Mood and Cognitive Changes During Menopause

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Learning Objectives

To recognize the complexity and multi-faceted aspects of depression in midlife women

To understand the mechanisms by which hormone changes may affect mood and cognition in women

To review existing, evidence-based treatment strategies for this population
A Closer Look at Depression in Women

Depression is more common in women than in men 2-2.5:1 ratio

Unique psychosocial stressors: transitional roles, stressful life events

Reproductive-related windows of vulnerability periods of hormone changes – PMS, PPD, peri-menopause
Windows of Vulnerability

- Heightened prevalence of psychiatric conditions during periods of intense hormone variability, fluctuation (e.g., premenstrual, postpartum, menopausal transition).

- Symptoms, adverse outcomes resulting from the disruption of hormone milieu.

Windows of Opportunity

- A stable hormone milieu or a hormone intervention may exert a *prophylactic* effect.

- Hormone intervention/modulation may exert a *therapeutic* effect.

The Menopausal Transition
Interface between Psychiatry and Gynecology

C. Soares
M. Warren

The interplay of hormones, health and behavior across the female life cycle, especially during the menopausal transition, poses a special challenge to health care professionals.

Written by experts, this book brings together the knowledge gained on the menopausal transition from clinical experience and medical research. Topics like ‘what to expect’ from the menopausal transition, sexuality, sociocultural changes, impact of life stressors, and emergence of depression are discussed. The physiology of thermoregulation and the occurrence of hot flashes are reviewed to promote a better understanding of vasomotor complaints. Another chapter offers an update on hormonal and nonhormonal treatment strategies by presenting an overview of the management of mood and anxiety during the menopausal transition. The emergence of psychotic symptoms associated with peri- and postmenopausal changes in sex hormone levels is also addressed. Lastly, the book includes an excellent review on the pros and cons of hormonal therapy in the post-Women’s Health Initiative era.

This book is essential for gynecologists, psychiatrists, endocrinologists, epidemiologists involved in the clinical care of mature women as well as researchers and students interested in obtaining an up-to-date overview of this topic.
“Depression of gradual onset occurring during the involutional years (40-55 in women and 50-65 in men)......marked anxiety, agitation, restlessness, somatic concerns, hypochondriasis....somatic or nihilistic delusions, insomnia, anorexia, and weight loss”

The empty nest period is defined as the phase of life when the children are grown but no longer live at home (Harkins, 1978). ... a time of crisis for mothers, with high levels of marital conflict and low marital satisfaction (Barber, 1989).

In macaques, TPH-2 mRNA levels were measured in the raphe region after chronic estrogen treatment.... ...there was an increase in the relative abundance of TPH-2 mRNA when compared to spayed controls (Sanchez et al 2005).
Menopause-Associated Pathways to Depression

Risk for New Onset of Depression During the Menopausal Transition

The Harvard Study of Moods and Cycles

Lee S. Cohen, MD; Claudio N. Soares, MD, PhD; Allison F. Vitonis, BA; Michael W. Otto, PhD; Bernard L. Harlow, PhD

**Context:** Transition to menopause has long been considered a period of increased risk for depressive symptoms. However, it is unclear whether this period is one of increased risk for major depressive disorder, particularly for women who have not had a previous episode of depression.

**Objective:** To examine the association between the menopausal transition and onset of first lifetime episode of depression among women with no history of mood disturbance.

**Design:** Longitudinal, prospective cohort study.

**Setting:** A population-based cross-sectional sample.

**Participants:** Premenopausal women, 36 to 45 years of age, with no lifetime diagnosis of major depression (N=460), residing in 7 Boston, Mass, metropolitan area communities.

**Main Outcome Measure:** Incidence of new onset of depression based on structured clinical interviews, Center for Epidemiologic Studies Depression Scale scores, and an operational construct for depression.

**Results:** Premenopausal women with no lifetime history of major depression who entered the perimenopause were twice as likely to develop significant depressive symptoms as women who remained premenopausal, after adjustment for age at study enrollment and history of negative life events. The increased risk for depression was somewhat greater in women with self-reported vasomotor symptoms.

**Conclusions:** The current study suggests that within a similarly aged population of women with no lifetime history of depression, those who enter the menopausal transition earlier 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 occurrence of adverse life events, independently modify this risk. Physical symptoms associated with the menopausal transition and mood changes seen during this period may affect many women as they age and may lead to a significant burden of illness.

