Mental Health and Menopause: Focus on Depression

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Overview

• Background/context
  - Menopause
  - Mental health/depression
  - Public health significance
• Why study depression during menopausal transition (and after)?
• Risk of depression during the menopausal transition
• Study of Women’s Health Across the Nation (SWAN)
What is Menopause?

Menopause
• Cessation of menses for >12 consecutive months (FMP)

Perimenopause (menopausal transition)
• Transition period into menopause
• Menstrual irregularity
• Fluctuations in reproductive hormones

Median age of transition onset: 47 years
Median age at final period: 51 years
Duration of transition: avg of 4 years
What is Depression?

• A syndrome or mental disorder characterized by low mood as well as a number of other emotional and somatic symptoms that can vary from person to person

• It is often a chronic condition, remitting and recurring multiple times during a person’s life
Depression is an important public health problem

- Common among women – lifetime prevalence over 20%
- Leading cause of health-related disability in women
- ↑ morbidity and mortality - ↑ risk of CVD, diabetes, poor health behaviors
- US cost = $83.1 billion per year in treatment expenses and lost productivity

12-Month Prevalence of Major Depression by Country & Age

Developed Countries combined prevalence range: 2.1-9.4
Developing Countries combined prevalence range: 3.7-11.8
Brazil
Ukraine

Kessler et al, Depress Anxiety. 2010
Why focus on depression during (and after) the menopausal transition?

• 20-25% of women in their fifties have had ≥ 1 past MDD episode

• MDD is recurrent illness in 50%-80%

• ~ 25% women in midlife have ↑ depression sx

• Early and midlife exposures, e.g., depression and adversity, may influence mental & physical health in older age
Spectrum of mood symptoms/disorders associated with reproductive hormone related events and patterns across a woman’s life:

- Menarche
- Menstrual cycle - premenstrual symptoms and disorder
- Pregnancy and Postpartum
- Menopause?

Estradiol & progesterone receptors in brain, effect neurons implicated in depression – serotonin & noradrenergic neurotransmitters
• Little evidence of direct relationship between hormone levels and depressed mood

• No clear underlying pathophysiologic abnormalities

• Current hypotheses:
  – decrease, dysregulation or imbalance of ovarian hormones that occur during periods of significant or rapid changes in levels

• Normal changes in estrogen and/or progesterone may trigger mood-perturbing symptoms in women sensitive to the effects of these gonadal steroids
Mental Health, Depression and Menopause Studies

• Most studies around the world focused on psychological or depression symptoms, not disorder

• Mostly cross-sectional with mixed results –
  - Some found elevations in depressive, irritable, and nervous symptoms during the menopausal transition (MT)
  - Others found no association
  - A few reported elevations during post –

• Varying methodologies

Obermeyer et al, 2000; 2007; Avis et al, 2001;
Past 2 decades – 6 prospective studies of menopause

- United States
- Netherlands
- Australia
- United Kingdom
### Risk of depression symptoms and major depression in peri/postmenopause

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Outcome</th>
<th>Depression Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Depressive Symptoms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eindhoven Osteoporosis Study, Netherlands, 2002</td>
<td>2,103</td>
<td>EPD</td>
<td>peri &gt; pre</td>
</tr>
<tr>
<td>Seattle Midlife Women’s Health Study, 2008</td>
<td>508</td>
<td>CES-D</td>
<td>late peri &gt; pre</td>
</tr>
<tr>
<td>The Penn Ovarian Aging Study, 2004</td>
<td>436</td>
<td>CES-D</td>
<td>peri &gt; pre, peri &gt; pre</td>
</tr>
<tr>
<td>Study of Women’s Health Across the Nation, 2010</td>
<td>3,302</td>
<td>CES-D</td>
<td>peri &gt; pre, post &gt; pre</td>
</tr>
<tr>
<td><strong>Major Depression</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The Penn Ovarian Aging Study, 2004</td>
<td>436</td>
<td>PRIME-MD</td>
<td>peri = pre</td>
</tr>
<tr>
<td>Study of Women’s Health Across the Nation, 2011</td>
<td>221</td>
<td>SCID</td>
<td>peri &gt; pre, early post &gt; pre, late post?</td>
</tr>
</tbody>
</table>

## Risk of Psychological Symptoms

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Outcome</th>
<th>Depression Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australian Longitudinal Study on Women’s Health, 2009</td>
<td>6,814</td>
<td>Mental Health Index from SF-36</td>
<td>peri- 1-4 yrs before FMP &gt;pre post- 1-4 yrs after &gt;pre</td>
</tr>
<tr>
<td>1946 British Cohort Study, 2009</td>
<td>1,569</td>
<td>Psychological symptom score (0-12)</td>
<td>Pre- = peri = post</td>
</tr>
</tbody>
</table>
Study of Women’s Health Across the Nation (SWAN)

A multi-center, multi-ethnic, community based longitudinal study of menopause and aging that began in 1995 to:

• Characterize the biological, symptomatic, and psychosocial changes that occur during the menopausal transition (MT)
• Understand the effects of these changes on women’s health during and after the MT
Study Sample

Recruitment of community women at 7 sites: standard methods

Eligibility

• 42-52 years
• Intact uterus
• No hormone use
• At least 1 menstrual period in past 3 mos.

