Women's Mood Disorders Across the Lifespan

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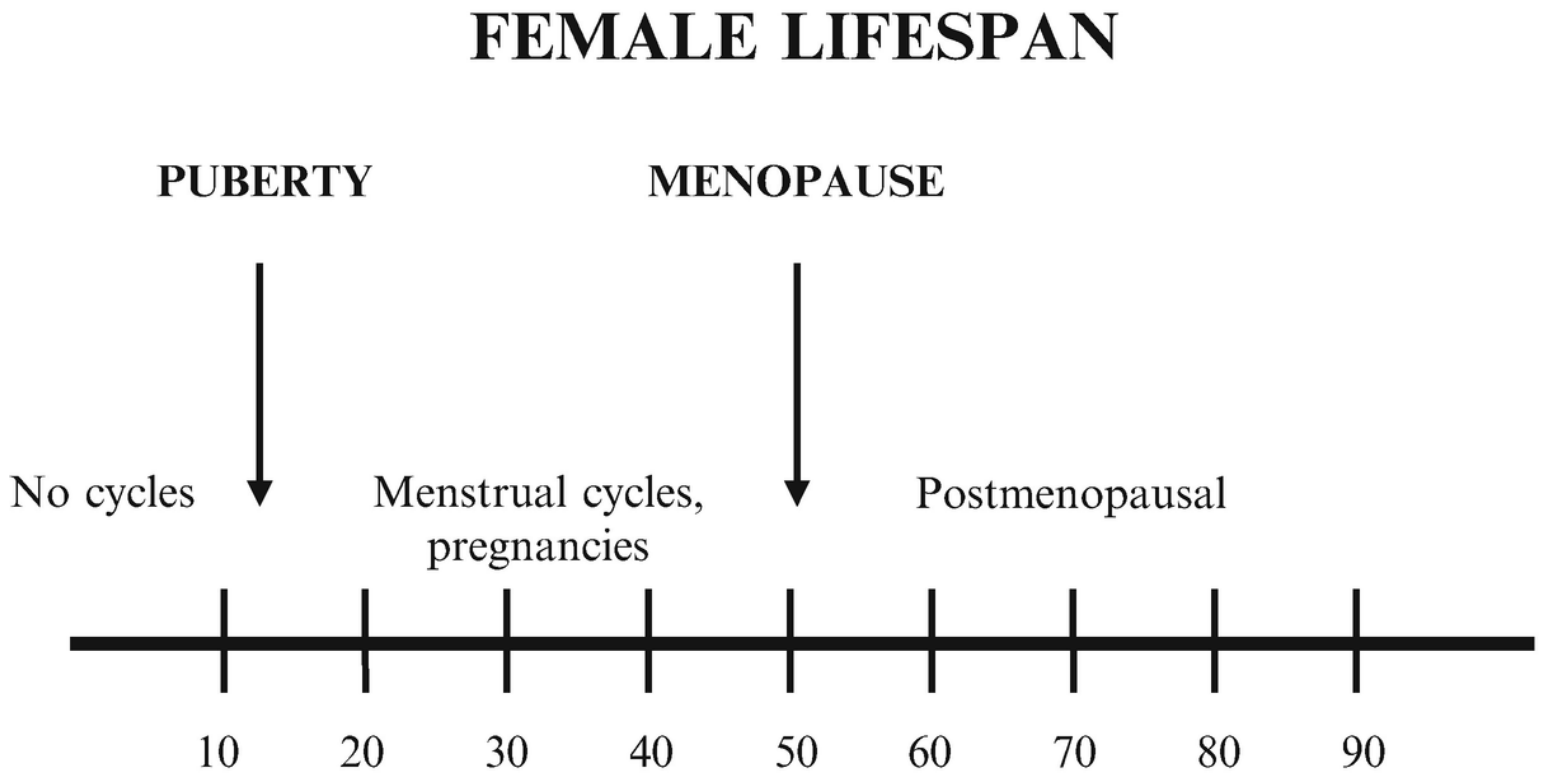
Objectives

To discuss the epidemiology, clinical presentation, and general approach to the management of perimenstrual and perimenopausal disorders



I have no disclosures

The increased risk for depression in women begins at puberty

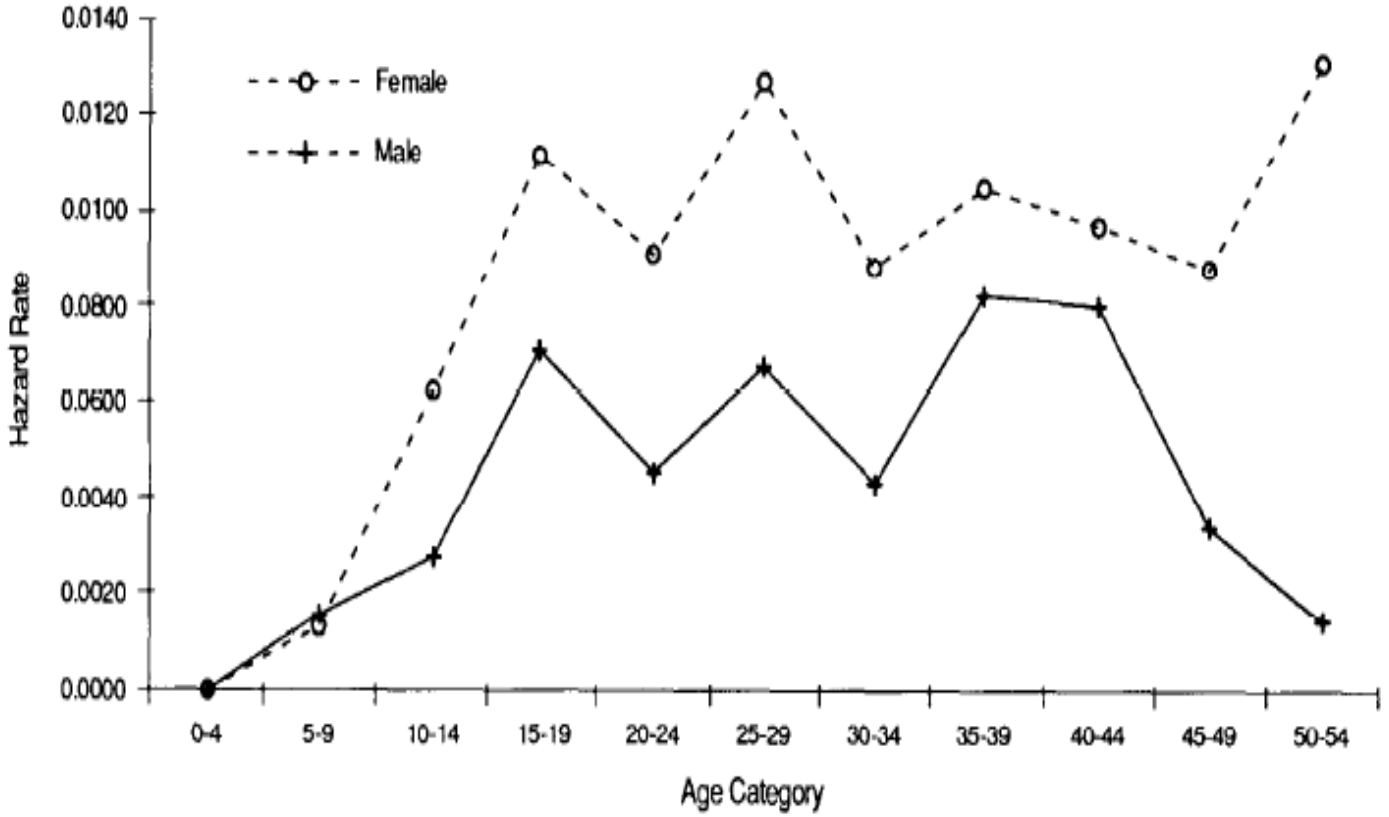


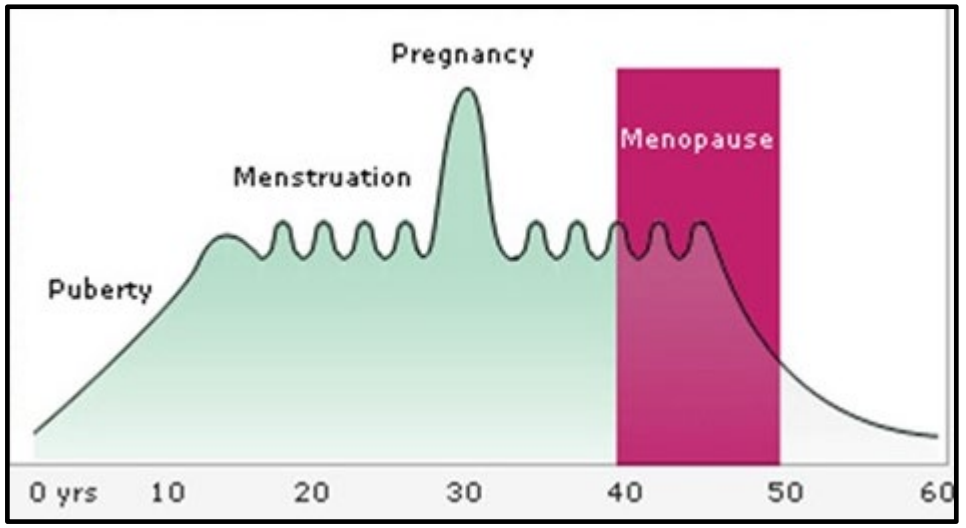
Fig. 1. MDE hazard rates by age and sex.

