The Menopausal Transition and Depression

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Disclosures

Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose.
Affective Disorders in Women

Risk for Depression by Age and Sex

Depression Across the Female Reproductive Cycle

- Menarche
- Pregnancy
- Menopause

- Depression during pregnancy
- Postpartum Depression
- Premenstrual exacerbation of depression or Premenstrual dysphoric disorder (PMDD)
- Depression during the perimenopausal period
Risk for Mood Disorder During the Menopause Transition

Are Women At increased Risk for New Onset of Depression?
### NEW ONSET Of Depression and Menopause Transition: Population Studies

<table>
<thead>
<tr>
<th>Studies</th>
<th>Population</th>
<th>References</th>
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<tbody>
<tr>
<td>The Study of Women’s Health Across the Nation (SWAN)</td>
<td>N=266 midlife women with no history of depression for 7 years</td>
<td>Bromberger et al. Psychol Med. 2009;39:55-64.</td>
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<td>The Harvard Study of Moods and Cycles</td>
<td>N=460 women with no history of depression for up to 8 years</td>
<td>Cohen et al. Arch Gen Psychiatry. 2006;63:385-390.</td>
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<td>The Penn Ovarian Aging Study</td>
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Menopausal status was significantly associated with incidence of higher depressive symptoms. The highest risk was observed in transition phases.

**Penn Ovarian Aging Study, N=436**

- Menopausal status was significantly associated with incidence of higher depressive symptoms.
- Highest risk observed in transition phases.

CES-D = Center for Epidemiologic Studies Depression Scale.
CES-D score $\geq 16$ signify high depressive symptoms.

Freeman EW. Arch Gen Psychiatry. 2004;61:62-70.
The risk for depressive onset starts increasing in early perimenopause with the greatest risk in late perimenopause.

N=29

Relative Risk of Depressive Onset

- Premenopause: 6-36 years prior to FMP
- Early perimenopause: 2-5 years prior to FMP
- Late perimenopause: 0-24 months surrounding FMP

FMP = final menstrual period
Risk for New Onset of Depression During the Menopausal Transition

The Harvard Study of Moods and Cycles

Lee S. Cohen, MD; Claudio N. Soares, MD, PhD; Allison F. Vitonis, BA; Michael W. Otto, PhD; Bernard L. Harlow, PhD

Context: Transition to menopause has long been considered a period of increased risk for depressive symptoms. However, it is unclear whether this period is one of increased risk for major depressive disorder, particularly for women who have not had a previous episode of depression.

Objective: To examine the association between the menopausal transition and onset of first lifetime episode of depression among women with no history of mood disturbance.

Design: Longitudinal, prospective cohort study.

Setting: A population-based cross-sectional sample.

Participants: Premenopausal women, 36 to 45 years of age, with no lifetime diagnosis of major depression (N=460), residing in 7 Boston, Mass, metropolitan area communities.

Main Outcome Measure: Incidence of new onset of depression based on structured clinical interviews, Center for Epidemiologic Studies Depression Scale scores, and an operational construct for depression.

Results: Premenopausal women with no lifetime history of major depression who entered the perimenopause were twice as likely to develop significant depressive symptoms as women who remained premenopausal, after adjustment for age at study enrollment and history of negative life events. The increased risk for depression was somewhat greater in women with self-reported vasomotor symptoms.

Conclusions: The current study suggests that within a similarly aged population of women with no lifetime history of depression, those who enter the menopausal transition earlier have a significant risk for first onset of depression. Further studies are needed to determine more definitively whether other factors, such as the presence of vasomotor symptoms, use of hormone therapy, and the occurrence of adverse life events, independently modify this risk. Physical symptoms associated with the menopausal transition and mood changes seen during this period may affect many women as they age and may lead to a significant burden of illness.

Arch Gen Psychiatry. 2006;63:385-390
Increased Risk for First Episode of MDD During Menopausal Transition (cont’d)

• Risk of MDD during menopausal transition is high (OR=1.9), even among women with no history of MDD

• Risk for MDD higher among women with vasomotor symptoms (OR=2.5)

• Adverse life events may exacerbate the risk for depression, BUT are not necessary for its occurrence

Menopausal Transition* (lasts average of 5 y)

<table>
<thead>
<tr>
<th>Perimenopause</th>
<th>Early</th>
<th>Late‡</th>
<th>Postmenopause (recognized 12 months post-FMP)</th>
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<tbody>
<tr>
<td>Variable cycle length§</td>
<td>≥2 skipped cycles &amp; interval of amenorrhea⊥</td>
<td>FMP Amenorrhea x 12 mos</td>
<td>Early‡</td>
</tr>
</tbody>
</table>

Postmenopause

Postmenopause

Higher depressive symptoms (CES-D) associated with increased variability (within subject) of levels of:

- Estradiol ($P = .03$)
- FSH ($P < .001$)
- LH ($P = .005$)
Treatment of Perimenopausal and Menopausal Women with Depression

