# Pharmacotherapy of Menopausal Depression and PMDD

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# ARS Questions

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# Disclosure Statement

- Research Funding:
  - Takeda
- Consulting Fee/Advisory Boards:
  - Takeda Pharmaceuticals, Sunovion, JDS Therapeutics
- Medical Editing:
  - GOED Newsletter
- I will be discussing off-label use and/or investigational use of prescription medications/medical devices in the presentation and will identify those issues

# Lecture Content

- Premenstrual Dysphoric Disorder (PMDD) and Related Conditions
- Treatments for PMDD/PMS
- Lifestyle/“Natural” Treatments
- Depression During the Menopausal Transition and Associated Symptoms

# Premenstrual Dysphoric Disorder (PMDD) and Related Conditions

# Premenstrual Mood Problems: Risk Factors

- Age: onset typical in late 20's to mid-30's
- History of psychiatric disorder(s):
  - Increased risk in individuals with history of major depression, postpartum mood episodes, bipolar disorder
- Family history
- Psychosocial stressors

Steiner M, Born L. *Curr Psychiatry Rep.* 2002;3(6):463-469.

# Definitions

- **Premenstrual syndrome (PMS)**
  - Premenstrual emotional, behavioral and physical symptoms; remit after menses; mood changes generally minor
  - Majority of women; do not usually need medical or psychiatric intervention
- **Premenstrual dysphoric disorder (PMDD)**
  - DSM-5™ diagnosis, signifies significant psychiatry morbidity; interference with function
- **Other psychiatric disorders**
  - May have cyclic exacerbations of other DSM disorders (Premenstrual Exacerbation [PME])

Steiner M, Born L. *Curr Psychiatry Rep.* 2002;3(6):463-469.

# Premenstrual Dysphoric Disorder (PMDD)

- 5 or more during most menstrual cycles during last week of luteal phase (remit within days of onset of menses)
  - Depressed mood
  - Anxiety
  - Lability
  - Irritability
  - Decreased interest
  - Poor concentration
  - Decreased energy
  - Change in appetite
  - Change in sleep
  - Feeling overwhelmed
  - Other physical symptoms (bloating, breast pain, headaches)
- Interferes with function, activities, relationships
- Not merely an exacerbation of another disorder
- 3% to 5% of women

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Fifth Edition. Arlington, VA: American Psychiatric Publishing, Inc.; 2013.

# Core Premenstrual Symptoms

- **Most consistent symptoms across cycles**
  - Anxiety
  - Irritability
  - Mood lability

Bloch M et al. *Am J Psychiatry*. 1997;154(12):1741-1746.

# PMDD and Neurobiology

- Higher allopregnanolone levels (neuroactive progesterone metabolite) in women with PMDD, lower cortisol levels
- Normal ovarian function appears to trigger symptoms in some vulnerable individuals

Girdler SS et al. *Biol Psychiatry*. 2001;49(9):7887-7897.
Rubinow DR et al. *Biol Psychiatry*. 1998;44(9):839-850.
Steiner M, Born L. *Curr Psychiatry Rep*. 2002;3(6):463-469.

# Screening and Diagnosis

- History
- Prospective documentation—prospective daily mood ratings (at least 2 months)

# Treatments for PMDD/PMS

# SSRIs for PMDD

- Cochrane Database Systematic Reviews (2009 and 2013):
  Reviews of efficacy of SSRIs in severe PMS/PMDD
- Selection criteria:
  Trials with prospective diagnosis of PMS, PMDD or late luteal phase dysphoric disorder (LPDD); randomized to SSRI or placebo
- Results
  - SSRIs highly efficacious compared to placebo (P<0.00001)
  - Secondary analysis: efficacious on symptom subsets: physical, functional, behavioral (P<0.00001 each)
  - Luteal phase only and continuous administration both effective
  - All SSRIs efficacious: fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, and clomipramine
  - Withdrawals due to side effects were twice as likely with SSRI compared to placebo (P<0.00001)
  - Small to moderate effect sizes: -0.36 with change score, -0.65 with end scores

Brown J et al. *Cochrane Database Syst Rev*. 2009;(2):CD001396.
Marjoribanks J et al. *Cochrane Database Syst Rev*. 2013;6:CD001396.

