



# Women's Mood Disorders Across the Lifespan

Margo Nathan, MD

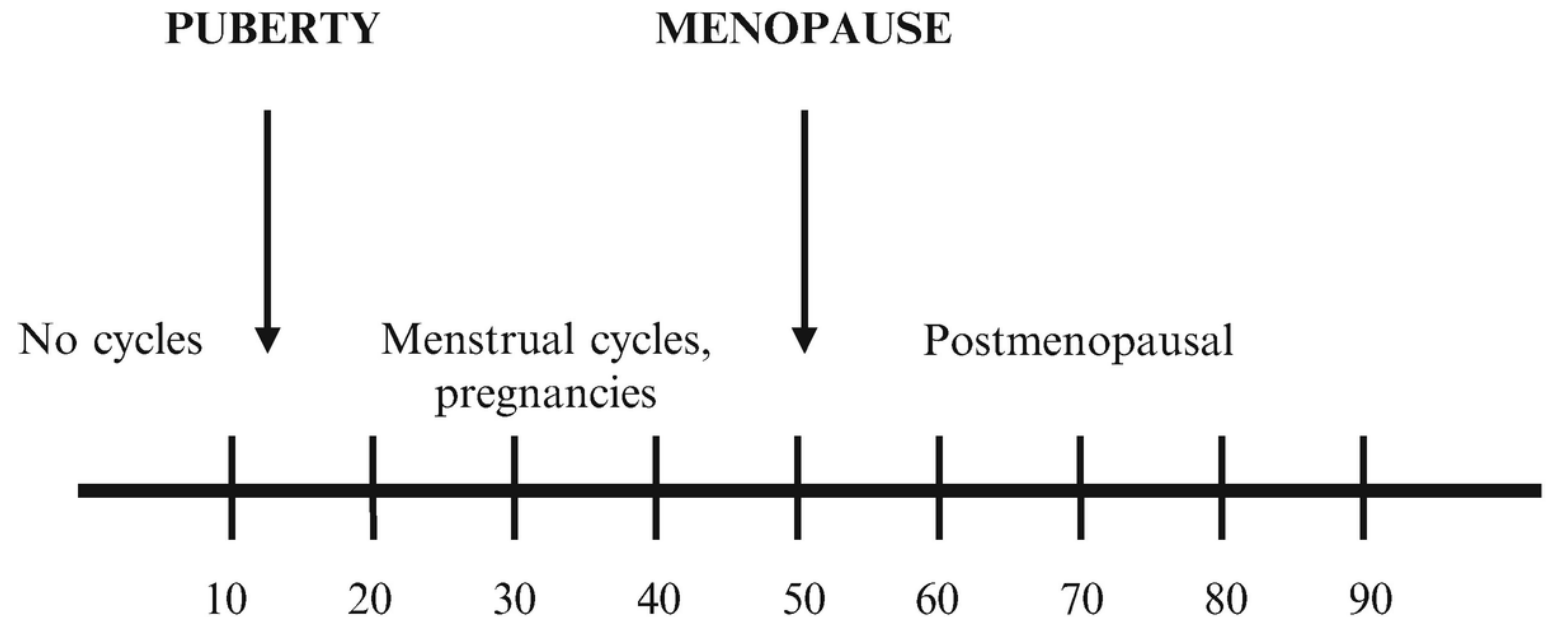
Assistant Professor

UNC Center for Women's Mood Disorders

# Objectives

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

## FEMALE LIFESPAN



# The Increased Risk for Depression in Women Begins at Puberty

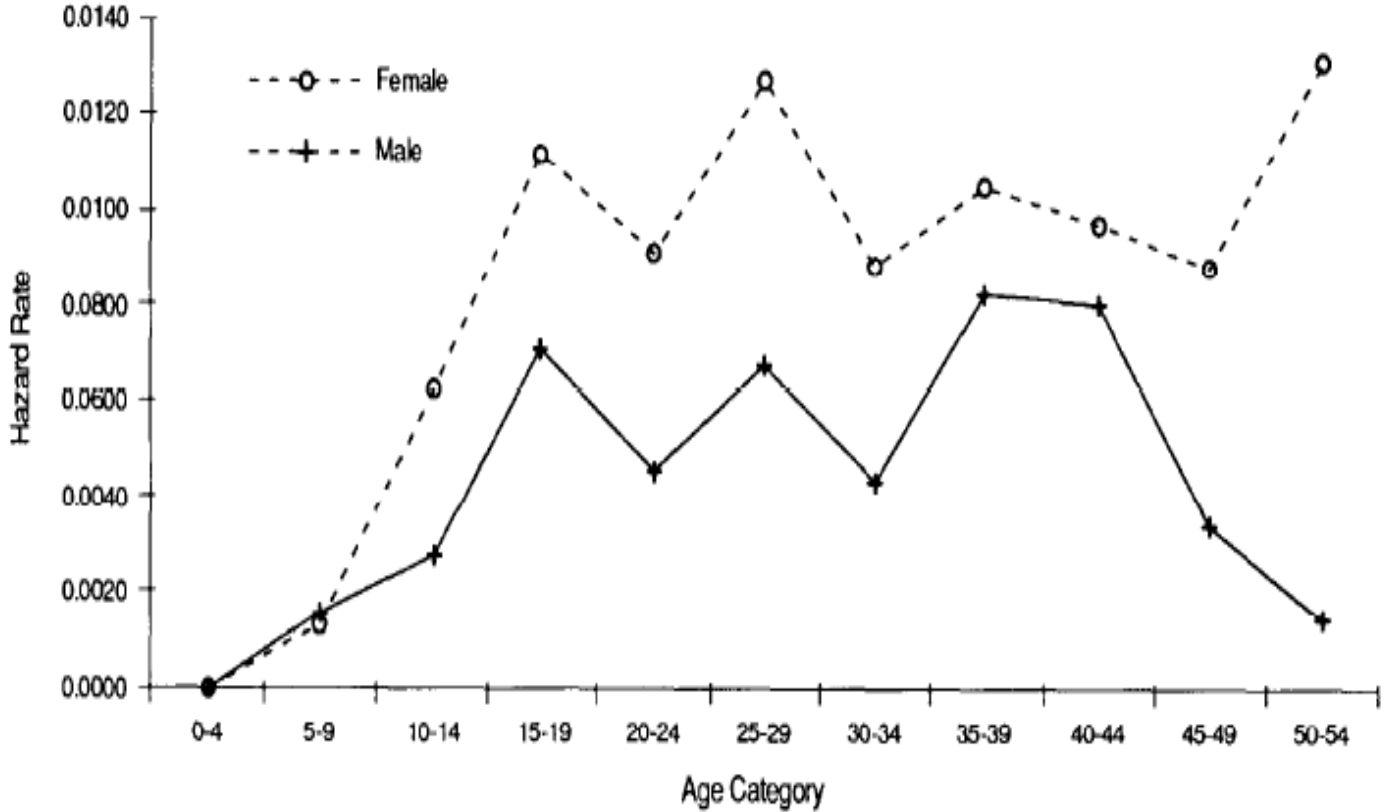
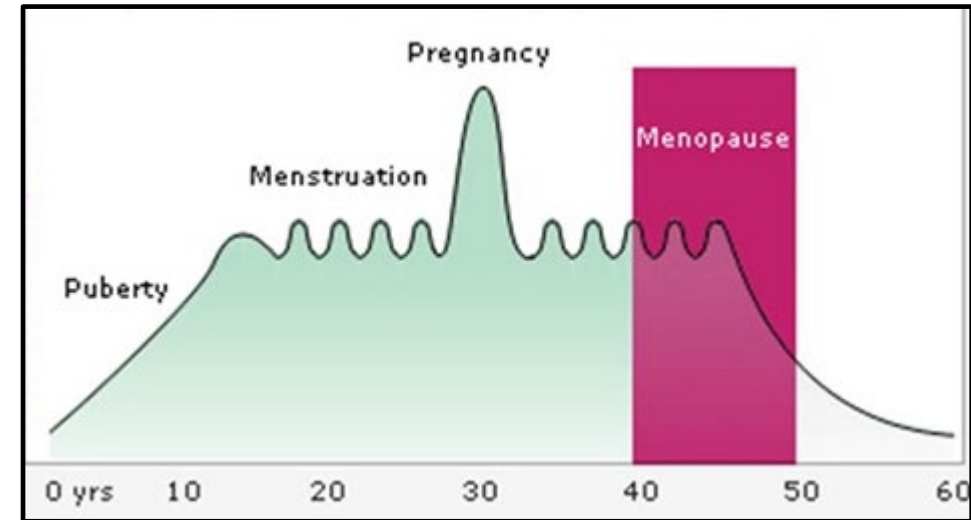


Fig. 1. MDE hazard rates by age and sex.

