Mood and Menopause

Karen E Adams, MD, FACOG, NCMP, FISSWSH
Professor Emeritus, Department of Obstetrics and Gynecology
Oregon Health and Science University

Disclosures

- Today I will discuss both on- and off-label uses of drugs
- No financial conflicts
- Acknowledgement: ISSWSH and Nicole Cirino MD
- When I use the terms “woman” and “female” I am referring to people who have ovaries and are experiencing the cessation of ovarian function either due to normal aging or medical intervention.

Learning Objectives:
After this talk, you will be able to:

1) Explain how reproductive hormones influence anxiety and depression

2) Differentiate Perimenopausal Mood Instability (PMI) from Major Depressive Disorder (MDD) and Generalized Anxiety Disorder (GAD)

3) List behavioral and pharmacologic treatment options for mood disorders in perimenopause and menopause

4) Consider PMI as frequently as you consider PMS!

Amanda

- 47 yo married mom of 2 teens
- Not on hormones
- Skipped 2 periods in the past year
- Feels anxious, more irritable and moody than usual
- Flushing day and night
- Nighttime waking, can’t go back to sleep
- Difficulty concentrating at work

- History of postpartum depression successfully txd w SSRI and therapy, none since


PERI
MENOPAUSE
AHEAD

Natural History of Hot Flashes

Transition Stage	% affected*	Age
Premenopause	20-45%	<45
Pre- to-Early Perimenopause	25-55%	45-47
Early-to-Late Perimenopause	50-80%	47-49
Late Peri-to-Postmenopause	35-75%	49-55
Late Postmenopause (>5yr)	16-44%	56+

References:
Barnabei V et al. Obstet Gynecol 2002; 100:1209-18
Gold EB, et al, Am J Pub Health 2006; 96:1226-35
Politi MC, et al. J Gen Intern Med 2008;23:1507–13

OHSU

WHICH IS IT??

Major Depression

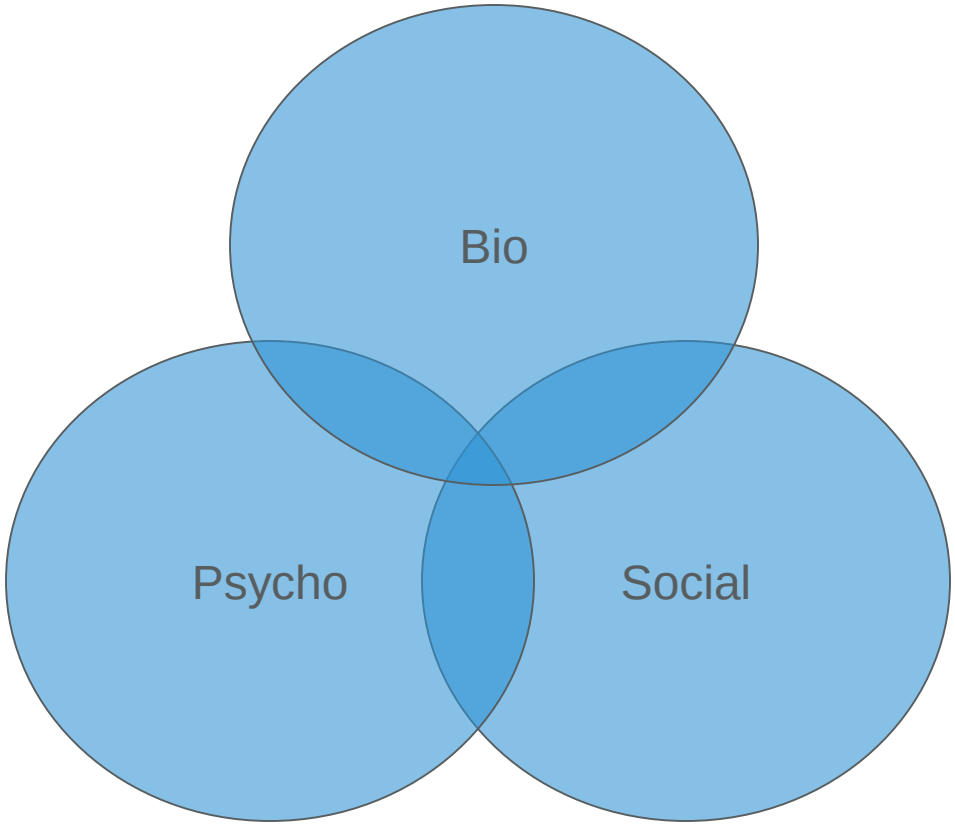
✓	SIGNS AND SYMPTOMS OF DEPRESSION
	Sadness or an "empty" mood
	Feeling guilty, worthless, or helpless
	Problems concentrating, remembering, or making decisions
	Change in eating habits and/or weight changes
	Feeling hopeless
	Lack of energy or feeling tried and "slowed down"
	Problems with sleep: Trouble getting to sleep, staying asleep, or sleeping too much
	Easily angered or irritable
	Wanting to be alone or spending much time alone
	Loss of interest or pleasure in hobbies and activities, including sex, that were once enjoyed

