



PSYCHIATRIC UPDATE ON REPRODUCTIVE MOOD DISORDERS

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Disclosures

Dr. Yonkers discloses that she is an author for UpToDate and editor for Psychiatric Research and Clinical Practice. She has grants from NIMH, NIAAA and PCORI.

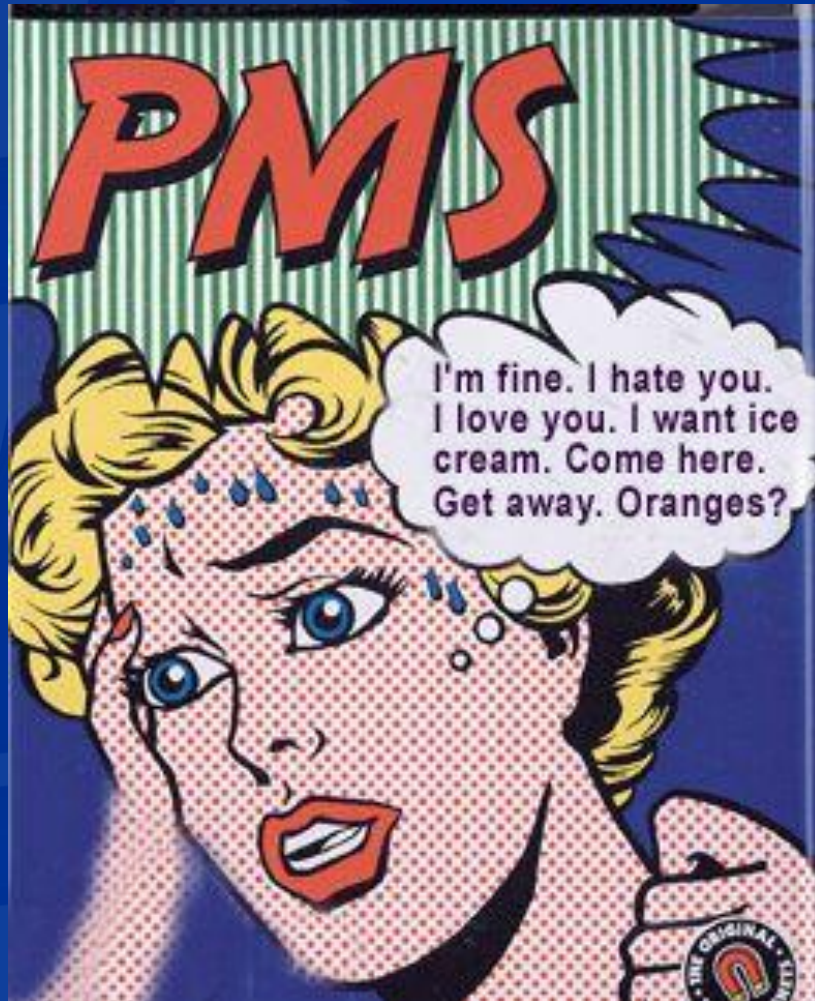
Dr. Savella has nothing to disclose.

The listener will be able to:

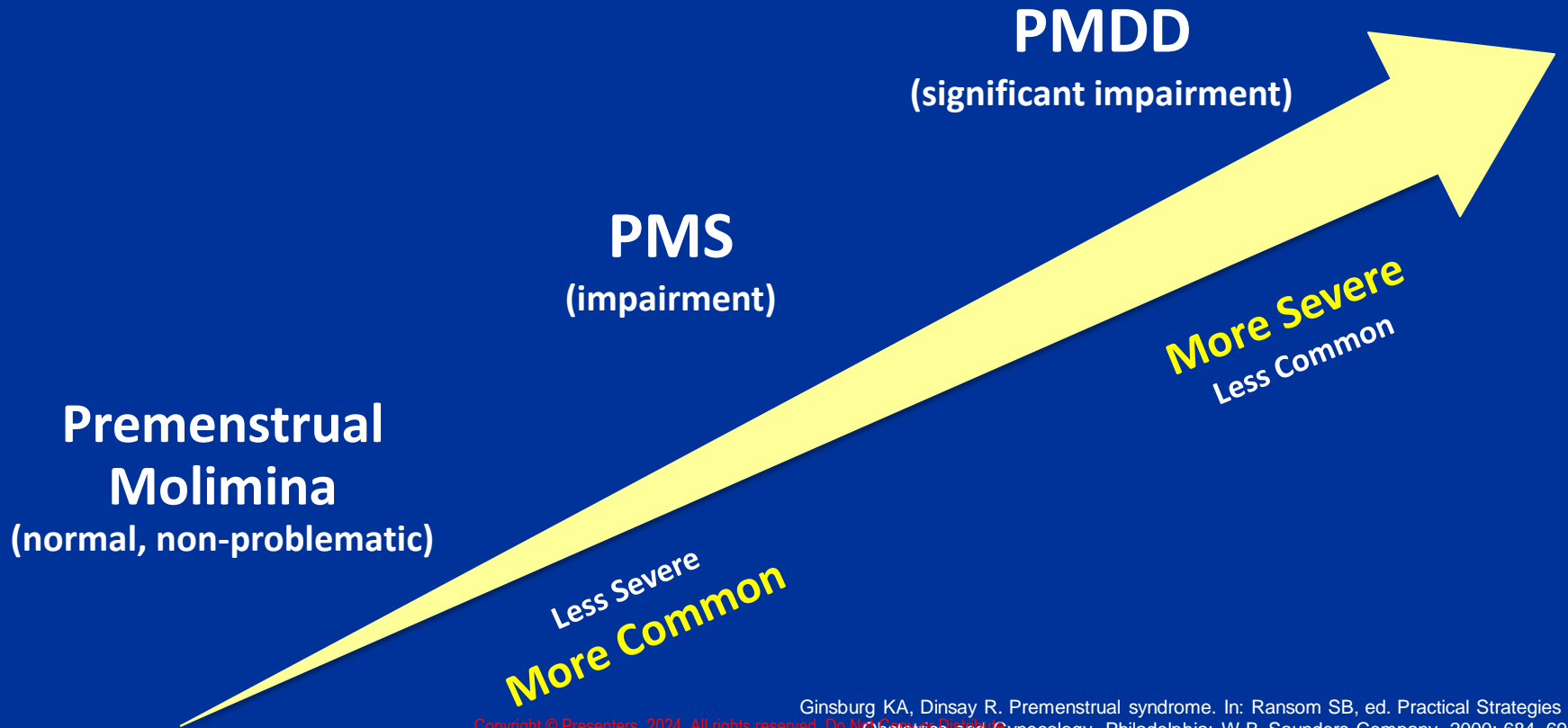
- Understand the current definitions and epidemiology of mood disorders influenced by the female reproductive cycle.
- Appreciate what is known about the biological underpinnings of these mood disorders.
- Make evidence-based decisions about effective treatments for reproductive-related mood disorders.