# 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**

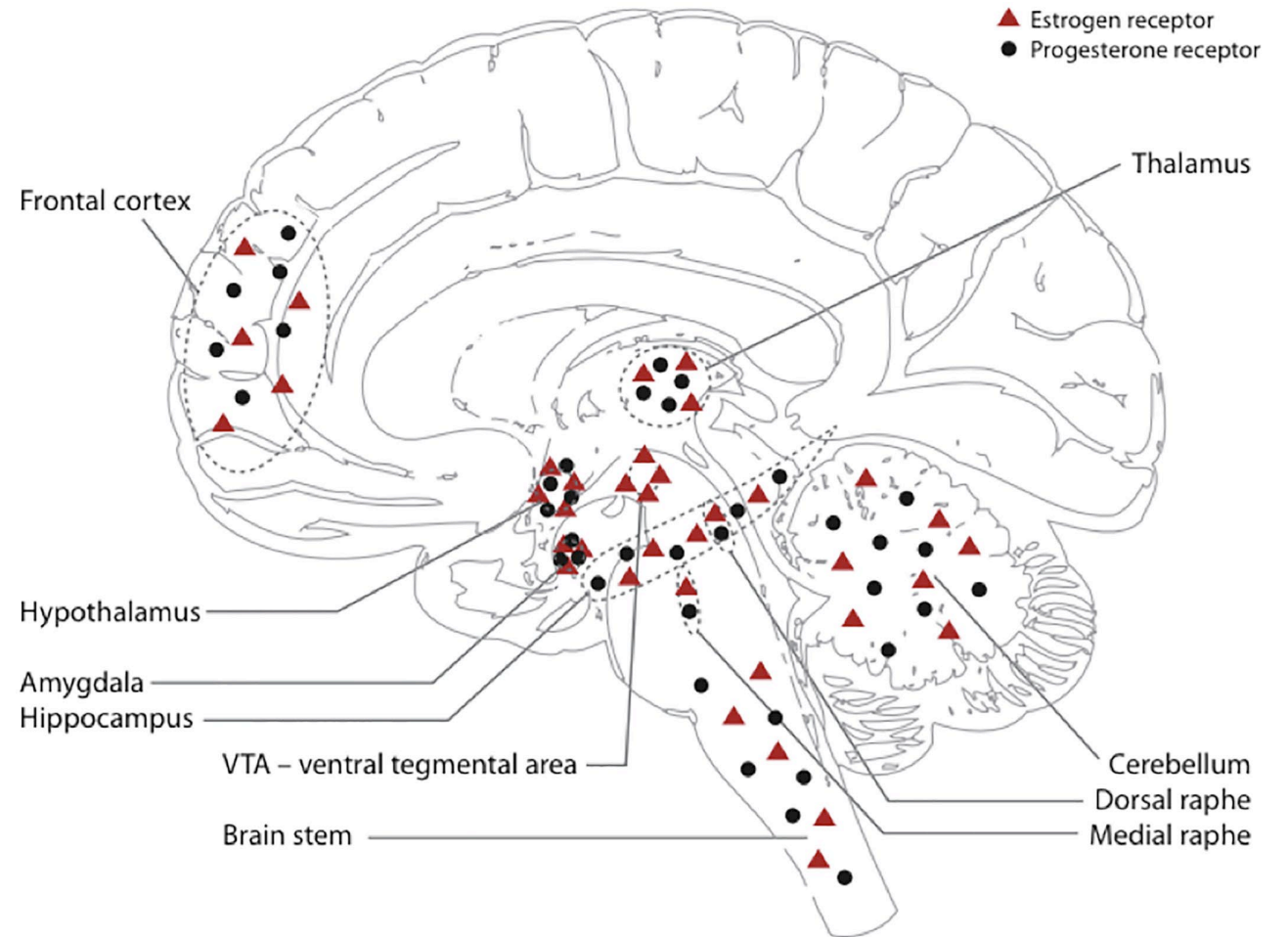


# Gonadal steroid hormones impact neurotransmitter pathways and structural brain regions

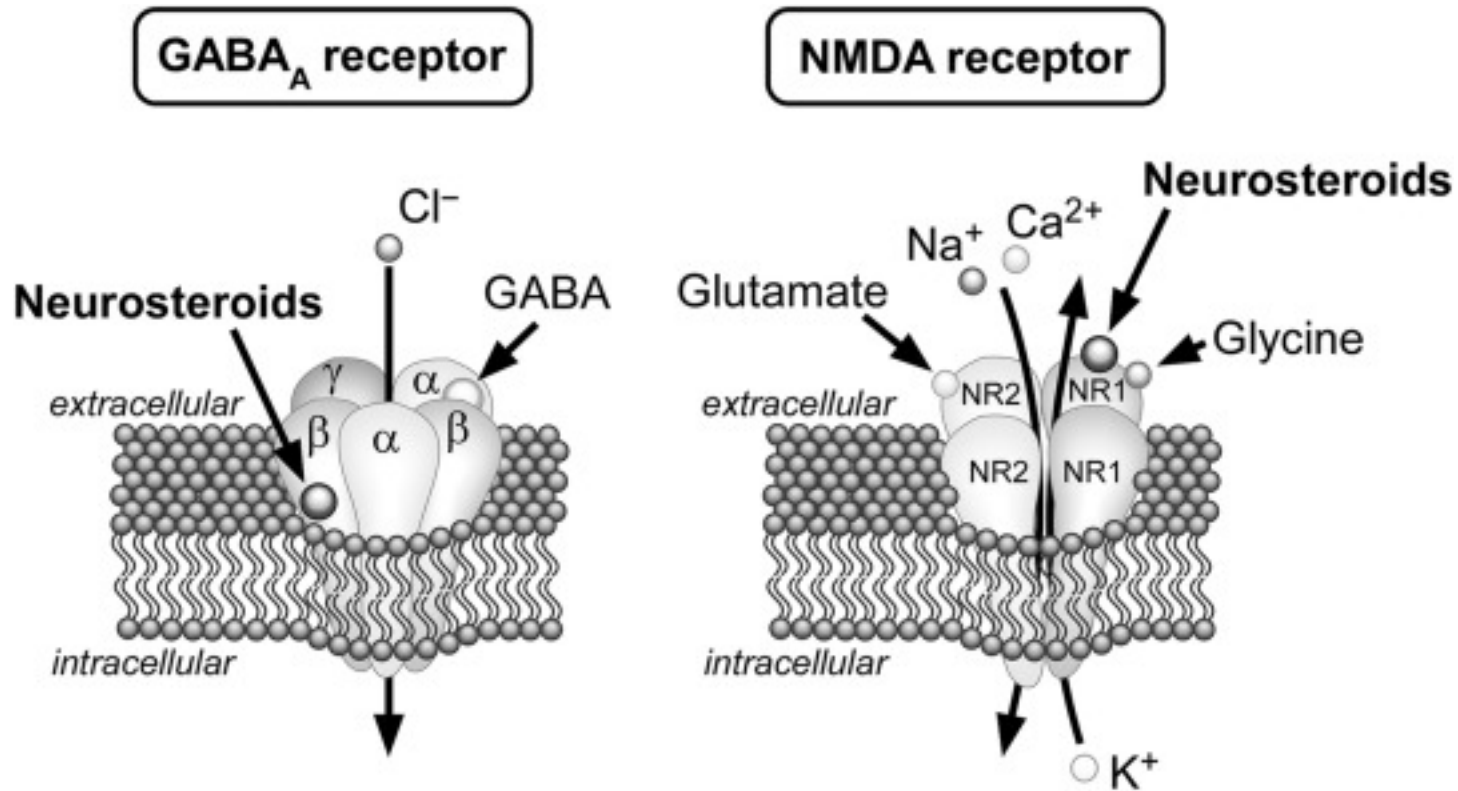
**Progesterone acts on GABA-A receptor complex**