# Antidepressant Dosing Strategies

- Relatively lower doses may be enough
- Dosing options
  - Daily
  - Daily with higher dosing premenstrually
  - Intermittent, scheduled
  - Intermittent PRN

PRN, as needed.

Kornstein SG et al. *J Clin Psychiatry*. 2006;67(10):1624-1632.

# Reproductive Hormones

- Estrogen appears beneficial
- In general, progesterone ineffective in some controlled studies (despite anecdotal reports), may even worsen symptoms
- Mixed results with oral contraceptives
  - For women on oral contraceptives, type of progesterone may affect PMS

Smith RN et al. *Br J Obstet Gynaecol.* 1995;102(6):475-874.
Gunston KD. *S Afr Med J.* 1995;85(9):851-852.
Magill PJ. *Br J Gen Pract.* 1995;45(400):589-593.
Tiemstra JD, Patel K. *J Am Board Fam Pract.* 1998;11(5):378-381.
Andersch B. *Int J Gynaecol Obstet.* 1982;20(6):463-469.

# Oral Contraceptives for PMDD

- **Combined oral contraceptives (COCs)** have both progestin and estrogen; recent studies in COCs containing drospirenone and low estrogen (approval for treating PMDD)
- **Cochrane Review (2009)**
  - 5 trials, N=1,600;  2 placebo-controlled trials of women with PMDD showed less severe premenstrual symptoms after 3 months with drospirenone (plus ethinyl estradiol [EE] 20 g) than with placebo
  - The drospirenone group had greater decreases in impairment of productivity, social activities, and relationships
  - Side effects: nausea, intermenstrual bleeding, breast pain
  - Little effect on less severe symptoms when comparing drospirenone to another COC. A 6-month study showed fewer symptoms with drospirenone, while a 2-year trial found the groups to be similar

Lopez  LM et al. *Cochrane Database Syst Rev*. 2009;(2):CD006586.

# Oral Contraceptives for PMDD

- **Best studied in**
  - Short trials (3 cycles)
  - Severe premenstrual dysphoria/PMDD
- **Limitations**
  - Placebo responses, need more long-term studies, unclear regarding add-on benefits to antidepressants
  - Safety: not considered safe in women over 35 who smoke
- **Response rate may be modest compare with placebo**
  - COC responders: 48%
  - Placebo responders: 36%
  - Number needed to treat: 8

Lopez LM et al. *Cochrane Database Syst Rev*. 2009;(2):CD006586.
Yonkers KA et al. *Obstet Gynecol*. 2005;106(3):492-501.

# Lifestyle/“Natural” Treatments

# Light Therapy

- Reduction of depressive symptoms in PMDD reported, small amount of data
- May decrease carbohydrate cravings along with improved mood
- Evidence limited to date, may have small effect size
- Small number of trials, small number of subjects, unclear efficacy

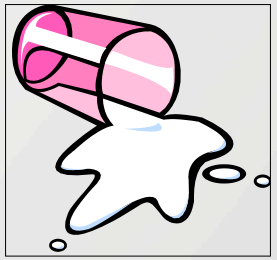
Krasnik et al. *Am J Obstet Gynecol*. 2005;193(3 Pt 1):658-661.
Lam RW et al. *Psychiatry Res*. 1999;86(3):185-192.
Parry BL et al. *Am J Psychiatry*. 1993;150(9):1417-1419.
Bylesjo EI et al. *Int J Eat Disord*. 1996;20(4):443-446.

# Exercise

- Observational studies suggest women who exercise experience less emotional distress premenstrually
- Intervention studies (reviewed by Daley, 2009)
  - 4 intervention studies, small number of participants; promising preliminary data
  - Adequately powered, controlled studies needed

Aganoff JA, Boyle GJ. *J Psychosom Res*. 1994;38(3):183-192.
Steege JF, Blumenthal JA. *J Psychosom Res*. 1993;37(2):127-133.
Daley A. *J Womens Health (Larchmt)*. 2009;18(6):895-899.

# Calcium



- **Calcium: impact on premenstrual symptoms**
- Including mood symptoms
- Approximately 500 to 1,500 mg/d
- Large study N=497
  - Calcium carbonate 1,200 mg/day or placebo
  - Significant benefit in 2nd and 3rd cycles
  - 48% reduction in calcium group, 30% in the placebo group (included affective symptoms)
- Calcium regulation may be altered in women with PMDD across cycle

Thys-Jacobs S et al. *Am J Obstet Gynecol*. 1998;179(2):444-452.
Penland JG, Johnson PE. *Am J Obstet Gynecol*. 1993;168(5):1417-1423.
Thys-Jacobs S et al. *J Clin Endocrinol Metab*. 2007;92(8):2952-2959.

