The Menopausal Transition and Depression

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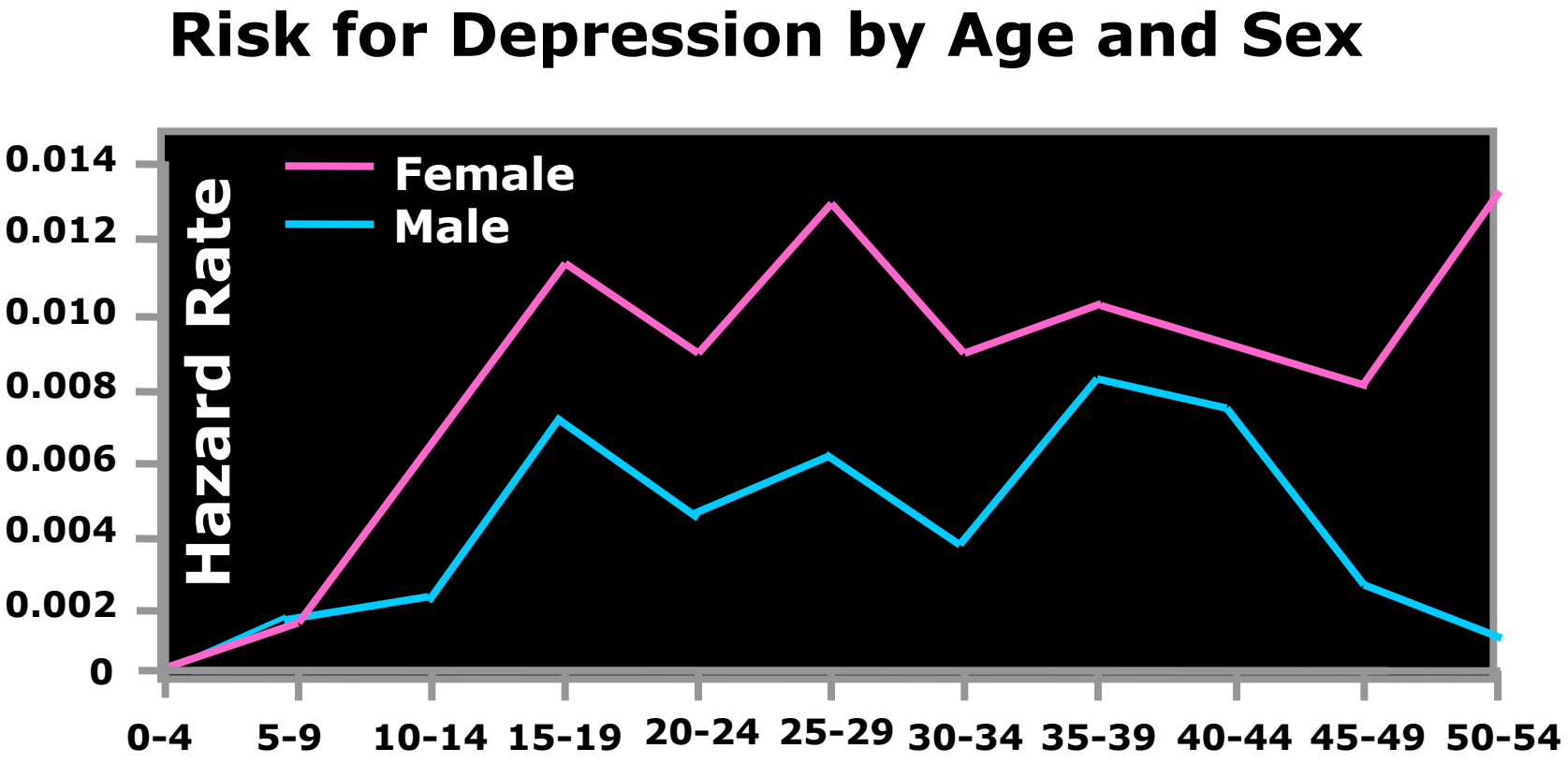
Disclosures

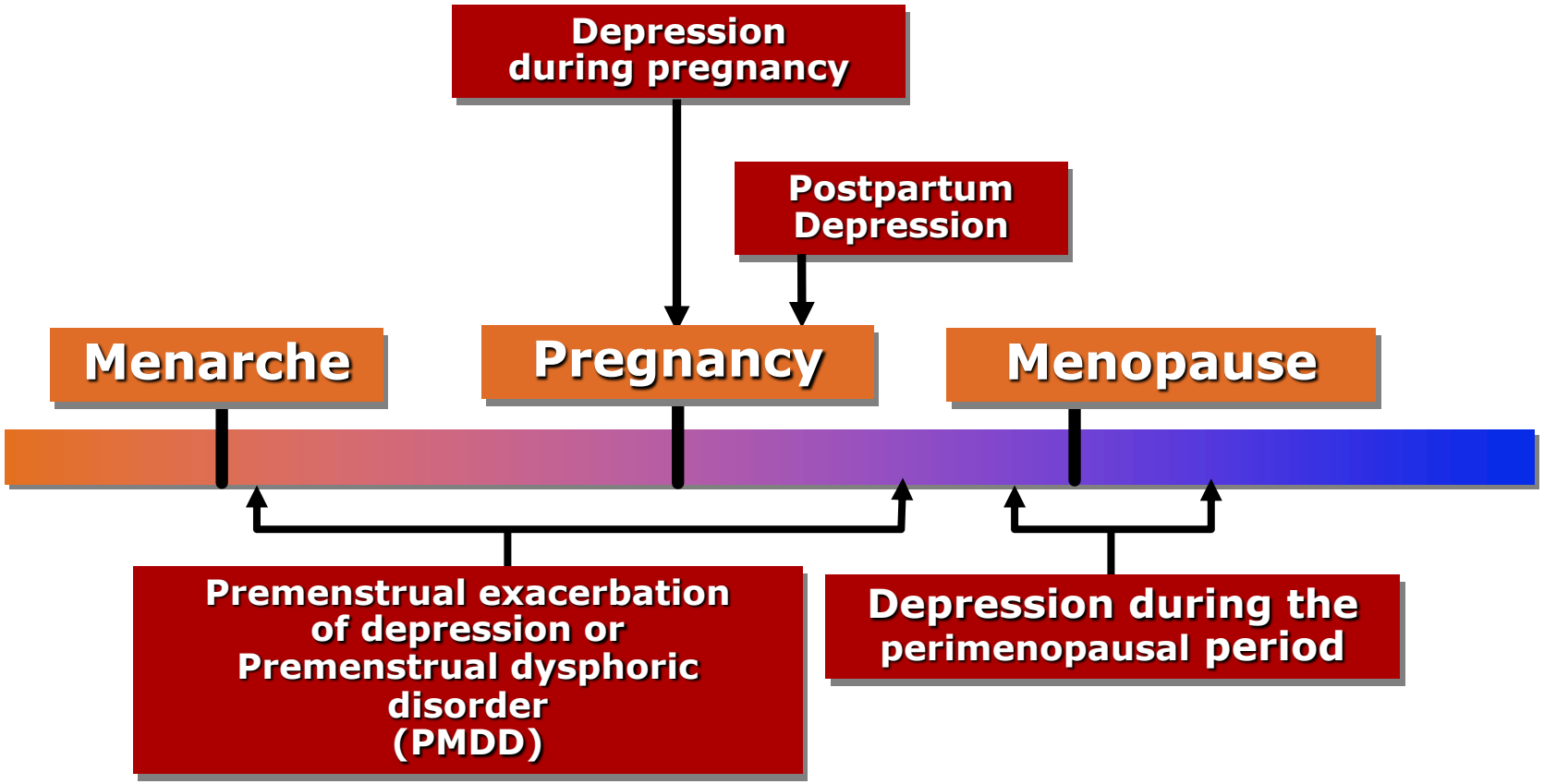
Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose.

