

Perimenopausal depression? Ask how she's sleeping

Consider insomnia in workup of midlife mood disorders

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Trying to treat depression or anxiety in a midlife woman without asking how she's sleeping may doom your treatment plan. Asking about sleep addresses issues that affect her quality of life and can provide valuable insight into effective interventions.

Psychiatric, psychosocial, and medical problems can disturb sleep during perimenopause.¹ To help you diagnose and treat both mood disorders and insomnia, this article:

- describes how irregular hormone levels and psychosocial changes are linked to perimenopausal mood and sleep disorders
- offers evidence-based strategies for hormone replacement therapy (HRT), antidepressants, hypnotics, and psychotherapy.

DEPRESSION AND INSOMNIA AT MIDLIFE

Sixty-five percent of women seeking outpatient treatment for depression report disturbed sleep.² Even mild anxiety and depression can undermine sleep quality, whereas insomnia can precede other symptoms of an evolving major depression.

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Algorithm

Managing mood and sleep symptoms during perimenopause

Identify onset of signs and symptoms

- Last menstrual period
- Episode of depressed mood
- Timing and quality of sleep disturbance
- Possible snoring
- Timing and intensity of hot flashes

Depression
Initial options:

- Sedating antidepressant
- Any antidepressant; wait 3 weeks for stimulant effect to resolve
- Antidepressant + hypnotic
- Psychotherapy

Nocturnal hot flashes
Initial options:

- HRT/ST
- Antidepressant
- Gabapentin
- Soy
- Black cohosh

Sleep-disordered breathing
Polysomnography to gauge severity

Partial or nonresponse
Nasal CPAP, weight loss, dental appliance, or ENT surgery

Partial or nonresponse

- Consider adding HRT/ST, especially in first lifetime depressive episode
- More-intensive psychotherapy

Partial or nonresponse

- Combine approaches
- Consider adding hypnotic

Partial or nonresponse
Consider adding hypnotic

HRT/ST: hormone replacement therapy, short-term (reassess at least annually); ENT: ear, nose, and throat (otolaryngology); CPAP: continuous positive airway pressure

Depressive disorders affect up to 29% of perimenopausal women (depending on the assessment tool used), compared with 8% to 12% of premenopausal women. Menopausal symptoms—hot flashes, poor sleep, memory problems—and not using HRT are associated with depression.³

Causes of midlife depression. Gonadal hormone changes have been implicated as a cause of increased depression in midlife women; declines in serum estradiol and testosterone are inversely associated with depression.⁴ The natural menopause transition (perimenopause) begins during the mid-40s, persists to the early 50s, and lasts an average 2 to 9 years. Estradiol produced by the ovary becomes erratic then decreases. Follicle-stimulating hormone (FSH) and luteinizing hor-

monone (LH) serum levels increase, then plateau and serve as laboratory markers of menopause.⁵