Kessler, McGonagle, Swartz, Blazer, & Nelson (2003)

A subset of women have mood symptoms associated with reproductive transitions

Fluctuations in gonadal steroids are a part of normal reproductive events

Some women are more sensitive to these normal hormonal shifts



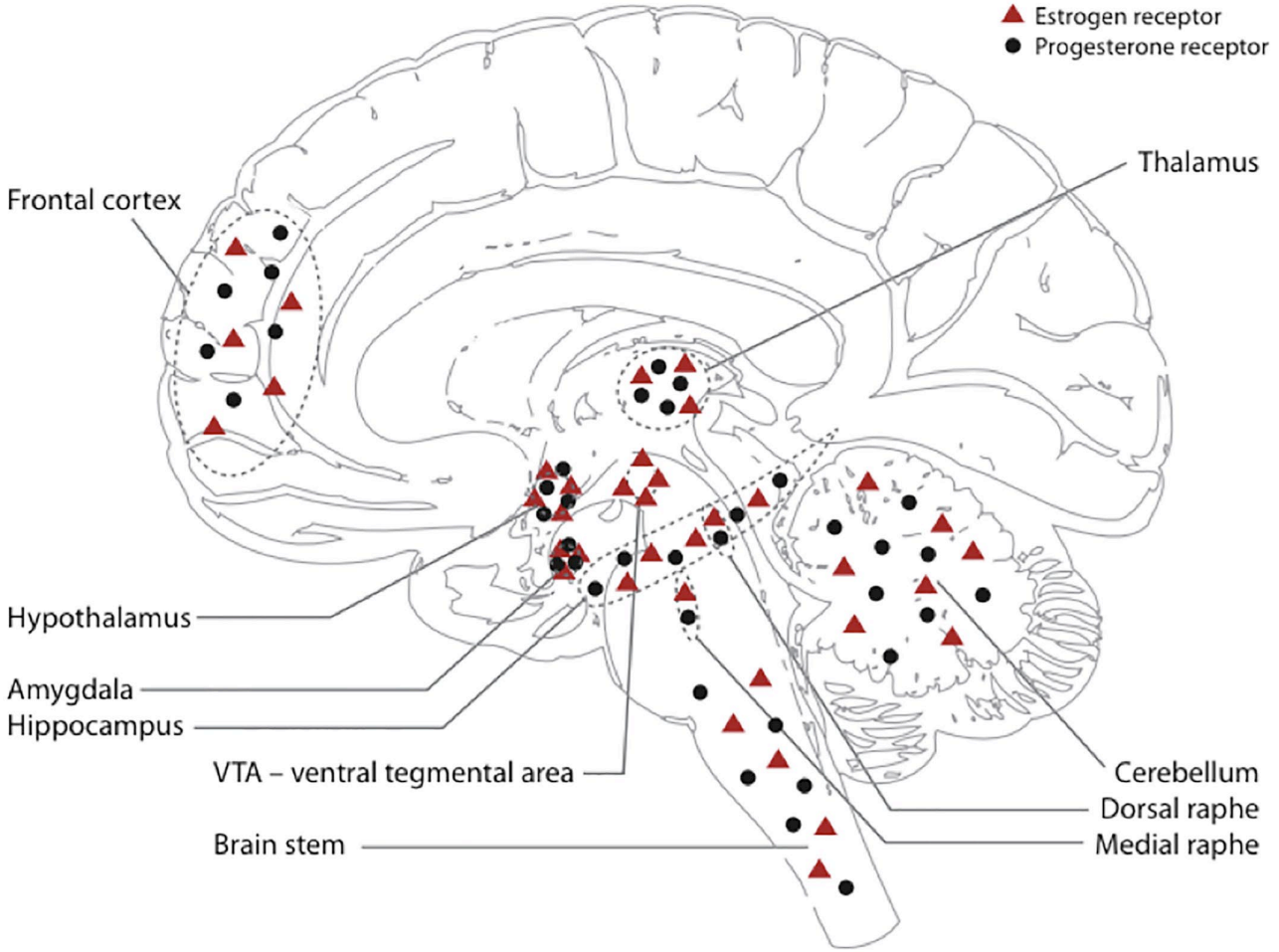
Schmidt et al, New Engl J Med, 1998; Bloch et al, Am J Psychiatry, 2000

Gonadal steroid hormones impact neurotransmitter pathways and structural brain regions

Progesterone acts on GABA-A receptor complex

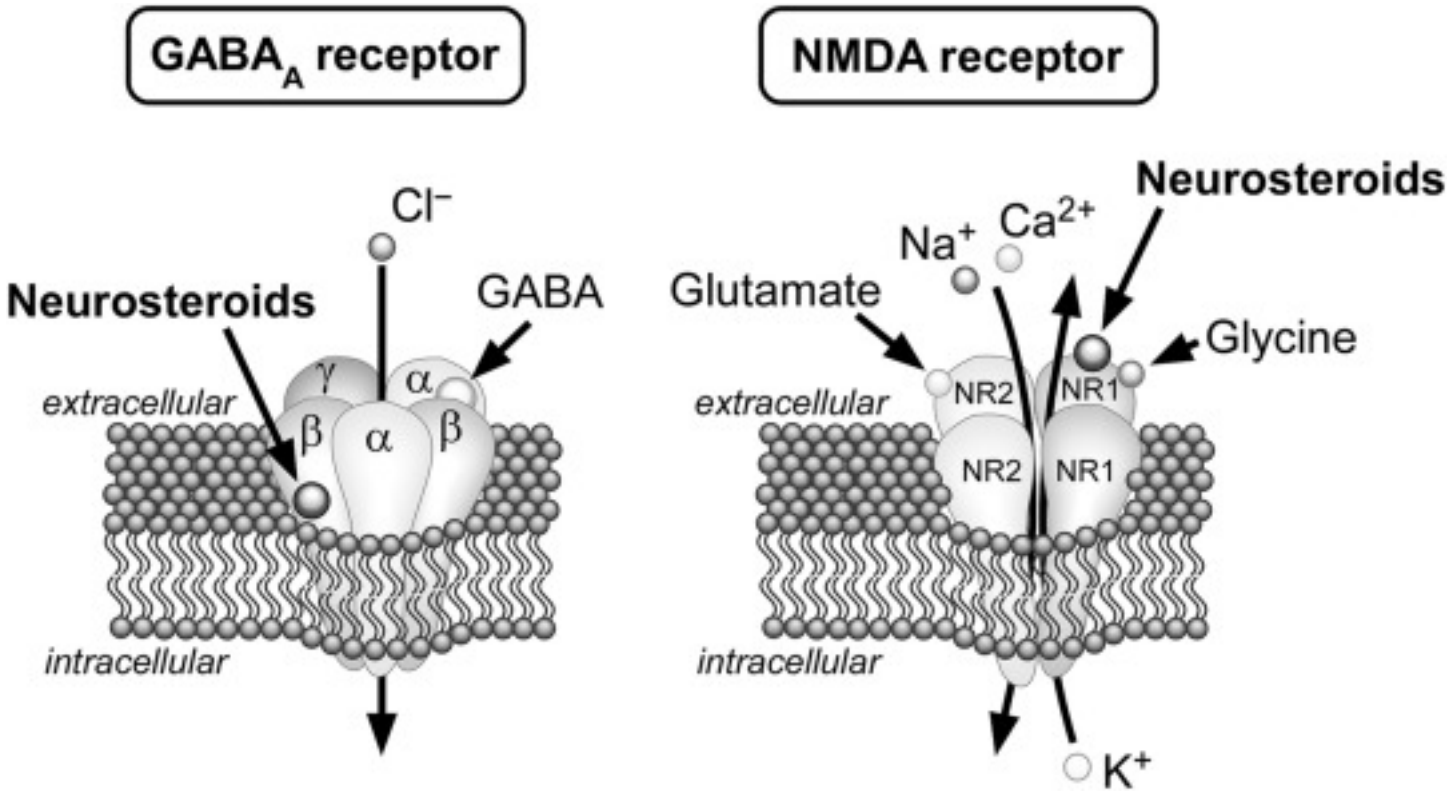
Estradiol may act on serotonin transporter

Estrogen receptors are present on brain structures linked to emotion processing



Ruehr et al, Front Neuroendocrinol, 2024; Boyle, Human Brain Mapping, 2021

Role of neuroactive steroids: allopregnanolone



Taking a reproductive history is currently the best method of assessing risk

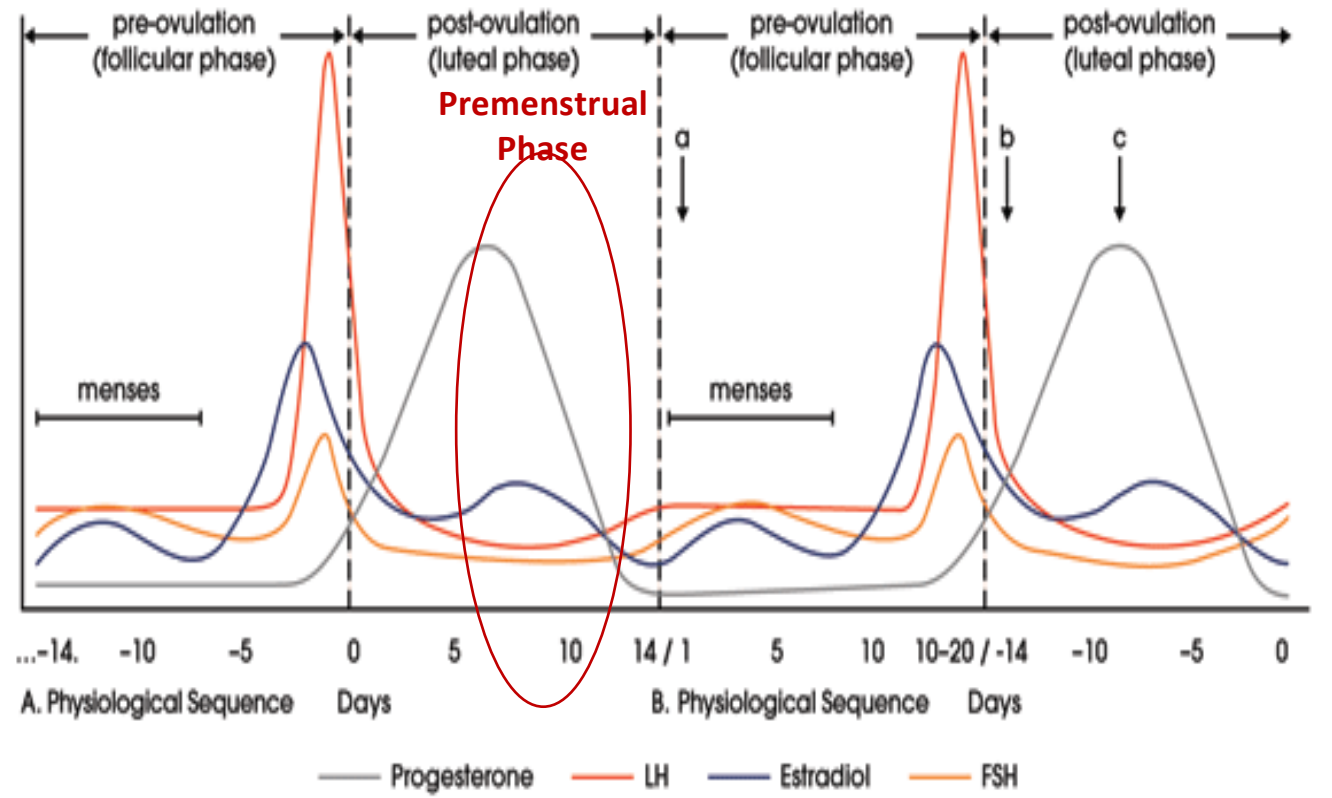
- **Family history of reproductive exacerbations**
- **Personal history of mood symptoms during reproductive transitions**
- **Sensitivity during changes in hormonal medications**
- **Exposure to early life stressors/trauma**

