

Premenstrual Dysphoric Disorder and Depression During the Menopausal Transition – New Insights

Laura Fagioli Petrillo, Ed.M., M.D.

Director of Training, The Ammon-Pinizzotto Center for Women's
Mental Health

Massachusetts General Hospital

Instructor in Psychiatry, Harvard Medical School

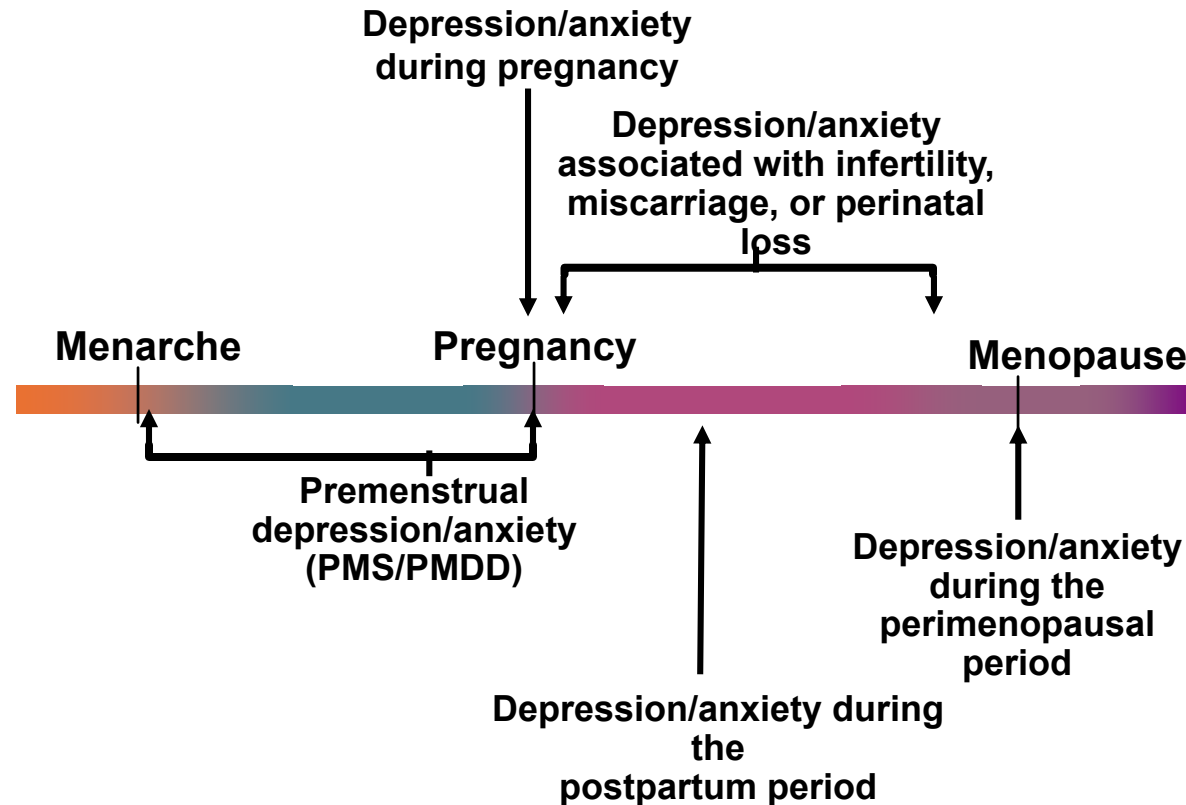
www.womensmentalhealth.org

Disclosures

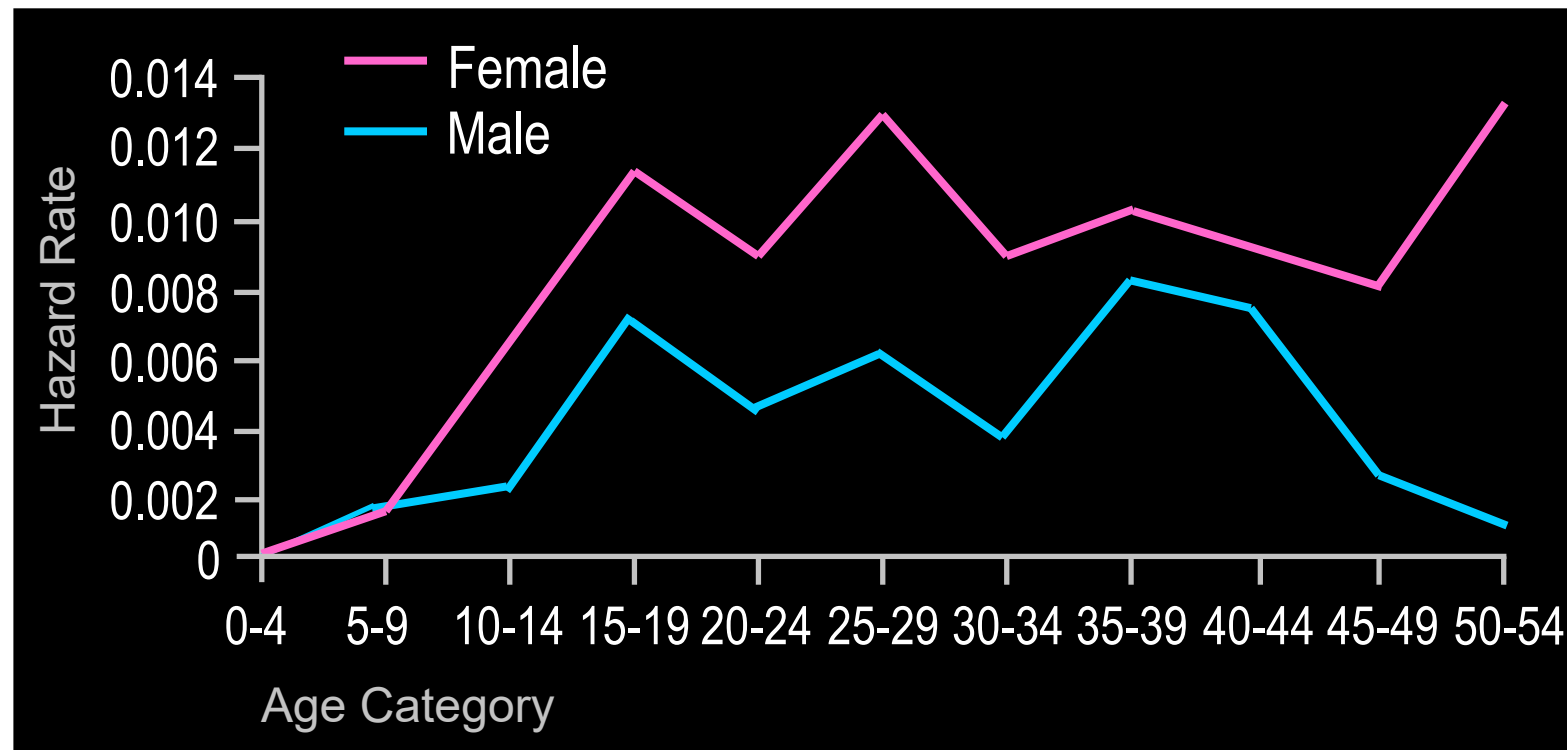
My spouse/partner and I have the following relevant financial relationship with a commercial interest to disclose:

Educational activities (speaking): WebMD

Depression and Anxiety Across the Female Reproductive Cycle



Risk for Depression by Age in Females and Males



Kessler R. *J Affect Disord.* 1993;29:85-96.

