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BRIGHAM AND WOMEN'S
Connors Center for Women's Health & Gender Biology

Women's Hormones and Aging Research Program
WHARP

HARVARD MEDICAL SCHOOL

Depression in the Menopausal Transition: Understanding Causal Factors and Translating to Therapeutics

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- Spouse:
  - Employee: Arsenal Biosciences employee
  - Equity: Merck Research Labs

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Learning Objectives

1. Recognize importance of understanding factors that contribute to menopause-related depression
   a. Hormonal / menopause-specific
   b. Psychiatric / mental health
   c. Stress / life stage

2. Translate knowledge of causal factors to treatment approaches
   a. Pharmacologic
      - Hormonal
      - Nonhormonal
   b. Behavioral / psychotherapy / lifestyle

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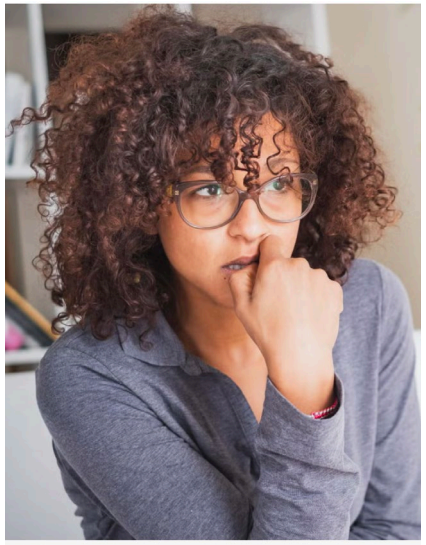
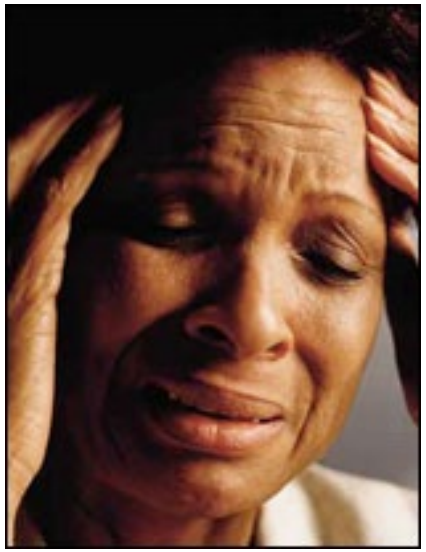
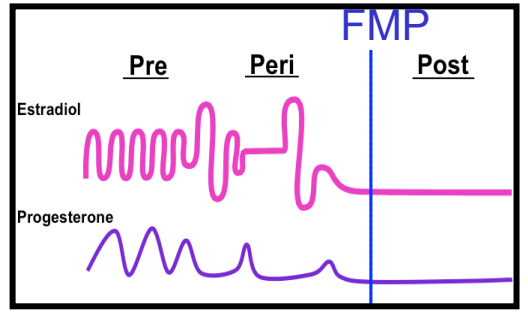
Brain symptoms of menopause

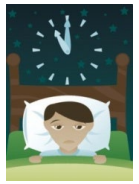




Most common symptoms of menopause

1. Menstrual cycle irregularities and bleeding abnormalities
2. Thermoregulatory disturbance: hot flashes, night sweats, vasomotor symptoms (VMS)
3. Sleep interruption
4. Mood: depressive symptoms >> major depression
5. Vulvo-vaginal and urinary symptoms

