MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

PMDD and Depression During the Menopausal Transition: New Insights

Ruta Nonacs, MD PhD

Editor-in-Chief, womensmentalhealth.org

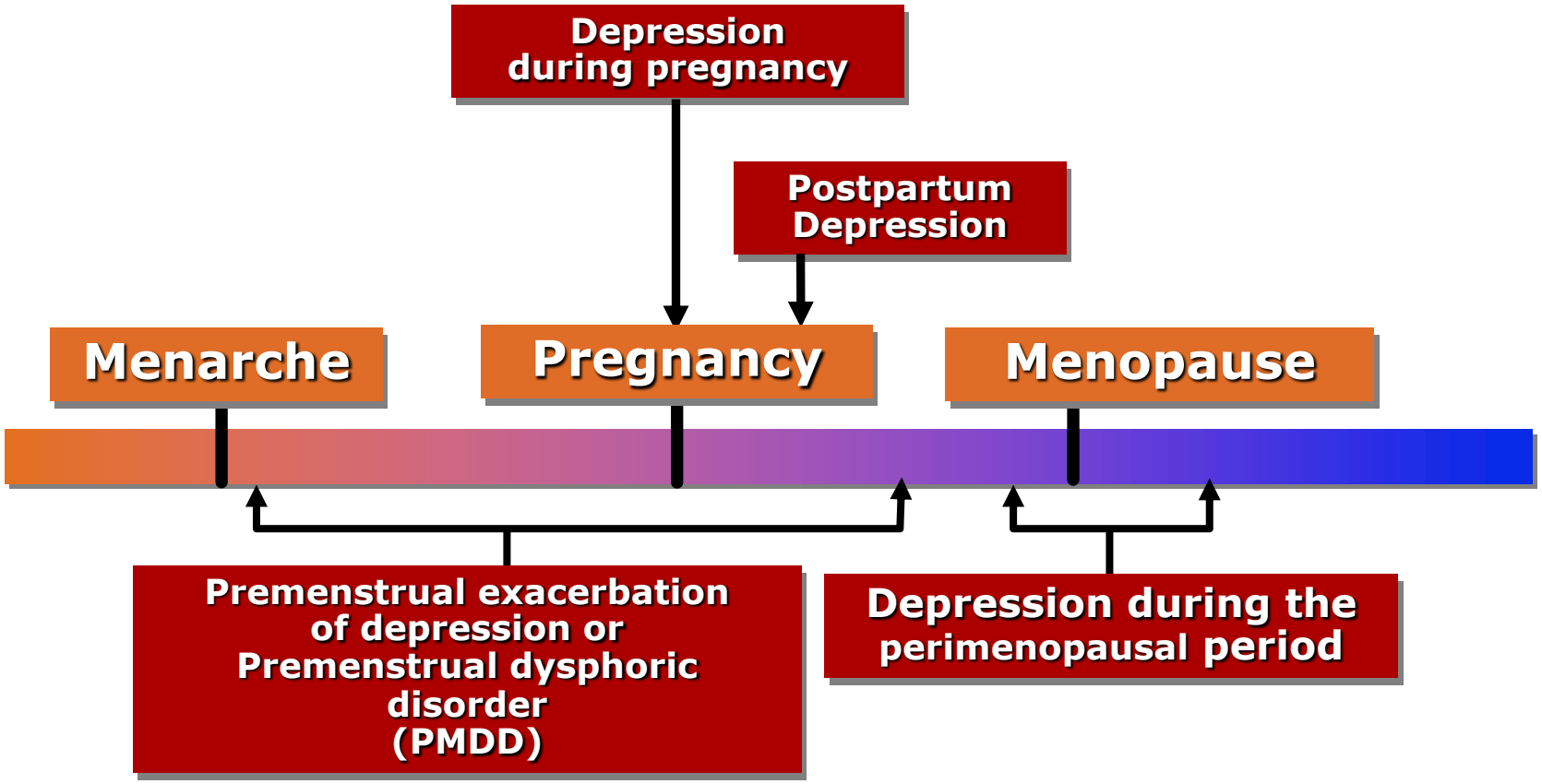
The Ammon-Pinizzotto Center for Women's Mental Health, Massachusetts General Hospital