Affective Disorders in Women



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

Depression Across the Female Reproductive Cycle



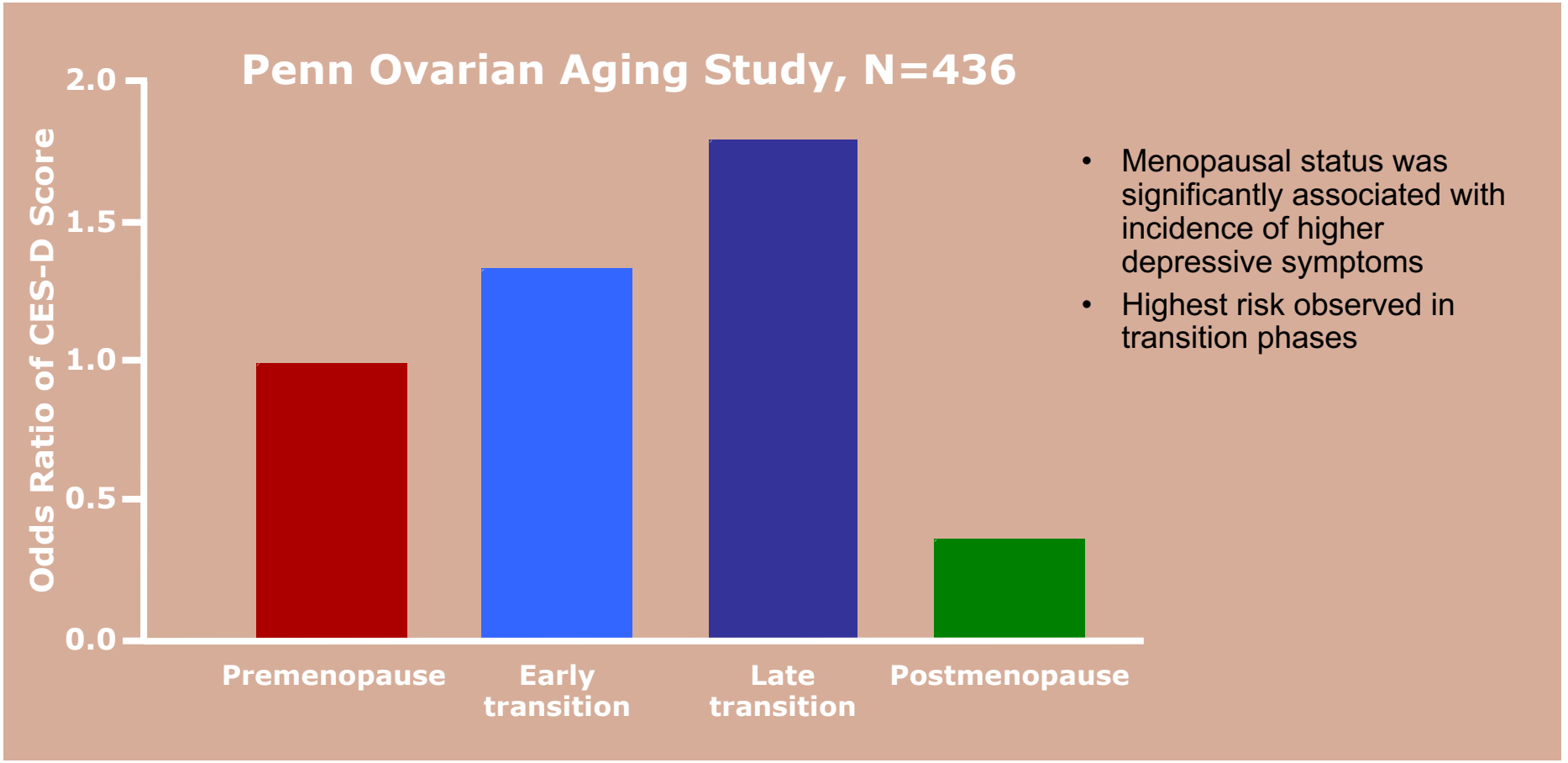
Risk for Mood Disorder During the Menopause Transition

Are Women At increased Risk for New Onset of Depression?

NEW ONSET Of Depression and Menopause Transition: Population Studies

Studies	Population	References
The Study of Women's Health Across the Nation (SWAN)	N=266 midlife women with no history of depression for 7 years	Bromberger et al. Psychol Med. 2009;39:55-64.
The Harvard Study of Moods and Cycles	N=460 women with no history of depression for up to 8 years	Cohen et al. Arch Gen Psychiatry. 2006;63:385-390.
The Penn Ovarian Aging Study	N=231 women with no history of depression for up to 8 years	Freeman E et al. Arch Gen Psychiatry. 2006;63:375-382.

Menopausal Status is Associated With Increased Depressive Symptoms



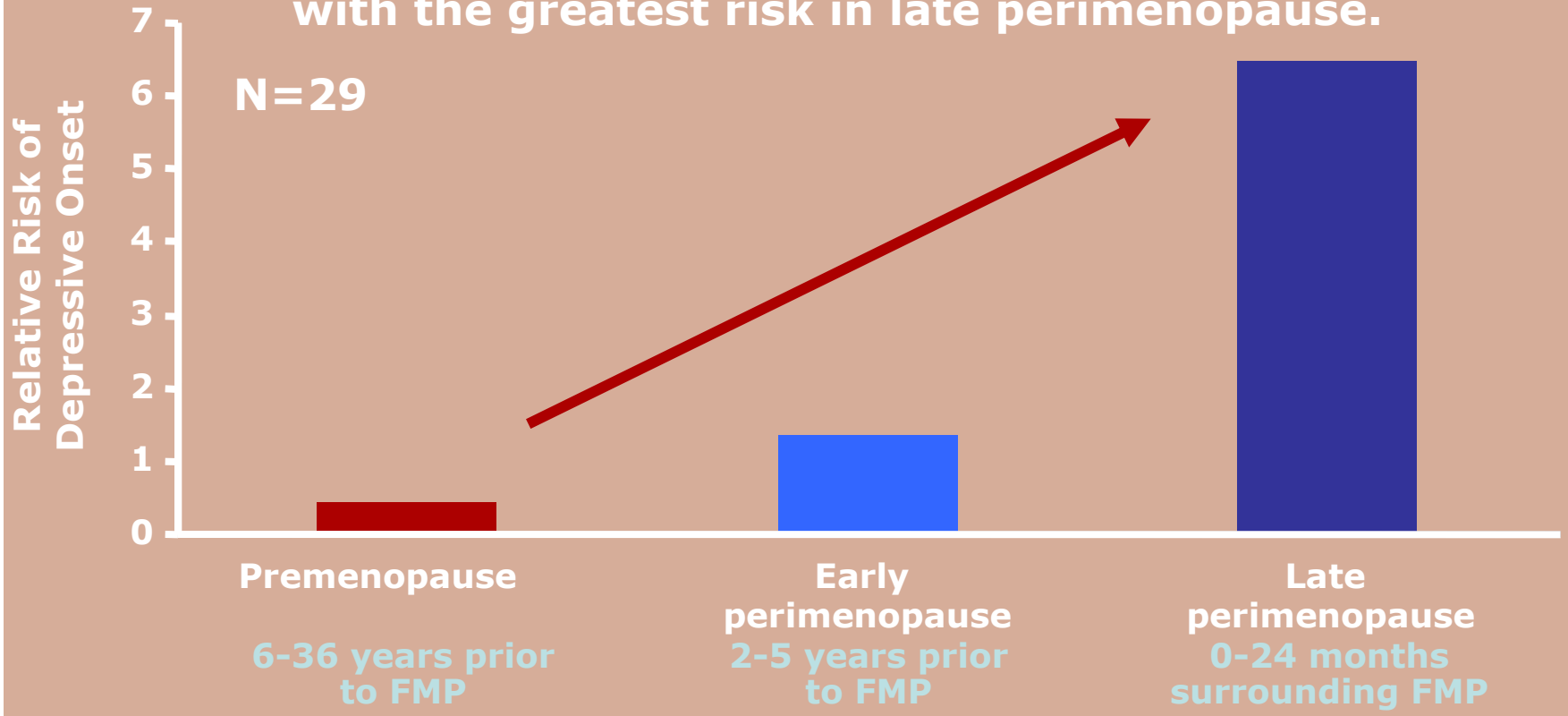
- Menopausal status was significantly associated with incidence of higher depressive symptoms
- Highest risk observed in transition phases

CES-D=Center for Epidemiologic Studies Depression Scale.
CES-D score ≥16 signify high depressive symptoms.

Freeman EW. *Arch Gen Psychiatry.* 2004;61:62-70.

Risk for Depression Among Perimenopausal Women

The risk for depressive onset starts increasing in early perimenopause with the greatest risk in late perimenopause.



FMP = final menstrual period

Schmidt PJ, et al. *Am J Psychiatry*. 2004;161:2238-2244.

ORIGINAL ARTICLE

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.