**Estradiol may act on serotonin transporter**

**Estrogen receptors are present on brain structures linked to emotion processing**



# 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**

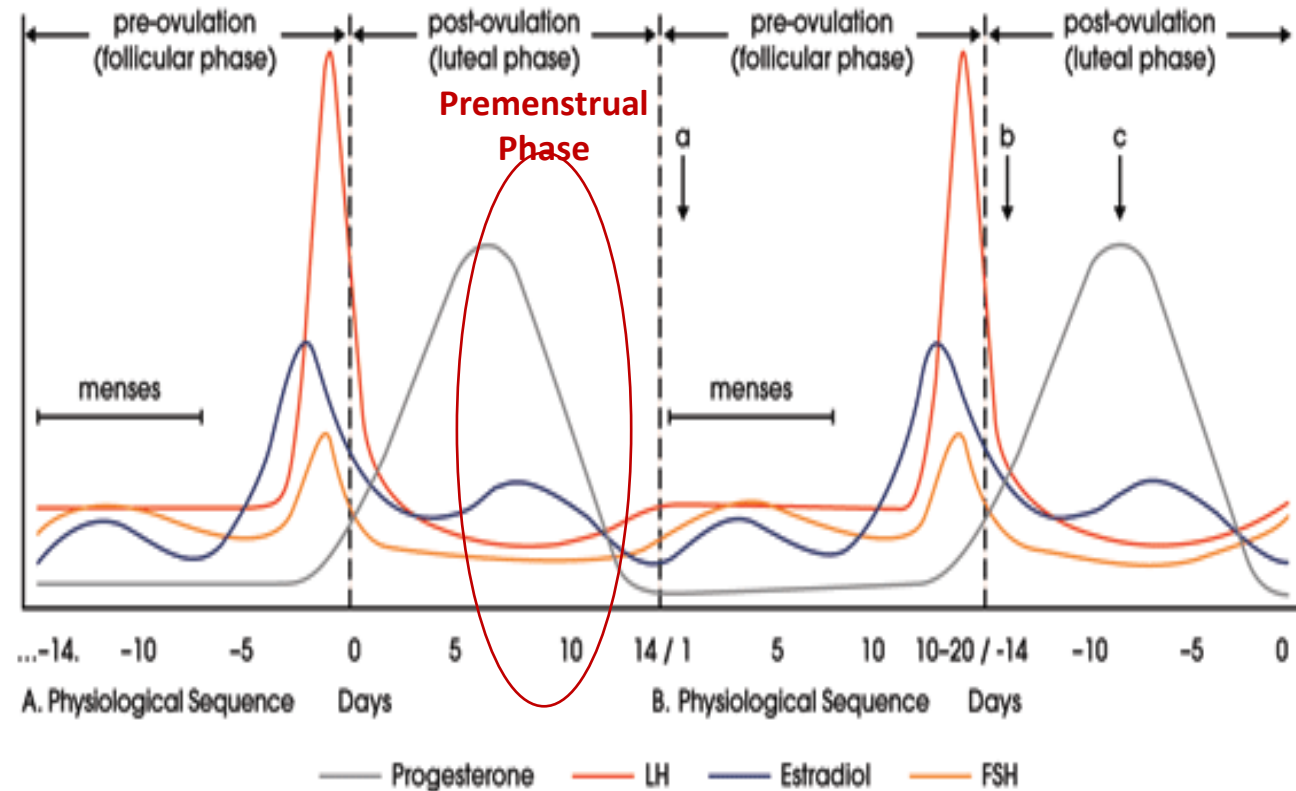


# Menstrual disorders

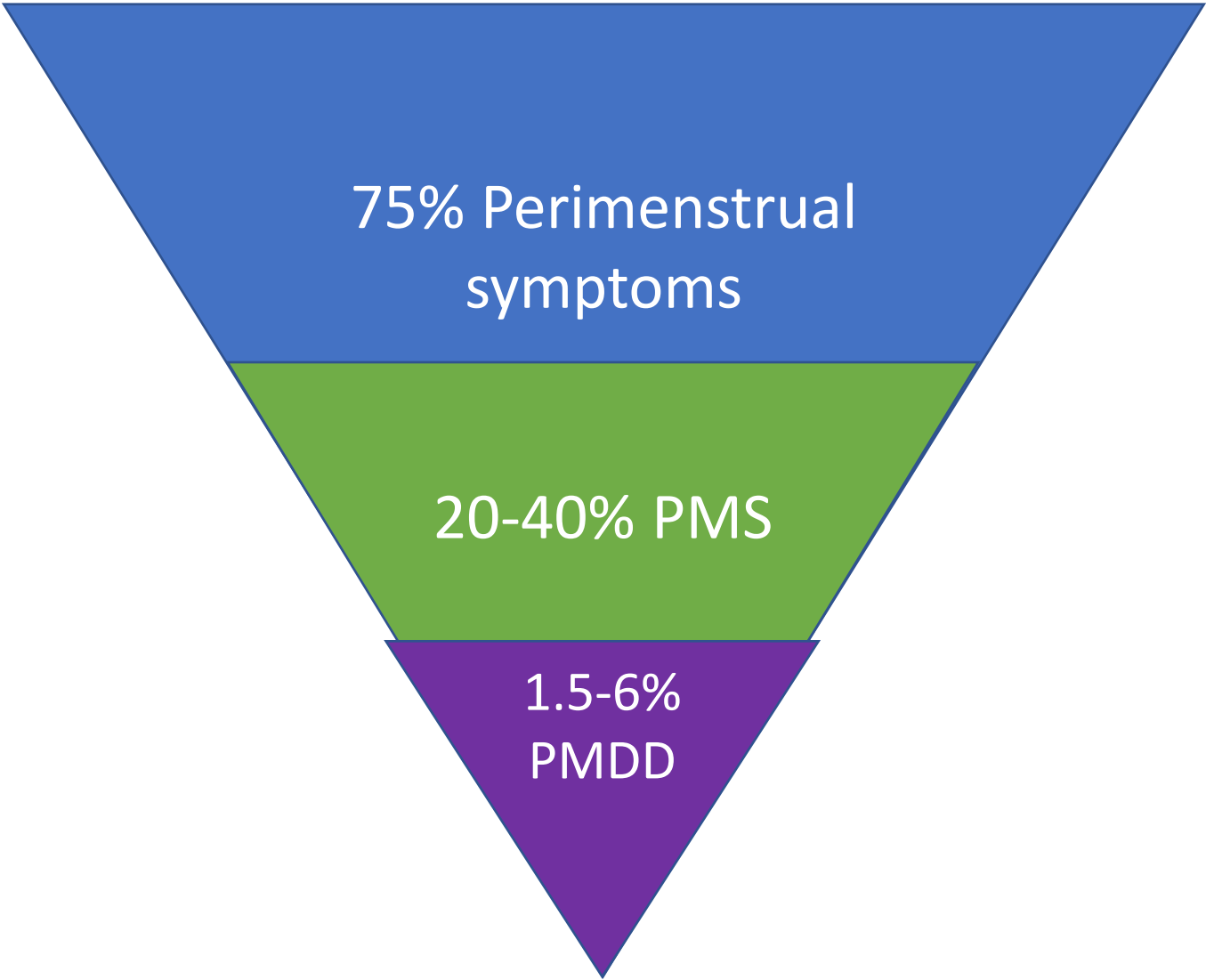


# Menstrual Cycle

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.



# Premenstrual Syndrome

Not listed in DSM-5

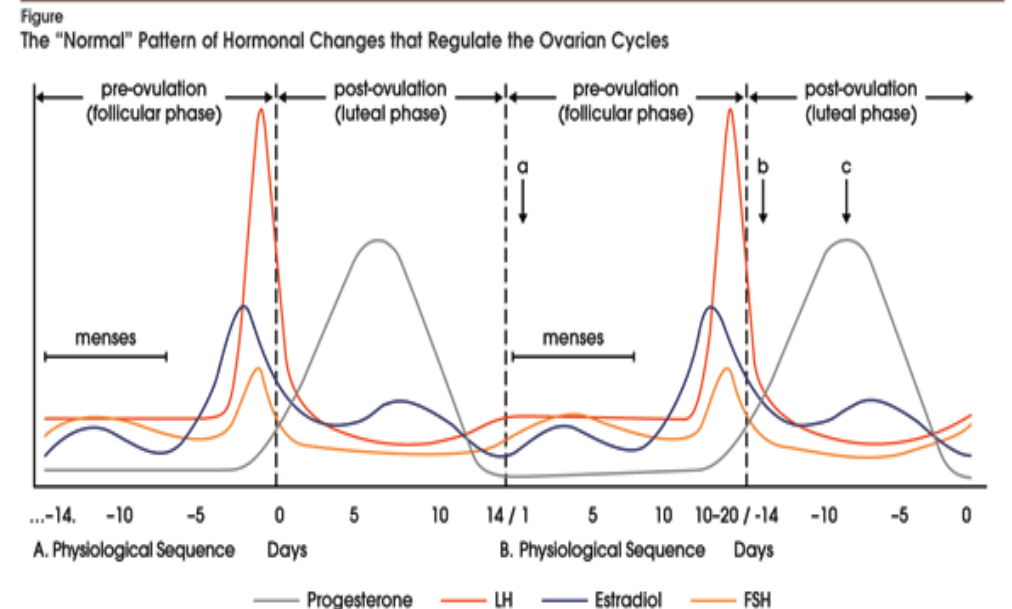
ACOG definition of PMS:

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

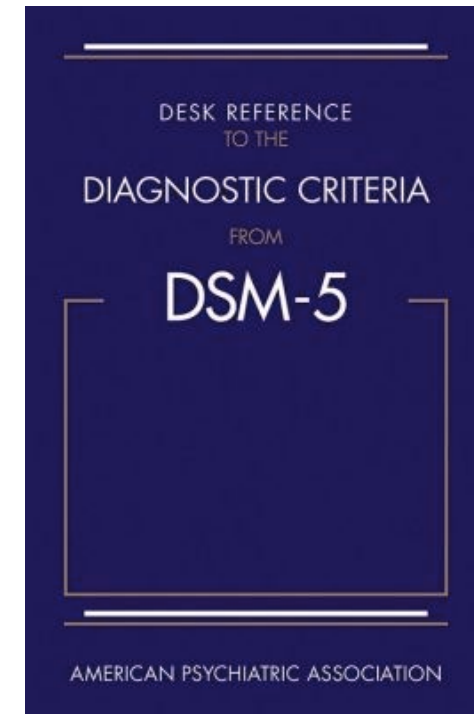
Clinically significant distress or impairment

