Gender-Informed Psychopharmacology for Women Across the Lifespan

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Disclosures/Conflicts of Interest

- I have no conflicts of interest to disclose
- Generative AI was not used for the development or content of this presentation

Learning Objectives

1. Describe how sex-based biological differences and gendered social factors influence medication metabolism, efficacy, and side effects in women across the lifespan.
2. Discuss the impact of hormonal changes on psychopharmacological treatment during critical life stages such as adolescence, pregnancy, postpartum, and menopause.
3. Describe evidence-based approaches to optimize psychopharmacological treatment plans for women, addressing unique risks, benefits, and patient-centered consideration.

Why Gender-Informed Psychopharmacology Matters

- Gender influences medication access, expectations, adherence, and experience of care
- Women underrepresented in medication trials
- Depression incidence 2x women vs men, more persistent/severe symptoms
    - Differences emerge in adolescence, resolve in postmenopause

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Lifespan Approach to Pharmacology

- Puberty-pregnancy-postpartum-perimenopause-postmenopause

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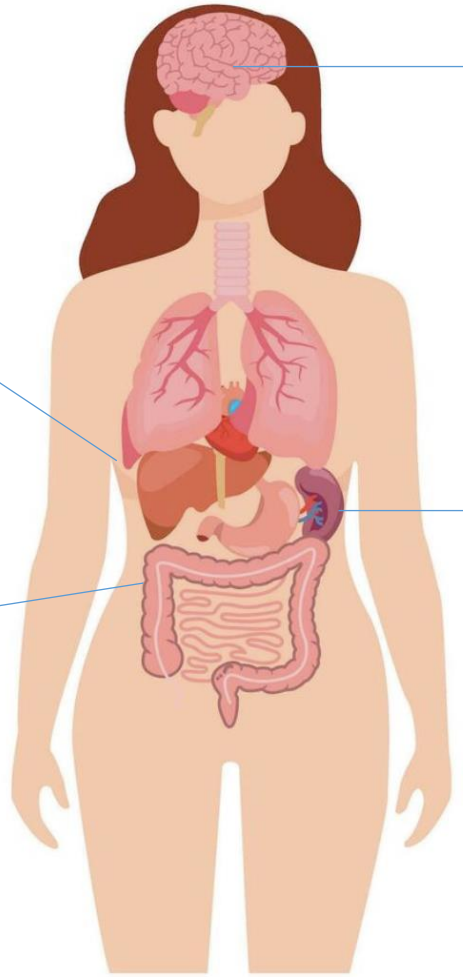
Pharmacokinetics Differences By Sex

Liver metabolism:
Higher CYP3A4 activity
Lower CYP2D6 activity
Mixed CYP1A2 activity

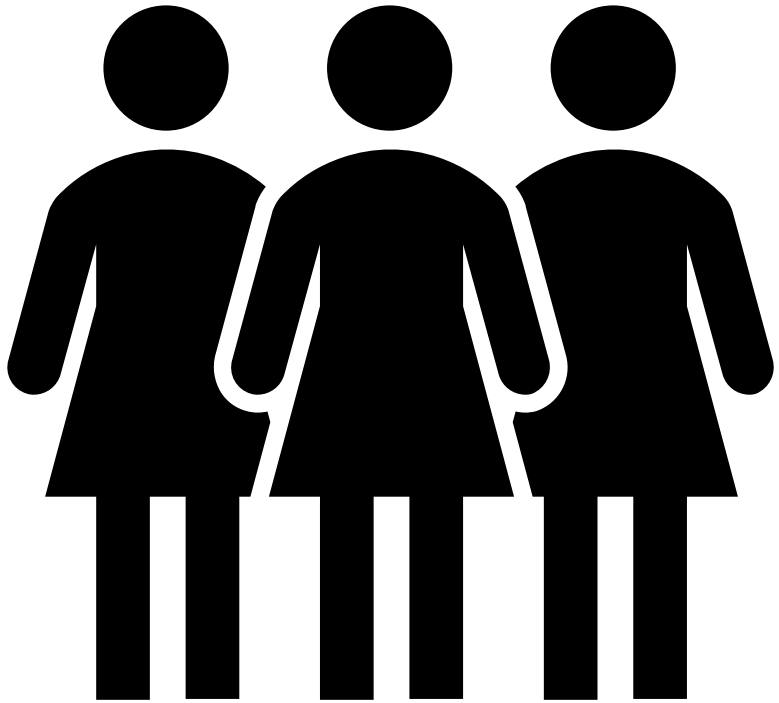
Absorption:
Increased gastric pH (?)
Slower GI transit time