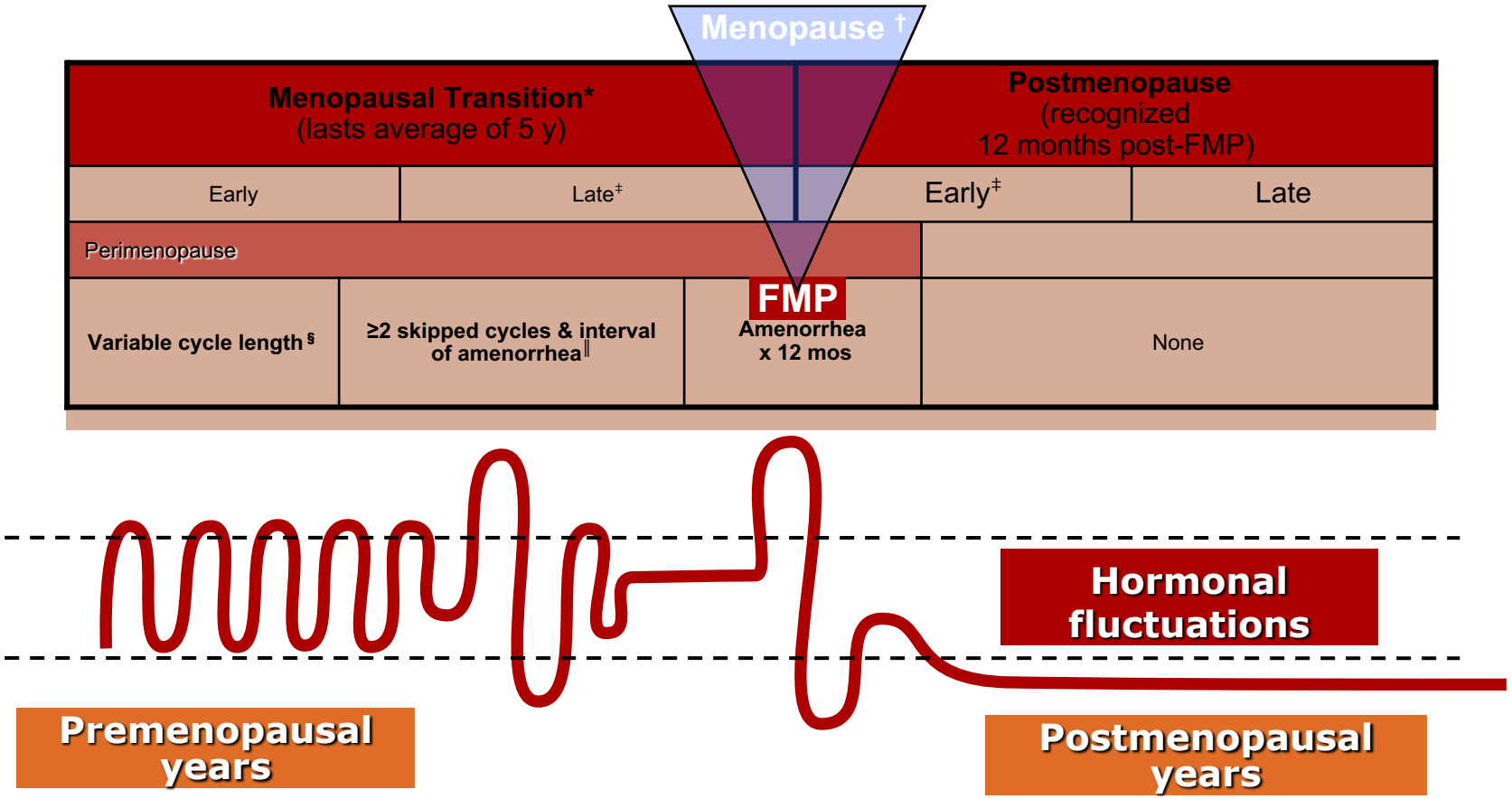
Conclusions: The current study suggests that within a similarly aged population of women with no lifetime history of depression, those who enter the menopausal transition earlier have a significant risk for first onset of depression. Further studies are needed to determine more definitively whether other 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

Increased Risk for First Episode of MDD During Menopausal Transition (cont'd)

- Risk of MDD during menopausal transition is high (OR=1.9), even among women with no history of MDD
- Risk for MDD higher among women with vasomotor symptoms (OR=2.5)
- Adverse life events may exacerbate the risk for depression, BUT are not necessary for its occurrence

Cohen LS, Soares CN, Otto MW, et al. *Arch Gen Psychiatry 2006*; 63:385-390.



Santoro N, et al. *J Clin Endocrinol Metab.* 1996;81:1495-1501.
Kronenberg F. *Ann N Y Acad Sci.* 1990;592:52-86.

Onset of Depressive Symptoms and Hormone Changes

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GENERAL PSYCHIATRY

Higher depressive symptoms (CES-D) associated with increased variability (within subject) of levels of:

- Estradiol (P = .03)
- FSH (P<.001)
- LH (P = .005)

Table 6. Odds Ratios (ORs) of Hormones From the Final Multivariable Model for Onset of Depressive Symptoms (CES-D Scale Score ≥ 16) for 116 Participants

	OR			
Hormone*	Unadjusted	Adjusted	95% CI	*P* Value
Estradiol				
Mean	1.10	1.06	(0.63-1.78)	.83
SD†‡	1.30	1.36	(1.02-1.80)	.03
FSH				
Mean	4.38	4.58	(2.03-10.35)	<.001
SD†‡	1.90	2.09	(1.70-3.41)	<.001
Inhibin B				
Mean	0.34	0.37	(0.20-0.66)	<.001
SD†‡	1.32	1.20	(0.89-1.60)	.21
LH				
Mean	2.98	3.00	(1.52-5.93)	.002
SD†‡	1.57	1.57	(1.18-2.22)	.005

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 colinearity 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.

Freeman, E. W. et al. Arch Gen Psychiatry 2006;63:375-382.

Treatment of Perimenopausal and Menopausal Women with Depression

Diagnostic Challenges

Clinical Presentation

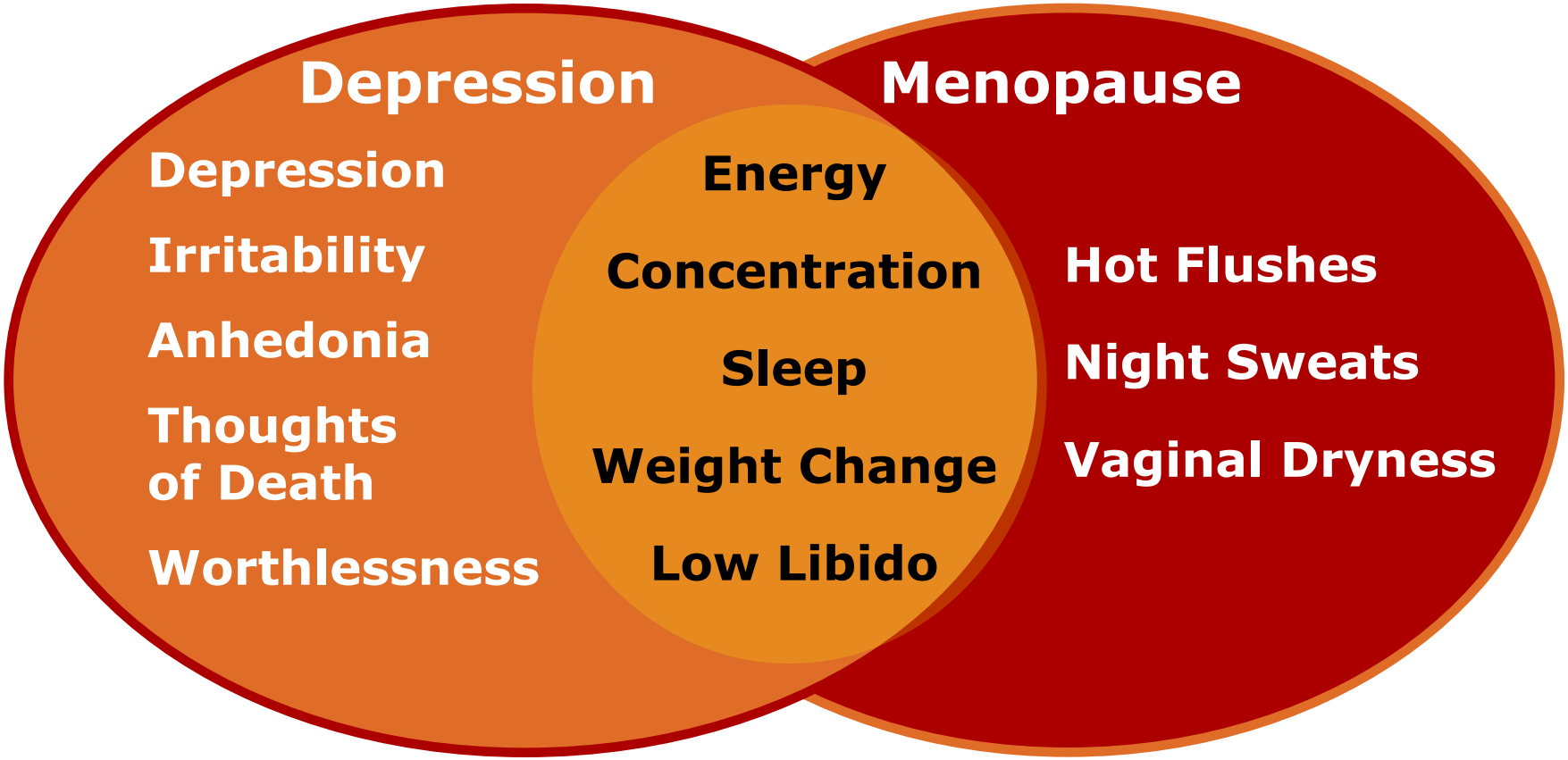
- Most women have a history of MDD, recurrence of depression during transition, similar symptoms
- Typical symptoms: anhedonia, irritability, sleep disruption, fatigue, poor concentration
- “Mood swings” - rule out bipolar disorder
- Psychosocial factors specific to midlife (e.g., caring for aging parents, children leaving home, decline in health)
- Comorbid medical illness

