WOMEN'S HEALTH:
Beyond the Annual Visit

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Advances in Postpartum Depression: What You Need to Know

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The faculty reported the following financial relationships or relationships to products or devices they have with ineligible companies related to the content of this CME/CE activity:

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Learning Objectives

- Describe validated tools for identifying patients with postpartum depression (PPD)
- Outline the current evidence-based strategies for optimal treatment of mild, moderate, and severe PPD
- Discuss the efficacy and safety findings from clinical trials of approved and emerging therapies for PPD

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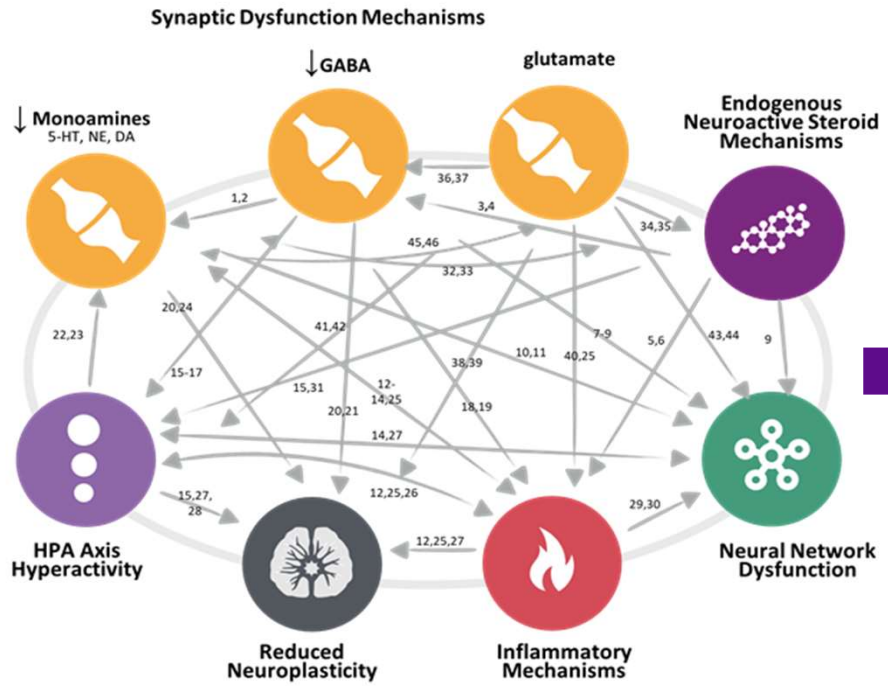
A Unified Theory of Depression

Genetic Susceptibility

Epigenetics

Environmental Triggers



MDD
PPD

Etiology → Pathophysiology → Clinical Phenotype

Dean J, et al. *Asian J Psychiatr*. 2017;27:101-111. Duman RS, et al. *Neuron*. 2019;102(1):75-90. Fischer AS, et al. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2016;1(3):262-270. Williams LM. *Lancet Psychiatry*. 2016;3(5):472-480.

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Perinatal Depression Is Common

- Overall, the highest rates for MDD in women occur between 25-44 years[1]
- 10%-16% of pregnant women have MDD[1]
  - After the first trimester, MDD is 2x the rate in the general population
  - Often associated with a prior history of depression, specifically reproductive-related mood disorders (eg, premenstrual dysphoric disorder, depression during prior pregnancy)
  - When antidepressant medication is discontinued with planning for or onset of pregnancy, ~70% of women relapse with MDD.[2] The relapse rate is significantly higher for populations with severe or recurrent depression (RR: 2.3; 95% CI: 1.58-3.35)