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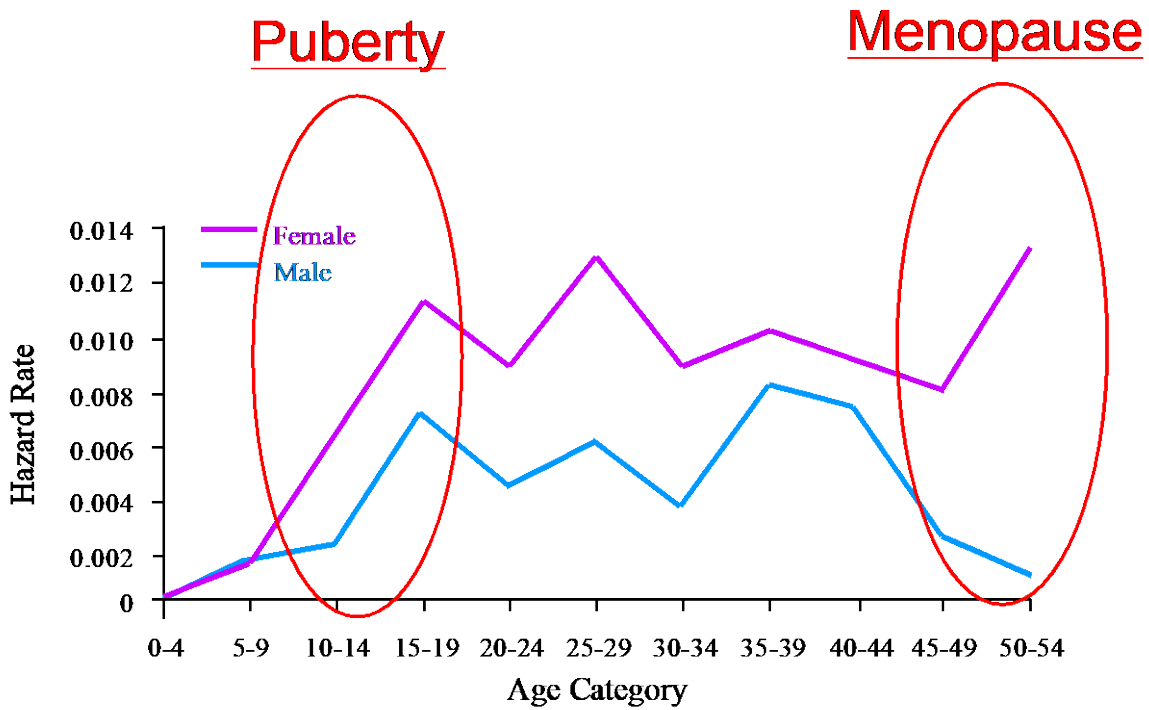
♀ vs. ♂: 2x lifetime risk of depression

World Health Organization Mental Health Surveys
Association of gender with lifetime risk of DSM-IV depression (15 countries, n=73,099)

		All countries combined
		F:M OR (95% CI)
I. Mood disorders		
Major depressive disorder	♀ vs. ♂	1.9* (1.8–2.0)
Dysthymic disorder		1.9* (1.6–2.2)
Bipolar disorder		0.9 (0.8–1.0)
Any mood disorder		1.8* (1.7–1.8)

Seedat S, *JAMA Psych* 2009



Kessler R. *J Affect Disord.* 1993

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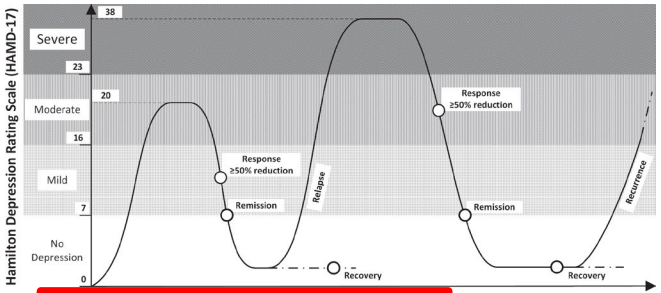
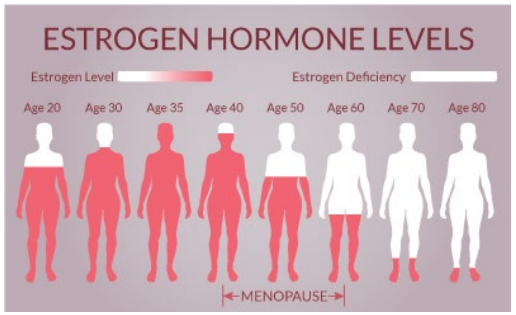
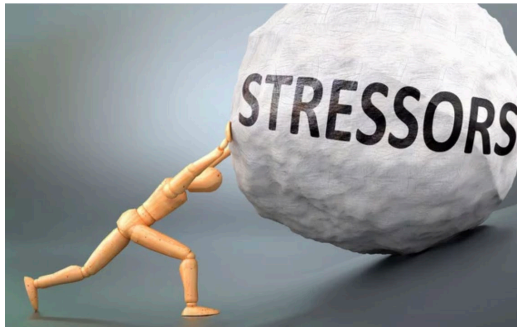
Longitudinal and Cross-sectional Frameworks