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**



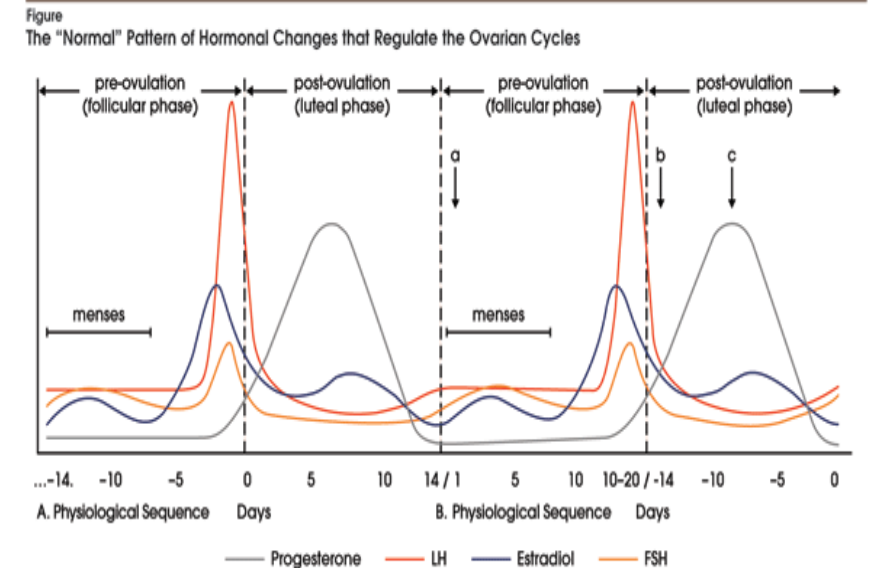


# Role of Hormones in PMDD

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!**



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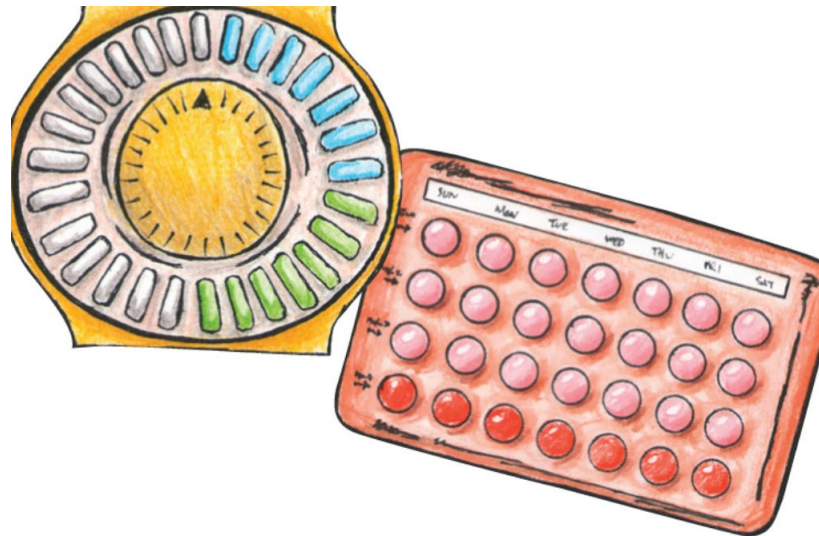
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# Menstrual Disorder Treatment Options

Psychiatric Medications

Hormonal Treatments

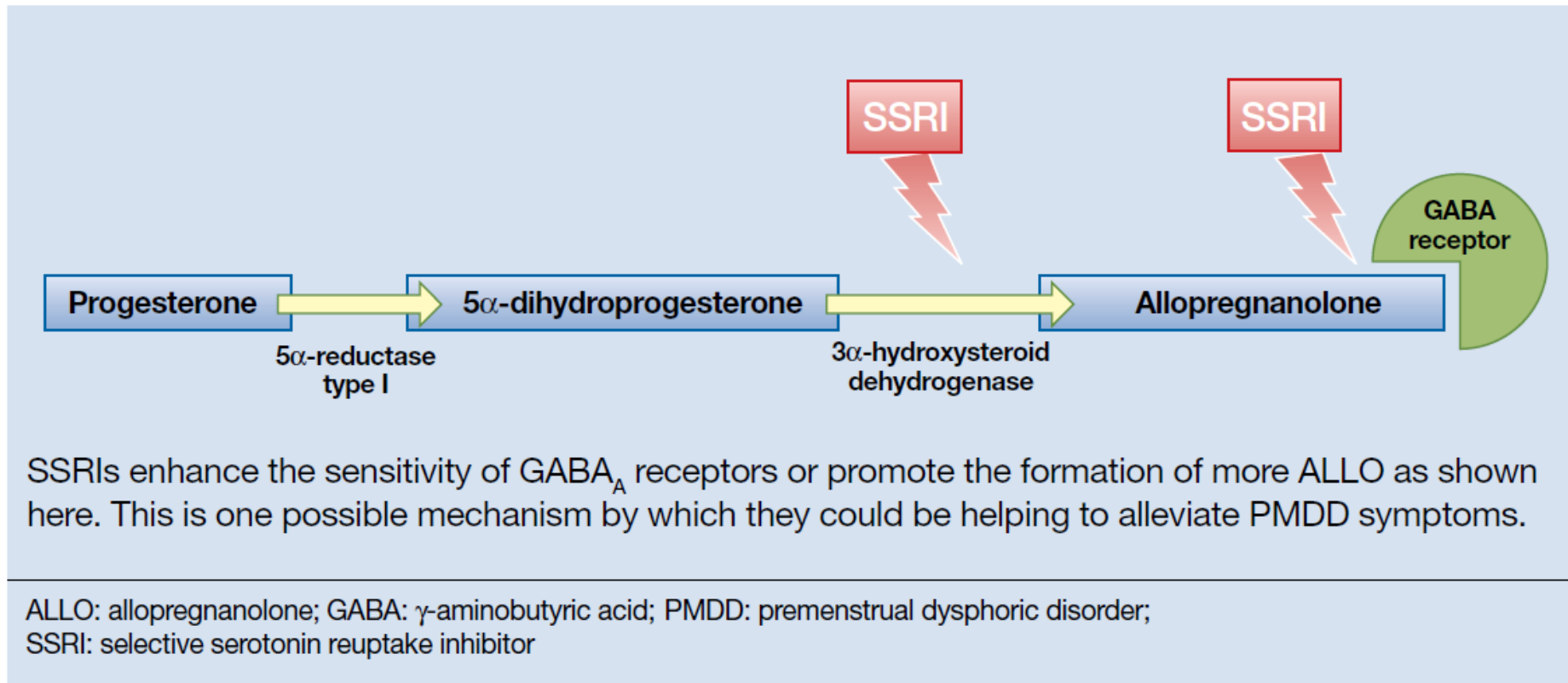
Supplements/Behavioral  
Modification



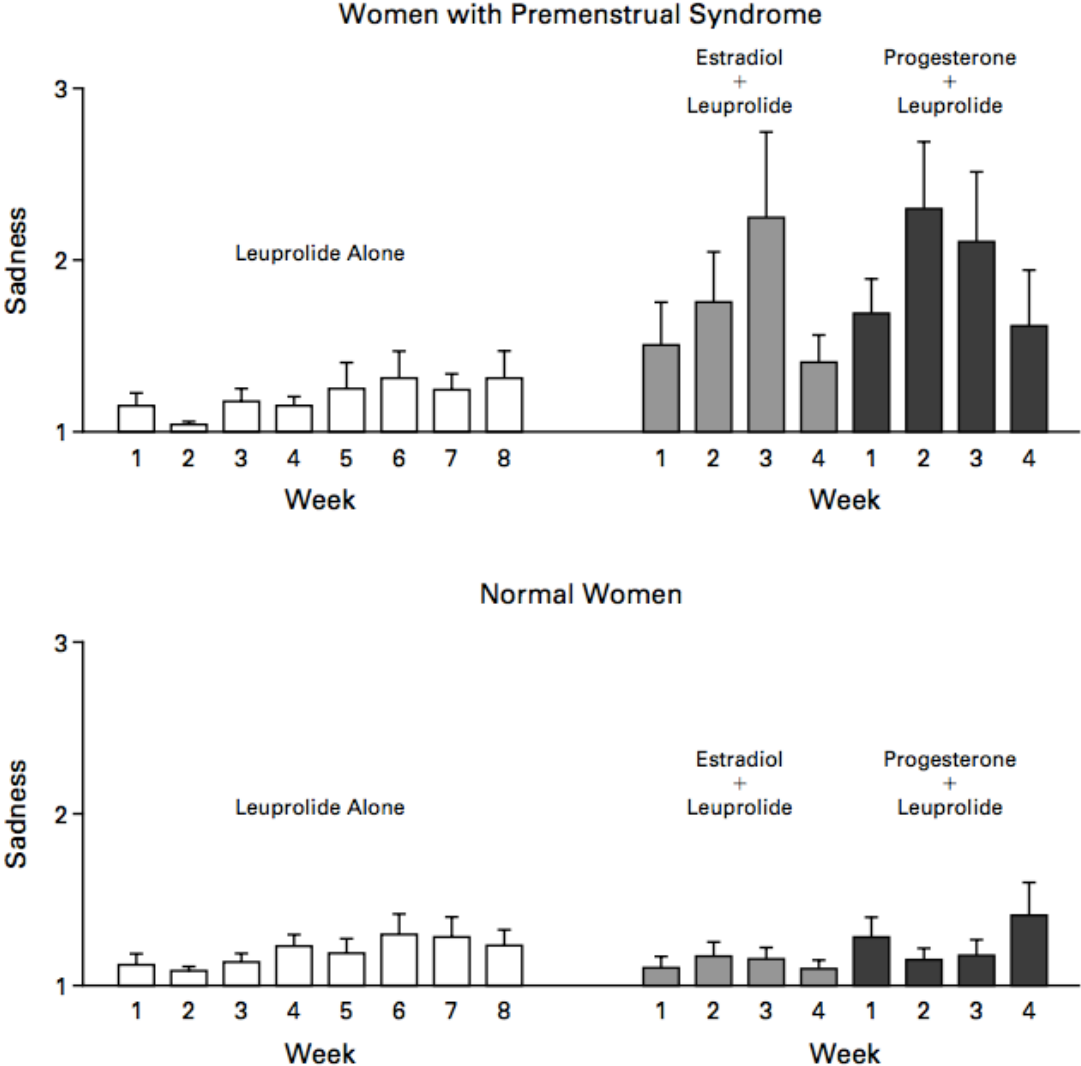
# Why serotonergic antidepressants?