Perimenopause

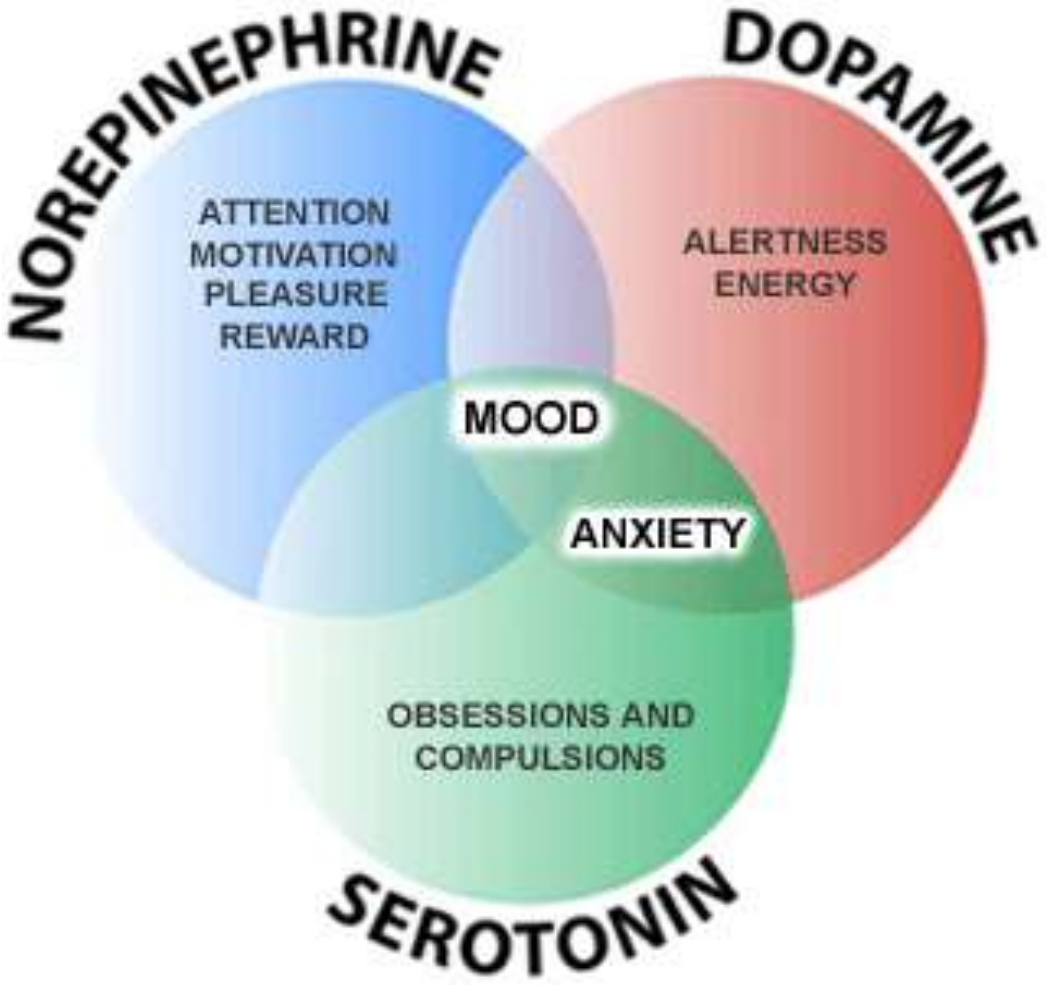
- Irregular periods 100%
- Hot flushes 80%
- Urinary/vaginal symptoms
- Sleep disturbance
- Sexual disturbance
- Weight changes
- Energy changes
- Brain fog/cognitive disturbance