Depression recurrence is the norm





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Mood Disturbance Across Menopause Transition

Major Depressive Disorder (MDD)

- 2.7x risk within-person risk as progress into perimeno
- No increased risk of first-lifetime episode of MDD
  - When present, linked with VMS and stressful life events
- Greater risk if
  - Psychiatric risk factors
    - History of MDD → Recurrence
    - Anxiety
    - Medical illness
  - Menopause/hormonal risk factors
    - Sleep disruption

Depressive Symptoms

- 17-28% in perimeno vs. 14-21% in late premeno for entire population
- 2-4x risk within-person risk as progress into perimeno
- Greater risk if
  - Psychosocial risk factors
    - History of MDD
    - Stressful life events, financial stress, low social support
    - Racial minority, higher BMI, smoking, lower activity levels
  - Menopause/hormonal risk factors
    - Reproductive hormone dynamics
    - Longer time in perimenopause
    - Hot flashes
    - Sleep disruption

Subgroup problem

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Bromberger. *Psych Med* 2015; Freeman. *Arch Gen Psych Med* 2006

Maki. *Menopause* 2018

Depression during menopause transition is not universal: A subgroup problem

The trade off

- Empowerment
- Anticipation, fear
- Preparation
- Education
- Cross-sectional attribution
- Implication for treatment

The Washington Post
Democracy Dies in Darkness

Subscri

Depression risks of menopause have been overstated, study finds

By Caren Chesler
Updated March 5, 2024 at 7:40 p.m. EST | Published March 5, 2024 at 2:14 p.m. EST