Dube et al, Am J Prevent Med, 2005; CDC 2011

Menstrual disorders

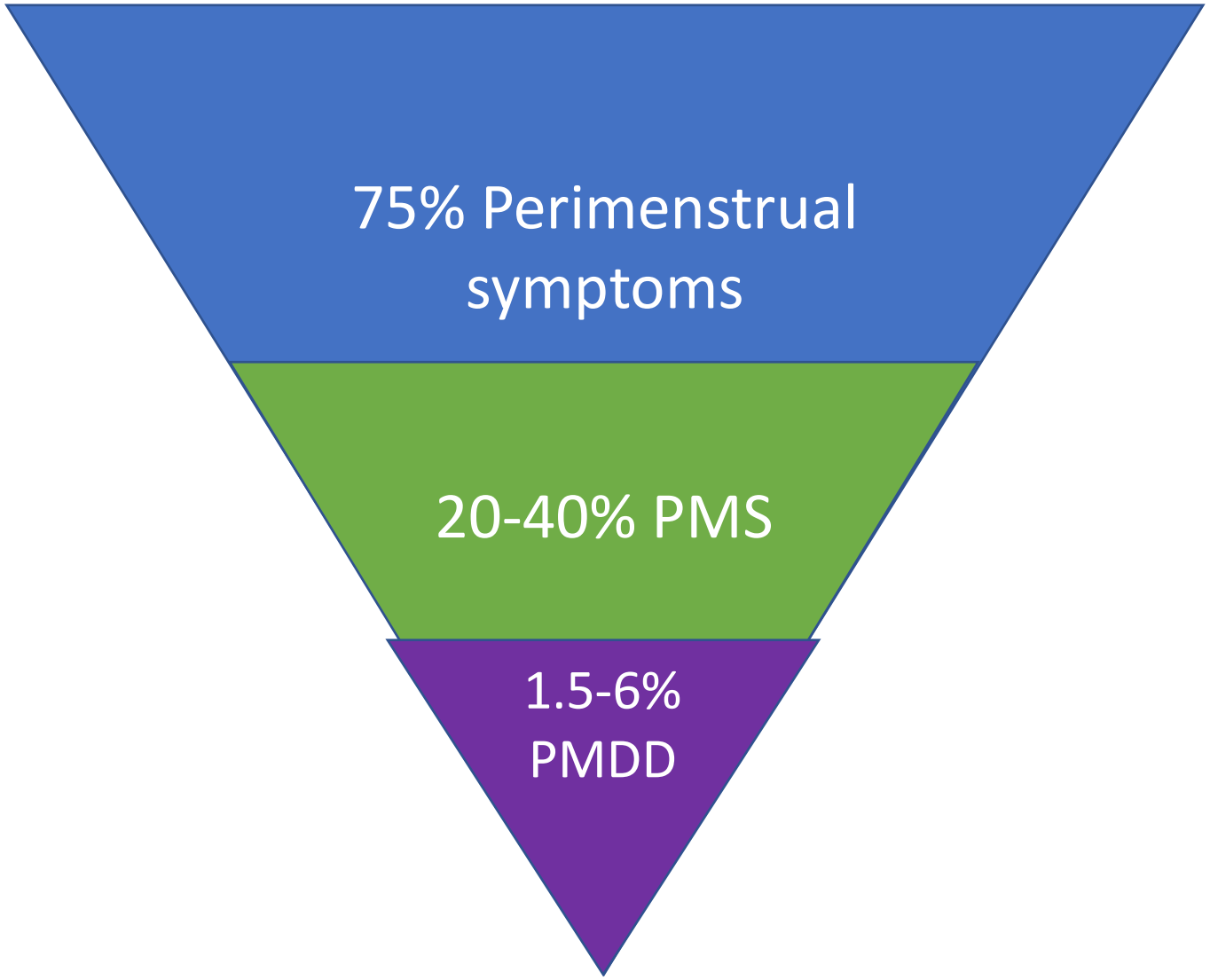
Menstrual Cycle

Figure
The "Normal" Pattern of Hormonal Changes that Regulate the Ovarian Cycles



a=gonadotropin-releasing hormone analogues, continuous psychotropics; b=Intermittent psychotropics, possible progesterone antagonists, possible progestin antagonists; c=Possible symptomatic interventions (eg, anxiolytics); LH=luteinizing hormone; FSH=follicle-stimulating hormone.

Halbreich U, Monacelli E. *Primary Psychiatry*. Vol 11, No 12. 2004.



Steiner et al, J Psychiatry and Neuroscience 2000

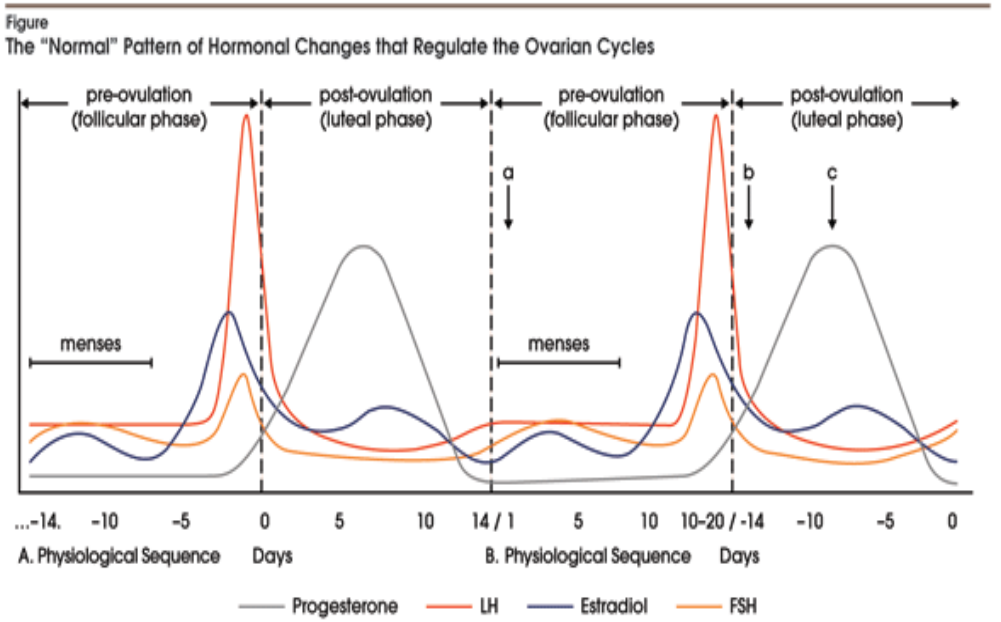
Premenstrual Syndrome

Not listed in DSM-5

ACOG definition of PMS:

- At least 1 symptom associated with economic or social dysfunction
- Occurs during the 5 days before onset of menses and is present at least 3 consecutive menstrual cycles
- Symptoms may be affective or physical

Impacts 20-40% of women



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Halbreich U, Monacelli E. *Primary Psychiatry*. Vol 11, No 12. 2004.

Premenstrual Dysphoric Disorder (PMDD)

Timing of symptoms is central

Combination of somatic symptoms and severe mood symptoms

Clinically significant distress or impairment

MUST be confirmed prospectively

Prevalence estimates range from 1.8% to 5.8% of menstruating women

Association with seasonal affective symptoms

Differential: rule-out mood disorder with premenstrual exacerbation

Rubinow, Am J Obstet Gynecol, 1988; Epperson et al, American Journal of Psychiatry, 2012

Tracking Symptoms is Key to making the diagnosis

Premenstrual Mood Chart

Name_____
Doctor_____ Year_____

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Jan																															
Feb																															
Mar																															
April																															
May																															
June																															
July																															
Aug																															
Sept																															
Oct																															
Nov																															
Dec																															

☐ = menstrual flow

Rating scale for mood/depression, irritability, anxiety, other_____
1 = good
2 = ok
3 = poor
4 = terrible

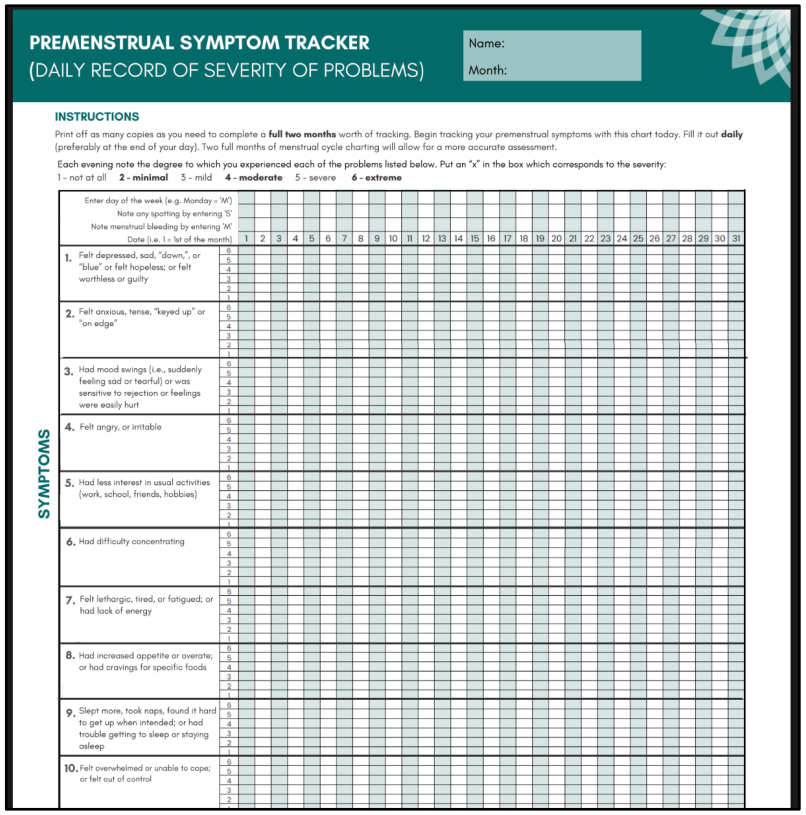
Examples:

#1 probable PMS

1	2	3	4	4	4	2	1	1	2

#2 probable depression

2	3	4	3	3	4	3	3	4	2



PREMENSTRUAL SYMPTOM TRACKER
(DAILY RECORD OF SEVERITY OF PROBLEMS)

Name:
Month:

INSTRUCTIONS

Print off as many copies as you need to complete a **full two months** worth of tracking. Begin tracking your premenstrual symptoms with this chart today. Fill it out **daily** (preferably at the end of your day). Two full months of menstrual cycle charting will allow for a more accurate assessment.