Figure 4

## Conversion of progesterone to ALLO and the SSRI influence



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



# Menopause



# Reproductive Lifespan

## Premenopause:

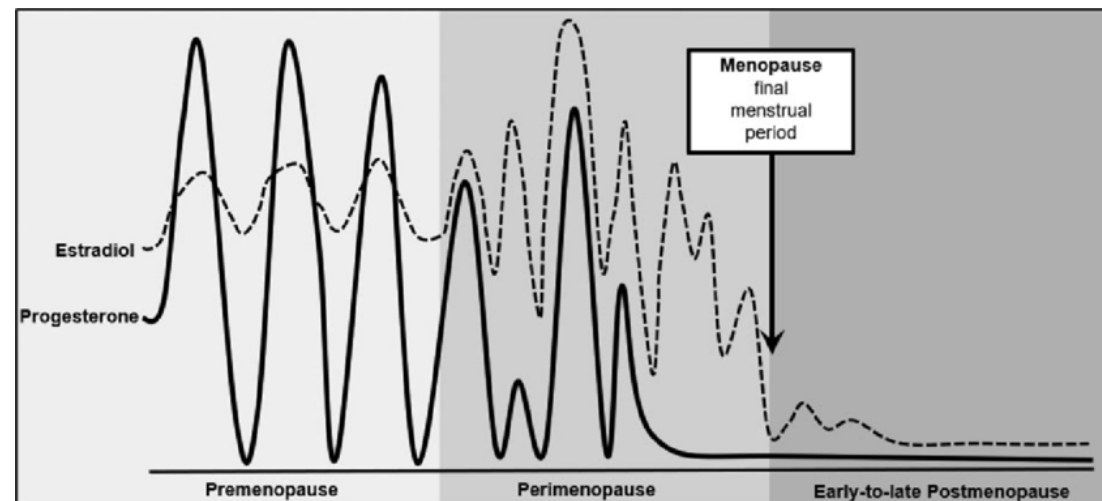
- Time of reproductive fertility
- Regular menstrual cycles
- Pubertal transition until early 40s

## Perimenopause:

- Reduced and irregular periods due to naturally waning estrogen
- 40s to 50s

## Postmenopause:

- 12 months after last period
- Symptoms can persist after this point
- Age 51-53