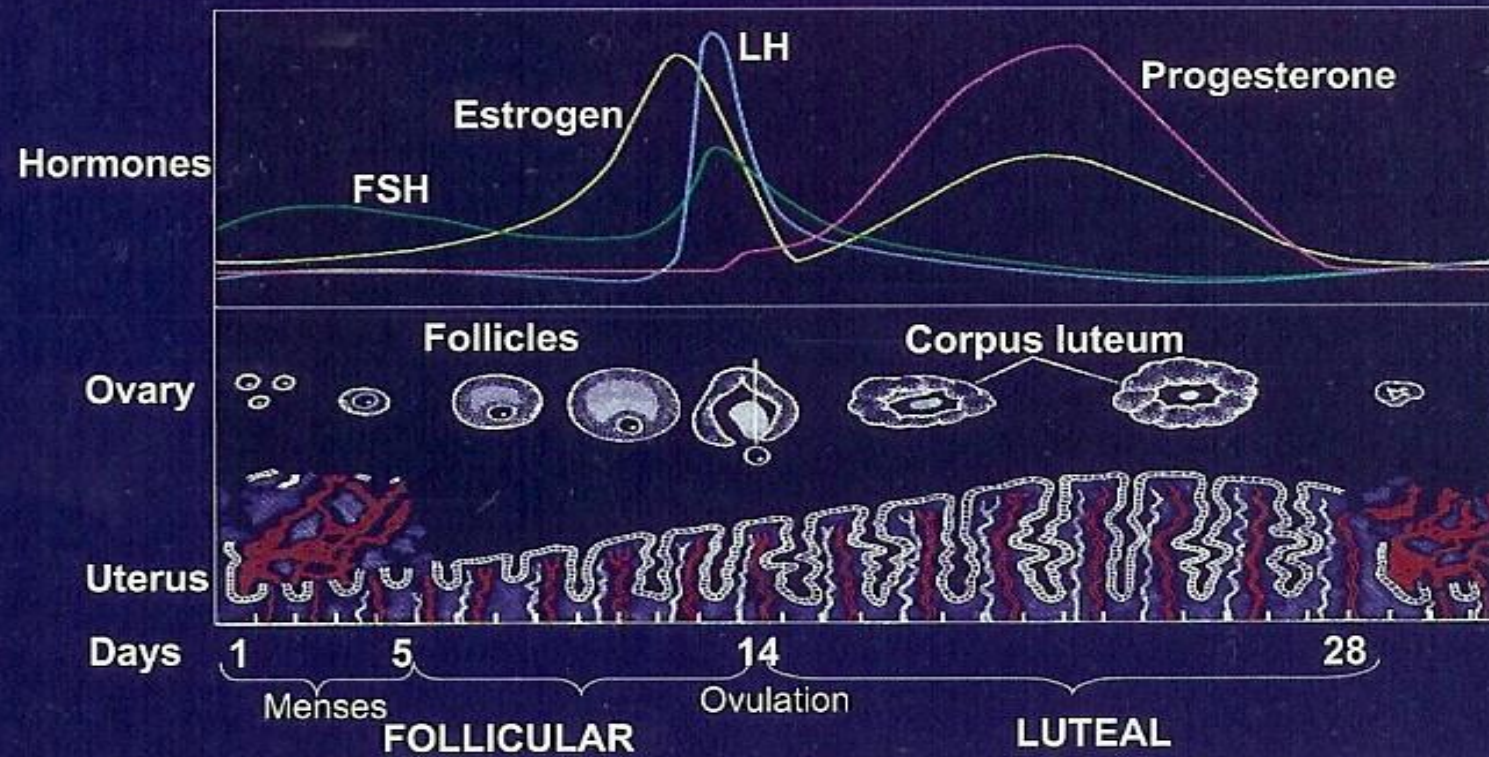
Why are rates of depression higher in women?

- Reproductive transitions
- Neurosteroids and hormones
- Inflammation
- Symptom report
- Stress
- Genetics
- Cultural factors/societal roles

PREMENSTRUAL DYSPHORIC DISORDER



The Menstrual Cycle



Adapted from Solomon EP, Davis PW. *Human Anatomy and Physiology*. Philadelphia: Sanders College; 1982.

Case 1

- 35 year old married female
- 2 prior pregnancies, with children 2 and 4 years old
- Reports “always had PMS” which was manageable (3 days premenstrually had physical symptoms, cramps treated with ibuprofen, felt more emotional, craved sweets)
 - Felt this was normal because her two sisters also experienced it
- Since having second child, she has noticed a week premenstrually feels enraged, sad, tearful, with low frustration tolerance
 - In work, she feels disorganized, can not get things done, has poor focus
 - Normally eats a healthy diet, but at this time craves sugar and salt
- Noted for the past 18 months but in the 2 months, used her babysitter for the week premenstrually since she did not want to shout at her children
 - She and her husband had a significant argument and she left the house to take a long walk
- Cycles are regular and she is not taking birth control (husband had vasectomy)

Case 1

- Mentioned to her PCP at her annual appointment who thought she might have severe PMS
- No psychiatric history, no medical issues
- Routine labs including TSH were normal
- History of trauma – family experienced a house fire as a teenager
- Recommend tracking for two months, adding Calcium 600 mg bid

Case 1

- Returns to review tracking
- Clear pattern of severe symptoms along multiple domains for 7 days premenstrually with resolution on the day of menstruation
- Asymptomatic the rest of the month
- Feels “so much better” that she can now predict her symptoms and alter her behaviors and supports at a specific time of the month
- Discuss adding SSRI intermittently and agrees to try fluoxetine 10 mg for 7 days premenstrually and discontinuation with menstruation

Premenstrual Mood Changes

- Majority of reproductive age women report unpleasant symptoms around the time of menstruation
 - Physical and psychological symptoms
 - “More emotional”
 - Minimal effect on functioning
- 2.5 million women affected annually



Clayton, *Jnl of Psych Prac.* 2008;14:13-21.
Winer & Rapkin, *Jnl Reproductive Med.* 2006;51(4): 339-347.