Core Menopause Symptoms

- **Vasomotor Symptoms: Night sweats, hot flashes**
  - Affect 60% to 80%of perimenopausal women
- **Sleep Disturbance**
  - 2-fold increase vs. premenopausal women
- **Depressive Symptoms**
  - 2-fold increase vs. premenopausal women
- **Vaginal Dryness, Changes in Sexual Function**
  - 25% to 60% of women report moderate to severe vaginal dryness or dyspareunia

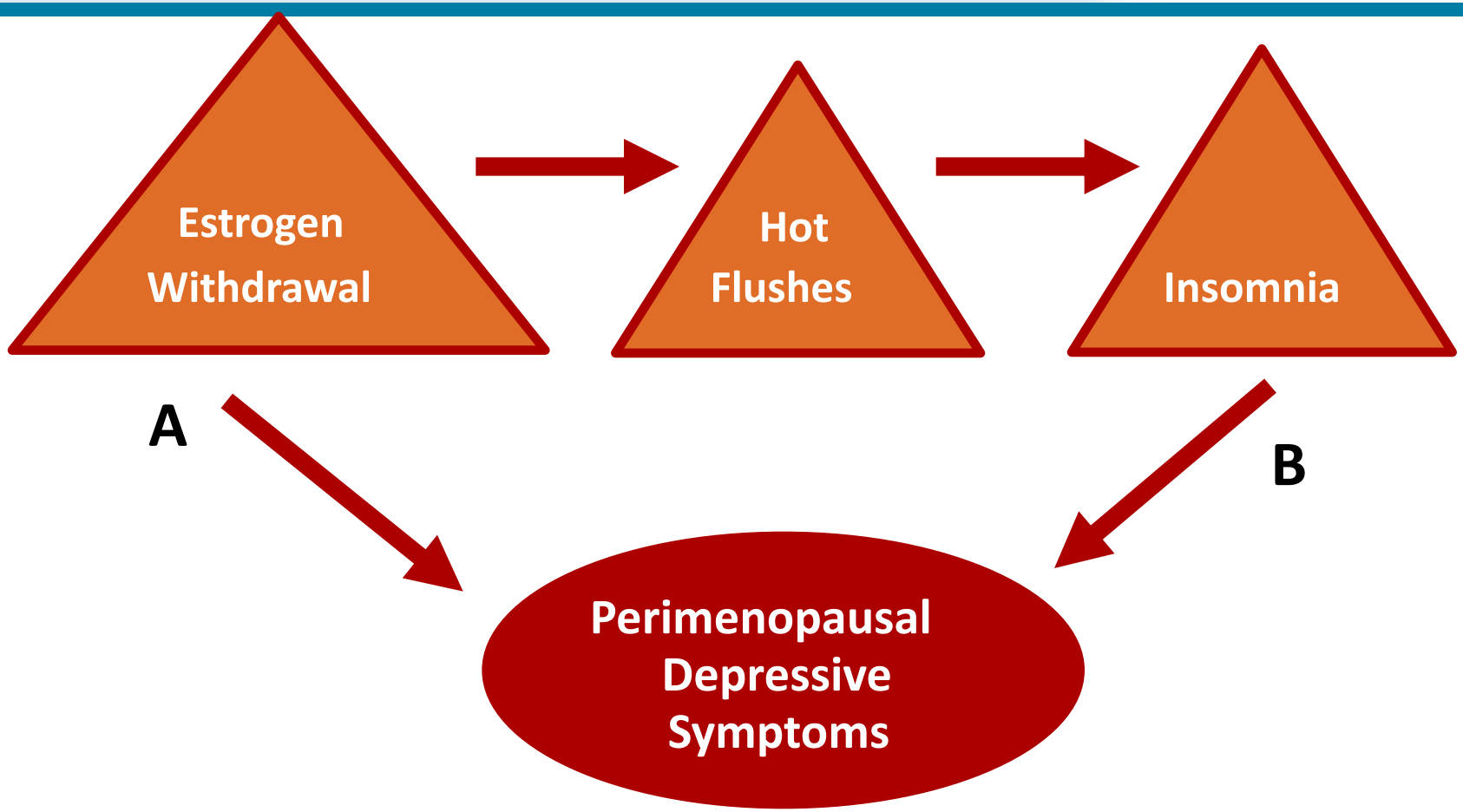
- Gold EB et al. *Am J Public Health*. 2006;96(7):1226-1235.
  Ohayon MM. *Arch Intern Med*. 2006;166(12):1262-1268.
  Freeman EW et al. *Arch Gen Psychiatry*. 2006;63(4):375-382.
  Cohen LS et al. *Arch Gen Psychiatry*. 2006;63(4):385-390.

Menopause vs. Depression-Related Symptoms



Soares CN, et al. *CNS Spectr*. 2005 Jun;10(6):489-497.
Joffe H, et al. *Psychiatr Clin North Am.* 2003;26:563-580.

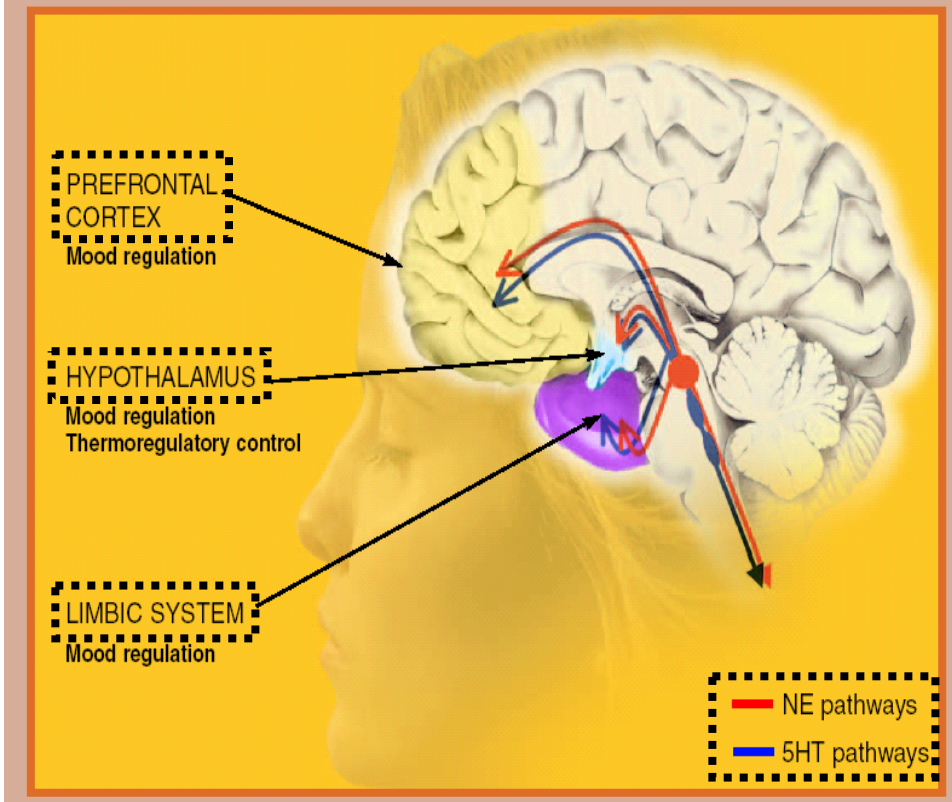
Potential Mechanisms of Perimenopausal Depressive Symptoms