*Arch Gen Psychiatry.* 2006;63:385-390
Risk for First Onset of MDD

Menopausal Status

- Premenopause (n = 95)
- Perimenopause (n = 326)
- Perimenopause with VMS (n = 135)

VMS = vasomotor symptoms

First-onset of depression in women with no depression history at the time of entry to perimenopause: The Harvard Study of Moods and Cycles

835 women 36-49 years of age with no lifetime history of depression followed for 3-14 years

✓ Women entering perimenopause experienced first onset of depression at rates nearly twice that of women who remained premenopausal (HR=1.8, 95%CI 1.1-3.0)

✓ The incidence was highest at or within two years following entry to 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, et al., submitted
Hot Flashes: A Red Flag for Depression

• Vasomotor symptoms have been consistently associated with the emergence of depressive symptoms / episodes in prospective and retrospective population-based studies
  - VMS should raise the index of suspicion of depression in perimenopausal women

• ~ like a fever that often precedes symptoms of infection
**Odds Ratios (ORs) of Hormones From the Final Multivariable Model for Onset of Depressive Symptoms (CES-D Scale Score >= 16) for 116 Participants**

<table>
<thead>
<tr>
<th>Hormone*</th>
<th>Unadjusted</th>
<th>Adjusted</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol</td>
<td>1.10</td>
<td>1.06</td>
<td>(0.63-1.78)</td>
<td>.83</td>
</tr>
<tr>
<td></td>
<td>1.30</td>
<td>1.36</td>
<td>(1.02-1.80)</td>
<td>.03</td>
</tr>
<tr>
<td>FSH</td>
<td>4.38</td>
<td>4.58</td>
<td>(2.03-10.35)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>1.90</td>
<td>2.09</td>
<td>(1.70-3.41)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Inhibin B</td>
<td>0.34</td>
<td>0.37</td>
<td>(0.20-0.66)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>1.32</td>
<td>1.20</td>
<td>(0.89-1.60)</td>
<td>.21</td>
</tr>
<tr>
<td>LH</td>
<td>2.98</td>
<td>3.00</td>
<td>(1.52-5.93)</td>
<td>.002</td>
</tr>
<tr>
<td></td>
<td>1.57</td>
<td>1.57</td>
<td>(1.18-2.22)</td>
<td>.005</td>
</tr>
</tbody>
</table>

Abbreviations: CES-D, Center for Epidemiological Studies of Depression; CI, confidence intervals; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

*Each hormone was examined separately in the final model because of high collinearity of the hormones.

† Standard deviation (SD) is the deviation of the hormone measures around the subjects' mean, calculated for each subject at each assessment period.

‡ Refers to odds per 1 unit change in SD.

High CES-D scores were associated with greater variability (within subject) of levels of estradiol (P = .03), FSH (P<.001), and LH (P = .005) compared to prior high CES-D scores.
Effects of Estrogens on Serotonergic and Noradrenergic Neurons

Effects on Serotonergic System
- Modulates serotonin neuronal firing
- Increases serotonin synthesis
- Decreases serotonin breakdown
- Affects serotonin receptor subtypes
- Desensitizes serotonin autoreceptors

Effects on Noradrenergic System
- Increases available norepinephrine
- Increases norepinephrine synthesis
- Alters adrenergic receptor gene expression
- Reduces norepinephrine turnover rate

Depression in Women: Windows of Vulnerability and New Insights Into the Link Between Estrogen and Serotonin

Sonali Lokuge, MSc; Benicio N. Frey, MD, PhD; Jane A. Foster, PhD; Claudio N. Soares, MD, PhD, FRCPC; and Meir Steiner, MD, PhD, FRCPC

- E2 administration decreases the activity of monoamine oxidases (MAO-A and MAO-B), which are enzymes involved in 5-HT degradation and increases both isoforms of tryptophan hydroxylase (TPH-1 and TPH-2) involved in serotonin synthesis i.e. increases 5-HT synthesis and availability.

- E2 also regulates the 5-HT transporter, fundamental in 5-HT reuptake from the synaptic cleft to the pre-synaptic neuron.

- By down-regulating 5HT_{1a} auto-receptors and up-regulating 5HT_{2a} receptors, E2 increases the amount of 5-HT found in the synapse and increases the amount available for postsynaptic transmission.