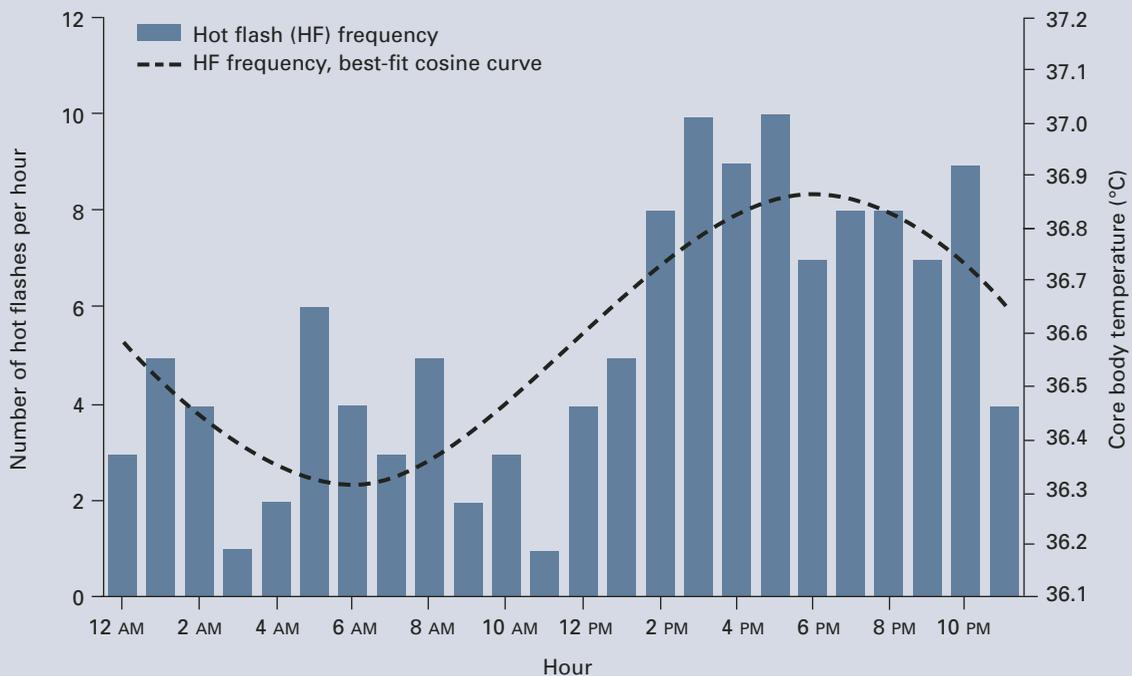
Sociodemographic factors also may contribute to depression, anxiety, and insomnia. A midlife woman may experience role transitions—such as children leaving home and aging parents needing care. She may be adapting to her or her spouse’s retirement or to the loss of her partner by divorce or death. She may be grappling with her own aging and questions about mortality and life purpose.

In the workup, consider medical factors that may worsen sleep problems, such as hot flashes, sleep apnea, thyroid disease, urinary frequency, chronic pain, restless leg syndrome, caffeine use, sedentary lifestyle, and primary insomnia. Some women lose sleep from a bed partner’s snoring or

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Figure 1
Hot flashes are associated with core body temperature changes



Climacteric hot flashes increase in relative frequency in the afternoon and evening. Slight core body temperature changes, as measured with an ingested telemetry pill in this study of 10 symptomatic women, are hypothesized as the hot-flash triggering mechanism.

Source: Reprinted with permission from reference 13.

movement (“spousal arousal”). Stimulating drugs such as theophylline can also play a role.

SLEEP CHANGES AT PERIMENOPAUSE

Sleep changes are among the most common physical and psychological experiences healthy women describe during perimenopause:

- 100 consecutive women surveyed at a menopause clinic reported fatigue (91%), hot flashes (80%), insomnia and early awakenings (77%), and depression (65%).⁶
- Sleep problems were reported by >50% of 203 women interviewed for the Decisions at Menopause Study (DAMES).⁷

- Difficulty sleeping across 2 weeks was reported by 38% of a multi-ethnic population of 12,603 women ages 40 to 55.⁸

Sleep problems occur more often during perimenopause than earlier in life. In a clinic sample of 521 women, Owens et al¹ found insomnia in 33% to 36% of those in premenopause and in 44% to 61% of women during perimenopause. In the total sample of healthy middle-aged women, 42% had sleep complaints, including:

- initial insomnia: 49%
- middle insomnia: 92%
- early morning awakening: 59%.

No association? Individuals experience sleep



Box

Hot flashes: Thermoregulatory changes may set scene for noradrenergic spark

Estrogen deficiency is thought to cause hot flashes via decreased serotonin synthesis and up-regulated 5HT_{2A} receptors—the mediators of heat loss. As a result, a woman's thermoregulatory zone narrows during perimenopause, reducing her tolerance for core body temperature changes. The thermoregulatory nucleus resides in the medial preoptic area of the anterior hypothalamus.