Brain:
Brain monoamine functioning

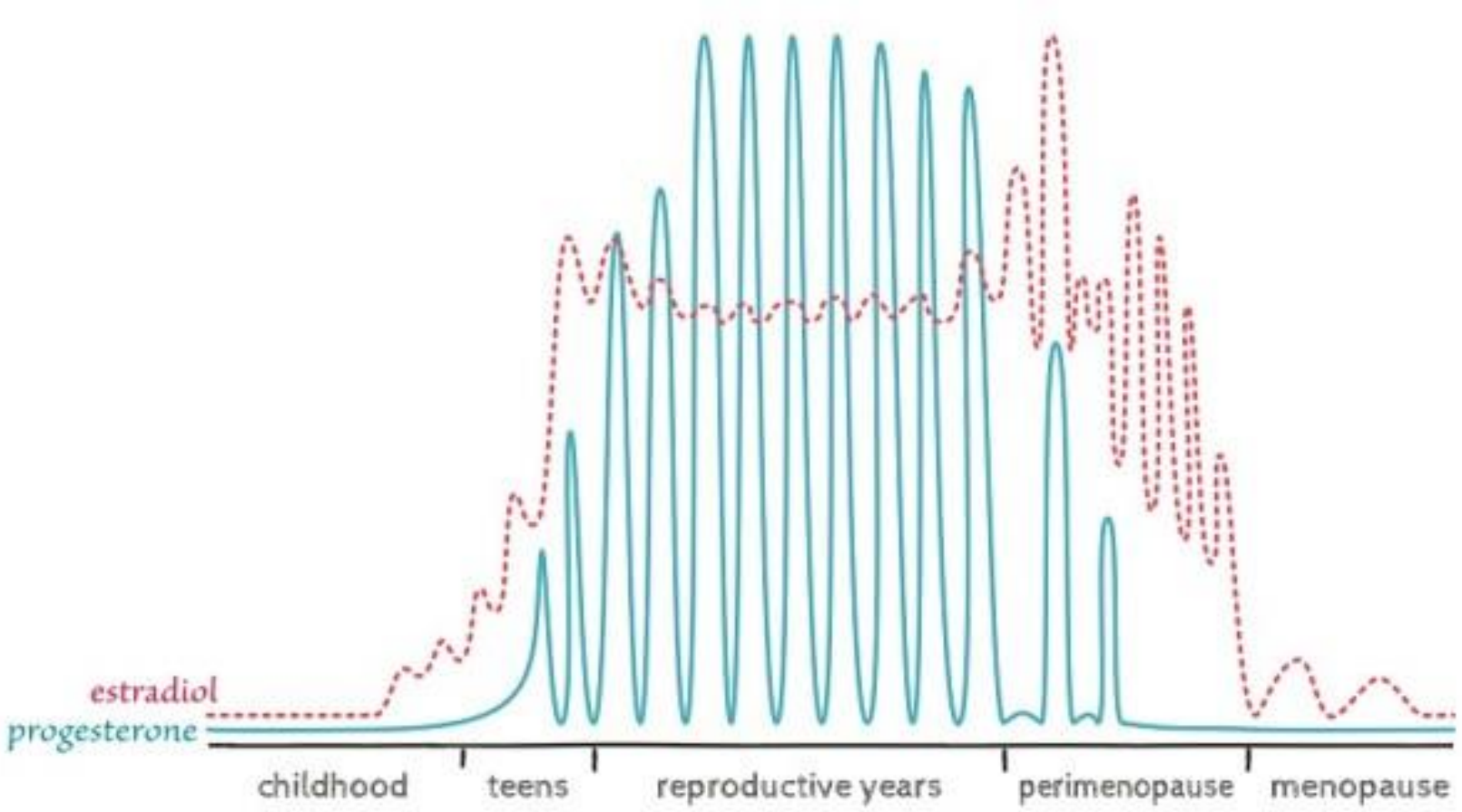
Excretion:
Slower renal clearance

Pharmacodynamic Differences By Sex



- No consensus on whether sex influences medication efficacy
  - Study design differences, confounding variables
- Mixed data on response to specific categories of medications in men vs women
  - Females may have higher response rate to SSRIs Males may have a greater response specifically with imipramine
  - SSRI efficacy may be higher in younger women vs women >age 44
- The clinical relevance of these findings is unclear

Hormonal Influences On Neurotransmission



Estrogen

- E2 receptors distribute throughout brain
- Modules serotonin, dopamine, norepinephrine
- Promotes brain plasticity (BDNF)