J Clin Psychiatry 2011
It is plausible to speculate that in times of intense hormone fluctuations (i.e., the menopausal transition), the crosstalk between estrogen and monoaminergic systems could be affected and could ultimately alter mood and behaviour regulation.
Prescriptions of HRT and Antidepressants* Prior To and After WHI Results

Bottom: Linear regression models of the number of prescriptions against time, for each prescription type (HRT and SA) and for each time period (11 months before and 11 months after July 2002).

*Citalopram, fluoxetine, sertraline, fluvoxamine, paroxetine, venlafaxine, nefazodone, and trazodone. HRT = hormone replacement therapy; WHI = Women’s Health Initiative; SA = serotoninergic antidepressant. McIntyre RS, et al. CMAJ. 2005;172:57-59.
Pharmacotherapy for Midlife Women

- Treatment of midlife women (peri- and early postmenopausal women) presenting with mood, vasomotor, and somatic symptoms might pose a significant challenge to physicians and health professionals
- No general consensus or comprehensive guidelines available

**Diagram**

- Antidepressant
- HT/ET
- HT/ET + Antidepressant

ET, estrogen therapy; HT, hormone therapy.
Depression During the “Menopausal Window”: Clinical Considerations

• Antidepressants are still the treatment of choice for depression across the female life cycle. Behavioral interventions (CBT, IPT) can also be helpful

• Hormonal strategies can be helpful for the treatment of menopause-related depressive symptoms

• Adequate management of other menopause-related symptoms (eg, VMS) is important to achieve full recovery in menopause-associated depression

• Nonhormonal strategies can be helpful for the treatment of menopause-related symptoms (eg, VMS)

CBT, cognitive behavioral therapy; IPT, interpersonal psychotherapy; VMS, vasomotor symptoms.
Hormonal Management of Hot Flashes

• Hormone therapy is the most efficacious therapy for VMS
• Cochrane database review showed\textsuperscript{1}
  - 75\% reduction in frequency
  - Significant reduction in hot flash severity
  - Combination of E+P slightly more effective than E alone
• Progestin alone has also demonstrated efficacy\textsuperscript{2}

E, estrogen; P, progestin; VMS, vasomotor symptoms.
# Efficacy of Nonhormonal Treatments for Vasomotor Symptoms

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Main Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black cohosh</td>
<td>No significant improvement of VMS</td>
</tr>
<tr>
<td>Soy</td>
<td>No significant improvement of VMS or QOL</td>
</tr>
<tr>
<td>Clonidine</td>
<td>Reduction of hot flushes in 80% (PL=36%)</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Reduction of hot flushes in 45% (PL=29%)</td>
</tr>
<tr>
<td>Paroxetine CR</td>
<td>Reduction of hot flushes in 62% to 65% (PL=38%)</td>
</tr>
<tr>
<td>Venlafaxine XR</td>
<td>Reduction of hot flushes in 37% to 61% (PL=27%)</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Reduction of hot flushes in 76% (PL=64%)</td>
</tr>
<tr>
<td>Desvenlafaxine</td>
<td>Reduction of hot flushes in 68%-75% (PL=48%)</td>
</tr>
</tbody>
</table>

VMS, vasomotor symptoms; QOL, quality of life; PL, placebo.
Efficacy of Herbals, Soy, and Botanicals for Vasomotor Symptoms

HT, hormone therapy.
Treatment of Core Menopause-Associated Symptoms

Hot Flashes
- Gabapentin
- Estrogen therapy

Sleep Disturbance
- Gabapentin
- GABA-A agents
- SSRI/SNRI

Depression
- Atypicals

Solid lines indicate support from randomized controlled trials.
Dotted lines indicate support from preliminary/open-label studies.
SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.
Normal Aging & the Brain

*Not all domains are equally affected*

**REMAINS INTACT**
- Non-declarative memory
  - How to brush one’s teeth, drive a car, etc.
- Semantic memory
  - Names of presidents

**DECLINES WITH AGE**
- Declarative memory
  - Personal history, experiences
  - Delayed recall of information, working memory
  - Degree of difficulty
- Spatial learning memory

Estrogen and Cognition

Effects on Layer III Pyramidal Cells in BA 46 (DLPFC)

