstrual period.
- The menopausal transition (perimenopause) begins up to 10 years before menopause.
- Average duration of perimenopausal symptoms is 4 years.

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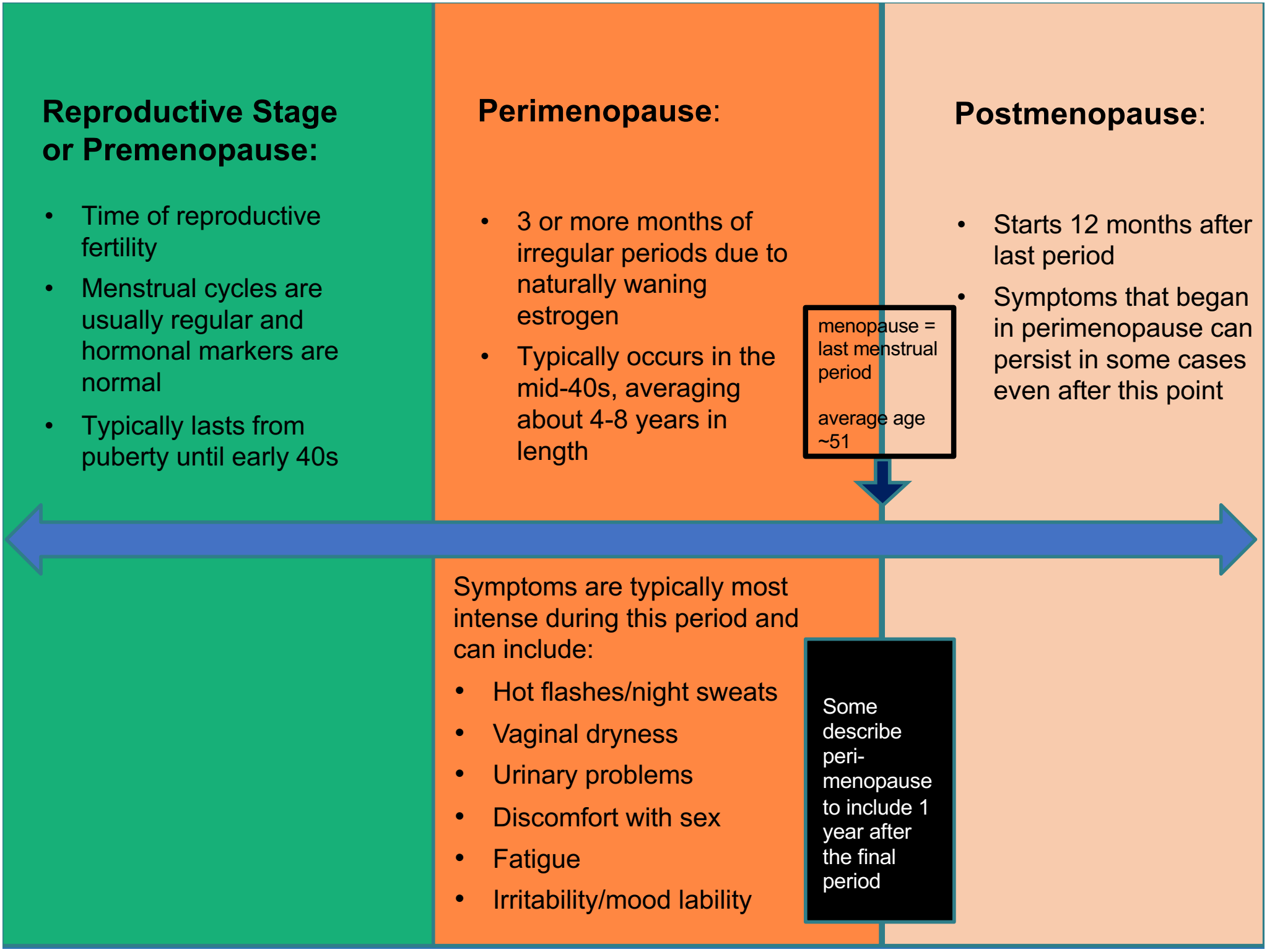
Reproductive Stage or Premenopause:
Time of reproductive fertility
Menstrual cycles are usually regular and hormonal markers are normal
Typically lasts from puberty until early 40s
Perimenopause:
3 or more months of irregular periods due to naturally waning estrogen
Typically occurs in the mid-40s, averaging about 4-8 years in length
menopause = last menstrual period
average age ~51
Postmenopause:
Starts 12 months after last period
Symptoms that began in perimenopause can persist in some cases even after this point
Symptoms are typically most intense during this period and can include:
Hot flashes/night sweats
Vaginal dryness
Urinary problems
Discomfort with sex
Fatigue
Irritability/mood lability
Some describe peri-menopause to include 1 year after the final period