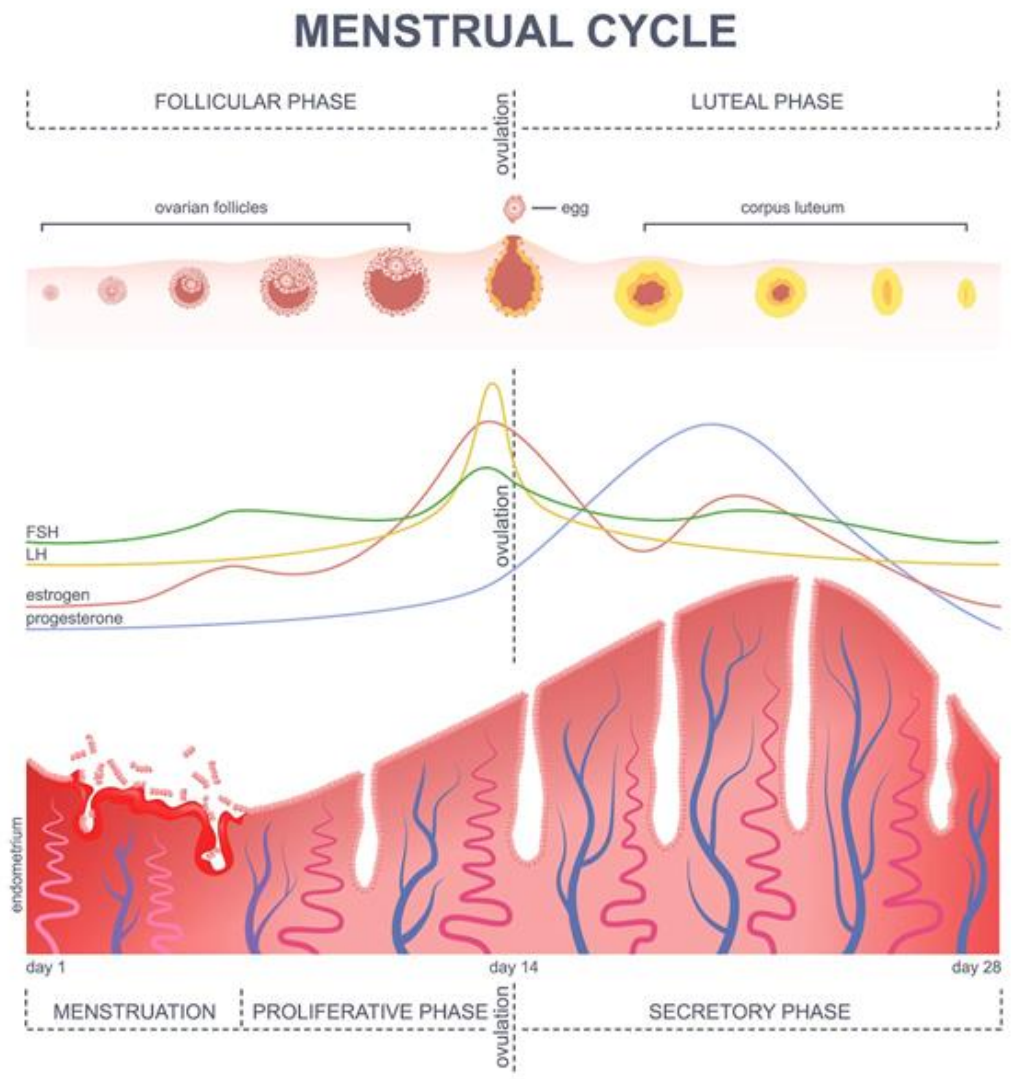
Progesterone

- Allopregnanolone
  - Modules GABA-A
  - Potential anxiolytic/sedative effects and mood benefit
- Can also worsen mood for some

Adverse Effects and Tolerability

- Side effects profiles may affect women differently vs men, though studies are mixed
- Different medication classes should be considered separately
  - Antipsychotic use:
    - Women more vulnerable to antipsychotic-related metabolic syndrome
    - Hyperprolactinemia symptoms (vaginal dryness, dyspareunia, menstrual irregularities, infertility) can go underrecognized in women
- Societal expectations placed on women can influence tolerability
  - Weight gain
  - Sexual dysfunction

Adolescence: Puberty and Menstrual Cycle



- Mood sensitivity to hormonal changes
- Sex differences in depression prevalence emerge in adolescence
  - May be due to hormone changes, social factors, etc
- Menstrual cycle physiologic effects:
  - Alters gastric contractions + fluid retention, esp during luteal phase
  - Theoretical dilution of antidepressant levels across cycle
  - Unclear clinical relevance

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Case 1

- Gabby is a 19-year-old with bipolar 2 disorder currently on lamotrigine 200mg daily who is seeing you for therapy. She had been doing well until 2 months ago when she switched out her Mirena IUD for an oral contraceptive pill called Yaz, which she hoped would help address her acne. She had taken Yaz when she was 15 and done well on it before.
- However, this was before she was diagnosed with bipolar disorder. She feels more irritable and is sleeping less. She feels like her lamotrigine just isn't working the way it did. She wants to know if the birth control is causing her to act "crazy."

Reproductive Years and Contraception: Hormonal Contraceptives and Mood

- Slight increase in risk of depression:
  - Within 6 months of starting
  - Adolescents
  - Personal or family history of mood disorders
- Risk declines over time (possibly due to discontinuation by sensitive individuals)
- Mechanism unclear:
  - Hormonal sensitivity
  - Social/contextual factors
- Progestin-only methods (Depo, POPs, IUD/implant) may pose higher risk
- Most users do not experience significant mood changes