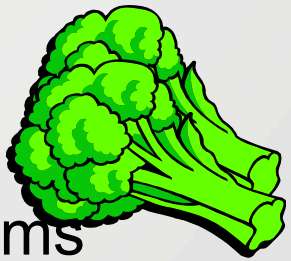
# Omega-3 Fatty Acids and Premenstrual Symptoms

- Omega-3 fatty acids: treatment with fish oil (1.8 g/d EPA + DHA) reduced PMS symptoms in adolescents after 2 months
- Menstrual symptoms (pain) associated with low omega-3 fatty acid intake
- No benefit with general formulation of essential fatty acid
- Evening primrose oil (omega-6) not more beneficial than placebo

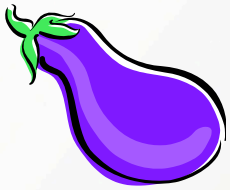
DHA, docosahexaenoic acid. EPA, eicosapentaenoic acid.

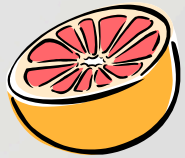
Harel Z et al. *Am J Obstet Gynecol*. 1996;174(4):1335-1338.
Deutch B. *Eur J Clin Nutr*. 1995;49(7):508-516.
Collins A et al. *Obstet Gynecol*. 1993;81(1):93-98.
Khoo SK et al. *Med J Aust*. 1990;153(4):189-192.
Whelan AM et al. *Can J Clin Pharmacol*. 2009;16(3):e407-429.
Budieri D et al. *Control Clin Trials*. 1996;17(1):60-68.

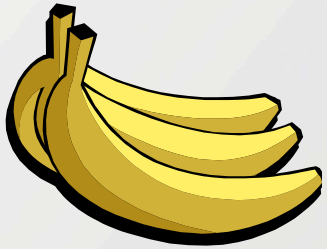
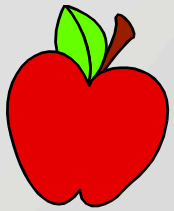
# Treatment—Diet

- Low-fat, vegetarian diet beneficial for PMS symptoms
- Also increased concentration of sex hormone binding globulin (SHBG) (N=33, diet for 2 cycles)



Barnard ND et al. *Obstet Gynecol*. 2000;95(2):245-250.

# "Chocolate: Food or Drug?"

- 40% to 50% of women who crave sweets and chocolate do so primarily premenstrually
- Refractory to treatment!
  - Trial of progesterone vs. alprazolam vs. placebo; none helpful in decreasing cravings
- Self-medication?
  - Correct dietary deficiencies (e.g., magnesium)
  - Increase levels of neurotransmitters
  - Biologically active compounds (methylxanthines, biogenic amines, cannabinoid-like fatty acids)

Bruinsma K, Taren DL. *J Am Diet Assoc*. 1999;99(10):1249-1256.
Michener W et al. *Physiol Behav*. 1999;67(3):417-420.

# Treatment Strategies for PMDD, Premenstrual Mood Exacerbation

| Treatment | How to add | Comments |
|---|---|---|
| **Antidepressants First line** | Monotherapy: Intermittent or daily Dosing: Can increase dose premenstrually | Serotonergic antidepressants, SSRIs best studied |
| **Oral contraceptives First line** | Variable results—monotherapy or adjunctive therapy | Results vary between women and OCP preparation; watch for OCP dysphoria, contraindicated in smokers over 35 |
| **Exercise** | Adjunctive strategy | |
| **Nutrition— general, decrease fat** | Adjunctive strategy | Overall improved nutrition, decrease saturated fat, increased fruit, vegetables |
| **Omega-3 fatty acids** | Adjunctive strategy | 1 to 3 g EPA+DHA per day |
| **Calcium** | Adjunctive strategy | 1,200-1,500 mg calcium per day |