The Harvard Gazette

Menopause depression risk has been exaggerated

March 11, 2024

Some groups are more vulnerable but symptoms far from universal, review finds

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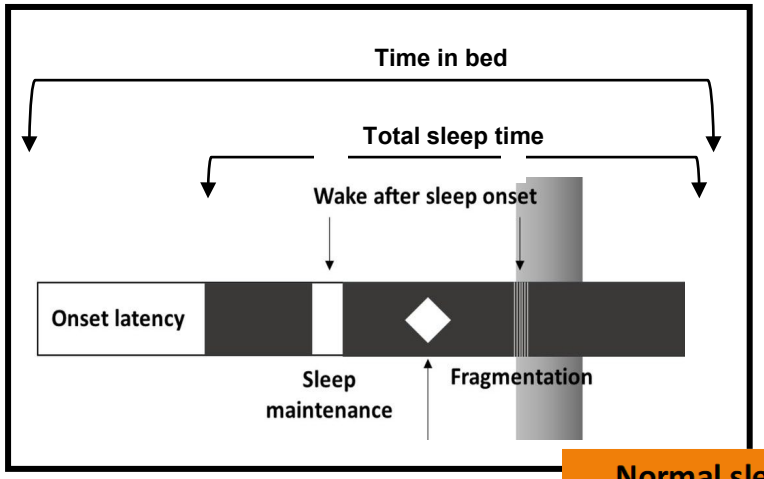
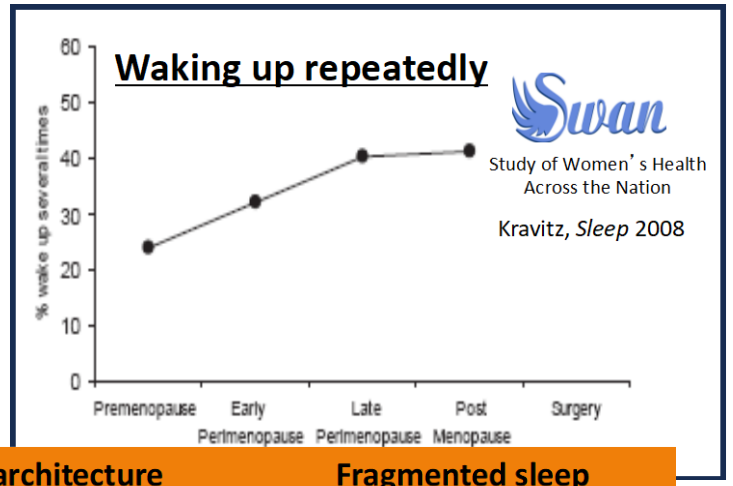
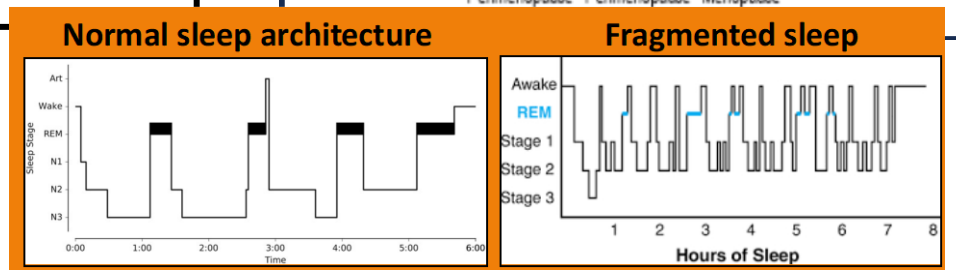
Brown. *Lancet* 2024

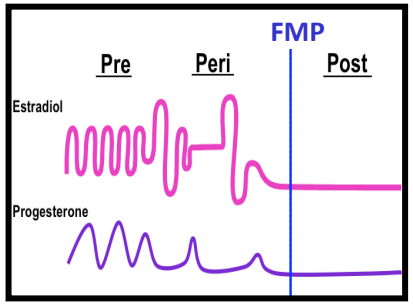
Sleep is multi-dimensional: Alterations in menopause-associated major depression and depressive symptoms







Menopause-associated sleep fragrmentation 2nd VMS and hypo-estrogenism



VMS = vasomotor symptoms; FMP=final menstrual period

Subthreshold depressive symptoms:

↑ sleep fragmentation (↑#minutes awake after sleep onset, ↑ #wakes episodes)

Major/clinical depression:

↓ Total sleep time, ↑ sleep onset
NOT sleep fragmentation

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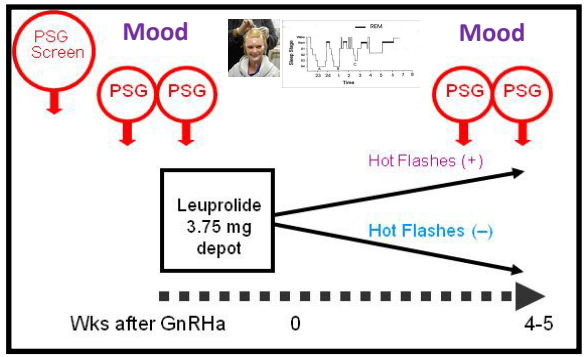
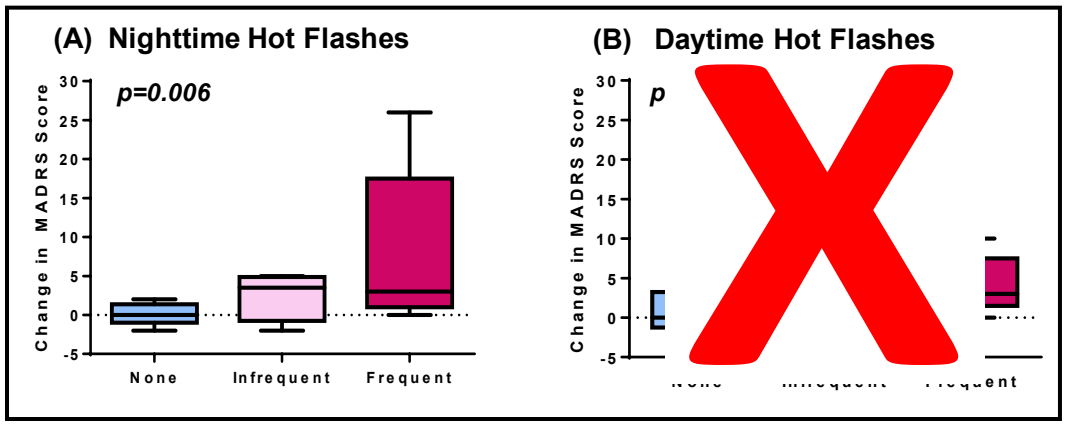
Joffe, *Sleep* 2013; Coborn J, de Wit A, et al, *JCEM* 2022; Joffe, *Menopause* 2009; Kravitz, *Menopause* 2003; Kravitz, *Sleep* 2008; De Zambotti, *Fert Ster* 2014; Bianchi, *J Clin Sleep Med* 2016

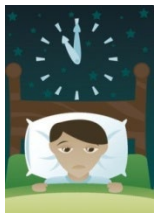
Effect of nighttime hot flashes and sleep disruption on depressive symptoms

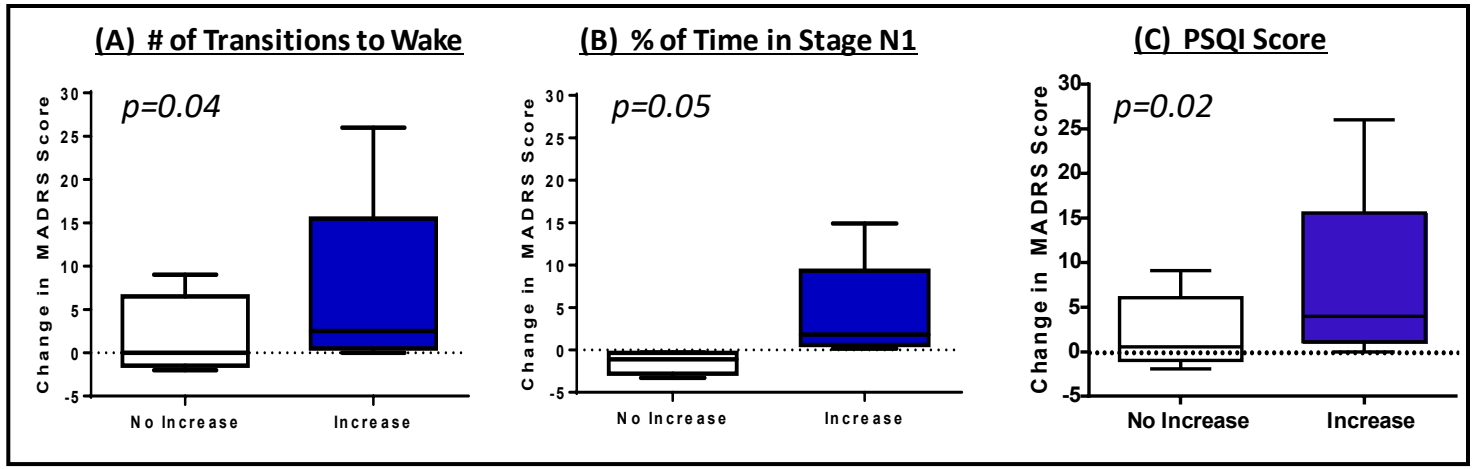


Nocturnal, but not daytime, hot flashes, result in an increase in depressive symptoms