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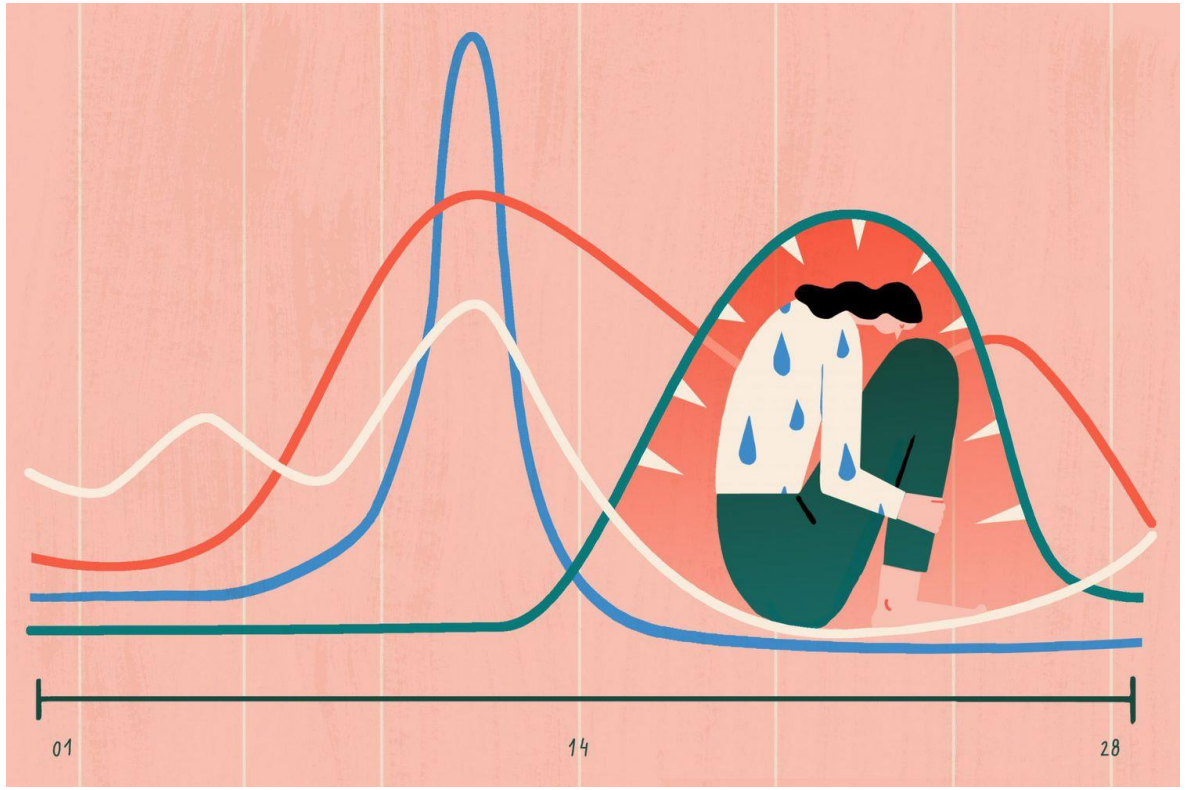
Reproductive Years and Contraception: Psychotropics and Contraception

- Mood stabilizers and contraceptive efficacy:
  - Carbamazepine and oxcarbazepine induce CYP3A4 → reduced efficacy of COCPs + risk of contraception failure
  - Consider IUDs or other non-hormonal options for contraception
- Lamotrigine and oral contraception interactions:
  - Estrogen increases lamotrigine clearance
  - Levels can decrease by 50% after 1 week of co-administration
  - During placebo pill week, blood levels can double
  - Lamotrigine does not affect OCP efficacy

PMDD and Menstrual Related Mood Disorders

- Premenstrual dysphoric disorder (PMDD)
  - SSRIs: gold standard, continuous or luteal phase
  - OCPs: combined, continuous COCPs, Drosperinone-containing COCP (Yaz, FDA-approved)
  - Lupron: severe cases
- Premenstrual exacerbation
  - Pulse dosing during luteal phase
  - OCP augmentation (limited evidence)
  - Adjunctive treatment targeted toward stabilizing the underlying disorder
  - Cautious SSRI augmentation during luteal phase with select bipolar patients



Case 1: Co-administration of COCP + lamotrigine

- Clinical considerations for Gabby:
  - Tolerated Yaz before, so less likely adverse mood effect from COCP
  - Lamotrigine + COCP has led to drop in lamotrigine levels, decreased efficacy
  - If pt prefers to stay on COCP, will need lamotrigine dose increase + continuous COCP dosing
  - If pt open to stopping COCP, can switch back to IUD and continue lamotrigine at current dose

Case 2

- Allison is a 32-year-old with recurrent major depression who recently found out she was pregnant. Prior to pregnancy, she was stable on fluoxetine 40mg daily. She had previously not responded to trials of sertraline and escitalopram. When her depression is active, she struggles to get out of bed, function at work, and has passive suicidal thoughts. She is worried that she cannot stay on her medication during the pregnancy, since she was told by another doctor that antidepressants cause withdrawals for baby and sertraline is her only option. She feels distraught and wonders if you have thoughts on what she should do. She doesn't want to hurt her baby.