We will review material on:

- Premenstrual Syndrome/Premenstrual Dysphoric Disorder
- Perinatal Mood Disorders
- Perimenopausal Depression



Premenstrual Symptoms ≠ An Illness

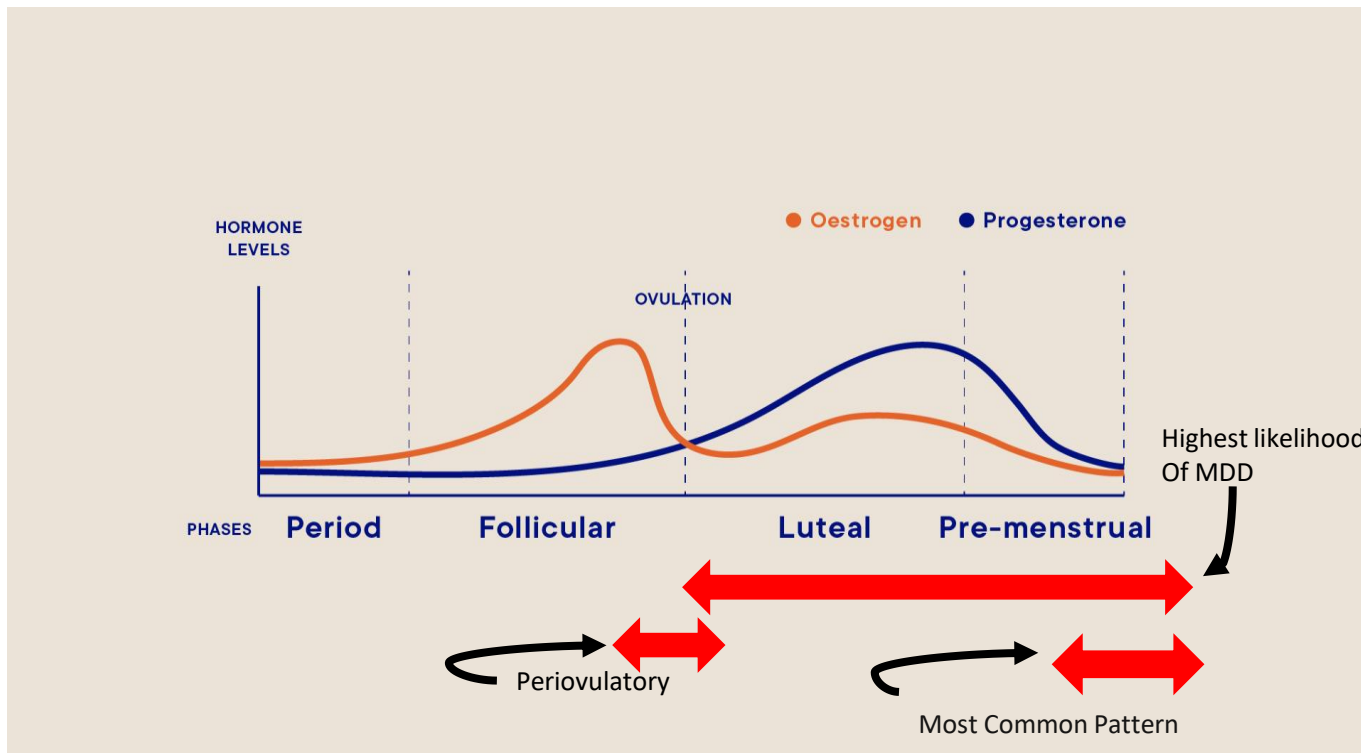


PMS and PMDD Can Have Similar Symptoms But At Least One Mood Symptom Is Obligatory in PMDD

5 Total Symptoms Required for PMDD

1 Mood symptom is required	
Affective Lability	Decreased Interest
Anger/Irritability	Difficulty Concentrating
Depression/Hopelessness	Fatigue
Anxiety/Tension/On Edge	Over or Under Sleeping
	Change in Appetite
	Feeling Out of Control
	Physical Sxs (e.g. Breast Pain)

Diagnostic Criteria for PMDD Require “On-Offness” That Can Follow Several Patterns



New Findings Related to the Diagnosis of PMDD

- 4 symptoms predict a PMDD dx
- Symptom severity is greatest 4 days before and 2 days after menses
- Depressed mood is less common than irritability and mood swings

There are Two Mainstays of Treatment for PMDD

Serotonin Reuptake Inhibitors

- Strongest evidence base
- Some with FDA approval
- Can be used for full cycle, half cycle or symptom onset

Oral Contraceptives

- Evidence for compounds with shortened hormone interval is the strongest
- Good choice for individuals who desire contraception
- Not as effective for mood symptoms as physical symptoms

How Do I Treat PMDD?



Medical & Psychiatric History



Ask patient to keep a menstrual calendar that confirms the diagnosis, documents **symptoms and illustrates onset/offset of symptoms**

Have the patient identify the most bothersome symptoms and any cues to the onset of symptoms



Discuss with the patient whether she would like to have daily, half cycle or symptom onset treatment

Prospective Symptom Tracking Can Help Confirm PMDD Diagnosis And Provide Useful Data

Table A. Daily Record of Severity of Problems for Diagnosis of Premenstrual Dysphoric Disorder

Day of menstrual cycle (day 1 is the start of the menstrual period)

Symptoms	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	32	33	34	35	
Felt depressed or sad																																				
Felt hopeless																																				
Felt worthless or guilty																																				
Felt anxious or tense																																				
Had mood swings																																				
Feelings were more easily hurt																																				
Felt angry or irritable																																				
Had conflicts with people																																				
Had less interest in activities																																				
Had trouble concentrating																																				
Felt tired or lacked energy																																				
Had increased appetite																																				
Had food cravings																																				
Slept more or had trouble waking up																																				
Had trouble getting to sleep or staying asleep																																				
Felt overwhelmed																																				
Felt out of control																																				
Had breast tenderness																																				
Had breast swelling or weight gain, or felt bloated																																				
Had headache																																				
Had joint or muscle pain																																				
At least one of the problems noted above caused reduced productivity at work, school, or home																																				
At least one of the problems noted above interfered with hobbies or social activities																																				
At least one of the problems noted above interfered with relationships with others																																				
Menstrual flow: H = heavy, M = medium, L = light or spotting (leave blank for no bleeding)																																				

PREMENSTRUAL SYMPTOM TRACKER (DAILY RECORD OF SEVERITY OF PROBLEMS)

Name:

Month:

INSTRUCTIONS

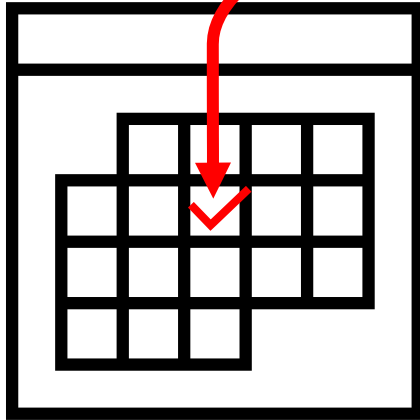
Print off as many copies as you need to complete a **full two months** worth of tracking. Begin tracking your premenstrual symptoms with this chart today. Fill it out **daily** (preferably at the end of your day). Two full months of menstrual cycle charting will allow for a more accurate assessment.

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)		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						
1. Felt depressed, sad, "down," or "blue" or felt hopeless; or felt worthless or guilty	6																																					
	5																																					
	4																																					
	3																																					
	2																																					
2. Felt anxious, tense, "keyed up" or "on edge"	6																																					
	5																																					
	4																																					
	3																																					
	2																																					
3. Had mood swings (i.e., suddenly feeling sad or tearful) or was sensitive to rejection or feelings were easily hurt	6																																					
	5																																					
	4																																					
	3																																					
	2																																					
4. Felt angry, or irritable	6																																					
	5																																					
	4																																					
	3																																					
	2																																					
5. Had less interest in usual activities (work, school, friends, hobbies)	6																																					
	5																																					
	4																																					
	3																																					
	2																																					
6. Had difficulty concentrating	6																																					
	5																																					
	4																																					
	3																																					
	2																																					

How Can I Initiate Half Cycle Treatment?