Instructor in Psychiatry, Harvard Medical School

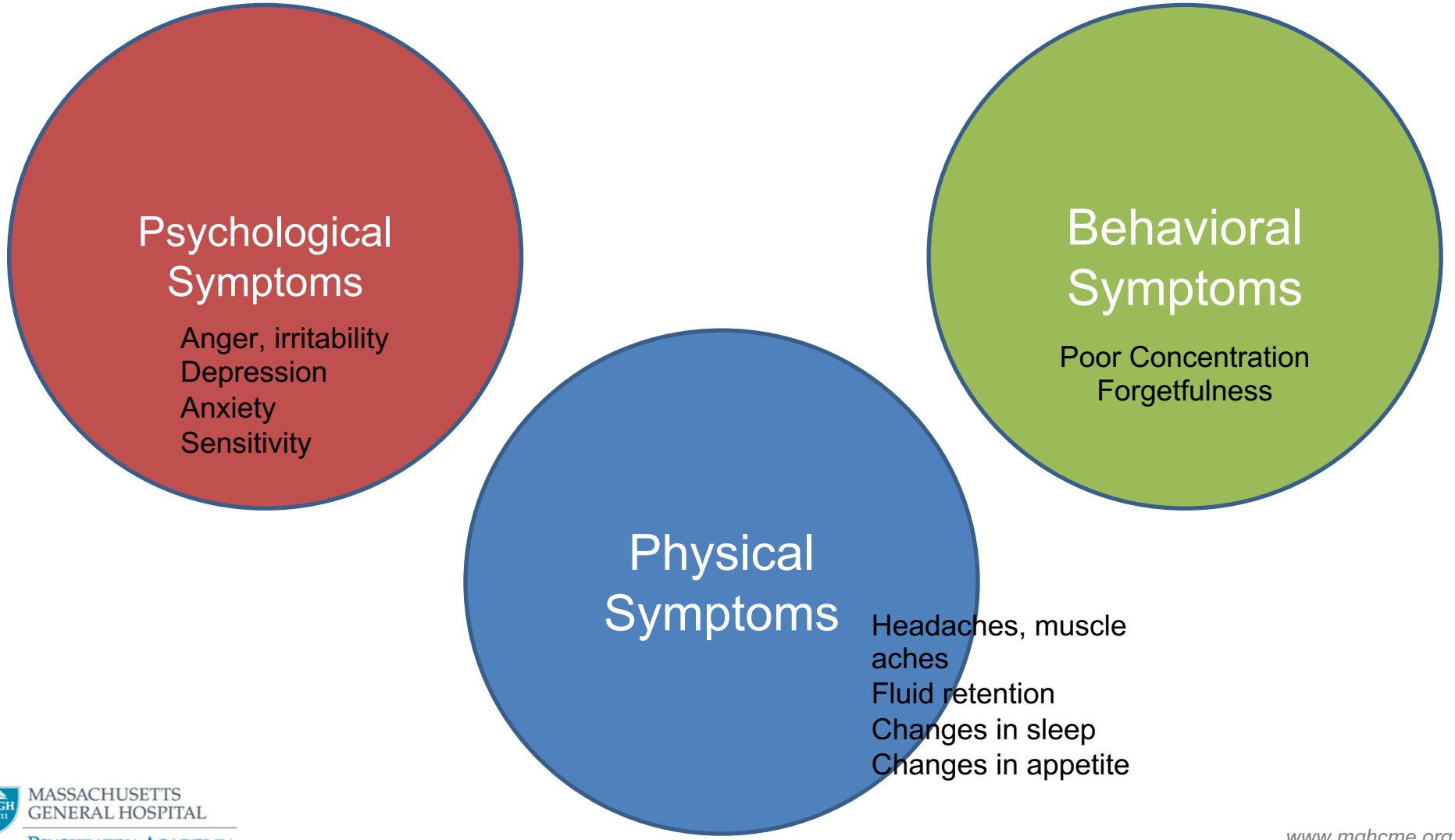
Disclosures

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

Depression Across the Female Reproductive Cycle



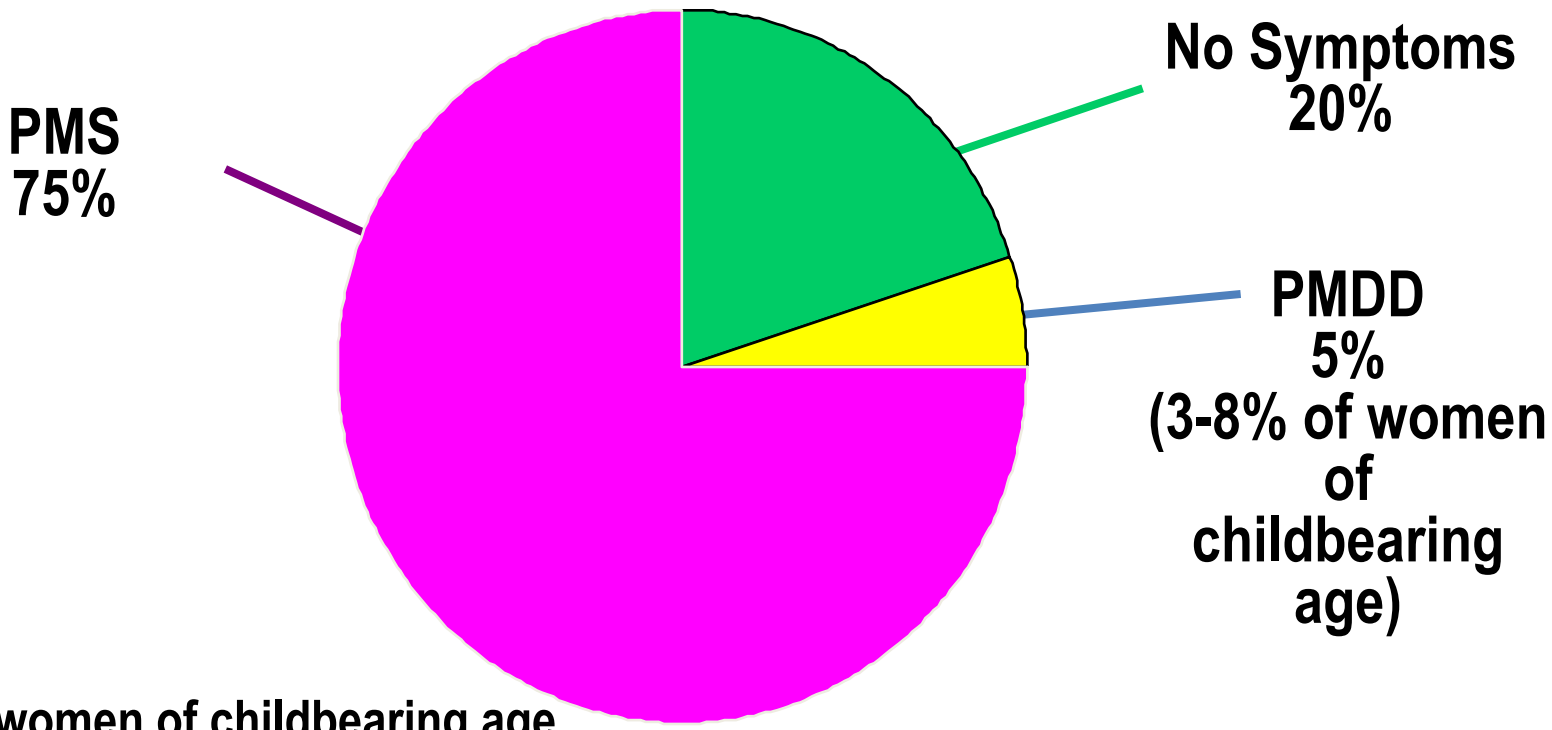
Premenstrual Symptoms



Premenstrual Syndrome (PMS)

- Pattern of physical, emotional and behavioral symptoms 1-2 weeks before menstruation
- Remit with the onset of menses
- 30-80% of reproductive age women
- Minimal interference with functioning
- More severe symptoms in 3-8% of women

Prevalence of Premenstrual Conditions



100%=all women of childbearing age.

Haskett RF. *Prog Neuropsychopharmacol Biol Psychiatry.* 1987;11(2-3):129-135.
Johnson SR, et al. *J Reprod Med.* 1988;33(4):340-346.
Rivera-Tovar AD, Frank E. *Am J Psychiatry.* 1990;147(12):1634-1636.
Ramcharan S, et al. *J Clin Epidemiol.* 1992;45(4):377-392.

PMDD - DSM-V 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

Timing: 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.

DSM-V Criteria

- Criterion B: Symptoms must be severe enough to interfere significantly with social, occupational, sexual, or scholastic functioning.
- Criterion C: is 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: 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.

PMS/PMDD Longitudinal Course

- First treatment in late 20s/early 30s
- Symptoms peak around 30-39 years old[1]
- Physical/mood symptoms stable from cycle to cycle[2]
- Diagnosis appears stable over time[3]
- Chronic course; symptoms may worsen over time [with age[4], after pregnancy[5]]
- Remission during pregnancy

1Johnson. *Clin Obstet Gynecol.* 1987;30:369.
2Block. *Am J Psychiat.* 1997;154:1741. 3Roca et al. *J Clin Psychiatry.* 1999;60:763.
4Ramcharan. *J Clin Epidemiol.* 1992;45:377. 5Campbell. *J Reprod Med.* 1997;42:637.

Risk Factors for PMDD and PMS

- Family history of PMS and PMDD[1,2]
- History of postpartum depression[3]
- Major depression past[3,4] or future[5]
- Mood changes induced by oral contraceptives

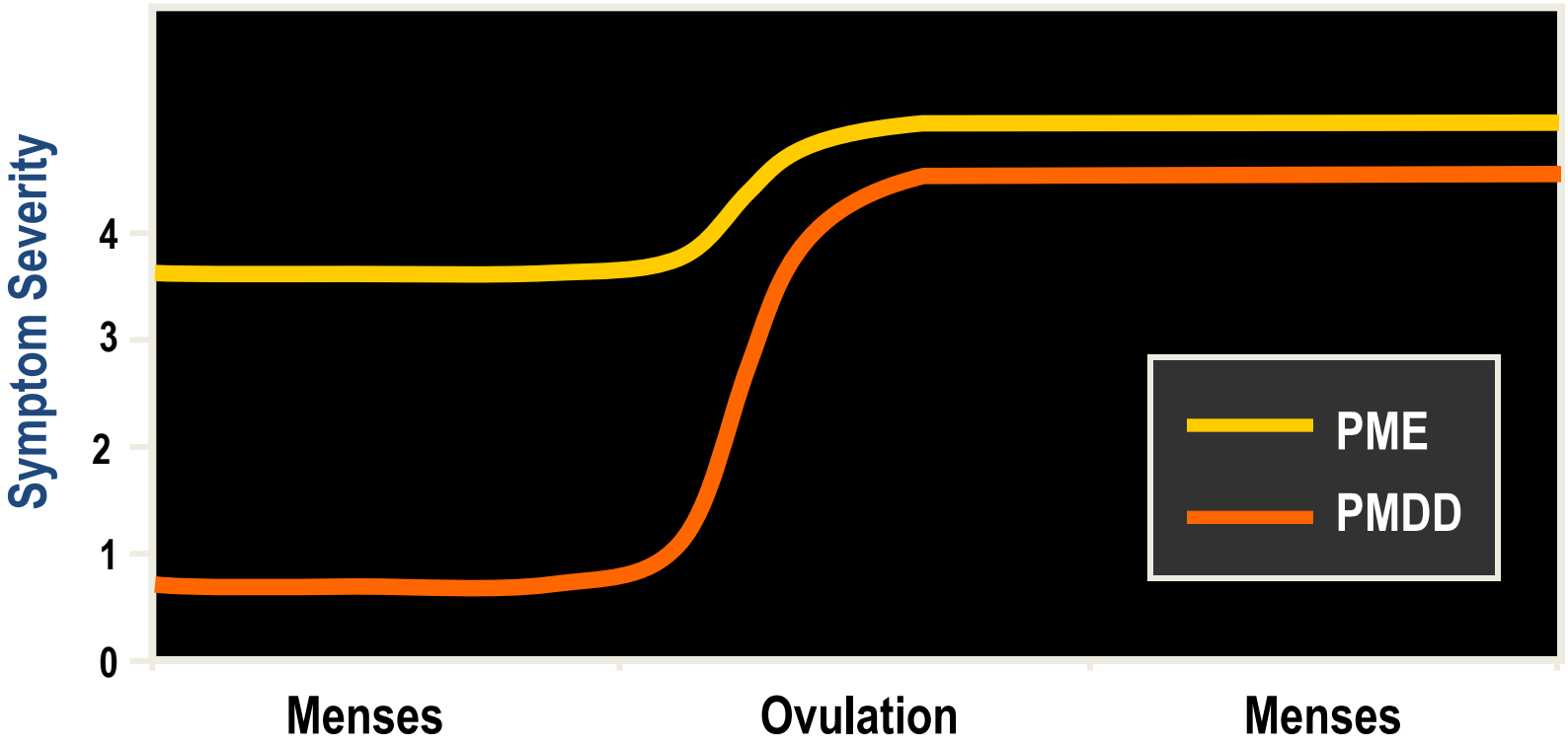
1. van den Akker OB, et al. *Acta Genet Med Gemellol (Roma).* 1987;36(4):541-548.
2. Kendler KS, et al. *Psychol Med.* 1992;22(1):85-100.
3. Warner P, et al. *J Affect Disord.* 1991;23(1):9-23.
4. Bancroft J, et al. *Psychosom Med.* 1994;56(3):225-231.
5. Graze KK, et al. *Acta Psychiatr Scand.* 1990;81(2):201-205.

Premenstrual Exacerbation (PME)

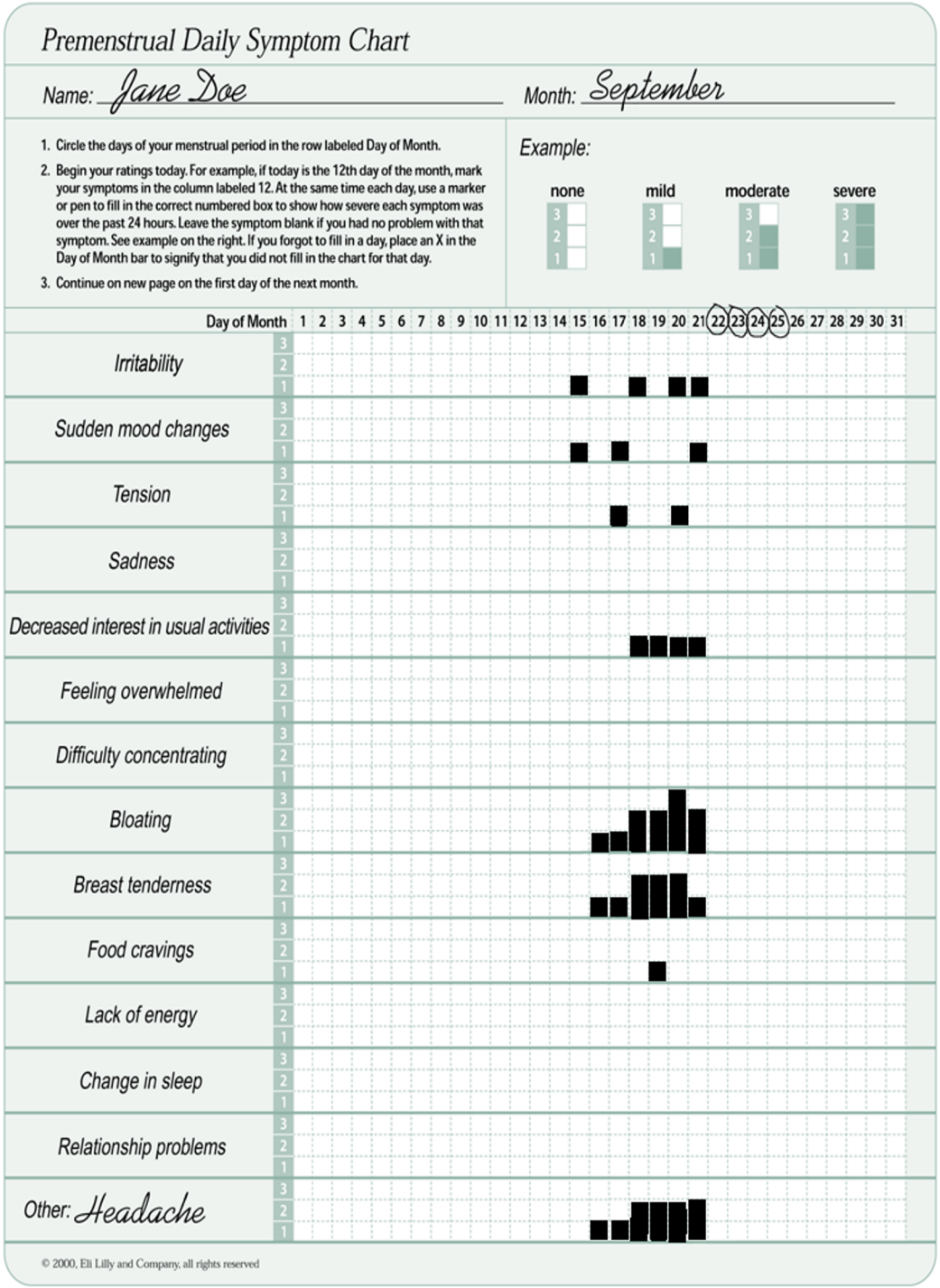
- Significant symptom overlap between MDD and PMDD
- Mood disorders can worsen premenstrually
- PMDD vs. PME
- 40% of women screened for PMDD have an underlying mood disorder with PME
- Charting to determine timing of symptoms