OHSU

What causes Perimenopausal Mood Changes?



Brain Neurotransmitters implicated in Depression and Anxiety



Hormones and Neurotransmitters

Depression during perimenopause is likely due to fluctuating levels of estrogen and progesterone

Estrogen modulates serotonin and norepinephrine

- Possible reason why women are protected from some forms of psychosis

OHSU

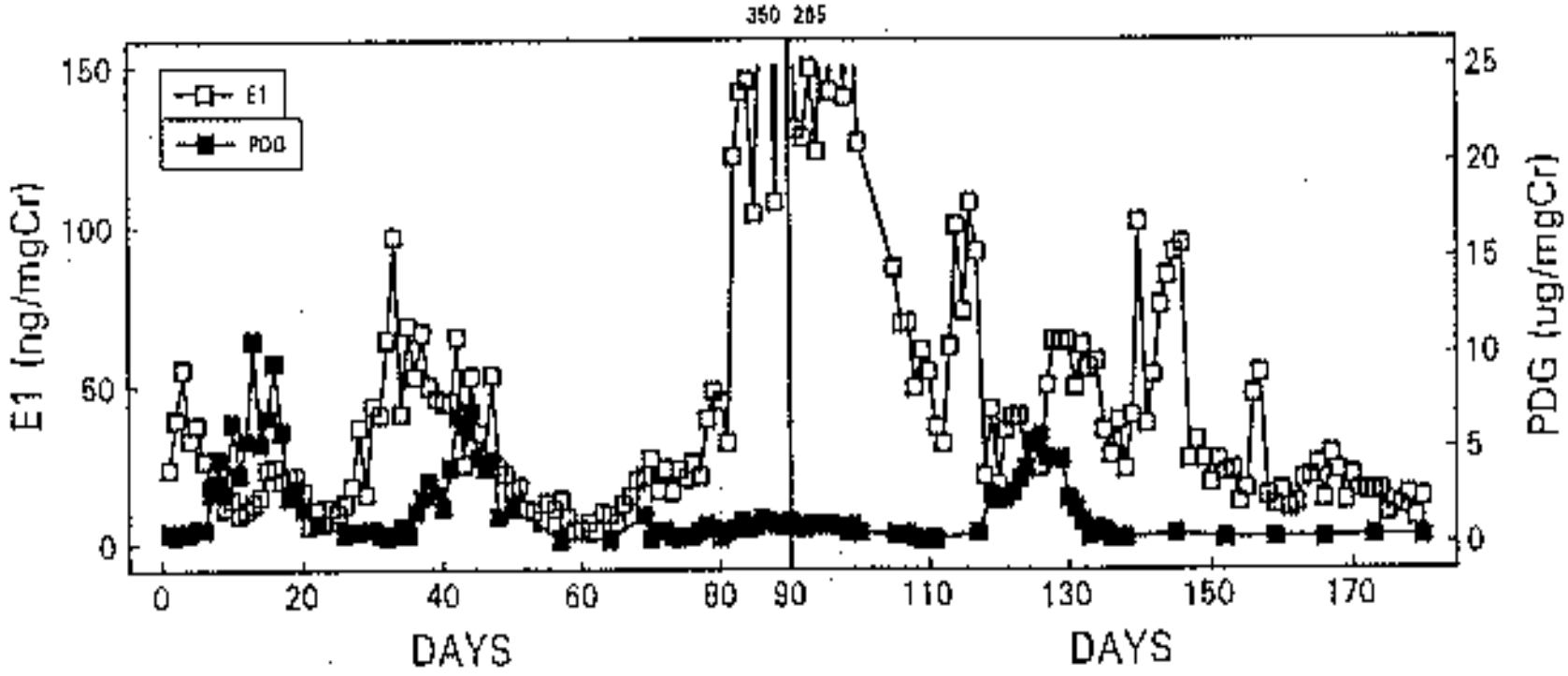
Progesterone – Anti-anxiety effects

Progesterone targets areas of the brain similar to anti-anxiety, pain and sleep medications

Progesterone has calming/sleep promoting effects in postmenopausal women

- Possible explanation for “pregnancy glow”
- Improvement of some anxiety disorders

Hormonal Changes in the Perimenopause



Santoro NF, et al J Clin Endocrinol Metab 1996

Perimenopausal Mood Instability (PMI)

Fluctuating mood symptoms: irritability, low mood, tearfulness, decreased energy, poor concentration

45-68% of perimenopausal women get mood symptoms (compared to 28-31% of premenopausal women)

NOT Major Depression

OHSU

Key point:
it could be MDD!

- 1 in 4 women will experience an episode of major depression at some point during perimenopause or menopause
- Women with no history of depression are still at 2x risk for new onset depression in perimenopause
- You may be the only one she is seeing! Essential to be able to determine the diagnosis and treat accordingly

OHSU

Psychiatry for the gynecologist:

Diagnosis of major depressive disorder (MDD)

OHSU

PHQ-9

5 or more symptoms in past 2 weeks

PATIENT HEALTH QUESTIONNAIRE-9

Over the last 2 weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING

0 + _____ + _____ + _____

=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

Point total characterizes depression:

5-9	mild
10-14	moderate
15-19	severe
20+	very severe