Identify ovulation:

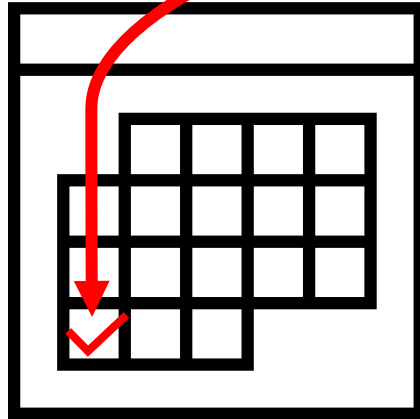
Many individuals experience physical symptoms at ovulation; pills should start then

Or count about 14 days from onset of menses in prior cycle and start pills then

Continue pills until menses

Evaluate outcome and adjust or switch platforms

How Can I Initiate Symptom Onset Treatment?



Identify physical or other cues to symptom onset

Start pills and continue until onset of menses or few days after onset

Evaluate outcome and adjust or switch platforms if it is difficult or unsuccessful

Take Note!



Physical symptoms do not respond to intermittent treatment as effectively as daily treatment throughout the cycle



Patients may have difficulty determining the time to start symptom onset treatment



If one SRI does not work or is not well tolerated you can try a different SRI

What About Hormonal Treatment?

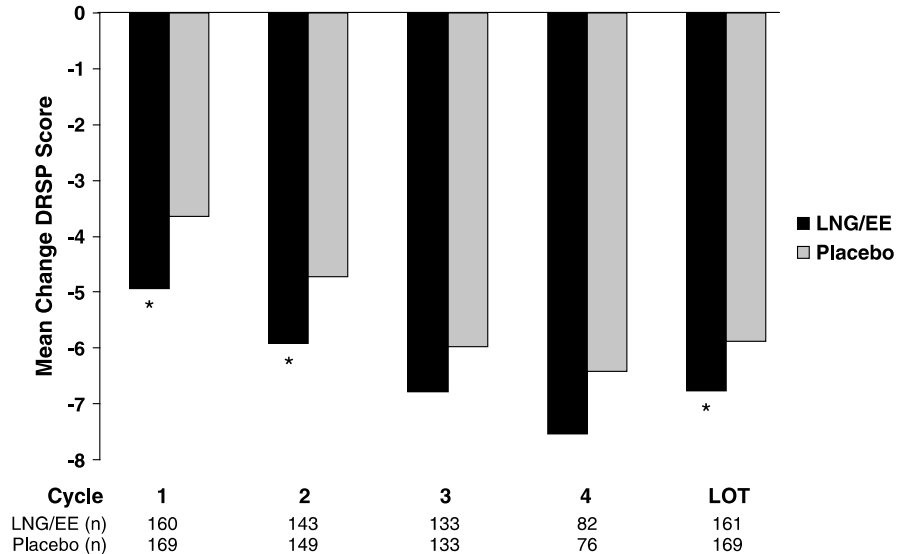
There is evidence for efficacy of contraceptives with either a shortened hormone free interval (4 rather than 7) OR no hormone free interval

U. Halbreich et al. / Contraception 85 (2012) 19–27



Patch for daily Rx

A Physical Symptoms



24 Days of Drospirenone and Ethinyl Estradiol

Individual Symptom Items	Drospirenone/Ethinyl Estradiol [†]	Placebo [‡]	Adjusted Mean Difference	95% CI	<i>P</i> §
1a. Depressed, b. hopeless, c. worthless/guilty	4.0	4.6	-0.8	-1.38 to -0.30	.005
2. Anxious/tense	1.9	2.4	-0.4	-0.66 to -0.23	< .001
3a. Mood swings, b. feel sensitive	3.3	4.5	-1.0	-1.43 to -0.57	< .001
4a. Angry/irritable, b. conflicts	3.7	4.7	-0.9	-1.36 to -0.49	< .001
5. Diminished interest	1.7	1.8	-0.3	-0.52 to -0.10	.003
6. Difficulty concentrating	1.5	1.9	-0.4	-0.58 to -0.15	.001
7. Tired/fatigued	2.1	2.5	-0.3	-0.51 to -0.07	.010
8a. Increased appetite, b. food cravings	3.3	3.8	-0.8	-1.32 to -0.35	.010
9a. Slept more, b. trouble sleeping	3.5	3.9	-0.4	-0.79 to -0.12	.033
10. Overwhelmed/lack of control	2.8	3.3	-0.7	-1.15 to -0.35	< .001
11a. Breast tenderness, b. breast swelling, c. bloated sensation, d. headache, e. muscle pain	7.4	8.6	-1.4	-2.11 to -0.77	< .001

New Treatments On the Horizon

Agonists of allopregnanolone or antagonists of allopregnanolone (isoallopregnanolone) may be effective

T. Bäckström et al.

Psychoneuroendocrinology 133 (2021) 105426

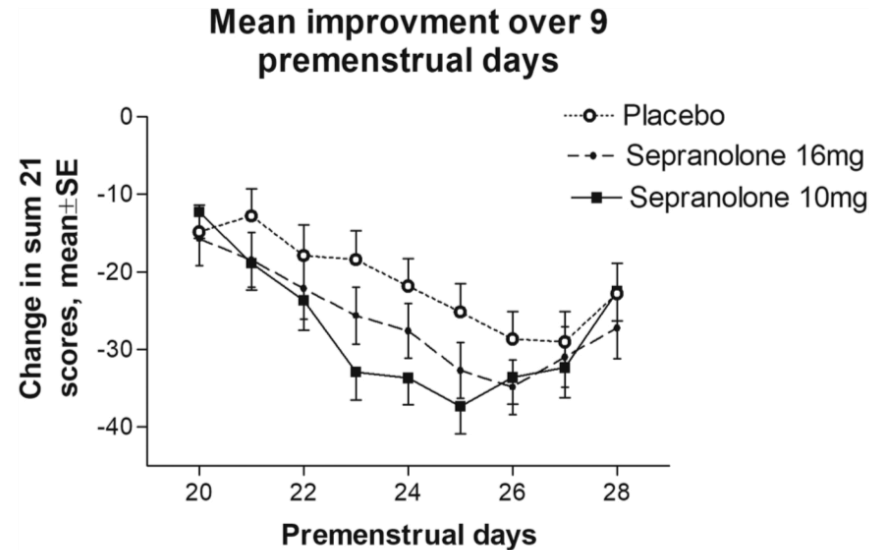


Fig. 4. Change in Sum21 during nine luteal phase days from baseline to the 3rd treatment cycle in the PP population. Comparison between women treated with sepranolone, 10 mg or 16 mg, or placebo.

Summary: PMDD

- PMDD is treatable
- SRIs remain the first line treatment
- Some contraceptives may be helpful, particularly for physical symptoms
- New treatments are on the horizon

HOW TO CARE FOR PREGNANT INDIVIDUALS WITH DEPRESSION

- 3%-9% of women experience an episode of major depression in pregnancy
- An additional 5% develop minor depressive disorder
- 6-9% of women are depressed after delivery
- 50% of postpartum episodes begin during pregnancy

My Patient Is Pregnant!! What Do I Do?



A Mother's Dilemma?

Can depression harm
my baby?

Can antidepressant
medication harm my
baby?