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

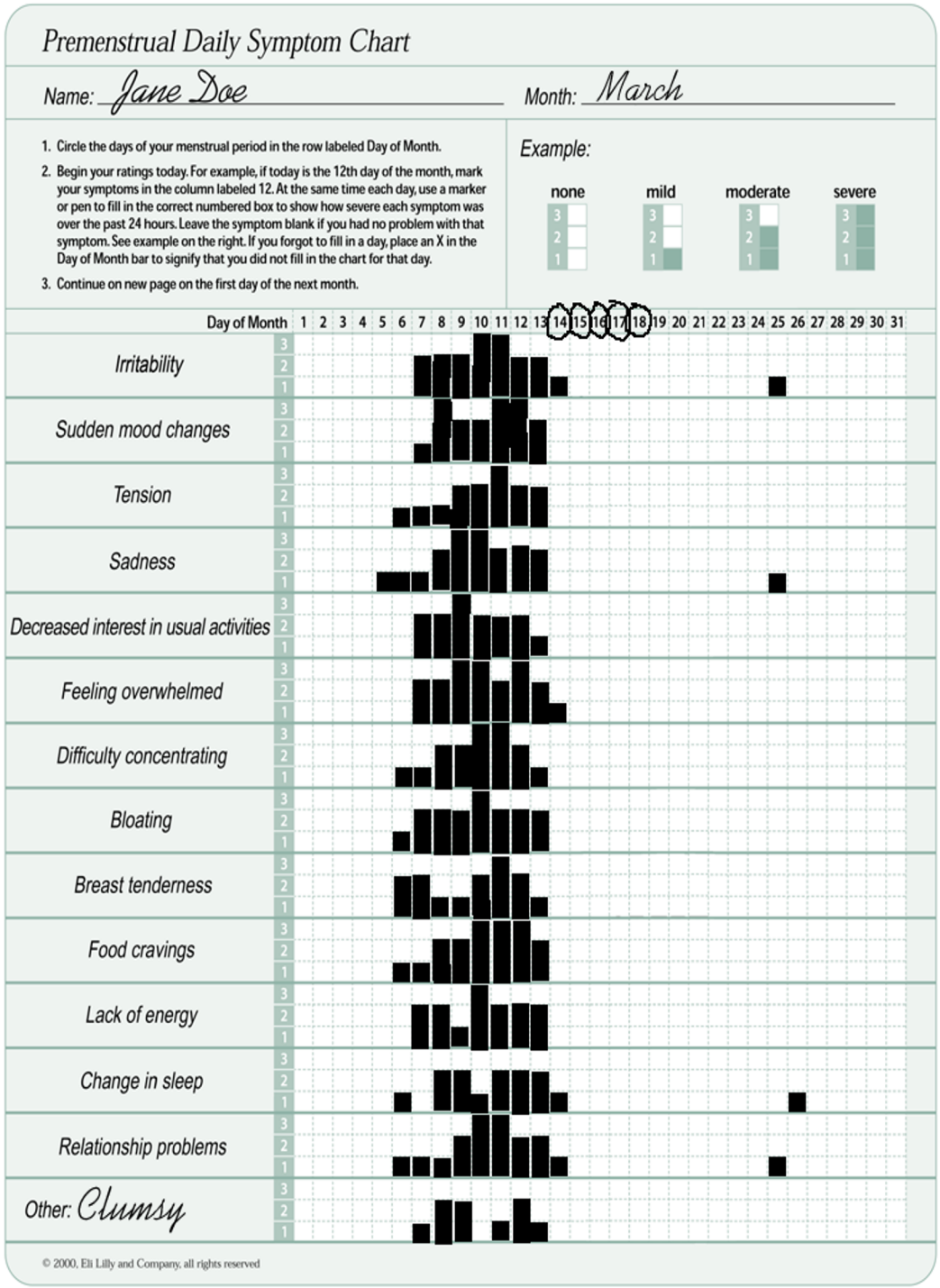
PMDD vs. Premenstrual Exacerbation (PME)



