



# Perimenopause: Mood and Cognition

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## Objectives

- Review the definition and diagnosis of perimenopause.
- Review common symptoms of perimenopause, including vasomotor symptoms, disrupted sleep, cognitive concerns, mood changes, and sexual dysfunction.
- Review available treatments for common symptoms of perimenopause and the evidence base for interventions.

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## Meet Sarah: 47-Year-Old Executive

- **Chief Complaint:** "I feel like I'm losing my mind"
- **History of Present Illness:**
  - Irregular menses for 8 months with 35-50 day cycles
  - Persistent nighttime awakenings with drenching sweats
  - Daily word-finding difficulties
  - Severe irritability affecting her work



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## Sarah's History

- **Past Medical & Psychiatric History**
  - Mild postpartum depression 14 years ago, now resolved
  - No prior psychiatric hospitalizations
  - BMI 27.2
  - Non-smoker
  - No cardiovascular history



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## Workup and Treatment

- How do we differentiate perimenopause from a major depressive episode or early dementia?
- What education should we provide for Sarah regarding her word-finding difficulties?
- What treatment options could we offer Sarah?



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## Perimenopause Basics

- Average age of menopause in US: 45-51 years
- Transition to menopause can last 7-14 years
- Multiple factors affecting length and timing of transition
  - Body habitus
  - Race/ethnicity
  - Smoking

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## Perimenopause Course

- Four stages cover the transition per Stages of Reproductive Aging Workshop +10 (STRAW+10)
  - Late reproductive (regular/slightly irregular cycles, normal to variable FSH)
  - Early menopause transition ( $\geq 7$  day difference in cycles, variable FSH)
  - Late menopause transition (cycles  $\geq 60$  days apart, high FSH)
  - Early postmenopause (12 months after final menstrual period, high FSH)

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## Perimenopause: A Clinical Diagnosis

- **Hormonal Dynamics:** Wide fluctuations in estradiol and follicle-stimulating hormone (FSH) from cycle to cycle, with physiologic changes that can occur **before** changes in the menstrual cycle
  - Point testing of hormones not usually clinically useful
- **Routine Testing:** not recommended for women over age 45

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## Differential Diagnosis

- **Essential rule-out labs:**

- **Thyroid-stimulating hormone (TSH)**- rule out hypo/hyperthyroidism mimicking vasomotor symptoms and fatigue
- **Prolactin**- rule out hyperprolactinemia in secondary amenorrhea
- **hCG**- be sure to rule out pregnancy in sexually active perimenopausal women
- **FSH**- check if age <40 with amenorrhea to check for primary ovarian insufficiency, history of hysterectomy with ovaries intact, and for diagnostic ambiguity in women <45

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## Next Steps for Sarah

- Sarah requests a "full hormone panel to check my estrogen levels." How do you proceed?
  - A. Order serum estradiol, serum FSH, and luteinizing hormone (LH) to confirm perimenopause stage
  - B. Reassure Sarah that perimenopause is a clinical diagnosis; order TSH and hCG.
  - C. Start high-dose oral estrogen.

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## Common Symptoms of Perimenopause

- Vasomotor symptoms
- Sleep concerns
- Cognitive concerns
- Mood concerns
- Sexual dysfunction

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## Vasomotor Symptoms (VMS)

- Most common physical complaint of perimenopause
- Risk factors:
  - Black or Hispanic
  - Higher BMI
  - Smoking
  - Symptoms of anxiety or depression
  - Medical interventions

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## Diagnosing VMS

- Sudden onset of heat, most often in face/neck/chest
- Followed by sweating, flushing, and occasionally chills
- May be accompanied by tachycardia, anxiety, and dread
- Last 1-5 min
- May occur multiple times per day and through the night

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## Course of VMS

- Last a mean of 5 years, but may last longer (up to 10)
- Late 40s to early 50s
- Black women more likely to experience longer duration
- Must be differentiated from:
  - Thyroid disorders
  - Pheochromocytoma
  - Carcinoid syndrome
  - Medication side effects

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## Biology of VMS

- Not fully understood
- Estrogen withdrawal, serotonin involved
- Hypotheses:
  - Temperature dysregulation at the hypothalamus
  - Changes in local control of skin blood flow
  - Sensitivity to small rises in body temperature

