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Premenstrual Dysphoric Disorder and Menopausal Mood Disorders

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DISCLOSURES



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 - Eli Lilly
- Spouse employment: Arsenal Biosciences, F-Prime



Learning Objectives

1. Understand premenstrual dysphoric disorder and premenstrual exacerbation of mood disturbance
2. Describe prevalence, course and common precipitating and co-occurring factors of major depression and subthreshold depressive symptoms across menopause transition
3. Review treatment options for mood disturbance related to menopause and the premenstruum



Women's Hormones and Aging
Research Program



Beth Israel
Deaconess Medical Center



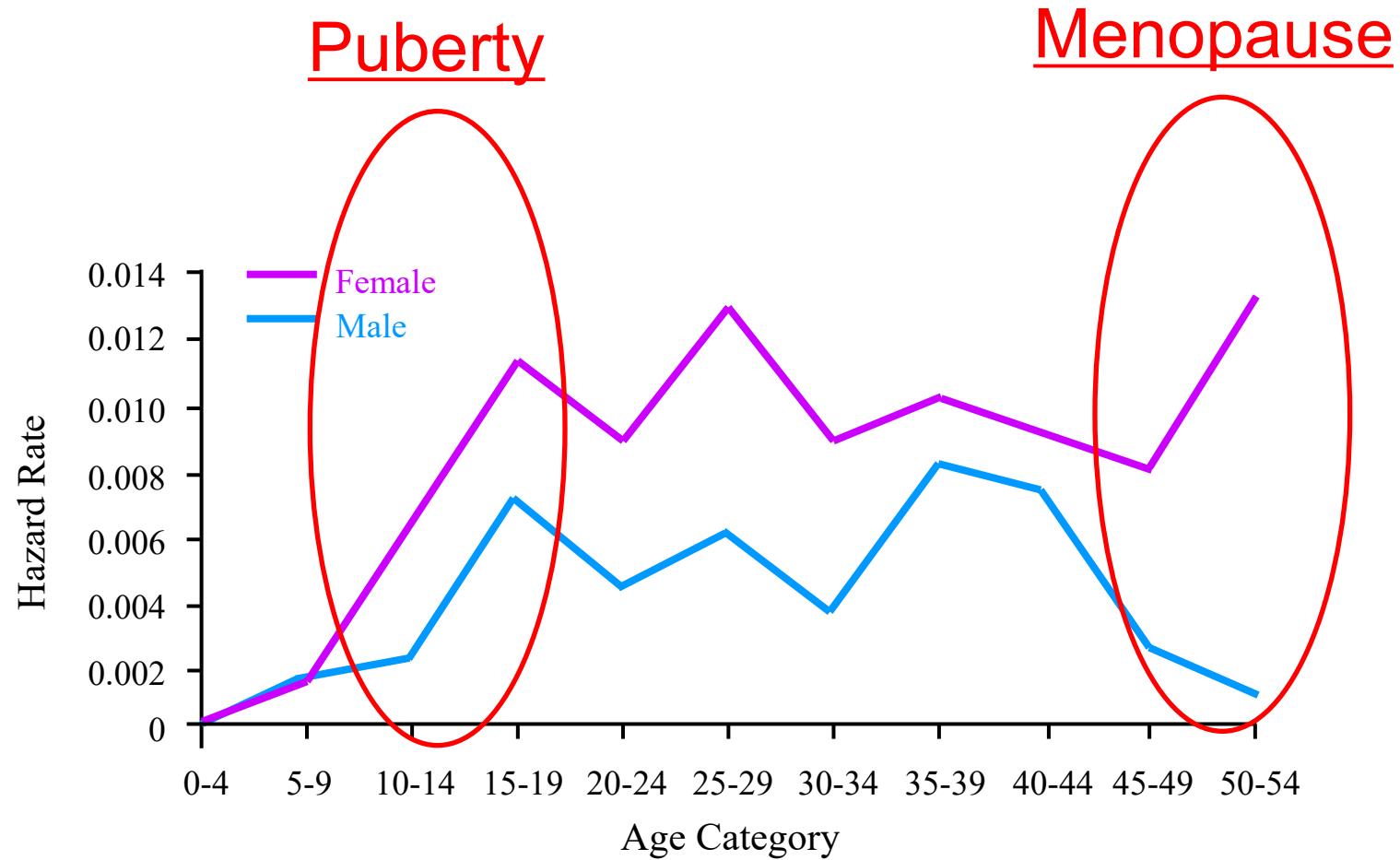
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♀ vs. ♂: 2x lifetime risk of depression

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

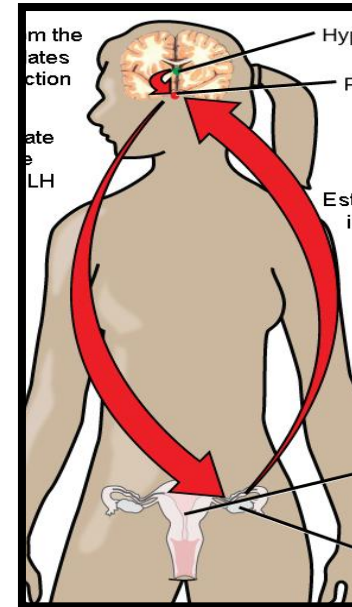
All countries combined		
F:M OR (95% CI)		
I. Mood disorders		
Major depressive disorder	♀ vs. ♂	1.9* (1.8–2.0)
Dysthymic disorder		1.9* (1.6–2.2)
Bipolar disorder		0.9 (0.8–1.0)
Any mood disorder		1.8* (1.7–1.8)

Risk of major depression by age in ♀ and ♂

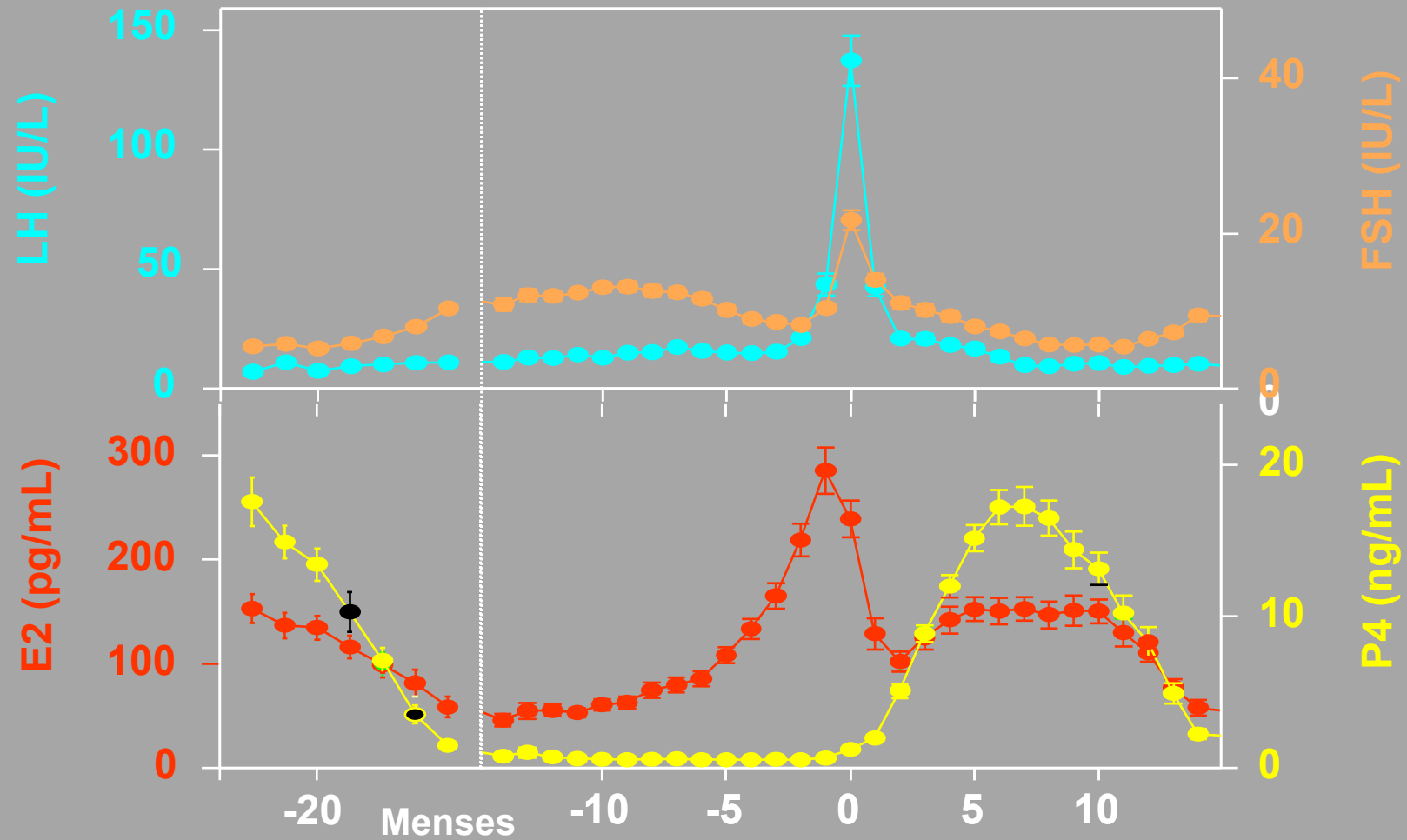


What explains excessive risk of depression in women?