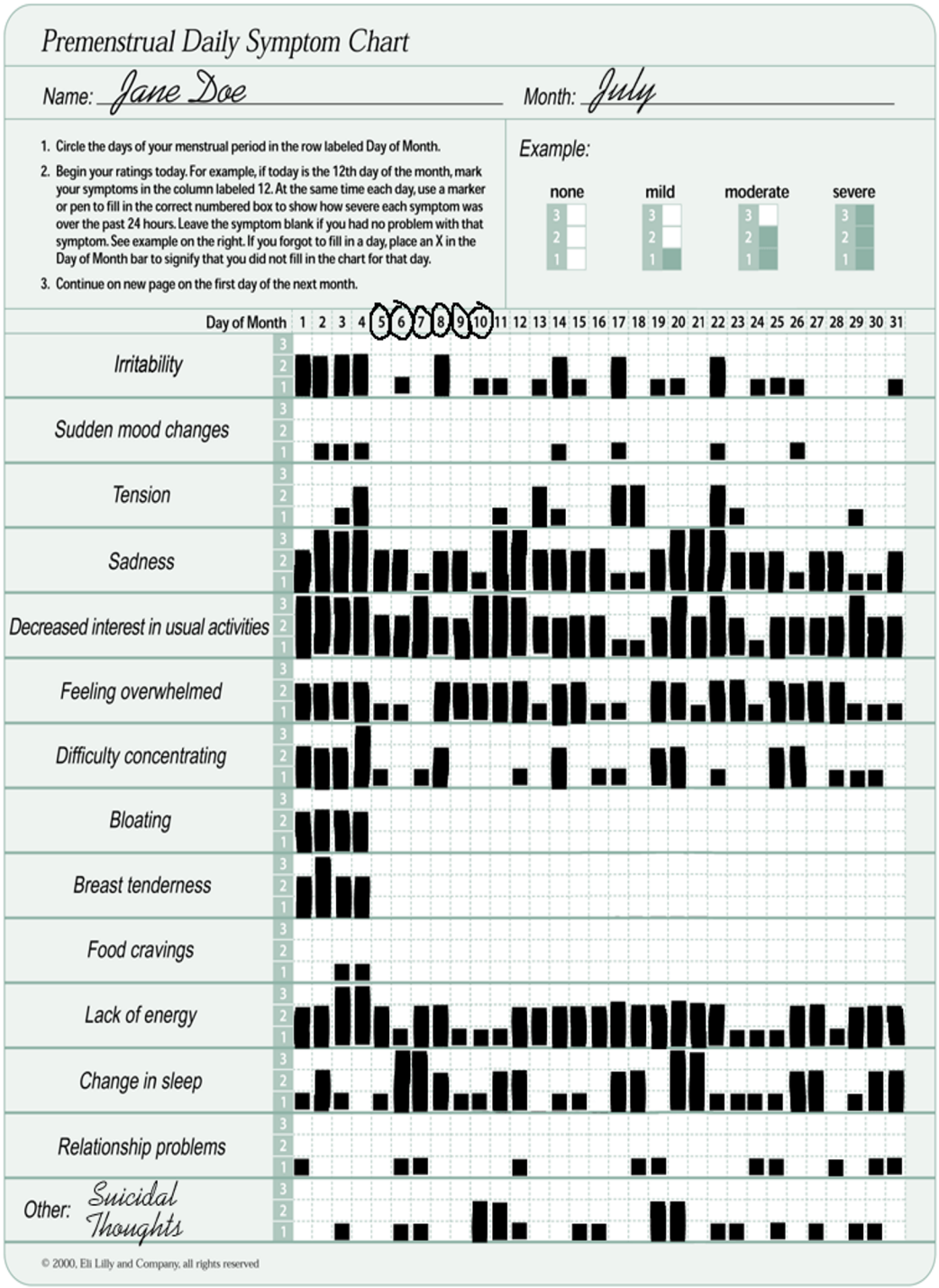
Prospective Rating for Patient With PMS



Prospective Rating for Patient With PMDD

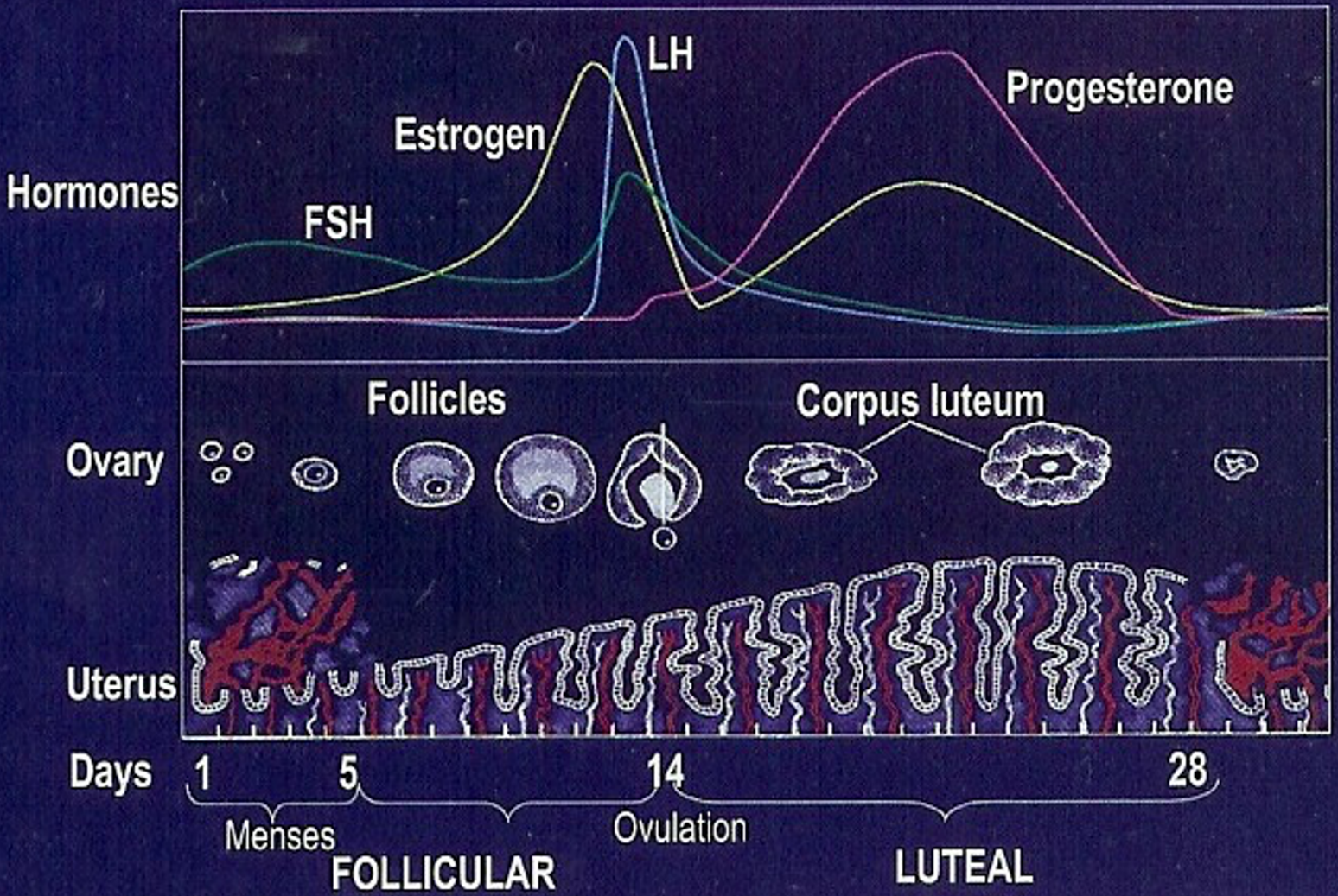


Prospective Rating for Patient With Depression



Why do some women experience PMDD?

The Menstrual Cycle



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

Pathophysiology of PMDD

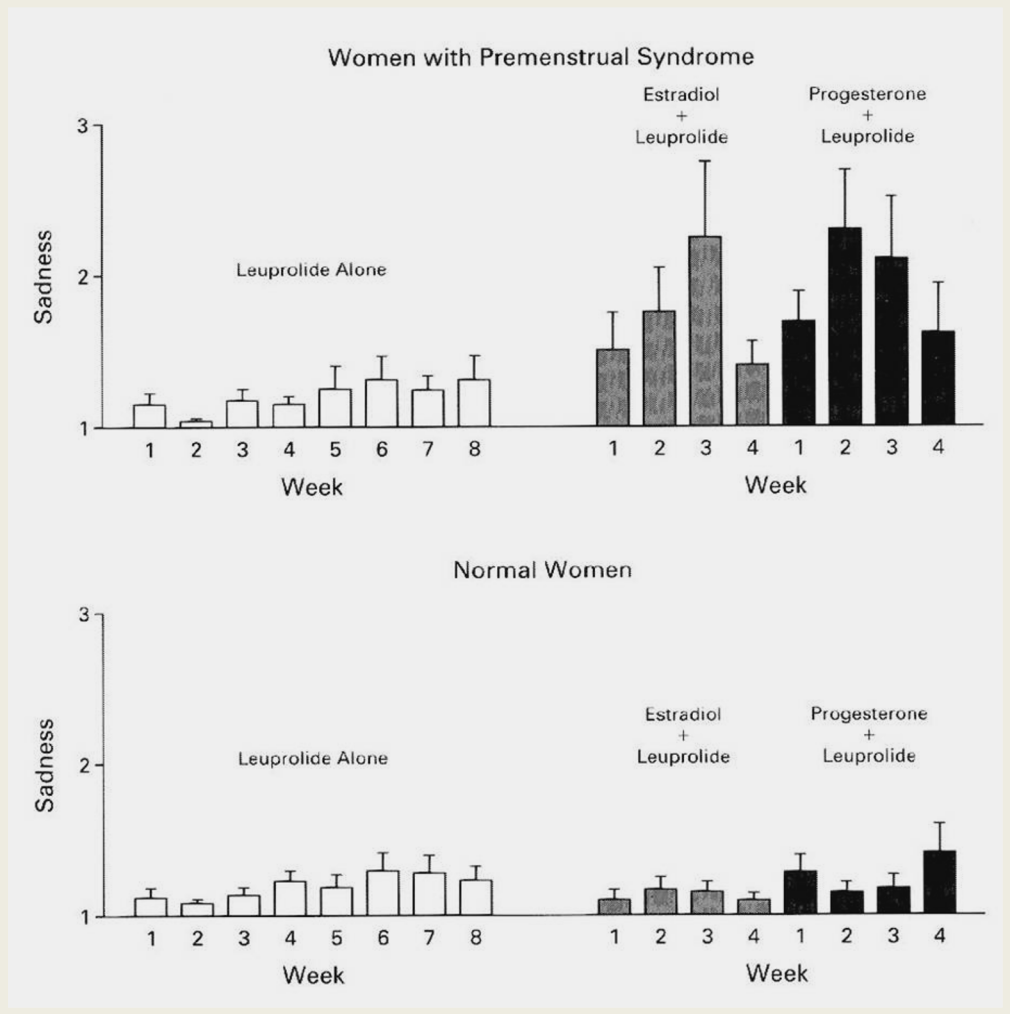
- No clear evidence of “hormonal dysregulation”
- Hormone levels similar in women with and without PMDD

- PMS/PMDD may represent an abnormal response to normal fluctuations of gonadal steroids

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

Hormonal Basis of PMDD

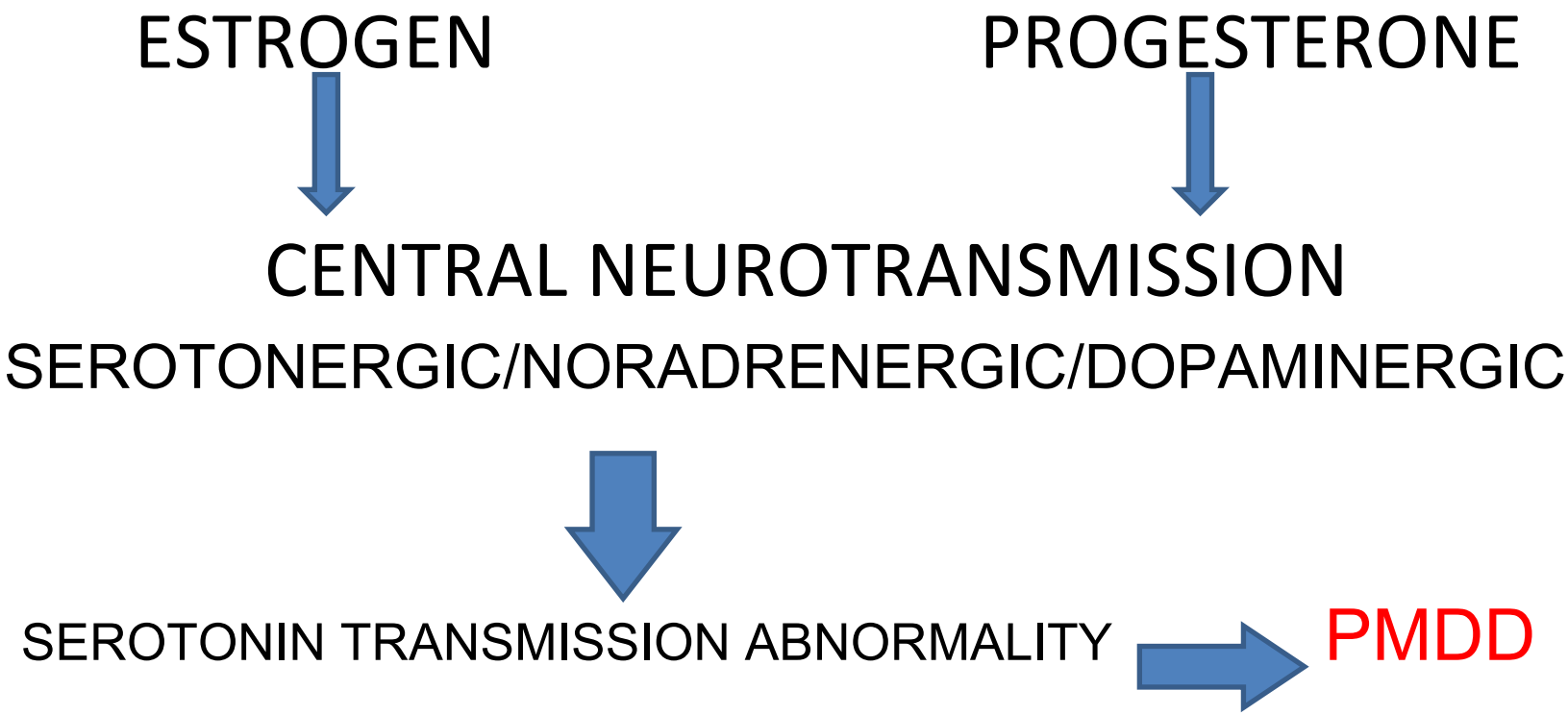
- Suppression of cycles with GnRH agonist leuprolide
- Alleviates PMDD
- PMDD re-occurs with add-back therapy
- Differential sensitivity to normal changes in estrogen and progesterone



GnRH = gonadotropin-releasing hormone.