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## Sleep Concerns in Perimenopause

- Second most common physical complaint
- 39-60% of women in peri-/post-menopause
- Most severe during the perimenopause transition and tend to improve post-menopause
- Often related to VMS (not necessarily the result of VMS)
- Rule out sleep apnea and restless leg syndrome

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## Sleep Concerns: Risk Factors

- Risk Factors:

- ☐ VMS
- ☐ Depression and anxiety
- ☐ Surgical menopause and breast cancer treatment
- ☐ Increased perceived stress
- ☐ Smoking

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## Cognitive Symptoms in Perimenopause

- **Subjective** complaints - "brain fog"
  - Verbal memory deficits (word-finding difficulty)
  - Difficulty with working memory (mental math)
  - Delayed processing speed
  - Difficulties with attention and concentration
- Objective measures typically within normal range
  - Subjective reports of effects on work performance, relationships, daily function BUT not typical for measurable decrements in work and ability to care

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## Cognitive Symptoms in Perimenopause

- Mechanism unclear:
  - Hormonal changes (estradiol **variability**, rising LH + FSH)
  - Structural neurologic changes (hippocampal volume loss)
- Cognitive changes are an independent process
- Factors that can worsen these symptoms:
  - Depression
  - Poor sleep
  - VMS

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## Cognitive Symptoms in Perimenopause

- How to distinguish from normal aging?
  - Symptoms are typically transient and stabilize or revert in postmenopausal phase
- **For most women, cognitive symptoms do not represent a dementia prodrome**
- Who are we more concerned about symptoms representing underlying dementia?
  - APOE4 carriers
  - Early menopause (<45)
  - If symptoms cause **functional impairment**, consider another etiology (depression, sleep disorder, thyroid disorder, cardiovascular effects, medications, dementia)
    - Medical work-up + refer to neuropsychology

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## Mood Symptoms in Perimenopause

- **A Window of Vulnerability**

- Hormonal fluctuations in perimenopause increase risk for depression

- **Depression in Perimenopause is Common**

- Women in perimenopause have a significantly higher rate of depression than premenopausal women (OR = 1.4)
  - 5x more likely to experience first-episode depression than premenopausal women
  - Possible increased risk of suicidal ideation

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## Depression and Perimenopause Symptoms Overlap

- Low energy, low concentration, weight changes, and decreased interest can all be seen in perimenopause
- Differentiators:
  - Low mood, anhedonia, guilt, worthlessness, hopelessness, and suicidal ideation are **not** seen in typical perimenopause

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## Risk Factors for Mood Symptoms

- Prior history of depression
- Greater degree of hormonal change (FSH and estradiol)
- History of anxiety
- History of premenstrual syndrome
- Adverse experiences
- Childhood trauma history
- Black race or Hispanic ethnicity
- Financial stress and low social support
- History of abusive relationships
- VMS
- Perimenopausal symptoms of poor sleep
- Elevated BMI
- Smoking cigarettes
- Social changes (caring for aging family, challenges at work, children in transition, challenges in intimate relationships)

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## Mental Illness in Perimenopause

- **Perimenopause increases risk of new onset or exacerbation of other mental illnesses**
  - Increased risk of depression in bipolar I or II
  - Increased rates of schizophrenia diagnosis
    - "Second wave" of diagnosis ages 45-54
  - Increased anxiety in perimenopause for women who previously had low levels
  - Possible increased risk for alcohol use disorder

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## Sexual Symptoms of Perimenopause

- Commonly present in perimenopause
- Decreased sexual interest and arousal
- Difficulty with orgasm and emotional satisfaction
- Vaginal dryness and atrophy with pain with intercourse
  - Highly prevalent symptom that is often not reported to physicians
  - Can be improved with over the counter lubricants, topical hormones, and hormone replacement therapy

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## Treatment Options

- Pharmacologic Interventions
  - Hormonal replacement therapy (HRT)
  - Non-hormonal
- Non-pharmacologic Interventions