1. Endorsement of symptoms
2. Gender roles, socio-cultural biases, economics
3. Genetics
4. Inflammation
5. Stress exposure & response
6. Reproductive transition-related risk factors
7. Sex hormones
8. Neurosteroids



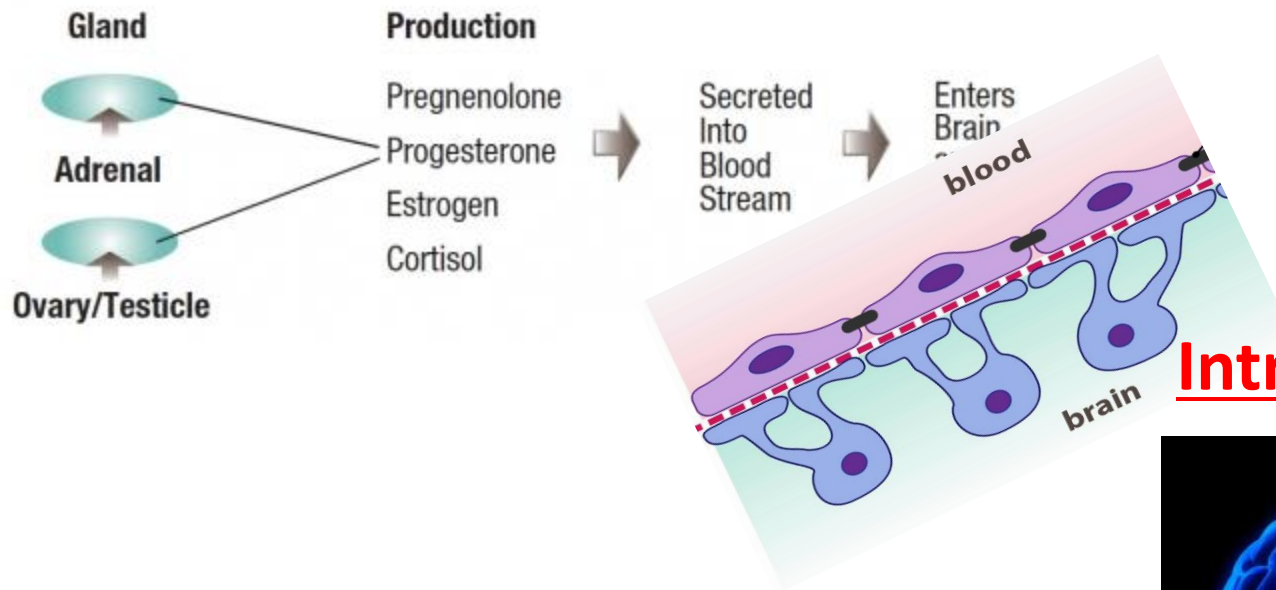
Reproductive hormone changes across the menstrual cycle



Neurosteroids:

Sources of female reproductive hormones

Extra-CNS production



Intra-CNS production



Estradiol
Progesterone
Allopregnenolone

Premenstrual dysphoric disorder (PMDD)



PMDD Case: Do you use SSRI or HC?

26-year-old woman presenting with PMDD symptoms

- One prior depression episode 6 years ago
- Advised against using HC because of brittle depression

Questions:

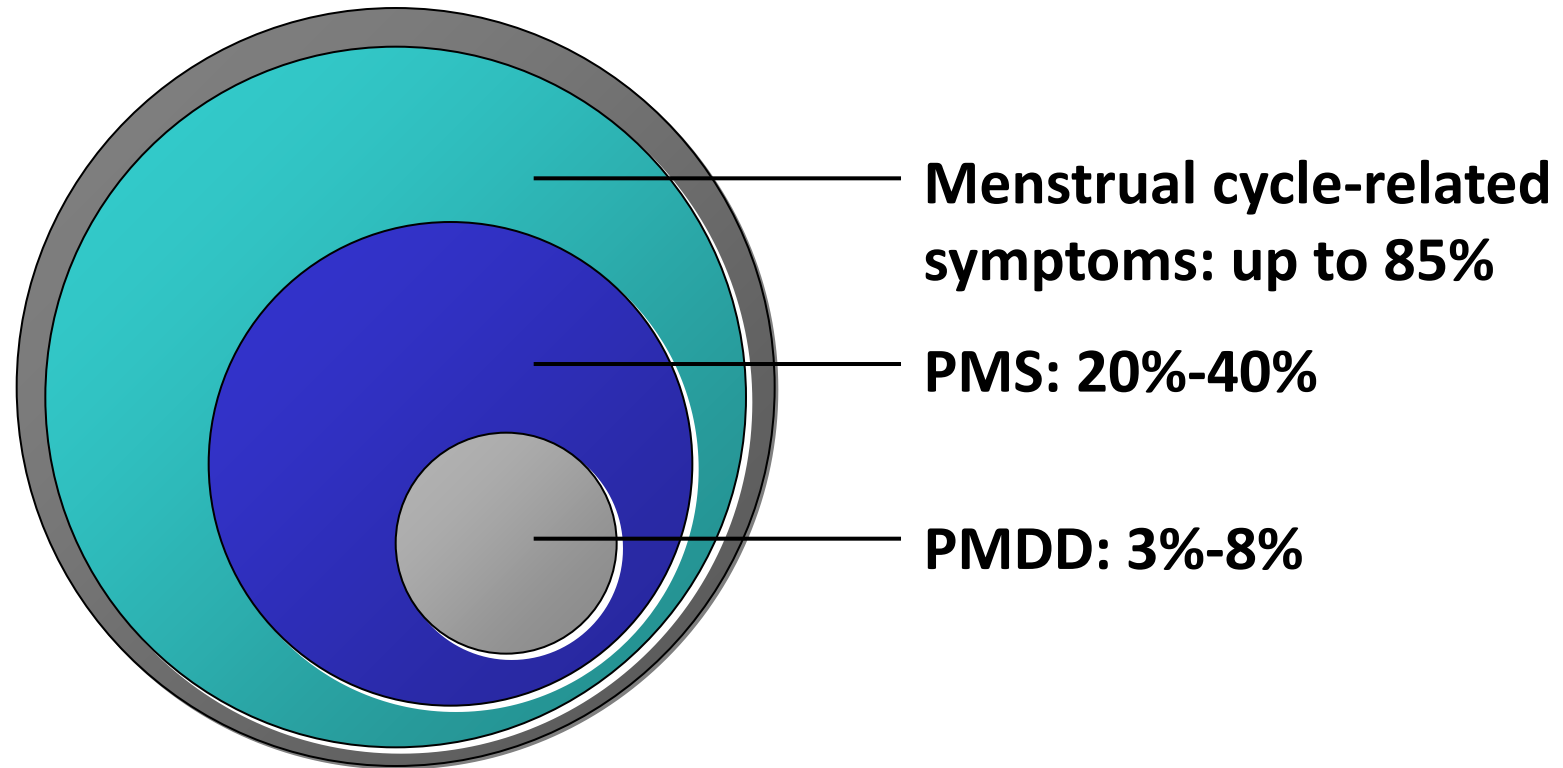
1. Should she be treated with an SSRI or an HC?
2. Can she go on HC?
For contraception?
For premenstrual symptoms?



HC = hormonal contraceptives

- Oral contraceptives plus other routes of administration
- Systemic (penetrating CNS)
- Local (IUD)
 - Note: vaginal ring is systemically absorbed
- Estrogens + progestin
- Progestin alone

PMS and PMDD: A spectrum of symptoms



PMS = premenstrual syndrome; PMDD = premenstrual dysphoric disorder.

A Clayton. *J Psychiatr Pract* 2008; Epperson et al. *Am J Psych* 2012

PMDD Diagnosis in DSM-5 TR

A. In most menstrual cycles during the past year, five (or more) of the following symptoms occurred during the final week before the onset of menses, started to improve within a few days after the onset of menses, and were minimal or absent in the week postmenses, with at least one of the symptoms being either (1), (2), (3), or (4):

1. marked affective lability (e.g., mood swings; feeling suddenly sad or tearful or increased sensitivity to rejection)
2. marked irritability or anger or increased interpersonal conflicts
3. markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts
4. marked anxiety, tension, feelings of being “keyed up” or “on edge”
5. decreased interest in usual activities (e.g., work, school, friends, hobbies)
6. subjective sense of difficulty in concentration
7. lethargy, easy fatigability, or marked lack of energy
8. marked change in appetite, overeating, or specific food cravings
9. hypersomnia or insomnia
10. a subjective sense of being overwhelmed or out of control
11. other physical symptoms such as breast tenderness or swelling, joint or muscle pain, a sensation of “bloating,” weight gain

B. The symptoms are associated with clinically significant distress or interference with work, school, usual social activities, or relationships with others (e.g., avoidance of social activities, decreased productivity and efficiency at work, school, or home).