Schmidt et al. *N Engl J Med.* 1998;338:209.

Pathophysiology of PMDD



Pathophysiology of PMDD: GABA

- Allopregnanolone – metabolite of progesterone
- Positive modulator of $GABA_A$ receptor
- Treatment with allopregnanolone antagonist during the luteal phase reduces PMDD scores
- Analogies of allopregnanolone for PMDD

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

Non-Pharmacologic Treatment

- Mood Charting
- Lifestyle Modification – aerobic exercise, avoidance of alcohol
  - Calcium (1200 mg daily)
  - Magnesium (200-460 mg daily)
- Psychotherapy - CBT

Andrzej, M & Diana, J. *Maturitas*. 2006;55:S47-S54.
Thys-Jacobs S et al. *Am J Obstet Gynecol.* 1998;179: 444–52.

Pharmacologic Treatment

- SSRIs are first line treatment
  - Low dose
  - Rapid response
  - Fluoxetine, sertraline, and controlled release paroxetine are FDA approved

- Other antidepressants with serotonergic activity are also effective:
  - Venlafaxine
  - Duloxetine
  - 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.

Antidepressant Dosing

- Continuous
  - Steady dose throughout the month
  - For PME, PMDD with recurrent MDD
- Intermittent
  - Luteal phase
- Luteal phase increase
  - Continuous with luteal phase “bump up”

Oral Contraceptives (OC) and PMS/PMDD

- Most commonly prescribed treatment for PMDD
- Ddouble-blind, randomized, placebo-controlled trials supports use of some OCs for treatment of PMDD
- OCs containing drosperinone (Yaz, Yazmin) may be more effective
- Avoid triphasic preparations
- Continuous dosing (skip placebo pills)

Duration of Treatment in PMDD

- Most women relapse when they stop treatment–as early as 1 to 2 cycles[1-5]
- Well tolerated, efficacious when used longer than 6 months in open-label studies[1-3]
- Maintenance of treatment may be necessary

1. De la Gandara Martin JJ. *Actas Luso Esp Neurol Psiquiatr Cienc Afines.* 1997;25(4):235-242.
2. Pearlstein TB, Stone AB. *J Clin Psychiatry.* 1994;55(8):332-335.
3. Elks ML. *South Med J.* 1993;86(5):503-507.
4. Yonkers KA. *Psychopharmacol Bull.* 1998;34(3):261-266.
5. Freeman EW, et al. *Am J Psychiatry.* 1992;149(4):531-533.

Gonadotropin-Releasing Hormone Agonists for PMDD

- Subcutaneous leuprolide, intranasal buserelin
- Down-regulate gonadotrophin receptors in pituitary to create a hypogonadotropic state
- Induce a reversible medical menopause
- Treatment usually restricted to six months
- Side effects: hot flashes, vaginal dryness, osteoporosis
- Estrogen add-back may trigger PMS/PMDD symptoms, better after 2-3 cycles

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

Nutritional Supplements

- Calcium (1200 mg daily)
- Magnesium (200-460 mg daily)
- Vitamin B6 (50-100 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.

Herbal Remedies

- Vitex Agnus Castus (Chasteberry)
  - Association of Reproductive Health Professionals includes *VAC* as a treatment option
  - Potential benefits
  - Unclear mechanism: D2 receptor, estrogen receptor
- St. John's Wort
  - Physical symptoms > emotional symptoms
  - 13-15% reduction in the level of OCS

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.

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 treatments that can be beneficial.
- Treatments can be non-pharmacologic or pharmacologic.
  - Hormonal or psychotropic

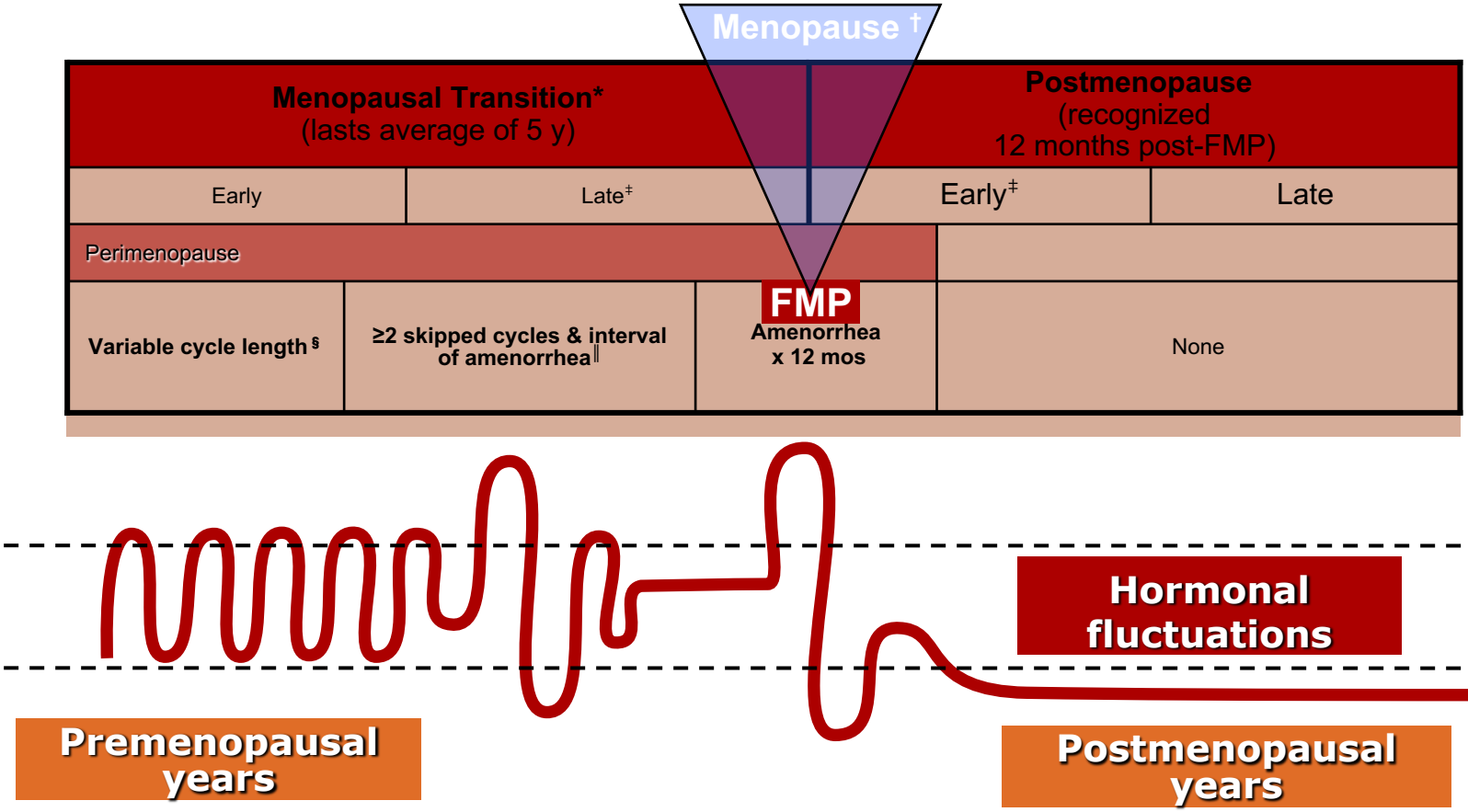
What is Menopause?

- 12 months without menses
- Menopausal transition– endocrinologic, somatic, psychological changes
- Average age is 51 (lower for smokers)
- Severity, frequency and variety of symptoms vary widely
- Perimenopause = passage from reproductive to non-reproductive life

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

The Menopausal Transition and Depression

Ruta Nonacs, MD, PhD
Ammon-Pinizzotto Center for Women's Mental Health
Massachusetts General Hospital, Harvard Medical School