Definitions of Premenstrual Disorders

Premenstrual Syndrome/PMS

- Emotional, behavioral, and physical symptoms
- Symptoms can be disturbing but functioning is preserved
- Does not require psychiatric intervention
- Remission after menstruation

Premenstrual Dysphoric Disorder/PMDD

- DSM-5 diagnosis
- Impairment in functioning
- Significant psychiatric morbidity
- Remission after menstruation

Premenstrual Exacerbation/PME

- Cyclic worsening of another DSM-5 condition

DSM-5 Criteria

- Criterion A: in most menstrual cycles during the past year, at least 5 of 11 symptoms (including at least 1 of the first 4 listed) were present:

- Markedly depressed mood, hopelessness, or self-deprecating thoughts
- Marked anxiety, tension, feelings of being “keyed up” or “on edge”
- Marked affective lability
- Persistent/marked anger or irritability or interpersonal conflicts
- Decreased interest in usual activities
- Subjective sense of difficulty in concentrating
- Lethargy, easy fatigability, or marked lack of energy
- Marked change in appetite, overeating, or specific food cravings
- Hypersomnia or insomnia
- A subjective sense of being overwhelmed or out of control
- Other physical symptoms, such as breast tenderness or swelling, headaches, joint or muscle pain, a sensation of bloating, or weight gain

At least one mood/anxiety symptom

- The symptoms must have been present for most of the time during the last week of the luteal phase, begun to remit within a few days of the onset of menstrual flow, and absent in the week after menses

Occurrence during the luteal phase

DSM-5 Criteria

Significant functional impairment

- Criterion B is that the symptoms must be severe enough to interfere significantly with social, occupational, sexual, or scholastic functioning.
- Criterion C is that the symptoms must be discretely related to the menstrual cycle and must not merely represent an exacerbation of the symptoms of another disorder, such as major depressive disorder, panic disorder, dysthymic disorder, or a personality disorder.
- Criterion D is that criteria A, B, and C must be confirmed by prospective daily ratings during at least 2 consecutive symptomatic menstrual cycles. The diagnosis may be made provisionally before this confirmation.

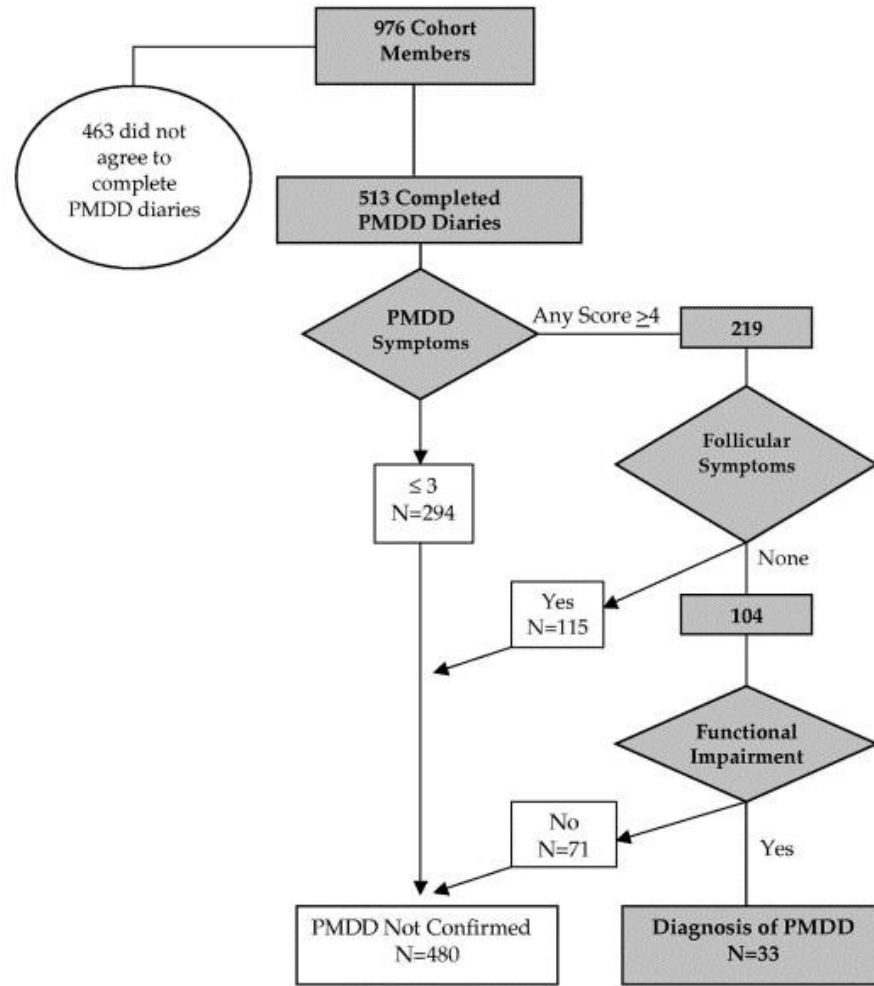
Not a worsening of another
psychiatric disorder

Suicidal Ideation and Premenstrual Disorders

- Women with PMDD and PMS are at higher risk of suicidality compared with women without premenstrual disturbances
 - Suicide risk assessments should be performed with women who exhibit these symptoms
- Women with PMDD are almost 7x at higher risk of suicide attempt and almost 4x as likely to exhibit suicidal ideation
- In one study where the diagnosis of PMDD was confirmed prospectively, 40% of women reported SI in the late luteal phase
- Women with PMS are also at increased risk of suicidal ideation, but not suicide attempts

Prasad D, et al. J Womens Health (Larchmt). 2021 Dec;30(12):1693-1707.
Wikman A, et al. BMC Womens Health. 2022 Feb 11;22(1):35.

Prevalence of PMDD



- SCID used to assess psychiatric morbidity
- 513 women completed a prospective evaluation of premenstrual symptoms
- PMDD was confirmed in 33 of 513 women (6.4%)
- Of note, 2.7% did not have a prior history of depression

Cohen LS, et al. *J Affect Disord.* 2002 Jul;70(2):125-32.

Premenstrual Symptoms and Age

- Symptoms commonly begin in 20s but onset may be earlier
- Often more disturbing in 30s through menopause
- Prevalence of moderate to severe symptoms
 - Ages 25-34 → 8.6%
 - Ages 35-44 → 11.2%
 - Ages 45-54 → 10.8%

Tschudin et al., *Archives Women's Mental Health*, 2010
Johnson. S. *Clin Obstet Gynecol*. 1987



PMS/PMDD Longitudinal Course

- Women seek treatment in their late 20s/early 30s
- Physical/mood symptoms stable from cycle to cycle¹
- Diagnosis appears stable over time²
- **Chronic course** although symptoms may improve during suppression of the ovarian cycle (lactation, pregnancy, post-menopause)³

1Block. JA. *Am J Psychiat*. 1997;154:1741.