Worsening of sleep fragmentation and sleep quality result in an increase in depressive symptoms





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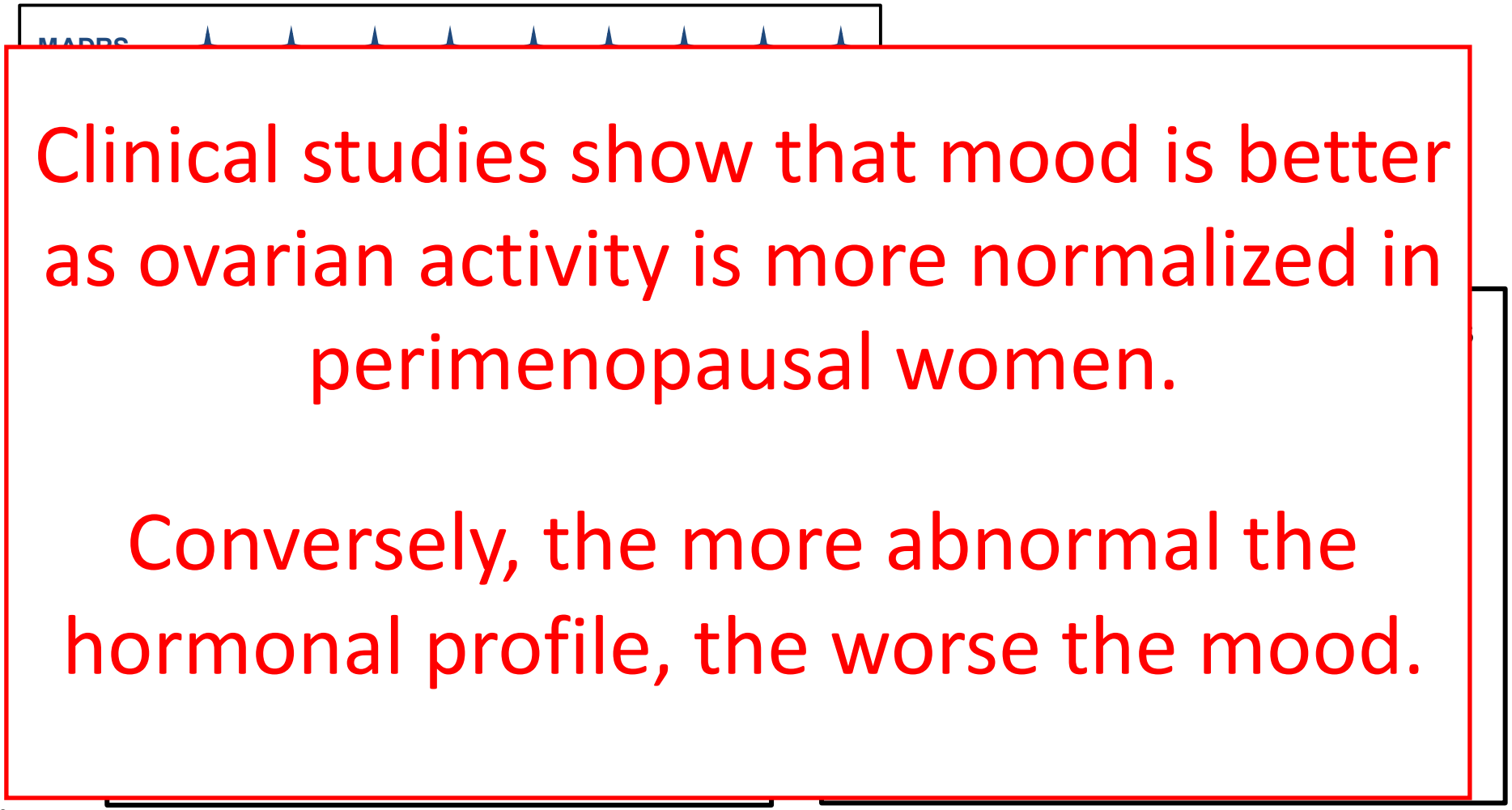
Joffe, *J Clin Endo Metab* 2016