First Things First: Unhealthy Habits Can Be More Problematic Than Any Psychotropic Treatment



Smoking: low birth weight



Drinking: fetal alcohol effects and fetal alcohol syndrome

Other substance use:

- ▶ Cocaine, stimulants: intrauterine growth restriction; preterm birth; abruption
- ▶ Opioids: preterm birth



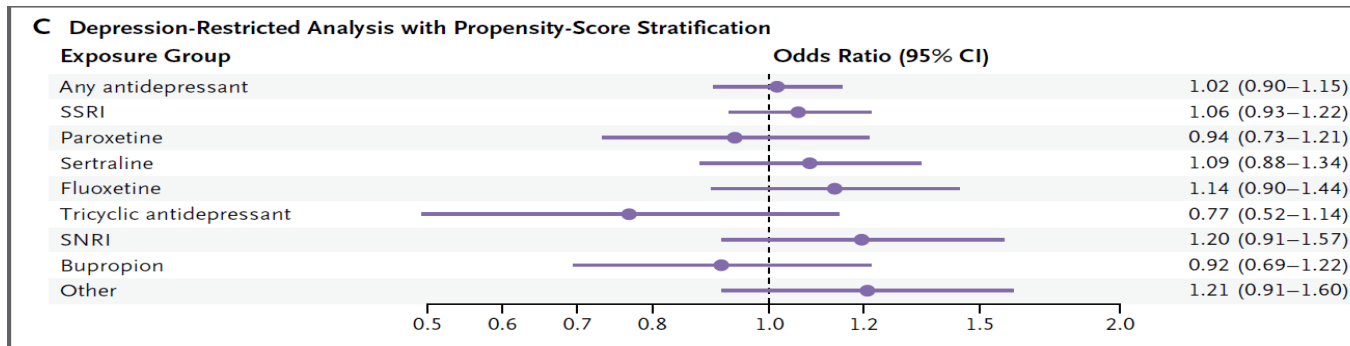
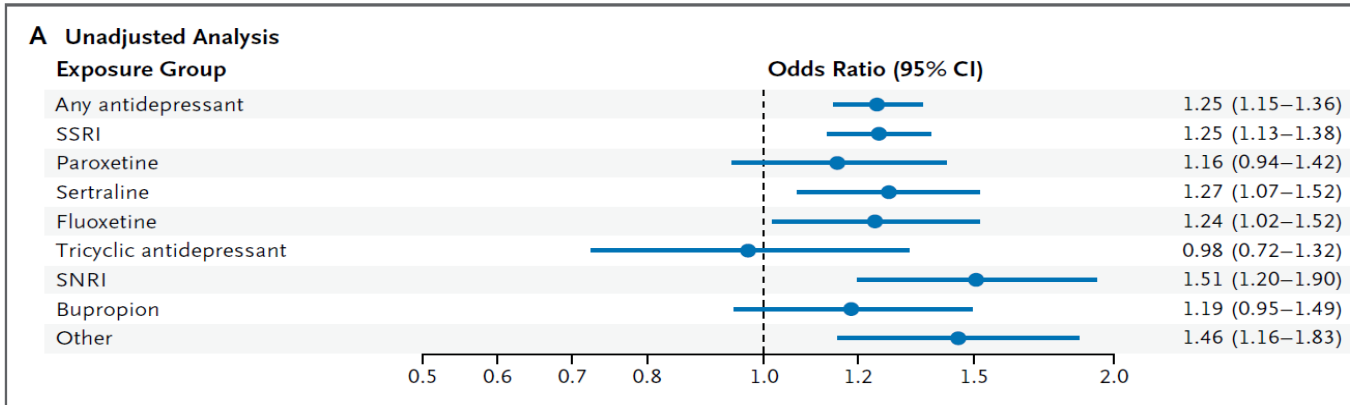
- Over half of pregnant women take prescription medication in pregnancy
- More than half take a non-vitamin over the counter treatment
- 5% take an antidepressant medication

WHAT ARE THE CONSEQUENCES OF ANTIDEPRESSANT USE DURING PREGNANCY ?

Reported Associations between Antidepressant Use in Pregnancy and Adverse Fetal Outcomes

Outcome	Strength of Finding
Spontaneous miscarriage	Mixed results
Fetal demise	Not associated
Preterm Birth	Highly replicated but small effects
Small for Gestational Age/Low Birth Weight	Mixed but weak results; better controlled studies are negative
Major Congenital Anomalies	Mixed by weak results; greater consistency with paroxetine
Persistent Pulmonary Hypertension	Mixed but better replicated in late pregnancy
Neonatal adaptation	Moderately well replicated
Autism	Mixed but weak results; better controlled studies are negative
Pre-eclampsia, gestational hypertension	Replicated
Attention Deficit Hyperactivity Disorder	Mixed but weak results; better controlled studies are negative

Controlling For Confounders Eliminates Associations Between Antidepressant Use And Cardiac Malformations



Adjusted And Sibling Comparisons Of 1st Trimester Antidepressant Exposure Nearly Attenuates Estimated Associations Between Preterm Birth/Small For Gestational Age

Any Antidepressant	Baseline	Adjusted	Sibling Comparison
Preterm Birth	1.47 (1.40-1.55)	1.35 (1.28-1.42)	1.32 (1.18-1.52)
Small for Gest Age	1.15 (1.06-1.25)	1.12 (1.03-1.22)	1.01 (0.81-1.25)
SSRI Antidepressant	Baseline	Adjusted	Sibling Comparison
Preterm Birth	1.38 (1.30-1.46)	1.27 (1.20-1.35)	1.33 (1.16-1.53)
Small for Gest Age	1.11 (1.01-1.21)	1.09 (0.99-1.20)	0.88 (0.70-1.12)

Baseline controlled for parity and year; **Adjusted** controlled for parity, year of birth, maternal/paternal country, age, education, psychiatric illness, criminality and suicide attempts; **Sibling** controlled for parity, year of birth, paternal country, age, education, criminality, psychiatric illness, suicide attempts

Absolute Risk For Birth Defects With Established Teratogens Is Much Greater Than SRIs

Exposure	Outcome	Estimated absolute risk
valproic acid	Any major defect (3/100 births in population)	11/100 exposed
isotretinoin	Heart, CNS, ear thymus defects	18/100 exposed
alcohol	Craniofacial, brain, growth defects: Fetal Alcohol Spectrum Disorders	25/100 heavily exposed
serotonin reuptake inhibitors	Any malformation	3/10000

Poor Neonatal Adaptation Syndrome



All antidepressants are associated with neonatal complications including jaundice, hypoglycemia, low APGAR scores and convulsions, neonatal ICU admission



PNAS Meta-analysis

- 2.2-fold increased risk of respiratory distress (CI=1.81-2.66)
- 7.9 fold increase in tremors (CI=3.33-18.73)

Confounding Factors May Explain Associations With ADHD And Autism Spectrum Disorder Risk

ADHD

Comparison	Crude risk ratio	No. of studies	Adjusted risk ratio	No. of studies
Maternal exposure during pregnancy vs. unexposed women	2.04 (1.62–2.56)	5	1.38 (1.13–1.69)	7
Maternal exposure pre-pregnancy vs. unexposed women	1.42 (1.09–1.84)	2	1.38 (1.14–1.69)	5
Maternal exposure during pregnancy vs. unexposed women with a history of affective disorder	1.01 (0.80–1.27)	1	0.98 (0.77–1.24)	1
Sibling design	0.8 (0.5 to 1.2)	1	0.88 (0.70–1.11)	3
Paternal exposure during the maternal pregnancy period vs. unexposed women	–	0	1.71 (1.31–2.23)	1