2Roca, C. et al. *J Clin Psychiatry*. 1999;60:763.

3Reid RL. Endotext [Internet]. MDText.com, Inc.; 2017.

Risk Factors for PMDD and PMS

- Family history of PMS and PMDD^{1,2}
- History of postpartum depression³
- Major depression past^{3,4} or future⁵
- Trauma history⁶

1. van den Akker OB, et al. *Acta Genet Med Gemellol (Roma)*. 1987;36(4):541-548. 2. Kendler KS, et al. *Psychol Med*. 1992;22(1):85-100. 3. Warner P, et al. *J Affect Disord*. 1991;23(1):9-23. 4. Bancroft J, et al. *Psychosom Med*. 1994;56(3):225-231. 5. Graze KK, et al. *Acta Psychiatr Scand*. 1990;81(2):201-205. 6. Perkonig A, Yonkers KA, Pfister H, et al. *J Clin Psychiatry*. 2004;65:1314-1322.

Pathophysiology

Role of gamma amino-butyric acid (GABA)

Increasingly investigated as a contributor to PMDD¹

Paradoxical effect of allopregnanolone mediated via the GABA-A receptor => neg mood symptoms²

PMDD = greater ALLO/prog ratio vs. controls in luteal phase³

Treatment with ALLO antagonist during the luteal phase reduced PMDD scores on the DRSP⁴

1. Hantsoo, L & Epperson, Neill. *Neurobiology of Stress*, 2020; 12.

2. Bäckström T, et al. *Prog Neurobiol*. 2014;113:88-94.

3. Girdler SS, et al. *Biol Psychiatry*. 2001;49(9):788-797.

4. Bixo M, et al. *Psychoneuroendocrinology*. 2017;80:46-55.

Pathophysiology

- PMS/PMDD may represent an abnormal response to normal fluctuations of gonadal steroids
- Minimizing the fluctuations may be helpful

Schmidt et al., *American Journal of Psychiatry*:2017;174(10), 980-989

Pharmacologic Treatment

SSRIs are first line treatment in patients without bipolar disorder

Superior to placebo in 31 RCTs

FDA approved

- fluoxetine
- sertraline
- controlled release paroxetine

Antidepressants with serotonergic activity

- venlafaxine
- duloxetine
- fluvoxamine
- citalopram
- clomipramine

Sundblad et al. *Acta Psychiatr Scand*. 1992;85:39-47.

Freeman et al. *Obstet Gynecol*. 2001;98:737-44.

Ramos & Hara. *Int J Neuropsychopharmacol*. 2009;12(8):1081-8.

Cochrane Database Syst Rev 2002.

Antidepressant Dosing

- Continuous
 - Steady dose throughout the month
- Intermittent
 - Luteal phase (day 14 to onset of menstruation)
 - fluoxetine 20 mg
 - sertraline 50-100 mg
 - controlled release paroxetine 10-20 mg
 - escitalopram 10-20 mg
- Symptom onset
 - Women with irregular cycles
 - May be more effective for reducing anger/irritability than other symptoms
- Luteal phase increase
- Studies comparing luteal phase vs. continuous dosing have found both to be effective

Landén M, et al. *Neuropsychopharmacology*. 2007;32(1):153–161.

Yonkers KA, et al. *J Clin Psychopharmacol*. 2023 Jul-Aug 01;43(4):320-325.

Adjunctive Psychopharmacology

- Benzodiazepines
 - Alprazolam – mixed results
- Buspirone
 - Mixed results; benefit may be modest
- Gabapentin
 - Anecdotally helpful
- Quetiapine SR
 - Modest benefit
 - Small sample size



Schmidt PJ, Grover GN, Rubinow DR. *Arch Gen Psychiatry*. 1993;50(6):467-473.
Harrison WM, Endicott J, Nee J. *Arch Gen Psychiatry*. 1990;47(3):270-275.
Freeman EW. *CNS Drugs*. 2004;18(7):453-468.
Jackson C, Pearson B, Girdler S, et al. *Hum Psychopharmacol*. 2015;30(6):425-434.

Oral Contraceptives (OC)

- ◆ Evidence from double-blind, randomized, placebo-controlled trials supports drospirenone/estradiol for treating PMDD¹
 - No trials have shown efficacy vs. placebo for standard OCP dosing - 21 days of active pill followed by 7 days placebo
 - 48% response, risk for VTE
- ◆ OCPs with non-drospirenone progestin have less data
- ◆ Progesterone only pill unlikely to be helpful²⁻⁴
 - Suppress ovulation in 50% of women
 - Prog only pill contains drospirenone, ? if it will help PMDD symptoms⁵

1. Yonkers KA, et al. *OBGYN* 2005 2. Ford O, et al. *Cochrane Database Syst Rev*. 2006;(4):CD003415. 3. Wyatt K, et al. *BMJ*. 2001;323:776-780. 4. Freeman E, et al. *JAMA*. 1990;264(3):349-353. 5. Caruso S, et al. *Eur J Obstet Gynecol Reprod Biol*. 2023 Jul 6; 288:73-77.

OC Dosing

- Cyclic
- Continuous
 - Consecutive pill packs without a placebo
- Begin with cyclic dosing; move to continuous dosing if symptoms persist
- Comparison of dosing strategies is limited

Always consider medical risks of OCP

Freeman et al. *Contraception*. 2012;85(5): 437-445

Skovlund et al. *Am Jnl Psychiatry*. 2018;175(4): 336-342

Eisenlohr-Moul TA, et al. *Depress Anxiety*. 2017;34(10):908-917

Gonadotropin-Releasing Hormone Agonists

- ◆ Leuprolide – depot injection every 1-3 months
- ◆ Buserelin – intranasal spray daily

PLUS add-back of estrogen, progestin or both

- ◆ Down-regulate gonadotropin receptors in pituitary to create a hypogonadotropic state
- ◆ Treatment usually restricted to six months
- ◆ Long term effects are unknown; SE in some patients

Mortola JF et al. *J Clin Endocrinol Metab.* 1991; 72: 252A–252F

Ripps BA et al. *J Reprod Med.* 2003;48:761–766.