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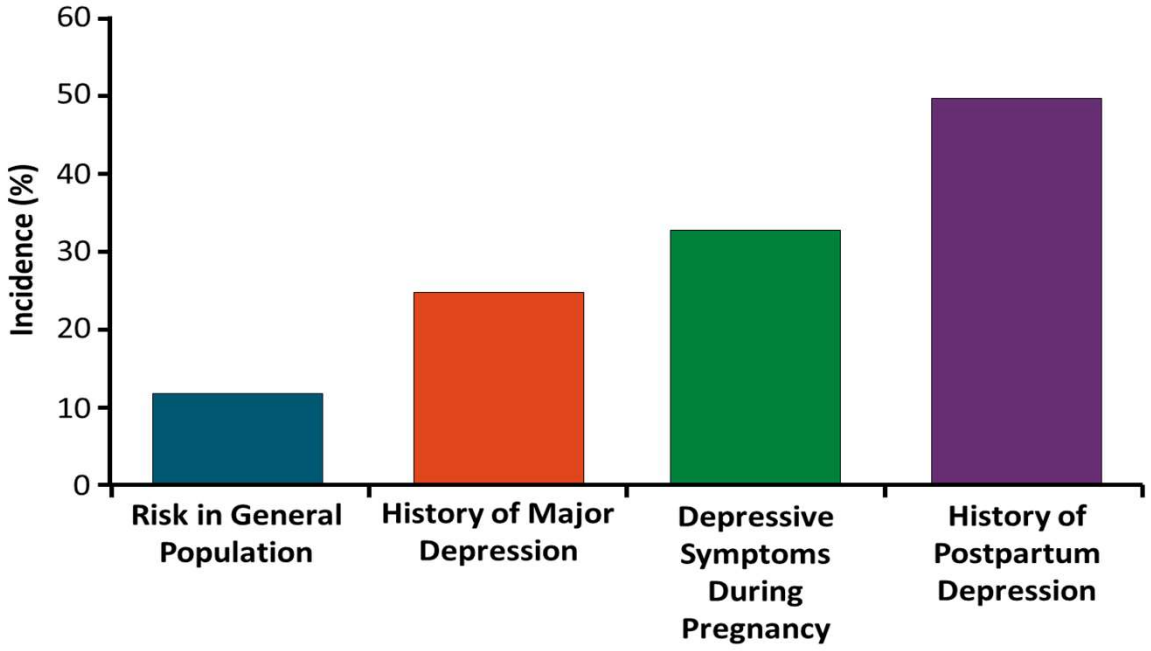
1. ACOG Committee on Practice Bulletins--Obstetrics. *Obstet Gynecol*. 2008;111(4):1001-1020.
2. Cohen LS, et al. *JAMA*. 2006;295(5):499-507.

Psychiatric History Predicts Risk of Perinatal Depression



O'Hara MW, et al. *J Abnorm Psychol*. 1984;93(2):158-171. O'Hara MW. *Postpartum Depression: Causes and Consequences*. Springer; 1995.

Postpartum Depression

- The baby blues may affect up to 80% of new mothers; characterized by a brief period (1-2 weeks) of mild worry, unhappiness, emotional lability, crying, fatigue
- Postpartum depression is a major depressive episode beginning within 4 weeks of childbirth (clinicians may observe later onset after weaning in breastfeeding women)
  - Appears to be related to rapid (in first 3 days after delivery) drop from extremely high levels of estrogen and progesterone during pregnancy to pre-pregnancy levels
  - Some women are particularly sensitive to normal hormonal changes
- PPD is seen in 10%-15% of women

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Schiller CE, et al. *CNS Spectr*. 2015;20(1):48-59. Wisner KL. *JAMA Psychiatry*. 2013;70(5):490-498.

Postpartum Depression Screening

- 10,000 women 4-6 weeks postpartum completed the Edinburgh Postnatal Depression Scale
- 14% were screen positive with a score ≥10
- **40% of episodes began postpartum, 33% during pregnancy, 27% before pregnancy**
- 70% had MDD, 2/3 had comorbid anxiety disorders, and almost 1/4 had BPAD (increased risk of postpartum psychosis)
- **Almost 20% had self-harm ideation;** drug-related deaths/overdose and suicide are major contributors to maternal death in the 12 months after delivery

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Wisner KL. *JAMA Psychiatry*. 2013;70(5):490-498. Goldman-Mellor S, et al. *Am J Obstet Gynecol*. 2019;221(5):489.e1-489.e9.