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

Estrogen Modulation of Key Regions/Systems

Brain regions involved in MDD and Menopausal Symptoms

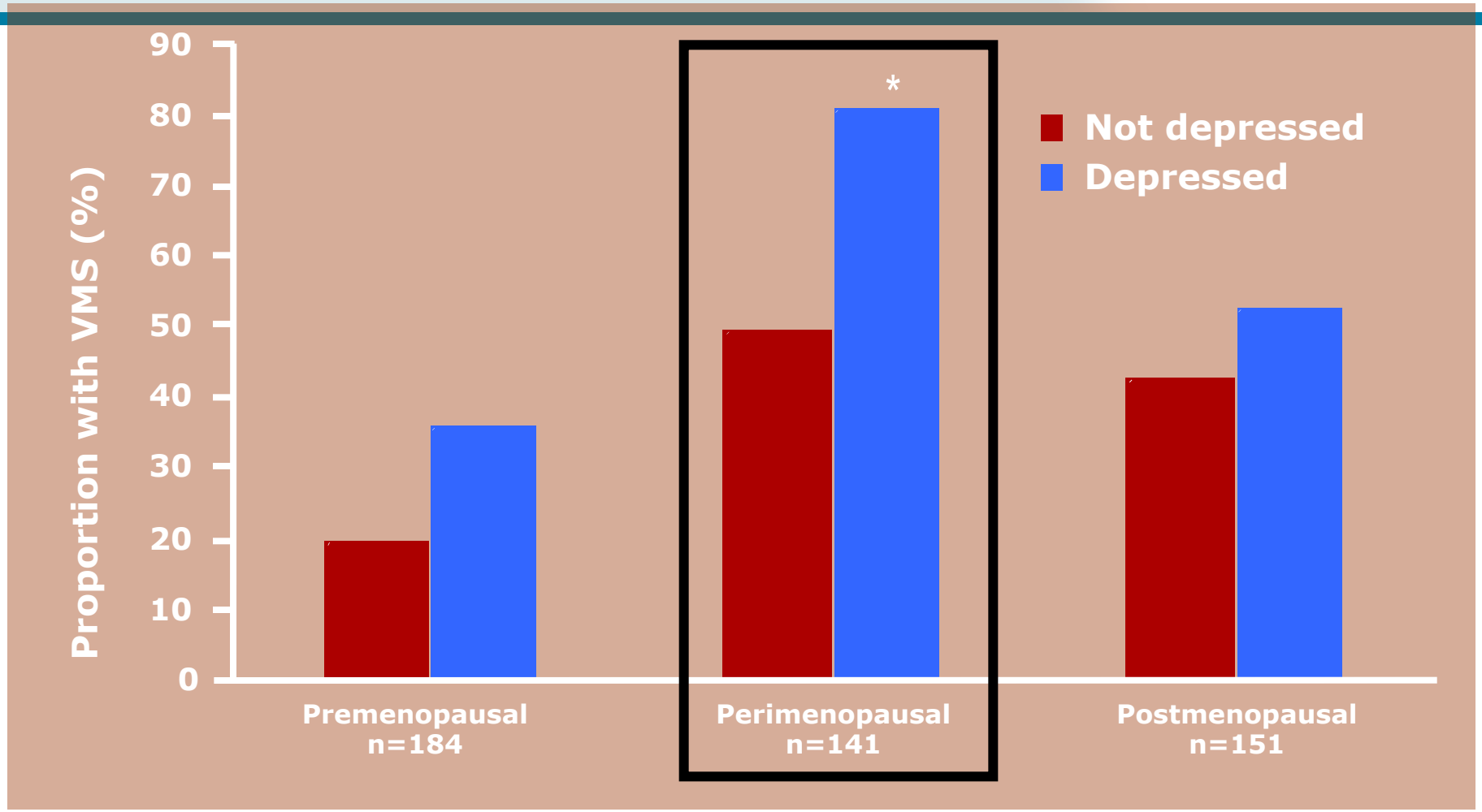


Estrogen has multiple effects on neurotransmitter systems and brain regions involved in MDD and menopausal symptoms (VMS)

During times of estrogen fluctuations/decline, loss of these effects might predispose some women to dysregulation of affected brain regions

Figure adapted from Charney DS. *Am J Psychiatry.* 2004;161:195–

Perimenopausal women with depression are more likely to have hot flashes than peri women without depression.

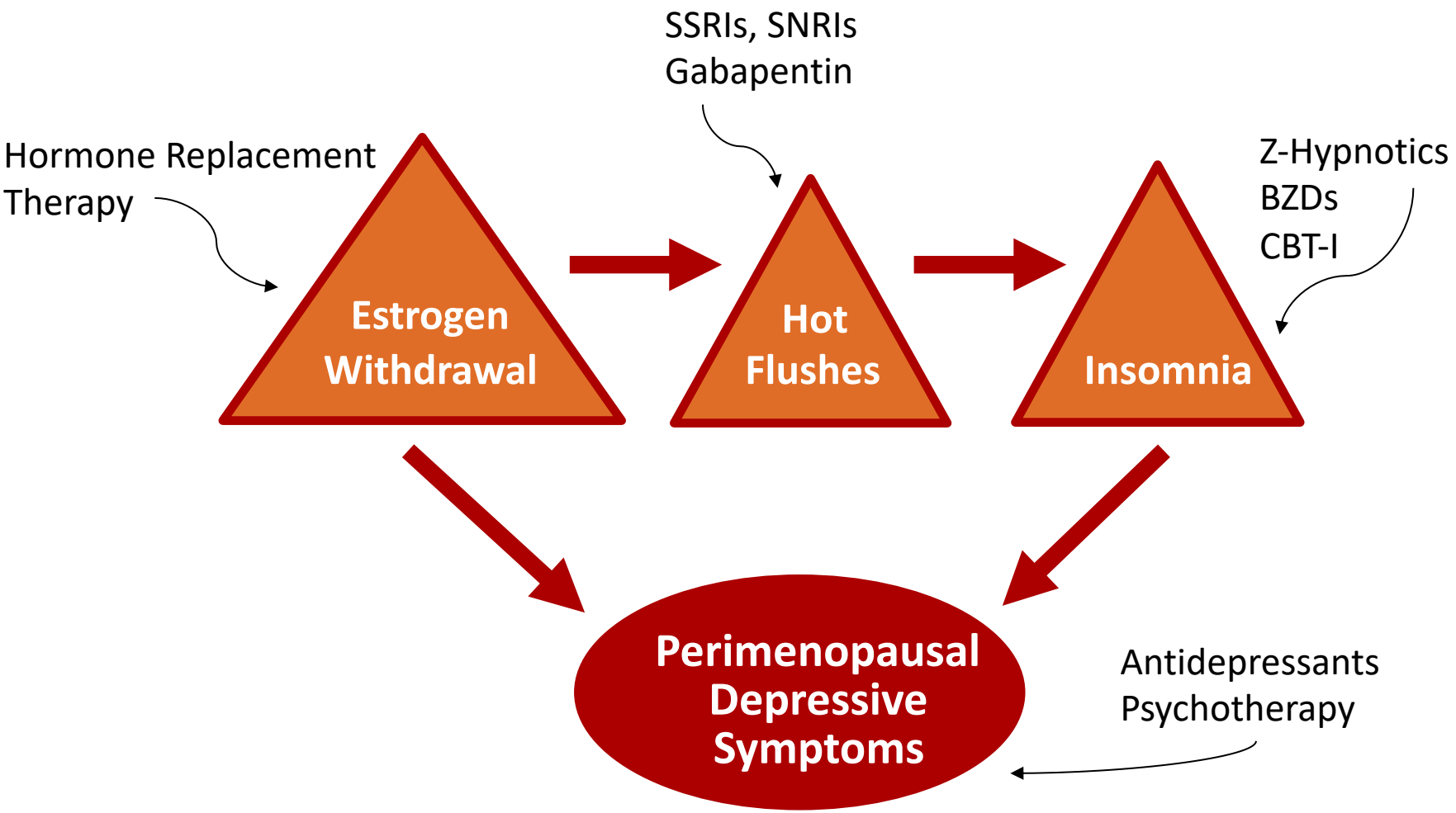


***P*=0.008 vs. nondepressed perimenopausal.**
Joffe H, et al. *Menopause.* 2002;9:392-398.

Treatment of Perimenopausal and Menopausal Women with Depression

Selecting the Appropriate Intervention

Multiple Targets for Intervention



Estrogen-Based Therapies for the Treatment of MDD in Perimenopausal Women

DEPRESSION AND ANXIETY 32:539–549 (2015)

Research Article

EFFICACY OF ESTRADIOL IN PERIMENOPAUSAL DEPRESSION: SO MUCH PROMISE AND SO FEW ANSWERS

David R. Rubinow, M.D.,[1]* Sarah Lanier Johnson, B.S.,[1] Peter J. Schmidt, M.D.,[2] Susan Girdler, Ph.D.,[1] and Bradley Gaynes, M.D. M.P.H.[1]

- 25 RCT on the effects of estrogen therapy on mood
- Only 5 included symptomatic (depressed) women
- Only 2 E2 RTCs for perimenopausal depression

