

New Treatments for Postpartum Depression: Brexanolone & Zuranolone

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Disclosures

- We have no disclosures.

Diagnosis [1]

A. Five (or more) of the following symptoms have been present during the same two-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

NOTE: Do not include symptoms that are clearly attributable to another medical condition.

1) Depressed mood most of the day, nearly every day, as indicated by either subjective report (eg, feels sad, empty, hopeless) or observations made by others (eg, appears tearful). (NOTE: In children and adolescents, can be irritable mood.)

2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).

3) Significant weight loss when not dieting or weight gain (eg, a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (NOTE: In children, consider failure to make expected weight gain.)

4) Insomnia or hypersomnia nearly every day.

5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).

6) Fatigue or loss of energy nearly every day.

7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).

8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by their subjective account or as observed by others).

9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

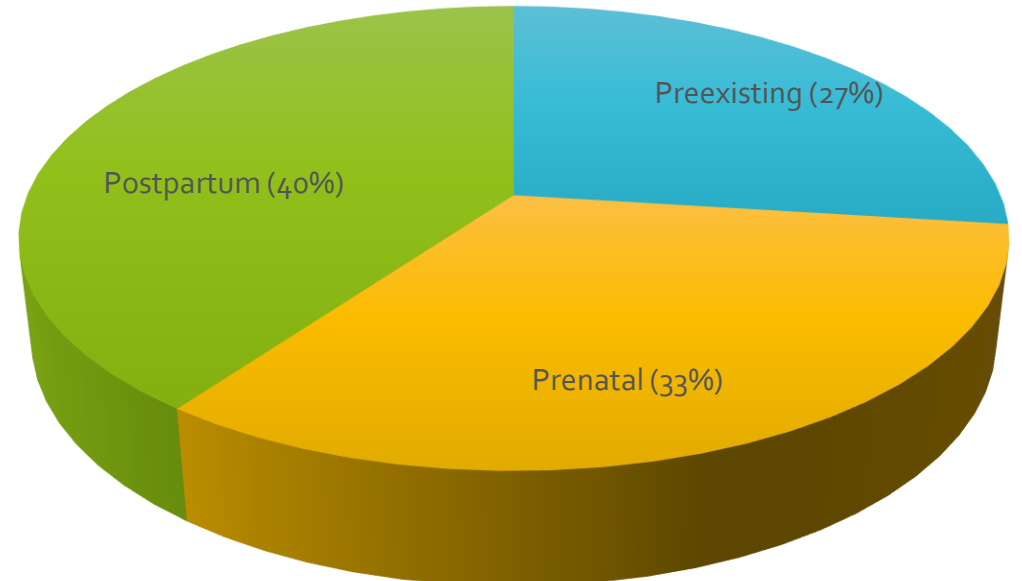
C. The episode is not attributable to the direct physiological effects of a substance or to another medical condition.

Risk Factors for Perinatal Mood and Anxiety Disorders

- History of:
 - Depression or anxiety
 - Bipolar disorder
 - Psychosis
 - Diabetes
 - Thyroid disease
 - PMS
 - Sexual trauma
 - Abuse
 - Traumatic pregnancy/delivery
- Family h/o mental illness
- Unintended pregnancy
- Teen mother
- Medicaid Insurance
- Multiples
- NICU admissions
- Pregnancy or Infant Loss
- Relationship Discord
- Financial Insecurity
- Life stress and/or limited social support or away from home
- Breastfeeding difficulty

Incidence of Perinatal Mood and Anxiety Disorders (PMAD)

- Wisner et al followed 10,000 women [2]
 - If PMAD present:
 - 68.5% unipolar depression
 - 66% of these had comorbid anxiety disorder
 - 22.6% bipolar disorder
 - 19% endorsed thoughts of self harm



