 Effects of Transdermal Estradiol in the Prevention of Depressive Symptoms in the Menopause Transition: A Randomized Clinical Trial

Jennifer L. Gordon\textsuperscript{1,2}, David R. Rubinow\textsuperscript{1}, Tory A. Eisenlohr-Moul\textsuperscript{1}, Kai Xia\textsuperscript{1}, Susan S. Girdler\textsuperscript{1}

\textsuperscript{1}Psychiatry, University of North Carolina, Chapel Hill, NC
\textsuperscript{2}Psychology, University of Regina, Regina, Saskatchewan
Disclosures

- None
Depression in the Menopause Transition

- The years leading up to menopause are accompanied by an increased risk of depressed mood
  - 2-fold increased risk of first-onset MDD, affecting 9-17%\(^1,2\) of women
  - 2-4-fold increased risk of clinically significant depressive symptoms, affecting 24-33%\(^1,3\) of women
- The perimenopausal hormonal environment thought to play a role

HRT Effects on Perimenopausal Mood

- A few trials suggest that hormone therapy is an effective treatment for perimenopausal depression\textsuperscript{1-4}

- No studies have examined whether hormone therapy can prevent the development of depressive symptoms in initially euthymic women

Perimenopausal Estrogen Replacement Therapy Study

RCT evaluating the cardiovascular and mood benefits of 12 months of transdermal estradiol

NIH #R01 MH087619

PIs: David Rubinow & Susan S. Girdler
Current Study Aims

- Among initially euthymic perimenopausal women:
  - To examine the efficacy of hormone therapy in preventing depressive symptom onset.
  - Identify baseline characteristics predicting hormone therapy’s beneficial mood effects.
Participants

- Women aged 45-60 from the community
- Perimenopausal or early postmenopausal (meeting STRAW -1, -2 or +1a criteria)
- Medically healthy
- No current diagnosis of major depressive disorder, bipolar or psychotic disorder
- Not taking psychotropics or medications affecting cardiovascular or endocrine profile
Intervention

- Treatment Group (TE+IMP)
  - Transdermal estradiol
    - 0.025 mg for two weeks
    - 0.05 mg for four weeks
    - 0.1 mg for the remainder of the study
  - Micronized progesterone (200 mg) for 12 days every 2-3 months

- Placebo Group
  - Placebo patch
  - Placebo pills
Flow of Participants

4166 Women Initiated Screening

350 Provided Consent and Underwent Additional Screening

172 Randomized

86 Randomized to Placebo

86 Randomized to TE+IMP
Participant Visits

• Enrollment session
  • Baseline depressive symptoms
    • Center for Epidemiologic Studies – Depression Scale (CES-D)

• Potential predictors of treatment response assessed:
  • Reproductive stage (early peri, late peri, early post)
  • History of depression
    • SCID-IV
  • History of physical or sexual abuse
    • Validated structured trauma interview¹
  • Vasomotor symptom bother
    • Greene Climacteric Scale
  • Stressful life events in the last 6 months
    • Life Experiences Survey

Participant Visits

- Post-Randomization Visits: months 1, 2, 4, 6, 8, 10, 12
  - Depressive symptoms
    - Center for Epidemiologic Studies – Depression Scale
    - Rate of CES-D score $\geq 16^1$
  - Vasomotor symptom bother
    - Greene Climacteric Scale

Statistical Analyses

- Test the efficacy of TE+IMP in preventing depressive symptom onset
  - Logistic regression comparing rates of CES-D ≥ 16
  - Repeated measures regression comparing mean post-randomization CES-D score
- Covariates
  - Enrollment CES-D score
  - Change in vasomotor symptom bother at each visit
- Identify baseline predictors of TE+IMP’s effects
  - Treatment-by-predictor interaction term
Results
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n=86)</th>
<th>TE+IMP (n=86)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>51.0 (3.2)</td>
<td>51.0 (3.0)</td>
<td>.71</td>
</tr>
<tr>
<td>Race (% Caucasian)</td>
<td>70%</td>
<td>81%</td>
<td>.20</td>
</tr>
<tr>
<td>Income ($K)</td>
<td>80-100</td>
<td>80-100</td>
<td>.52</td>
</tr>
<tr>
<td>CES-D Score</td>
<td>5.5 (4.9)</td>
<td>5.3 (5.1)</td>
<td>.92</td>
</tr>
<tr>
<td>Any physical or sexual abuse (%)</td>
<td>34%</td>
<td>34%</td>
<td>1.0</td>
</tr>
<tr>
<td>Total current stress score (/5)</td>
<td>1.8 (1.8)</td>
<td>2.3 (1.6)</td>
<td>.12</td>
</tr>
<tr>
<td>History of depression (%)</td>
<td>33%</td>
<td>33%</td>
<td>.87</td>
</tr>
<tr>
<td>GCS Vasomotor Subscale score</td>
<td>2.2 (1.6)</td>
<td>2.0 (1.8)</td>
<td>.58</td>
</tr>
<tr>
<td>No. total stressful life events (%)</td>
<td></td>
<td></td>
<td>.36</td>
</tr>
<tr>
<td>0</td>
<td>40%</td>
<td>42%</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>29%</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>31%</td>
<td>34%</td>
<td></td>
</tr>
</tbody>
</table>
Main Effect of Treatment
Main Effect of Treatment

% CES-D Score ≥16

Placebo: 32.3
TE+IMP: 17.3

* p < .05
Main Effect of Treatment

![Graph showing CES-D Score over time for TE+IMP and Placebo groups with p < .05](image)
Moderators of Treatment Effects
Treatment Effects by Reproductive Stage

- Significant treatment-by-reproductive stage interaction on CES-D scores ($p = .03$)
  - Beneficial effect of TE+IMP is only significant among early perimenopausal women
Treatment Effects by Reproductive Stage

<table>
<thead>
<tr>
<th>Reproductive Stage</th>
<th>% CES-D Score ≥16</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Peri (n = 36)</td>
<td>48.1%</td>
<td>0.001</td>
</tr>
<tr>
<td>Late Peri (n = 99)</td>
<td>27.9%</td>
<td></td>
</tr>
<tr>
<td>Early Post (n = 37)</td>
<td>18.5%</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* p < .05
Treatment Effects by Recent Stressful Life Events

- Significant treatment-by-SLE interaction on CES-D scores ($p < .01$)
  - Beneficial effect of TE+IMP becomes more evident with increasing # of SLEs
Treatment Effects in Low Stress Women

CES-D Score

n = 70; p = .70
Treatment Effects in High Stress Women

CES-D Score

- TE+IMP
- Placebo

n = 56; p < .01
Non-Significant Treatment Moderators

- Past depression history
- Abuse history
- Baseline vasomotor symptom bother
Conclusions

- The first study to suggest that TE+IMP prevents the development of depressive symptoms in peri- and early postmenopausal women

- Secondary analyses suggest the prophylactic mood benefits of TE+IMP may be greatest in
  - Early perimenopausal women
  - Women experiencing multiple stressful life events

- If confirmed in future research, clinicians may consider TE+IMP as a prophylactic treatment for depressive symptoms in the menopause transition
Thank You!

- Coauthors
  - Susan Girdler
  - David Rubinow
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