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

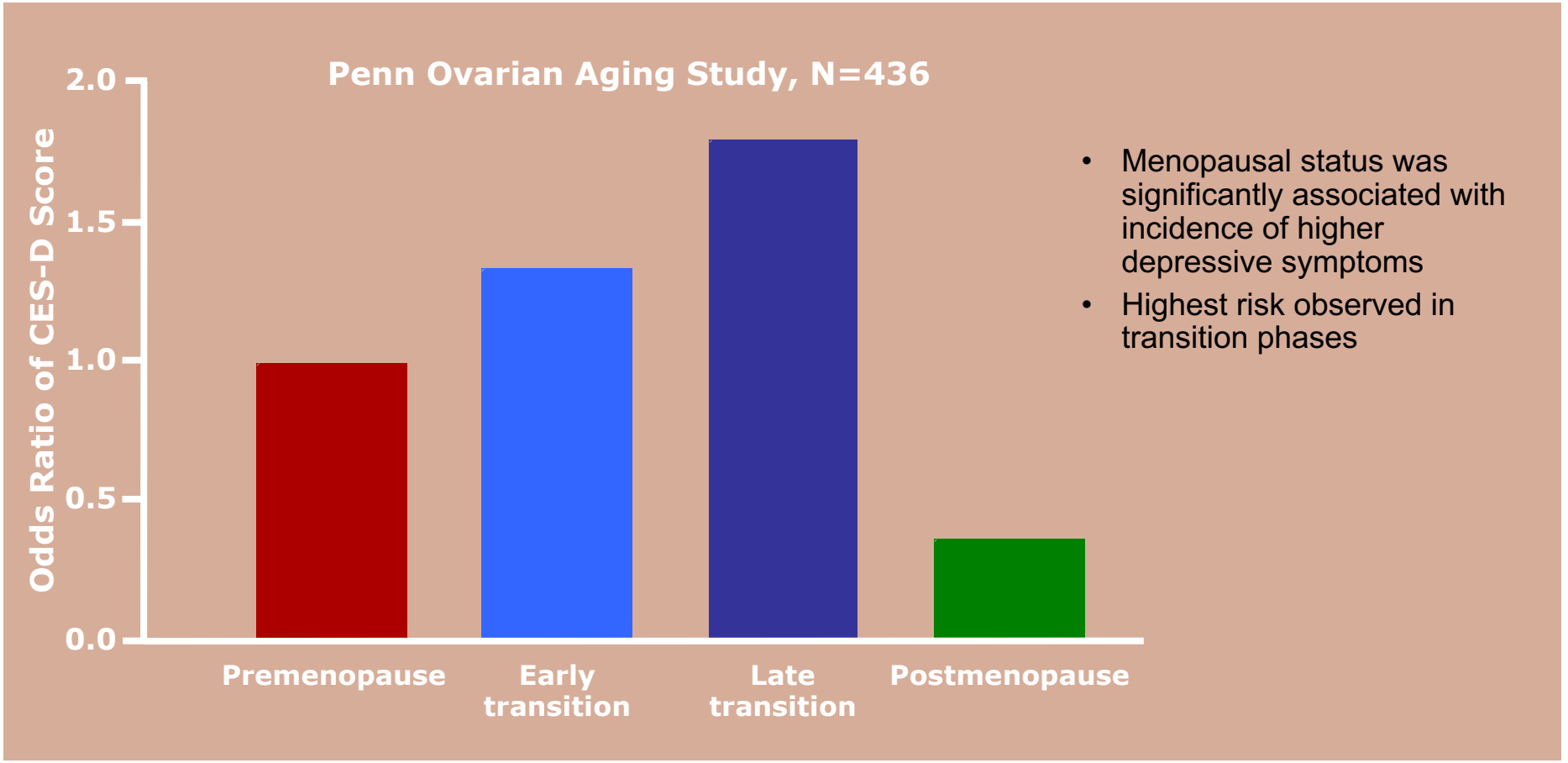
Risk for Mood Disorder During the Menopause Transition

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.

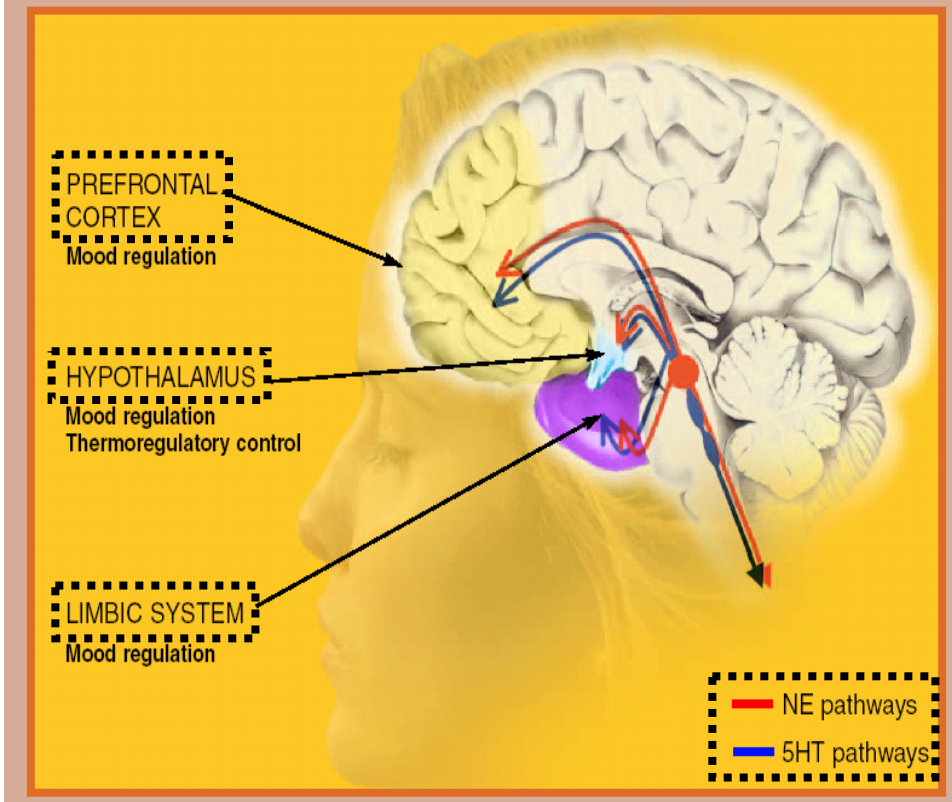
Increased Risk for First Episode of MDD During Menopausal Transition

- 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.

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–

Treatment of Perimenopausal and Menopausal Women with Depression

Diagnostic Challenges

Clinical Presentation

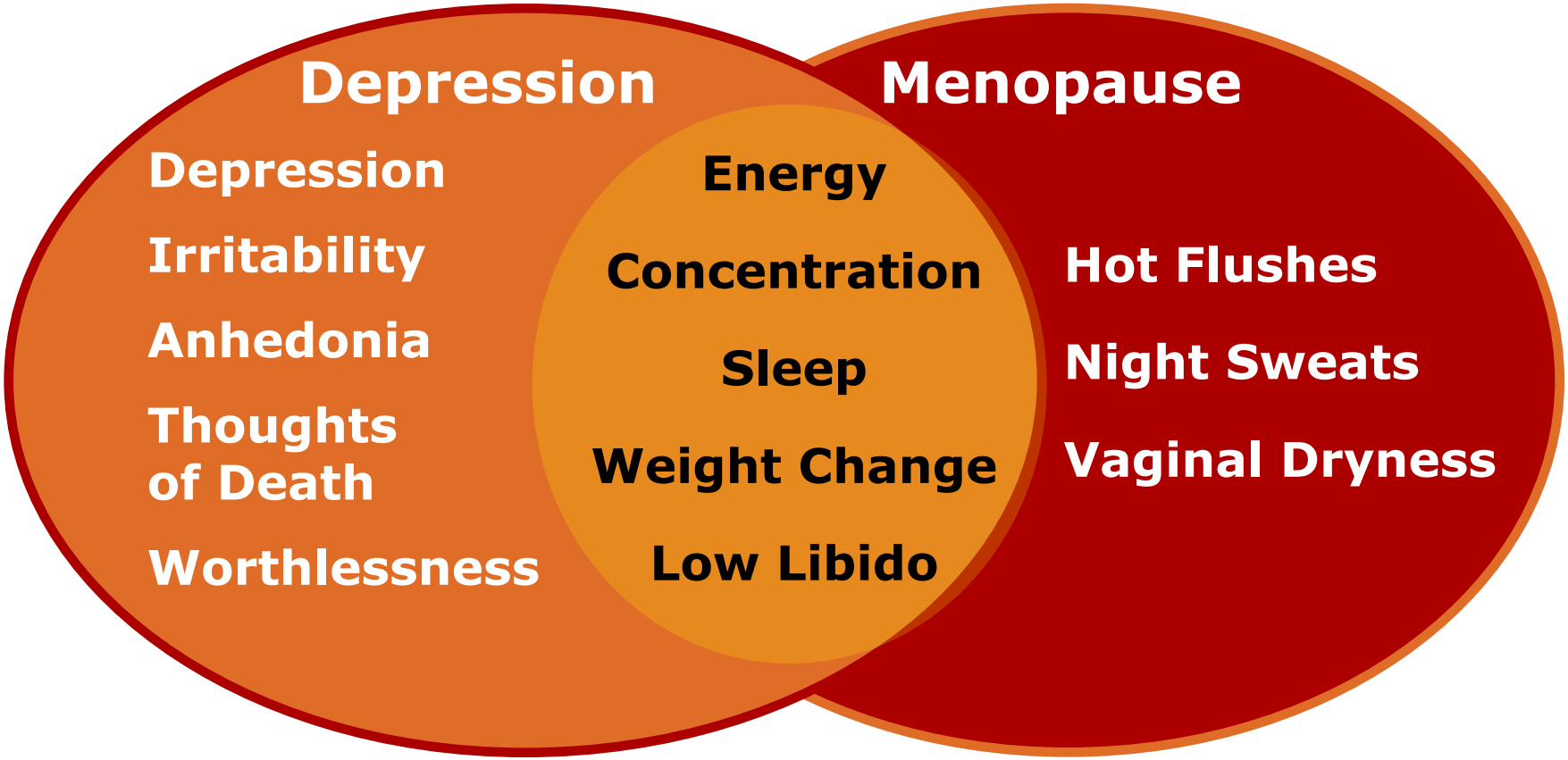
- Most women have a history of MDD, recurrence of depression during transition, similar symptoms
- Typical symptoms: anhedonia, irritability, sleep disruption, fatigue, poor concentration
- “Mood swings” - rule out bipolar disorder
- Psychosocial factors specific to midlife (e.g., caring for aging parents,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

