

Postpartum Mood and Anxiety Disorders

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36 mo (some represent relationships dating further back in time; many not current):

As an employee of MGH, I work with the MGH CTNI and MGH Center for Women's Mental Health, which has had research funding from multiple pharmaceutical companies and NIMH. My spouse and I have the following relevant financial relationships with a commercial interest to disclose:

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- Updated sponsors can be found at: <https://womensmentalhealth.org/research/pregnancyregistry/>

Research through MGH: Sage, NIA, NIMH. Consulting through CTNI through MGH (included below).

Advisory boards or consulting, Data Safety Committees/Independent Data Safety and Monitoring Committees: Janssen (Johnson & Johnson), Novartis, Neurocrine; Eliem, Sage; Brainify; Everly Health; Tibi Health; Relmada; Beckley Psytech; Brie Biotech; Reunion; Vistagen; Mycomedica.

Educational activities (speaking, planning): MGH Psych Academy, WebMD, Medscape, Pri-Med, Postpartum Support International, PRIME, HMP Global, CME Institute

Postpartum Mood and Anxiety Disorders

Postpartum Blues

Postpartum Depression (PPD)

- DSM5: Peripartum onset specifier
- Onset during pregnancy or within 4 weeks of delivery

Postpartum Psychosis

Postpartum Episodes of Bipolar Disorder

Postpartum Anxiety Disorders or Symptoms

Postpartum Depression

- 10-15% of women experience major depressive episodes after delivery (25-40% of women with histories of MDD)
- Symptoms can be similar to non-puerperal major depressive episodes
- Impairment of functioning
- The chief complaint is often not depressed mood
- Co-occurring anxiety or anxiety disorders/OCD are common

PPD: Diagnostic and Research Considerations

Major depressive episode occurring postpartum

- What is PDD anyway?
- Definitions vary
- DSM-5 specifier vs others that allow for later onset
 - DSM-5: defined by onset within four weeks of childbirth or late pregnancy

Not one homogeneous condition

- Ideal treatment may work more generally for MDD;
- Few specific treatments to target PPD (unique target or just indication?)
- different phenotypes - PPD onset, recurrent MDD, index episode bipolar depression, MDD + anxiety
- What about treatment refractoriness- patients on antidepressants already, in therapy
- Need to monitor for emergent mania/hypomania/psychosis, OCD

Context: Pregnancy and the Postpartum

- Breastfeeding or not;
- Multiple contacts with health care providers
- Opportunities for screening, diagnosis, education, treatment and treatment planning, prevention
- Who is most likely to be identified and seek treatment

Postpartum Depression: MDD +

Anxiety

Obsessions

Guilt

Insomnia

Irritability and
anger

Impairment of
transition to
motherhood

Impact on
bonding

Negative Effects of PPD and Maternal Depression on the Child

- Insecure attachment
- Behavioral problems
- Cognitive function
- Increased risk of abuse, neglect
- Childhood psychiatric diagnoses & symptoms
- Compliance with preventative measures
- Thoughts of harming infant

Civic & Holt, 2000; Cicchetti et al., 1988; Feldman et al., 1999; Murray et al., 1999; Murray et al., 1996; Sharp et al., 1995; Kotch et al., 1999; Cadzow et al., 1999; Jennings et al., 1999; McLennan & Kotelchuck, 2000; Weissman et al., 2006.

Long term Toll of PPD

- Risks of untreated PPD broadly impactful
- Can last months to years; implications for maternal MDD
- Risks to mother, baby, children, family: suicide, bonding and attachment problems, behavioral, emotional, and developmental problems, etc.

Follow up of women with histories of MDD who were euthymic at pregnancy onset:

Long term follow up of women with MDD followed throughout pregnancy and postpartum

- ~1/3 reported sustained remission
- ~2/3 reported subsequent depressive episodes
- ~1/5 (~12% of the total sample) endorsed depression more than 50% of the time following their index pregnancy
- 6.3% of the women with previous diagnoses of MDD reported new diagnoses of bipolar disorder

