Natural History of Mood Changes Across the Menopause Transition

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Menopause and the Brain: Maximizing Cognitive and Psychological well-being at midlife

Overview

• Study of Women’s Health Across the Nation (SWAN)
• Depression symptoms & menopause, risk factors, patterns across 13 years
• Clinical depression & menopause, risk factors, patterns across 13 years
• Conclusions/Clinical implications

Study of Women’s Health Across the Nation (SWAN)

• A multicenter, multi-ethnic, community-based longitudinal study of menopause and aging in 3,302 pre-/early perimenopausal women, aged 42 to 52 years at baseline in 1996

Major Aim

• To characterize the endocrinologic/biologic, symptomatic, and psychosocial changes that occur during the menopausal transition

Sample: Recruitment of community women by standard methods at 7 sites –

Eligible

• 42-52 years old
• intact uterus
• no hormone use
• at least 1 menstrual period in past 3 months

Study design: 3,302 women assessed at study entry & annually with a common standardized protocol at 7 field sites, 1996-present
SWAN Cohort Composition

Study Entry and Annual Assessments with a common standardized protocol.

- SWAN (N=3302)
  - Behaviors, psychosocial
  - Medical/reproductive history
  - Physical measures
  - Symptoms
  - E2, FSH, T lipids, inflammatory markers

- SWAN Mental Health (N=443)
  - SCID
  - Family history of depression
  - CTQ: Child abuse

The Menopause Transition

Two SWAN Studies of Depression

Depression symptoms
Women at all sites (n=3,200+)
Outcome: Center for Epidemiological Studies of Depression (CES-D) Scale
- Level of depressive symptoms
- Screen for clinical depression, CES-D score ≥ 16

Clinical depression
Women at Pittsburgh site (n=443)
Outcome: Structured Clinical Interview of DSM IV Axis I Disorders (SCID) diagnoses major and minor depression
Objectives of Depression Studies

- To determine if risk of depression is greater during the MT or postmenopause than premenopause - independent of socio-demographics, stressful events, and health conditions.
- To identify psychosocial, endocrine, physical, and behavioral risk factors for depression during MT and postmenopause.

Does the prevalence of depressive symptoms vary by menopausal status, by ethnicity?

Is an association between higher depressive symptoms and menopausal status accounted for or independent of known risk factors for depression?

What is the relative importance of menopausal status?

Across 9 Years, Do Peri- and Postmenopause ↑ Odds of CES-D Scores ≥ 16 (n=3,296)?

Adjusted for multiple variables

Bromberger et al. Arch Gen Psychiatry. 2010
Overall, depressive symptom levels average a CES-D score =10-12 and are relatively stable. – BUT are there groups of women with different patterns of depressive symptoms through early peri- and into postmenopause?

**Multiple factors contribute to risk of ↑ depression symptoms over 9 years**

<table>
<thead>
<tr>
<th>Status</th>
<th>Race/Ethnicity</th>
<th>Vasomotor Symptoms</th>
<th>Social Support</th>
<th>1 Life Event</th>
<th>2+ Life Events</th>
<th>Upsetting Life Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Peri</td>
<td>African American</td>
<td>1</td>
<td>0.05</td>
<td>1.15</td>
<td>1</td>
<td>1.23</td>
</tr>
<tr>
<td>Late Peri</td>
<td>Chinese</td>
<td>2</td>
<td>0.05</td>
<td>1.15</td>
<td>1</td>
<td>1.23</td>
</tr>
<tr>
<td>Post</td>
<td>Hispanic</td>
<td>3</td>
<td>0.05</td>
<td>1.15</td>
<td>1</td>
<td>1.23</td>
</tr>
<tr>
<td>Post</td>
<td>Japanese</td>
<td>4</td>
<td>0.05</td>
<td>1.15</td>
<td>1</td>
<td>1.23</td>
</tr>
</tbody>
</table>

Note: Referent for early peri, late peri, and post was premenopausal. Adjusted for education, concurrent testosterone, age, smoking status, psychotropic medications, body mass index, and site.

**Are hormone levels/changes independently associated with ↑ CES-D**

Across 9 yrs: No association of E2, FSH
- $T_{\log}$ was associated with ↑ OR of ↑ CES-D (OR=1.15).
- ↑ increase in log T from baseline to each annual visit was associated with ↑ OR of ↑ CES-D (OR=1.23).
- independent predictors of ↑ CES-D: social support, stressful life events, peri- and postmenopause

Bromberger et al, Arch Gen Psych. 2010

Overall, depressive symptom levels average a CES-D score =10-12 and are relatively stable. – BUT are there groups of women with different patterns of depressive symptoms through early peri- and into postmenopause?

Women Can be Classified Into 5 Trajectory Groups

Multivariable analysis:
Compared to the low sx group,
- Asians vs whites have less predictable patterns over time
- < HS less likely to be in very low group and more likely to be in moderate
- Financial strain and smoking are less likely to be in very low group

Bromberger et al, Arch Gen Psych. 2010
Summary

• Women are at greater risk of depression symptoms when peri-or early postmenopausal than when premenopausal, independent of sociodemographic & health factors, stress, & VMS

• Multiple psychosocial & health factors associated with greater risk: ↓ education, smoker, ↑ BMI, stressful life events, vasomotor symptoms, ↓ social support, poor/fair perceived health

• Over 13 yrs, mean depression symptoms low on average and low for 75% of women, but nearly ¼ had increasing, decreasing or moderate trajectories

What about Clinical Depression?