Diagnostic Challenges
Clinical Presentation

• Most women have a history of MDD, recurrence of depression during transition, similar symptoms
• Typical symptoms: anhedonia, irritability, sleep disruption, fatigue, poor concentration
• “Mood swings” - rule out bipolar disorder
• Psychosocial factors specific to midlife (e.g., caring for aging parents, children leaving home, decline in health)
• Comorbid medical illness
Core Menopause Symptoms

• **Vasomotor Symptoms: Night sweats, hot flashes**
  – Affect 60% to 80% of perimenopausal women

• **Sleep Disturbance**
  – 2-fold increase vs. premenopausal women

• **Depressive Symptoms**
  – 2-fold increase vs. premenopausal women

• **Vaginal Dryness, Changes in Sexual Function**
  – 25% to 60% of women report moderate to severe vaginal dryness or dyspareunia

*Ohayon MM. *Arch Intern Med.* 2006;166(12):1262-1268.*
*Freeman EW et al. *Arch Gen Psychiatry.* 2006;63(4):375-382.*
*Cohen LS et al. *Arch Gen Psychiatry.* 2006;63(4):385-390.*
Menopause vs. Depression-Related Symptoms

**Depression**
- Depression
- Irritability
- Anhedonia
- Thoughts of Death
- Worthlessness

**Menopause**
- Energy
- Concentration
- Sleep
- Weight Change
- Low Libido
- Hot Flushes
- Night Sweats
- Vaginal Dryness

Potential Mechanisms of Perimenopausal Depressive Symptoms

Estrogen has multiple effects on neurotransmitter systems and brain regions involved in MDD and menopausal symptoms (VMS).

During times of estrogen fluctuations/decline, loss of these effects might predispose some women to dysregulation of affected brain regions.
Perimenopausal women with depression are more likely to have hot flashes than peri women without depression.
Treatment of Perimenopausal and Menopausal Women with Depression

Selecting the Appropriate Intervention
Multiple Targets for Intervention

Perimenopausal Depressive Symptoms

- Estrogen Withdrawal
  - SSRIs, SNRIs
  - Gabapentin

- Hot Flushes
  - Hormone Replacement Therapy

- Insomnia
  - Z-Hypnotics
  - BZDs
  - CBT-I

Antidepressants
Psychotherapy
Estrogen-Based Therapies for the Treatment of MDD in Perimenopausal Women

Research Article

Efficacy of Estradiol in Perimenopausal Depression: So Much Promise and So Few Answers

David R. Rubinow, M.D., 1* Sarah Lanier Johnson, B.S., 1 Peter J. Schmidt, M.D., 2 Susan Girdler, Ph.D., 1 and Bradley Gaynes, M.D. M.P.H. 1

- 25 RCT on the effects of estrogen therapy on mood
- Only 5 included symptomatic (depressed) women
- Only 2 E2 RTCs for perimenopausal depression
Treatment of Perimenopausal:
Hormonal Interventions

- RCTs with 17β-estradiol
  - Response in 80% of women on estradiol vs. 20% in placebo \textit{(Schmidt 2000)}
  - Remission in 68% of women on estradiol vs. 20% with placebo \textit{(Soares 2001)}
- Primarily in women with vasomotor symptoms
- Secondary to antidepressant effects or to improvements in hot flashes and sleep?
- Perimenopausal women: estrogen superior to placebo
- Little evidence to indicate that estrogen is effective for POST-menopausal depression
- Studies were carried out in women with unopposed estrogen
- No RCTs of combination estrogen plus progestogen for depression

\textsuperscript{1} Schmidt, \textit{Am J OBGYN} 2000; \textsuperscript{2} Soares, \textit{Arch Gen Psych} 2001;
Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results From the Women’s Health Initiative Randomized Controlled Trial

[Original Contribution: JAMA-EXPRESS]

Writing Group for the Women’s Health Initiative Investigators

Estrogen Plus Progestin and the Incidence of Dementia and Mild Cognitive Impairment in Postmenopausal Women: The Women’s Health Initiative Memory Study: A Randomized Controlled Trial

[Original Contribution: JAMA-EXPRESS]

Shumaker, Sally A. PhD; Legault, Claudine PhD; Rapp, Stephen R. PhD; Thal, Leon MD; Wallace, Robert B. MD; Ockene, Judith K. PhD, MEd; Hendrix, Susan L. DO; Jones, Beverly N. III MD; Assaf, Ann Louise R. PhD; Jackson, Rebecca D. MD; Kotchen, Jane Morley MD, MPH; Wasserheit-Smoller, Sylvia PhD; Wactawski-Wende, Jean PhD; WHIMS Investigators
Increased risk of breast cancer a factor, government says

August 14, 2002 Posted: 11:56 AM EDT (1556 GMT)

WASHINGTON (CNN) -- In a move that may affect millions of women, U.S. government scientists Tuesday stopped a major study of hormone replacement therapy on the risks and benefits of combined estrogen and progestin in healthy menopausal women, citing an increased risk of invasive breast cancer.