Symptoms of Perimenopause

- Hot flushes and night sweats (vasomotor symptoms)
- Menometrorrhagia
- Headache
- Palpitations
- Breast tenderness
- Musculoskeletal pain
- Restless legs
- Vaginal dryness
- Dyspareunia

- Insomnia
- Fatigue
- Low mood
- Irritability
- Impaired concentration
- Memory complaints

Note the overlap between the symptoms in this column and the symptoms of depression.

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Assessment of Perimenopause

- Perimenopause is a clinical assessment, based on changes in the menstrual cycle and appearance of other symptoms.
- Menses start to vary in frequency, length, and amount of flow.
- Hormone testing is not necessary to determine perimenopause, as levels of follicle stimulating hormone, estradiol, progesterone and luteinizing hormone vary significantly day by day, and even across a single day, and so levels obtained will not be helpful.
- Symptoms of perimenopause should be discussed with an Ob/Gyn or primary care provider, as other potential etiologies should be considered.

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Vasomotor Symptoms

- Vasomotor symptoms (VMS) consist of hot flashes/flushes and night sweats.
- VMS are the most common symptoms of perimenopause and the ones for which treatment is most often sought.
- VMS are a sudden sensation of extreme heat in the upper body, generally lasting a few seconds to several minutes, but sometimes up to an hour. (Thus some prefer *hot flush* over *hot flash*.)
- VMS occur spontaneously but can also be triggered by stress, alcohol, caffeine, hot drinks, or an abrupt change in ambient temperature.
- Flushing, sweating, palpitations and anxiety often accompany the sensation of extreme heat and are sometimes followed by chills.
- Night sweats can interrupt sleep and can be associated with anxiety, irritability, depression, impaired concentration and memory.

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Epidemiology of Vasomotor Symptoms

- Up to 80% of women have VMS during the transition to menopause; most rate them moderate to severe, and 1/3 have > 10/day.
- The Study Of Women's Health Across the Nation (SWAN), a multiracial/multiethnic observational study, assessed women through the menopausal transition.
- 3302 women were recruited at 7 sites, and followed from 1996 until 2013.
- Median total duration of VMS was 7.4 years.
- For women with an observable final menstrual period, VMS lasted for a median of 4.5 years after that date.
- African American women had longest VMS duration (median 10.1 years) and Japanese and Chinese American women had shortest (median 4.8 and 5.4 years).
- Other factors associated with longer duration of VMS include history of smoking, higher BMI, anxiety, perceived stress, depressive symptoms, lower educational level, and lower levels of social support.

Avis 2015

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Differential Diagnosis of Vasomotor Symptoms

Workup includes clinical history, review of symptoms, and lab studies to rule out:

- Thyroid disease (TSH)
- Subacute/chronic infection (CBC, C-reactive protein)
- Psychosomatic disorder, stress (stress questionnaire, clinical interview)
- Leukemia (CBC)
- Pheochromocytoma (Urine vanillylmandelic acid)
- Carcinoid (Chromogranin A, urine 5-hydroxy indole acetic acid)
- Other malignancies (CT or MRI)

Krause & Nakajima 2015

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History of Menopausal Hormone Therapy

- First reported in Germany in 1886: a small study described women injected with bovine ovarian tissue experiencing a dramatic reduction in sexual dysfunction.
- The first commercially available product, Emmenin, made from the urine of pregnant women, was introduced in the US in 1933; in 1941 it was replaced by Premarin, made from conjugated equine estrogens.
- By 1975, estrogen was the fifth most prescribed drug in the US.
- In the late 1970s, reports of an increased risk for endometrial cancer led to decreased use; with the addition of progesterone to decrease endometrial hypertrophy use again increased.
- Data from 16 prospective cohort studies, many of which showed reduced incidence of Coronary Heart Disease (CHD), encouraged the prescription of menopausal hormone therapy (MHT) for chronic disease prevention as well as symptoms of perimenopause.

