Depression in the Menopause Transition: Role of Female Reproductive Hormones, Hot Flashes, and Sleep

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1. Depressive symptoms vs. clinical depression
2. Causal factors
   - Prior depression
   - Impact of reproductive hormones
   - Role of hot flashes and sleep disruption
3. Treatment approaches

Depressive symptoms vs. major depression

Not just a matter of degree

Depressive symptoms
- Milder
- Emotions out of control
- Brief awakenings
- Hot flashes
- On/off distress
- Variable trajectories

Major depression
- Clinical syndrome
- Worthlessness, guilt
- Pervasive, persistent
- More extensive sleep disruption
- Interference with function
- Suicide risk

Clinical considerations when evaluating contribution of menopause to depression

1. Depressive symptoms vs. clinical depression
2. Extent of interference with function
3. Past history of depression
4. Co-occurring / precipitating stressful life events
5. Presence of / temporal relationship to
   - Menstrual pattern changes
   - Hot flashes & night sweats
   - Associated sleep interruption
6. Severity and nature of sleep disturbance
   - Brief awakenings only
   - Insomnia: Sleep onset +/- or maintenance / early morning awakening
   - Hypersomnia
   - Snoring, gasping, kicking, daytime sleepiness

Hickey M, Menopause 2016
Factors associated with depressive symptoms and major depression during peri/postmenopause

<table>
<thead>
<tr>
<th>Menopause symptoms</th>
<th>Hot flashes and night sweats</th>
<th>Sleep disturbance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormone dynamics</td>
<td>↑ FSH, ↑ LH, ↓ inhibin</td>
<td>Variability in estradiol and FSH</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>Prior depression</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Demographic factors</td>
<td>↑ BMI, smoking, ↓ education, Hispanic, Japanese</td>
<td></td>
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<tr>
<td>Psychosocial factors</td>
<td>Stressful life events, financial strain, poor social support</td>
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FSH = follicle-stimulating hormone; LH = luteinizing hormone

Associations with hormones, hot flashes, & sleep disturbance vary by depression presentation

**Depressive symptoms associated with:**
1. Perimenopausal hormone profile
2. Hot flashes
3. Demographic and psychosocial factors

**Recurrent clinical depression associated with:**
1. Anxiety preceding menopause
2. Demographic and psychosocial factors typical of clinical depression
3. Not with perimenopausal hormone profile
4. Not with hot flashes

**First lifetime clinical depression associated with:**
1. Hot flashes (trend)
2. Demographic and psychosocial factors typical of clinical depression
3. Medical problems preceding menopause

Risk of Depressive Symptoms and Major Depression Decreases With Time After Final Menstrual Period

**Good News!**

Bromberger, J. Psychol Med 2011

Risk of major depressive episodes decreases with time after FMP

Years from FMP

- OR 5.0 ≤2 yrs
- OR 2.93 >2 yrs

**Potential pathways to menopausal depression**

1. Changes in reproductive hormones
2. Standard CNS factors
3. Psychosocial and other factors
4. Depression

- Hot flashes
- Sleep disturbance


Bromberger, J. Psychol Med 2011
Perimenopausal hormone changes are dynamic

Aims
1. To determine if perimenopausal hormone dynamics are associated with depressive symptom severity
   a. Estradiol variability
   b. Progesterone peaks

Clinical studies show that mood is better as ovarian activity is more normalized in perimenopausal women. Conversely, the more abnormal the hormonal profile, the worse the mood.

Aims
1. To determine if hot flashes are associated with depressive symptom onset
   a. Nighttime hot flashes?
   b. Daytime hot flashes?
2. To examine if sleep fragmentation mediates the association between hot flashes and depressive symptoms

MADRS = Montgomery Asberg Depression Rating Scale
Perimenopause and depression

1. Depressive symptoms and clinical depression during the perimenopause are distinct entities with different risk profiles
2. Major depression associated with:
   • Prior depression episodes
3. Depressive symptoms associated with:
   • Changing hormone dynamic
   • Hot flashes and sleep disturbance
4. Implications for treatment approaches

Patient considerations

Relevance of menopause to mood state?
1. Coincident vs. linked vs. susceptibility factor
2. Stressful life events, precipitants
3. Midlife and menopause experience and attitudes

Menopause and risk profile
1. Perimenopause (early vs. late) vs. postmenopause
2. Presence of hot flashes
3. Psychiatric history/antidepressant benefits and risk
4. Estrogen therapy risk profile

Symptom presentation
1. Temporal relationship to hormonal and perimenopausal changes
2. Co-occurrence of hot flashes and sleep disturbance
3. Mild depressive symptoms vs. 1st lifetime onset clinical depression vs. recurrent depression episode
Hormone therapy and menopause-associated depression

- Peri- and early postmenopausal women with hot flashes with depressive symptoms are main group to benefit from hormone therapy\(^1,2\)
  - Ineffective for older postmenopausal women further from FMP without hot flashes\(^3\)

- Estrogen is not primary therapy for women with an episode of clinical depression
  - Secondary benefit in women with hot flashes?

\(^{1}\) Soares, Arch Gen Psych 2001; \(^{2}\) Schmidt, Am J OB/GYN 2000; \(^{3}\) Morrison Bio Psych 2004

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Treatment of Menopause-Associated Depression

1. Antidepressants (all serotonergic agents)
   - Desvenlafaxine, citalopram, escitalopram, mirtazapine, duloxetine, venlafaxine\(^1,5\)
   - Response to SSRI and SNRI does not vary by menopause status or co-treatment with hormone therapy\(^6,7\)
     - No advantage of specific agents

2. Psychotherapy

3. May need to augment with specific therapy targeting nighttime hot flashes and sleep disturbance

\(^{1}\) Kornstein, J Clin Psych 2010; \(^{2}\) Joffe, J Clin Psych 2007; \(^{3}\) Joffe, J Women’s Health Genit Based Med 2001; \(^{4}\) Soares, J Clin Psych 2003; \(^{5}\) Dias, Menopause 2006; \(^{6}\) Kornstein, Menopause 2014; \(^{7}\) Kornstein, JCP 2014

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SSRI and SNRI RCT for menopause-associated major depression
Summary: Depression during peri/postmenopause

1. Mood disturbance is a common problem during the menopause transition

2. Presents as major depression or mild subsyndromal depressive symptoms
   - Risk factors and treatment implications

3. Major depression
   - Primarily recurrent episodes
   - Not associated with perimenopausal hormone changes or hot flashes
   - Sleep disturbance not restricted to brief awakenings
   - First line therapy is traditional psychotropic agents (SSRI/SNRI) and psychotherapy

4. Depressive symptoms
   - Associated with changing perimenopausal hormone dynamics
   - Associated with nighttime (not daytime) hot flashes and sleep interruption
   - Off-label benefit of estrogen therapy (and hormonal contraceptives)