OHSU

Panic disorder/Generalized Anxiety Disorder (GAD)

New Panic Disorder and Generalized Anxiety Disorder more common during perimenopause

More common in women with physical symptoms of menopause (esp hot flushing)

GAD-7

GAD-7

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

Total Score ___ = Add Columns ___ + ___ + ___

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

Point total characterizes anxiety:

5-9	mild
10-14	moderate
15+	severe

Over 8 is clinically significant

OHSU

Be aware!

- Perimenopause is a window of vulnerability for mood changes (68%!)
- Risk of major depression goes up even in women with no history of mood disorders
- Mood disturbance earlier in life is a significant risk factor

OHSU

What can we do??

Menopause
Vol 25, No. 10, 2018

First-ever guidelines for detecting, treating perimenopausal depression

by University of Illinois at Chicago

Menopause: The Journal of The North American Menopause Society
Vol. 25, No. 10, pp. 000-000
DOI: 10.1097/GME.0000000000001174
This article is being co-published in the journals *Journal of Women's Health* and *Menopa*

CONSENSUS RECOMMENDATIONS

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

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

OHSU

The panel addressed 5 topics:

- Epidemiology of depression in peri- and post-menopause
- Presentation of depression in this population
  - *No different but dx complicated by perimenopausal symptoms*
- Effectiveness of antidepressants
  - *No difference in younger vs older women, both effective*
- Effects of HT on mood symptoms
  - *Effective in perimenopause, not in postmenopause*
- Effectiveness of other treatment modalities (psychotherapy, somatic or physical treatments, natural products)
  - *Some work, some do not*

Epidemiology—who's at risk?