Screening Tool: Edinburgh Postnatal Depression Scale

1. I have been able to laugh and see the funny side of things
- ❑ As much as I always could
- ❑ Not quite so much now
- ❑ Definitely not so much now
- ❑ Not at all

2. I have looked forward with enjoyment to things
- ❑ As much as I ever did
- ❑ Rather less than I used to
- ❑ Definitely less than I used to
- ❑ Hardly at all

***3. I have blamed myself unnecessarily when things went wrong**
- ❑ Yes, most of the time
- ❑ Yes, some of the time
- ❑ Not very often
- ❑ No, never

4. I have been anxious of worried for no good reason
- ❑ No, not at all
- ❑ Hardly ever
- ❑ Yes, sometimes
- ❑ Yes, very often

***5. I have felt scared of panicky for no very good reason**
- ❑ Yes, quite a lot
- ❑ Yes, sometimes
- ❑ No, not much
- ❑ No, not at all

***6. Things have been getting on top of me**
- ❑ Yes, most of the time I haven't been able to cope well
- ❑ Yes, sometimes I haven't been coping as well as usual
- ❑ No, most of the time I have coped quite well
- ❑ No, I have been coping as well as ever

***7. I have been so unhappy that I have had difficulty sleeping**
- ❑ Yes, most of the time
- ❑ Yes, sometimes
- ❑ Not very often
- ❑ No, not at all

***8. I have felt sad or miserable**
- ❑ Yes, most of the time
- ❑ Yes, quite often
- ❑ Not very often
- ❑ No, not at all

***9. I have been so unhappy that I have been crying**
- ❑ Yes, most of the time
- ❑ Yes, quite often
- ❑ Only occasionally
- ❑ No, never

***10. the thought of harming myself has occurred to me**
- ❑ Yes, quite often
- ❑ Sometimes
- ❑ Hardly ever
- ❑ Never

Item scores: range from 0-3;
* indicates reverse scoring;
Total score ≥10 suggests depression; always check #10.
Scores of 7-13 indicate mild depression, 14-19 indicate moderate depression, 19-30 indicate severe depression

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Cox JL, et al. *Br J Psychiatry*. 1987;150:782-786. McCabe-Bean JE, et al. *J Reprod Infant Psychol*. 2016;34(3):293-303.

Mechanism of Action (MOA) of Treatment Options

- Standard oral antidepressants act on neurotransmitters (serotonin, dopamine, norepinephrine) primarily as reuptake inhibitors (RI) which boost neurotransmitter activity and/or make the activity last longer at the synapse, improving neurotransmission
- Neuroactive steroids (NAS) evaluated in PPD bind to gamma-aminobutyric acid type A (GABA-A) positive allosteric modulators (PAMs) at
  - Synaptic receptors (benzodiazepine binding site on the gamma subunit) which lead to rapid but brief (phasic) effects AND
  - Extrasynaptic receptors (binding site on the delta subunit for the PAMs including the progesterone metabolite, allopregnanolone, and brexanolone/zuranolone) which leads to rapid and sustained (tonic) effects
  - These effects open the chloride ion channel through the membrane and keep it open to enhance GABA inhibition of hyperactive neurotransmitter systems and restore neuroendocrine network functioning to relieve symptoms of PPD