# The Menopausal Transition

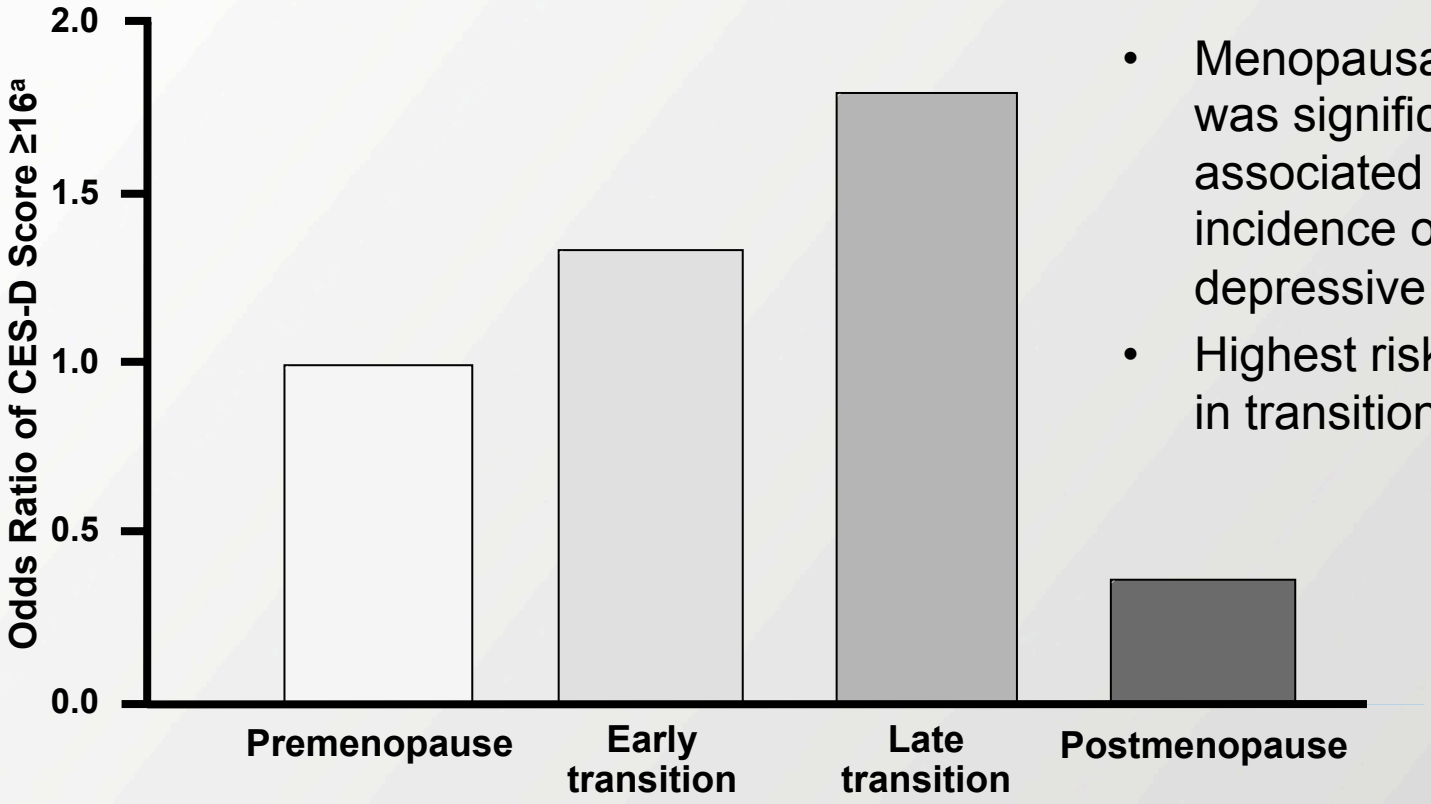
# Perimenopause

- 2 to 8 years preceding menopause; may last 1 year after final menses
- Biological, hormonal, and clinical changes
  - Typically begin after age 40
- Hormonal assays are unreliable
- Risk of depression increased **perimenopausally**

World Health Organization. WHO Technical Report Series 866. Geneva, Switzerland: World Health Organization; 1996.
Stellato RK et al. *Endocr Pract.* 1998;4(3):137-141.

# Menopausal Status Is Associated with Increased Depressive Symptoms

## Penn Ovarian Aging Study, N=436




- Menopausal status was significantly associated with incidence of higher depressive symptoms
- Highest risk observed in transition phases

CES-D, Center for Epidemiologic Studies Depression Scale.
[a]CES-D score ≥16 signifies high depressive symptoms.
Freeman EW et al. *Arch Gen Psychiatry.* 2004;61:62-70.

