Disclosure

Relevant Financial Relationships
None

Off-Label/Investigational Uses
No antidepressants or hormonal therapies are specifically approved for treating depression during the menopause transition
Learning Objectives

• Summarize the main findings of studies linking clinically significant depression with the menopause transition

• Describe key etiological hypotheses linking clinically significant depression with the menopause transition

• Define treatment options for women with depression during the menopause transition
Outline

• Does the menopause transition increase the risk for clinically significant depression?
• If so, who is at higher risk?
• What are the major hypotheses linking the two?
• How is depression related to the menopause transition (D-MT) diagnosed?
• How is it treated?
Natural menopause

- **Natural menopause**
  - Permanent cessation of menstruation
  - 12 consecutive months of amenorrhea
  - Median age (U.S.), 51 years

- **Endocrine changes**
  - Tonic elevation of gonadotropins (FSH, LH)
  - Tonic reduction of ovarian steroids (E2, progesterone)
Menopause transition

• **Menopause transition**
  • Defined by menstrual cycle irregularity
  • Generally between 45-49 years
  • ~4 years (range 0-11 years)

• **Stages**
  • Early- follicular phase shortens
  • Middle- menstrual cycle irregularity ensues
  • Late- more prolonged amenorrhea

# Prevalence of increased depressive symptoms (peri- vs. pre-menopause)\textsuperscript{a}

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Age range</th>
<th>Measure</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown et al. 2009</td>
<td>639</td>
<td>45-54 yrs.</td>
<td>CES-D\textsuperscript{b}</td>
<td>Early/late: 1.50 (1.02-2.21)\textsuperscript{*}</td>
</tr>
<tr>
<td>Gallicchio et al. 2007</td>
<td>634</td>
<td>45-54 yrs.</td>
<td>CES-D\textsuperscript{b}</td>
<td>Early/late: 1.24 (0.83-1.86)</td>
</tr>
<tr>
<td>Bromberger et al. 2004</td>
<td>3,015</td>
<td>42-52 yrs.</td>
<td>CES-D\textsuperscript{b}</td>
<td>Early: 2.45 (1.32-4.55)\textsuperscript{†}</td>
</tr>
<tr>
<td>Maki et al. 2012</td>
<td>1,170</td>
<td>30-65 yrs.</td>
<td>CES-D\textsuperscript{b}</td>
<td>Early: 1.74 (1.17-2.60) Late: 1.18 (0.63-2.22)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Age range</th>
<th>Measure</th>
<th>F, p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mauas et al. 2014</td>
<td>376</td>
<td>35-60 yrs.</td>
<td>BDI-II</td>
<td>Early: (F_{(1,349)} = 4.6, p=0.03) Late: (F_{(1,349)} = 3.8, p=0.05)</td>
</tr>
</tbody>
</table>

\textsuperscript{*} Unadjusted analysis only; \textsuperscript{†} Hispanic women; overall sample, OR 1.22 (95% CI 1.00-1.50)

\textsuperscript{a} U.S. samples only; \textsuperscript{b} Elevated depressive symptoms defined as CES-D score $\geq 16$.

BDI-II = Beck Depression Inventory-II; CES-D = Center for Epidemiologic Studies Depression scale.
Increased depressive symptoms and MDD diagnosis: pooled effect size estimates

- Meta-analysis of 4 longitudinal studies (4,002 subjects)
- Depressive symptoms measured by standard symptom inventories
- MDD diagnoses made using structured interviews

<table>
<thead>
<tr>
<th>Main exposure group</th>
<th>Depressive symptoms</th>
<th>MDD diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>vs. premenopause</td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Early perimenopause</td>
<td>1.34</td>
<td>1.14 – 1.57</td>
</tr>
<tr>
<td>Late perimenopause</td>
<td>1.82</td>
<td>1.38 – 2.41</td>
</tr>
<tr>
<td>Any perimenopause</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>Postmenopause</td>
<td>1.54</td>
<td>1.14 – 2.10</td>
</tr>
</tbody>
</table>
Risk factors for perimenopausal depressive symptoms or major depression

• **Demographic**
  - Caucasian race
  - Lower SES

• **Clinical**
  - History of major depression or anxiety disorder
  - More severe/persisting vasomotor symptoms
  - History of postpartum depression/PMDD

• **Psychosocial**
  - Stressful life events
  - Sleep problems
  - Negative attitudes (M)
  - Lower physical functioning
  - Marital stress/family violence

Depression in the menopause transition: major etiologic theories

• Empty nest hypothesis

• Domino theory
  • Vasomotor symptoms → Sleep problems → Depression

• Greater sensitivity to hormonal fluctuation
  • Postpartum depression/PMDD are risk factors
  • ↑↓ FSH
  • ↑↓ E2 (estradiol) → 5-HT, NE neurotransmission?