Pearls in Pregnancy

- Utilize the EPDS for screening/early detection to follow through the pregnancy and beyond and to monitor treatment response/outcomes
- If stopped antidepressant due to pregnancy and depression recurs, restart previously effective medication **(past history guides treatment)**
- If never treated before, most data available for use of fluoxetine during pregnancy unless she plans to breastfeed, then use sertraline (low AD levels in breastmilk)
- **Don't undertreat:** Risks of medication exposure are not dose related
  - Maximize the use of one medication as opposed to polypharmacy
  - Increase dose as pregnancy progresses if symptoms increase related to increased volume of distribution and drug metabolism
- **Avoid exposure to both drug and continued depression (worst fetal outcomes)**
  - Do not reduce dose or stop antidepressant in third trimester

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Pearls for Postpartum

- Plan in advance if hx of prior episode; if not depressed during the pregnancy and desire to avoid any symptoms of PPD, start antidepressant at delivery
- If first episode of PPD is mild to moderate per EPDS, start oral antidepressant or initiate psychotherapy (CBT=cognitive behavioral therapy). Utilize SSRI, SNRI, bupropion, or mirtazapine. Titrate to therapeutic dose and continue for 6-8 weeks to ensure adequate treatment.
- If previously treated for MDD:
  - Use medication that was effective
  - Do not withhold treatment due to breastfeeding; exposure is much lower than in utero and self-tapering will occur with weaning
- If PPD is moderate to severe, especially if rapid response is desirable, treat with brexanolone

ACOG Practice Guidelines: https://www.acog.org/womens-health/faqs/postpartum-depression

Specific Treatments in PPD: Brexanolone Phase 3 Trials

- Brexanolone is a neuroactive steroid (NAS) GABA-A receptor agonist positive allosteric modulator (PAM) administered in 60-hr inpatient IV infusion; women ≤6 mo postpartum with PPD willing to temporarily stop breastfeeding were enrolled
- Primary efficacy measure: change in HAM-D 17 score at 60 hr

Study 1:
Inclusion HAM-D 17 score ≥26
138 subjects
60 µg/kg/hr BRX, 90 µg/kg/hr BRX or PLA
60: HAM-D ↓19.5; *P* = .0013 vs PLA
90: HAM-D ↓17.7; *P* = .0252 vs PLA
PLA: HAM-D ↓14.0
SAE: SI + OD in 1 patient

Study 2:
Inclusion HAM-D 17 score of 20-25
108 subjects
60µg/kg/hr BRX or PLA
60: HAM-D ↓14.6; *P* = .0160 vs PLA
PLA: HAM-D ↓12.1
SAE: altered MS + syncope in 1 patient

- No difference in % AEs from placebo; most common: HA, dizziness, somnolence

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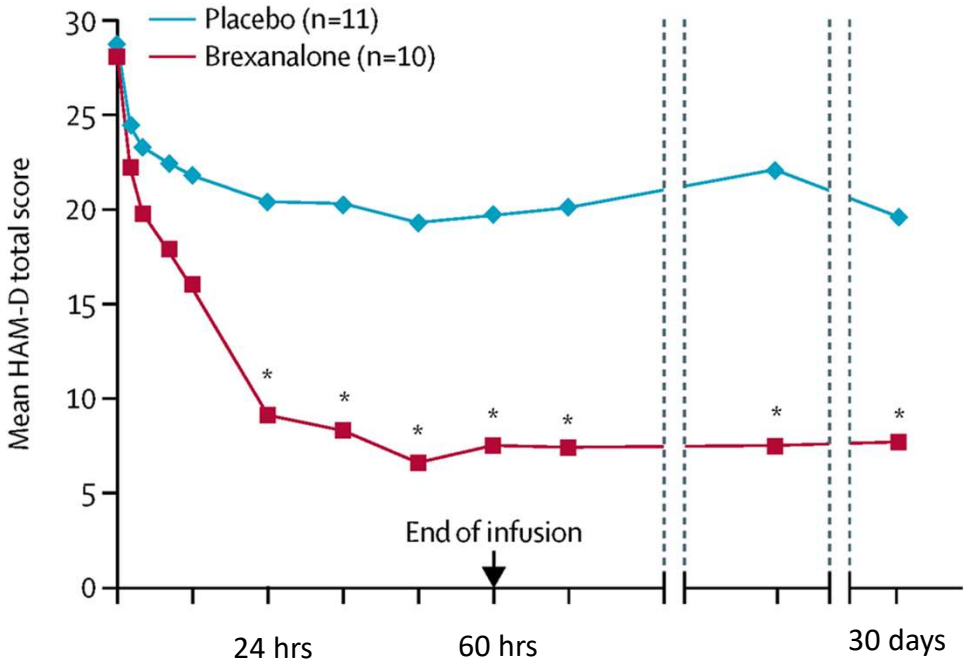
Meltzer-Brody S, et al. *Lancet.* 2018;392(10152):1058-1070.
Study 1 (NCT02942004); Study 2 (NCT02942017) at ClinicalTrials.gov