Kohn 2019

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The Women's Health Initiative Trial: Design

- The Women's Health Initiative (WHI) was designed to assess the risks and benefits of MHT in healthy postmenopausal women.
- Randomized controlled primary prevention trial with a planned duration of 8.5 years.
- Between 1993-1998, 27,347 postmenopausal women aged 50-79 were recruited by 40 US clinical centers.
- The 16,608 participants with an intact uterus received conjugated equine estrogen (CEE),0.625 mg/d, plus medroxyprogesterone acetate (MPA), 2.5mg/d, or placebo. The 10,739 women with a prior hysterectomy received CEE alone.
- Primary outcome was coronary heart disease; invasive breast cancer was the primary adverse outcome. Global index summarizing balance of risks and benefits included these plus stroke, pulmonary embolus, endometrial cancer, colorectal cancer, hip fracture, and death due to other causes.

The Women's Health Initiative: Initial Results

- In May 2002 the WHI was stopped as in the estrogen plus progestin group (after a mean of 5.2 years of follow-up) the test statistic for invasive breast cancer exceeded the stopping boundary and the global index statistic suggested risks exceeding benefits.
- Absolute excess risks per 10,000 person-years: 7 more coronary heart disease events, 8 more strokes, 8 more pulmonary emboli, 8 more invasive breast cancers.
- Absolute risk reductions per 10,000 person-years: 6 fewer colorectal cancers, 5 fewer hip fractures.
- In July 2002 the initial data were published in the Journal of the American Medical Association and widely covered in the press. Prescriptions for MHT fell by as much as 80%, and provision of training in prescribing MHT dwindled rapidly.

The Women's Health Initiative: Further Considerations

- The average age of WHI participants at enrollment was 63; many were not experiencing vasomotor symptoms.
- The overall WHI cohort thus differed significantly from the younger, symptomatic population of earlier observational studies.
- Analysis of WHI data by age showed a *reduction* in myocardial infarction (MI) and all-cause mortality in women 50-59 years treated with CEE alone; only women 70-79 years had increased risks.
- For the group treated with CEE + MPA, the increased risk of MI was minimal in women <10 years from menopause and age <60 years. Risk of MI increased with age and time since menopause.
- Women with vasomotor symptoms early in menopause had a lower risk of cardiovascular disease and all-cause mortality, while women still having hot flushes 14 years after menopause on average had a higher risk of coronary heart disease and all cause mortality. *When women experience symptoms may be correlated with their health risks.*

Chester, Kling and Manson 2018

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Research Since The Women's Health Initiative

- The results of the WHI contradict those of prior observational studies; research since the WHI has addressed reasons for this.
- More recent studies have investigated younger women, used lower doses of estrogen, and compared transdermal with oral estrogen.
- The "timing hypothesis" posits that age and time since menopause is key; risks of MHT are lower when it is prescribed closer to the menopausal transition.
- Women 50-59 years old or < 10 years from menopause at initiation of MHT have lower hazard ratios for coronary heart disease than women starting MHT at an older age.
- Studies have continued to find an increased risk of breast cancer associated with MHT, which decreases with intermittent or no use of a progestogen.

Kling 2017 and Collaborative Group on Hormonal Factors in Breast Cancer 2019

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KEEPS and ELITE Studies

- The Kronos Early Estrogen and Prevention Study (KEEPS), a 4-year randomized, double blind prospective trial included 727 women aged 42-58 (mean 52) and had 3 arms (all given cyclical micronized progesterone) plus: oral CEE (0.45mg/d), transdermal estradiol (50µg/d) or placebo. Findings showed no significant effects on progression of atherosclerosis in either treatment arm compared with placebo.
- The ELITE (Early Versus Late Intervention Trial) compared women <6 years past menopause with women ≥10 years past menopause started on MHT. 643 women were randomized to oral estradiol (1mg/d) plus cyclical vaginal progesterone gel for women with a uterus, versus placebo for 6-7 years. For women closer to menopause, markers of cardiovascular disease progressed more slowly in group on MHT. For women further from menopause, the rate of progression of atherosclerosis was similar in estradiol and placebo groups.

Chester, Kling and Manson 2018

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Current Recommendations for MHT

- WHI sub-analysis and post-WHI studies have adjusted recommendations for MHT in healthy women early in menopause.
- Multiple expert organizations, including the North American Menopause Society, The Endocrine Society, and the American Society for Reproductive Medicine, agree.
- Recommendations are no longer “the smallest dose possible for the shortest period of time” but instead focus on the type, dose and duration appropriate for each woman.
- “For women aged younger than 60 years or who are within 10 years of menopause onset and have no contraindications, the benefit-risk ratio is most favorable for treatment of bothersome [vasomotor symptoms] and for those at elevated risk for bone loss or fracture.”