C. The disturbance is not merely an exacerbation of the symptoms of another disorder, such as major depressive disorder, panic disorder, dysthymic disorder, or a personality disorder (although it may co-occur with any of these disorders).

D. Criteria A, B, and C should be confirmed by prospective daily ratings during at least two symptomatic cycles. (The diagnosis may be made provisionally prior to this confirmation.)

E. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).

- 5+ of 11 symptoms
 - 1+ of 5 is mood symptom
- Psychological > physical symptoms
- Interfere with role functions
- Symptoms restricted to luteal-phase
 - During the week before menses and remit within days of menses
 - Establish “on and off-ness”
- Not an exacerbation of another psychiatric disorder

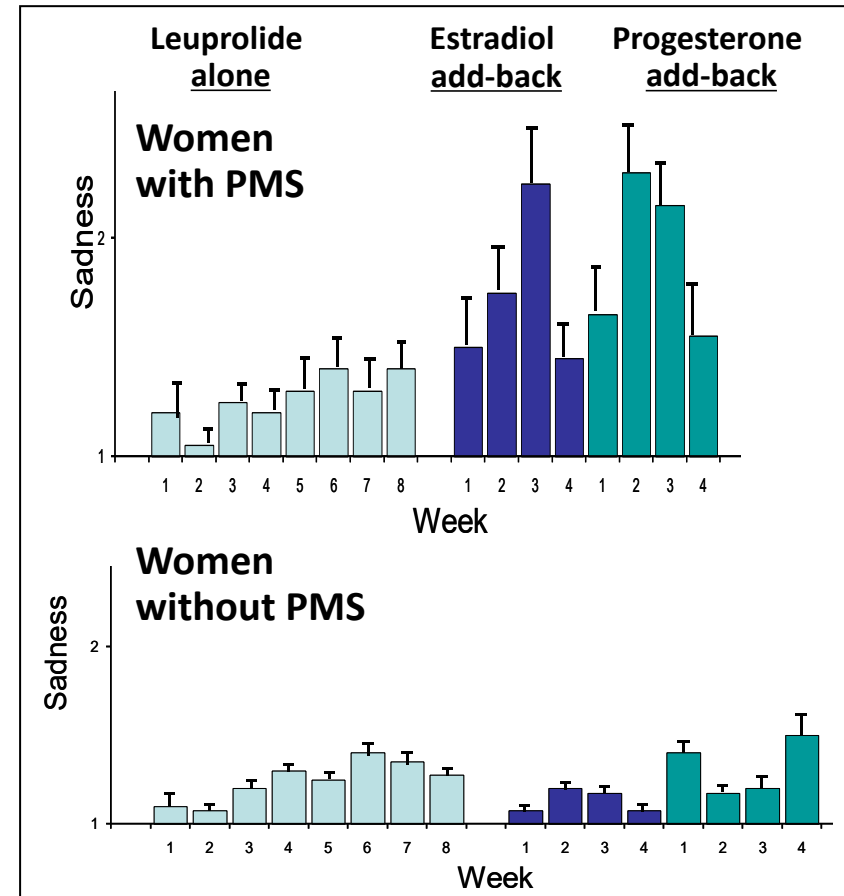
PMDD: Hormonal basis



- No abnormality in hormone levels¹
- Susceptibility to fluctuation of estrogen and progesterone^{2,3}
- Vulnerability may be serotonin mediated²
- Gonadotropin releasing hormone (GnRH) agonists are effective therapy
 - Eliminate hormonal fluctuation
 - PMS re-occurs with add-back therapy
- Role of impaired GABA_A-R response to dynamic ALLO fluctuations across the menstrual cycle?⁵

⁵ Hantsoo, Epperson. *Neurobiol Stress* 2020

Recurrence of Sxs of PMS during the Addition of Estradiol or Progesterone to the Leuprolide Regimen⁴



PMDD: Treatment options



Serotonin-based

- Cochrane Database of Systematic Reviews¹
 - Identified 31 RCT
 - SSRIs > placebo
 - Response rates ~ 60%

Other

PMDD: cognitive behavioral therapy

PMS: benzodiazepine (alprazolam),
buspirone, calcium, GnRH agonists

RCT = randomized controlled trials

VTE = venothrombotic events

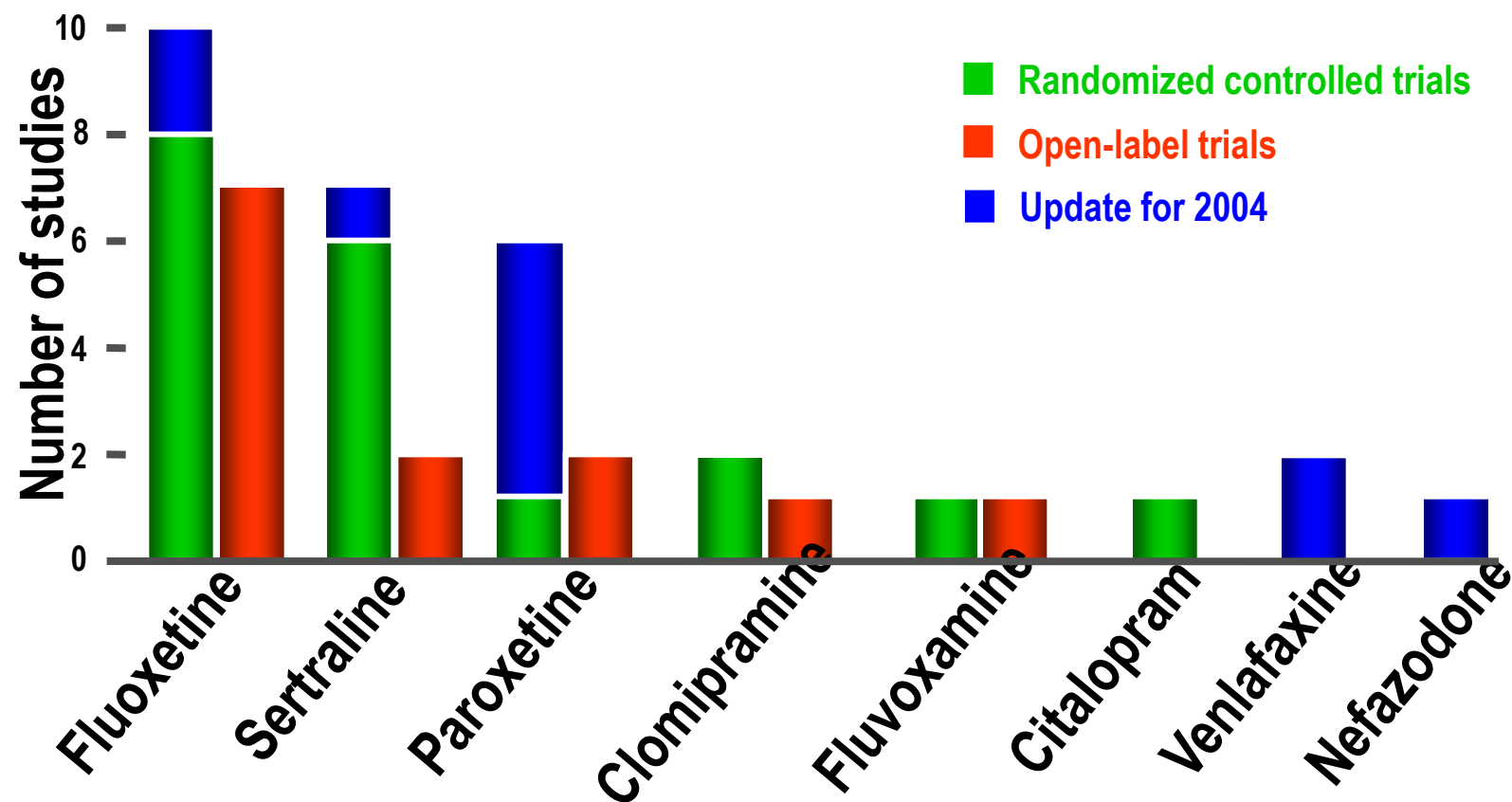
OC = oral contraceptives

GnRH = gonadotropin releasing hormone

Hormone-based

- Systemic hormonal contraceptives
 - Only drospirenone / estradiol pill FDA approved²
 - But higher VTE risk
 - Response rate 48%²
- Shorter hormone-free interval (24/4 day)
 - Reduces adverse symptoms during the hormone-free interval³
 - Long-cycle treatment (6 month) effective⁴
- Other HC with different progestins less well studied and with conflicting results⁵⁻⁷
 - Monophasic may be more effective than triphasic OC⁵