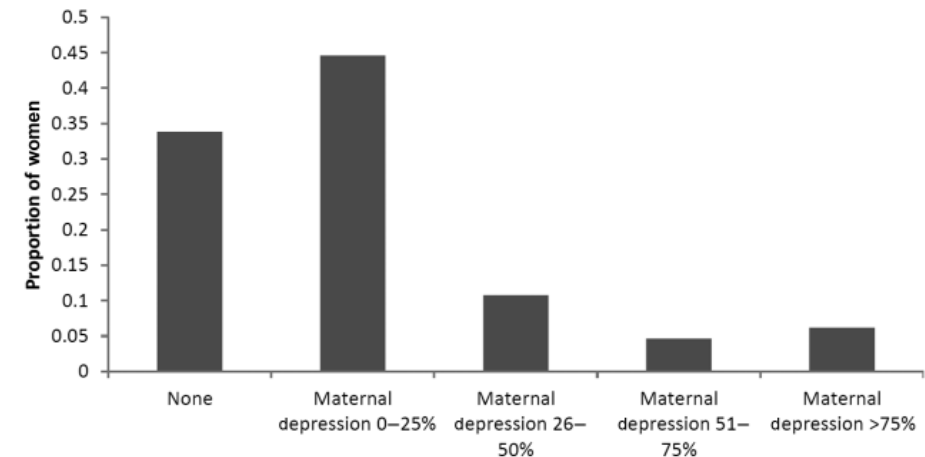


FIGURE 1 Extent of recurrence of major depression in reproductive age women previously followed across pregnancy or the postpartum period

Freeman MP, Claypoole LD, Burt VK, Sosinsky AZ, Moustafa D, Noe OB, Cheng LJ, Cohen LS. Course of major depressive disorder after pregnancy and the postpartum period. *Depress Anxiety*. 2018 Dec;35(12):1130-1136.

Postpartum Bipolar Depression

- Bipolar depression: most common type of postpartum bipolar mood episode
 - Often missed
 - Up to half of women who screen positive for PPD may have bipolar disorder
- Pharmacologic prevention strongly recommended after delivery (or earlier)
- Index episode of bipolar disorder common in the postpartum (PPD)
- Bipolar/mania/hypomania not typically screened for
- Ideal treatment for PPD would not pose risk of “switch”

Sharma V, Khan M, Corpse C, Sharma P. Bipolar Disord. 2008; Kim B, Wang HR, Son JI, Kim CY, Joo YH. Compr Psychiatry. 2008; Sharma V, Doobay M, Baczynski C. J Affect Disord. 2017; Sharma V, Al-Farayedhi M, Doobay M, Baczynski C. 2018; Tebeka S et al. Prog Neuropsychopharmacol Biol Psychiatry. 2021; Masters et al., J Clin Psychiatry 2022.

Postpartum Anxiety, OCD

Postpartum anxiety and OCD often severe

Postpartum Anxiety Disorders

- Estimated 20% of women experience maternal anxiety disorders

Postpartum OCD

- Obsessions are often present with PPD
- Obsessions more common than compulsions/rituals
- Prevalence : up to 17%, risk of recurrence and of new onset

Fairbrother, N., Janssen, P., Antony, M. M., Tucker, E., & Young, A. H. (2016). Perinatal anxiety disorder prevalence and incidence. *Journal of Affective Disorders*, 200, 148–155.

<https://doi.org/10.1016/j.jad.2015.12.082>

Fairbrother, N., Challacombe, F. L., Collardeau, F., & Truong, T. T. (2021). Perinatal and Postpartum Obsessive-Compulsive Disorder. In E. A. Storch, J. S. Abramowitz, & D. McKay (Eds.), *Complexities in Obsessive Compulsive and Related Disorders: Advances in Conceptualization and Treatment* (p. 0). Oxford University Press. <https://doi.org/10.1093/med-psych/9780190052775.003.0014>

Postpartum OCD: with or without PPD

- OCD symptoms may occur in context of PPD; or prominently without depressive episode
- Obsessions more common in the postpartum than general population
- Obsessions more common than compulsions/rituals
- Estimates: OCD in up to 9-11% of postpartum women; 38% report subsyndromal OCD
- Aggressive obsessions > contamination > checking rituals
- Treatment options: similar to non-perinatal treatments (first line: psychotherapy, antidepressants)
- Thoughts of harming infant common; do not elevate risk of violence

Miller et al., *J Women's Health* 2015; Wisner et al. *J Clin Psychiatry* 1999; Zambaldi et al. *Compr Psychiatry* 2009; Arnold *Prim Care Companion J Clin Psychiatry* 1999; Hudepohl et al., *Curr Psychiatry Rep* 2022; Brok et al., *J Clin Psychiatry* 2017

Differentiating OCD and Psychosis

- Postpartum OCD
 - Thoughts are ego-dystonic
 - Disturbed by thoughts
 - Avoid objects or being with their newborn
 - Very common disorder
 - Low risk of harm to baby
- Postpartum Psychosis
 - Thoughts are ego-syntonic
 - May not be distressed by thoughts
 - May not show avoidant behaviors
 - Not common disorder
 - High risk of harm to baby