Hormones/menopausal status & depressed mood in women without history of depression

- 8-year cohort study (1996-2004), 231 premenopausal women, No history of depression at enrollment
- Depressive symptoms (CES-D), MDD (PRIME-MD)
- Nonfasting blood samples for hormone assays taken at each visit

Estradiol and mood in women with past perimenopausal depression

- RCT – 56 postmenopausal women (45-65 yrs.)

- With or without history of perimenopausal depression, current remission

- 3 wks. open transdermal (TD) E2 → randomized to 3 wks. TD E2 or TD placebo

Perimenopausal depression: diagnosis

MDD unrelated to reproductive events

- Depressed mood
- Anhedonia
- Lower self-esteem
- Sleep problems
- Low libido
- Rumination
- Vegetative change

Depression related to menopause transition

- Depressed mood
- Anhedonia
- Lower self-esteem
- Lower self-esteem
- Low libido
- Vegetative change

If diagnostic criteria for MDD are met, MDD should be diagnosed

Perimenopausal depression: formulation

- **Bi-directional relationship**
  - Severity of perimenopausal symptoms ↔ Severity of depression

- **Psychosocial challenges** unique to midlife
  - Dual and at times conflicting roles
  - Negative view of midlife and beyond
  - Higher risk of spousal death, marital conflict, lack of support, divorce/separation

# Perimenopausal depression: clinical trials with perimenopausal samples

<table>
<thead>
<tr>
<th>N</th>
<th>Sample</th>
<th>Dx(s)</th>
<th>Exposure</th>
<th>Control</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rasgon 2002</td>
<td>16</td>
<td>Peri</td>
<td>MDD</td>
<td>AD + ERT&lt;sup&gt;a&lt;/sup&gt; (n=6)</td>
<td>ERT&lt;sup&gt;b&lt;/sup&gt; (n=10)</td>
<td>8 wks</td>
</tr>
<tr>
<td>Morgan 2005</td>
<td>17</td>
<td>Peri</td>
<td>MDD</td>
<td>AD+ERT</td>
<td>AD + Placebo</td>
<td>6 wks.</td>
</tr>
<tr>
<td>Ladd 2005</td>
<td>16</td>
<td>Peri</td>
<td>MDD</td>
<td>Vlfx. XR</td>
<td>...</td>
<td>8 wks.</td>
</tr>
<tr>
<td>Freeman 2006</td>
<td>20</td>
<td>Peri</td>
<td>Dep.&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Escital.</td>
<td>...</td>
<td>8 wks.</td>
</tr>
</tbody>
</table>

<sup>a</sup> Exposed enrollees had history of poor overall response to antidepressants; no climacteric symptoms.

<sup>b</sup> Controls had no prior history of antidepressant treatment.

<sup>c</sup> Defined as having perimenopausal depression and somatic symptoms.

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Interventions for hot flushes: role of serotonergic antidepressants

• Pooled analysis of individual-level data from 3 randomized trials

• 899 peri- and postmenopausal women, ≥ 14 bothersome VMSs/wk

Intervention effects on change in mean vasomotor symptom frequency vs. controls.

Guthrie KA et al. Obstet Gynecol. 2015;126:413-422.
Cognitive behavioral therapy for D-MT

  • 44 outpatients (mean age, 49 years, 52% perimenopausal) not taking HRT
  • 2x/wk group CBT (16 sessions) vs. an undefined control condition.
  • ↓ in BDI-II with CBT; no significant improvement in the control group.
  • Same results after restricting to only perimenopausal women.