Serotonergic agents shown to be effective for treating PMDD/PMS



SSRI/SNRI dosing for PMDD



Treatments proven effective

1. **Continuous dosing**^{1,2}
 - Daily use throughout the menstrual cycle
 - Treats both psychological and physical symptoms of PMDD¹
2. **Intermittent/luteal-phase dosing**^{1,2}
 - 14 days prior to menses until cycle day
2. **Symptom-onset dosing**³
 - Sertraline 50-100mg/d during symptomatic and first few days of cycle (~6 days total)
more effective than placebo
 - No discontinuation symptoms

¹ Cochrane Database Syst Rev 2002; ² Steiner M, et al. *Br J OBGYN* 2001; ³ Yonkers KA, et al. *JAMA Psych* 2015

Consideration in selecting SSRI vs. HC for PMDD treatment



SSRI

- Advantages
 - Extensive investigation with multiple trials showing efficacy
 - Continuous and intermittent dosing options
 - 3 FDA-approved agents (fluoxetine, sertraline, and paroxetine CR)
 - Treat concurrent depression and/or reduce the risk of depression recurrence
- Disadvantages
 - Pregnancy during treatment
 - Potential long-term adverse effects of weight gain and sexual dysfunction

Hormonal contraceptive pills

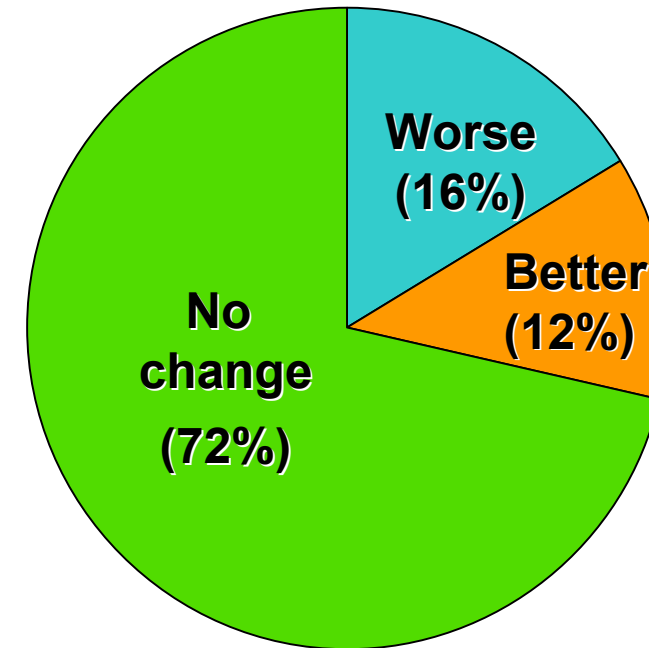
- Advantages
 - Concurrent benefits
 - Contraception
 - Acne treatment
 - Reduced menstrual flow
 - Long-cycle treatments (no benefit over cycles with hormone-free intervals for PMDD)
- Disadvantages
 - Less extensive study
 - HC side effects and risks
 - Smoking contraindication >35 years old
 - Rare mood side effects

HC = hormonal contraceptives

Impact of oral contraceptives on premenstrual mood



- Epidemiologic study of 658 women 36–45 years, who previously used a variety of OC preparations
- OC's do not affect premenstrual mood in the majority of women
- History of depression is strongest predictor of worse mood on OC
 - But only 25% of women with depression histories had mood worsening on OC
 - 61% had no change in mood
 - 14% experienced improvement in mood



OC = oral contraceptives

Hormonal contraceptives and long-term risk of depression



Table 2. Rate Ratio of First Use of Antidepressants and First Diagnosis of Depression In All Women^a

Type of Hormonal Contraception	Person-years	First Use of Antidepressants			First Diagnosis of Depression		
		No. of Events	RR ^b	RR (95% CI) ^c	No. of Events	RR ^b	RR (95% CI) ^c
Nonuse	3 041 595	50 346	1	1 [Reference]	9310	1	1 [Reference]
All oral combined	3 518 381	74 126	1.2 ^d	1.2 (1.22-1.25) ^d	12 211	1.0 ^d	1.1 (1.08-1.14) ^d
All progestin-only	74 540	1884	1.3 ^d	1.3 (1.27-1.40) ^d	296	1.1	1.2 (1.04-1.31) ^d
Nonoral							
Levonorgestrel IUS	81 281	2373	1.4 ^d	1.4 (1.31-1.42) ^d	397	1.4 ^d	1.4 (1.22-1.50) ^d

Abbreviations: IUS, Intrauterine system; RR, incidence rate ratio.

^a Includes 1 061 997 women aged 15 to 34 years.

^b Adjusted for age and calendar year.

^c Adjusted for age, calendar year, educational level, polycystic ovary syndrome, and endometriosis.

^d Indicates statistical significance.

Systemic hormonal
contraceptives

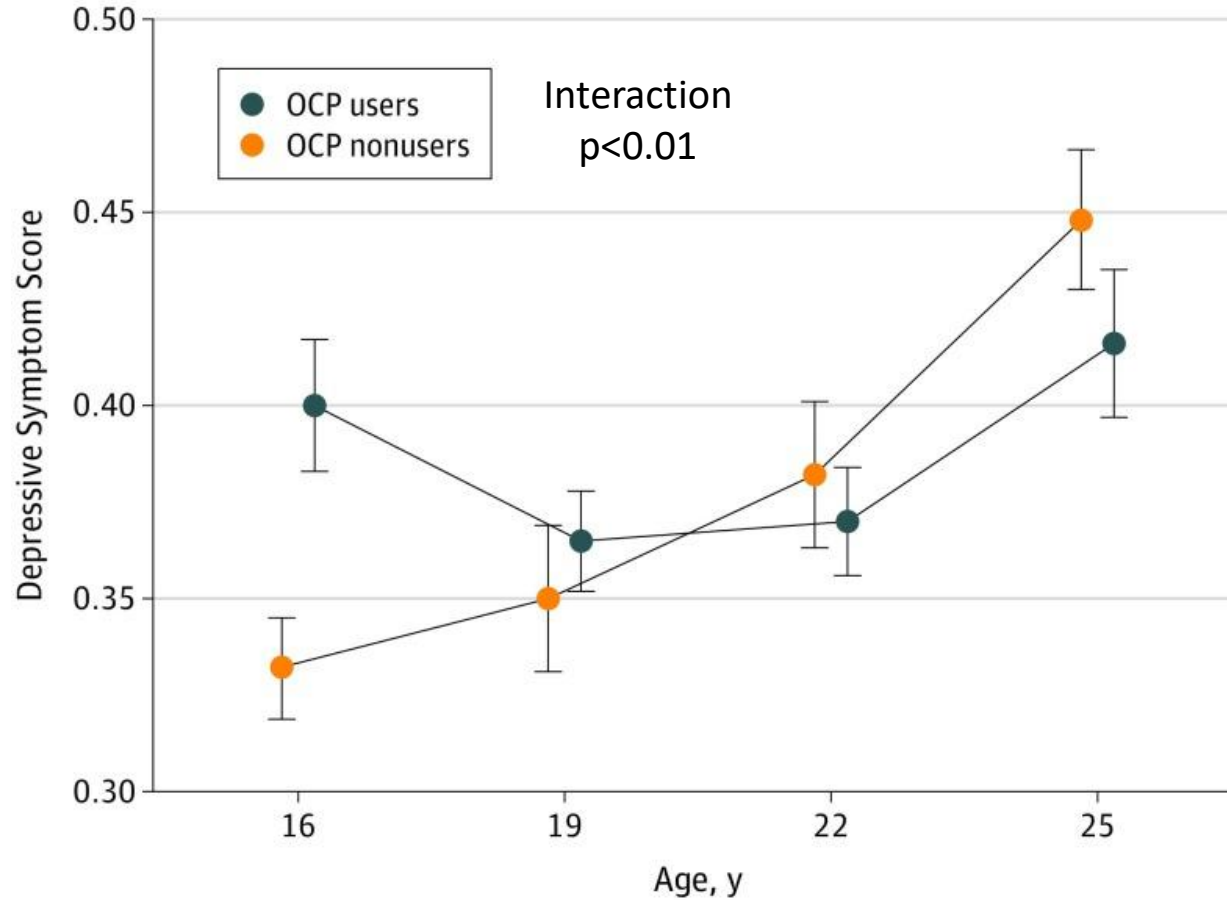
Estrogen + progestogen

Progestogen only

Local (IUD)

- Risk of antidepressant use and of depression diagnosis is years later
- HC use in teens associated with greater risk of subsequent depression