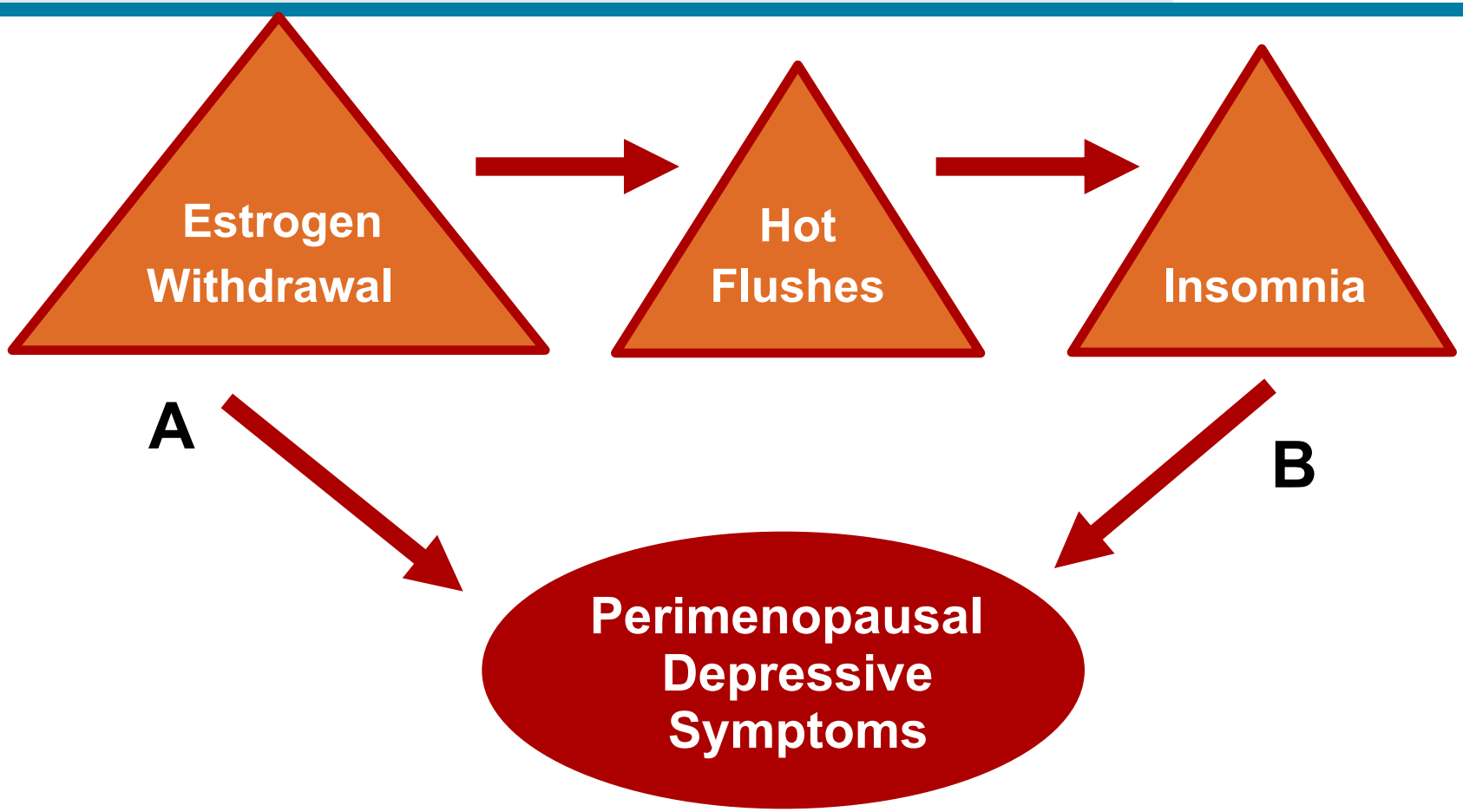
Gold EB et al. *Am J Public Health*. 2006;96(7):1226-1235.
Ohayon MM. *Arch Intern Med*. 2006;166(12):1262-1268.
Freeman EW et al. *Arch Gen Psychiatry*. 2006;63(4):375-382.
Cohen LS et al. *Arch Gen Psychiatry*. 2006;63(4):385-390.

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

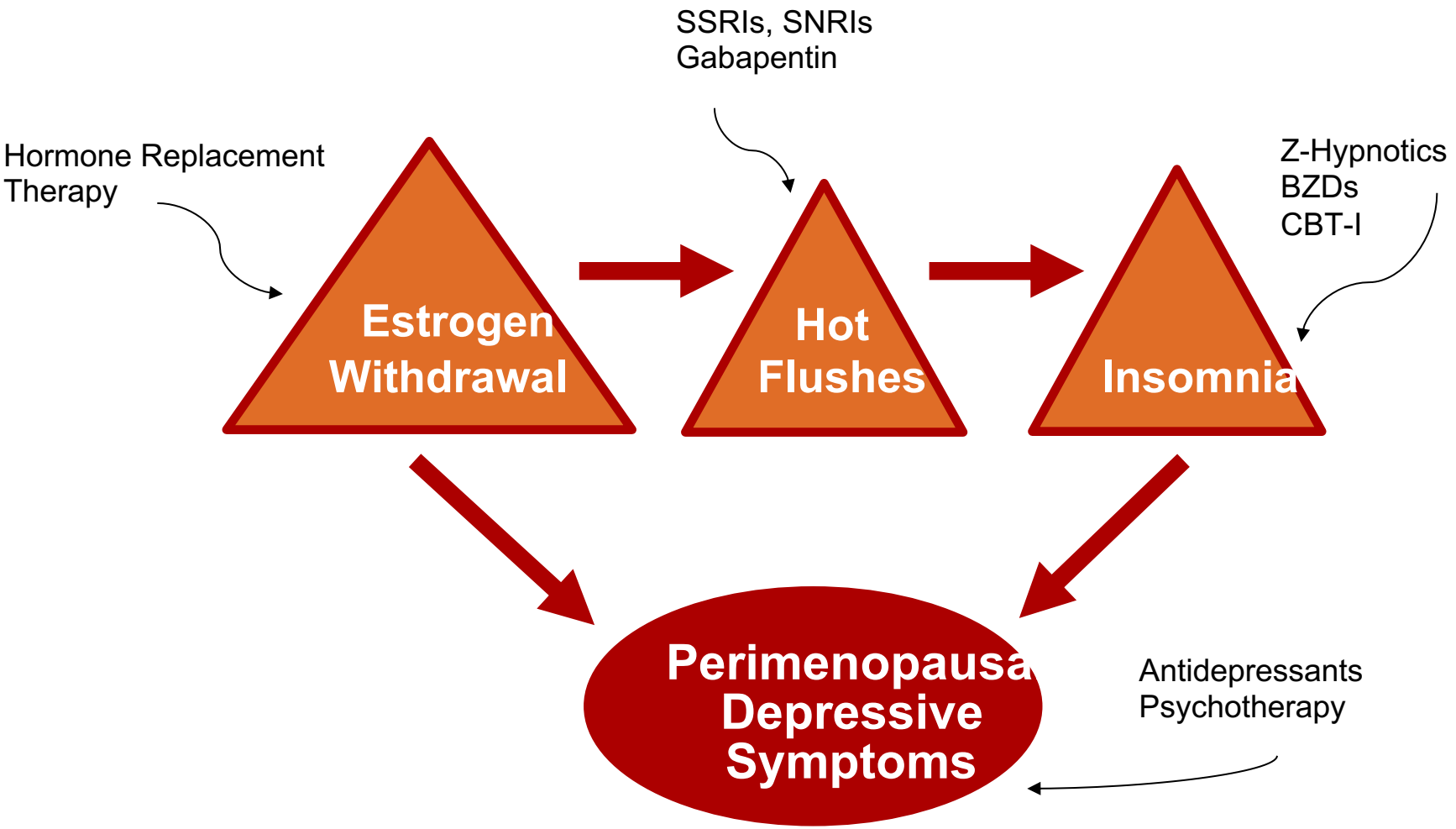


Joffe H and Cohen LS. *Biological Psychiatry.* 1998;44:798-811.

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.

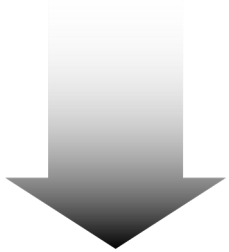
Researchers from the National Heart, Lung and Blood Institute of the National Institutes of Health also found increases in coronary heart disease, stroke and pulmonary embolism.

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

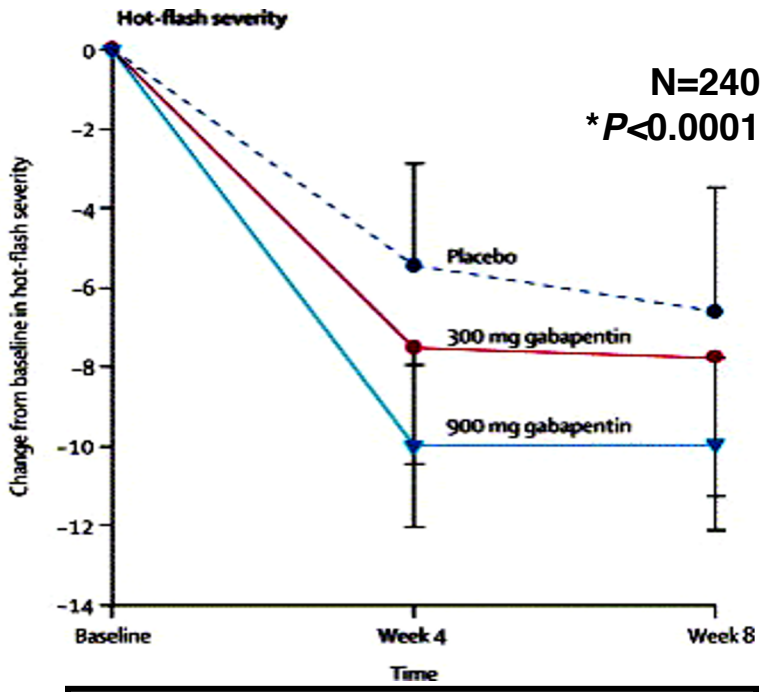
Joffe, *J Clin Psych* 2007; Joffe, *J Women's Health Gend Based Med* 2001; Soares, *J Clin Psych* 2003; Dias, *Menopause* 2006; Kornstein, *J Clin Psych* 20

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 hot flashes with gabapentin