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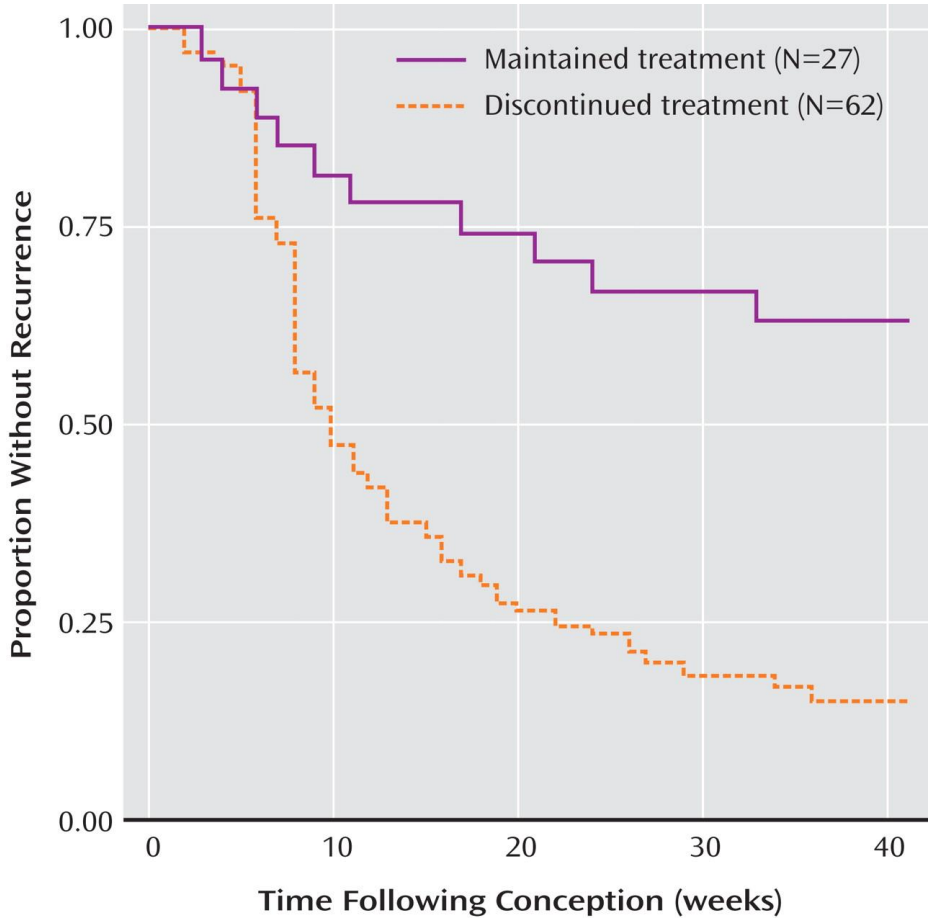
Perinatal Period

- PMADs are one of the most common complications of pregnancy and childbirth
- Suicide and accidental overdose are leading cause of maternal mortality
- Pregnancy is NOT protective against mental illness
- Postpartum is high risk for new onset or recurrence of mental illness, including more severe symptomatology
- High risk of relapse when medications discontinued
  - MDD: 68% relapse rate in med discontinuers vs 26% for med continuers
  - Bipolar: 86% relapse rate in med discontinuers vs 37% for med continuers



Viguera et al, 2007.

Viguera et al 2007.

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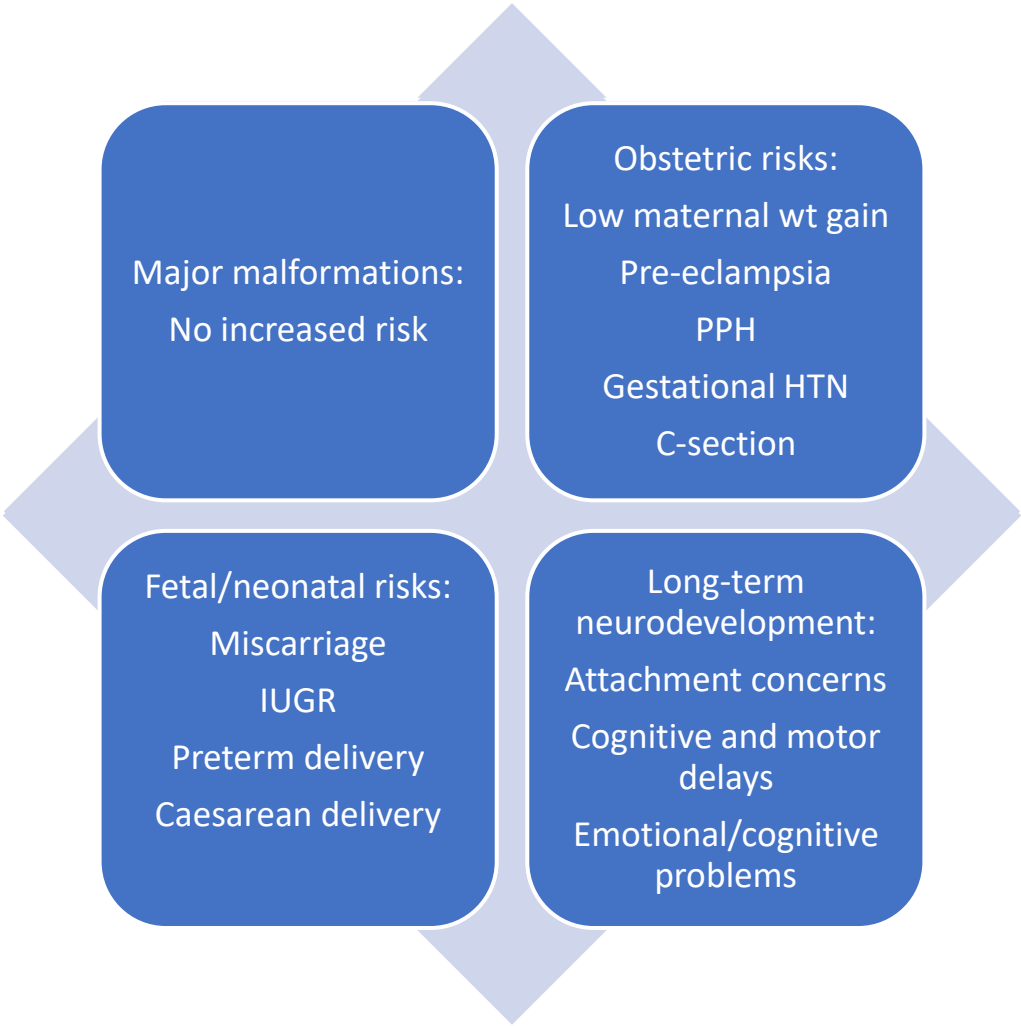
Perinatal Period: Reasons for Medication Use