Hormonal contraceptives and risk of concurrent depressive symptoms by age



Use in teens associated with risk of **concurrent** depressive symptoms

OCP = oral contraceptives pills

***"My PMS is so bad that it
lasts all month long"***

Premenstrual worsening of mood disorder



- 64% of women with major depression not taking an HC report premenstrual worsening of depression¹
- Ask about mood symptoms in the follicular phase
- Prospectively document temporal relationship between mood symptoms and menses
- Don't miss underlying mood disorder
 - Continuous versus luteal-phase SSRI therapy
- Treatment: HC augmentation may not be effective²

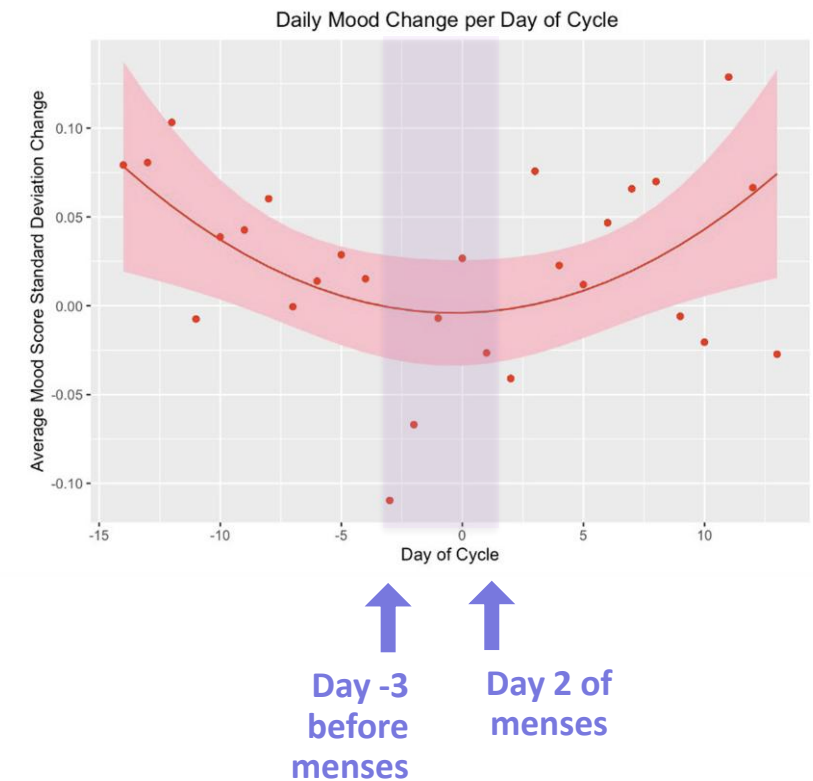
HC = hormonal
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Premenstrual worsening of mood disorder

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Mood worsens surrounding menses in 54% of women with depression (72% on antidepressants)³



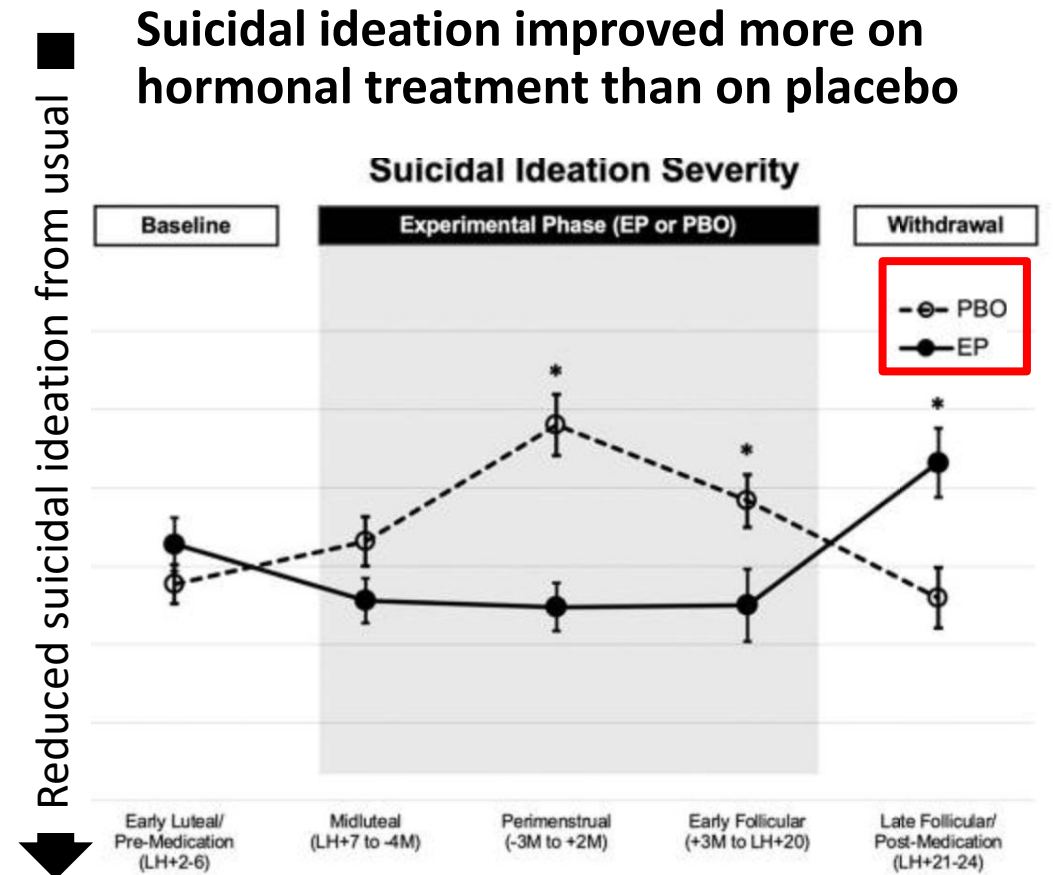
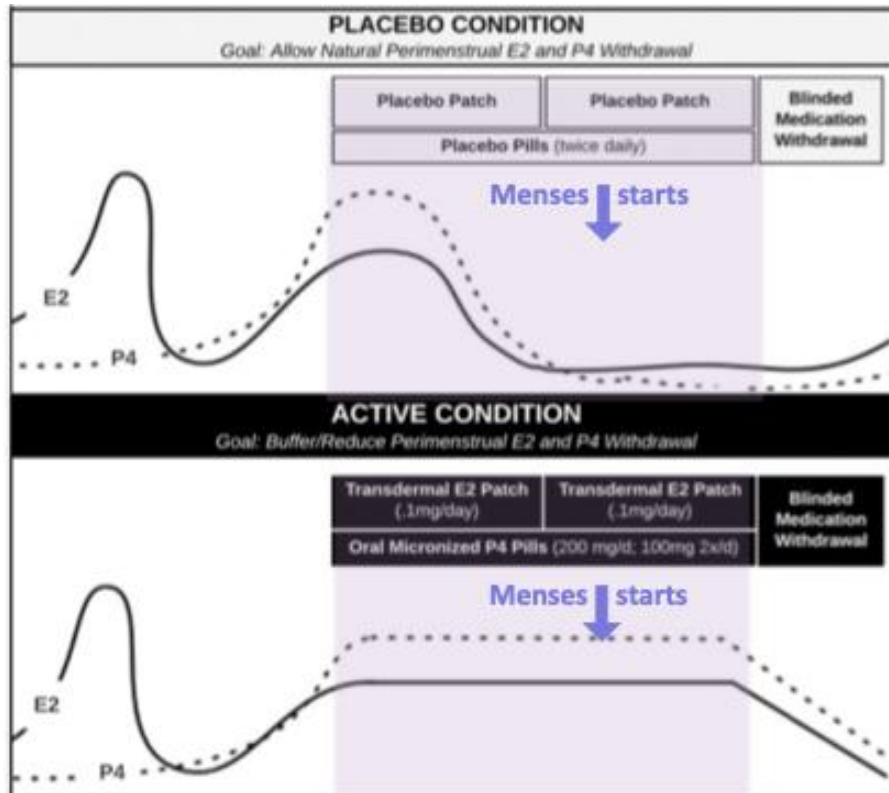
¹ Kornstein SG, et al. *Psychol Med* 2005; ² Peters W, et al. *J Clin Psychopharm* 2017; ³ Delray K, et al. *BMJ Mental Health* 2017

Perimenstrual suicidal ideation



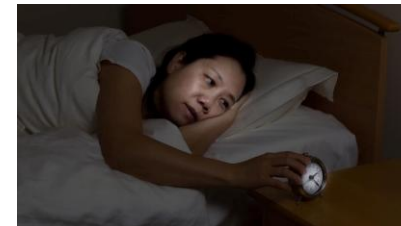
- Peak suicidal ideation occurs perimenstrually (preceding and during menses) transdiagnostically
- Role of decline in both estradiol and progesterone concurrently?