# Stages of Reproductive Aging Workshop (STRAW)

- Menopause: >12 months amenorrhea, reflects a complete but natural decrease in ovarian hormone secretion
- Menopausal transition: menstrual cycle and endocrine changes, begins with menstrual cycle changes, <12 months since last menses
- Postmenopause
  - Early postmenopause: 5 years since last menses, further dampening of ovarian hormone function
- Perimenopause: “about or around the menopause,” includes menopausal transition, until 1 year past final menses

Soules MR et al. *Fertil Steril.* 2001;76:874-878.

# Risk of Core Menopause Symptoms

- **Hot flashes**
  - Affect 60% to 80%
- **Sleep disorder**
  - 2-fold increase vs. premenopausal women
- **Major depression**
  - 2-fold increase vs. premenopausal women

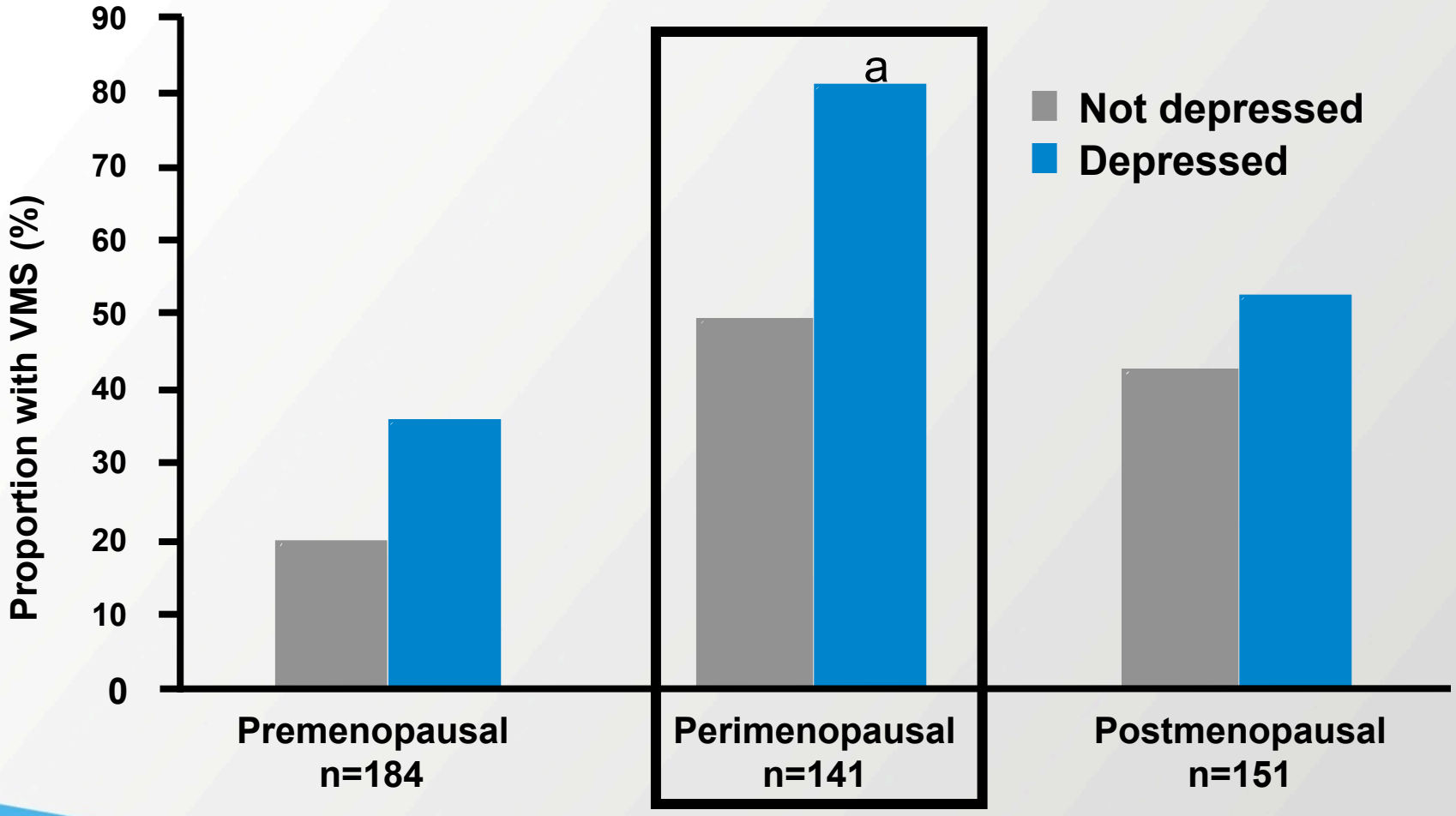
Gold EB et al. *Am J Public Health*. 2006;96(7):1226-1235.
Ohayon MM. *Arch Intern Med*. 2006;166(12):1262-1268.
Freeman EW et al. *Arch Gen Psychiatry*. 2006;63(4):375-382.
Cohen LS et al. *Arch Gen Psychiatry*. 2006;63(4):385-390.