Brexanolone vs Placebo in Reducing HAM-D Scores



- HAM-D Effect size = 1.2
- Similar results for MADRS & CGI
- Remission: 70% brexanolone vs 9% placebo
- Difference at 24 hours (*P* = 0.056), 60 hours (*P* = 0.0364), 30-day follow-up (*P* = 0.0499)

Kanes S, et al. *Lancet*. 2017;390(10093):480-489.

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Brexanolone FDA-Approved for PPD

- The NAS $GABA_A$ receptor agonist positive allosteric modulator, brexanolone, is given as a 60-hour IV infusion titrated from 30 µg/kg/hr x 4 hours to 60 µg/kg/hr or 90 µg/kg/hr (24-52 hrs) then titrated down to 30 µg/kg/hr x 4 hours
- Most common AEs with brexanolone were somnolence (12.8%), headache (9.0%), dizziness (7.7%), upper respiratory tract infection (7.7%), diarrhea (6.4%), sedation (5.1%), and nausea (3.8%)
- In women with postpartum depression (PPD), both rapid (phasic) effects in 24 hours and sustained (tonic) effects out to Day 30 were seen with brexanolone

FDA Advisory Committee and Dosing Guidelines

- Brexanolone: First FDA-approved treatment for postpartum depression
- Advisory Committee left decision of dosing (60 or 90 µg/kg/hr) up to FDA
- REMS: To be administered in medically supervised settings with a pulse oximeter through 60-hr infusion and for 12 hr after by HCP who could intervene for sedation or loss of consciousness
  - Assess for excessive sedation every 2 hr during planned nonsleep periods
  - Monitor for 12 hr after infusion completed for any adverse events, specifically sedation or loss of consciousness
  - If the baby is present, an additional caregiver should be present in case mom is sedated with infusion
  - Suggest pausing breastfeeding during infusion and for 36 hours after completion of infusion

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Brexanolone prescribing information. Hoffman E, et al. *Am J Obstet Gynecol.* 2019;220(1):S554. Hoffmann E, et al. *Obstet Gynecol.* 2019;133(Suppl 1):115S. Abstract 30J.

Zuranolone Phase 3 ROBIN Study

- Zuranolone is an oral NAS GABA-A receptor agonist PAM; 153 women with severe PPD (HAM-D 17 ≥26) randomized to placebo (n = 76) or zuranolone 30 mg (n = 77) daily in the evening for 14 days; ~20% on oral antidepressant
- At Days 3, 15 (primary endpoint), 45, found significant differences in reduction in HAM-D 17 total scores for zuranolone vs placebo; differences in response and remission rates were also significant and favored zuranolone
- Well tolerated with similar rates of AEs reported, 60% with zuranolone vs 52% with placebo. Most common AEs with zuranolone: somnolence (15%), headache (9%), dizziness (8%), upper respiratory tract infection (8%), diarrhea (6%), sedation (5%), nausea (4%)