Each evening note the degree to which you experienced each of the problems listed below. Put an "x" in the box which corresponds to the severity:
1 - not at all **2 - minimal** 3 - mild **4 - moderate** 5 - severe **6 - extreme**

Enter day of the week (e.g. Monday = 'M')
Note any spotting by entering 'S'
Note menstrual bleeding by entering 'M'
Date (i.e. 1 = 1st of the month)

SYMPTOMS

1. Felt depressed, sad, "down,", or "blue" or felt hopeless; or felt worthless or guilty
2. Felt anxious, tense, "keyed up" or "on edge"
3. Had mood swings (i.e., suddenly feeling sad or tearful) or was sensitive to rejection or feelings were easily hurt
4. Felt angry, or irritable
5. Had less interest in usual activities (work, school, friends, hobbies)
6. Had difficulty concentrating
7. Felt lethargic, tired, or fatigued; or had lack of energy
8. Had increased appetite or overate; or had cravings for specific foods
9. Slept more, took naps, found it hard to get up when intended; or had trouble getting to sleep or staying asleep
10. Felt overwhelmed or unable to cope; or felt out of control

Checking hormones levels is not currently recommended!

iampmd.com

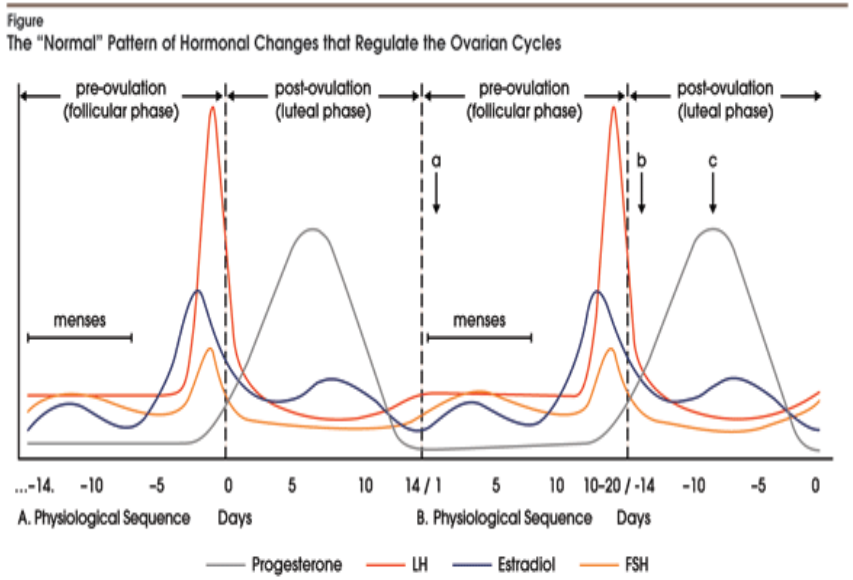
Pearlstein, J Psychiatry Neuroscience, 2007

Role of Hormones in PMDD

No evidence of menstrual hormone irregularity or disturbance

Reproductive hormones may trigger mood dysregulation in the context of an antecedent susceptibility

Checking hormones levels is not currently recommended!

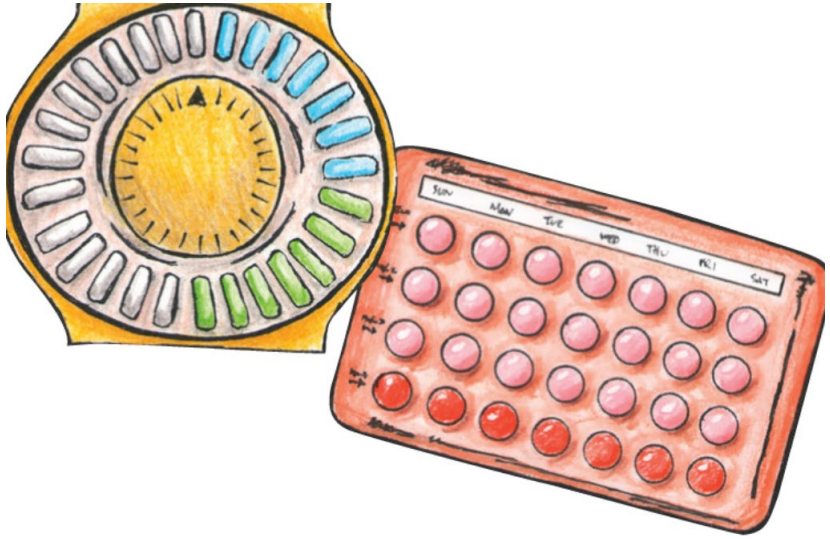


Menstrual Disorder Treatment Options

Psychiatric Medications

Hormonal Treatments

Supplements/Behavioral Modification

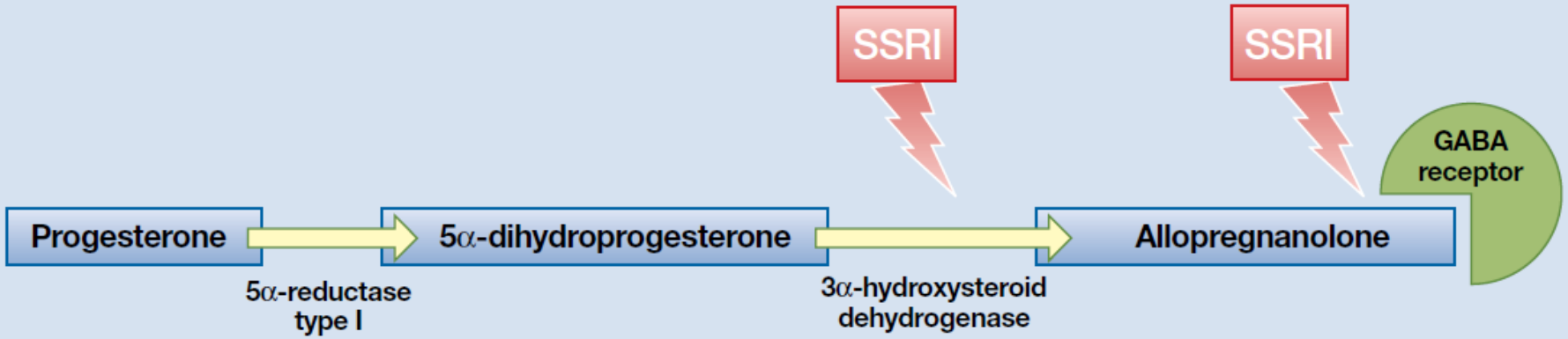


Joffe, Clinical Psychiatry, 2007

Why serotonergic antidepressants?

Figure 4

Conversion of progesterone to ALLO and the SSRI influence

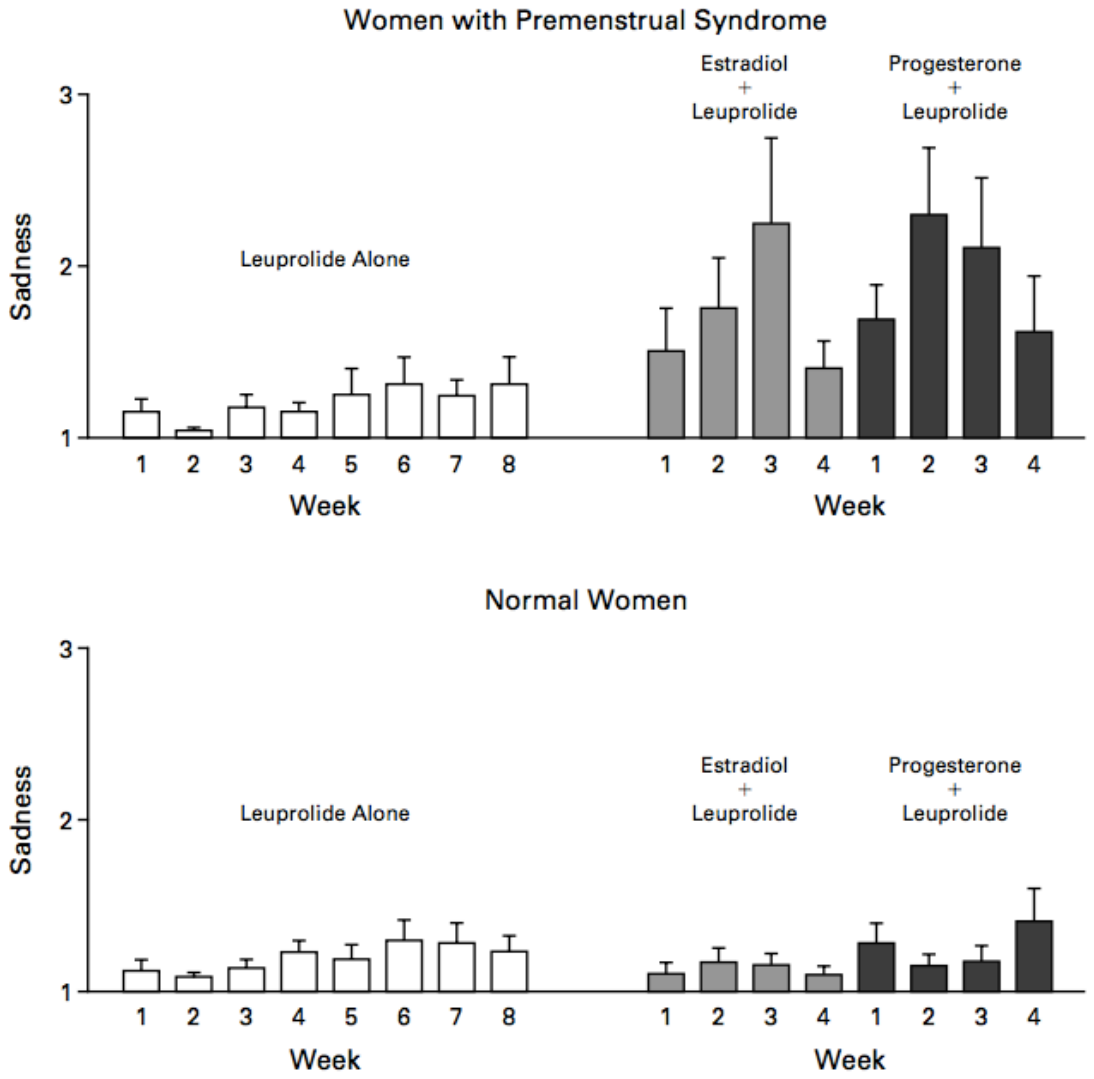


SSRIs enhance the sensitivity of $GABA_A$ receptors or promote the formation of more ALLO as shown here. This is one possible mechanism by which they could be helping to alleviate PMDD symptoms.