Researchers from the National Heart, Lung and Blood Institute of the National Institutes of Health also found increases in coronary heart disease, stroke and pulmonary embolism.
Prescriptions of HRT and Antidepressants* Prior to and After WHI Results

Bottom: Linear regression models of the number of prescriptions against time, for each prescription type (HRT and SA) and for each time period (11 months before and 11 months after July 2002)

*Citalopram, fluoxetine, sertraline, fluvoxamine, paroxetine, venlafaxine, nefazadone, and trazodone.

HRT = hormone replacement therapy; WHI = Women’s Health Initiative; SA = serotonergic antidepressant.

Impact of WHI on Treatment of Women During Menopause Transition

Decreased hormone therapy use

+ Lowest dose, shortest duration

More symptomatic women

WHI = Women’s Health Initiative.
Can estrogen replacement therapy prevent perimenopausal depression?

- 172 euthymic perimenopausal and early postmenopausal women
- Randomly assigned to receive either transdermal estradiol (0.1 mg/d) plus intermittent oral micronized progesterone or placebo
- After 12 months, women receiving active HRT were less likely to develop depressive symptoms compared with women receiving placebo (32.3% vs. 17.3%)
- Greater benefits for women with stressful life events in the preceding 6 months
- Trend toward increased benefit in peri- vs. post-menopausal women
Treatment of Perimenopausal MDD: Antidepressants

- Two large RCTs support the use of desvenlafaxine, superior to placebo
- Positive results in open trials of SSRIs and SNRIs: citalopram, escitalopram, venlafaxine, vortioxetine, mirtazapine
- Dosage range similar to non-menopausal MDD
- Beneficial effects on sleep, VMS, anxiety, pain
- Effective for peri- and postmenopausal women

Treatment of Menopausal Symptoms

• Hormone replacement therapy – gold standard
  – For severe symptoms in healthy younger women
  – Limit treatment to 5 years
• SSRIs, SNRIs improve vasomotor symptoms, depression
• Gabapentin improves VMS and sleep, pain
Black cohosh, a multibotanical herbal product, and soy intake did not appear to significantly reduce the frequency or severity of menopause-related hot flushes or night sweats.
Treatment of hot flashes with gabapentin

Low-dose (900mg/d) effective

N = 240

*P < 0.0001

Hot flash score reduction

Gabapentin 900-mg/day: 46%*
Gabapentin 300-mg/day: 31%
Placebo: 15%

Moderate-dose (2400mg/d) as effective as estrogen

N = 60

*P = 0.01

Hot flash score reduction

Gabapentin 2400-mg/day: 71%*
Estrogen (CEE 0.625-mg/day): 72%
Placebo: 54%

Pandya KJ et al, Lancet 2005

Reddy SY et al. OBGYN 2006
Sleep Disturbance in Peri/Postmenopausal Women

Sleep maintenance is most common symptom

Waking up repeatedly
Falling asleep

1 Kravitz, Menopause 2003; data for Caucasians
2 Kravitz, Sleep 2008

* p<0.005 vs. premenopause
Treatment of Sleep Disturbance in Perimenopausal Women

- Non-benzodiazepine sedative hypnotics
  - Ezopiclone improved sleep, decreased VMS
- SSRIs – Not sedating but may improve anxiety, VMS
- Gabapentin – Mildly Sedating, improves anxiety, RLS
- CBT-I – Effective and non-menopausal patients, CBT may also be used to treat VMS
Treatment of Menopause-Associated Symptoms

Hot Flashes
- Estrogen therapy
- Anti-epileptics

Sleep Disturbance
- GABA-A agents

Depression
- Serotonergic agents
Novel Strategies for the Treatment of Menopausal Symptoms

- Stellate ganglion blockade – VMS
- Acupuncture- VMS
- Neurokinin 3 Receptor Antagonists – VMS
- Amodafenil – fatigue, cognitive function
- New Study: Pregnenolone (neurosteroid) for menopausal depression
Conclusions

1. Etiology of menopause-associated depression is not precisely known

2. Co-occurrence of hot flashes, sleep disturbance, and depression suggests
   - Shared mechanisms
   - Cascade of effects
Current State of Treatment Options

- Antidepressants remain the treatment of choice for depression across the female life cycle.
  - Limited by side effect profile
  - Not effective or fully effective for all patients

- Hormonal strategies can be helpful for the treatment of menopause-related depressive symptoms
  - Either alone or in combination with anti-depressant
  - Risks associated with long-term treatment

- Limited evidence for integrative/complementary and alternative medicine treatment options despite popularity
Treatment Guidelines

- Antidepressants first line treatment for MDD
  - Past response guides selection
  - Consideration of side effects (sexual side effects with SSRIs, paroxetine, weight gain with mirtazapine)

- Menopausal symptoms may affect response
  - Assess for VMS – gabapentin
  - Assess sleep – gabapentin, Z-hypnotics, BZDs, CBT-I

- Consider adjunctive psychotherapy
Unmet Needs

1. Available treatments are limited to serotonergic antidepressants and traditional hormone replacement therapy

2. No treatments target all aspects of symptom domains- mood, VMS, sleep, anxiety

3. Many patients prefer non-SSRI/SNRI and non-estrogen related treatments

4. Available treatments are not rapidly acting

5. No treatments have received a specific FDA indication for perimenopause-related MDD