Estrogen & Cognition- Timing or Critical Window Hypothesis

- ET administered after surgically induced menopause preserves cognitive function\(^1\)
- No effect if initiated several years after surgical or natural menopause\(^2\)
- The risk for developing cognitive impairment or dementia increased among women who underwent unilateral or bilateral oophorectomy compared with the referent group. \(^3\)
- Risk increased with younger age at surgery; e.g., women who had surgery before age 38 had an almost 3-fold increased risk compared with the referent group. \(^3\)
- Women who had surgery before age 48 but received treatment with estrogen until at least age 50 had no increased risk. \(^3\)

\(^1\) Phillips & Sherwin Psychoneuro 2002; 17:485-495
\(^2\) Almeida et al. Neurobiol Aging 2006; 27:141-149
\(^4\) Rocca WA et al. Neurology 2008; 64:1458-64.
# Hormone therapy and cognitive function

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<table>
<thead>
<tr>
<th>Verbal Memory</th>
<th>Executive Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beneficial effect of estrogen on verbal memory in younger naturally post-menopausal women, particularly in surgically post-menopausal women</td>
<td>Evidence for benefits on executive functions such as working memory, problem solving and source memory</td>
</tr>
<tr>
<td>Detrimental effects of CEE/MPA on verbal memory in younger and older post-menopausal women</td>
<td>Benefits are evident even in the absence of hippocampus-mediated tasks</td>
</tr>
<tr>
<td>No beneficial or detrimental effects of estrogen alone in older postmenopausal women</td>
<td>Estrogen as a memory retainer or protector rather than memory enhancer</td>
</tr>
</tbody>
</table>
Effects of E2 administration on Cognitive Function

✓ 52 peri and postmenopausal women – most with vasomotor symptoms & sleep disruption were randomized to ET 50 ug/d or placebo x 12 weeks
✓ California Verbal Learning Test: ET decreased perseverative errors
✓ Final 11 women (5 ET & 6 placebo) underwent fMRI at 1.5T.

Contrast between ET and placebo yielded significant activation in the inferior frontal cortex and parietal regions during completion of a verbal recall task (at T ≥ 3.4, p < 0.001).

Objective hot flashes are negatively related to verbal memory performance in midlife women.

Relationship between Logical Memory delayed free recall and average objective hot flashes during sleeping hours controlling for verbal knowledge and sleep duration.

MC-SYSTEM - McMaster Systematic Screening and Treatment Evaluation of Menopause

- Multi-approach to diagnosis and treatment of menopause-related mood symptoms
- Women’s Health Concerns Clinic (WHCC), The Brain-Body Institute (BBI), The Imaging Research Centre (IRC) and the Mood Disorders Program (MDP) at St. Joseph’s Healthcare Hamilton, McMaster University.

- DIAGNOSTIC STRATEGIES – standardized interviews that capture female-specific triggers (i.e. reproductive life cycle changes)
- STRUCTURAL AND FUNCTIONAL BRAIN IMAGING - effects of depression and vasomotor symptoms on cognition, mood and behavior in menopause
- THERAPEUTIC INTERVENTIONS – improvement of medical and functional outcomes in midlife women

Initiative supported by 2 CIHR R&D fellowships and 3 investigator-initiated research grants
Acute Tryptophan Depletion (ATD) Paradigm

Utilized to investigate the pathophysiology of depression and the mechanism of action of antidepressant treatments.

Plasma Tryp are reduced by 70-90%; Peak effect 5-7 hours post-ingestion of mixture of LNAAs.

Most commonly observed effect on mood is NO EFFECT.

Minimal effects of healthy volunteers and/or MDD subjects receiving NON 5-HT- based treatments (e.g., ECT, lithium, desipramine).

Significant worsening of mood in subjects receiving 5-HT based treatments

Adapted from original material developed by N. Epperson
NEW DIRECTIONS

Monoamine Depletion Paradigms
The role of 5-HT and NE/DA transmission for the effects of E2 on mood, cognition and thermoregulation in midlife women

Biomarkers of Menopause-Associated Changes
BDNF, oxidative stress, inflammatory

Clinical and mechanistic studies to clarify the pathways for E2 effects
Development of novel, safe, hormone-analogous treatments
The need for further investigation and better understanding of common mechanisms seems intuitive.....

An ultimate goal could include preventative strategies for women presenting with various risk factors for cardiovascular, cognitive and mood disorders..... as well as treatments that could be tailored to multiple symptom domains during the menopause transition.
Thank you

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