Treatment of Perimenopausal: Hormonal Interventions

- RCTs with 17β-estradiol
  - Response in 80% of women on estradiol vs. 20% in placebo *(Schmidt 2000)*
  - Remission in 68% of women on estradiol vs. 20% with placebo *(Soares 2001)*
- Primarily in women with vasomotor symptoms
- Secondary to antidepressant effects or to improvements in hot flashes and sleep?
- Perimenopausal women: estrogen superior to placebo
- Little evidence to indicate that estrogen is effective for POST-menopausal depression
- Studies were carried out in women with unopposed estrogen
- No RCTs of combination estrogen plus progestogen for depression

[1] Schmidt, *Am J OBGYN* 2000; [2] Soares, *Arch Gen Psych* 2001;

JAMA
The Journal of the American Medical Association

Volume 288(3) 17 July 2002 p 321–333

Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results From the Women's Health Initiative Randomized Controlled Trial

[Original Contribution: *JAMA*-EXPRESS]

Writing Group for the Women's Health Initiative Investigators

Volume 289(20) 28 May 2003 p 2651–2662

Estrogen Plus Progestin and the Incidence of Dementia and Mild Cognitive Impairment in Postmenopausal Women: The Women's Health Initiative Memory Study: A Randomized Controlled Trial

[Original Contribution: *JAMA*-EXPRESS]

Shumaker, Sally A. PhD; Legault, Claudine PhD; Rapp, Stephen R. PhD; Thal, Leon MD; Wallace, Robert B. MD; Ockene, Judith K. PhD, MEd; Hendrix, Susan L. DO; Jones, Beverly N. III MD; Assaf, Annlouise R. PhD; Jackson, Rebecca D. MD; Kotchen, Jane Morley MD, MPH; Wassertheil-Smoller, Sylvia PhD; Wactawski-Wende, Jean PhD; WHIMS Investigators

Hormone Replacement Therapy Study Halted

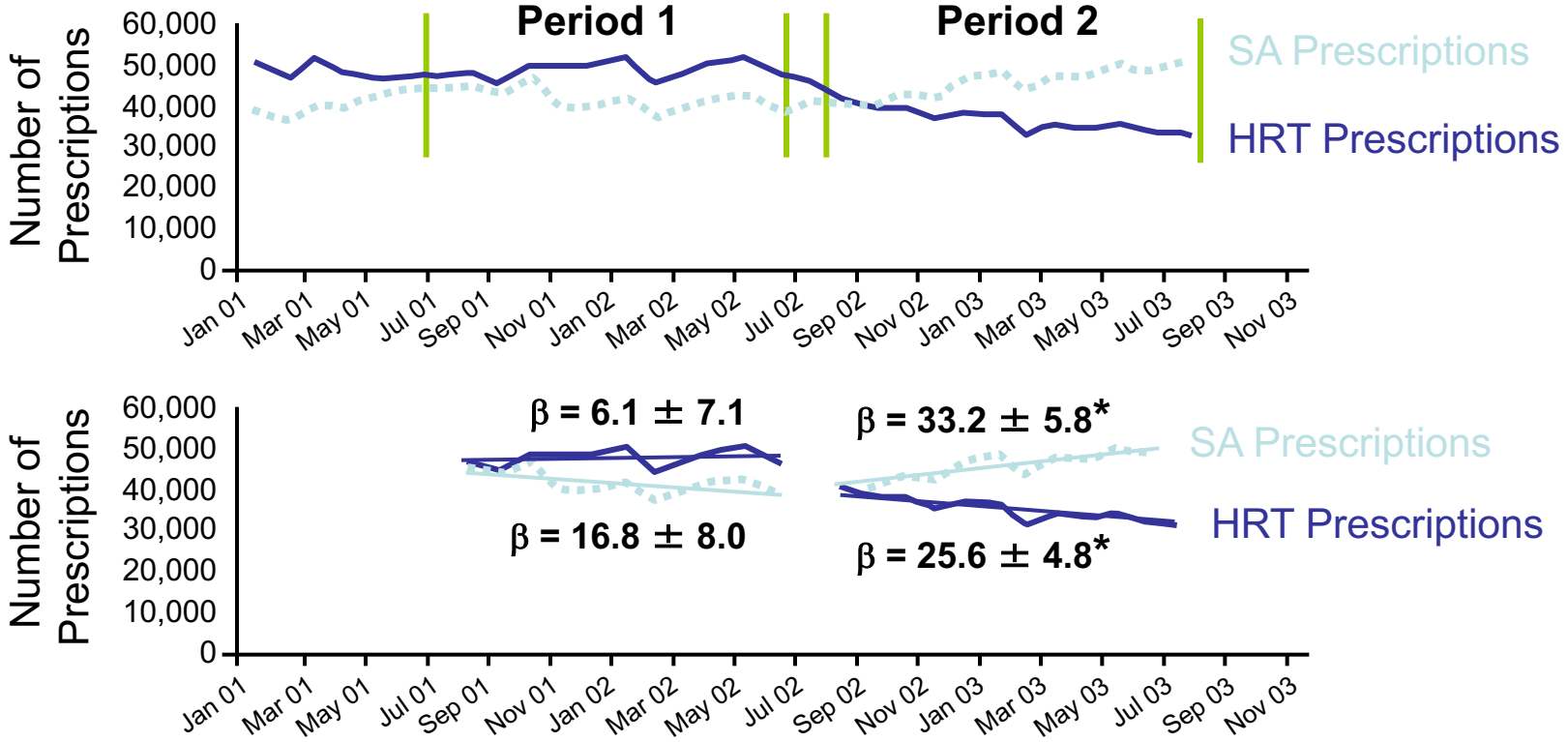
Increased risk of breast cancer a factor, government says

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.

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, nefazadone, and trazodone.**

HRT = hormone replacement therapy; WHI = Women's Health Initiative; SA = serotoninergic antidepressant.

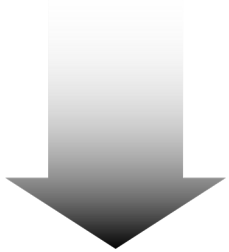
McIntyre RS, et al. *CMAJ.* 2005;172:57-59.

Impact of WHI on Treatment of Women During Menopause Transition

DecreasedHormone therapy use

+

Lowest dose, shortest duration



More symptomatic women

WHI = Women's Health Initiative.

Can estrogen replacement therapy prevent perimenopausal depression?

- 172 euthymic perimenopausal and early postmenopausal women
- Randomly assigned to receive either transdermal estradiol (0.1 mg/d) plus intermittent oral micronized progesterone or placebo
- After 12 months, women receiving active HRT were less likely to develop depressive symptoms compared with women receiving placebo (32.3% vs. 17.3%)
- Greater benefits for women with stressful life events in the preceding 6 months
- Trend toward increased benefit in peri- vs. post-menopausal women