- **45-68% of perimenopausal women** report depressive symptoms
- Higher in Hispanic women
- "Overall **multiple and varying factors** including socioeconomic, personal psychologic and social characteristics, and health status are associated with increased risk."
- Elevated risk w hysterectomy (w and w/o BSO)
- Elevated risk w POI

OHSU

Therapeutic Approaches: Psycho/Pharmacotherapies

OHSU

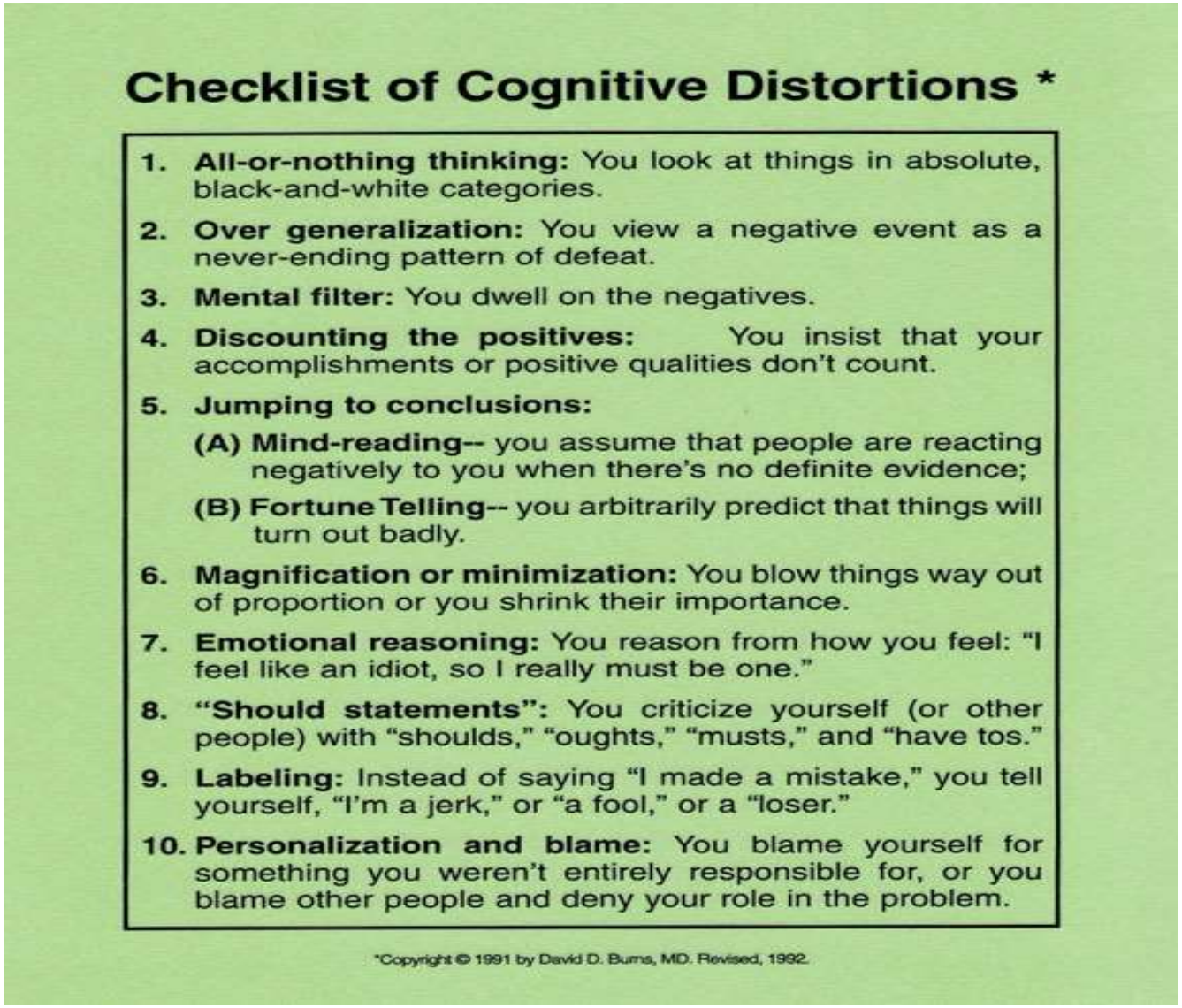
Psychological Treatments

- CBT (Cognitive Behavioral Therapy) reduces
  - frequency of hot flashes (now 7 RCTs!)
  - sexual dysfunction
  - depression and anxiety sxs
  - insomnia

- MBSR (Mindfulness-based stress reduction) therapy
  - Improves distress in women experiencing severe hot flashes and night sweats

- CBT-I (CBT for insomnia):
  - Fall asleep quicker and stay asleep longer

CBT Interventions



Checklist of Cognitive Distortions *

1. **All-or-nothing thinking:** You look at things in absolute, black-and-white categories.
2. **Over generalization:** You view a negative event as a never-ending pattern of defeat.
3. **Mental filter:** You dwell on the negatives.
4. **Discounting the positives:** You insist that your accomplishments or positive qualities don't count.
5. **Jumping to conclusions:**
   - **(A) Mind-reading--** you assume that people are reacting negatively to you when there's no definite evidence;
   - **(B) Fortune Telling--** you arbitrarily predict that things will turn out badly.
6. **Magnification or minimization:** You blow things way out of proportion or you shrink their importance.
7. **Emotional reasoning:** You reason from how you feel: "I feel like an idiot, so I really must be one."