Randomized crossover trial of estradiol + progesterone vs placebo x 14 days (midluteal through early follicular)



Summary: PMDD, premenstrual exacerbation of depression, and use of hormonal contraceptives

1. **PMDD is severe menstrually-linked, hormonally-based mood-dominant form of PMS with adverse impact of function**
 - Can be treated with systemic hormonal contraceptives or serotonergic antidepressants
2. **Premenstrual exacerbation of depression is common**
3. **Hormonal contraceptives have concurrent and long-term risks of depression**
 - May or may not be biologically driven risk
 - Hormonal contraceptives should not be withheld from individuals with depression
4. **Hormonal therapies may improve suicidal ideation**

A close-up photograph of a woman's face, focusing on her eyes and forehead. She has brown hair and is looking upwards with a concerned expression. A piece of yellowed, torn paper is stuck to her forehead with the words "OUT OF ORDER" written in black marker. The background is plain white.



Perimenopause and depression

CONSENSUS RECOMMENDATIONS

Menopause: The Journal of The North American Menopause Society
Vol. 25, No. 10, pp. 1069-1085

Guidelines for the evaluation and treatment of perimenopausal depression: summary and recommendations

Pauline M. Maki, PhD,^{1*} Susan G. Kornstein, MD,^{2*} Hadine Joffe, MD, MSc,³ Joyce T. Bromberger, PhD,⁴ Ellen W. Freeman, PhD,⁵ Geena Athappilly, MD,⁶ William V. Bobo, MD, MPH,⁷ Leah H. Rubin, PhD,⁸ Hristina K. Koleva, MD,⁹ Lee S. Cohen, MD,¹⁰ Claudio N. Soares, MD, PhD, MBA,¹¹ on behalf of the Board of Trustees for The North American Menopause Society (NAMS) and the Women and Mood Disorders Task Force of the National Network of Depression Centers

Menopause terms & definitions

Menopause marks end of reproductive potential

Menopause

=12 months without menses

Age ~52 years

Perimenopause

Irregular, unpredictable, then infrequent menstrual cycles

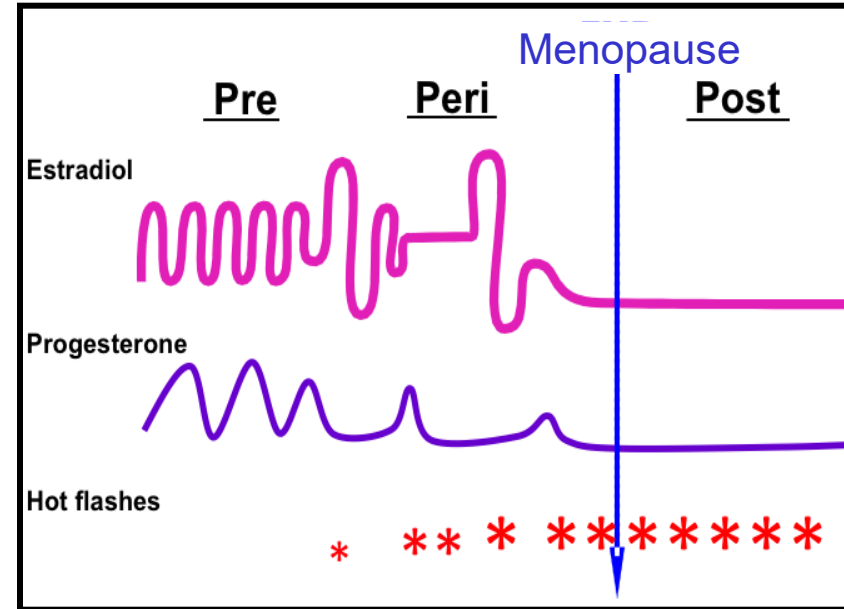
Begins ~48 years

Last ~4 years

Postmenopause

More than 12 months past final menstrual period

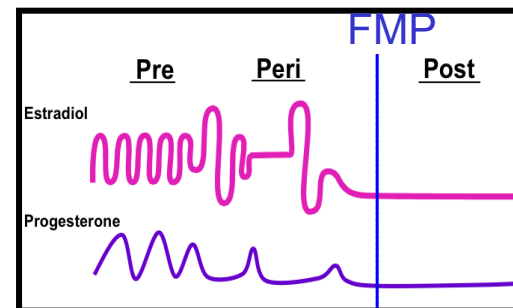
Hormone changes across menopause



Pre/peri/postmenopausal
FMP = final menstrual period

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. Cognitive dysfunction / brain fog
6. Vulvo-vaginal and urinary symptoms



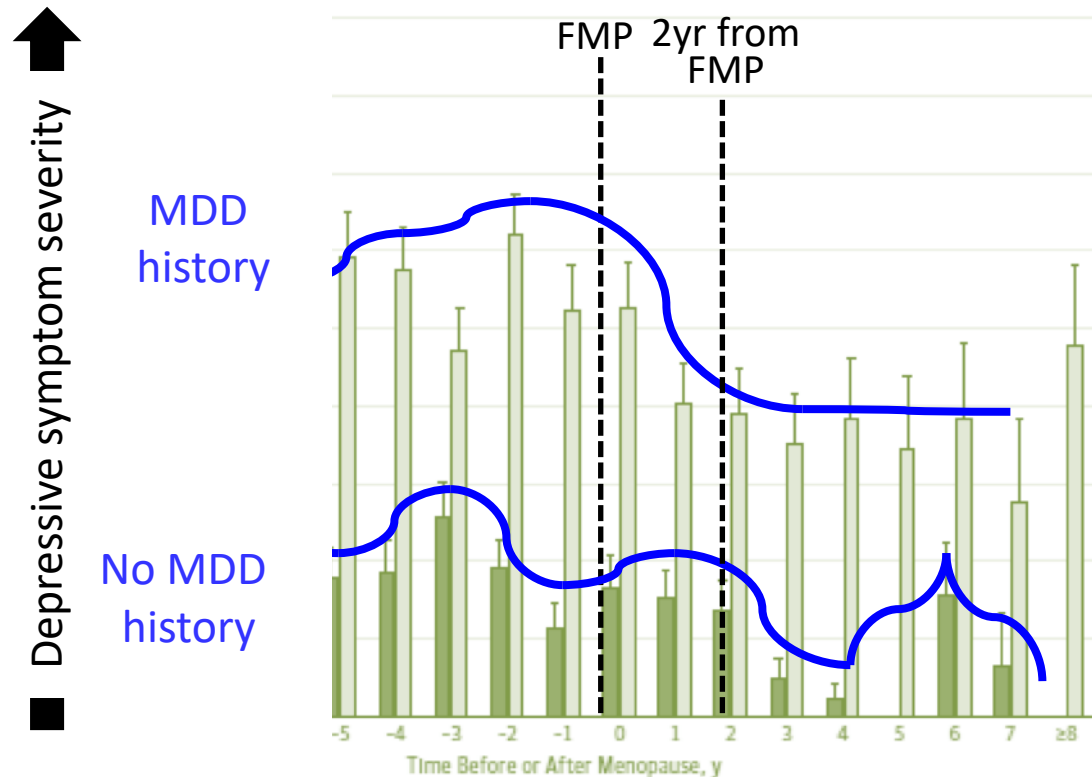
Menopause transition is a period of vulnerability for depression in women: doubling of risk of depression of peri/early post

1. ↑ risk of depressive symptoms in peri & early post
2. ↑ risk of clinical depression in peri & early post
3. ? ↑ risk of 1st lifetime onset of clinical depression in peri & early post
 - Data are mixed

Brown L, *Lancet* 2024; Freeman E, *Arch Gen Psych* 2006; Cohen LS, *Arch Gen Psych* 2006 ; Bromberger JT & Kravitz HM. *Obstet Gyn Clinics* 2011; Harlow, *Am J Epidemiol* 2013; Bromberger JT, *Psychol Med* 2014

Perimenopause is a Transient Period of Risk for Depressive Symptoms in Subset of Women

Good
News!