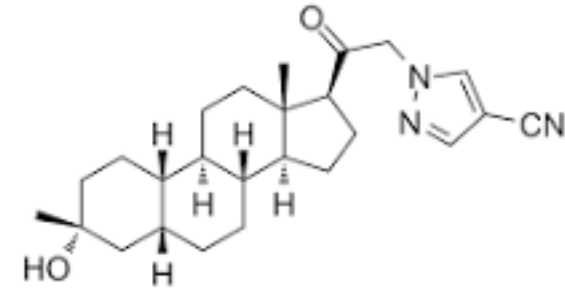
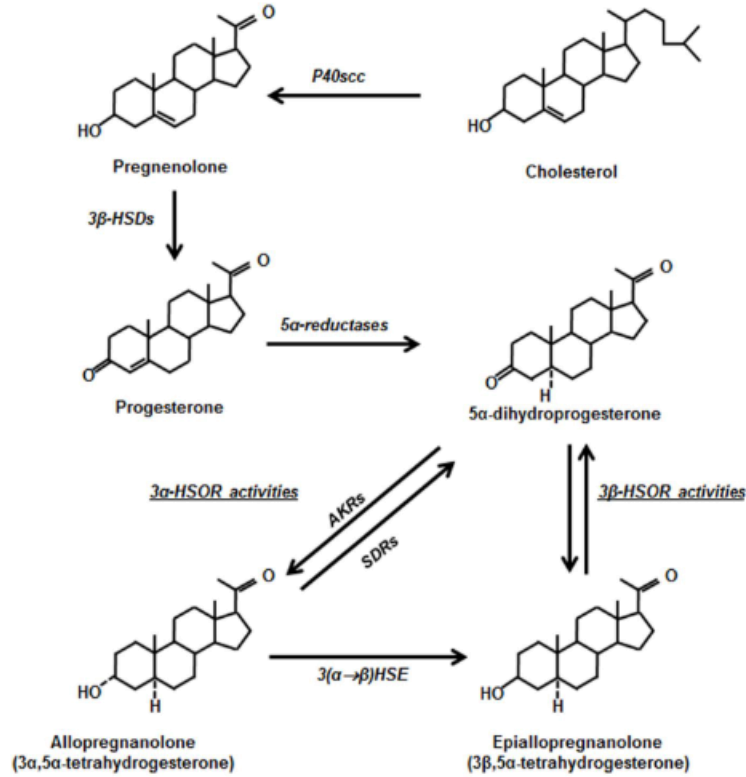
Breastfeeding Is Generally Recommended With Antidepressant Use



- Exposure can be minimized by breastfeeding, taking medication, pumping and not using next feed but this may be difficult to do
- Rather than monitor levels, the baby should be monitored for problems feeding or sleeping

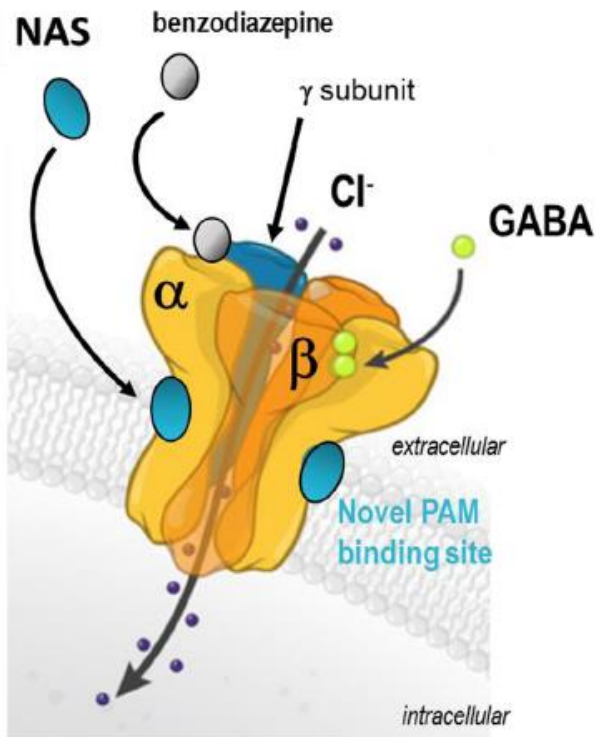
TREATMENT OF POSTPARTUM DEPRESSION

Update: Neurosteroids As Treatments



Zuranolone

Gamma-Amino-Butyric Acid Receptor



Neuroactive steroids (NAS) bind to a unique site and are positive allosteric modulators (PAMs) of the receptor; can modulate the receptor in synaptic and extra synaptic sites

RCT: Effect of Zuranolone vs Placebo in Postpartum Depression: A Randomized Clinical Trial

POPULATION

150 Women



Women ages 18-45 y with postpartum depression and Hamilton Rating Scale for Depression (HAM-D-17) score ≥ 26

Mean (SD) age, 28.3 (5.4) y

INTERVENTION

153 Individuals randomized



76 Zuranolone

Oral zuranolone, 30 mg, every evening with food for 14 d

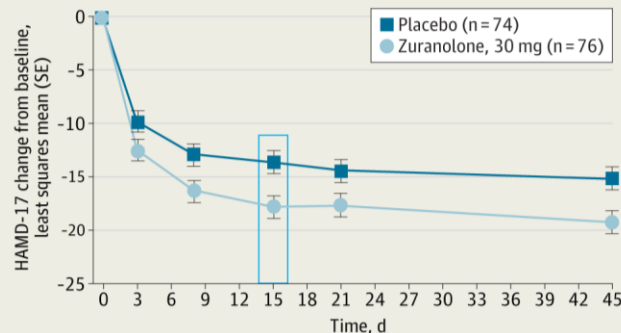


74 Placebo

Oral placebo capsule every evening with food for 14 d

FINDINGS

Individuals with postpartum depression who received zuranolone for 2 wk displayed significantly greater reductions in depressive symptoms compared with placebo at day 15



Difference in change in depressive symptoms at 15 wk, zuranolone vs placebo:

-4.2 (95% CI, -6.9 to -1.5); $P = .003$

SETTINGS / LOCATIONS



27 Clinical sites
in the US

PRIMARY OUTCOME

Change from baseline in depressive symptoms at day 15, as measured by HAM-D-17 score (range, 0-52, with higher scores indicating more severe depression)

How To Treat With Zuranolone?



- Zuranolone (Zurzuvae) comes in 20 mg, 25 mg and 30 mg capsules
- 50 mgs daily for 2 weeks is the recommended dose
- Adjust dose to 40 mgs for significant side effects
- Take medication at night because it can cause sedation; take with food
- Avoid driving or using potentially hazardous machinery for 12 hours



- Can 14 days of treatment protect against relapse for months, years?
- Should zuranolone be first line treatment?
- What if the individual has recurrent depression?
- What about cost?

Bipolar Disorder In Pregnancy

- Bipolar disorder is about 1% of the female population
- Bipolar disorder is related to postpartum psychosis: ~ 50% of perinatal individuals who become psychotic go on to express a clinical course consistent with bipolar disorder
- Onset can happen pre-delivery or after deliver and is rapid with an escalation to mania