# Risk of Major Depressive Disorder in Perimenopause

- Risk for new onset of depression during the menopause transition: the Harvard study of moods and cycles and Penn Study
- Longitudinal, prospective studies; premenopausal women without histories of depression
- Over course of studies, women who entered the perimenopause were 2 to 4 times as likely to develop depression as those who remained premenopausal during the follow-up
- Increased hormonal variability associated with increased risk of depression

Cohen LS et al. *Arch Gen Psychiatry*. 2006;63(4):385-390.
Freeman EW et al. *Arch Gen Psychiatry*. 2006;63(4):375-382.

# Hot Flashes Among Perimenopausal Women With and Without Depression




[a]*P*=0.008 vs. nondepressed perimenopausal.
VMS, vasomotor symptoms.
Joffe H et al. *Menopause.* 2002;9:392-398.

# Sex Hormones and Perimenopausal Depression

- **Role of sex hormones in perimenopausal MDD**
  - Stages of the menopausal transition characterized by hormonal fluctuation, estradiol withdrawal most likely those of MDD onset
  - Trials demonstrating antidepressant effects of estradiol, at least in short-term studies (3 to 6 weeks)
  - Experimentally induced estradiol withdrawal triggers mood symptoms in some women

MDD, major depressive disorder.

Schmidt PJ, Rubinow DR. *Ann NY Acad Sci*. 2009;1179:70-85.

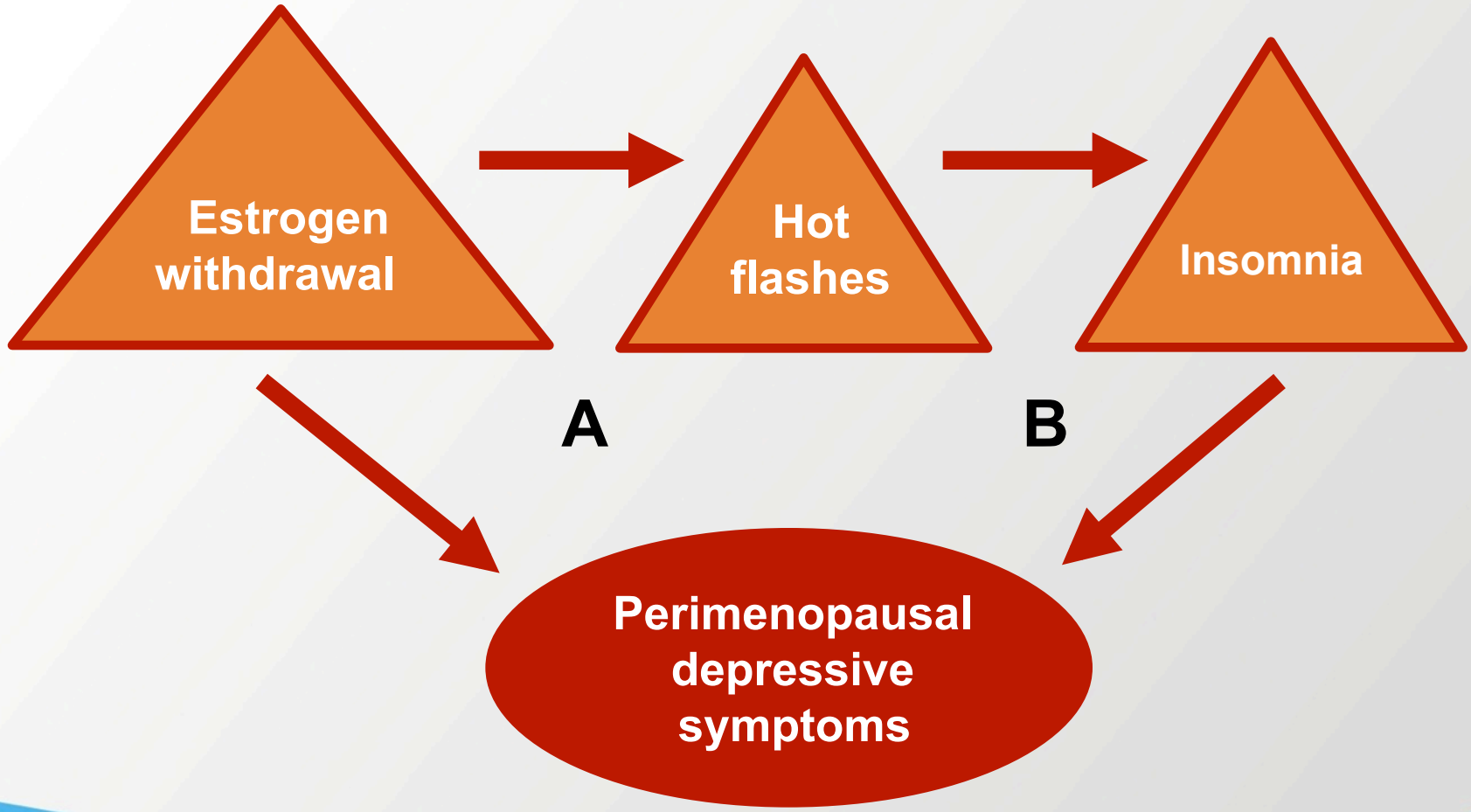
# Sex Hormones and Perimenopausal Depression