Wyatt et al. *Br J Obstet Gynaecol.* 2004; 111: 585-593

Wagner-Schuman M, et al.. *J Clin Psychiatry.* 2023

Gonadotropin-Releasing Hormone Agonists

- Double-blind, placebo-controlled trials
 - Several show superiority of GnRH agonists over placebo^{1–8}
 - Some show GnRH agonists equal to placebo^{9,10}
 - Not first line due to significant side effects
 - Consider after failure of non-pharmacologic agents, SSRIs and OCs

1. Brown CS, et al. *Obstet Gynecol*. 1994;84(5):779-786. 2. Freeman EW, et al. *Psychopharmacol Bull*. 1997;33(2):303-309. 3. Hammarback S, Backstrom T. *Acta Obstet Gynecol Scand*. 1988;67(2):159-166. 4. Hussain SY, et al. *Gynecol Endocrinol*. 1992;6(1):57-64. 5. Leather AT, et al. *Gynecol Endocrinol*. 1999;13(1):48-55. 6. Muse KN, et al. *N Engl J Med*. 1984;311(21):1345-1349. 7. Schmidt PJ, et al. *N Engl J Med*. 1998;338(4):209-216. 8. Sundstrom I, et al. *Acta Obstet Gynecol Scand*. 1999;78(10):891-899. 9. Helvacioğlu A, et al. *J Reprod Med*. 1993;38(11):864-870. 10. West CP, Hillier H. *Hum Reprod*. 1994;9(6):1058-1063.

IUD and PMDD

- Hormonal and non-hormonal IUDs
- Lack of research on IUDs and PMDD
- Hormonal IUD does not consistently prevent ovulation (<15% of women stop ovulating by 1 year)

Since PMDD is related to ovulation, there is no clear reason an IUD would help PMDD

Some women are sensitive to the progesterone in OCPs and might also react adversely to the progestin in the hormonal IUD

Rapkin AJ, Korotkaya Y, Taylor KC. *Open Access J Contracept*. 2019 Sep 20;10:27-39.

Non-Pharmacologic Treatment

- Mood Charting
- Lifestyle Modification
 - Diet, exercise, sleep
- Psychotherapy
 - CBT, MBCT, iCBT
- Nutritional Supplements

Andrzej, M & Diana, J. *Maturitas*. 2006;55:S47-S54.

Panahi, F & Faramarzi, M. *Depress Res Treat*. 2016.

Samadi, Z., et al. *Iran J Nurs Midwifery Res*. 2013;18:14–19.

Weise, C., et al. *Psychother Psychosom*. 2019;88(1):16-29.

Nutritional Supplements

- ◆ Calcium (1200 mg daily)
- ◆ Vitamin B6 (50-100 mg daily)
- ◆ Magnesium (200-460 mg daily)
- ◆ Vitamin E (400 IU daily)

Thys-Jacobs S et al. *Am J Obstet Gynecol*. 1998;179: 444–52. Chocano-Bedoya P et al. *The Am Jnl Clin Nutr*. 2011;93(5):1080-1086. Fathizadeh N et al. *Iran J Nurs Midwifery Res*. 2010;15:401-5. Shobeiri et al. *Obstetrics & Gynecology Science*, 2018;60:100–105.

Premenstrual Exacerbation (PME)

- Mood and anxiety disorders
- 40% of women screened for PMDD have an underlying mood disorder with PME
 - Community samples, 60% of women with mood disorders report PME
 - Worsening around ovulation
- Charting to determine cyclicity of symptoms
- Epidemiology, mechanism and treatment understudied
 - PMDD treatments not helpful
 - Adjusting existing regimen can help

Bailey & Cohen. *J Women's Health Gender Based Med.* 1999;8(9):1181.

Kuehner C, Nayman S. *Curr Psychiatry Rep.* 2021;23(11):78.

Premenstrual Worsening of Other Conditions

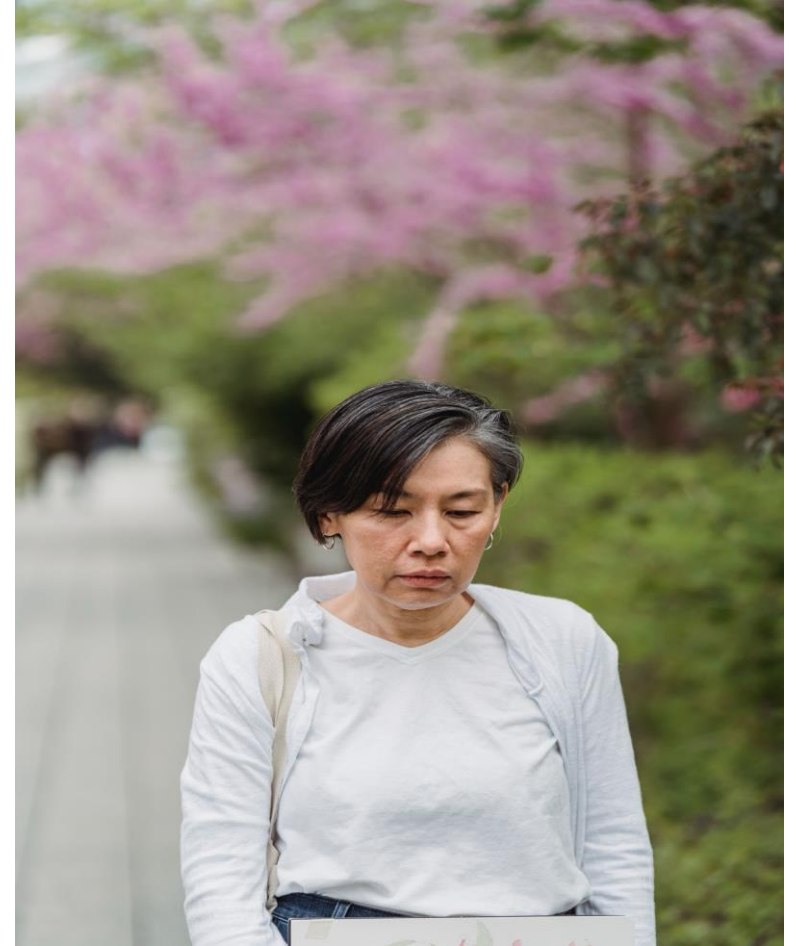
- 44-68% of women with bipolar disorder report premenstrual worsening
 - Depressive, manic, or hypomanic symptoms
 - Fluctuations can affect ovulation, menstruation and premenstruation
 - No data supports using SSRI for the treatment of PME in bipolar disorder
- 1.5-fold increase in psychiatric hospitalization during the premenstrual phase in women with psychotic disorders
- Limited study of premenstrual worsening of ADHD
 - When stimulant increased premenstrually, women reported improved mood and ADHD symptoms
 - Inattention, irritability and energy

Teatero ML, Mazmanian D, Sharma V. Bipolar Disord. (2014) 16:22–36. Dias RS, et al. Am J Psychiatry. (2011) 168:386–94. Camara B, et al. Arch Womens Ment Health. 2022 Feb;25(1):1-8. de Jong M, Wynchet al. Front Psychiatry. 2023 Dec 13;14:1306194. Reilly TJ, et al. Schizophr Bull, May 2019.