8. **"Should statements":** You criticize yourself (or other people) with "shoulds," "oughts," "musts," and "have tos."
9. **Labeling:** Instead of saying "I made a mistake," you tell yourself, "I'm a jerk," or "a fool," or a "loser."
10. **Personalization and blame:** You blame yourself for something you weren't entirely responsible for, or you blame other people and deny your role in the problem.

Mindfulness Interventions

- Paced Breathing (NOT for VMS)
- APPs - Body Scan, Progressive Muscle Relaxation

  (Headspace, Simply being, Breathe2Relax)
- (MBSR) Mindfulness Based Stress Reduction course

OHSU

Pharmacotherapies: what doesn't work

- Black cohosh
- Calcium, Vit B6, Vit E
- Chasteberry
- Evening primrose oil
- Gingko
- Magnesium
- St John's wort

OHSU

Pharmacotherapy: Prescribing Pearls

- **Estrogen is not FDA-approved to treat PMI** but it works!
  - HT
  - Continuous OCs (sxs recur in the pill-free week)
- **Treat menopausal symptoms** if co-presenting in women with MDD
- Address **sleep disturbance**
  - Consider the role of **progestins** in sleep promotion
- **Always recommend exercise**, particularly when combined with psycho- and pharmacotherapies

Medication treatment for Depression

SSRIs or SNRIs

- FIRST LINE for moderate to severe depression or anxiety
- History of depression
- Most effective if in combination with psychotherapy
- Start low and go slow, warn of SE of sweating, insomnia

- Effect in 2-6 weeks

vs. Estrogen

- Start with this if **perimenopausal and symptoms include PMI** or mild depression/anxiety
- In combination with SSRIs for severe depression in **perimenopause and menopause**
- ALWAYS in **early menopause**