1. High baseline depression symptoms: Trajectory toward improved mood across and after FMP slows transiently surrounding the FMP
2. Low baseline depression symptoms: Vulnerability to small increase in depressive symptoms across FMP

MDD = major depressive disorder
FMP = final menstrual period

Mood Disturbance Across Menopause Transition



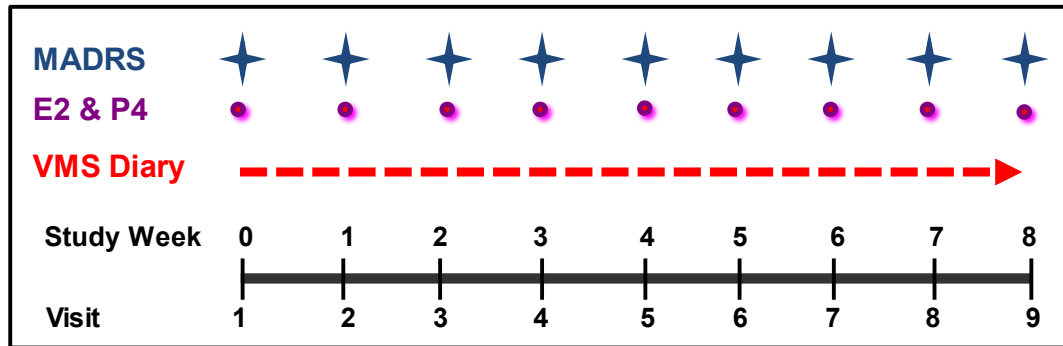
■ Major Depressive Disorder (MDD)

- 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
 - Anxiety
 - Medical illness
 - Sleep onset, total sleep time
 - Menopause/hormonal risk factors

■ Depressive Symptoms

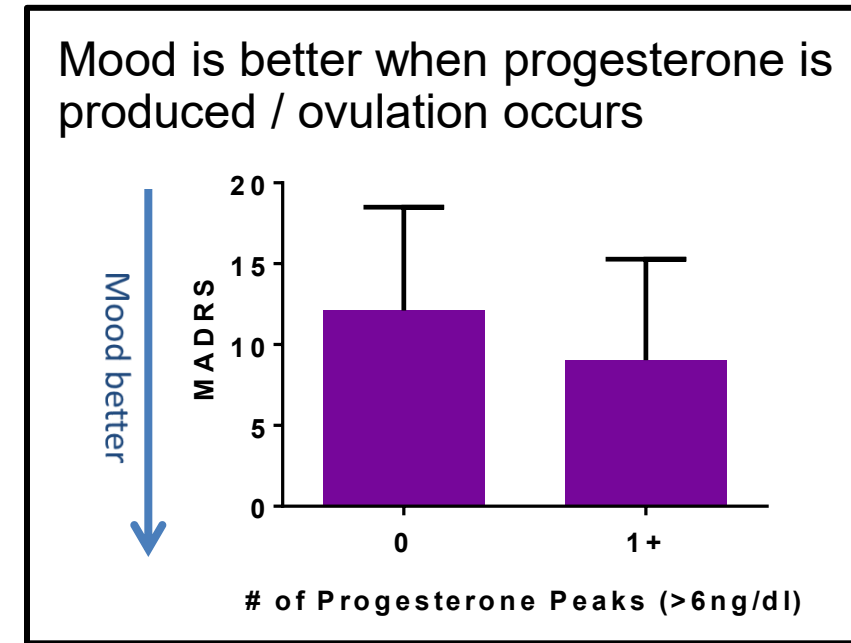
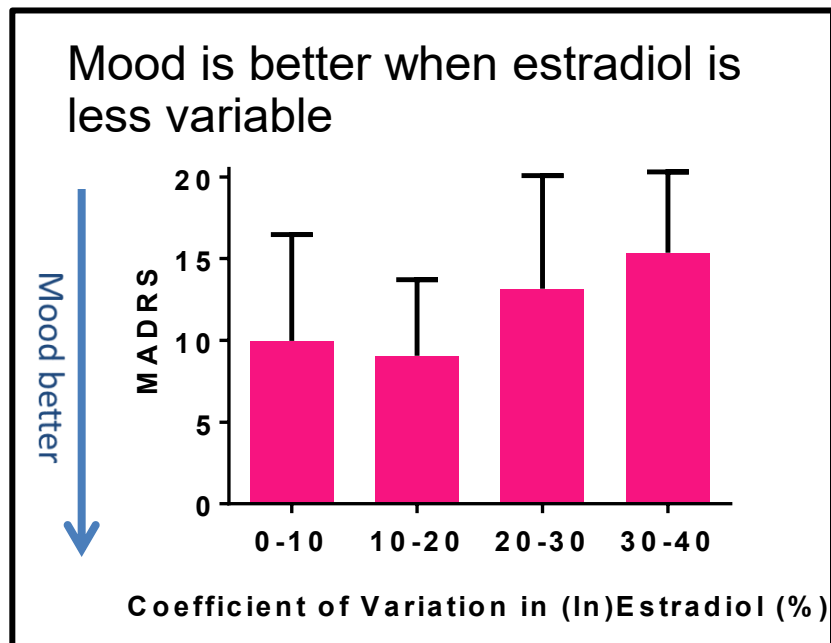
- 17-28% in perimeno vs. 14-21% in late premeno for entire population
- 2-4x risk within-person risk as progress into perimeno
- Greater risk if
 - Psychosocial risk factors
 - History of MDD
 - Stressful life events, financial stress, low social support
 - Racial minority, higher BMI, smoking, lower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

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.



Depression not universal: A subgroup problem



The trade off

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



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 Washington Post
Democracy Dies in Darkness

Subscribe

Menopause depression risk has been exaggerated

The
Harvard
Gazette

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

March 11, 2024



How do you know if depression occurring in peri/postmenopausal woman is related to her being peri/postmenopausal?

True, true, related?

True, true, unrelated?

Clinical considerations when evaluating contribution of menopause to depression



1. Depressive symptoms vs. clinical depression
2. Extent of interference with function
3. Past history of depression
4. Co-occurring / precipitating stressful life events
5. No diagnostic test or hormone profile to establish association
6. Presence of / temporal relationship to
 - Menstrual pattern changes
 - Hot flashes & night sweats
 - Associated sleep interruption
7. Sleep disturbance
 - Brief awakenings only
 - Early morning awakening

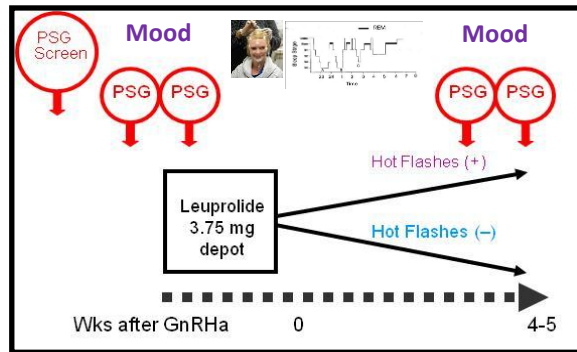
True, true, related?

True, true, unrelated?

Effect of nighttime hot flashes and sleep disruption on depressive symptoms

Hot
flashes
↓
Depression

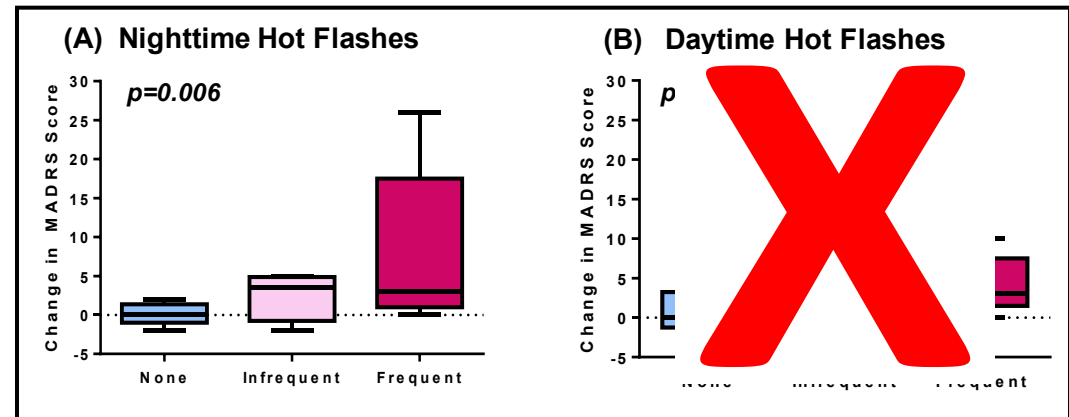
Sleep
↓



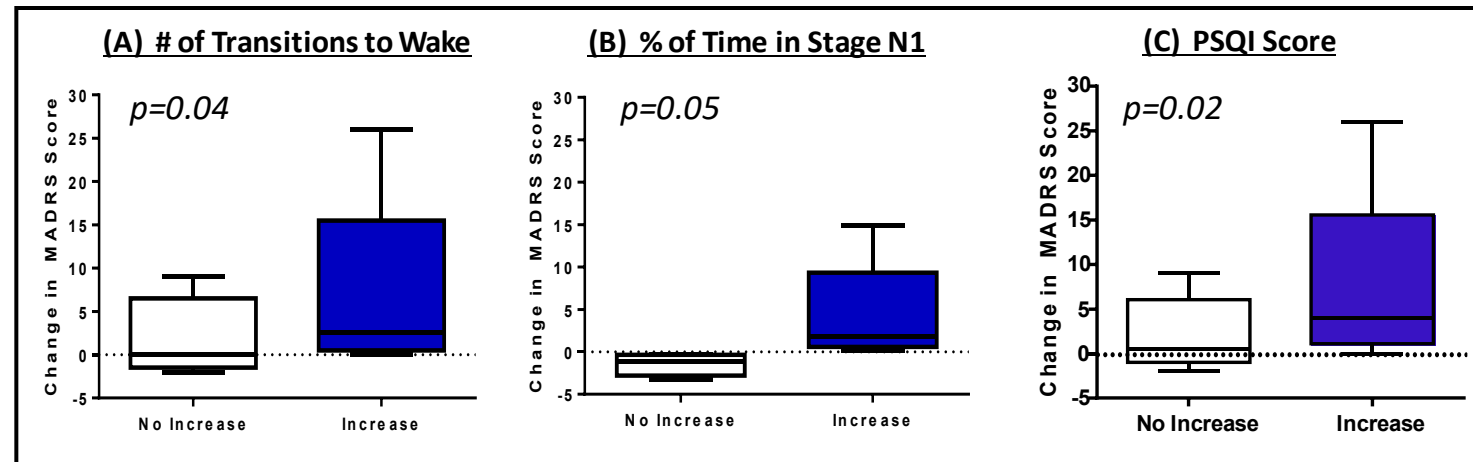
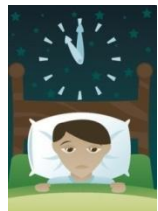
Nocturnal, but not daytime, hot flashes, result in an increase in depressive symptoms