A hot flash begins with facial warmth when core temperatures exceed the thermoregulatory line. Heat spreads to the chest, often accompanied by flushing, diaphoresis, and headache. A woman may feel agitated, irritable, and distressed.

CNS noradrenergic activity may initiate hot flashes. Freedman et al¹³ compared the effects of IV clonidine (an alpha₂ adrenergic agonist) plus yohimbine (an alpha₂ adrenergic antagonist) or placebo in menopausal women with or without vasomotor symptoms. Among 9 symptomatic women, 6 experienced hot flashes when given yohimbine, and none did with placebo. No hot flashes occurred in asymptomatic women. Clonidine increased the duration of peripheral heating needed to trigger a hot flash and reduced the number of hot flashes in symptomatic women, compared with baseline.

quality subjectively, and these assessments may not match those obtained objectively. The Wisconsin Sleep Cohort Study,⁹ for example, found no association between menopause and diminished sleep quality in polysomnographic studies of 589 community-dwelling women. Even so, the peri- and postmenopausal women in the study reported less sleep satisfaction than premenopausal women did.

Most clinicians agree that a woman's subjective experience of sleep is clinically relevant. Thus, rule out underlying sleep disorders before you

attribute a midlife woman's depressive signs and symptoms primarily to menopause.¹⁰

Treatment. Combination therapy may be useful, depending on the patient's psychiatric and medical comorbidities (*Algorithm, page 40*).

TREATING PERIMENOPAUSAL DEPRESSION

HRT. Before the Women's Health Initiative (WHI),¹⁰ guidelines recommended HRT for a first depressive episode during perimenopause and antidepressants for severe depressive symptoms and for women with a history of depression.¹¹ This practice changed when the WHI found risks of thromboembolism, breast cancer, stroke, and coronary artery disease that increased over time with HRT.

HRT remains a short-term treatment option but is no longer considered the first or only approach to mood symptoms at perimenopause. Discuss with your patient potential benefits of short-term HRT for a first episode of depression—especially if she has vasomotor symptoms—versus potential risks.

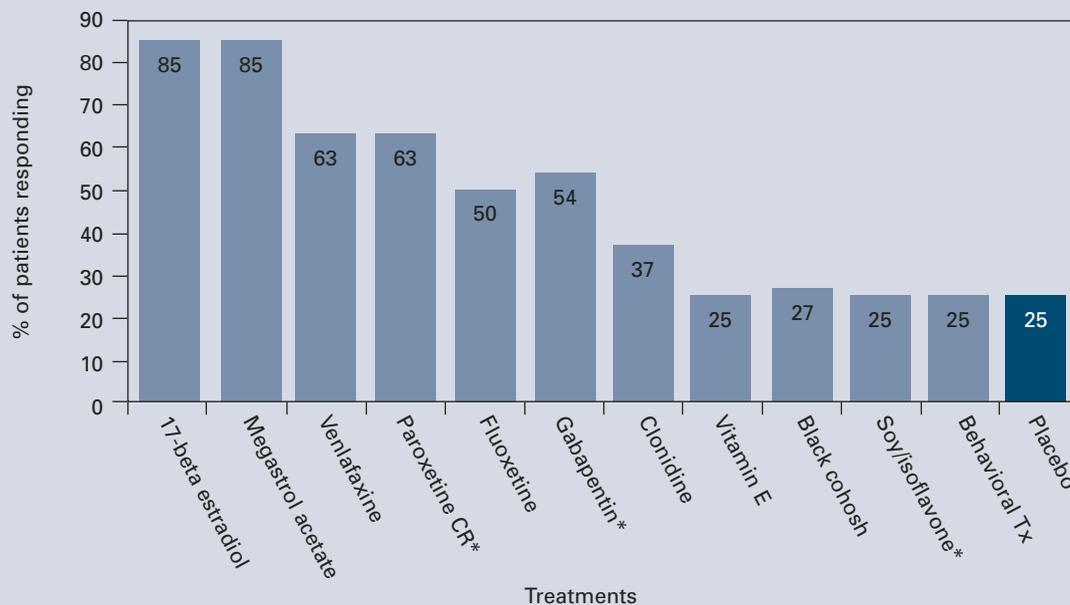
Antidepressants can improve perimenopausal depression, but few studies have tested these agents' effects on sleep. To reduce treatment-associated insomnia:

- select a relatively sedating antidepressant such as mirtazapine
- accept some insomnia for 3 to 4 weeks, until a stimulating antidepressant has had a full effect on mood and its associated side effects would be expected to resolve
- or augment the antidepressant with a hypnotic such as zolpidem, zaleplon, eszopiclone, or trazodone.

When choosing therapy, consider patient factors and insomnia severity. For example, mirtazapine is typically associated with weight gain, so consider other options for overweight patients. Those with severe insomnia may prefer not to wait 3 to 4 weeks for improved sleep. With

Figure 2

Efficacy of hormones, antidepressants, and other hot flash therapies



In randomized clinical trials, hormone therapies were most effective in suppressing hot flashes, followed by antidepressants. In women being treated for natural menopause symptoms (*) or cancer, alternative therapies and placebo showed similar efficacy.

Source: Adapted from reference 16.

hypnotics, consider cost, any coexisting chemical dependency, and potential for morning hangover.

Psychotherapy can help perimenopausal patients accept aging, evaluate relationships, and examine their roles in the lives of more-dependent parents and less-dependent children.

HOT FLASHES AND INSOMNIA

Persistent hot flashes that disturb sleep may cause depression.¹² They can wake a perimenopausal woman repeatedly (*Figure 1, page 43*). The awakenings may be brief—90% last <3 minutes—but a severely affected woman can lose an hour of sleep in a night.¹³ Even after a hot flash resolves, other factors such as anxiety may keep her awake.

Up to 85% of perimenopausal women experience hot flashes, especially during the first year

after menses cease. Hot flashes persist for 5 years after menopause in 25% of women and indefinitely in a minority (*Box*).¹⁴

Risk factors for nocturnal hot flashes include surgical menopause, Caucasian versus Asian ethnicity, lack of exercise, and nicotine use.⁸ Women suffering anxiety and stress also are at increased risk.¹⁵

HOT-FLASH THERAPIES

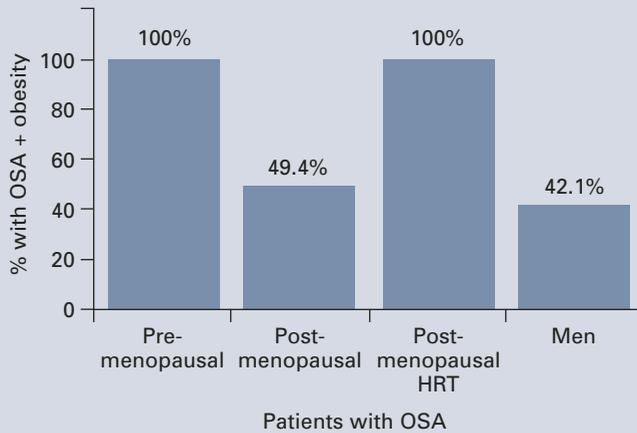
Placebo-controlled trials of hot flash therapies have found efficacies from 85% for HRT to 25% for placebo, vitamin E, black cohosh, soy, and behavioral therapy (*Figure 2*).¹⁶ Most trials were not designed to test the link between hot flashes and sleep, and many enrolled cancer patients not experiencing natural menopause. With the 25% placebo response rate, some therapies' efficacy is unclear.