Other Major Areas for Attention

Postpartum PTSD

- 1/3 of women experience childbirth as traumatic, 3-6% develop new onset postpartum PTSD
- Prevalence of postpartum PTSD ranges from 1-30%

Postpartum Depression and SUDs

- High rates of PPD among individuals with SUDs
- High rates of relapse across pregnancy and postpartum

Grekin R, O'Hara MW. Prevalence and risk factors of postpartum posttraumatic stress disorder: a meta-analysis. Clin Psychol Rev. 2014

Slade P, Murphy A, Hayden E. Identifying post-traumatic stress disorder after childbirth *BMJ* 2022

Pacho M et al. Substance use during pregnancy and risk of postpartum depression: a systematic review and meta-analysis. Front Psychiatry. 2023;

Freeman MP et al. Predictors of Depressive Relapse in Women Undergoing Infertility Treatment. J Womens Health. 2018

Breastfeeding

Public health initiatives vs. individual situations

“Baby friendly” hospital initiatives

What is it: education around breastfeeding, rooming in 24 hours/day, no use of infant nursery, emphasis on exclusive breastfeeding on demand, no bottles or pacifiers

Overemphasis over maternal wellbeing may increase risk of postpartum depression and anxiety

Data do not support 24 hr/day rooming in and breastfeeding success



Diez-Sampedro et al., 2019; Jaafar et al., Cochrane Database Syst Review 2012 & 2016;
babyfriendlyusa.org

Sleep deprivation can be a major trigger for psychiatric disorders and hinder recovery

Emphasis to Screen and Prevent

Screening for Depression in Adults

US Preventive Services Task Force Recommendation Statement

DESCRIPTION Update of the 2009 US Preventive Services Task Force (USPSTF) recommendation on screening for depression in adults.

METHODS The USPSTF reviewed the evidence on the benefits and harms of screening for depression in adult populations, including older adults and pregnant and postpartum women; the accuracy of depression screening instruments; and the benefits and harms of depression treatment in these populations.

POPULATION This recommendation applies to adults 18 years and older.

RECOMMENDATION The USPSTF recommends screening for depression in the general adult population, including pregnant and postpartum women. Screening should be implemented with adequate systems in place to ensure accurate diagnosis, effective treatment, and appropriate follow-up. (B recommendation)

JAMA. 2016;315(4):380-387. doi:10.1001/jama.2015.18392

JAMA | US Preventive Services Task Force | **RECOMMENDATION STATEMENT**

Interventions to Prevent Perinatal Depression

US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force

IMPORTANCE Perinatal depression, which is the occurrence of a depressive disorder during pregnancy or following childbirth, affects as many as 1 in 7 women and is one of the most common complications of pregnancy and the postpartum period. It is well established that perinatal depression can result in adverse short- and long-term effects on both the woman and child.

OBJECTIVE To issue a new US Preventive Services Task Force (USPSTF) recommendation on interventions to prevent perinatal depression.

EVIDENCE REVIEW The USPSTF reviewed the evidence on the benefits and harms of preventive interventions for perinatal depression in pregnant or postpartum women or their children. The USPSTF reviewed contextual information on the accuracy of tools used to identify women at increased risk of perinatal depression and the most effective timing for preventive interventions. Interventions reviewed included counseling, health system interventions, physical activity, education, supportive interventions, and other behavioral interventions, such as infant sleep training and expressive writing. Pharmacological approaches included the use of nortriptyline, sertraline, and omega-3 fatty acids.

FINDINGS The USPSTF found convincing evidence that counseling interventions, such as cognitive behavioral therapy and interpersonal therapy, are effective in preventing perinatal depression. Women with a history of depression, current depressive symptoms, or certain socioeconomic risk factors (eg, low income or young or single parenthood) would benefit from counseling interventions and could be considered at increased risk. The USPSTF found adequate evidence to bound the potential harms of counseling interventions as no greater than small, based on the nature of the intervention and the low likelihood of serious harms. The USPSTF found inadequate evidence to assess the benefits and harms of other noncounseling interventions. The USPSTF concludes with moderate certainty that providing or referring pregnant or postpartum women at increased risk to counseling interventions has a moderate net benefit in preventing perinatal depression.