Case 2

- 45 year old female reports she has been struggling with PMDD since the birth of her son 6 years ago
- She has no history of depression/anxiety/psychiatric treatment prior to the past two years
- Since then, she has tried 3 SSRIs, 2 OCPs (continuously and intermittently), vitamins through a functional medicine doctor, and benzodiazepines prn with no symptom relief
- Symptoms are depressed mood and intense anxiety, which occur for 3 days around ovulation and 3 days premenstrually, severe enough that she has missed work and can not leave her bed
- Between these times, she feels completely well
- Regimen: bupropion SR 150 mg, Trazodone 50 mg, lorazepam 0.5 mg prn

MENOPAUSE



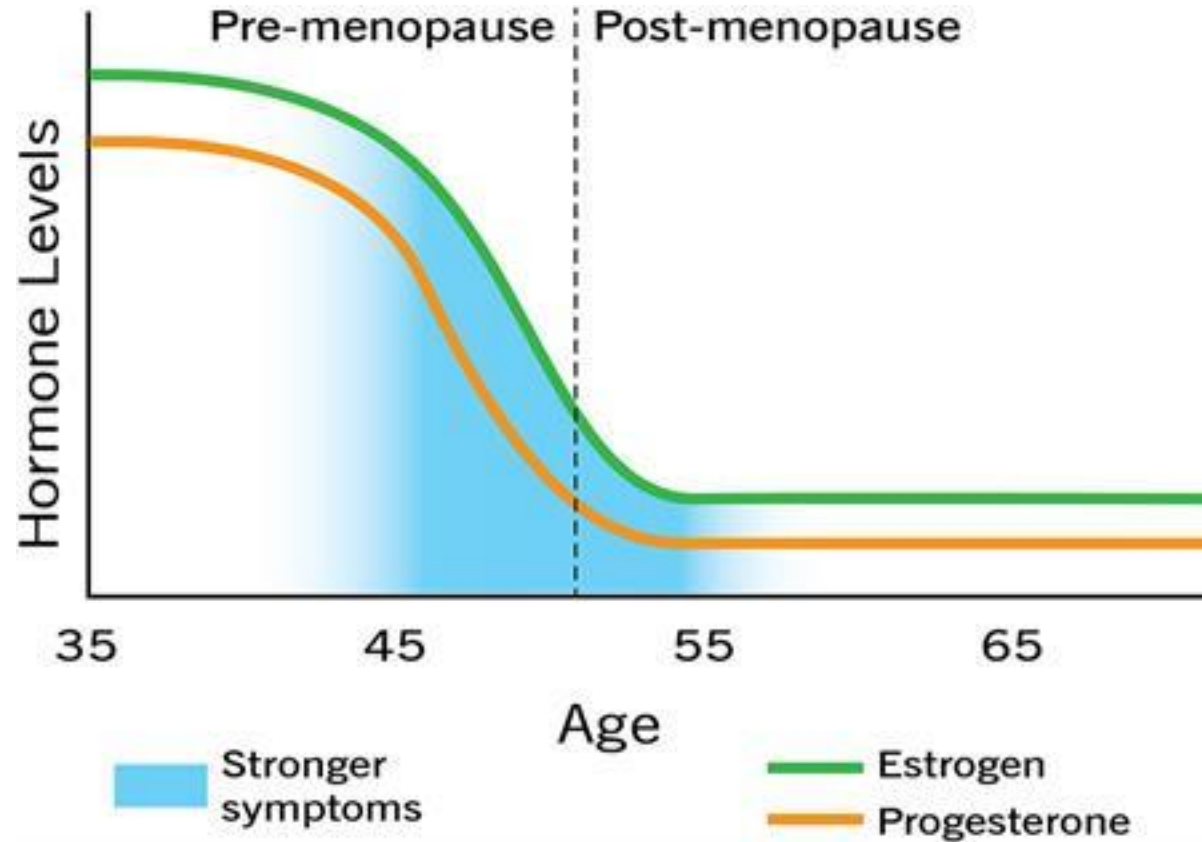
Case 3

- 52 yo female with diagnoses MDD, PTSD, migraine headaches
- Remote history of a suicidal gesture
- 10 year history of venlafaxine monotherapy which worked well
- At age 44 had an episode of irregular bleeding for 2 weeks and hormonal IUD was begun resulting in cessation of menses
- In the past year, has begun to experience vasomotor symptoms (day and night), worse migraines, hopelessness, isolative behavior, fatigue, ruminations and passive SI
- Alcohol: 15/week, cannabis on weekends

What is Menopause?

- 12 months without menses
 - 5-6 years lead up
- Menopausal transition– endocrinologic, somatic, psychological changes
- Average age is 51 (lower for smokers)
 - Most women ages 42-55
 - Premature menopause if before age 40
 - Oophorectomy can be a cause of early menopause
- Severity, frequency and variety of symptoms vary widely

What is Menopause?



Perimenopause – cycles irregular, ages 48-52 (roughly)

Menopause – 12 months without menstruation, age 52 (roughly)

Postmenopause - >12 months after last menstrual period (LMP)

<https://my.clevelandclinic.org/health/diseases/15224-menopause-perimenopause-and-postmenopause>

Symptoms of Menopause

- Hot flashes (60-80%)
- Sleep changes (2-fold increase)
- Depression (2-fold increase)
- Vaginal dryness
- Anxiety
- Osteopenia/osteoporosis
- Fatigue
- Concentration difficulty
- Weight gain



Gold, EB, et al. *Am Jnl Public Health*. 2006.

Ohayon, MM. *Arch Intern Med*. 2006.

Freeman, EW, et al. *Arch Gen Psych*. 2006.

Are symptoms of depression/anxiety related to the menopausal transition?