- Effect in 2-4 weeks

- **Not for postmenopausal depression** in the absence of other indications

Antidepressants -Menopause

SSRIs	SNRIs/Others	Others
Brintellix (vortioxetine) **Celexa** (citalopram)* **Lexapro** (escitalopram) **Luvox** (fluvoxamine) **Paxil** (paroxetine) **Prozac** (fluoxetine)* **Viibryd** (vilazodone) **Zoloft** (sertraline) *	**Cymbalta** (duloxetine)* **Effexor** (venlafaxine)* **Fetzima** (levomilnacipran) **Pristiq** (desvenlafaxine)** **Wellbutrin** (bupropion) **Remeron** (mirtazapine)	**Wellbutrin (**Bupropion) **Remeron (**Mirtazapine)
Inhibit the reuptake of serotonin (5HT)	Inhibit serotonin and norepinephrine reuptake	

- Studied and shown efficacy in peri/post menopause
- ** Only RCT

OHSU

Drug	Anticholinergic	Drowsiness	Insomnia/agitation
Selective serotonin reuptake inhibitors[¶]			
Citalopram	0	0	1+
Escitalopram	0	0	1+
Fluoxetine	0	0	2+ Prozac
Fluvoxamine	0	1+	1+
Paroxetine	1+	1+ Paxil	1+
Sertraline	0	0	2+ Zoloft
Atypical agents			
Agomelatine[§] (not available in United States)	0	1+	1+
Bupropion	0	0	2+ (immediate release) 1+ (sustained release)
Mirtazapine	1+	4+	0
Serotonin-norepinephrine reuptake inhibitors[¶,**]			
Desvenlafaxine[‡]	0	0	1+
Duloxetine	0	0	1+
Levomilnacipran[‡]	0[†]	0	0 to 1+
Milnacipran[‡]	0	1+	0
Venlafaxine[‡]	0	1+ Effexor	1+

OHSU

My personal approach to antidepressants in perimenopause:

- Zoloft and Prozac are activating
  - good for the draggy, fatigued person
  - don't use for the anxious, sped-up person
- Paxil and Effexor are calming
  - Good for the anxious, sped-up person
  - don't use for the draggy, fatigued person
- Wellbutrin is activating
  - take in the morning or they won't sleep
  - Sex-positive