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Figure 3

Increased OSA in postmenopausal women is unrelated to obesity (BMI >32)



Obstructive sleep apnea (OSA) in 1,000 women and 741 men was associated exclusively with obesity in premenopausal women and postmenopausal women using HRT, but nearly one-half of the postmenopausal women with OSA were not obese.

Source: Adapted from reference 23.

blind, placebo-controlled trial (RCT). Hot flashes in those receiving black cohosh decreased from 4.9 to 0.7 daily, compared with reductions of 5.2 to 3.2 in women receiving estrogen and 5.1 to 3.1 in those receiving placebo.²¹ As a result, the National Institutes of Health is funding a 12-month, RCT to determine whether black cohosh reduces hot flash frequency and intensity.

Alternative agents are widely used and warrant study. Those shown to be safe can be used alone or with other therapies, but advise the patient that these agents may not be effective. Relaxation and exercise may decrease hot flashes,²² although some outcomes have been similar to a placebo response.

SLEEP APNEA AT PERIMENOPAUSE

Obstructive sleep apnea (OSA), although more common in men than women, appears to increase during perimenopause. Women with untreated

OSA are twice as likely as men to be treated for depression, less likely to report excessive daytime sleepiness and snoring, and more likely to present with depression, anxiety, and morning headache.

Bixler et al²³ interviewed 12,219 women and 4,364 men ages 20 to 100 and conducted 1-night sleep studies in 1,000 women and 741 men. OSA rates were 3.9% in men, 0.6% in premenopausal women, 2.7% in postmenopausal women not taking HRT, and 0.5% in postmenopausal women taking HRT.

The risk of sleep-disordered breathing is lower during early menopause and peaks at approximately age 65. Declining hormones likely play a role; progesterone increases ventilatory drive, and estrogen increases ventilatory centers' sensitivity to progesterone's stimulant effect. In small studies, exogenous progesterone has shown a slight effect in improving OSA.²⁴

OSA's transient, repetitive upper airway collapse increases inspiratory effort and may cause hypoxemia. Repeated arousals can lead to prolonged awakenings and unrefreshing sleep. Snoring and increased body mass index are strongly associated factors, although the Wisconsin Sleep Cohort Study¹⁰ showed an increase in sleep apnea in perimenopausal women that was unrelated to increased body mass index.

Obesity may not explain the increase in obstructive sleep apnea at perimenopause (*Figure 3*),²⁸ although body fat distribution does change with aging. Women at perimenopause are likely to develop abdominal weight distribution.

Treatment. In the Sleep Heart Health Study²⁵ of 2,852 women age 50 or older, HRT users had one-half the apnea prevalence of nonusers (6% vs 14%). HRT users were less likely to awaken at night and to get inadequate sleep. Snoring rates were similar (25% for HRT users, 23% for nonusers).

Nasal continuous positive airway pressure

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Related resources

- ▶ American College of Obstetricians and Gynecologists. www.acog.org
- ▶ The North American Menopause Society. www.menopause.org

DRUG BRAND NAMES

Conjugated estrogens • Premarin
Eszopiclone • Lunesta
Fluoxetine • Prozac
Gabapentin • Neurontin
Medroxyprogesterone • Provera
Micronized progesterone • Prometrium

Mirtazapine • Remeron
Trazodone • Desyrel
Venlafaxine • Effexor
Zaleplon • Sonata
Zolpidem • Ambien

DISCLOSURES

Dr. Krahn reports no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

(CPAP) is the mainstay of apnea treatment, although some women appear to have difficulty accepting CPAP.²⁶ Weight loss and moderate exercise can help manage weight and improve sleep quality by increasing slow-wave sleep. Regular exercise also may improve depressed mood.

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Disturbed sleep in perimenopause overlaps with depression, hot flashes, and obstructive sleep apnea. Sleep assessment is needed to formulate a treatment plan. HRT eases symptoms, but long-term use is not recommended. Antidepressants may relieve depression and hot flashes but worsen insomnia.

BottomLine