Treatment of Perimenopausal MDD: Antidepressants

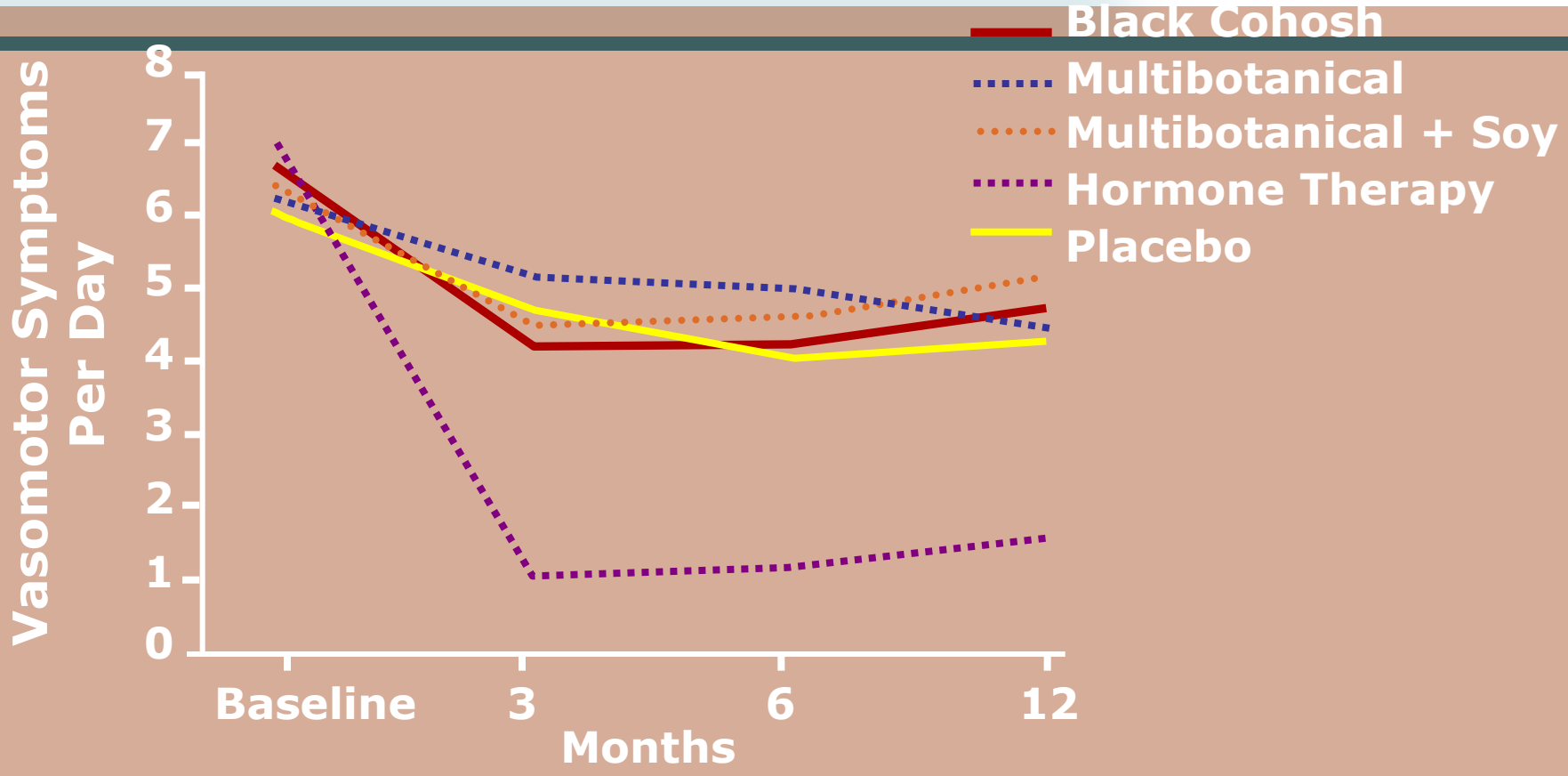
- Two large RCTs support the use of desvenlafaxine, superior to placebo
- Positive results in open trials of SSRIs and SNRIs: citalopram, escitalopram, venlafaxine, vortioxetine, mirtazapine
- Dosage range similar to non-menopausal MDD
- Beneficial effects on sleep, VMS, anxiety, pain
- Effective for peri- and postmenopausal women

Joffe, *J Clin Psych* 2007; Joffe, *J Women's Health Gend Based Med* 2001; Soares, *J Clin Psych* 2003; Dias, *Menopause* 2006; Kornstein, *J Clin Psych* 2010

Treatment of Menopausal Symptoms

- Hormone replacement therapy – gold standard
  - For severe symptoms in healthy younger women
  - Limit treatment to 5 years
- SSRIs, SNRIs improve vasomotor symptoms, depression
- Gabapentin improves VMS and sleep, pain

Treatment of Vasomotor Symptoms With Black Cohosh, Multibotanicals, Soy, Hormone Therapy or Placebo

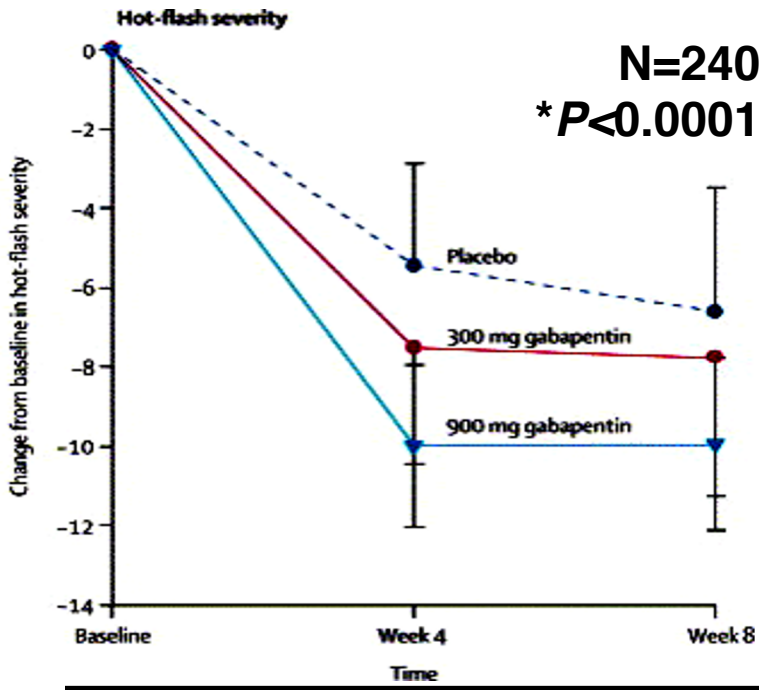


- Black cohosh, a multibotanical herbal product, and soy intake did not appear to significantly reduce the frequency or severity of menopause-related hot flushes or night sweats

Newton KM, et al. *Ann Intern Med.* 2006;145:869-879.

