**Learning Objectives**

- To understand the concepts of continuum of risk and "window of vulnerability" for midlife depression
- To recognize the role of VMS, Sleep and Anxiety
- To explore neurobiology models for depression in midlife women - Where should we go next?

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**Depression During Menopause: An Evolving Conceptual Framework**

- Structural
  - Involutional Melancholia
- Psychosocial
  - Empty Nest Syndrome
- Neurobiology
  - Regulatory effects of E2 on TPH-2
Depression During Menopause

- Risk factors
  - Continuum of risk/Window of vulnerability
  - Trajectories over time

- Co-occurrence or causality?
  - Vasomotor Symptoms
  - Sleep
  - Anxiety

- The Role of Estrogen
  - Biology
  - Modulation of neurotransmitters
  - Therapeutic value

Most women will NOT develop significant depressive symptoms during the menopause transition.

Continuum of Risk:
- Previous depression (diagnosis and/or treatment)
- History of anxiety (past, current)
- Previous exposure to trauma, history of abuse

Window of Vulnerability:
- Previous reproductive-related mood disturbances (PMS, PPD)
- Menopause-related symptoms - VMS, sleep, pain
- Context and time-related stressful life events


Depression During Menopause: Is there a lifetime risk or is this a context-related problem?

Editorial
Depression during the menopausal transition: window of vulnerability or continuum of risk?


Personal Perspective
Menopausal transition, mood, and cognition: an integrated view to close the gap
Claudio N. Soares, MD, PhD, FRCPsych and Pauline M. Mah, PhD
Menopause 2010; 17(6):812-14

Risk for New Onset of Depression During the Menopausal Transition

The Harvard Study of Moods and Cycles

Objective: To examine the association between the menopausal transition and onset of new lifetime episodes of depressive symptoms among women with a history of mood disturbances.

Design: Longitudinal, prospective cohort study.

Setting: A population-based cross-sectional sample.

Participants: 2,846 women aged 55-75 years of age, with no lifetime diagnosis of major depression (N=500), residing in 7 Boston, Mass., metropolitan area communities.

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

Results: Premenopausal women with no lifetime history of major depression who entered the menopausal transition were at lower risk of new lifetime episodes of depression. The presence of vasomotor symptoms in women who entered menopause was associated with higher risk of new lifetime episodes of depression. This risk was higher in women who entered menopause with a history of reproductive-related mood disturbances.

Conclusion: The current study suggests that within a normally aged population of women with a lifetime history of depression, those who enter the menopausal transition 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 experience of adverse life events, independently modify this risk. Physical symptoms associated with the menopausal transition and mood changes were present during the premenopausal period and may lead to a significant burden of illness.
First-onset of depression and time of menopause transition: The Harvard Study of Moods and Cycles

- 835 women (36-49 years of age)
- 3-14 years of follow up
- NO history of depression at enrollment

Highest incidence of depression within two years into the menopause transition

Rate of depression (per 100 person years) in 2 year time periods relative to entry to menopause transition

Harlow BL, MacLehose RF, Soares CN. Am J Epidemiology, 2013

Depressive symptoms across the menopause transition: Findings from a large population-based cohort study

Hickey M et al. Menopause in press

Around 11% of the sample (N=6,000) showed stable high or increasing depressive symptoms over time

Continuum of risk' previous diagnosis or treatment for depression, presence of enduring, challenging socio-economic issues

Depression During Menopause

- Risk factors
  - Continuum of risk/Window of vulnerability
  - Lessons learned from epidemiologic data
  - Trajectories over time

- Co-occurrence or causality?
  - Vasomotor Symptoms
  - Sleep
  - Anxiety

- The Role of Estrogen
  - Etiology
  - Modulation of neurotransmitters
  - Therapeutic value

Table 5: Results from Multivariable Multinomial Regression Model

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Persistent/Recurrent Major vs. No Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Age (per 1 unit increase)</td>
<td>1.06 (1.00, 1.13)</td>
</tr>
<tr>
<td>Black vs. White</td>
<td>1.05 (1.00, 1.11)</td>
</tr>
<tr>
<td>Low risk physical</td>
<td>0.65 (0.52, 0.82)</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>1.40 (1.05, 1.87)</td>
</tr>
<tr>
<td>Low risk emotional</td>
<td>1.37 (1.03, 1.84)</td>
</tr>
<tr>
<td>(95% CI) (per 1 unit increase)</td>
<td>1.08 (1.03, 1.13)</td>
</tr>
<tr>
<td>Sleep problems</td>
<td>(1.04 (1.00, 1.07)</td>
</tr>
<tr>
<td>≥ two or more very stressful life events vs. none vs. one vs. none</td>
<td>≥ two or more medical conditions vs. none</td>
</tr>
<tr>
<td>Lifetime major/minor depression</td>
<td>3.78 (1.13, 1.68)</td>
</tr>
<tr>
<td>Family history depression</td>
<td>3.25 (1.14, 9.46)</td>
</tr>
</tbody>
</table>