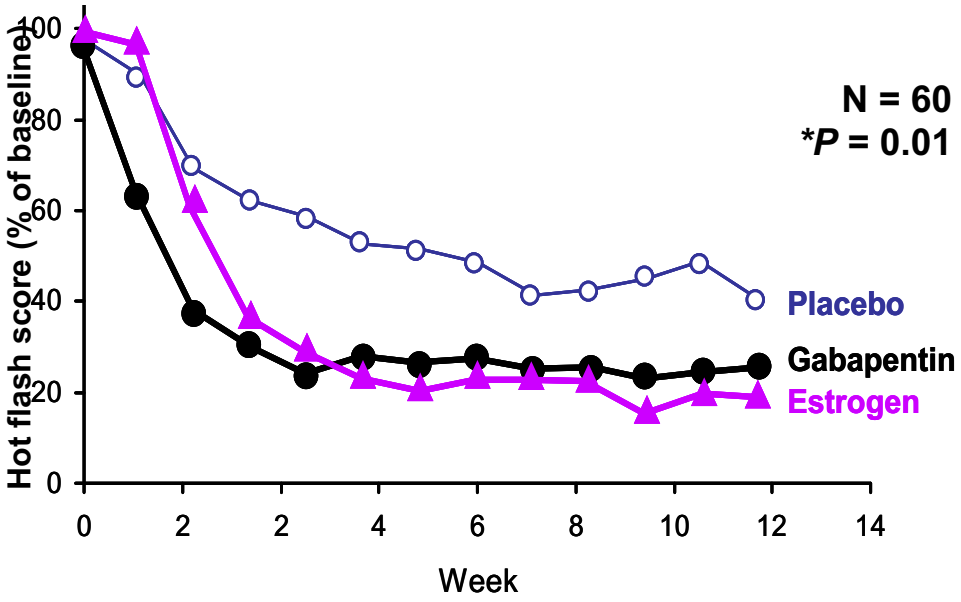
Low-dose (900mg/d) effective



Hot flash score reduction
Gabapentin 900-mg/day: 46%*
Gabapentin 300-mg/day: 31%
Placebo: 15%

Pandya KJ et al, *Lancet* 2005

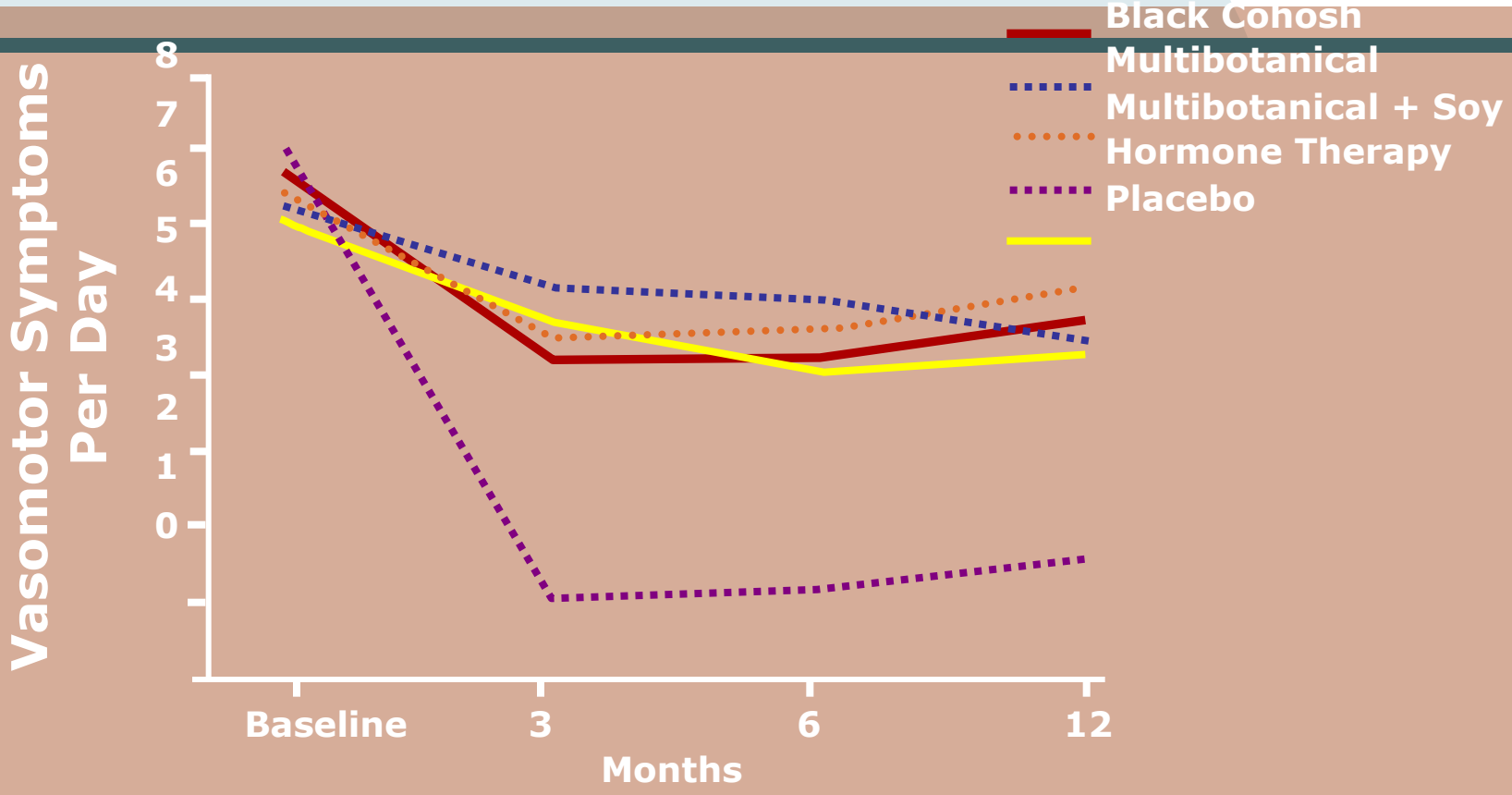
Moderate-dose (2400mg/d)
as effective as estrogen



Hot flash score reduction
Gabapentin 2400-mg/day: 71%*
Estrogen (CEE 0.625-mg/day): 72%
Placebo: 54%

Reddy SY et al. *OBGYN* 2006

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



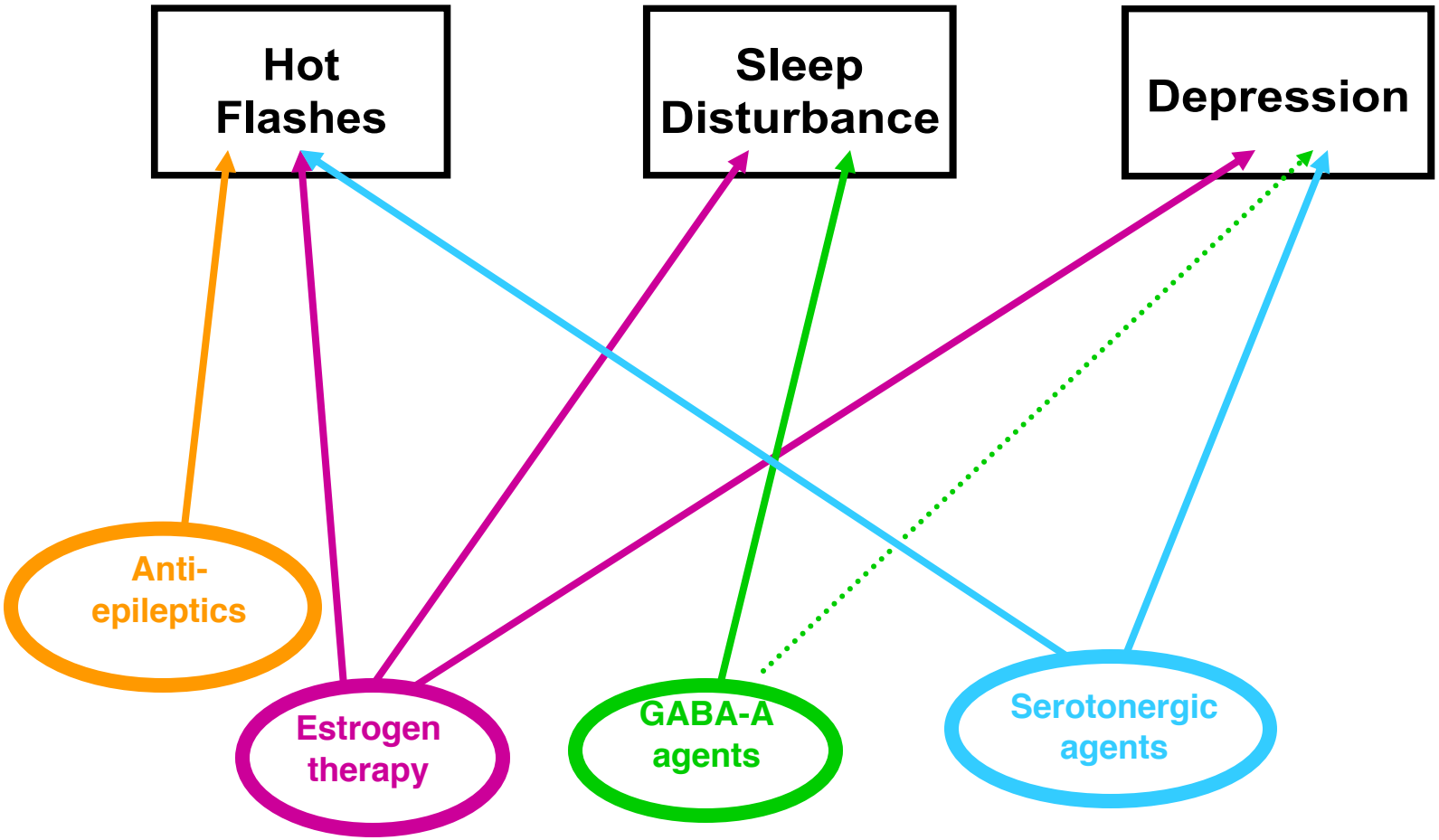
- Black cohosh, a multibotanical herbal product, and soy intake did not appear to significantly reduce the frequency or severity of menopause-related hot flushes or night sweats

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

Treatment of 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



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

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

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

Conclusions

1. Etiology of menopause-associated depression is not precisely known
2. Co-occurrence of VMS, sleep disturbance, and depression
3. Antidepressants first line treatment for MDD
4. Menopausal symptoms (sleep, VMS) may affect response, require other interventions
5. Hormonal strategies for the treatment of