ALLO: allopregnanolone; GABA: γ-aminobutyric acid; PMDD: premenstrual dysphoric disorder; SSRI: selective serotonin reuptake inhibitor

Griffin, PNAS, 1999; Sundstrom, Psychoneuroendocrinology, 1998

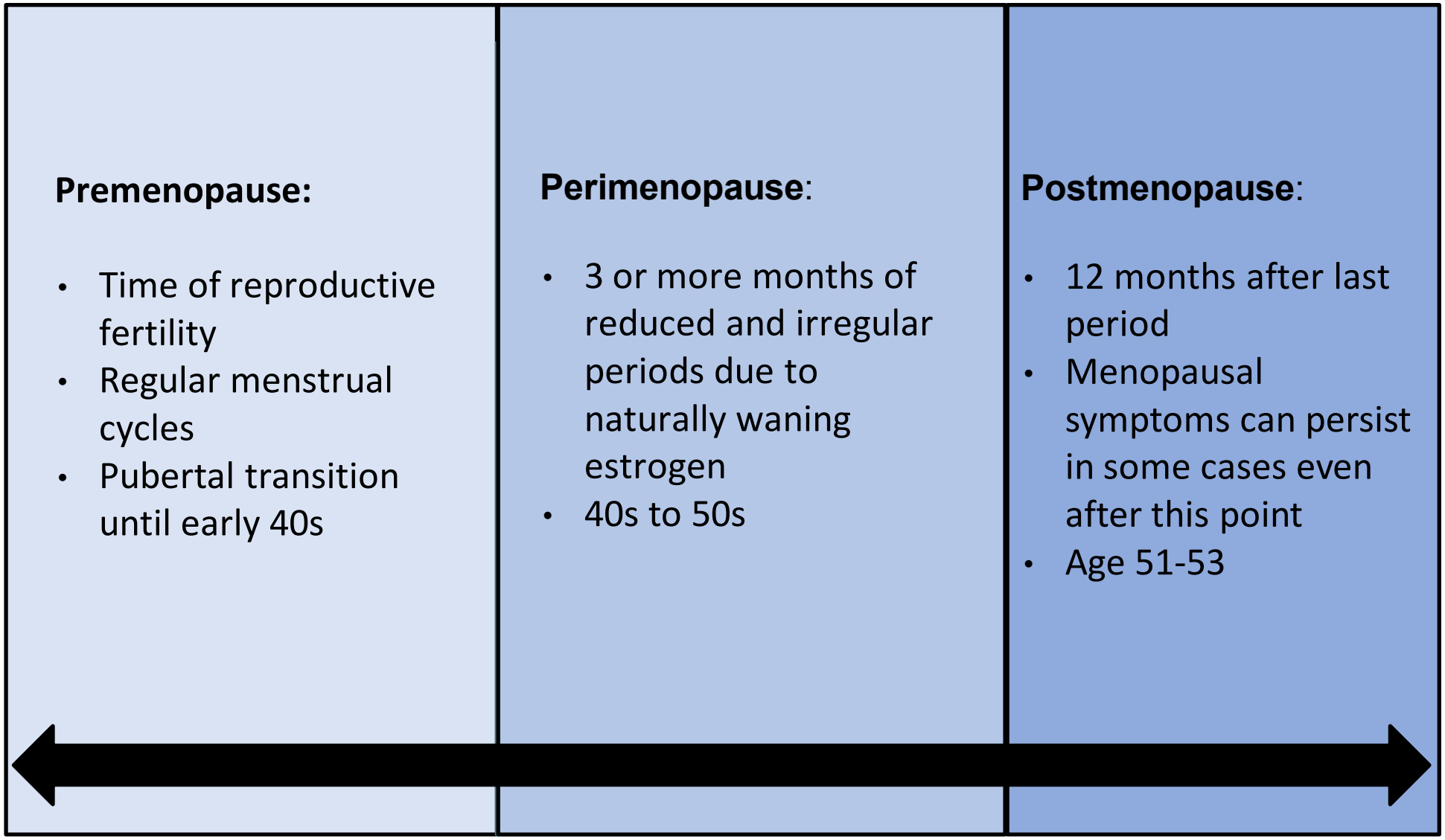
PMDD Symptoms Remit with Leuprolide Treatment and Recur During during Estradiol/Progesterone Addback



Schmidt et al (1998) NEJM 338: 209-216

Menopause

Reproductive Lifespan



Harlow, Climacteric, 2012

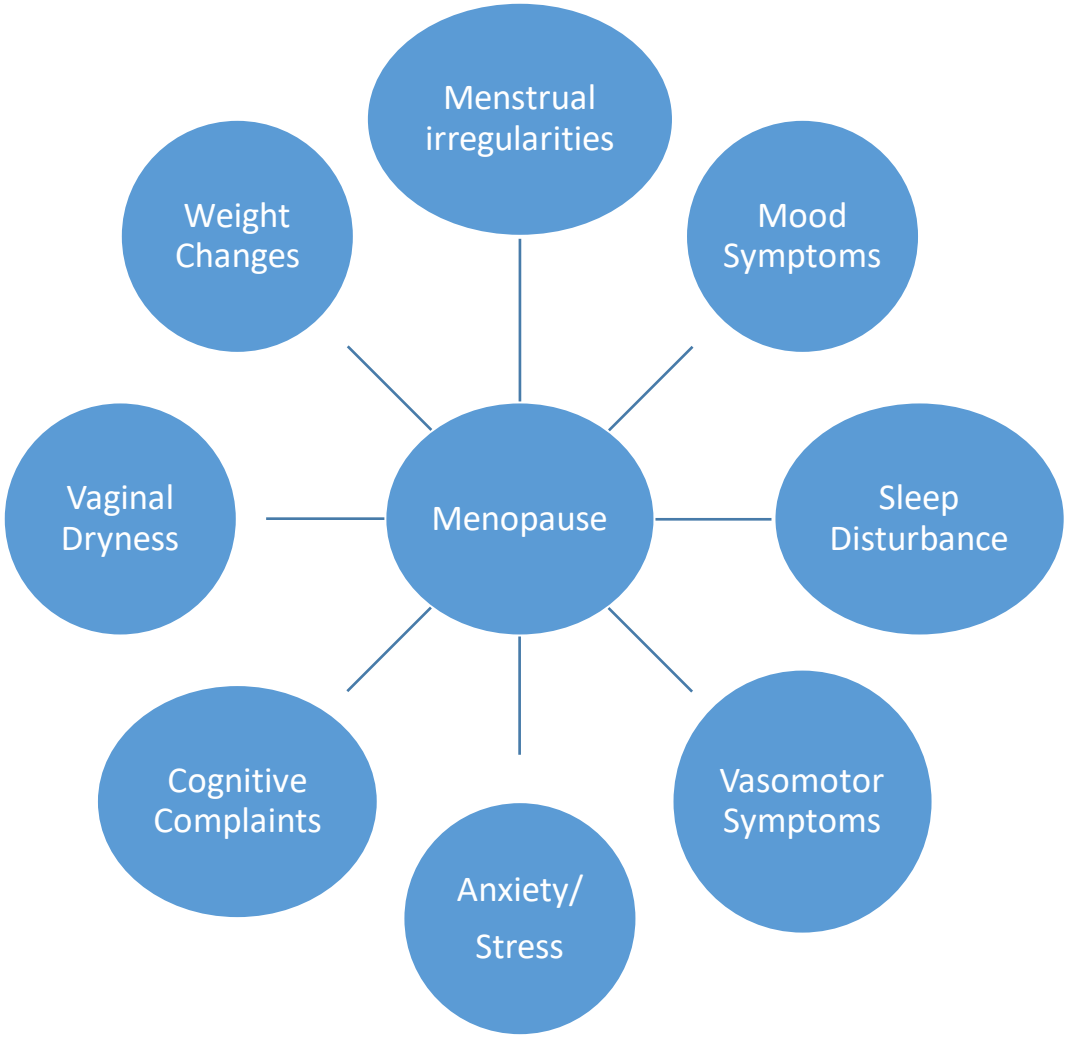
Common Menopausal Symptoms

Study of Women's Health Across the Nation

Seattle midlife Women's Health Study

Penn Ovarian Aging Study

MsFLASH



Avis, An Epidemiol, 1994; Freeman, Arch Gen Psych, 2004; Kravitz, Psychol Med, 2014; Bromberger, Psychol Med, 2015; Joffe, J Clin Endocrin and Metab, 2016