31% developed Persistent/recurrent Depression
continuum of risk factors (depression, past, current, family, medical conditions) and context-related factors (e.g. life stressors)
• 29 premenopausal women
• 27.3 ± 7.2 years old
• Non-depressed

GnRHα (leuprolide) 4 weeks Mood, HF, Sleep assessments

• 20 subjects (69%) developed HFs
• Only 1 subject developed clinical depression

• Association between changes in depressive symptoms and nighttime HF
• Association with sleep changes

Women with LOW Anxiety at Baseline
Anxiety peaked at Perimenopause - 4.6% to 13.6%

Women with HIGH Anxiety at Baseline
Those remained anxious over time (16-21%), with symptoms declining after menopause (from 71% to 40%)

Menopause 2013;20(5) 488-95.
Vasomotor Symptoms remain strongly associated with Anxiety over time (2-3 fold increased risk) at both groups

Depression During Menopause

• Risk factors
  • Continuum of risk/ Window of vulnerability
  • Lessons learned from epidemiologic data
  • Trajectories over time

• Co-occurrence or causality?
  • Vasomotor Symptoms
  • Sleep
  • Anxiety

The Role of Estrogen
  • Biology
  • Modulation of neurotransmitters
  • Therapeutic value

Role of Estrogen for Depression during the Menopause Transition

Greater changes, fluctuations in estrogen levels

Vulnerability to depression during the menopausal transition

Administration of estrogen (17β Estradiol)

Presence/severity of mood symptoms during the menopausal transition

Onset of Depressive Symptoms and Hormone Changes

High CES-D scores were associated with increased variability (within subject) of levels of:
- Estradiol (P = .03)
- FSH (P < .001)
- LH (P = .005)

Table 6. Odds Ratios (OR) of Hormones From the Final Reversible Model for Onset of Depressive Symptoms (CES-D Suicide Score > 10) for 110 Participants

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Unadjusted</th>
<th>Adjusted</th>
<th>OR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol</td>
<td>1.13</td>
<td>1.06</td>
<td>(1.00-1.30)</td>
<td>.06</td>
</tr>
<tr>
<td>FSH</td>
<td>1.30</td>
<td>1.29</td>
<td>(1.05-1.50)</td>
<td>.05</td>
</tr>
<tr>
<td>LH</td>
<td>1.00</td>
<td>1.00</td>
<td>(0.85-1.16)</td>
<td>.92</td>
</tr>
</tbody>
</table>

Effects of Estradiol Withdrawal on Mood in Women with Past Perimenopausal Depression: A Randomized Clinical Trial

Estrogen Withdrawal caused depressive response ONLY in women with history of perimenopausal depression treated with ET

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

- Over 2,300 searches (1997-2014)
- 25 RCT on the effects of estrogen therapy on mood
- 5 included symptomatic (depressed) women
- Only 2 E2 RTCs for perimenopausal depression

Estrogen-Based Therapy (Transdermal 17β-E2) for the Treatment of MDD in Perimenopausal Women
To identify early biomarkers for PPD among at-risk women
Biomarker panel of 116 transcripts unique to PDD in the third trimester (89% accuracy)
- controlled for anxiety
- controlled for lifetime MDD or BPD
- Replicated in another dataset

Higher numbers of transcripts were linked to estrogen signaling – i.e., dysregulation of estrogen signaling in PPD


Exploring an E2 \(\rightarrow\) 5H-T pathway for mood regulation: The Acute Tryptophan Depletion (ATD) Paradigm

ATD has been used to investigate the pathophysiology of depression and the MOA of antidepressant treatments
- ingestion of large neutral amino acids (NO tryptophan) resulting in 70-90% reduction in brain tryptophan within 5-7 hours.
- Decline in central 5-HT behavioral and physiological correlates.

ATD procedure was successful – 93% reduction in Trp availability 6 hours after mixture ingestion

Figure 1a. Contrast between post-therapy with antidepressant (AD) and acute post-surgery (No AD) trial (Emotional Conflict Resolution) by functional magnetic resonance imaging (fMRI). Top row shows regional brain changes in baseline condition (pre-Acute Tryptophan Depletion [ATD]). Emotional conflict resolution involved detection (values from blue to green in anterior cingulate, bilateral thalamus, and thalamus). Bottom row shows the regional brain changes 6 hours after ATD, when subject reported increased energy, low motivation and difficulty concentrating. Emotional conflict resolution involved anticipation (values from blue to yellow) in the right dorsolateral prefrontal cortex. Color bar represents reliability in the correlation (\(p<0.05\)).