CONCLUSIONS AND RECOMMENDATION The USPSTF recommends that clinicians provide or refer pregnant and postpartum persons who are at increased risk of perinatal depression to counseling interventions. (B recommendation)

The Perinatal Depression Treatment Cascade: Baby Steps Toward Improving Outcomes

Bradley N. Gaynes, MD, MPH; Elizabeth Q. Cox, MD; Nathaniel A. Sowa, MD, PhD; Samantha E. Meltzer-Brody, MD, MPH

J Clin Psychiatry 2016;77(9):1189–1200

RELATED ARTICLES ▾

Article Abstract

Objective: Perinatal depression is a common and costly health concern with serious implications for the mother and child. We sought to quantify the “Perinatal Depression Treatment Cascade”—the cumulative shortfalls in clinical recognition, initiation of treatment, adequacy of treatment, and treatment response for women with antenatal (AND) and postpartum depression (PPD).

Data Sources: A systematic search was conducted to identify articles about diagnostic rates, treatment rates, adequate treatment rates, and remission rates for AND and PPD. We searched PubMed and EMBASE through March 2015.

Study Selection: Articles were included if they were in English and examined rates of detection, treatment, adequate treatment, or remission for AND or PPD.

Data Extraction and Analysis: Mean rates of diagnosis, treatment, adequate treatment, and remission were calculated and weighted based on the number of subjects in each study. Search results were dually reviewed for confirmation of study eligibility and data abstraction.

Results: Decrements occur at each branch of the cascade. Data suggest that 49.9% of women with AND and 30.8% of women with PPD are identified in clinical settings; 13.6% of women with AND and 15.8% of women with PPD receive treatment; 8.6% of women with AND and 6.3% of women with PPD receive adequate treatment; and 4.8% of women with AND and 3.2% of women with PPD achieve remission.

Conclusions: Application of the treatment cascade model suggests multiple opportunities for improving perinatal depression management, informing optimal allocation of resources, and providing adequate treatment to this underrecognized and undertreated population..

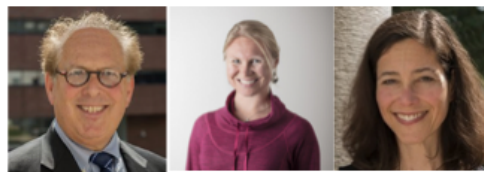


Screening and Treatment Enhancement for Postpartum Depression in the MGB System

Postpartum depression (PPD) affects roughly 15% of women after the birth of a child, impacting not only the mother, but also the infant and family. To facilitate early detection of PPD, universal screening for postpartum depression with an evidence-based tool has been recommended. Building from the Center's previous research on PPD screening, STEPS for PPD (Screening and Treatment Enhancement for Postpartum Depression), funded by the **Marriott Foundation**, is dedicated to furthering our understanding of systems for screening, referral and treatment of PPD. This is a joint investigation between the Center for Women's Mental Health and multiple Departments of Obstetrics and Gynecology across Massachusetts General Brigham (MGB). This study seeks to ensure that MGB patients are universally screened for postpartum depression and, if they do screen positive, are referred to receive adequate care and treatment of symptoms. The knowledge gained from this study will illuminate factors associated with utilization of treatment services for postpartum depression and can inform how best to increase access and uptake of services for future patients.

Meet the STEPS for PPD Study Team

Read staff biographies [here](#)



THE J. WILLARD AND ALICE S. MARRIOTT FOUNDATION

This study is funded by the **J. Willard and Alice S. Marriott Foundation**

Safety: Need to monitor for suicide risk with a prespecified safety plan

Suicidal ideation

- Among women with PPD:
 - 5.4% thoughts of self harm sometimes or quite often

EPDS Suicide Item

10. The thought of harming myself has occurred to me	Yes, quite often (score of 3)
	Sometimes (score of 2)
	Hardly ever (score of 1)
	Never (score of 0)

Suicide attempts and suicide:

- In US: 1/20 maternal deaths during pregnancy or first postpartum year
- Suicide attempts in the postpartum year:
Risk Factors
 - Mood disorders: bipolar disorder, MDD
 - Anxiety disorders
 - Psychotic disorders
 - Substance use disorders
 - Comorbid diagnoses

Sit et al., 2015; Goldman-Mellor et al, 2025. Vanderkruik R, Freeman MP, Dunn KA, Clifford CA, Dimidjian S, Cohen LS. The Challenge of Clinical Research and Suicidality: Participant Feedback on a Safety Protocol. J Clin Psychiatry. 2023

Risk for PPD: Who is At Risk and Why?



No single known cause of postpartum depression

Inconsistent findings: no hormonal abnormality has been implicated in the cause of PPD

Thyroid dysfunction is common- either hypo- or hyperthyroidism (hypothyroidism more common; thyroiditis with acute hyperthyroidism may occur)



Major Risk Factors

Depression and anxiety during pregnancy

History of PPD or postpartum psychosis

psychosis

History of bipolar disorder

History of recurrent MDD

Cohen et al. *Psychiatr Clin North Am.* 2010; Pearlstein et al. *Am J Obstet Gynecol* 2009.