Hot flashes

None (n=9) Infrequent (n=10) Frequent (n=10)



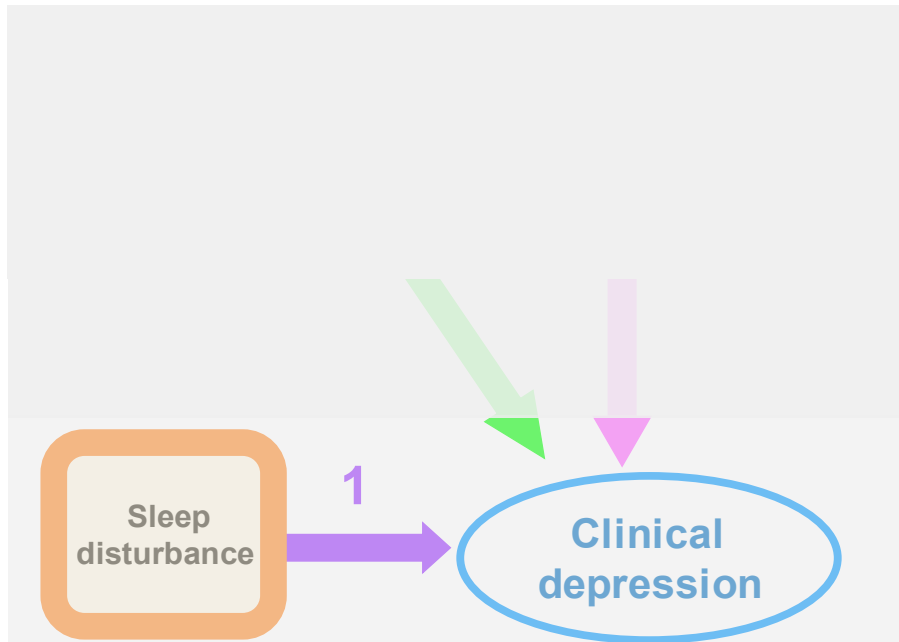
Worsening of sleep fragmentation and sleep quality result in an increase in depressive symptoms



Nature of sleep disturbance differs between major depression and subthreshold depressive symptoms



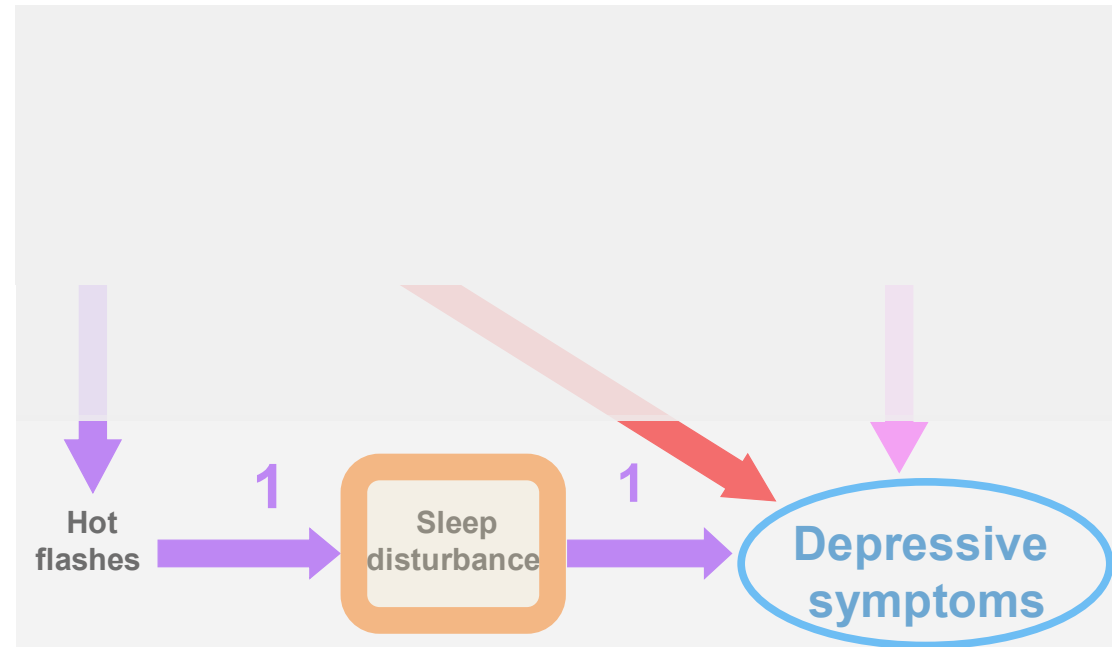
Major depression



Sleep disturbance in major depression

↓TST ↓TIB ↑SOL
(~WASO ~#wakes)

Depressive symptoms



Sleep disturbance in depressive symptoms

↑WASO ↑#wakes (~↑TST ~↑TIB ~SOL)

Sleep Fragmentation

Antidepressants to Treat Menopause-associated Depression



1. Antidepressants (all serotonergic agents)

- Large RCT demonstrate efficacy over placebo:
 - Desvenlafaxine 50mg, 100mg, 200mg ¹⁻²
- Smaller and open-label studies supporting efficacy: citalopram, escitalopram, mirtazapine, duloxetine, venlafaxine, paroxetine, fluvoxamine ³⁻⁷
- No advantage of specific serotonergic agents
- Response to SSRI and SRNI does not vary by co-treatment with hormone therapy⁸⁻⁹
- Non-serotonergic agents (e.g., bupropion) not studied

2. No specific data for other prescribed therapies in this population

- Transcranial magnetic stimulation, ECT, esketamine, neurosteroids (allopregnanolone, ganaxolone ⁹)

¹ Clayton, *J Clin Psych* 2013; ² Kornstein, *J Clin Psych* 2010; ³ Joffe, *J Clin Psych* 2007; ⁴ Joffe, *J Women's Health Gen Based Med* 2001;

⁵ Soares, *J Clin Psych* 2003; ⁶ Dias, *Menopause* 2006; ⁷ Ushiroyama, *J Med* 2004; ⁸ Kornstein, *Menopause* 2014; ⁹ Kornstein, *JCP* 2014

¹⁰ Dichtel, *J Clin Psych* 2020

Treatment of depression 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)
- ? Neurokinin antagonists?



■ Psychotherapy



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

Treatment of menopause-related neurocognitive symptoms



	VMS	Sleep (2 nd VMS)	Mood	Cognition
Hormonal agents				
Psychotropic agents				
Neurokinin B antagonists				
Behavioral Interventions				

Summary: Depression during peri/postmenopause

- 1. Mood disturbance can present as major depression or mild subsyndromal depressive symptoms**
- 2. Mild depressive symptoms more common during the menopause transition**
 - Subthreshold depressive symptoms associated with perimenopausal hormone profile, nighttime hot flashes, and sleep interruption, poor social support, anxiety
- 3. Major depression is less common and typically represents recurrence**
- 4. Hormone therapy**
 - Effective for subthreshold symptoms and for clinical depression mostly when women are perimenopausal and have hot flashes
 - Not effective for postmenopausal women without hot flashes
- 5. Antidepressants are effective treatments of depression associated with the menopause transition**

It takes a village.....



RHYME Research Center

The Regulation of Hormones, Chronobiology, Mood, and Sleep (RHYME) Research Center is currently undergoing a transition from Brigham and Women's Hospital to Beth Israel Deaconess Medical Center.



<https://research.bidmc.org/rhyme/>



Women's Hormones and Aging
Research Program



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Psychiatry

Kate Burdick, PhD, Erynn Christensen, PhD, Laura Holsen, PhD, Margo Nathan, MD, Vera Spagnolo, MD PhD, Lee Cohen, MD, Marlene Freeman, MD, Irene Gonsalvez, MD, Jessica Harder, MD

OBGYN / Endocrinology

Clara Sailer, MD PhD, Blair Wylie, MD MPH, Janet Hall, MD, Ursula Kaiser, MD, Caroline Mitchell, MD, Victor Navarro, PhD, Jan Shifren, MD, Aviva Cohn, MD

Sleep Medicine

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