Reproductive hormone dynamics concurrent with perimenopause-associated depressive symptoms



Clinical studies show that mood is better as ovarian activity is more normalized in perimenopausal women.

Conversely, the more abnormal the hormonal profile, the worse the mood.

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MADRS = Montgomery Asberg Depression Rating Scale

Joffe H, *J Clin Endo Metab* 2020

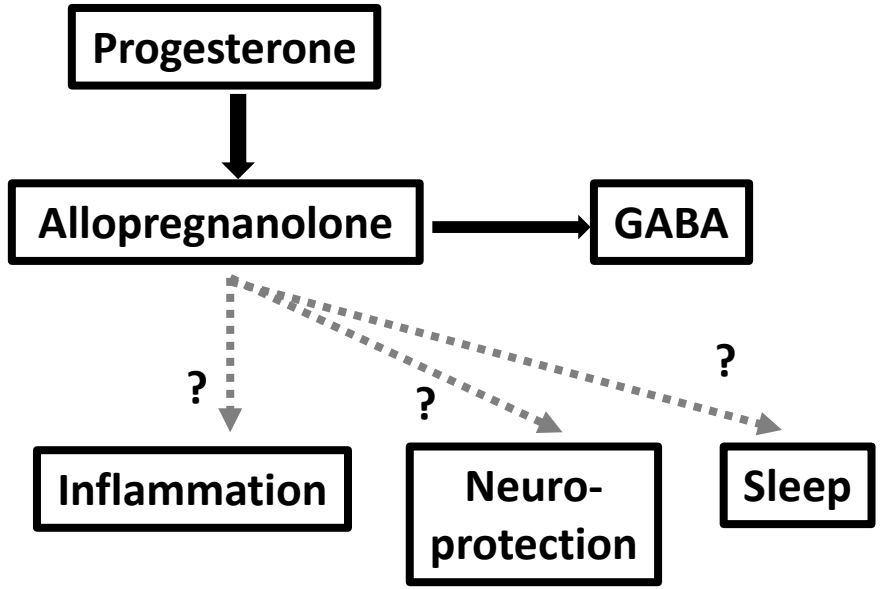
Susceptibility to hormonal contributors to menopause-related depressive symptoms

Why do some but not others develop depressive symptoms during menopause transition?

Possible explanations

1. Depressive symptoms ebb and flow based on recent/current reproductive hormone profile
2. Genetic susceptibility?
3. Stress mediation?
4. **Allopregnanolone (ALLO): metabolite of progesterone**
   - → **Extrapolating from data in postpartum depression**
   - → **ALLO is therapeutic**

As progesterone declines, does ALLO transmit perimenopausal depressive symptoms through



Joffe and Burdick (MPI): R01MH128617

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Joffe, *J Clin Endo Metabol* 2020; Gordon, *JAMA Psych* 2018; Schweizer-Schubert, *Front Med* 2020; McEvoy and Osborne, *Int Rev Psych* 2019;

Treatment approaches: menopause-associated depression

	Depression	VMS	VMS comments	Sleep (2nd VMS)
Hormonal				
Psychotropic or "non-hormonal"				
Novel compounds (neurokinin B antagonists)				
Behavioral alternatives				

TSEC = tissue selective estrogen complex = conjugated estrogens + SERM (selective estrogen receptor modulators (bazedoxifene))
DORA = dual orexin receptor antagonist; CBT = cognitive behavioral therapy; QOL = quality of life