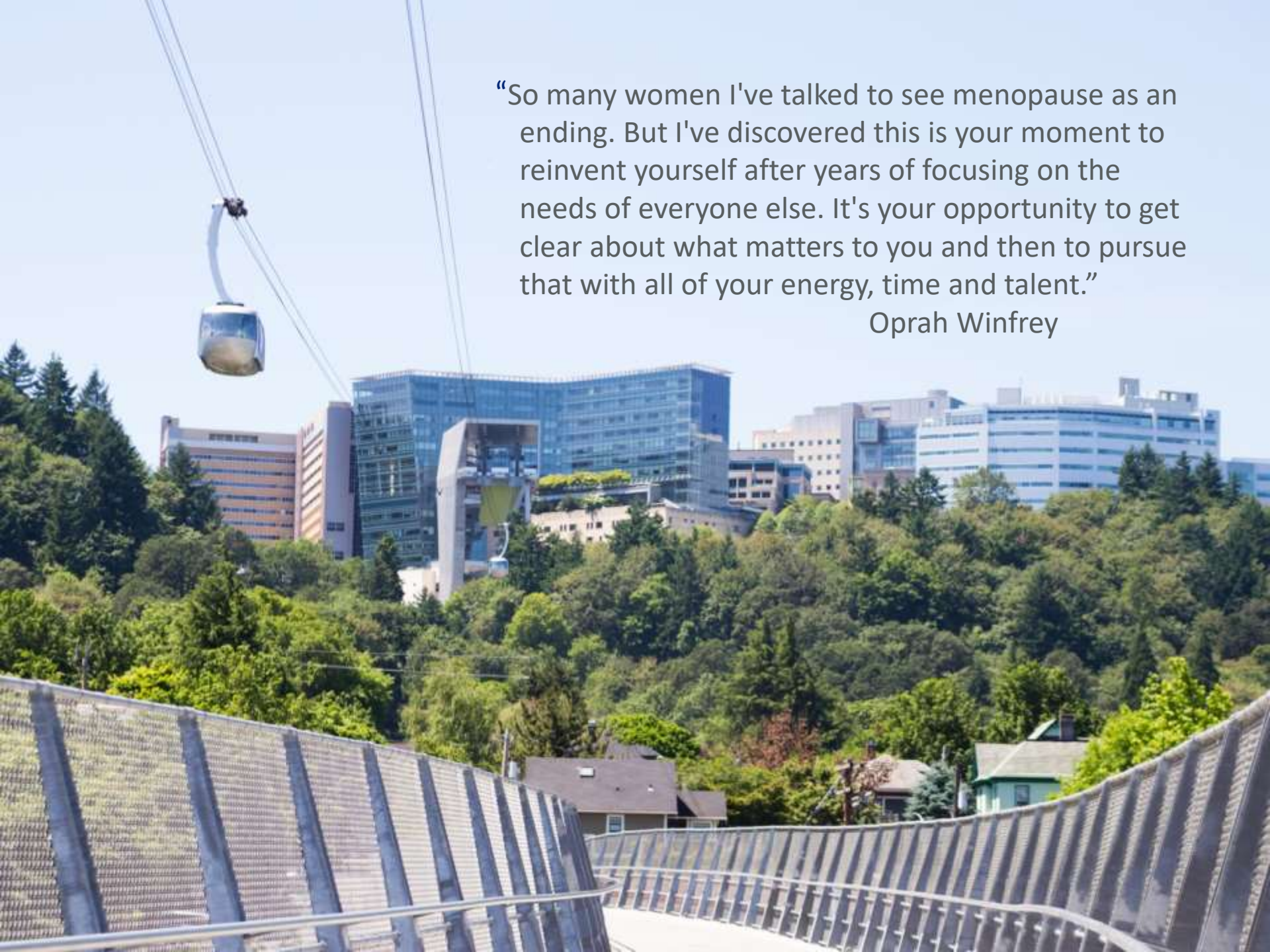
OHSU

Amanda revisited…

Amanda revisited

- Perimenopausal
- PHQ-9 c/w mild depression, not MDD
- No contrainds to estrogen
- Opted to start hormones and follow up shortly (TD E + oral P, TD E + mIUD, or cont OCs)
- Expect vasomotor sxs to improve, possibly mood and sleep
- Consider antidepressants at that time if no improvement in mood
- Could flip the order if depression is more severe
- SSRIs/SNRIs don't work as well for flushing as HT and have negative sexual side effects
  - Pros and cons of doing both simultaneously

OHSU



"So many women I've talked to see menopause as an ending. But I've discovered this is your moment to reinvent yourself after years of focusing on the needs of everyone else. It's your opportunity to get clear about what matters to you and then to pursue that with all of your energy, time and talent."

Oprah Winfrey

Summary:

1) Perimenopause is a window of vulnerability for mood disorders

2) There are many effective treatments for depression and anxiety-related symptoms of perimenopause

3) VALIDATE YOUR PATIENT'S EXPERIENCE

4) Pick either a hormonal approach or a mood approach, depending on most bothersome symptom(s), and reevaluate frequently

5) Partner with a mental health colleague for nonresponse to treatment or complex mental health history

OHSU

References

- Consensus Recs. Guidelines for the Evaluation and Treatment of Perimenopausal Depression: *Menopause*, Vol. 25, No. 10, 2018
- Leistikow *Advances in Psychiatry and Behavioral Health*, 2(2022) 107
- North American Menopause Society Hormone Therapy Position Statement, *Menopause*, 2022
- Soares *J Clin Psych* 2007. 68
- Spinelli *Clin Obstet Gynecol* 2004, June 47(2)
- Cohen LS *Arch Gen Psych* 2006 Apr 63(4)
- Soares *Arch gen Psych* 2001 58(6)
- www.womensmentalhealth.org
- Bhatt *Menopause and Mood Disorders* Medscape 2019 Jan

OHSU

Thank You

OHSU