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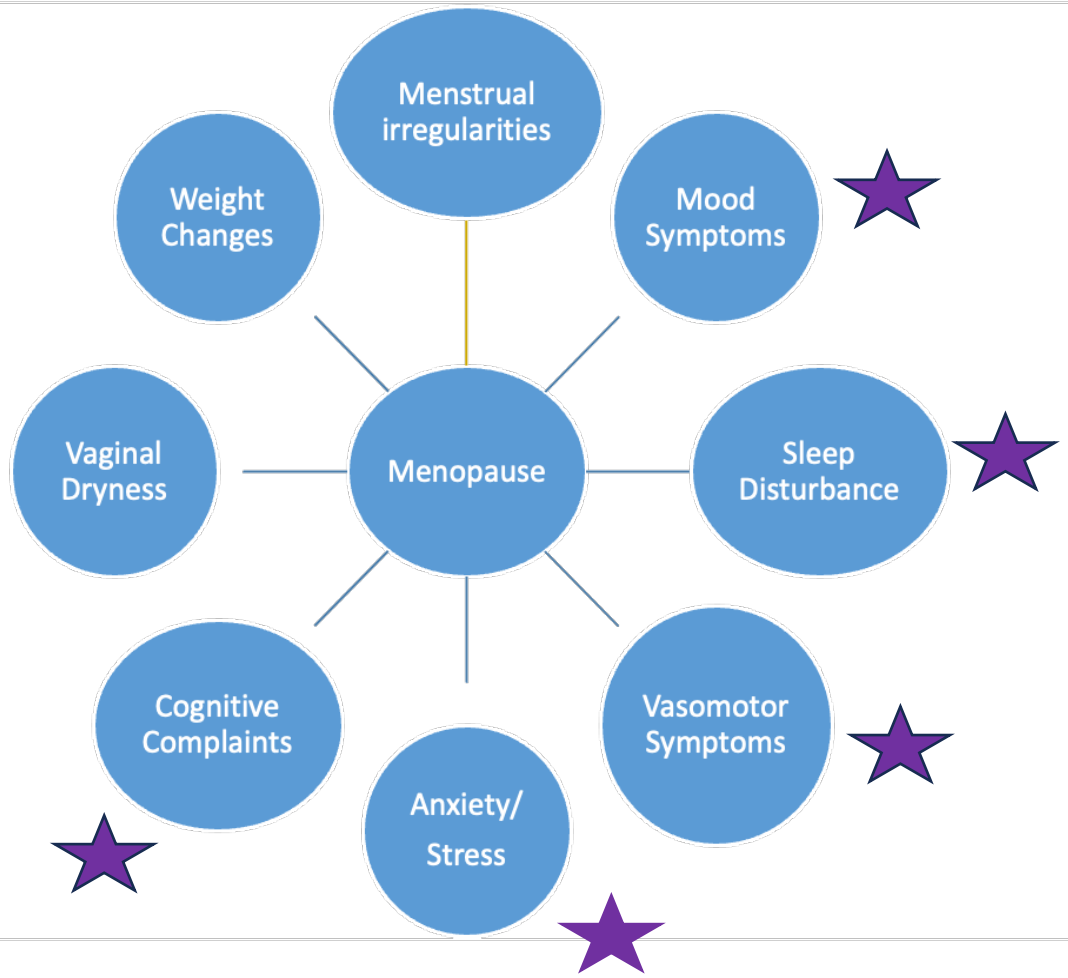
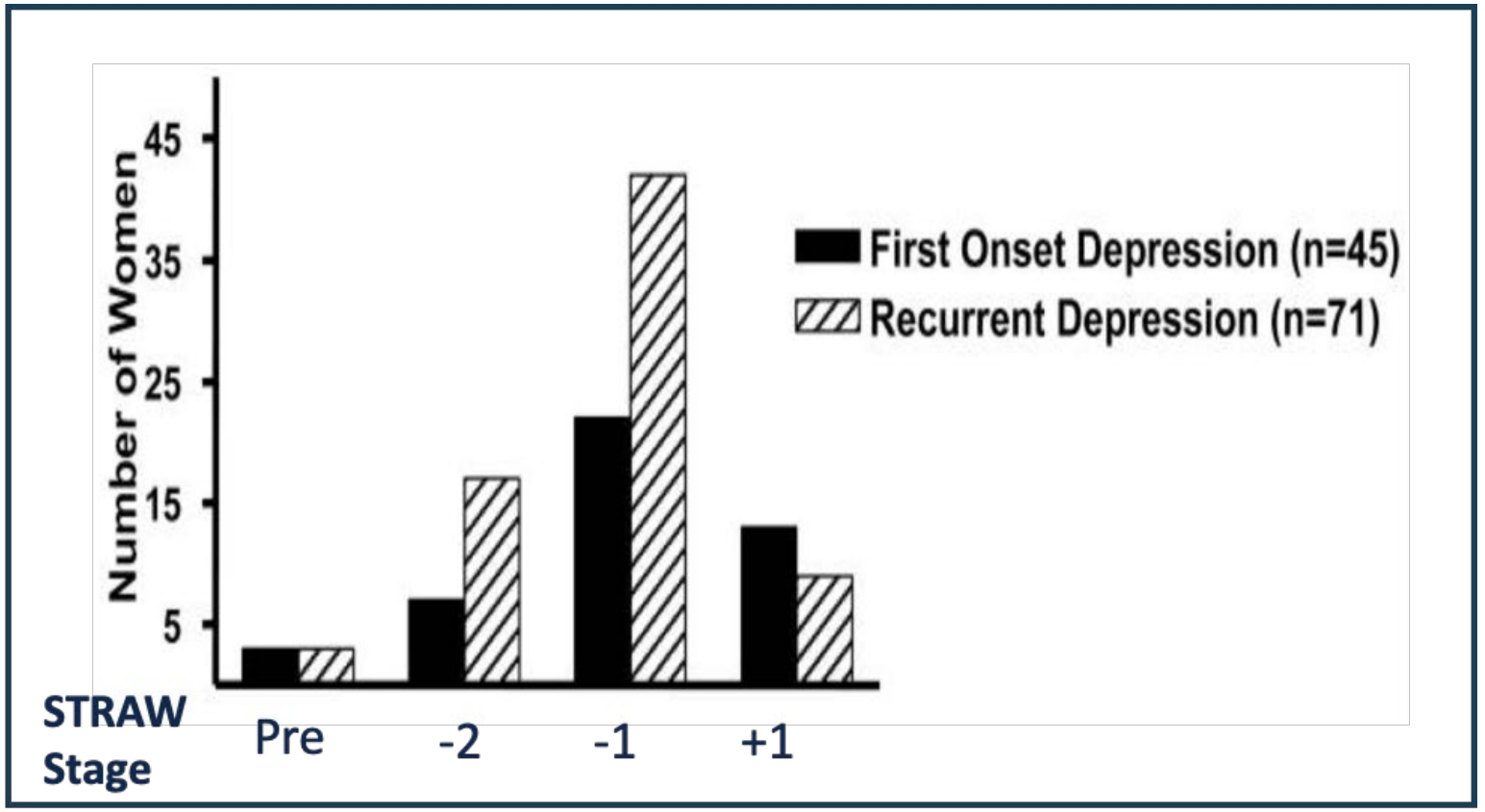


Avis, An Epidemiol, 1994; Freeman, Arch Gen Psych, 2004; Kravitz, Psychol Med, 2014; Bromberger, Psychol Med, 2015; Joffe, J clin Endocrin and Metab, 2016

Risk for depression increases across the perimenopause



Bromberger, J Affective Disorders, 2007; Steinberg, J Clin Psych, 2008

Depressive symptoms are common during perimenopause

‘sub-syndromal’ symptoms most common

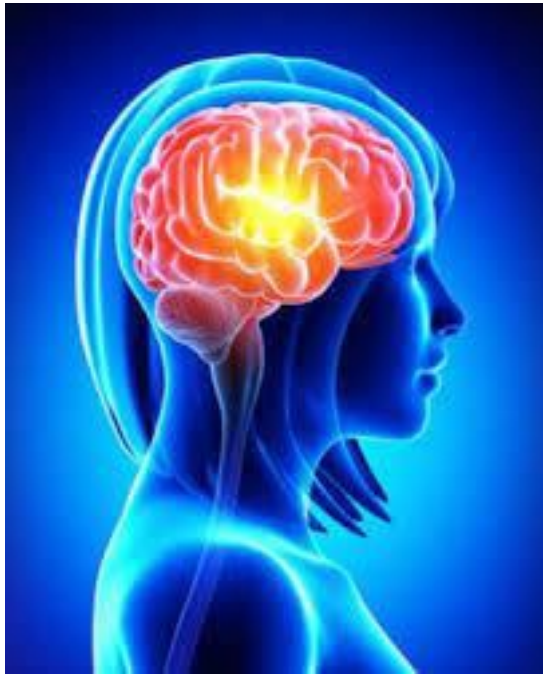
Women at highest risk for a MDE have a history of MDD

First lifetime MDE during the menopausal transition is less common

Independent of estradiol level

Maki, J of Women’s Health, 2019; Joffe, J Clin Endocrinol and Metab, 2019

Depression during midlife is linked to adverse medical outcomes



Thurston, Menopause, 2017

Who is most likely to develop symptoms?

Previously the '*domino theory*' was the prevailing theory for depression during perimenopause

Vasomotor symptoms (VMS)

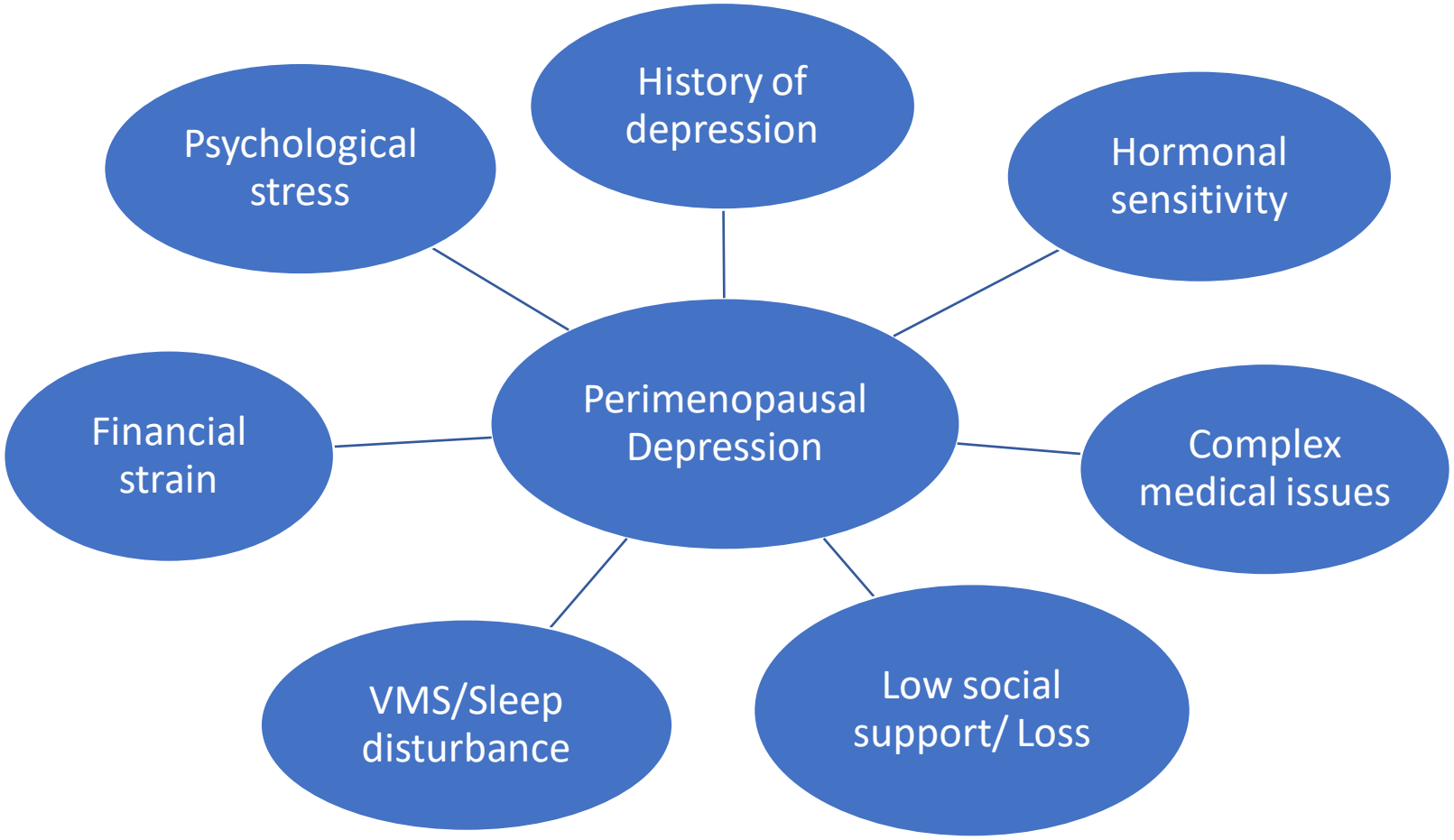
Sleep Disturbance

Depression

Severe VMS are not necessarily associated with depressive sx

Night VMS linked w/ depressive sx independent of sleep disturbance

Who is most likely to develop symptoms?