Lithium Treatment Of Pregnant Individuals

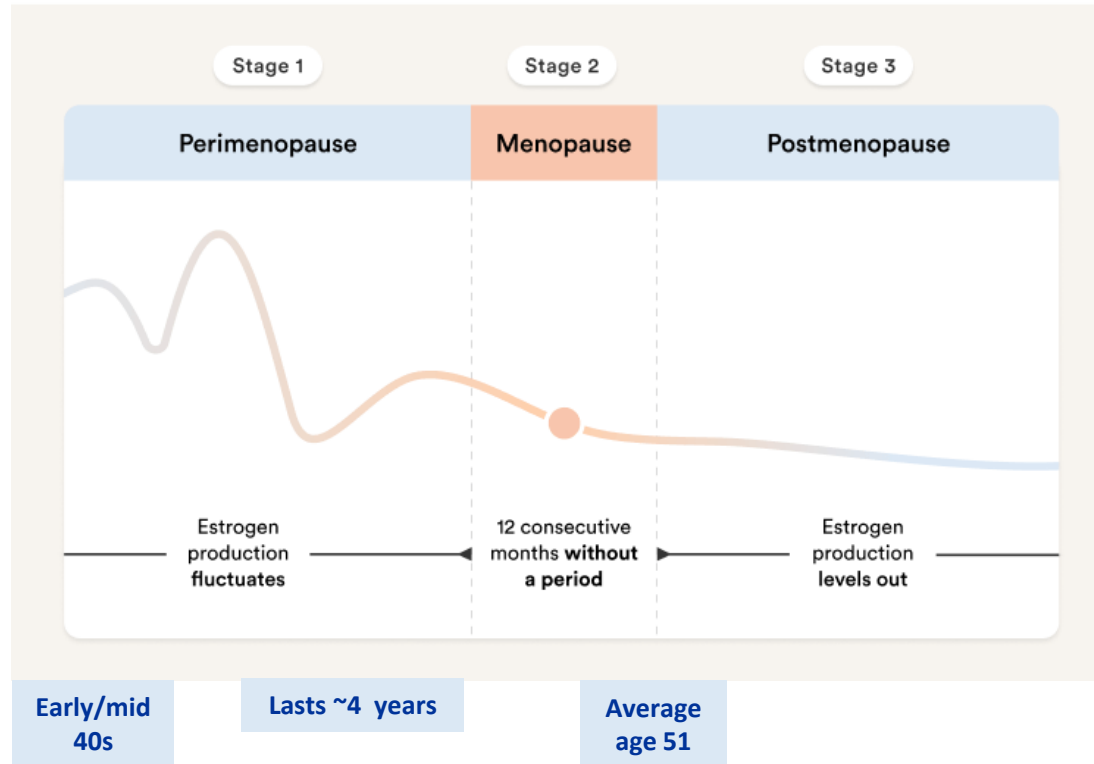
- People who are pregnant and undergoing lithium treatment
 - Try to avoid first trimester lithium use; antipsychotics may be a better choice
- Monitor levels throughout pregnancy and adjust dose; dosage may require increases because of increased GFR.
- Many experts suggest holding a dose or cutting it in half for a day or two prior to delivery; changing weight and hydration status can change levels
- Avoid breastfeeding if undergoing postnatal lithium treatment

Summary: Perinatal Depression






- Depression is common in pregnancy and after delivery
- Patients should be informed of any risks, but antidepressants such as SRIs should not be considered teratogens
- New treatments such as GABA agonists show promise but several issues need to be resolved before they are considered first line treatment

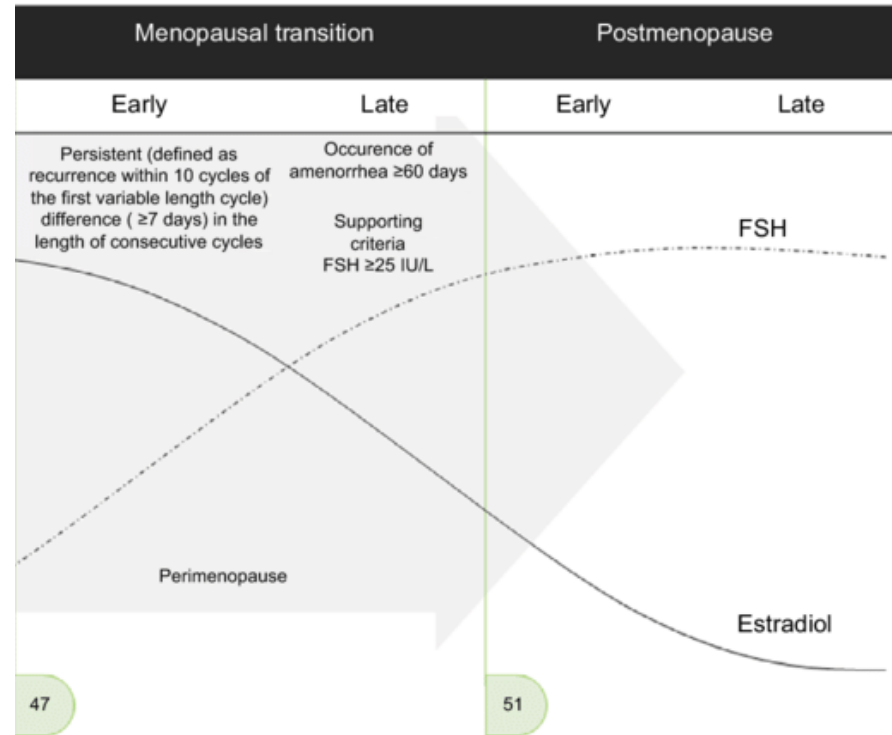
CARING FOR INDIVIDUALS IN THE MENOPAUSAL TRANSITION

Perimenopause (The Menopausal Transition) Precedes Menopause For Several Years



Perimenopause Is Marked By Hormone Fluctuations

-  Reduced ovarian reserve
-  Decreased estrogen
-  Increased FSH
-  Irregular menstrual cycles
-  Longer duration of amenorrhea





Vasomotor
Symptoms



Sleep Disturbances
& Fatigue



Mood
Changes

Up To 80% Of Individuals Experience Vasomotor Symptoms During The Menopausal Transition

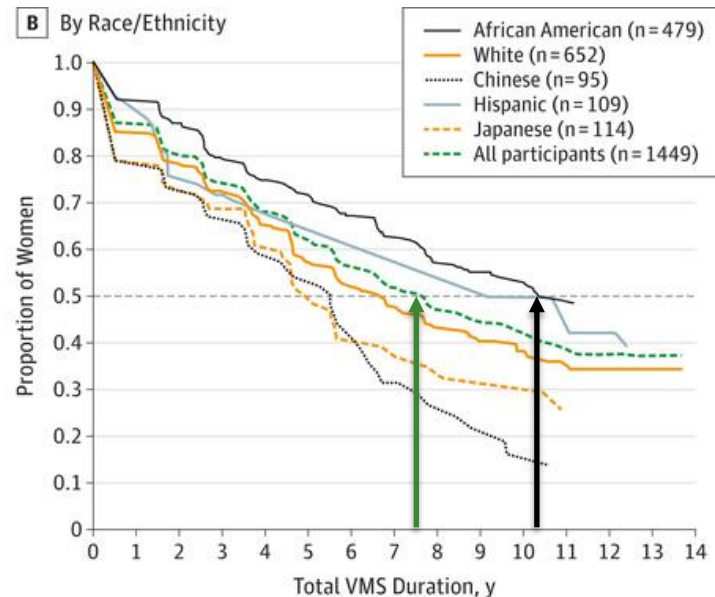
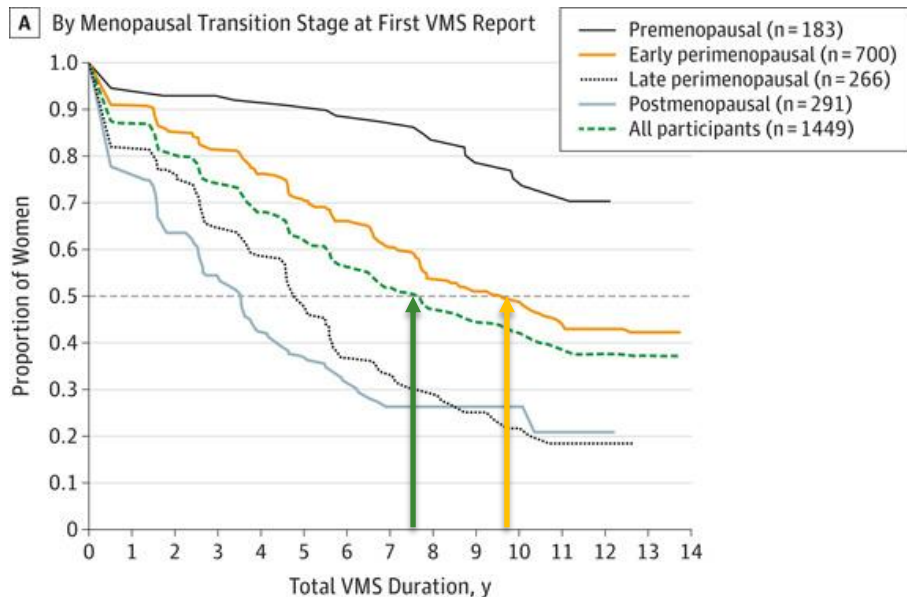


Disruptions in core body temperature homeostasis due to estrogen fluctuations and reduced HP axis sensitivity to feedback

Most common symptom menopausal women seek treatment for

Median duration of 7.4 years

Duration Of Vasomotor Symptoms Is Longer For...