3,302 participants assessed at study entry (baseline) and annually with a common standardized protocol over 12 years

• Lifestyle, demographics
• Health and functioning
• Psychosocial measures
• Physical measures
• Hormones, lipids, inflammatory markers
SWAN Cohort Composition

- Boston: 253 Afr Am, 301 281 Japanese, 248 250 Chinese, 218 286 Hispanic, 199 1,550 White
- UCLA: 209 Afr Am, 250 281 Japanese, 250 250 Chinese, 250 286 Hispanic, 209 1,550 White
- UC Davis: 146 Afr Am, 286 281 Japanese, 286 250 Chinese, 286 286 Hispanic, 146 1,550 White
- New Jersey: 146 Afr Am, 286 281 Japanese, 286 250 Chinese, 286 286 Hispanic, 146 1,550 White

Legend:
- Green: 935 Afr Am
- Red: 281 Japanese
- Yellow: 250 Chinese
- Blue: 286 Hispanic
- Black: 1,550 White
Objectives

• Determine if depression risk is greater during the MT or postmenopause than premenopause - independent of socio-demographics, stressful events, and health conditions

• Identify psychosocial, endocrine, physical, and behavioral risk factors for depression during MT and postmenopause
Two SWAN Studies of Depression

Depression symptoms
Included women at all sites (n=3,200+)
Outcome: Center for Epidemiological Studies of Depression (CES-D) Scale score $\geq 16$

Clinical depression
Included women at Pittsburgh site (n=443)
Outcome: Structured Clinical Interview of DSM-IV Axis - I Disorders (SCID) major and/or minor depression
Depression Symptoms & Menopause

**Depression Symptoms**: Center for Epidemiological Studies of Depression (CES-D) Scale - cut point ≥16 score.

- 20-items, self administered
- Level of depressive symptoms
- Screen for clinical depression
Peri- and postmenopause increase odds of CES-D Depression Scores ≥ 16 across 9 Years: SWAN

![Bar chart](chart.png)

- Pre-
- Early Peri-
- Late Peri-
- Post-

Menopausal Status

(n=3,296)

Early peri: change in menses;
late peri: 3 months with no menses;
post: 12 months with no menses

Bromberger et al. Arch Gen Psychiatry. 2010
Multiple factors contribute to risk of depression symptoms over 8 years

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.
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
- Included family history of depression and childhood abuse data
Pittsburgh SWAN site

- Recruited using random digit dialing, voter registration lists
- Participants self-identified as non-Hispanic White or African-American
- 463 women recruited (35% African-American)
Measurement of Clinical Depression

• Depression Diagnosis
  – Structured Clinical Interview for DSM-IV (SCID), semi-structured diagnostic interview
  – Trained, certified interviewers (Masters/PhD)
  – Diagnosis of history of minor or major depression made according to DSM-IV criteria

• Lifetime and current depression
  – Depression history obtained at baseline
  – Past-year and current episodes assessed at annual follow-ups
At study entry –

Depression history

• 17% recurrent depression
• 15% single episode of depression
• 12% subthreshold/minor depression

Current

• 4.3% major depression
• 4% subthreshold/minor depression

266 (60%) women without lifetime major or minor depression
Peri- & postmenopause increase odds of major depression over 9 years among 221 women premenopausal at baseline: SWAN Pittsburgh

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

Bromberger JT et al. Psychol Med. 2011
Adjusted Odds Ratios of a Major Depression Episode from Baseline Through Visit 9

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.95</td>
</tr>
<tr>
<td>Menopausal status (ref=pre)</td>
<td></td>
</tr>
<tr>
<td>Perimenopause</td>
<td>1.98</td>
</tr>
<tr>
<td>Postmenopause</td>
<td>3.86</td>
</tr>
<tr>
<td>African American</td>
<td>1.56</td>
</tr>
<tr>
<td>History of major depression at baseline</td>
<td>2.98</td>
</tr>
<tr>
<td>Psychotropic medication use annually</td>
<td>4.55</td>
</tr>
<tr>
<td>Very upsetting life event annually</td>
<td>2.62</td>
</tr>
<tr>
<td>BMI continuous annually</td>
<td>1.04</td>
</tr>
<tr>
<td>Frequent VMS (≥6days/past 2wks) annually</td>
<td>1.76</td>
</tr>
</tbody>
</table>

Bromberger JT et al. Psychol Med. 2011
Patterns of Depression During 12 Years of Annual Assessments

1) No mD / MD: no past year or current minor or major depression during study (n=239)

2) mD only: past year or current minor depression at least 1 annual visit, no major depression or dysthymia during study (n=47)

3) Single MD episode: past year or current major depression at only 1 annual visit (n=47)

4) Recurrent/persistent MD: past year or current major depression at 2 or more visits (n=35)

5) Major & minor depression: at least 1 episode of major & minor depression during the study (n=75)
Odds Ratios from Multinomial Regression Models for 4 patterns of major/minor vs. no depression over 12 years

Bromberger et al, unpublished data

*p < .05
What factors are associated with depression during the MT?