  • 353 women (mean age, 42 years, 22% perimenopausal) not taking psychotropic medication;
  • All participants received individual CBT
  • Response rates: 55% overall; peri- vs. postmenopause, 50% vs. 51%.
  • Remission rates: peri- vs. postmenopause, 26% vs. 28%.
Meta-analysis of the effect of HRT on depressed mood

- Meta-analysis of 26 studies (1966-1995), hormone therapy as exposure, at least one measure of depression or depressed mood as endpoint; ES expressed as Cohen’s $d$

<table>
<thead>
<tr>
<th>Main exposure</th>
<th>Control</th>
<th>P-value</th>
<th>Cohen’s $d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any HRT</td>
<td>Any control</td>
<td>&lt; 0.0001</td>
<td>0.74</td>
</tr>
<tr>
<td>Any HRT</td>
<td>Placebo</td>
<td>&lt; 0.0001</td>
<td>0.68</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Placebo</td>
<td>&lt; 0.0001</td>
<td>0.69</td>
</tr>
<tr>
<td>Estrogen + progesterone</td>
<td>Placebo</td>
<td>0.001</td>
<td>0.45</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Estrogen + progesterone</td>
<td>&lt; 0.0001</td>
<td>0.62</td>
</tr>
</tbody>
</table>

Women’s Health Initiative: Estrogen + progesterone risks vs. benefits

**Multi-site RCT (estrogen/progesterone vs. PLC)**


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**Table 2: Clinical Outcomes by Randomization Assignment**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Estrogen + Progesterone (n = 8,156)</th>
<th>Placebo (n = 8152)</th>
<th>Hazard Ratio</th>
<th>Nominal 95% CI</th>
<th>Adjusted 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD</td>
<td>164 (2.0)</td>
<td>122 (1.5)</td>
<td>1.30</td>
<td>1.05-1.63</td>
<td>0.65-1.97</td>
</tr>
<tr>
<td>CHD death</td>
<td>33 (0.4)</td>
<td>26 (0.3)</td>
<td>1.26</td>
<td>0.89-1.77</td>
<td>0.47-2.98</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>133 (1.6)</td>
<td>66 (0.8)</td>
<td>2.01</td>
<td>1.32-3.05</td>
<td>0.62-2.13</td>
</tr>
<tr>
<td>CAG/PTCA</td>
<td>183 (2.3)</td>
<td>171 (2.1)</td>
<td>1.08</td>
<td>0.84-1.38</td>
<td>0.71-1.51</td>
</tr>
<tr>
<td>Stroke</td>
<td>127 (1.6)</td>
<td>95 (1.2)</td>
<td>1.36</td>
<td>1.01-1.83</td>
<td>0.60-2.31</td>
</tr>
<tr>
<td>Fatal</td>
<td>16 (0.2)</td>
<td>13 (0.2)</td>
<td>1.29</td>
<td>0.92-1.80</td>
<td>0.32-4.49</td>
</tr>
<tr>
<td>Nonfatal</td>
<td>94 (1.2)</td>
<td>59 (0.7)</td>
<td>1.59</td>
<td>1.26-2.06</td>
<td>0.33-2.70</td>
</tr>
<tr>
<td>Vascular thromboembolic disease</td>
<td>151 (1.9)</td>
<td>87 (1.1)</td>
<td>1.76</td>
<td>1.58-3.62</td>
<td>0.99-5.06</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>115 (1.4)</td>
<td>53 (0.7)</td>
<td>2.37</td>
<td>1.49-3.77</td>
<td>1.14-3.51</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>70 (0.9)</td>
<td>51 (0.7)</td>
<td>2.02</td>
<td>1.39-3.25</td>
<td>0.99-5.06</td>
</tr>
<tr>
<td>Total cardiovascular disease</td>
<td>409 (5.2)</td>
<td>235 (3.0)</td>
<td>1.72</td>
<td>1.59-3.05</td>
<td>0.99-1.49</td>
</tr>
<tr>
<td>Cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>166 (2.0)</td>
<td>154 (1.9)</td>
<td>1.06</td>
<td>1.00-1.13</td>
<td>0.71-1.90</td>
</tr>
<tr>
<td>Endometrial</td>
<td>52 (0.6)</td>
<td>36 (0.4)</td>
<td>1.46</td>
<td>1.07-2.00</td>
<td>0.69-2.35</td>
</tr>
<tr>
<td>Cervical</td>
<td>45 (0.6)</td>
<td>67 (0.8)</td>
<td>0.63</td>
<td>0.43-0.92</td>
<td>0.35-1.24</td>
</tr>
<tr>
<td>Total</td>
<td>202 (2.5)</td>
<td>156 (1.9)</td>
<td>1.31</td>
<td>1.10-1.57</td>
<td>0.80-2.12</td>
</tr>
<tr>
<td>Fracture</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip</td>
<td>44 (0.6)</td>
<td>62 (0.8)</td>
<td>0.98</td>
<td>0.69-1.46</td>
<td>0.32-1.33</td>
</tr>
<tr>
<td>Vertebra</td>
<td>41 (0.5)</td>
<td>50 (0.6)</td>
<td>0.98</td>
<td>0.69-1.36</td>
<td>0.32-1.34</td>
</tr>
<tr>
<td>Other osteoporotic</td>
<td>579 (7.1)</td>
<td>739 (8.6)</td>
<td>0.77</td>
<td>0.69-0.86</td>
<td>0.45-0.94</td>
</tr>
<tr>
<td>Total</td>
<td>650 (8.1)</td>
<td>738 (9.0)</td>
<td>0.76</td>
<td>0.69-0.85</td>
<td>0.63-0.96</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Due to other causes</td>
<td>165 (2.0)</td>
<td>146 (1.8)</td>
<td>0.60</td>
<td>0.74-1.14</td>
<td>0.63-1.36</td>
</tr>
<tr>
<td>Total</td>
<td>251 (3.1)</td>
<td>250 (3.0)</td>
<td>0.98</td>
<td>0.82-1.18</td>
<td>0.70-1.37</td>
</tr>
<tr>
<td>Global index</td>
<td>283 (3.4)</td>
<td>283 (3.4)</td>
<td>1.00</td>
<td>1.00-1.00</td>
<td>0.98-1.00</td>
</tr>
</tbody>
</table>