Minuzzi, L et al, NAMS 2013
Impact of Tryptophan Depletion on Sleep Efficiency during the Menopausal Transition while on Estrogen Therapy

NAMS Meeting, 2016

Effects of ATD in Midlife Women on E2 with Current MDD or Past MDD (euthymic)

Poster presentation at NAMS 2016

Syan, S et al.

Allopregnanolone – a progesterone-derived neurosteroid, usually:
- Increases GABA activity through GABA_A receptors
- Negatively modulates the HPA axis to return it to homeostasis following stress
- Exerts anxiolytic and antidepressant actions

Am J Psychiatry 172:3, March 2015
**Shift in the brain network of emotional regulation in midlife women: is the menopausal transition the turning point?**

*Bruno R. Frys, MD, PhD,
Geoffrey R. Hall, PhD,
Sofiane Attard, BA,
Karin Yucel, MD, PhD,
Ivan Skarin, MD, PhD,
 and Claudine N. Seve, MD, PhD, FRCPC

Activation of DLPFC during emotional conflict resolution
Deactivation of amygdala during exposure to fearful faces

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**Precision Medicine: Potential Biomarker Candidates and Interventions**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Biomarker</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Cancer</td>
<td>EML4-ALK</td>
<td>Crizotinib</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>CYP2C19</td>
<td>Clopidogrel (Plavix)</td>
</tr>
<tr>
<td>Smoking Cessation</td>
<td>CYP2A6</td>
<td>Varenicline</td>
</tr>
<tr>
<td>Alcohol Abuse</td>
<td>GRIK1</td>
<td>Topiramate</td>
</tr>
</tbody>
</table>

*Jameson and Longo, New Engl J M 2015*

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**Biomarkers in Psychiatry: Barriers to progress**

- Limited by Syndromes/Disorders
  - Overlapping phenotypes across disorders
  - Heterogeneity within disorders
- Lack of in-vivo biopsy
- Naïve pursuit of single markers
  - No HbA1c
- Retrospective, generic
  - Lack of randomization on the basis of markers
- Failure to replicate
  - Common theme across areas of medicine
- Relatively small samples
  - Need Big Data to move forward

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**CAN-BIND**

Canadian Biomarker Integration Network In Depression

**CAN-BIND Academic Partners**

**Funding Partners**

[Logos of various institutions]
**CAN-BIND Integrated Platforms**

**Clinical Outcomes**
- Clinician administered scales
- Patient-reported outcomes
- Electronic data capture

**Molecular Profiling**
- Gene expression
- SNP analysis
- GWAS
- sRNA Microarray
- Whole genome mRNA
- Redox, methylation

**Neuroimaging**
- T1-weighted anatomical scan
- DTI series
- T2-weighted BOLD EPI series
- BOLD EPI series during tasks

**Data Science**
- Statistical tools coupled with machine learning tools to create biomarker models

**Preclinical**
- Rodent anhedonia models
- Zebrafish high-throughput pharmacology & electrophysiology

**M-Health**
- Behavioural Sensing
- Ecological momentary assessments

**CAN-BIND Approach**

Identify key markers that predict treatment response in the most accurate and efficient manner using an iterative process.

**Treatment Approaches**
- Cross-platform data collection
  - Clinical
  - Imaging
  - Molecular
  - EEG
  - M-Health

**Response Biomarkers**

**Data Science**

**Validate and Retest**

**Knowledge Translation**
- Public and provider education
- Patient Advisory Committee
- Social media strategy
- Implementation science

**Towards a Predictive Model: Summary**

**Baseline Severity (MADRS, QIDS)**

**Clinical inputs:**
- Anxiety Co-morbidity
- Anhedonia (DARS)

**Molecular inputs:**
- Inflammatory Markers

**Check for No Predictive Value**

**Predicts Slow Responders with 72% Accuracy**

**Predicts Fast vs. Non-responders with 76% Accuracy**

**Summary of Model**

**Accuracy = 72%**

**AUC = 0.73**

**Accuracy = 76%**

**AUC = 0.77**

**Patient**
- Yes
- Slow
- Fast

**No**
- No
- In between
Search for Biomarker Panels for Depression in Midlife Women

NEW ONSET of MDD during Midlife

E2 Responder

- Anxiety -
  - VMS +
  - Sleep -

- Anxiety +
  - VMS -
  - Sleep -

E2 Non Responder

- Anxiety -
  - VMS -
  - Sleep +

- Anxiety +
  - VMS +
  - Sleep +