North American Menopause Society (2017)

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Treatment for Vasomotor Symptoms

- MHT is the most effective treatment for the vasomotor symptoms of the menopausal transition. A 2004 Cochrane meta-analysis of 24 randomized controlled trials found a 75% reduction in weekly hot flush frequency compared with placebo.
- An intermittent progestogen[1] must be added to estrogen in women with a uterus to prevent endometrial hyperplasia and endometrial cancer.
- A continuous progestogen is not recommended due to data suggesting an increased risk of breast cancer.
- A progestogen can be taken orally, or through vaginal gel or IUD (latter equivalent or superior to systemic therapy but not FDA approved).

1. A class of steroid compounds that bind to and activate the progesterone receptor.

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Estrogen Dose

- Oral and transdermal low-dose estrogen (<0.3mg of conjugated estrogen, <0.5mg of oral micronized estradiol, <2.5µg of ethinyl estradiol, <25µg or less of transdermal estradiol) effectively alleviate vasomotor symptoms in most women.
- Ultra-low dose options, e.g. 0.14 µg patch, have not been extensively studied but may reduce vasomotor symptoms.
- Dose is increased if initial dose is not sufficient to treat symptoms, and decreased before discontinuation.

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Estrogen Delivery Method

- Vaginal estrogen cream or gel is effective for dyspareunia and vaginal dryness, but not for hot flushes.
- Non-oral preparations avoid a first-pass hepatic effect and so may produce fewer changes in lipids, clotting factors, and inflammatory markers.
- Studies have shown transdermal estrogens to be associated with a lower risk of venous thromboembolism than oral estrogens. Forms include patches, gels and sprays.
- Transdermal estrogens may also have greater positive effect on mood.
- Intranasal and buccal options have also been developed but are not available in the US.

Canonico et al 2007

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Benefits of Menopausal Hormone Therapy

- Improvement of vasomotor symptoms
- Improvement in vaginal dryness
- Decreased risk for osteoporosis
- Decreased risk for hip and spine fractures
- Decreased risk for colorectal cancer
- Improvement in mood (see next slide)

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Menopausal Hormone Therapy and Mood

- The increased risk of depression during perimenopause provides a theoretical argument for MHT having an antidepressant effect.
- Disparate methodologies used by extant studies prevents the drawing of robust conclusions as to whether this occurs in practice.
- Data available provide limited evidence to support estradiol as having antidepressant effects in perimenopausal women with depression.

  Rubinow et al. 2015

- One recent RCT showed evidence of MHT preventing the development of perimenopausal depression. Given the well documented risks of MHT, until replicated, this study is an insufficient basis for employing MHT as prophylaxis against the development or recurrence of depression.

  Gordon 2018, Joffe 2018

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Risks of Menopausal Hormone Therapy

Current data suggests that for older women and those further from menopause there is a slightly increased risk in those on MHT of:

- Breast cancer
- Coronary heart disease
- Stroke
- Venous thromboembolic event

Therefore MHT is most commonly prescribed for women:

- with moderate to severe symptoms
- younger than 59 or <10 years post-menopause

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Contraindications to Menopausal Hormone Therapy

Relative contraindication: Smoking

- Absolute contraindications:
  - Current, past or suspected breast cancer
  - Known or suspected estrogen-sensitive malignant conditions
  - Untreated endometrial hyperplasia
  - Undiagnosed vaginal bleeding
  - Active liver disease
  - Uncontrolled hypertension
  - Thrombophilia
  - Previous or current venous thromboembolism (transdermal may be acceptable)
  - Active or recent arterial thromboembolic event (e.g. myocardial infarction)
  - Hypersensitivity to any ingredient of the formulation
  - Porphyria cutanea tarda

Krause & Nakajima 2017

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Alternatives to MHT for Vasomotor Symptoms

First line: SSRIs, SNRIs, gabapentin, clonidine, cognitive behavioral therapy.

If MHT for vasomotor symptoms is contraindicated, or if a patient needs an antidepressant for a mood disorder, there is evidence that the following medications can improve hot flushes.