Women whose VMS began in early perimenopause



African American women

Duration Of Vasomotor Symptoms Is **Longer** For...



Younger women



Ever-smokers

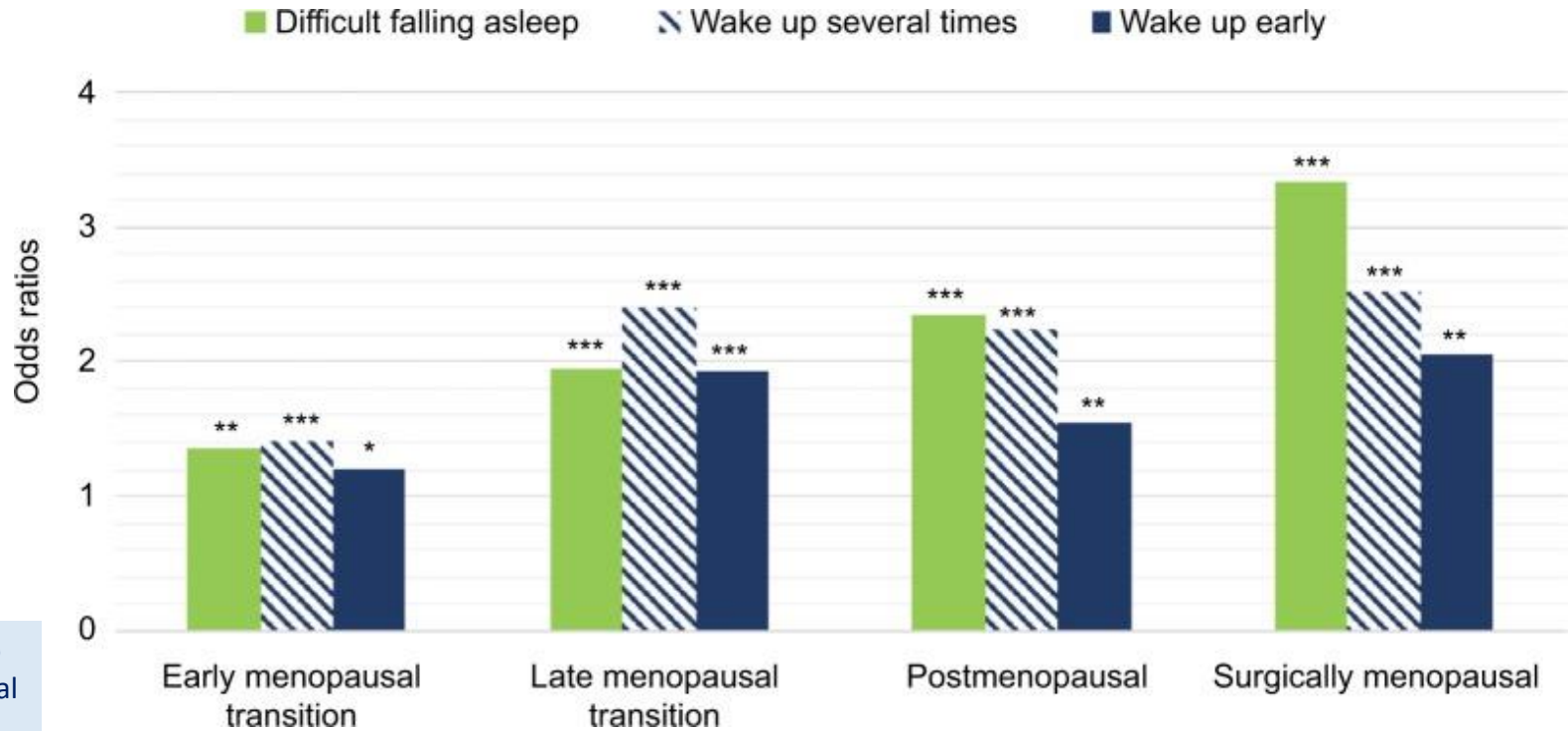


Women with greater perceived stress
or symptom severity



Women reporting higher anxiety and
depressive symptoms

Sleep Disturbances In The Menopausal Transition



Mood Symptoms Are Common In Perimenopause

Irritability, mood lability,
depression, anxiety

Odds of clinically significant
depressive symptoms

↑ 30-80%

(longitudinal studies)

History of a major
depressive episode
increases risk 4 to 6-fold

Other risk factors:

- Increased sensitivity to ovarian hormone fluctuations (h/o PMDD or postpartum depression)
- Poor sleep or VMS during perimenopause
- Longer duration of perimenopause
- Psychosocial stressors, smoking

MANAGEMENT OF VMS AND DEPRESSION IN PERIMENOPAUSE

Lifestyle Changes May Be Sufficient For Mild VMS



Lower the thermostat or use fans



Dress in layers



Avoid alcohol, caffeine, and spicy foods



Lose weight, if indicated

Hormone Therapy Should Be Considered For Bothersome VMS

Women <60 years of age or <10 years post-menopause with no contraindications or high cardiovascular or breast cancer risks

High CV risk: nonhormonal

Moderate CV risk: transdermal estradiol ± oral micronized progesterone

Hot flash frequency ↓ 75%

Hot flash severity ↓ 87%



estrogen + progesterone



estrogen

Hormone therapy is the most effective treatment for VMS
But for individuals who decline **or** have contraindications:

SSRI or SNRI

OR

Gabapentin or pregabalin

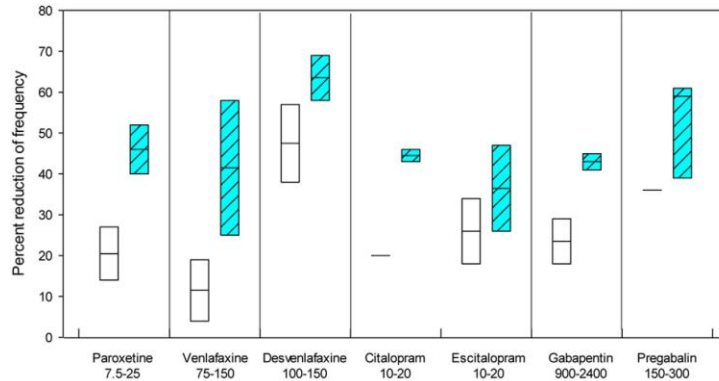


If ineffective or not tolerated

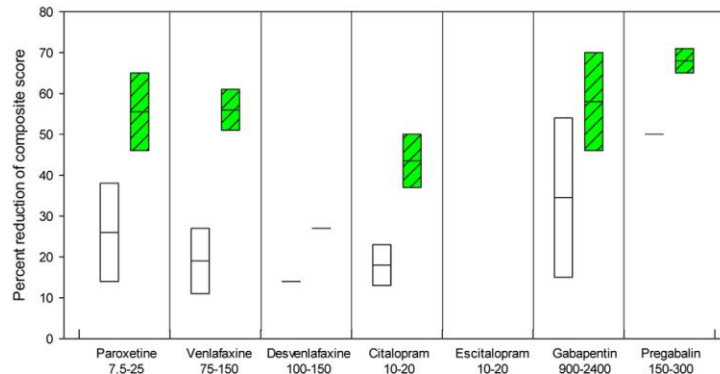
Clonidine (patch > oral)