Avis, An Epidemiol, 1994; Freeman, Arch Gen Psych, 2004; Kravitz, Psychol Med, 2014; Bromberger, Psychol Med, 2015; Joffe, J clin Endocrin and Metab, 2016

Pathophysiology

Greater variability in estradiol levels

May impact neurotransmitters involved in the pathophysiology of affective exacerbations and neuronal architecture

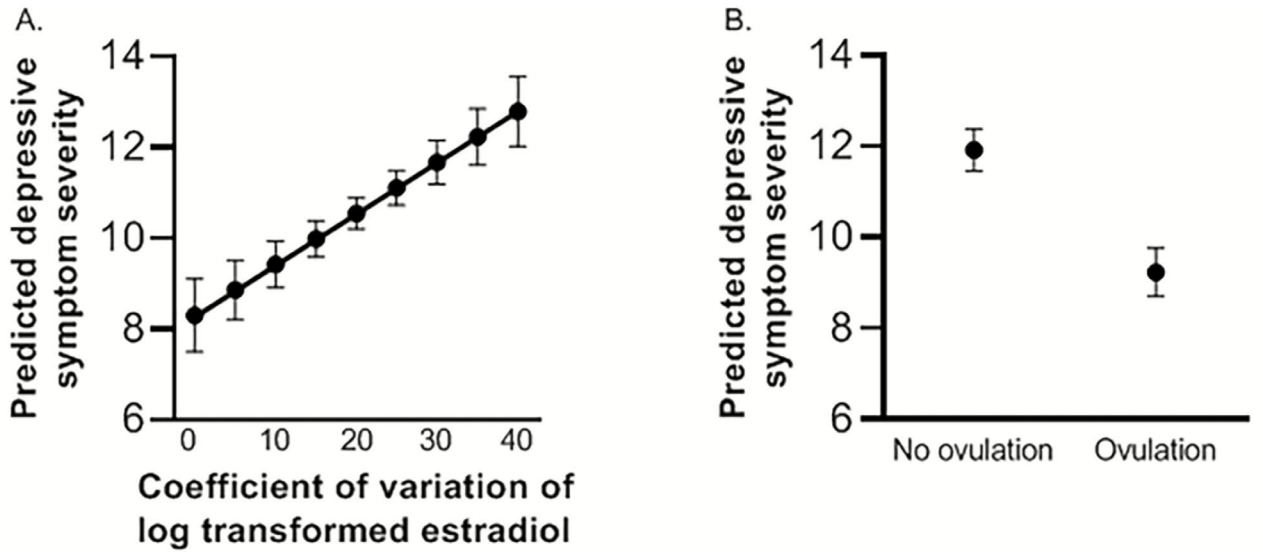
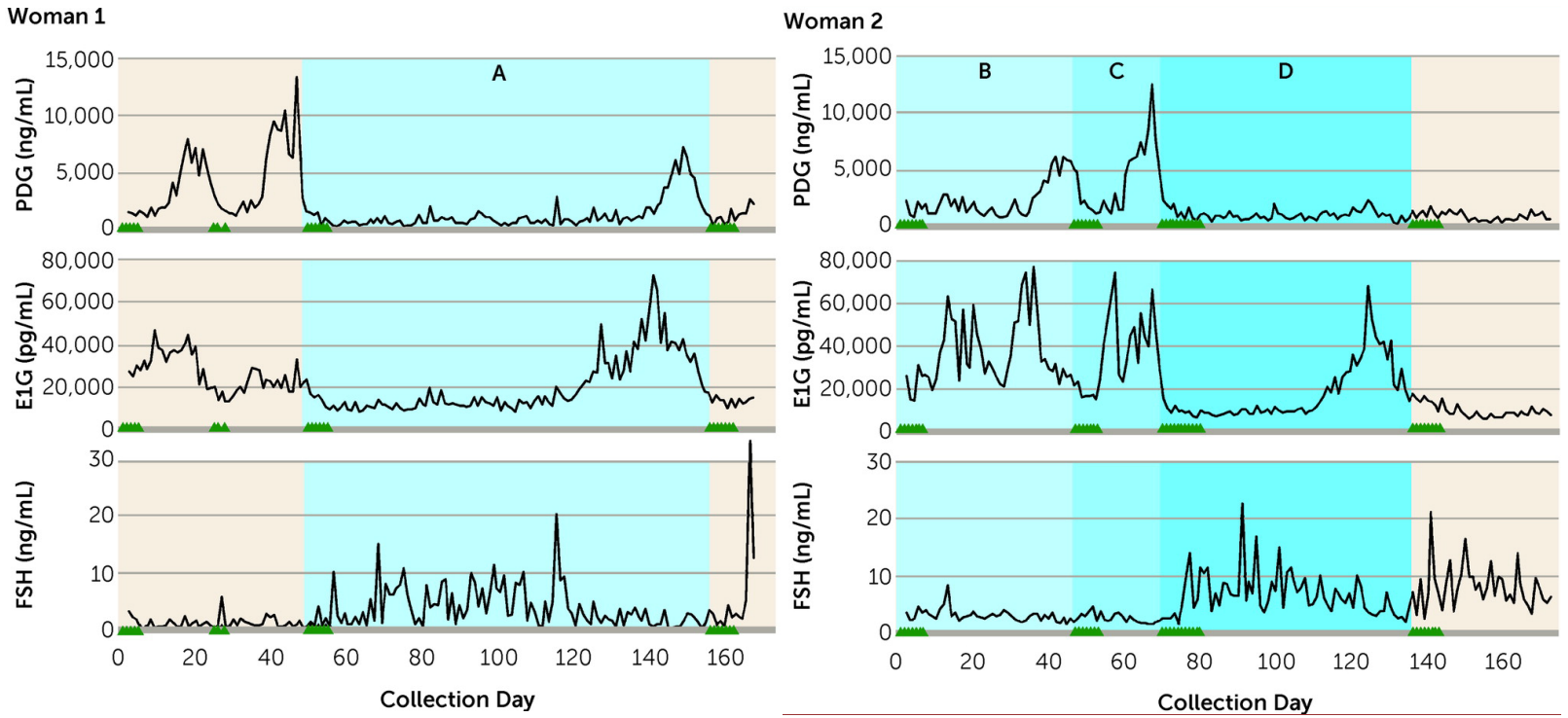


Figure 2. Predicted depressive symptom severity by A) variability in serum levels of estradiol and by B) detection or or not of serum progesterone indicating ovulation

Gordon et al, Am J Psychiatry, 2015; Joffe, J Clin Endocrinol and Metab, 2019

Sex steroid levels are highly variable during the perimenopause



b A, a long ovulatory cycle; B, a long ovulatory cycle with low luteal progesterone; C, a normal ovulatory cycle; and D, a long anovulatory cycle. Triangles on the x-axis represent days of menstrual bleeding. PDG, pregnanediol-glucuronide; E1G, estrone-glucuronide; FSH, follicle-stimulating hormone.

Gordon et al (2015) Am J Psychiat 172: 227-236

Available screening scales can be helpful

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

NAME:_____ DATE:_____

Over the last *2 weeks*, how often have you been bothered by any of the following problems?
(use "✓" to indicate your answer)

	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 figety 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	0	1	2	3
add columns		+	+	

(Healthcare professional: For interpretation of TOTAL, please refer to accompanying scoring card). TOTAL:

Which of the following symptoms apply to you at this time?

(X ONE Box For EACH Symptom) For Symptoms That Do Not Apply, Please Mark "None").

Symptoms:	none	mild	moderate	severe	extremely severe
Score =	**0**	**1**	**2**	**3**	**4**
1. Hot flashes, sweating (episodes of sweating)	☐	☐	☐	☐	☐
2. Heart discomfort (unusual awareness of heart beat, heart skipping, heart racing, tightness)	☐	☐	☐	☐	☐
3. Sleep problems (difficulty in falling asleep, difficulty in sleeping through the night, waking up early)	☐	☐	☐	☐	☐
4. Depressive mood (feeling down, sad, on the verge of tears, lack of drive, mood swings)	☐	☐	☐	☐	☐
5. Irritability (feeling nervous, inner tension, feeling aggressive)	☐	☐	☐	☐	☐
6. Anxiety (inner restlessness, feeling panicky)	☐	☐	☐	☐	☐
7. Physical and mental exhaustion (general decrease in performance, impaired memory, decrease in concentration, forgetfulness)	☐	☐	☐	☐	☐
8. Sexual problems (change in sexual desire, in sexual activity and satisfaction)	☐	☐	☐	☐	☐
9. Bladder problems (difficulty in urinating, increased need to urinate, bladder incontinence)	☐	☐	☐	☐	☐
10. Dryness of vagina (sensation of dryness or burning in the vagina, difficulty with sexual intercourse)	☐	☐	☐	☐	☐
11. Joint and muscular discomfort (pain in the joints, rheumatoid complaints)	☐	☐	☐	☐	☐

Heinaman, Health Qual Life Outcomes, 2003

Spectrum of symptoms in perimenopausal depression

Depressed mood

Irritability

Anhedonia

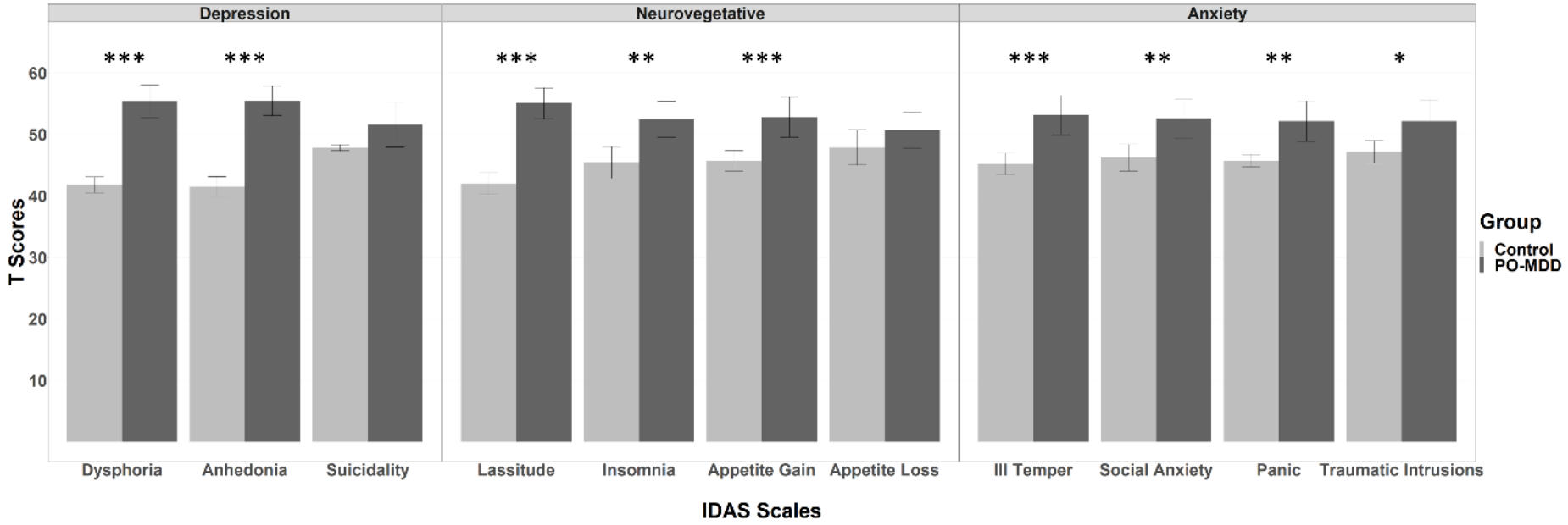
Fatigue

Insomnia

Appetite change

Anxiety

Panic attacks



Nathan et al., under review

Antidepressants are the mainstay of treatment

SSRI/SNRI best studied

Consider prior efficacy and tolerability

Hormone therapy can also be highly effective

OCPs not well studied

Joffe, J Women's Health Gend Based Med, 2003; Soares, J Clin Psychiatry, 2003; Kornstein, J Clin Psychiatry, 2010; Maki, J Women's Health, 2019

