Sleep in the Menopause Transition

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# Symptoms Attributed to Menopause Transition

**Strong evidence**

1. Vasomotor symptoms (hot flashes, night sweats)
2. **Sleep disturbance**
3. Depression
4. Vaginal dryness
5. Breast tenderness

**Weak evidence**

1. Cognitive problems
2. Sexual dysfunction
3. Menorrhagia
4. Urinary incontinence
5. Back pain
6. Stiff or painful joints

### Common Sources of Sleep Disturbance in Menopause Transition

<table>
<thead>
<tr>
<th>Menopause-specific</th>
<th>General</th>
<th>Sleep disorders</th>
<th>Mental health</th>
<th>Health</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hot flashes</strong></td>
<td>Stress</td>
<td>Primary insomnia</td>
<td>Depression</td>
<td>Chronic pain, fibromyalgia</td>
</tr>
<tr>
<td>↓ estradiol</td>
<td>Age-related</td>
<td>Obstructive sleep apnea</td>
<td>Anxiety</td>
<td>Obesity</td>
</tr>
<tr>
<td>↑ FSH</td>
<td>Caffeine</td>
<td>Periodic limb movement disorder</td>
<td></td>
<td>GERD</td>
</tr>
<tr>
<td>↓ inhibin B</td>
<td></td>
<td>Restless legs syndrome</td>
<td></td>
<td>HTN</td>
</tr>
<tr>
<td>↑ progesterone</td>
<td></td>
<td></td>
<td></td>
<td>Thyroid disease</td>
</tr>
<tr>
<td>↑ testosterone</td>
<td></td>
<td></td>
<td></td>
<td>Cancer</td>
</tr>
</tbody>
</table>

Overview

1. Hot flash associated sleep interruption

2. Are there sleep changes independent of hot flashes?
   - Hormone-related changes
   - Sleep apnea, restless legs syndrome, periodic limb movements

3. Treatment of sleep disturbance and insomnia associated with hot flashes and menopause
Overview—Part 1

1. Hot flash associated sleep interruption

2. Are there sleep changes independent of hot flashes?
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3. Treatment of sleep disturbance and insomnia associated with hot flashes and menopause
Impact of new-onset nighttime hot flashes on PSG sleep fragmentation

62% increase in WASO for every additional nighttime hot flash

3% increase in awakenings from baseline for every additional nighttime hot flash

Results for objective nighttime hot flashes are consistent

PSG = polysomnography
WASO = wake time after sleep onset (min)

Joffe, Sleep 2013
Moving Away from a 1-to-1 Link Between Hot Flashes and Sleep Interruption

1. Pairing of hot flashes with wakefulness
   - Approximately 2/3 of hot flashes linked with an awakening\(^1\)\(^-\)\(^3\)
   - Number of awakenings and sleep stage transitions exceeds number of hot flashes\(^1\)\(^,\)\(^2\)
   - Approximately ¼ of wake time attributed to hot flashes\(^3\)

   \[\text{Uncoupling of individual hot flashes from individual awakenings}\]

2. Physiologic processes underlying the hot flash state — *rather than the hot flash event per se* — may be responsible in part for sleep fragmentation
   a. Preceding cortical activation\(^4\)
   b. Autonomic system perturbation
      -↑ sympathetic\(^5\) and/or ↓ parasympathetic\(^6,\)\(^7\) tone
   c. Preceding temperature rise\(^8\)

   \[\rightarrow \text{Move from thinking of physiologic changes around hot flash event to the hot flashes state}\]
   \[\rightarrow\text{CNS activity may drive hot flashes and sleep interruption in parallel rather than exclusively through a linear relationship}\]

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Overview—Part 2

1. Hot flash associated sleep interruption

2. Are there sleep changes independent of hot flashes?
   - Hormone-related changes
   - Sleep apnea, restless legs syndrome, periodic limb movements

3. Treatment of sleep disturbance and insomnia associated with hot flashes and menopause
Is there a “menopausal sleep disorder”?  

<table>
<thead>
<tr>
<th>Hormonal factors</th>
<th>Primary sleep disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Menopause stage associations</td>
<td>1. Obstructive sleep apnea (OSA)</td>
</tr>
<tr>
<td>2. Link with reproductive hormone changes</td>
<td>2. Restless legs syndrome (RLS) and periodic limb movement disorder (PLMD)</td>
</tr>
<tr>
<td>3. Is there a mediating role of co-occurring hot flashes?</td>
<td></td>
</tr>
</tbody>
</table>
Summary of evidence for “menopausal sleep disorder” independent of hot flashes

Hormonal factors

☑ Evidence for a “menopausal sleep disorder”

☑ Independent of hot flashes

☒ Related to menopause stage or to biomarkers of reduced ovarian reserve

☑ Related to changing reproductive hormone dynamics of menopause transition

Primary sleep disorders

☑ Sleep apnea risk increases 2–3 fold

☑ Related to low estradiol and low progesterone

☑ PLMD associated with reduced sleep efficiency

1. Hot flash associated sleep interruption

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3. Treatment of sleep disturbance and insomnia associated with hot flashes and menopause
Co-occurring Causes of Sleep Disturbance

Spielman’s “3P model”: predisposing, precipitating, and perpetuating factors

- Hot flashes
- Stress
- Depression
- Primary insomnia
- Sleep apnea
- RLS/PLMD

RLS = restless legs syndrome
PLMD = period limb movement disorder

1 Spielman, Clin Psychol Rev 1986
Behavioral Treatment of Hot Flash-associated Sleep Disturbance

**CBTi for insomnia symptoms**

- 6-session telephone CBT-insomnia vs. menopause education control
- 106 peri/postmenopause with ISI ≥12 and hot flashes
- CBTi more effective at 8 weeks and effect sustained at 24 weeks (p<0.01)

**Small benefits in less symptomatic patients**

1. CBT for menopause
2. Exercise
3. Melatonin
4. Acupuncture

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ISI = insomnia severity index
CBT = cognitive behavioral therapy

Pharmacologic Approaches to Treating Hot Flash-associated Sleep Disturbance

Clinical trials supporting efficacy

1. Hormone therapy
   – Including estrogen + SERM combination

2. SSRI/SNRI

3. Gabapentin

4. GABA-A receptor non-benzodiazepines

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Summary of Pharmacological Approaches to Treating Sleep Disturbance in Women with Hot Flashes

Target both

- **SSRI/SNRI**
  - escitalopram\(^1\)
  - paroxetine mesylate\(^2\)
  - venlafaxine\(^3\)

- **Gabapentin**\(^4\)

- **Hormone therapy**\(^3,5\)
  - Bazedoxifene/CEE\(^6\)

- **Hypnotics**\(^7,8,9\)
  - CBTi\(^10\)

FDA warning 2013
- Suggest reducing zolpidem dose to 5-mg or 6.25-mg
- Because of persistent detectable levels and next morning side effects
- Especially in women

http://www.fda.gov/Drugs/DrugSafety/ucm334033.htm

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Conclusions

1. Sleep disturbance characterized primarily by sleep interruption is common during the menopause transition.

2. Hot flashes contribute importantly but not exclusively to sleep interruption in midlife women.

3. Links between hot flashes and awakenings suggest that it is not a 1-to-1 relationship.

4. Factors contributing to sleep disruption independent of hot flashes:
   - Changing reproductive hormone dynamics of menopause transition (but not progressive reproductive aging)
   - Obstructive sleep apnea, RLS/PLMD

5. Treatment of menopause-associated sleep disturbance can involve primary therapy for hot flashes and/or primary behavioral and pharmacologic therapies for insomnia.