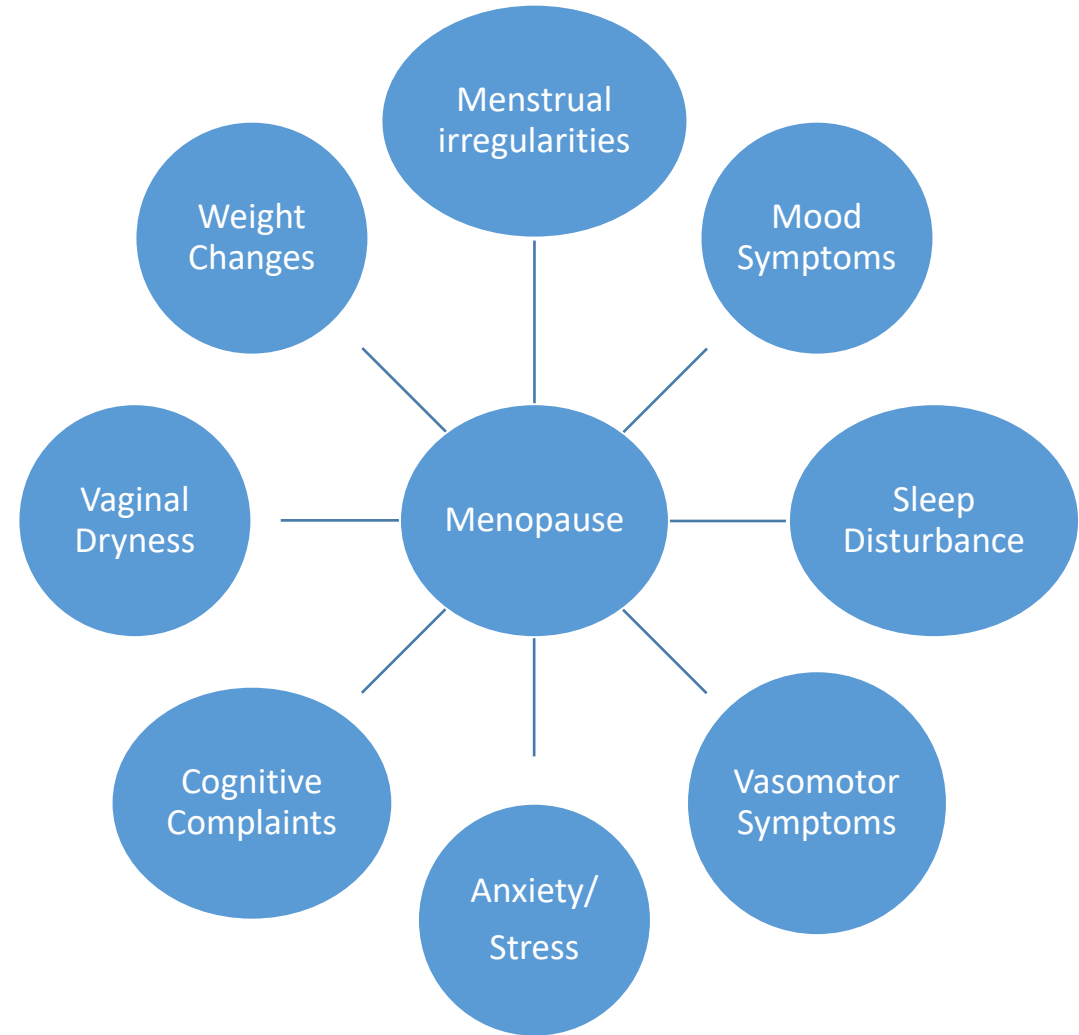
# Common Menopausal Symptoms

**Study of Women's Health  
Across the Nation**

**Seattle midlife Women's  
Health Study**

**Penn Ovarian Aging Study**

**MsFLASH**



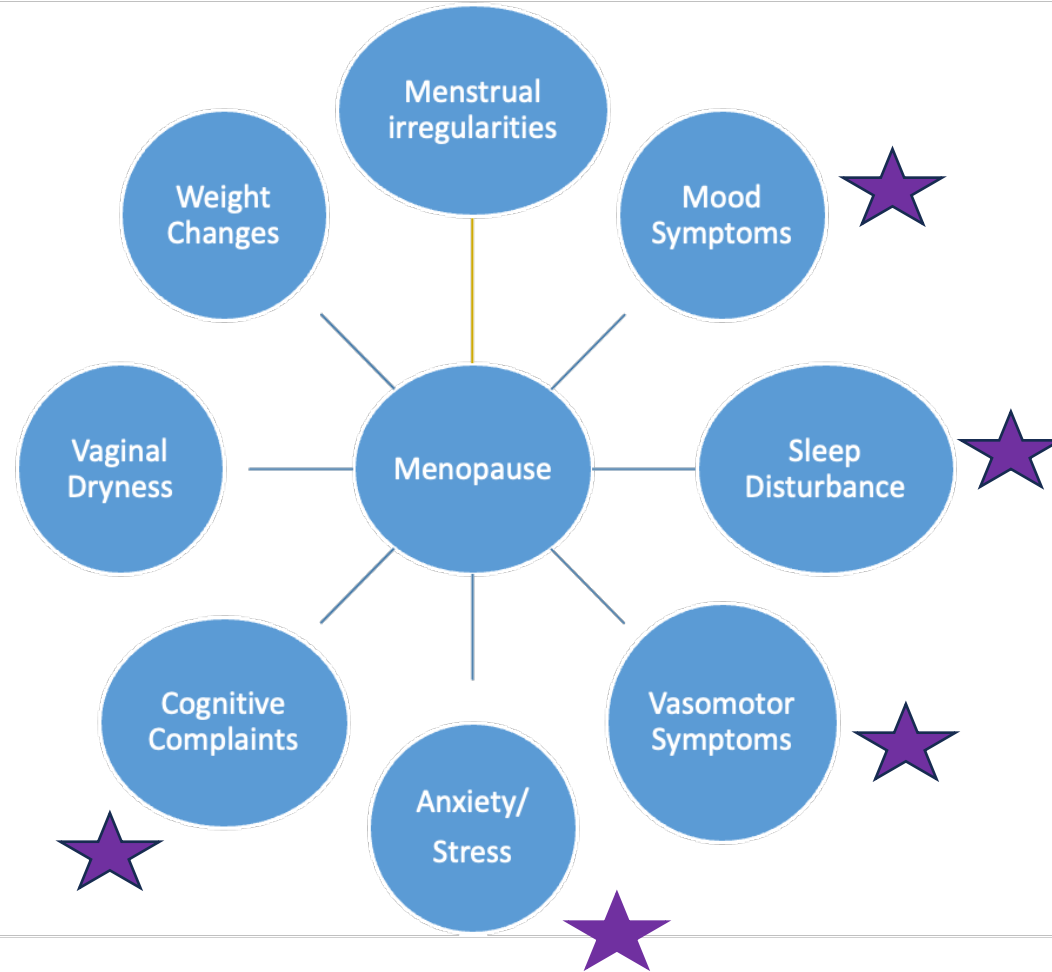
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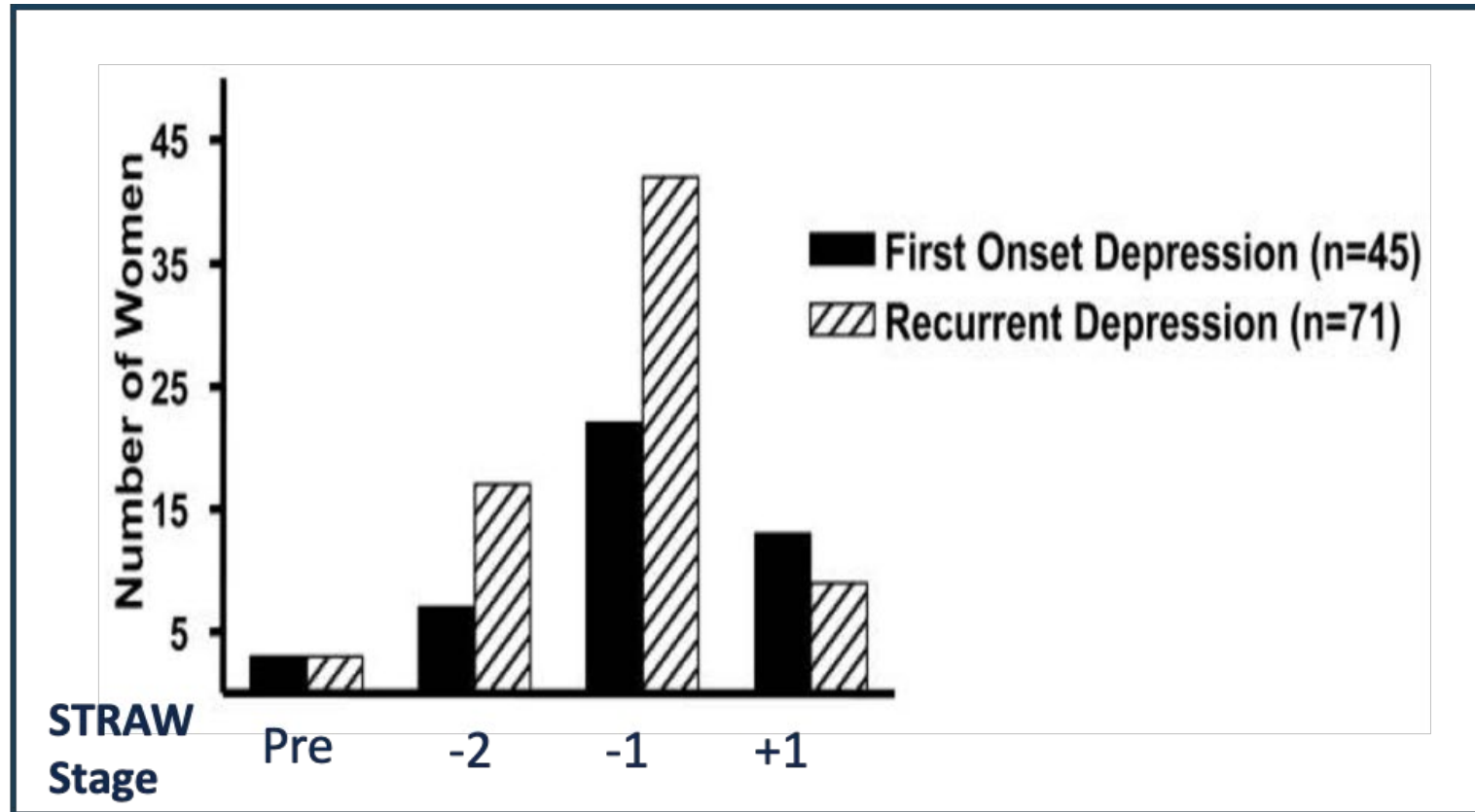
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# Risk for Depression increases across the perimenopause



# 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**



# Depression during midlife is linked to adverse medical outcomes



# Who is most likely to develop symptoms?

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

Vasomotor symptoms (VMS)