- Moderate-severe symptoms (EPDS 14+, PHQ9 10+)
- Suicidal ideation
- Psychotic symptoms
- Worsening symptoms
- Prior benefit from medication or recent stabilization
- Symptom relapse off medication
- History of severe depression or suicidal ideation/suicide attempts
- Unable to access therapy
- Functional impairment, inability to care for self/baby

Risk-Risk Analysis

Risk-Risk Analysis

- Increased risk of suicide
- Increased risk of substance use
- Low adherence with prenatal care
- Poor nutrition
- Loss of interpersonal and financial resources



Antidepressants in Pregnancy

Major malformations:	• No increased risk as a class • Paroxetine most controversy, larger studies reassuring
Obstetric risks:	• PPH, pre-eclampsia (SNRIs) • Also seen in depression
Fetal/neonatal:	• Preterm delivery (2-3 days less gestation, not clinically significant) • Also seen in depression

Antidepressants in Pregnancy

- Fetal/neonatal outcomes:

Neonatal adaptation syndrome (NAS)	Persistent pulmonary hypertension of the newborn (PPHN)
• 20-30% exposed infants, unclear mechanism (withdrawal? Toxicity? something else?) • Fussiness, irritability, jitteriness, feeding difficulties. Rarely hypoglycemia, tachypnea, seizures • Benign, time limited, hours to days	• Rate of 1-2/1000 in gen pop • Low absolute risk • Earlier studies- showed rate of 1/100 • Recent, better designed studies show no increased risk or very small increased risk (2-3/1000)

NOT recommended to taper off antidepressants to reduce risk

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Antidepressants in Pregnancy

Neurodevelopmental outcomes:

- Less data overall, small studies
- 2022 Suarez study:
  - Large, well-powered cohort study
  - NO increased risk of ASD, ADHD, learning disorders, intellectual disability, or behavioral problems after controlling for confounding by indication

Original Investigation

October 3, 2022

Association of Antidepressant Use During Pregnancy With Risk of Neurodevelopmental Disorders in Children

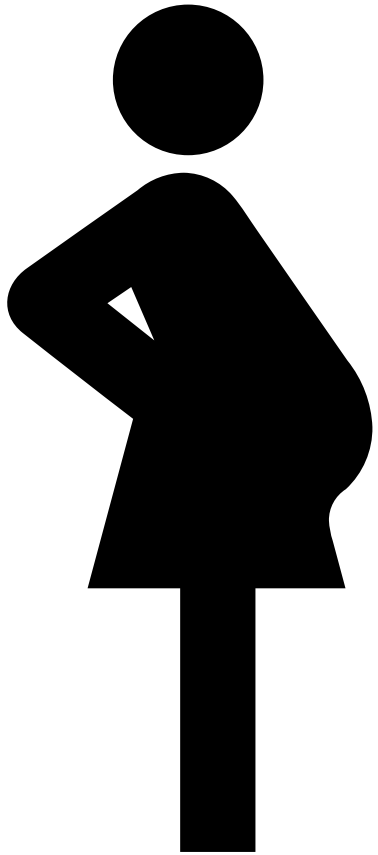
Elizabeth A. Suarez, MPH, PhD[1]; Brian T. Bateman, MD, MS[2]; Sonia Hernández-Díaz, MD, DrPH[3]; et al

» Author Affiliations

JAMA Intern Med. 2022;182(11):1149-1160. doi:10.1001/jamainternmed.2022.4268

Bottom line: Depression drives risk, not antidepressants

Perinatal Physiology



- Increased renal clearance, blood plasma volume, estrogen and progesterone levels
- Return to pre-pregnancy levels 2-3 wks postpartum
- Impacts management of medications
  - May need dose adjustment in third trimester (antidepressants, antipsychotics)
  - Increased lamotrigine clearance early in pregnancy due to estrogen, may need 2-3x pre-pregnancy dose
  - Increased lithium clearance and risk of toxicity around time of delivery
    - Obtain monthly levels in pregnancy, weekly starting week 36, immediately postpartum

Postpartum Considerations

Breastfeeding considerations:

- Goal is for relative infant dose <10%, virtually all antidepressants are <10%
  - Sertraline lowest, fluoxetine highest
- Do NOT switch antidepressants in postpartum to reduce risk of lactation exposure
- Monitor for irritability, sedation, poor feeding
- Riskier medications: lithium, clozapine, doxepin, alprazolam/diazepam

Zuranolone:

- Allopregnanolone analogue, modulates GABA-A R
- 2-week oral med course for postpartum depression, no data for pregnancy
- Very quick response (day 3), sustained remission 4 weeks after 2-week course
- Most common side effects- sedation, somnolence
- Limited lactation information, though RID <1% based on pharmaceutical analysis
- Unclear long-term outcomes

Case 2: SSRI in Pregnancy

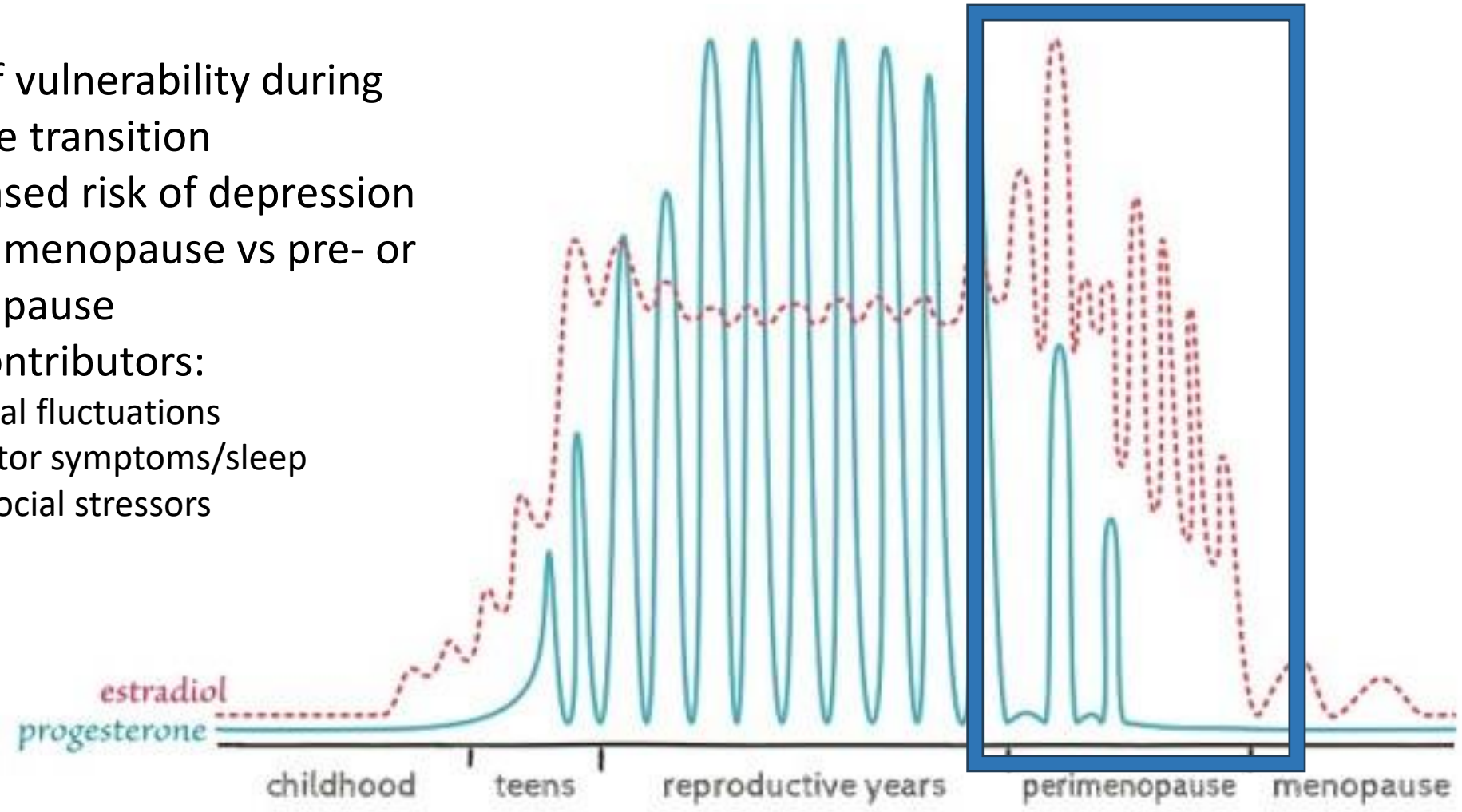
- Clinical considerations:
  - Allison has high risk features including recurrent major depression, 2 prior medication non-responses, moderate to severe depressive symptoms
  - High risk of mood recurrence off medications
  - Recommend continuing fluoxetine since that has kept her well
  - Risk of neonatal adaptation syndrome present, but symptoms typically benign and short-lived
  - Benefits of staying on medication in pregnancy outweigh risks

Case 3

Mia is a 47 y/o G2P2 with a prior history of postpartum depression who presents with concerns around mood. She has noticed increased tearfulness and irritability over past year coinciding with changes in her periods. She was prescribed sertraline in the past for her postpartum depression, but felt emotionally blunted and feels ambivalent about antidepressants. She is also having vasomotor symptoms at night, which are disrupting her sleep, and feels like her libido is lower. She is struggling with focus and just doesn't feel like herself. She wants to know what medication options could help her symptoms.