- But not the complete story
  - The majority of women do not experience MDD around the menopausal transition
  - No hormonal abnormality has been demonstrated to differentiate women who do develop depression vs. those who do not

MDD, major depressive disorder.

Schmidt PJ, Rubinow DR. *Ann NY Acad Sci.* 2009;1179:70-85.

# Potential Mechanisms of Perimenopausal Depressive Symptoms




Joffe H, Cohen LS. *Biological Psychiatry.* 1998;44:798-811.

# Sleep and Fatigue

- Complaints of fatigue, poor sleep
  - Do you snore
  - Suspect sleep apnea
- Risk factors
  - Age
  - Obesity/Body mass index (BMI)
  - Smoking
  - Menopause – an independent risk factor

Jordan et al. *Lancet*. 2014.

# Hormone Replacement Therapy Study Halted

Increased risk of breast cancer a factor, government says

August 14, 2002 Posted: 11:56 AM EDT (1556 GMT)

WASHINGTON (CNN) -- In a move that may affect millions of women, U.S. government scientists Tuesday stopped a major study of hormone replacement therapy on the risks and benefits of combined estrogen and progestin in healthy menopausal women, citing an increased risk of invasive breast cancer.

Researchers from the National Heart, Lung and Blood Institute of the National Institutes of Health also found increases in coronary heart disease, stroke and pulmonary embolism.

# Estrogen for Menopausal Depression: What is the evidence?

- Systematic Review; only 5 random control trials with depressed participants; only two of the study samples were solely perimenopausal
- Difficult to generalize
  - Little evidence to support the use of estradiol to improve mood in nondepressed patients
  - Some evidence to support the antidepressant efficacy of estradiol in perimenopausal but not postmenopausal women

Rubinow et al. *Depression and Anxiety*. 2015.

# Serotonin Reuptake Inhibitors—Perimenopause

- Fluoxetine: Decrease in hot flashes
- Citalopram: Open-label for perimenopausal depression; monotherapy or as augmentation of estrogen
- Paroxetine: Decreases in hot flashes (FDA- approval at low dose)
- Venlafaxine: Decrease in hot flashes; open-label for perimenopausal depression
- Mirtazapine: Open-label for perimenopausal depression
- Escitalopram: Open-label for perimenopausal depression
- Duloxetine: Open-label for perimenopausal depression


Loprinzi CL et al. *J Clin Oncol*. 2009;27(17):2831-2837.
Soares CN et al. *J Clin Psychiatry*. 2003;64(4):473-479.
Stearns V et al. *JAMA*. 003;289(21):2827-2834.
Barton D et al. *Oncol Nurs Forum*. 2002;29(1):33-40.
Ladd CO et al. *Depress Anxiety*. 2005;22(2):94-97.
Joffe H et al. *J Womens ealth end Based Med*. 2001;10(10):999-1004.
Freeman MP et al. *J Womens Health (Larchmt)*. 2006;15(7):857-861.
Joffe H et al. *J Clin Psychiatry*. 2007;68(6):9439-450.
Freeman MP et al. *Maturitas*. 2013;75(2):170-174.