Sleep Disturbance



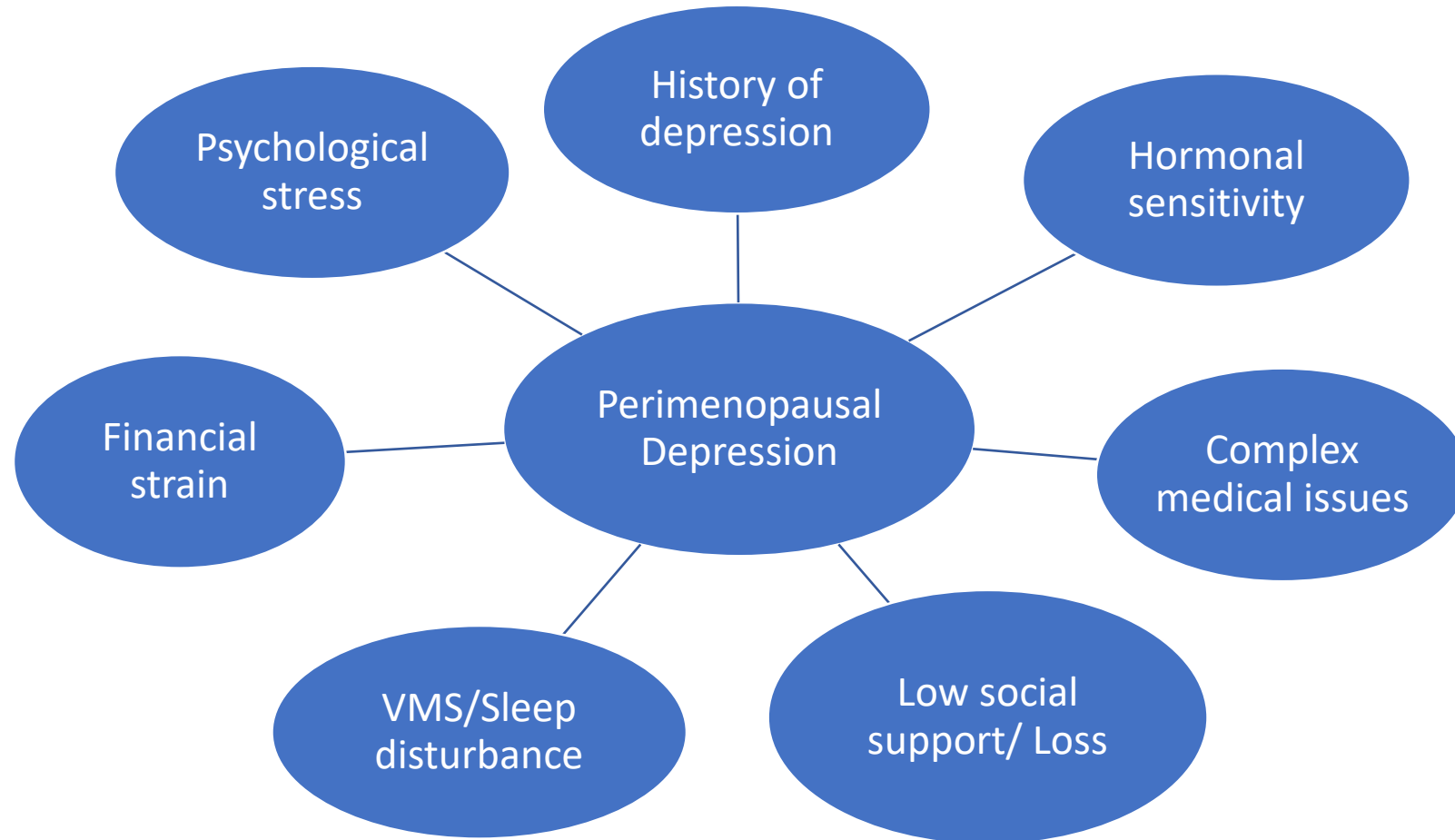
Depression



**Severe VMS are not necessarily associated with depressive sx**

**Night VMS linked w/ depressive sx independent of sleep disturbance**

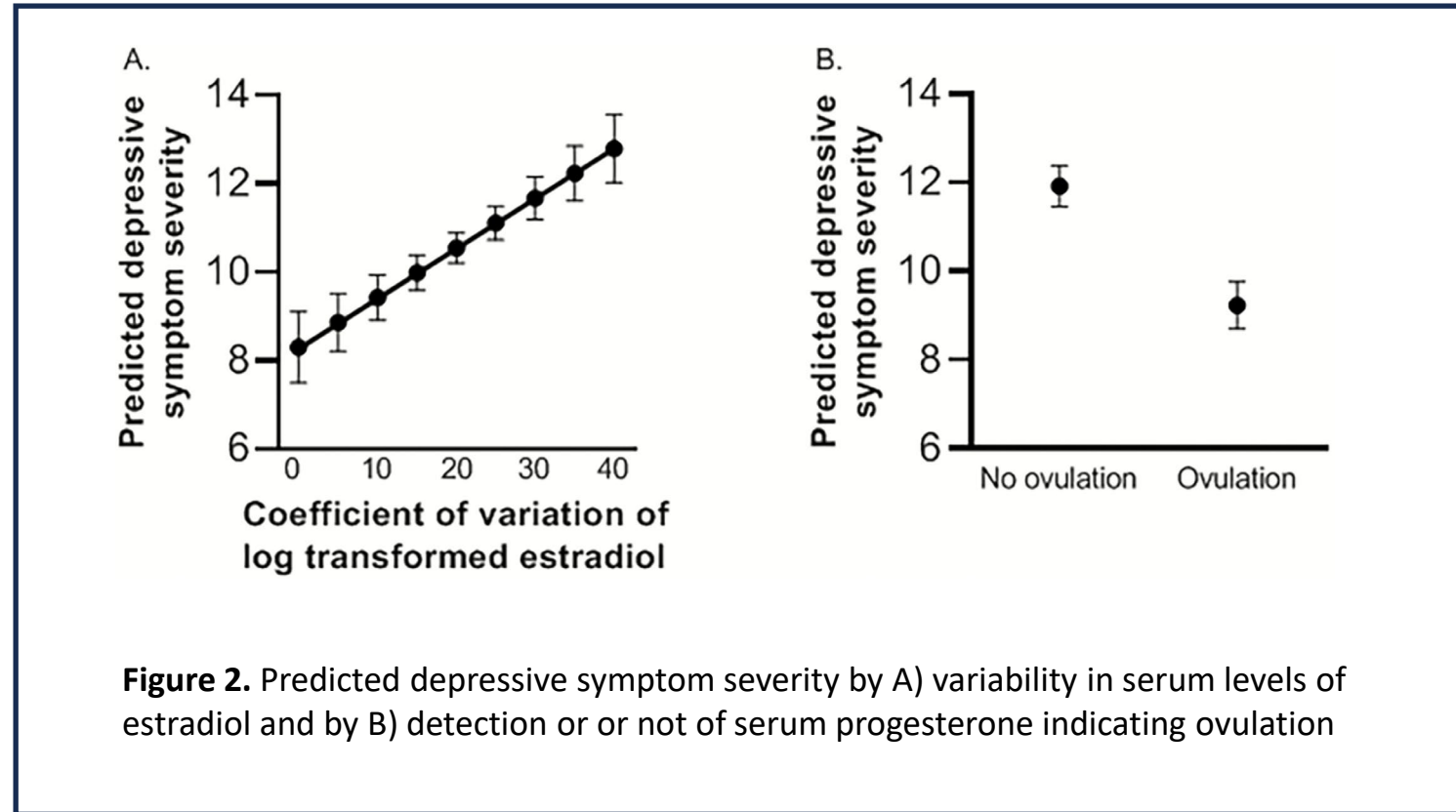
# Who is most likely to develop symptoms?



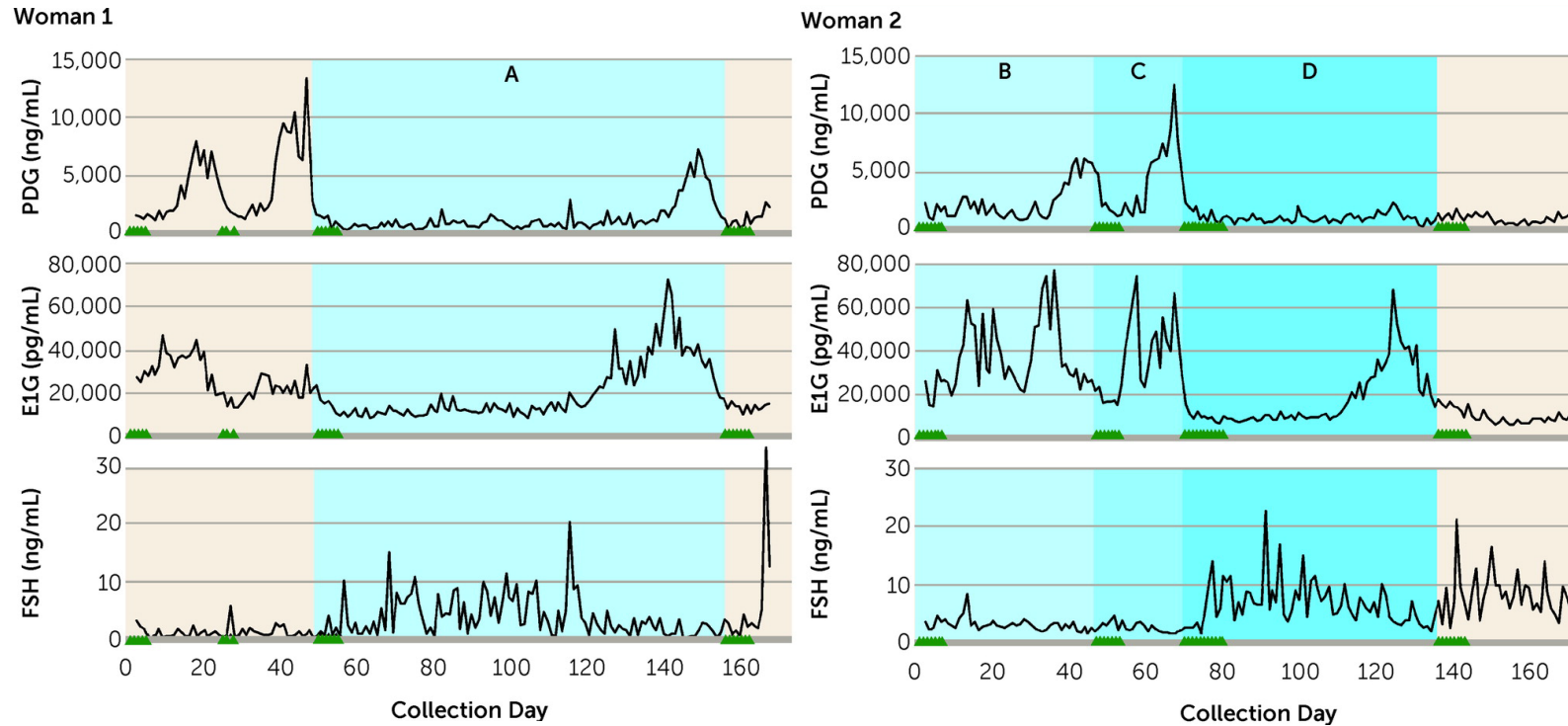
# Pathophysiology

**Greater variability in estradiol levels**

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



# 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.

# 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 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	0	1	2	3

add columns     +  +

TOTAL:

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

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).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Heart discomfort (unusual awareness of heart beat, heart skipping, heart racing, tightness).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Sleep problems (difficulty in falling asleep, difficulty in sleeping through the night, waking up early).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Depressive mood (feeling down, sad, on the verge of tears, lack of drive, mood swings).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Irritability (feeling nervous, inner tension, feeling aggressive) .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Anxiety (inner restlessness, feeling panicky) .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Physical and mental exhaustion (general decrease in performance, impaired memory, decrease in concentration, forgetfulness).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. Sexual problems (change in sexual desire, in sexual activity and satisfaction).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. Bladder problems (difficulty in urinating, increased need to urinate, bladder incontinence).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. Dryness of vagina (sensation of dryness or burning in the vagina, difficulty with sexual intercourse).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11. Joint and muscular discomfort (pain in the joints, rheumatoid complaints) .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