Among SRIs, Paroxetine And Venlafaxine Have The Greatest Efficacy In Reducing Hot Flashes

Frequency



Severity x frequency composite



- paroxetine
 - venlafaxine
 - desvenlafaxine
 - citalopram
 - escitalopram
- are associated with statistically significant reductions in hot flashes ↓ 27–61%

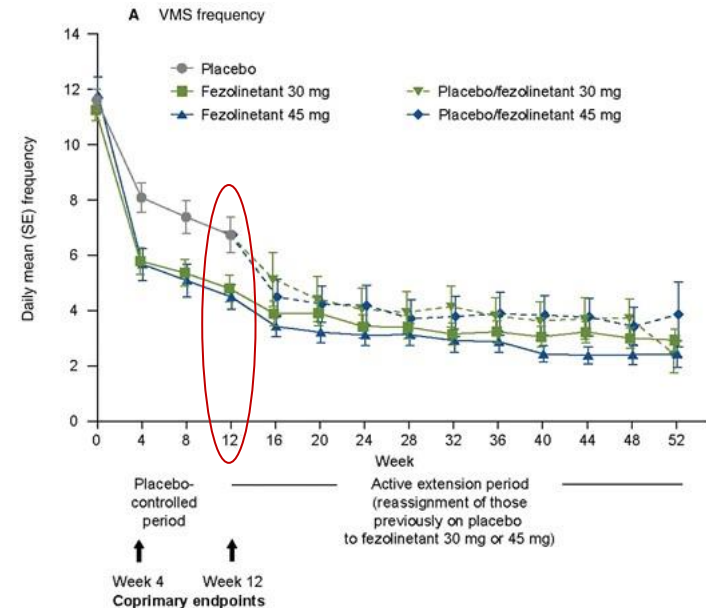
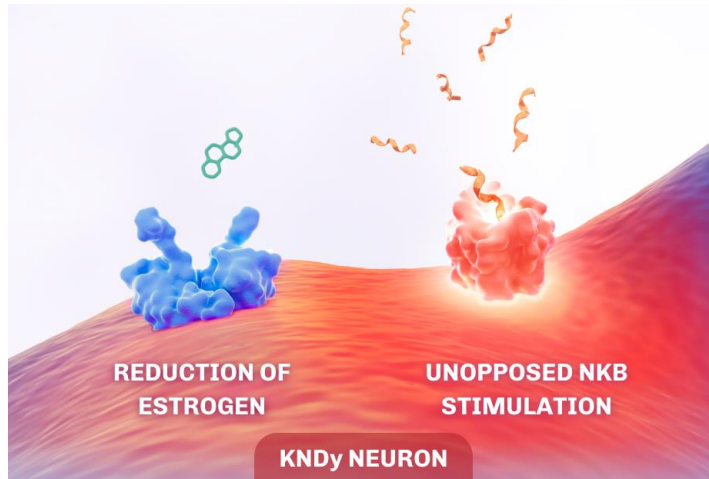
Efficacy data are mixed for fluoxetine and sertraline

Low-dose (7.5mg) paroxetine is FDA-approved for VMS in menopause



Fezolinetant Was FDA-approved In 2023 For Treatment Of Menopause Related VMS

- Fezolinetant (Veoza) is neurokinin 3 (NK3) receptor antagonist
- Aims to restore the estrogen-neurokinin signalling balance by blocking Neurokinin B in the hypothalamus thermoregulatory center





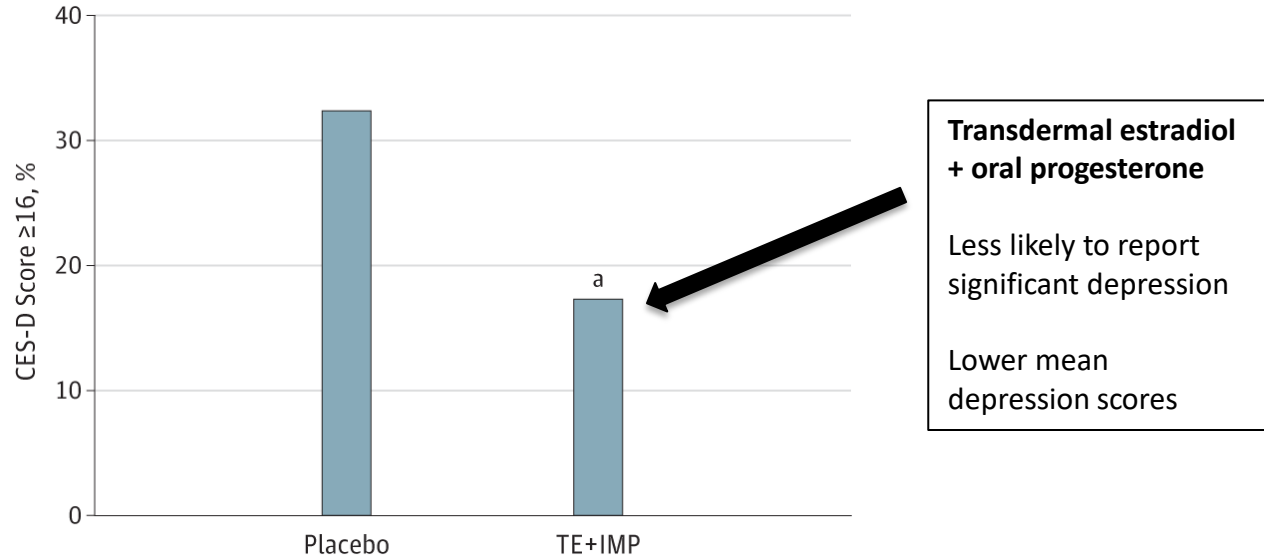
Standard Antidepressant Treatment Is Effective For Perimenopausal Depression

Hormone therapy has also been shown to improve depressive symptoms, independent of reductions in VMS

Hormone therapy was shown to **prevent** clinically significant depression in the early menopausal transition in a 12-month RCT

From: **Efficacy of Transdermal Estradiol and Micronized Progesterone in the Prevention of Depressive Symptoms in the Menopause Transition: A Randomized Clinical Trial**

JAMA Psychiatry. 2018;75(2):149-157. doi:10.1001/jamapsychiatry.2017.3998



Rate of Clinically Significant Depressive Symptoms by Treatment, Adjusting For Baseline Center for Epidemiological Studies–Depression Scale (CES-D) Score and Mean Change in Vasomotor Symptom Bothersomeness^a $P < .05$.

TE+IMP indicates transdermal estradiol plus intermittent micronized progesterone.

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Summary: Perimenopause

- Perimenopausal individuals are at risk for subclinical and clinically significant depression
- History of premenopausal depression, PPD, or PMDD increases risk for perimenopausal depression
- Hormone therapy with estradiol \pm progesterone is the most effective treatment for VMS in select populations
- Low-dose paroxetine is FDA approved for treatment of VMS
- SRIs should be utilized for treatment of perimenopausal depression
 - consider paroxetine, (des)venlafaxine, or (es)citalopram if comorbid VMS

THANK YOU!
QUESTIONS?