# Hot Flashes: Integrative Treatments

- Newton et al: Treatment of vasomotor symptoms of menopause with black cohosh, multibotanicals, soy, HRT, or placebo; randomized trial
- N=351 women age 45 to 55 with vasomotor symptoms
- Randomized to black cohosh, multibotanical with black cohosh, multibotanical + dietary soy counseling, estrogen, or placebo
- Patients followed for 1 year
- None of the complementary and alternative medicine treatments better than placebo; HRT significantly better than placebo at all follow-up points

HRT, hormone replacement therapy.
Newton KM et al. *Ann Intern Med*. 2006;145(12):869-879.

# Hot Flashes: Integrative Treatments

- Placebo-controlled study assessing omega-3 fatty acids (ethyl EPA vs. placebo) in the treatment of hot flashes in women who were experiencing "psychological distress" at baseline
- N=120 women, age 40 to 55; randomized to EPA vs. placebo for 8 weeks
  - All had hot flashes
  - After 8 weeks, hot flash frequency and score decreased significantly in the EPA group compared with placebo group
  - Menopause-specific Quality of Life scores improved significantly over time in both
  - Measures of Psychological Distress: at baseline, women with psychological distress were mildly to moderately depressed; 24% met criteria for a major depressive episode
  - After 8 weeks, mood outcomes improved in both groups, but no significant differences on HAM-D scores for women with major depressive episodes (N=29)

HAM-D, Hamilton Rating Scale for Depression.

Lucas M et al. *Menopause*. 2009;16(2):357-366.
Lucas M et al. *Am J Clin utr*. 2009;89(2):641-651.

# Hot Flashes: Integrative Treatments

- MsFlash: National Institutes of Health funded multi-site network, large study of **exercise, yoga, and omega-3 fatty acids** for hot flashes
  - 12-week study; N=355 women with an average of 7.6 HF per day
    - All randomized to either omega-3 or placebo
    - Also randomized to yoga, exercise, or usual activity
    - No efficacy for HF with any intervention

Newton et al. *Menopause*. 2014.
Cohen et al. *Menopause*. 2014.
Sternfeld et al. *Menopause*. 2014.

# Nonhormonal Treatments for Hot Flashes

| Agent | Indication | Study Designs, Comments |
|---|---|---|
| **Serotonergic antidepressants** | Hot flashes, MDD | RCTs, open trials, with and without HRT; fluoxetine, paroxetine, citalopram, escitalopram, venlafaxine, mirtazapine, duloxetine |
| **Gabapentin** | Hot flashes | Randomized, double-blind, placebo-controlled trials showing benefit for hot flashes |
| **Omega-3 fatty acids** | Hot flashes | One RCT showing benefit for hot flashes, not consistent across studies |
| **Isoflavones/soy** | Hot flashes | Randomized, double-blind, placebo-controlled trial; some positive and negative results |
| **Black cohosh** | Hot flashes | Several RCTs; no benefit over placebo |

RCT, randomized controlled trial.

Lammerink EA et al. *Maturitas*. 2012;73(3):265-268.
Hall E et al. *Drugs*. 2011;71(3):287-304.
Lucas M et al. *Menopause*. 2009;16(2):357-366.
Thacker HL. *J Womens Health (Larchmt)*. 2011;20(7):1007-1106.

# Treatment Strategies: Menopausal MDD and Hot Flashes

| Treatment | Efficacy for depression | Efficacy for hot flashes | Efficacy for sleep |
|---|---|---|---|
| Antidepressant – serotonergic activity | X | X | |
| Hormone therapy | X | X | |
| Gabapentin | | X | ? |
| Sleep medication | | | X |
| Omega-3 fatty acids | | X | |

# ARS Questions

# Q&A

Thank you