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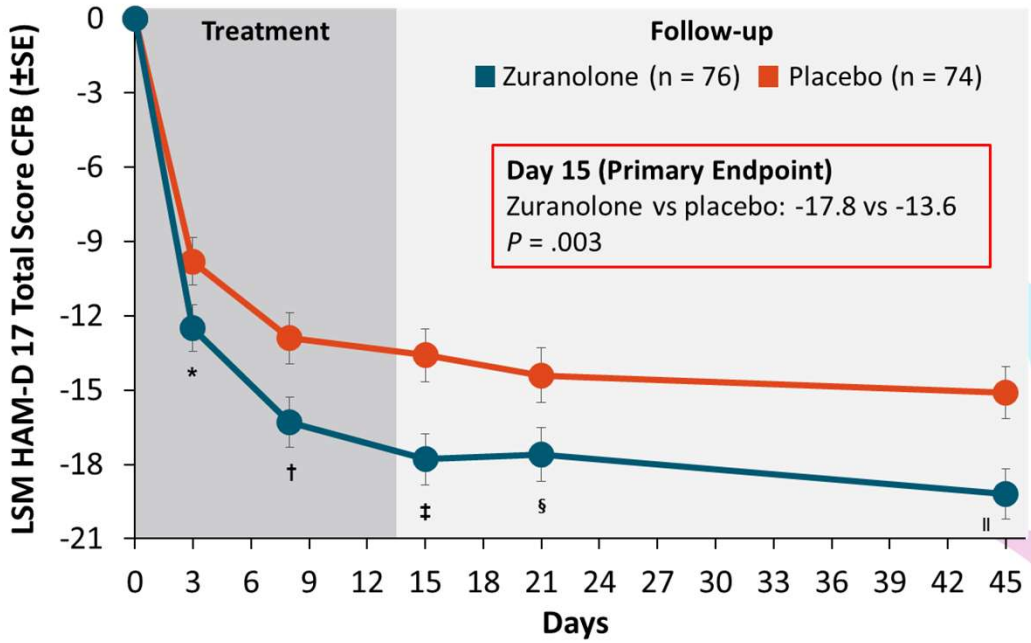
Deligiannidis KM, et al. *JAMA Psychiatry*. 2021;78(9):951-959.

Zuranolone in PPD (ROBIN Study)
Change from Baseline in HAM-D 17 Total

- Zuranolone 30 mg vs placebo once daily x 14 days
- Similar baseline demographics/ characteristics in zuranolone 30 mg (n = 76) and placebo (n = 74) groups; ~20% on baseline ADT
- Zuranolone met the primary endpoint, CFB in depressive symptoms in the HAM-D 17 total score at Day 15 vs placebo (CFB ± SE: ZUR, -17.8 ± 1.04; placebo, -13.6 ± 1.07; *P* = 0.003)
- Zuranolone was well tolerated



*P = .03; †P = .01; ‡P = .003 (effect size, 0.53); §P =0.03; ‖P = .002 vs placebo.

ADT, antidepressant therapy; CFB, change from baseline; HAM-D 17, Hamilton Rating Scale for Depression

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Deligiannidis KM, et al. *JAMA Psychiatry*. 2021;78(9):951-959.

Conclusions

- Some women are sensitive to normal hormonal changes that may represent a period of higher vulnerability for depressive episodes for these women; monitor for mood changes/depressive symptoms during risk periods
- Medications acting on serotonin, GABA, and dopamine/MAOI have a bidirectional relationship with sex steroids and appear more effective for hormonally mediated mood disorders
- For mild to moderate PPD, standard of care oral antidepressants are effective and well tolerated
- For moderate to severe PPD, the neuroactive steroid GABA-A receptor agonist positive allosteric modulators brexanolone and zuranolone have both phasic and tonic effects that enhance inhibition of a hyperactive HPA axis, restore neural network functioning, and rapidly relieve symptoms of PPD
- Other interventions such as lifestyle modifications, dietary changes, stress management, psychotherapy, and/or phototherapy combined with pharmacotherapy may provide the best outcomes


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