Choosing an antidepressant when a patient is on tamoxifen

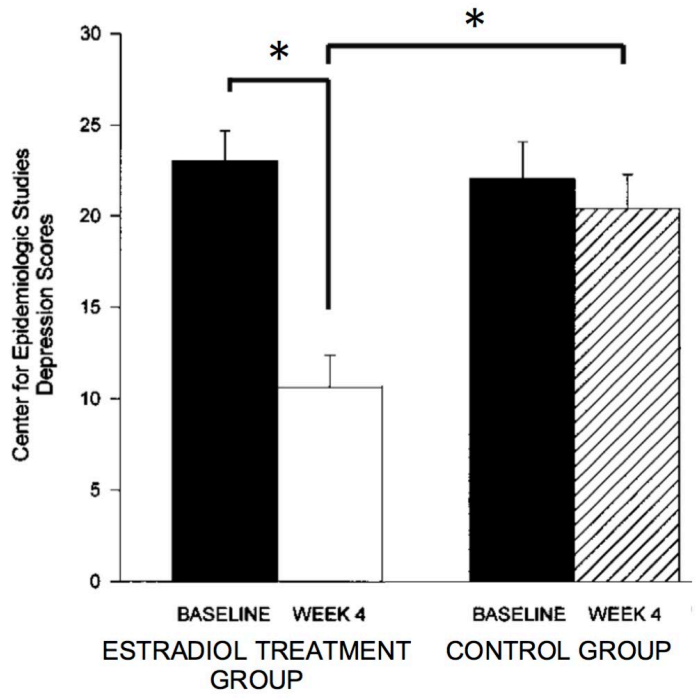
Avoid antidepressants that inhibit CYP2D6

Can be helpful to concurrently manage mood/VMS

Desmarais, J Clin Psychiatry, 2015

Estradiol treatment reverses depression in the perimenopause

c. Reduced depressive symptoms following estradiol treatment in women in STRAW Stage -1[15]

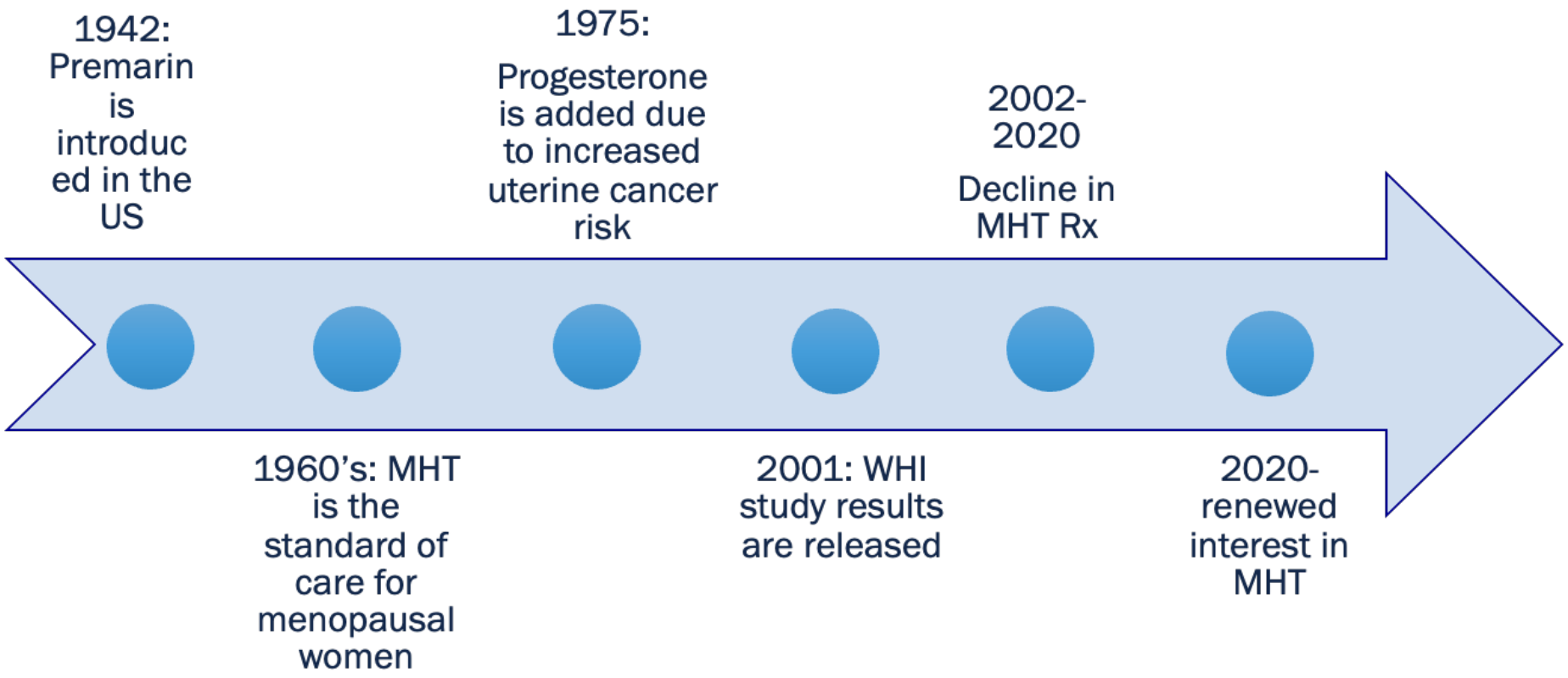


Schmidt, PJ *et al* (2000) *Am J Obs Gyn*183: 414–420

Tissue Selective Estrogen Complex (TSEC)

- Created to relieve vasomotor symptoms and treat osteoporosis while avoiding risks of HRT alone
- Combines conjugated estrogens with a SERM
- Maintains beneficial effects of estrogen, while SERM limits harmful effects on breast and endometrium

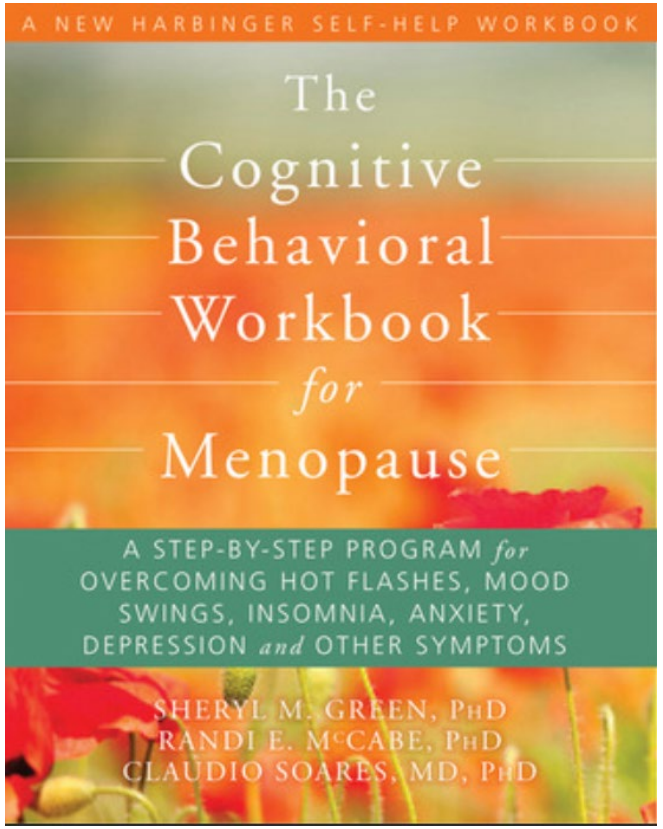
History of Hormone Therapy is Complex



Behavioral options are effective

Cognitive Behavioral Therapy (CBT) has been studied for:

- **Depression**
- **VMS**
- **Insomnia**



Hollon, JAMA Psychiatry, 2014; Nowokowski, Sleep Med Clin, 2019

Behavioral Activation Therapy

Behavioral activation therapy increases motivation and reduces depression at least as well as medication, even for severe depression

Behavioral activation works by helping people engage in their lives

Seek pleasure

Make connections

Celebrate accomplishments

VMS are common and burdensome for many women

~60% women experience VMS during the perimenopause

30% women experience severe VMS

Major impact on quality of life and function

Associated with perceived stress, +/- associated with physiological stress response

Gold, Am J Public Health, 2006; Thurston, Obset Gynecol Clin N America, 2011; Avis, JAMA Internal Medicine, 2015; Gordon, Menopause, 2016

Serotonergic antidepressants are helpful for vasomotor symptoms (VMS)

Venlafaxine, paroxetine, fluoxetine, escitalopram, citalopram studied

Any serotonergic agent (SSRI/SNRI) can work

Low dose is sufficient

Guthrie, Obstet and Gynecol, 2015

Other non-hormonal options for VMS

Gabapentin/pregabalin

Clonidine

Fezolinetant

Black cohosh

Joffe, J Women's Health Gend Based Med, 2003; Soares, J Clin Psychiatry, 2003; Kornstein, J Clin Psychiatry, 2010

Environmental modifications can help

Identify triggers

Reduce caffeine

Reduce alcohol

Exercise

Dress in layers

Sleep disturbance is prevalent during midlife

30-60% women experience sleep disturbance

Can occur in the absence of VMS

<u>Middle insomnia is most Common</u>

Major source of functional impairment

Rate of primary sleep disorders increase in midlife

Maki, J Women's Health, 2019

Cognitive symptoms are common…and understudied

Brain fog

Can occur with and without affective symptoms

<u>Screen for sleep disruption</u>

Limited studied treatments

- **--lisdexamphetamine or atomoxetine**
- **--MHT**
- **--testosterone?**

Maki, J Women's Health, 2019

Anxiety is common and more research is needed

Limited data

Anxiety during the menopausal transition linked with more significant vasomotor symptoms

Linked to increased risk for cardiovascular disease

Bipolar Disorder

Women with bipolar disorder are at an increased risk for affective exacerbation

***research is limited**

Some studies have identified the late perimenopause and early postmenopause as the periods of highest risk

Depressive episodes are the most common

Exacerbations not been correlated with specific hormone profiles

Conclusions

Some women are vulnerable to mood symptoms during reproductive transitions

PMDD is diagnosed clinically and there are both hormonal and non-hormonal options

Depressive symptoms during perimenopause are common

Antidepressants can be used to address both depressive and menopausal symptoms

Questions?