†C Indicate confidence intervals. NA, not applicable; CHD, coronary heart disease; MI, myocardial infarction; CAG, coronary artery bypass grafting; and PTCA, percutaneous transluminal coronary angioplasty.

‡CHD includes acute MI requiring hospitalization, silent MI determined from serial electrocardiograms, and coronary death. There were 6 silent MI.

Total cardiovascular disease is defined to events during hospitalization except venous thromboembolic disease reported after January 1, 1994.

††Vascular thromboembolic includes all fracture other than chest/thoracic, wrist/finger, ribs, and cervical spine, as well as hip and vertebral fractures reported separately.

§The global index represents the first event for each participant from among the following outcomes: CHD, stroke, pulmonary embolism, breast cancer, endometrial cancer, colorectal cancer, hip fracture, and death due to other causes.

Subsequent studies: selected findings

• **Reanalyses of WHI data**
  • No increased CAD risk with ERT (vs. HRT)
  • WHI hormones (CE+medroxy-progesterone) may be more risky than others
  • AE’s in older women not observed in perimenopausal women (critical window)

• **Transdermal E2** may not have prothrombotic or inflammatory effects
What do studies of estrogen for depression show?

• Very few RCT’s

• Transdermal E2 may have antidepressive effects similar to classic antidepressants…

  …in women with clinically significant depression.

• Ineffective for enhancing mood in depression-free women

• Transdermal 17β-E2 may be especially advantageous in perimenopausal women with clinically significant depression.
Randomized trials of E2 for depressed perimenopausal women

Randomized, PLC-controlled trial
31 women with PM-related depression
TD-E2 + medroxyprogesterone vs. PLC

E2 group

PLC group


Transdermal E2 not helpful for depressed post-menopausal women

Summary

• The MT is a period of heightened risk of new-onset depression for some women and recurrent illness for others

• Several risk factors identified; confluence of psychosocial factors (some unique to midlife) – underlying biological risk (role of hormonal flux?)

• Descriptive diagnosis of D-MT uses traditional criteria; case formulation accounts for perimenopausal symptom severity and psychosocial stressors

• Traditional treatments for MDD can be applied to D-MT

• Specific roles of E2, other hormonal therapies are being investigated
Questions & Discussion