Perimenopause and Menopause

- Window of vulnerability during menopause transition
- 2-4x increased risk of depression during perimenopause vs pre- or post-menopause
- Possible contributors:
  - Hormonal fluctuations
  - Vasomotor symptoms/sleep
  - Psychosocial stressors



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Antidepressants in Perimenopause

- Gold standard treatment for MDD, esp for mod-severe symptoms
- Helpful for both peri- AND post-menopausal women
- SSRI, SNRIs commonly used
  - Two large 8 week RCTs show support use of desvenlafaxine vs placebo in perimenopausal MDD
  - Open label trials support use of other SSRIs (citalopram, escitalopram, vortioxetine), SNRIs (venlafaxine, duloxetine), vortioxetine, and mirtazapine
  - Both SSRIs and SNRIs helpful for VMS, sleep, anxiety, and pain
- Bupropion often used in this population due to low risk of weight gain/sexual dysfunction/fatigue, but no RCTs

Hormone Therapy

- Estrogen is not FDA approved to treat mood disturbance
- Two small trials show benefit for transdermal estrogen (TDE) for depressive disorders in perimenopausal women w/ or w/o VMS
- Effect of combined MHT has not been studied
- No benefit of TDE for postmenopausal women
- Possible additive or accelerating effect with antidepressants
- Possible that HT prevents depression, though not recommended for this purpose yet
    - 2018 RCT: women receiving HT were significantly less likely to develop depression vs women receiving placebo (32.3% vs 17.3%) after 1 yr

Hormone Therapy

2002 study Women's Health Initiative (WHI) study:

- Study examined use for primary prevention
- Increased risk of all cause mortality, dementia, breast cancer, heart disease, stroke, blood clots
- Limitations:
  - Average age of cohort 63
  - Many not experiencing VM
  - One oral formulation
- Later analyses show risks were less in younger cohort in this study (age<60)

"Window of Opportunity"

- Start within 10 years of FMP or <age 60
- ACOG - use should be individualized and extended use may be reasonable if benefits>risks
- CV risks of transdermal estradiol are less versus oral estrogen

Contraindications to HT:

- Hx of ER+ breast cancer
- Unexplained vaginal bleeding
- CAD or prior MI
- History of clot or stroke
- Active liver disease
- Significant risk factors for CVD

Hormone Therapy

Practical points:

- Consider use for depression if:
  - Perimenopause status
  - Other reasons for use (VMS, osteoporosis prevention, etc)
  - No medical contraindications
  - Unable or unwilling to start antidepressant
- Close monitoring of mood with combination MHT
- Possible that mood symptoms may return when MHT discontinued
- NOT preferred for individuals with severe mood symptoms

Other Considerations In Midlife

Anxiety:

- Connection with vasomotor symptoms/panic
- No preferred medication
- Consider SSRIs/SNRIs, gabapentin, MHT, clonidine patches

Cognitive concerns

- Psychoeducation is key intervention
- Address modifiable factors (sleep, mood, etc) + encourage health lifestyle
- Unclear role of MHT
- Emerging role for lisdexamfetamine, atomoxetine

Case 3: Depression Treatment in Perimenopause

- Clinical considerations:
  - Mia is vulnerable to mood symptom worsening, given her prior history of PPD
  - She has many options available to her:
    - Therapy/lifestyle interventions
    - Antidepressants- could consider bupropion to start (less likely to cause emotional blunting, may help libido)
    - MHT- reasonable option given hot flashes, mild mood symptoms. Important to ensure she has no medical contraindications
  - Can engage in collaborative decision-making

Clinical Resources

- Mother to Baby: https://mothertobaby.org/fact-sheets/
- Lactmed: https://www.ncbi.nlm.nih.gov/books/NBK501922/
- Reprotox: https://reprotox.org/
- MGH blog: https://womensmentalhealth.org/

Q&A With Dr. Lebin

- We will now discuss select questions that were submitted via the Q&A feature throughout the presentation.
- Due to time constraints, we will not be able to address every question asked.

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References

- Sramek JJ, Murphy MF, Cutler NR. Sex differences in the psychopharmacological treatment of depression. Dialogues Clin Neurosci. 2016 Dec;18(4):447-457.
- Skovlund CW, Mørch LS, Kessing LV, Lidegaard Ø. Association of Hormonal Contraception With Depression. JAMA Psychiatry. 2016 Nov 1;73(11):1154-1162.
- Hantsoo L, Epperson CN. Premenstrual Dysphoric Disorder: Epidemiology and Treatment. Curr Psychiatry Rep. 2015 Nov;17(11):87.
- Suarez EA, Bateman BT, Hernández-Díaz S, Straub L, Wisner KL, Gray KJ, Pennell PB, Lester B, McDougle CJ, Zhu Y, Mogun H, Huybrechts KF. Association of Antidepressant Use During Pregnancy With Risk of Neurodevelopmental Disorders in Children. JAMA Intern Med. 2022 Oct 3;182(11):1149–60
- Lebin LG, Novick AM. Selective Serotonin Reuptake Inhibitors (SSRIs) in Pregnancy: An Updated Review on Risks to Mother, Fetus, and Child. Curr Psychiatry Rep. 2022 Nov;24(11):687-695.
- Lebin, LG, Blissett, G., Patel, K. *et al.* The Role of Menopause Hormone Therapy in Psychiatric Symptoms and Disorders: A Review of Evidence. Curr Treat Options Psych 12, 19 (2025). https://doi.org/10.1007/s40501-025-00351-2

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