



Perimenopause: Mood and Cognition

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1

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.

2

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



3

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



4

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?



5

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

6

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 (≥ 7 day difference in cycles, variable FSH)
 - Late menopause transition (cycles ≥ 60 days apart, high FSH)
 - Early postmenopause (12 months after final menstrual period, high FSH)

7

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

8

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

9

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.

10

Next Steps for Sarah

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11

Common Symptoms of Perimenopause

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

12



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13

Vasomotor Symptoms (VMS)

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

14

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

15

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

16

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

17

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

18

Sleep Concerns: Risk Factors

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

19



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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

21

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

22

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

23



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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

25

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

26

Risk Factors for Mood Symptoms

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

27

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

28



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29

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

30



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Treatment Options

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

32

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

33

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

34

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

35

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

36

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

37

VMS: Non-hormonal Options

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

38

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

39

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

40

VMS: Non-pharmacologic Options

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

41

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)

42

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

43

Mood: Non-pharmacologic Options

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

44

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

45

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

46

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

47

Cognition: Nonhormonal Options

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

48

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

49

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

50



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51

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.



52

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?

53

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.

54

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.

55

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

56

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

57

Resources

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58

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59