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Alternatives to MHT for Vasomotor Symptoms

Medication	Typical Daily Dose for Hot Flushes	Reduction in Hot Flushes
Desvenlafaxine		
Venlafaxine XR	37.5mg-75mg	45-63%
Paroxetine CR	12.5-25mg	58-63%
Fluoxetine	20mg	50%
Citalopram		
Escitalopram		
Gabapentin	900mg	54%3
Clonidine	.1mg	20-37%

Joffe *et al* 2003

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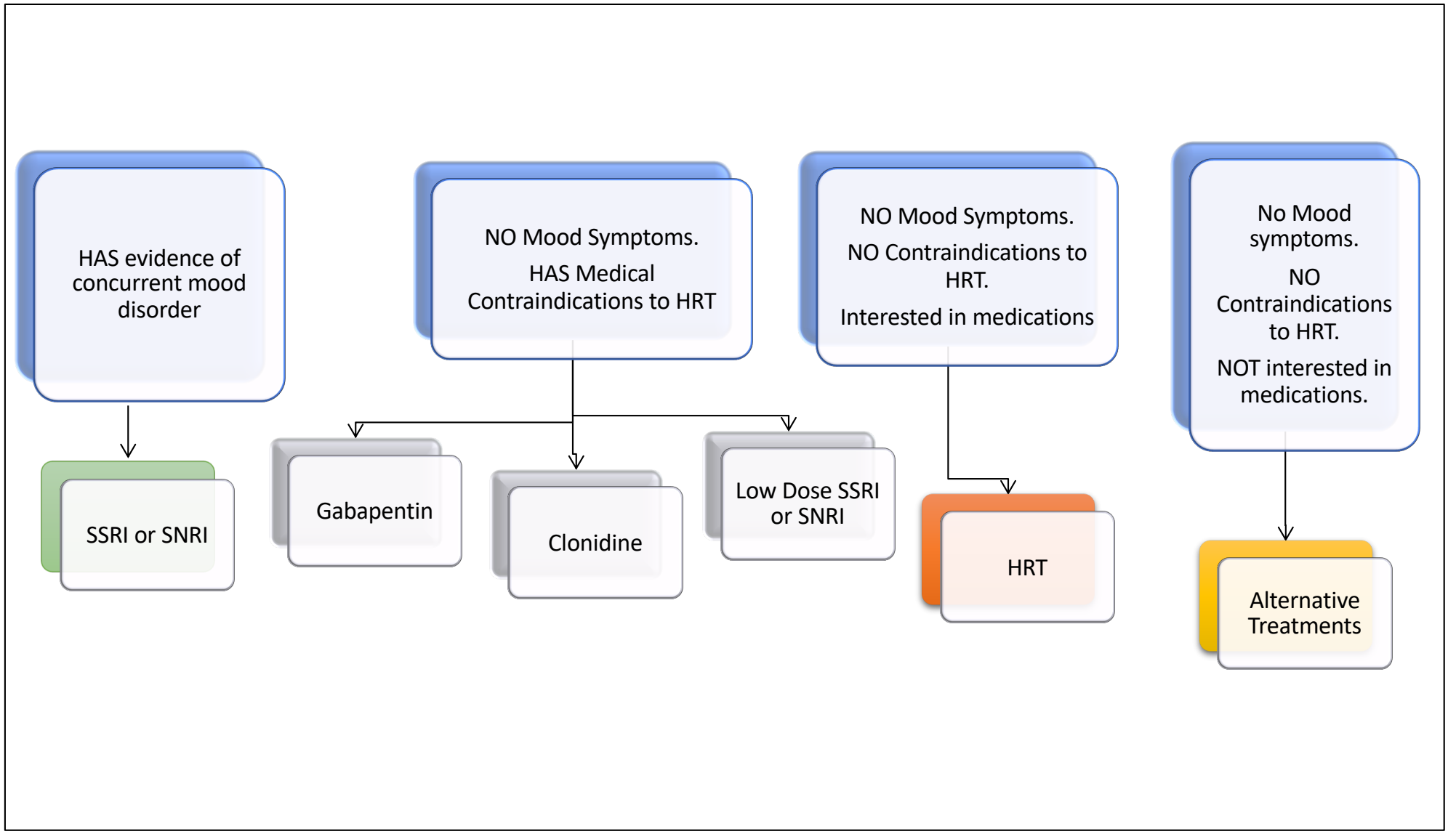
Perimenopausal Woman Presents with Vasomotor Symptoms affecting Sleep and Daily Life and….



Post-learning Self Assessment

1. What are the most common symptoms of perimenopause?
2. Which symptoms overlap with depression?
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