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## HRT: The Controversy

- **Women's Health Initiative (WHI):** Randomized controlled trial for evaluating use of HRT for chronic disease prevention in postmenopausal women
  - Two parallel trials
    - Intact uterus: Conjugated equine estrogen (CEE) + medroxyprogesterone acetate (MPA) vs. Placebo
    - No uterus: Conjugated equine estrogen vs. Placebo
  - **CEE+MPA: increased rates of breast cancer, stroke, pulmonary embolism/venous thromboembolism, coronary heart disease**
  - CEE-alone arm: increased stroke and VTE but reduced breast cancer and did not increase coronary events
- Resulted in significant drop in HRT prescriptions

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## HRT: The Controversy

- Why this may have been misinterpreted:
  - WHI only enrolled postmenopausal patients only
    - Participants older than typical perimenopausal patient + >10 years postmenopausal
  - Used single oral formulation (CEE) of hormones
  - Relative vs. absolute risk
- In 2025, previous FDA Black Boxed warnings surrounding cardiovascular disease, breast cancer, stroke and dementia were removed

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## HRT: The Controversy

- How to think about risk now:
  - **Shared decision-making**
  - "Timing **hypothesis**"
    - Benefit-risk balance is favorable if:
      - <60 years old
      - Within 10 years of menopause
  - Adjust formulation based on risk factors

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## HRT: Indications

- Indications: **moderate-to-severe VMS**, prevention of osteoporosis, premature ovarian insufficiency, genitourinary symptoms (vaginal estrogen)
- Contraindications\*:
  - **Absolute:** estrogen-sensitive malignancies, untreated endometrial hyperplasia, unexplained vaginal bleeding, active/severe liver disease, thrombophilic disorders, active/history of VTE, history of stroke/TIA, history of MI
  - **Relative:** smoking, migraine with aura, uncontrolled hypertension, severe hypertriglyceridemia, gallbladder disease, elevated breast cancer risk
  - \*May still permit low-dose vaginal estrogen for genitourinary symptoms given minimal systemic absorption

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## VMS: Hormonal Options

- HRT is the most effective treatment
  - Estrogen-only therapy if patient does not have uterus
  - Otherwise need progestin or tissue-selective estrogen complex
    - Risk of endometrial hyperplasia with unopposed estrogen
  - Micronized progesterone and synthetic progestins show benefit
    - No long-term studies
    - Concern for safety data
    - Not first-line and use is off-label

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## VMS: Non-hormonal Options

- FDA-approved options for moderate-to-severe VMS:
  - Paroxetine (Brisdelle): 7.5mg
  - Neurokinin (NK) Receptor Antagonists:
    - Fezolinetant (Veoza)
    - Elinzanetant (Lynkuet)

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## VMS: Non-hormonal Options

- Neurokinin receptor antagonists: Block neurokinin-B signaling in hypothalamus to restore temperature regulation
- **Fezolinetant (Veoza)** - 2023
  - First FDA-approved NK3 receptor antagonist for VMS
    - FDA Boxed Warning for hepatotoxicity
      - Monitor at baseline, monthly for first 3 months, then 6 and 9 months
      - Do not start if ALT or AST  $\geq 2 \times$  ULN or total bilirubin  $\geq 2 \times$  ULN
      - Discontinue if ALT or AST  $> 5 \times$  ULN, or ALT or AST  $> 3 \times$  ULN with total bilirubin  $> 2 \times$  ULN
- **Elinzanetant (Lynkuet)** - 2025
  - Dual NK1/NK3 receptor antagonist
    - Also thought to contribute to mood and sleep benefits
    - No hepatotoxicity associations thus far

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## VMS: Non-hormonal Options

- Off-label options:
  - Low-dose SSRI/SNRI: citalopram, escitalopram, venlafaxine, desvenlafaxine, duloxetine (limited)
    - Sertraline and fluoxetine do not show consistent benefit -> not recommended
  - Oxybutynin – very effective but concern with side effects
  - Gabapentin
  - Pregabalin – effective but limited evidence and concern with side effects
  - Clonidine - limited role given limited efficacy and side effects

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## **VMS: Non-pharmacologic Options**

- **Cognitive behavioral therapy (CBT) for menopausal symptoms**
- **Hypnosis**
- **Weight loss**
- **Not recommended: cooling techniques, yoga, relaxation techniques, paced breathing, acupuncture**

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## **Mood: Non-hormonal Options**