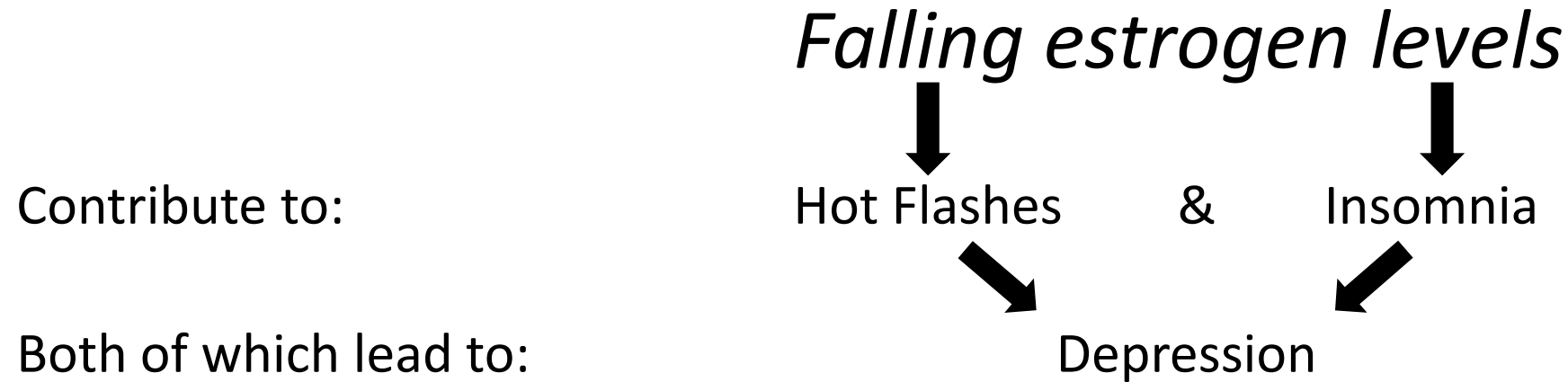


Menopause Assessment

- Menstrual History
 - Regularity of menses, changes in cycle length, absence of menses
- Symptoms and Severity/Interference with Functioning
 - Vasomotor, genitourinary, sleep, psychological
- Psychiatric Evaluation
 - MDD, GAD, bipolar disorder, substance use
- Rating Scales
 - Greene Climacteric Scale, MenQoL, PHQ-9
- Psychosocial Stressors
 - Health changes, family stressors, work



Mechanism – Perimenopausal Depression



BUT...not all women develop depression during the menopausal transition

Hot Flashes/Night Sweats

- Cause: falling levels of circulating estrogen
- Sensation: warmth of the upper body
- Duration: 30 seconds – 5 minutes
- Accompanying symptoms: palpitations, anxiety, dizziness, cold sensation and/or chills
- Timing: daytime and/or night (night sweats)
- Course: perimenopause through postmenopause
- Severity: 10-15% of women report as severe

Sleep

- Insomnia is highly correlated with depression
- Sleep disruption is the hallmark of menopause
- Nighttime vasomotor symptoms correlate with increased sleep fragmentation
- Sleep disordered breathing is more common during menopause (weight gain, unknown endocrine reasons)
- Menopausal sleep disruption can exacerbate other conditions (circadian disorders, restless leg syndrome)

•

Ford DE, Kamerow DB. *JAMA*. 1989; 262(11):1479-84. Breslau N, Roth T, Rosenthal L, Andreski P. *Biol Psychiatry*. 1996; 39:411-8. Morphy H, Dunn KM, Lewis M, Boardman HF, Croft PR. *Sleep*. 2007; 30:274-80. Joffe H, et al. *Sleep*. 2013;36:1977-85. . Eichling, P.S. and Sahni, J., *J Clin Sleep Med*, 2005;1, 291-300.

Vasomotor Symptoms and Depression

- Hot flashes have been associated with perimenopausal depression
 - Night sweats but not daytime hot flashes
- Women with moderate/severe depressive symptoms were twice as likely to report VMS vs. women with no/mild depressive symptoms
- Moderate to severe VMS = moderate to severe depression

Joffe, *J Clin Endo Metab* 2016.

Reed SD, et al. *Maturitas*. 2009;;62:306-10.

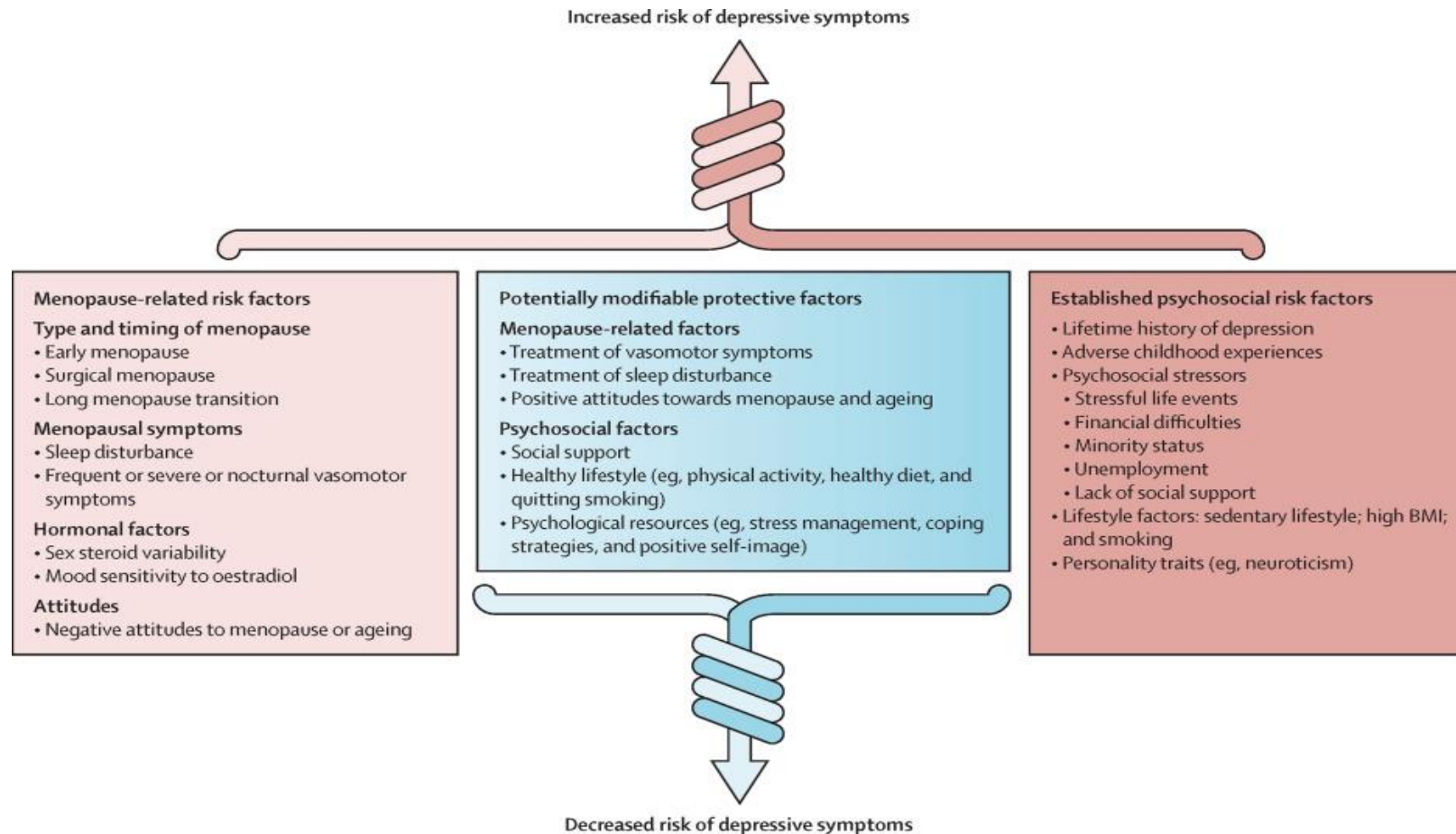
Worsley R, et al. *J Womens Health (Larchmt)*. 2017;26:712-718.