Treatment of hot flashes with gabapentin

Low-dose (900mg/d) effective



Hot flash score reduction

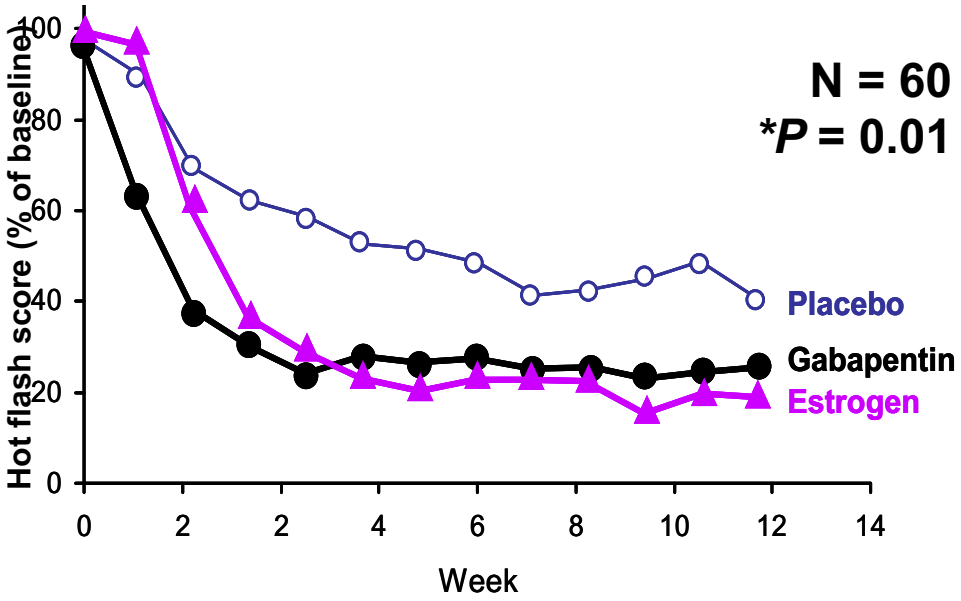
Gabapentin 900-mg/day: 46%*

Gabapentin 300-mg/day: 31%

Placebo: 15%

Pandya KJ et al, *Lancet* 2005

Moderate-dose (2400mg/d) as effective as estrogen



Hot flash score reduction

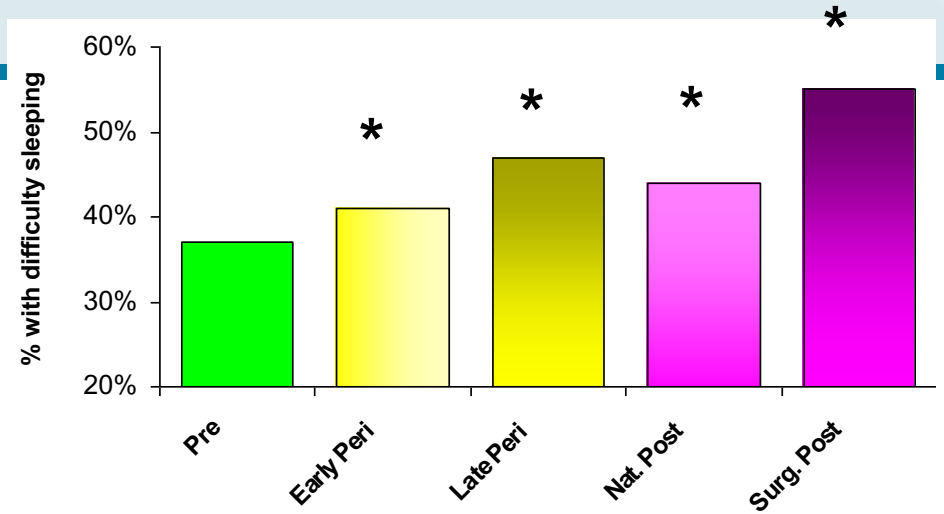
Gabapentin 2400-mg/day: 71%*

Estrogen (CEE 0.625-mg/day): 72%

Placebo: 54%

Reddy SY et al. *OBGYN* 2006

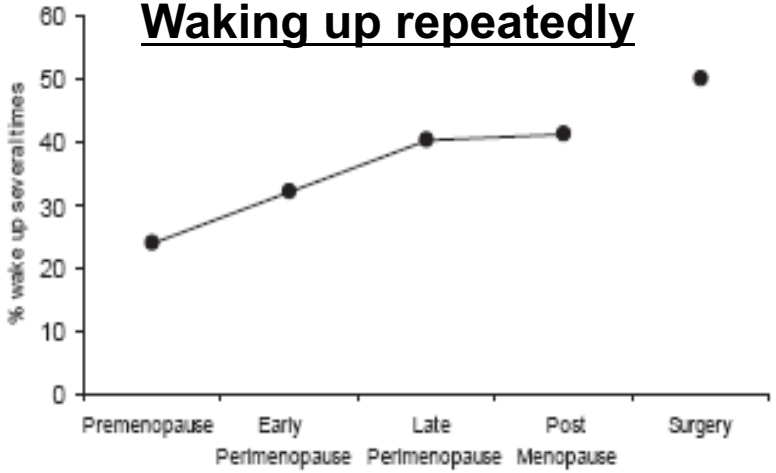
Sleep Disturbance in Peri/Postmenopausal Women



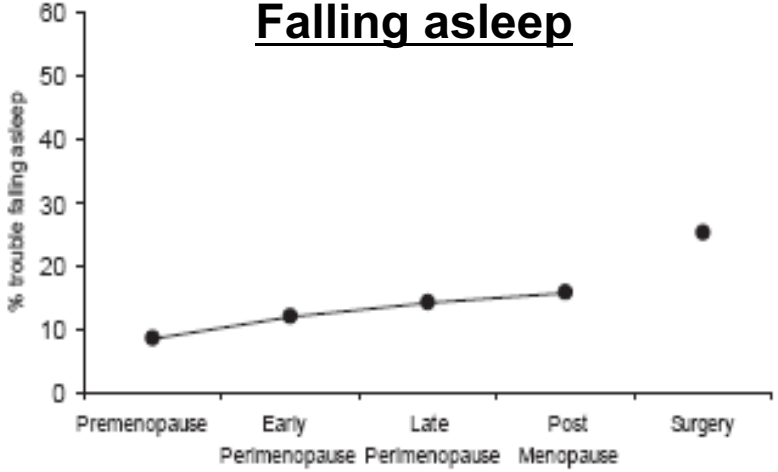
* p<0.005 vs. premenopause

Sleep maintenance is most common symptom[2]

Waking up repeatedly



Falling asleep



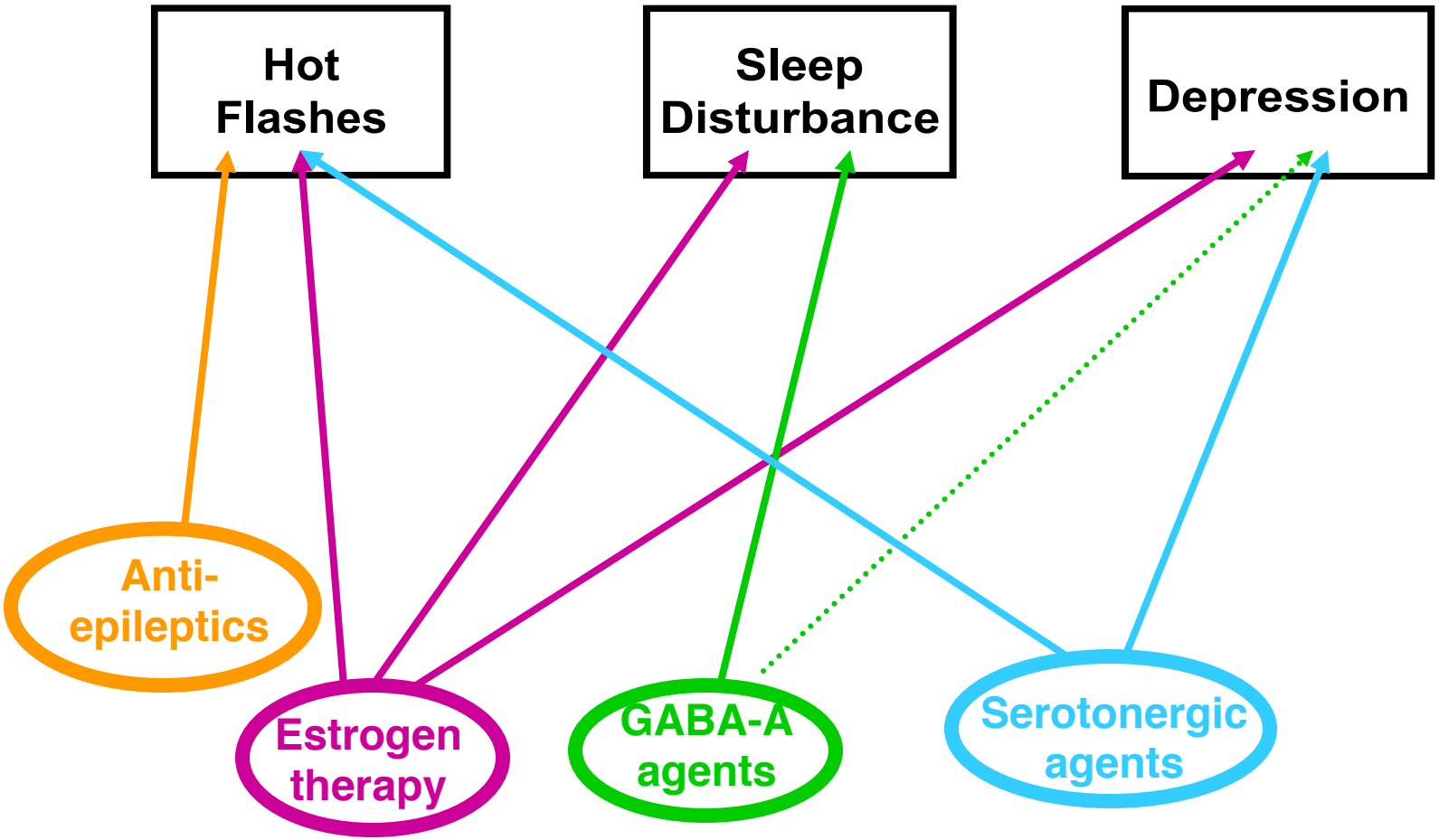
[1] Kravitz, *Menopause* 2003; data for Caucasians

[2] Kravitz, *Sleep* 2008

Treatment of Sleep Disturbance in Perimenopausal Women

- Non-benzodiazepine sedative hypnotics
  - Ezopiclone improved sleep, decreased VMS
- SSRIs – Not sedating but may improve anxiety, VMS
- Gabapentin – Mildly Sedating, improves anxiety, RLS
- CBT-I – Effective and non-menopausal patients, CBT may also be used to treat VMS

Treatment of Menopause-Associated Symptoms



Novel Strategies for the Treatment of Menopausal Symptoms

- Stellate ganglion blockade – VMS
- Acupuncture- VMS
- Neurokinin 3 Receptor Antagonists – VMS
- Amodafenil – fatigue, cognitive function
- New Study: Pregnenolone (neurosteroid) for menopausal depression

Conclusions

1. Etiology of menopause-associated depression is not precisely known

2. Co-occurrence of hot flashes, sleep disturbance, and depression suggests
   - Shared mechanisms
   - Cascade of effects

Current State of Treatment Options

- Antidepressants remain the treatment of choice for depression across the female life cycle.
  - Limited by side effect profile
  - Not effective or fully effective for all patients
- Hormonal strategies can be helpful for the treatment of menopause-related depressive symptoms
  - Either alone or In combination with anti-depressant
  - Risks associated with long-term treatment
- Limited evidence for integrative/ complementary and alternative medicine treatment options despite popularity

Treatment Guidelines

- Antidepressants first line treatment for MDD
  - Past response guides selection
  - Consideration of side effects (sexual side effects with SSRIs, paroxetine, weight gain with mirtazapine)
- Menopausal symptoms may affect response
  - Assess for VMS – gabapentin
  - Assess sleep – gabapentin, Z-hypnotics, BZDs, CBT-I
- Consider adjunctive psychotherapy

Unmet Needs

1. Available treatments are limited to serotonergic antidepressants and traditional hormone replacement therapy
2. No treatments target all aspects of symptom domains- mood, VMS, sleep, anxiety
3. Many patients prefer non-SSRI/SNRI and non-estrogen related treatments
4. Available treatments are not rapidly acting
5. No treatments have received a specific FDA indication for perimenopause-related MDD