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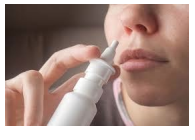
McCurry, *JAMA Int Med* 2016; Guthrie, *Sleep* 2018; Enrud, *Sleep* 2025; Lederman, *Lancet* 2023; Simon, *Menopause* 2023; Green, *Menopause* 2019

Treatment of depression and depressive symptoms in women with VMS

In women with VMS, approaches to major depression differ from approaches to depressive symptoms

Major/clinical depression

- Pharmacotherapies
  - ✓ Antidepressants (SSRI, SNRI, etc)
  - ✓ Interventional approaches (e.g., TMS, esketamine, ECT, hospitalization)
  - ? Neurosteroids (allopregnanolone, ganaxolone)
  - ✓ HT is not a first-line approach
    - May consider if peri, prominent VMS, no contra-indications
    - RCT used 0.1 mg TD
- Psychotherapy



Subthreshold depressive symptoms

- Pharmacotherapies
  - ✓ Antidepressants (SSRI, SNRI, etc)
  - ✓ Hormone therapies (if prominent VMS):
    - RCT used CEE 0.45mg/d + cyclic prog. 200mg/d
  - ? Neurosteroids (allopregnanolone, ganaxolone)
  - ? N
- Psych

R01MH12861 testing ALLO mechanisms

Summary of HT to treat mood

- ✓ HT (off-label) considered for subthreshold depressive symptoms when hot flashes are prominent/bothersome
- ✓ HT not 1st line for major depression

Gleason, *PLoS Med* 2015; Kornstein, *J Clin Psych* 2010; Joffe, *J Clin Psych* 2007; Joffe, *J Women's Health Gend Based Med* 2001; Soares, *J Clin Psych* 2003; Dias, *Menopause* 2006; Kornstein, *Menopause* 2014; Kornstein, *JCP* 2014; Soares, *Arch Gen Psych* 2001; Schmidt, *Am J OBGYN* 2000; Gordon, *JAMA Psych* 2018; Morrison, *Bio Psych* 2004

olled trials; TD = transdermal

TMS = transcranial magnetic stimulation; ECT = electroconvulsive therapy

Summary: Depression and depressive symptoms during peri/postmenopause

1. **Mood disturbance can present as major depression or mild subsyndromal depressive symptoms**
2. **Cross-sectional (menopause-related, stress/life events) and longitudinal factors (depression recurrence) must be considered to inform therapeutic strategies**
2. **Mild depressive symptoms commonly occur during the menopause transition**
    - Subthreshold depressive symptoms associated with perimenopausal hormone profile, nighttime hot flashes, and sleep interruption
3. **Major depression is less common and typically represents recurrence**
4. **Hormone therapy**
    - Effective for subthreshold symptoms
    - Clinical depression mostly when women are perimenopausal and have hot flashes (but not first-line)
    - Not effective for postmenopausal women without hot flashes
5. **Antidepressants are effective treatments of depression associated with the menopause transition**
6. **Role of allopregnanolone as progesterone metabolite under investigation**

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It takes a village……

WOMEN'S HORMONES AND AGING RESEARCH PROGRAM

THANK YOU

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MsFLASH MENOPAUSE STRATEGIES FINDING LASTING ANSWERS FOR SYMPTOMS & HEALTH

Kris Ensrud, MD MPH, Katherine Newton, PhD, Andrea LaCroix, PhD, Katherine Guthrie, PhD, Bette Caan, PhD, Barbara Sternfeld, PhD, Susan Reed, MD MPH, Janet Carpenter, PhD, Lee Cohen, MD, Ellen Freeman, PhD, Sue McCurry, PhD, and others

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Sybil Crawford, PhD, Jill Bromberger, PhD, Joel Finkelstein, MD, Martica Hall, PhD, Howard Kravitz, DO MPH, Karen Matthews, PhD, and others

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