Perimenopausal Depression

- Midlife is a time of increased risk for MDD
- Women WITHOUT history of MDD - lower risk for developing MDD during midlife (28%)
 - Risk factors: VMS, life stressors
- Women WITH history of MDD - elevated risk for MDD recurrence during midlife (59%)
 - Risk factors: Peri- and post-menopause, psychological symptoms, prior anxiety disorder
- Higher rates in Hispanic women - 2.45x higher risk of developing depression in early perimenopause

Maki PM, et al. *Menopause*. 2018;25:1069-1085. Schmidt PJ, et al. *JAMA Psychiatry*. 2015;72:714-26. Freeman EW, et al. *Gen Psychiatry*. 2006;63:375-82. Bromberger JT et al. *Am J Public Health* 2004; 94:1378–1385. Bromberger JT et al. *Psychol Med*. 2015 Jun;45(8):1653-64.

Depression Risk Factors



Brown L, et al.
The Lancet, 2024;
403, 969-983.

Treatment for Depression During Menopause

- Hormonal (estrogen +/- progesterone)
- Novel pharmacotherapy (Fezolinetant - NK3 antagonist)
- Psychotropic (SSRI, SNRI, gabapentin)
- Non-pharmacologic treatment (CBT)
- Complementary and alternative medications (CAM)



Hormonal Therapy

- VMS: FDA approved, beneficial
- Sleep: Modest benefit
- Depression: May be effective for mild depression and MDD
 - Limited studies
 - Not promising in postmenopausal women
 - Several small RCTs have been negative
- Prevention of depression: Data incomplete

Schmidt, P, et al. *Am J Obstet Gynecol*. 2000;183(2):414-420. Soares CN, et al. *Arch Gen Psychiatry* 2001; 58:529-534. Morrison MF, et al. *Biol Psychiatry* 2004; 55:406–412. Gordon JL, et al. *JAMA Psychiatry* 2018; 75:149-157. Rasgon, NL, et al. *Jnl Psych Res* 2007; 41:338-343.

Novel Pharmacotherapy

Fezolinetant (FDA approved) and Elinzanetant (not FDA approved)

- VMS:
 - Involved in the brain's regulation of body temperature
 - Antagonizes the signaling pathway → reduces hot flashes
 - Patients require monitoring of hepatic transaminases
 - Both Fezolinetant (NK3 antagonist) and Elinzanetant (NK3 and NK1 antagonist) effective
- Sleep: Elinzanetant improves sleep if co-occurring VMS
- Depression: Unknown

Morga A, et al. *Menopause*. 2024 Jan 1;31(1):68-76. Pinkerton JV, et al. *JAMA*. 2024;332(16):1343–1354.

Psychotropic Medications

- VMS: Paroxetine - FDA approved for hot flashes, other SSRIs, SNRIs, gabapentin and pregabalin helpful
- Sleep: zolpidem, eszopiclone, suvorexant effective
- Depression: SSRIs/SNRIs helpful, no data for others
- Cognitive function: Lisdexamfetamine studied in women undergoing surgical menopause
 - Surgical menopause associated with more severe cognitive impairments compared to natural menopause
 - Lisdexamfetamine 20-60 mg associated with improvements in attention and working memory per

Thase ME, et al. *J Womens Health (Larchmt)* 2005; 14:609–616.
Papakostas GI, et al. *Int Clin Psychopharmacol* 2007; 22:226–229.
Vermeiden M, et al. *J Psychopharmacol* 2010; 24:497–502.
Metcalf CA, et al. *Oncol* 2024 Aug 14;190:62-69.

Non-Pharmacologic Treatment/ Behavioral Practices

- CBT^{1,2} - effective for VMS (reduces distress from symptoms), sleep, potentially effective for mild depression but data limited
- Yoga - inconsistent results
- Exercise³ - limited data
- Hypnosis⁴ - reduced VMS, limited data
- Biofeedback and relaxation⁴ - inconsistent findings
- Acupuncture - limited study, potentially effective

1. Brandon AR, et al. *J Womens Health (Larchmt)* 2013; 22:58-66.

2. Khoshbooi R, et al. *Australian Journal of Basic and Applied Sciences* 2011; 5:991-995.

3. Perez-Lopez FR, et al. *Maturitas* 2017; 106:38-47.

4. Johnson A, et al. *J Evid Based Integr Med*. 2019 Jan-Dec;24.

Complementary and Alternative Medicine (CAM)

- During menopause, 51% of women use CAM, 60% find it effective, most do not discuss with their HCPs
- Natural products
- Omega-3
 - Limited data, potential benefit
- Vitex agnus-castus (Chasteberry)
 - Inconclusive data, potential benefit
- St. John's Wort
 - Physical symptoms > emotional symptoms, 13-15% reduction in the level of OCP

Cerqueira RO, et al. *Arch Womens Ment Health*. 2017;20:713-719. Verkaik S, et al. *Am J Obstet Gynecol*. 2017;217:150-166. Jang SH, et al. *BMC Complement Altern Med*. 2014;14:11. Sohrabi N, et al. *Complement Ther Med*. 2013;21(3):141-146. Krasnik C, et al. *Am Jnl of Obstetrics and Gyn*. 2005;193:658-661. Posadzki P, et al.. *Maturitas*. 2013 May;75(1):34-43.

Case 4

- 56 yo female with diagnosis of bipolar I disorder with psychosis
- Multiple hospitalizations over her lifetime
- Many medication trials, currently maintained on lithium 900 mg and aripiprazole 10 mg
- Has felt “unstable” for 3 years and during the same time frame has stopped menstruating – more episodes of paranoia, irritability, insomnia defined as difficulty falling asleep
- No vasomotor symptoms; no alcohol, no cannabis; caffeine “all day”
- Not working, has Master’s degree, lives with parents

Summary

- Premenstrual symptoms are common.
- A smaller percentage of women experience severe physical and emotional symptoms that interfere with their ability to function.
- Screening for these symptoms is important as it may lead to beneficial treatments.
- Treatments are non-pharmacologic and/or pharmacologic.
 - Hormonal or psychotropic
 - SSRIs/SNRIs are first line psychotropics
- More research is needed.

Summary

- It is important to identify mood symptoms premenstrually and during the menopausal transition.
- Menopausal symptoms other than mood (sleep, vasomotor) can significantly affect quality of life.
- Symptoms are treatable with pharmacologic and non-pharmacologic interventions.