Screening

- Frequency:
 - American Academy of Pediatricians: 1, 2, 4, 6 month visits [3]
 - ACOG: initial PNV, later in pregnancy, and postpartum visits [4]
 - AAFP: 6 week postpartum visit or 2 month well child visit [5]
 - Postpartum Support International [6]
 - once per trimester and postpartum
 - 6 and 12 months postpartum via FM and OB
 - 3, 9, and 12 months via peds
- Tools:
 - EDPS
 - PHQ-9
 - MDQ (Mood Disorder Questionnaire; used to screen for Bipolar Disorder)

Screening

- Edinburgh Postnatal Depression Scale (EDPS)
 - Used during pregnancy or postpartum
 - 10 item questionnaire
 - Asks about symptoms over the past 7 days
 - Each symptom given score of 1-3
 - 30 = maximum score
 - Using score of 11 as cut off = maximum specificity/sensitivity [7]

EDPS [8]

Below is an example already completed.

I have felt happy:
Yes, all of the time _____ (0)
Yes, most of the time (1)
No, not very often _____ (2)
No, not at all _____ (3)

This would mean: "I have felt happy most of the time" in the past week. Please complete the other questions in the same way.

- I have been able to laugh and see the funny side of things:
As much as I always could _____ (0)
Not quite so much now _____ (1)
Definitely not so much now _____ (2)
Not at all _____ (3)
- I have looked forward with enjoyment to things:
As much as I ever did _____ (0)
Rather less than I used to _____ (1)
Definitely less than I used to _____ (2)
Hardly at all _____ (3)
- I have blamed myself unnecessarily when things went wrong:
Yes, most of the time _____ (3)
Yes, some of the time _____ (2)
Not very often _____ (1)
No, never _____ (0)
- I have been anxious or worried for no good reason:
No, not at all _____ (0)
Hardly ever _____ (1)
Yes, sometimes _____ (2)
Yes, very often _____ (3)
- I have felt scared or panicky for no good reason:
Yes, quite a lot _____ (3)
Yes, sometimes _____ (2)
No, not much _____ (1)
No, not at all _____ (0)
- Things have been getting to me:
Yes, most of the time I haven't been able to cope at all _____ (3)
Yes, sometimes I haven't been coping as well as usual _____ (2)
No, most of the time I have coped quite well _____ (1)
No, I have been coping as well as ever _____ (0)

- I have been so unhappy that I have had difficulty sleeping:
Yes, most of the time _____ (3)
Yes, sometimes _____ (2)
No, not very often _____ (1)
No, not at all _____ (0)
- I have felt sad or miserable:
Yes, most of the time _____ (3)
Yes, quite often _____ (2)
Not very often _____ (1)
No, not at all _____ (0)
- I have been so unhappy that I have been crying:
Yes, most of the time _____ (3)
Yes, quite often _____ (2)
Only occasionally _____ (1)
No, never _____ (0)
- The thought of harming myself has occurred to me: *
Yes, quite often _____ (3)
Sometimes _____ (2)
Hardly ever _____ (1)
Never _____ (0)

TOTAL YOUR SCORE HERE ▶

Thank you for completing this survey. Your doctor will score this survey and discuss the results with you.

Verbal consent to contact above mentioned MD witnessed by:

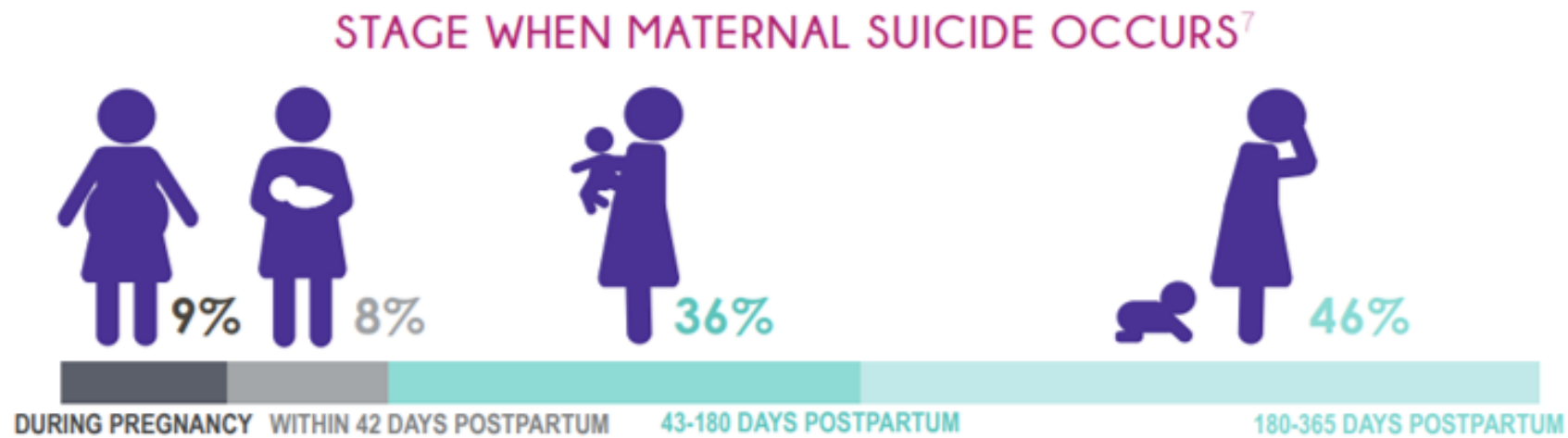
Depression in Pregnancy

- 10-15% of women effected during pregnancy [9]
- Effects if Untreated [10]:
 - Mother:
 - Poor participation in prenatal care
 - Substance use
 - Pre-eclampsia
 - Preterm labor/delivery and frequency of NICU admission
 - C-section
 - Postpartum depression
 - Fetus/Infant:
 - Increased activity across gestation and greater stress behavior after delivery
 - Epigenetic changes
 - Methylation
 - Increased cortisol and NE; decreased DA
 - Autonomic Instability
 - LBW
 - Preterm delivery and frequency of NICU admission

Postpartum Depression

- Effects if Untreated:
 - Mother [11]
 - Increased maternal substance use
 - Limited participation in follow up care (postpartum and pediatrics)
 - Impaired bonding within mother/infant pair
 - Maternal suicide
 - Breastfeeding challenges
 - Infant/Child [12]
 - Poorer cognitive functioning
 - Greater rate of illness by 3 months
 - Increased risk of colic
 - Disrupted sleep patterns/increased nightly awakenings
 - Negative impact on cognitive development

Suicide risk
highest 6-9
months
postpartum
[13]



THESE FINDINGS UNDERSCORE THE NEED FOR CONTINUED SCREENING FOR MENTAL HEALTH CONDITIONS THROUGHOUT PREGNANCY AND THE ENTIRE YEAR POSTPARTUM.

Treatment Options

- SSRI
- Zulresso
- Zuranolone
- Psychotherapy

Zulresso

Brexanolone

Pharmacology

[14]

- Positive allosteric modulator at GABA_A receptor --> increases gaba transmission
- No renal or hepatic adjustment required
- No data regarding use in breastfeeding
- Caution with use in combination with CNS depressants
- May cause fetal harm; preventative measures recommended

Administration

[14]

- REMS certified healthcare facility
- IV infusion over 60 hours --> patient cannot be primary caregiver during treatment
- Constant monitoring (pulse ox, sedation Q2 hours)
- Medication price without insurance is \$37,250; drug coverage program available through Sage

RCT [14]

- Significant placebo response and reduction in HAM-D scores
 - Difference of 2.5-5.5 points
 - Improvement in 2.5 days
 - 30 day outcomes positive
 - Black box: excessive sedation (5%); sudden LOC (4%)

Zurzuvae

Zuranolone

Basics

- FDA Approval: August 4, 2023
- Medication cost without insurance is \$15,900
- Mechanism of Action: Neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator



Eligibility

- Meets criteria for depression
- Onset in 3rd trimester (or)
- Within 4 weeks postpartum

Dosing [15]

- 20 mg, 25 mg, and 30 mg tablets
- 50 mg daily (25 mg tablet x 2)
 - If CNS depressant effects: decrease to 40 mg daily
- 30 mg daily dosing if:
 - Severe hepatic disease (Child-Pugh C)
 - Moderate to severe renal impairment (eGFR <60)
- Dose adjustments: strong CYP_{3A4} inhibitors
- Avoid use with CYP_{3A4} inducers
- Avoid use with CNS depressants (may need dose reduction)

CYP_{3A4} Inhibitors

Interactions [16]

- Might increase adverse reactions
- Use reduced dosing: 30 mg daily

Examples [17]

- Clarithromycin
- Erythromycin
- Diltiazem
- Itraconazole
- Ketoconazole
- Ritonavir
- Verapamil
- Goldenseal
- Grapefruit

CYP₃A₄ Inducers

Interactions [16]

- Might decrease efficacy of Zuranolone
- Avoid concomitant use

Examples [17]

- Phenobarbital
- Phenytoin
- Rifampicin
- St John's Wort
- Glucocorticoids

CNS Depressants

Interactions [16]

- May increase impairment or CNS depression.
- If unable to avoid, consider dose reduction

Examples [17]

- Alcohol
- Benzodiazepines
- Opioids
- Tricyclic Antidepressants

Patient Instructions [16,17]

- Take in evening with fatty meal x 14 days
- If missed dose: take the following evening
 - DO NOT take extra doses on the same day
 - Complete 14 days of treatment total
- Continue SSRI/SNRI if indicated
- Contraception during and 1 week following
- Activity restrictions x 12 hours after each dose

Warnings & Precautions [16]

- Impaired ability for hazardous activities
- CNS depression (somnolence, confusion)
- Suicidal thoughts/behaviors
- Embryo-fetal Toxicity

**WARNING: IMPAIRED ABILITY TO DRIVE OR ENGAGE IN
OTHER POTENTIALLY HAZARDOUS ACTIVITIES**

See full prescribing information for complete boxed warning.

ZURZUVAE causes driving impairment due to central nervous system (CNS) depressant effects. Advise patients not to drive or engage in other potentially hazardous activities until at least 12 hours after administration. Patients may not be able to assess their own driving competence or the degree of impairment caused by ZURZUVAE (5.1, 5.2).

Side Effects [16]

Incidence >5%:

- Somnolence (Drowsiness) (36%)
- Dizziness
- Diarrhea
- Fatigue
- Nasopharyngitis (common cold)
- Urinary tract infections

Breastfeeding [16,17]

- No data
- RID low
- Shared decision making: continue, cessation, pump and dump x 1 week following

How to Prescribe [15]

- Send prescription to specialty pharmacy
 - Accredo, CVS, Walmart
 - Pharmacy initiates approval process
 - Patient affordability program
- Patient MUST answer call from pharmacy
- Medication sent to patient's address following approval

Case Study

- 29 F, G2P2, Hx GAD and MDD with delivery on 3/19/23
- Symptoms:
 - began first few weeks after delivery and worsened at 3-4 months postpartum
 - depressed mood, anhedonia, excessive fatigue, poor sleep, feelings of hopelessness
- Medication Regimen:
 - Wellbutrin XL 300 mg daily and Atarax 25 mg as PRN
 - Continued during infusion
- Received Zulresso on 11/14/23:
 - Patient maximum dosage was 60 mcg/kg/hr due to patient report of chest pain and dyspnea in the setting of mild tachycardia following increase to 90 mcg/kg/hr
 - EKG and troponin unremarkable
- At Discharge:
 - Patient reported significant improvement in symptoms
 - Home medications continued
 - Follow up arranged with patient's referring psychiatrist

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