<table>
<thead>
<tr>
<th>Personal History</th>
<th>Environmental</th>
<th>Biological/Health behaviors</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of depression</td>
<td>Financial strain</td>
<td>↑ BMI, smoking, inactivity</td>
</tr>
<tr>
<td>History of child abuse</td>
<td>Low SES</td>
<td>Physical health problems, impaired functioning</td>
</tr>
<tr>
<td>Prior medical conditions</td>
<td>Lack of partner/single parent</td>
<td>Vasomotor symptoms</td>
</tr>
<tr>
<td>Family history of</td>
<td>Stressful events-family stress</td>
<td>Pain</td>
</tr>
<tr>
<td>depression</td>
<td>↓ Social support</td>
<td>Poor sleep</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reproductive hormones??</td>
</tr>
</tbody>
</table>
Menopause and Depression: Gaps in Knowledge

- Does depression persist into postmenopause
- What specific stressors are most salient during the menopausal transition
- Impact of environmental exposures
- Prevention of depression
- Reproductive hormones? Do they really matter? If so, for whom?
Addressing Research Gaps Overall and in Developing Countries

• Use of epidemiological and longitudinal methods in population sampling.

• Consistent use of standard measures of depression across countries & cultures

• Systematically collect data on reproductive hormones, biological factors & environmental/social circumstances

• Education about menopause & depression
Acknowledgments

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National Institute on Aging,
National Institute of Nursing Research
Office of Research on Women’s Health
National Institute of Mental Health

We thank the study staff at each site and all the women who participated in SWAN.
Menopausal Transition
- High risk?
- Hormone patterns
- Bleeding patterns
- Length of transition

Mood Disturbances
- Depression
- Irritability
- Mood lability
- Anxiety

Psychobiological and Psychosocial Factors
- Sociodemographics
- Medical morbidity
- Personality traits
- Stress

History of Depression
### Risk factors for MDD vary between women with and without a history of MDD at study entry

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>No Lifetime hx MDD</th>
<th></th>
<th>Lifetime history of MDD *</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio</td>
<td>p</td>
<td>Hazard ratio</td>
<td>p</td>
</tr>
<tr>
<td><strong>N=266:</strong></td>
<td></td>
<td></td>
<td><strong>N=145:</strong></td>
<td></td>
</tr>
<tr>
<td>57 Events,</td>
<td></td>
<td></td>
<td>67 Events</td>
<td></td>
</tr>
<tr>
<td>Baseline age</td>
<td>0.90</td>
<td>.05</td>
<td>0.87</td>
<td>.02</td>
</tr>
<tr>
<td>Close Friends 6+</td>
<td>0.55</td>
<td>.04</td>
<td>0.56</td>
<td>.05</td>
</tr>
<tr>
<td>Trait Anxiety (Spielberger)</td>
<td>1.10</td>
<td>&lt;.000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private Self Consciousness</td>
<td></td>
<td></td>
<td>1.07</td>
<td>.03</td>
</tr>
<tr>
<td>Lifetime medical condition(s)</td>
<td>2.19</td>
<td>.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifetime anxiety disorder(^2)</td>
<td></td>
<td></td>
<td>1.98</td>
<td>.01</td>
</tr>
<tr>
<td>Lifetime medications for emotions (SCID)</td>
<td>1.87</td>
<td>.08</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Unpublished data
<table>
<thead>
<tr>
<th>Lagged time varying characteristic</th>
<th>No Lifetime hx MDD</th>
<th>Lifetime history of MDD *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard ratio</td>
<td>p</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td><strong>N=266:</strong></td>
<td><strong>57 Events,</strong></td>
<td><strong>N=145:</strong></td>
</tr>
<tr>
<td>SF36 Low Composite RolePhy/RoleEmo/SocFx</td>
<td>1.69</td>
<td>.06</td>
</tr>
<tr>
<td>CES-D Continuous [0-60]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Very Upsetting Life Event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VMS (hot flashes/night sweats) 6+ days</td>
<td>1.72</td>
<td>.07</td>
</tr>
<tr>
<td>Concur. Early/Late Peri menopause (vs. Pre)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concurrent Post-meno menopausal (vs. Pre)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Cross-cultural Prevalence of Feeling Unhappy/blue or Depressed Varies

Anderson et al, Maturitas, 2011