• Will women will be more likely to develop a new or recurrent MDD during the MT or after than before?

• Will women with a history of MD be more likely to develop MDD than those without a history?

• Among women without a history of MDD at baseline, who will be most at risk for a first onset MDD? – will menopause stage or related symptoms contribute significantly?

• What is the course of clinical depression across the menopause transition?

SWAN Pittsburgh Mental Health Study

Ancillary study to collect detailed diagnostic psychiatric interview data annually from participants at the time of their SWAN core visit.

- 97% of SWAN Pittsburgh Cohort participated (n=443)
- Baseline +12 years of follow-up diagnostic psych data
  - At annual visit, evaluated for current and past year disorder
  - Included family history of depression and childhood abuse data

• Depression history at study entry
  - 19% recurrent depression
  - 17% single episode of depression
  - 14% minor depression

• Current at study entry
  - 3% major depression
  - 4% subthreshold depression
  - 414 women without current major or minor depression
Clinical Depression by Visit -
% Major or Minor Depression Current / Past Year

When Women Enter as Premenopausal, Will They ↑ Odds of MDD When They are Peri- or Postmenopausal over 9 yrs?

Independent Predictors of MDD from Baseline Through Visit 9

Risk Factors for Incident (first ever) or Recurrent MDD During Midlife: Are they the Same or Different?

In SWAN - during 13 years of annual follow up assessments:
- More than half (59%) of the women aged 42-52 with a history of MDD at study entry had a recurrence of MDD
- 28% of women without a lifetime history of MDD had their first episode of MDD

* 95% CI does not include 1

Adjusted for age, race, upsetting life event, BMI, frequent VMS

Bromberger JT et al., Psychosom Med 2011
**Risk Factors for Incident & Recurrent MDD**

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Incident MDD Hazard ratio</th>
<th>p</th>
<th>Recurrent MDD Hazard ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=411</td>
<td>N=266: 67 Events</td>
<td></td>
<td>N=145: 87 Events</td>
<td></td>
</tr>
<tr>
<td>Baseline age</td>
<td>1.00</td>
<td>.06</td>
<td>0.87</td>
<td>.23</td>
</tr>
<tr>
<td>6 or more close friends</td>
<td>1.04</td>
<td>.32</td>
<td>0.97</td>
<td>.28</td>
</tr>
<tr>
<td>Trait anxiety</td>
<td>1.30</td>
<td>&lt;.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1+ medical conditions</td>
<td>2.27</td>
<td>.04</td>
<td>1.06</td>
<td>.35</td>
</tr>
<tr>
<td>One vs. none</td>
<td>2.18</td>
<td>.04</td>
<td>1.05</td>
<td>.35</td>
</tr>
<tr>
<td>Two or more vs. none</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trait self-consciousness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1+ anxiety disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1+ psychotropic meds meds</td>
<td>1.50</td>
<td>.08</td>
<td>1.05</td>
<td>.35</td>
</tr>
</tbody>
</table>

**incident & recurrent MDD cont.**

<table>
<thead>
<tr>
<th>Time-varying (repeated at each visit)</th>
<th>Incident MDD Hazard ratio</th>
<th>p</th>
<th>Recurrent MDD Hazard ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low role funct. due to physical problems at last visit</td>
<td>1.88</td>
<td>.04</td>
<td>1.73</td>
<td>.07</td>
</tr>
<tr>
<td>Low role funct. due to emotional problems at last visit</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression sx at last visit</td>
<td>1.98</td>
<td>.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequent vasomotor symptoms at last visit</td>
<td>1.69</td>
<td>.08</td>
<td>2.67</td>
<td>.04</td>
</tr>
<tr>
<td>Early/late peri-menopause (vs. pre-menop.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-menopausal (vs. pre-menopause)</td>
<td>4.03</td>
<td>.03</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**What Were the Patterns of Clinical Depression Across 13 Years?**

1) NO MDD/MINOR: no past year or current minor or major depression during study (n=144)
2) MINOR D ONLY: past year or current minor depression at least 1 annual visit, no major depression or dysthymia during study (n=35)
3) SINGLE MD EPISODE: past year or current major depression at only 1 annual visit (n=27)
4) PERSISTENT/RECURRENT MD: past year or current major depression at 2 or more visits (n=91)

**Patterns of clinical depression during 13 yrs of annual assessments**
What are the Factors that Risk for Adjusted OR of Persistent/Recurrent MDD vs One Episode MDD Over 13 yrs?

Summary
Risk for depressive disorder increases during and after the menopause transition defined by bleeding patterns. The risk is not related to VMS or hormones.

Very upsetting life events have a greater influence on risk for MDD than VMS.

Women with depression history prior to midlife are at greatest risk for MDD during and after the menopause transition.

Risk factors for incident & recurrent MDD differ.
Persistent/recurrent MDD is common in midlife women.
45% of women had at least 1 MDD episode; 77% of these had a persistent/recurrent course - Major risk factors for persistence/recurrence are sleep problems, upsetting events.