# Spectrum of symptoms in perimenopausal depression

Depressed mood

Irritability

Anhedonia

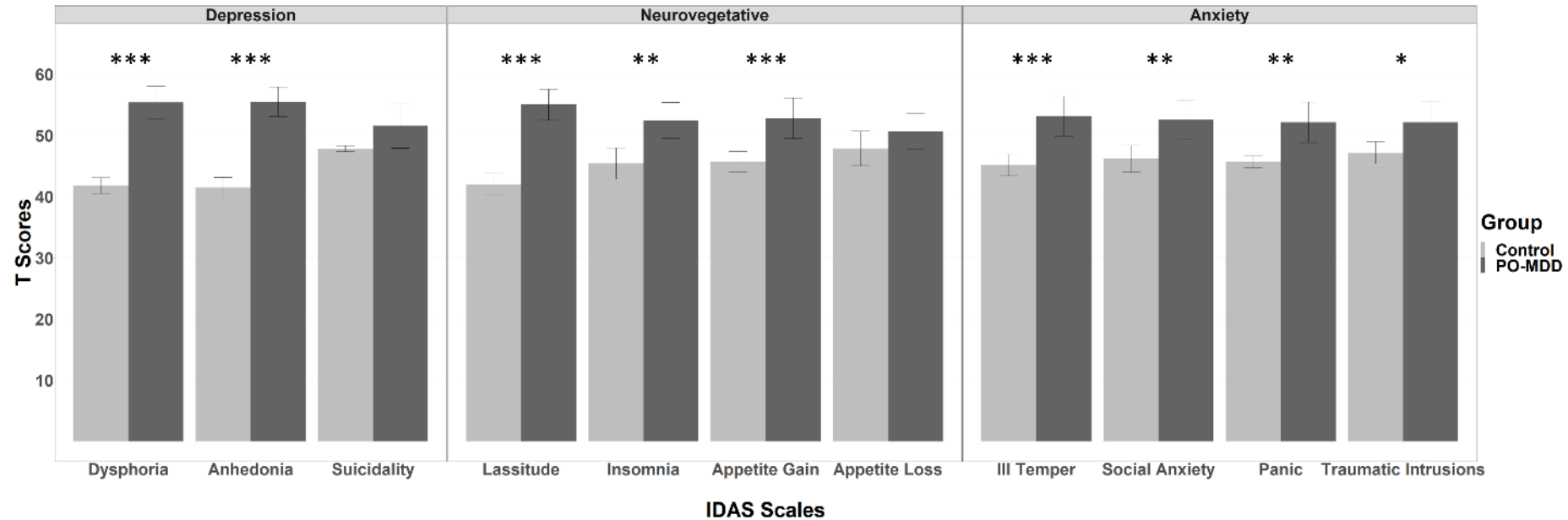
Fatigue

Insomnia

Appetite change

Anxiety

Panic attacks



# 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**



# Choosing an antidepressant when a patient is on tamoxifen

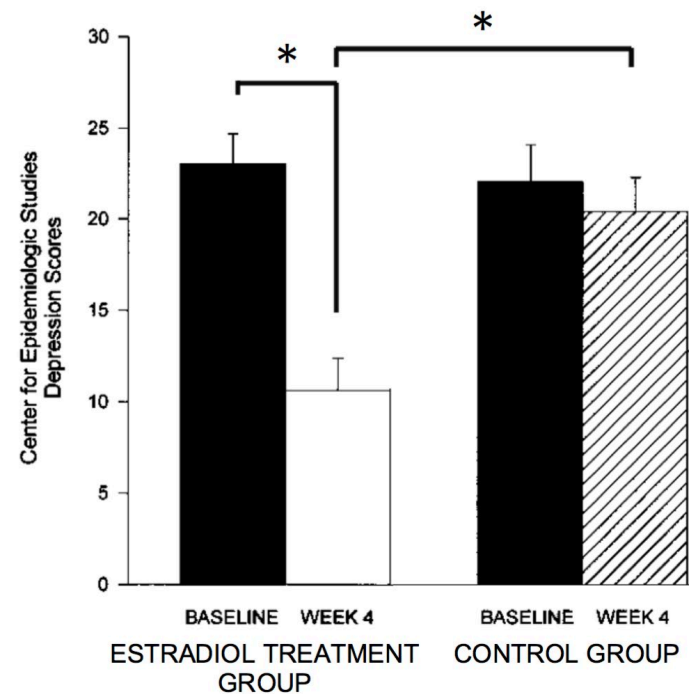
**Avoid antidepressants that inhibit CYP2D6**

**Can be helpful to concurrently manage mood/VMS**



# Estradiol treatment reverses depression in the perimenopause

c. Reduced depressive symptoms following estradiol treatment in women in STRAW Stage -1<sup>15</sup>



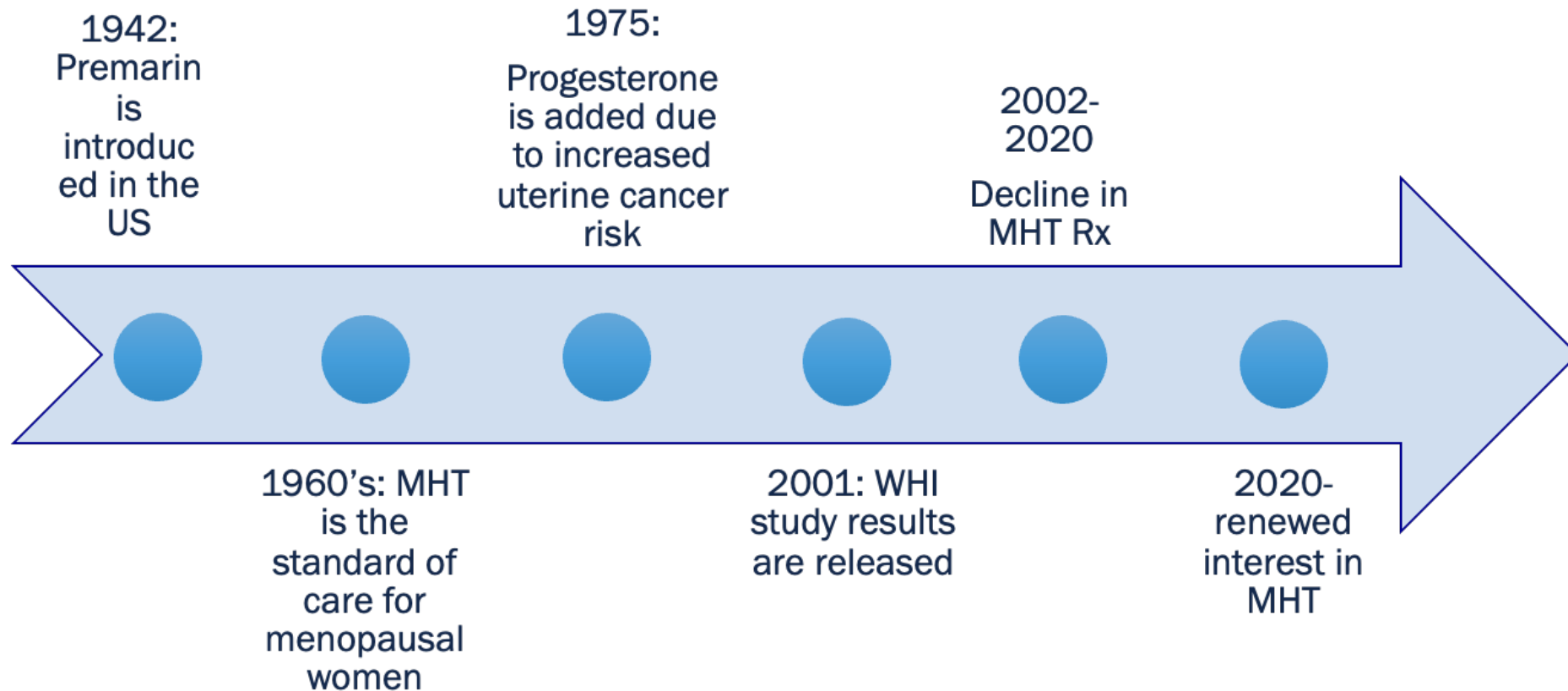
# Selective Estrogen Receptor Modulators (SERMS)

- Competitive partial agonists of the estrogen receptor
- Produce estrogenic or antiestrogenic effects depending on
  - the specific tissue
  - the intrinsic activity
- Examples:
  - Tamoxifen: estrogenic in bone and uterus
  - Bazedoxifene: estrogenic in bone, antiestrogenic in breast and endometrium

# 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



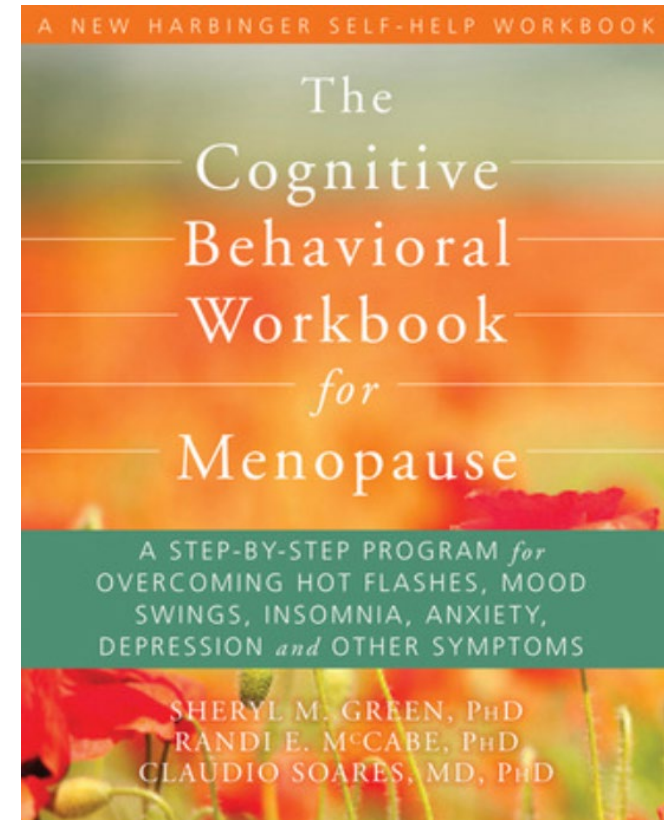
# Behavioral options are effective

**Cognitive Behavioral Therapy  
(CBT) has been studied for:**

**Depression**

**VMS**

**Insomnia**



# 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**



# 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**



# Other non-hormonal options for VMS

**Gabapentin/pregabalin**

**Clonidine**

**Fezolinetant**

**Black cohosh**



# 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**

**Middle insomnia is most Common**

**Major source of functional impairment**

**Rate of primary sleep disorders increase in midlife**



# Cognitive symptoms are common...and understudied

**Brain fog**

**Can occur with and without affective symptoms**

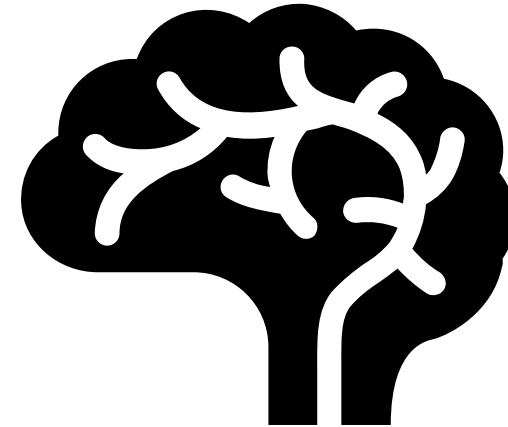
**Screen for sleep disruption**

**Limited studied treatments**

**--lisdexamphetamine or atomoxetine**

**--MHT**

**--testosterone?**



# 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?**