- Is this MDD or subclinical depression due to hormonal dysregulation / perimenopausal symptoms?
- If MDD, first-line is SSRI/SNRI antidepressants
  - Desvenlafaxine and venlafaxine have shown positive data
  - Favor prior positive response or targeting co-morbid symptoms
- Side effects to monitor: weight gain, sexual dysfunction
- Be sure to treat other factors (sleep, VMS)

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## Mood: Hormonal Options

- Not primary indication BUT can be helpful
  - Positive evidence in perimenopause, not postmenopause
  - Data is too limited to recommend primarily for this
- When to consider:
  - Subthreshold depressive symptoms and co-existing VMS
  - Partial response to antidepressant treatment
  - Non-response to antidepressants and hormonal timing of symptoms
- FYI: Progestogen choice may impact outcome
  - Micronized progesterone may be better tolerated than synthetic progestins

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## Mood: Non-pharmacologic Options

- Psychotherapy
  - CBT
  - Mindfulness-based therapy
  - Interpersonal psychotherapy
  - May be helpful single intervention for mild/subthreshold depression
- Exercise (aerobic)

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## Sleep: Nonhormonal Options

- Evaluate and treat underlying cause
  - VMS, depression, obstructive sleep apnea (OSA), restless leg syndrome (RLS)
- Otherwise treat sleep directly:
  - Prolonged-release melatonin
  - Low-dose doxepin
  - Non-benzodiazepine hypnotics
  - Ramelteon
  - Orexin antagonists (ex. suvorexant)
  - Mirtazapine
  - Trazodone

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## Sleep: Hormonal Options

- Most helpful through reducing VMS
- Mixed data on benefit independent of VMS
- Improved subjective sleep, usually not polysomnographic measures
- Formulations:
  - Transdermal estradiol > oral estrogen
  - Oral micronized progesterone
    - Improves sleep-onset latency through GABA modulation

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## **Sleep: Non-pharmacologic Options**

- CBT for insomnia
  - First-line over medications
- CBT for menopausal symptoms
  - Consider if this root of disrupted sleep
- Aerobic exercise
- Mindfulness/relaxation
- Yoga
- Acupuncture

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## **Cognition: Nonhormonal Options**

- No agent is established for this indication
- Preliminary data:
  - Lisdexamfetamine
  - Atomoxetine
- Be sure to treat underlying depression if present
  - Bupropion
  - Vortioxetine

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## Cognition: Hormonal Options

- It is **not** recommended for this indication
- RCTs are lacking in perimenopausal women
- Timing matters:
  - Late initiation possibly increases dementia risk
  - Early initiation has possible protective effects

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## Cognition: Non-pharmacologic Options

- Treat chronic medical issues (blood pressure, lipids, diabetes)
- Exercise
- Mediterranean diet
- Limit alcohol
- Smoking cessation
- Maintain social engagement
- Develop new skills, continue to learn

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## Back to Sarah

- Sarah reports her VMS are significantly disrupting her sleep, and she estimates 3-4 awakenings per night with a total of 5 hours of sleep per night.



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## Next Steps for Sarah

- Sarah denies suicidal ideation, hopelessness, and anhedonia at this time. She denies snoring and does not have other risk factors for OSA. What do you discuss next with Sarah?

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## Next Steps for Sarah

- Complete medical evaluation for consideration of HRT to treat VMS.
- Educate Sarah that improving her sleep may improve her mood, and discuss sleep hygiene practices.

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## Next Steps for Sarah

- What else should you discuss with Sarah?
  - Discuss that her word-finding difficulties are likely transient and will improve after the post-menopause transition.
  - Follow-up in 3 months to discuss if mood has improved; if not, consider SSRI for possible treatment of depression if she meets criteria for a recurrent depressive episode.

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## Summary

- VMS, sleep concerns, and mood concerns are very common in perimenopause
- Mental health disorders worsen in perimenopause
- Cognitive concerns are typically transient and resolve once menopausal transition is complete
- Mood should be treated like any other life period

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## Summary

- Be sure to adequately treat VMS and sleep for treatment of mood and cognition
- HRT has strongest evidence for treatment of VMS
- HRT is not primarily indicated for mood or cognition

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## Resources

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