Postpartum Depression Predictors Inventory

Stronger Predictors:

- History of depression
- Depression in pregnancy
- Anxiety in pregnancy
- Stressful life events
- Marital dissatisfaction
- Child-care stress
- Inadequate social supports
- Difficult infant temperament
- Low self-esteem
- Family History of Postpartum Depression – heritability 44-54% (from twin and sibling studies)

Weaker Predictors:

- Unwanted or unplanned pregnancy
- Lower socioeconomic status
- Being single
- Postpartum blues

Treatment: Postpartum Depression

- Moderate to severe depression
 - Antidepressants are first line
- Use lowest effective doses – aim for remission
- Consultation with perinatal psychiatry specialists as needed
- Maximize non-medication alternatives

Antidepressants and Breastfeeding

- Most studies of infant exposure to antidepressants show low levels of drug in breast milk and infant serum
- Variable quality of studies
 - Some rigorous mother-baby pair studies quantify exposure; case reports can be misleading
- Antidepressants as a class considered reasonable in breastfeeding
 - Some better known than others
 - Most data for sertraline, paroxetine (low levels of exposure)
 - Fluoxetine (more likely detectable but still compatible in breastfeeding)

Weissman et al., 2004; Burt et al., 2001; Orsolini and Bellantuono, 2015; Guille et al., 2013

Breastfeeding and Antidepressants

<u>Fluoxetine</u>	Due to long half life, may be more likely to be found at detectable levels in infant serum, especially at higher doses; Reasonable for use if a woman has had a good previous response to it and if used during pregnancy.
<u>Sertraline</u>	• Consistent reports of low levels of exposure, relatively large amount of study
Citalopram, escitalopram	• Less systematic study of mom-baby pairs compared with <u>sertraline</u> and <u>paroxetine</u>, observed low levels of exposure to infant via breastfeeding
<u>Paroxetine</u>	• Consistent reports of low levels of exposure, relatively large amount of study • Use limited by tolerability
<u>Bupropion</u>	• Paucity of systematic study; a few case reports in older infants that demonstrate low levels of exposure via breastfeeding; May be advantageous in smokers; Reasonable for use if women have had good previous response; One case report of possible infant seizure
Venlafaxine, Desmethyl venlafaxine	• Higher levels of <u>desmethylvenlafaxine</u> found in <u>breastmilk</u> than <u>venlafaxine</u> • No adverse events reported
Tricyclic Antidepressants	• Considered reasonable for breastfeeding if use clinically warranted; few adverse affects in babies and generally low levels of exposure reported
Newer antidepressants, MAOIs	• Systematic human lacking in the context of breastfeeding for MAOIs, most newer antidepressants • Case series for vortioxetine (N=3) showing low levels of exposure, duloxetine (N=1)

FDA approves first treatment for postpartum depression

For Immediate
Release

March 19, 2019

Release

[Español \(/NewsEvents/Newsroom/ComunicadosdePrensa/ucm634025.htm\)](#)

The U.S. Food and Drug Administration today approved Zulresso (brexanolone) injection for intravenous (IV) use for the treatment of postpartum depression (PPD) in adult women. This is the first drug approved by the FDA specifically for PPD.

"Postpartum depression is a serious condition that, when severe, can be life-threatening. Women may experience thoughts about harming themselves or harming their child. Postpartum depression can also interfere with the maternal-infant bond. This approval marks the first time a drug has been specifically approved to treat postpartum depression, providing an important new treatment option," said Tiffany Farchione, M.D., acting director of the Division of Psychiatry Products in the FDA's Center for Drug Evaluation and Research. "Because of concerns about serious risks, including excessive sedation or sudden loss of consciousness during administration, Zulresso has been approved with a Risk Evaluation and Mitigation Strategy (REMS) and is only available to patients through a restricted distribution program at certified health care facilities where the health care provider can carefully monitor the patient."

PPD is a major depressive episode that occurs following childbirth, although symptoms can start during pregnancy. As with other forms of depression, it is characterized by sadness and/or loss of interest in activities that one used to enjoy and a decreased ability to feel pleasure (anhedonia) and may present with symptoms such as cognitive impairment, feelings of worthlessness or guilt, or suicidal ideation.

Zulresso will be available only through a restricted program called the Zulresso REMS Program that requires the drug be administered by a health care provider in a certified

Brexanolone (SAGE-547)

Allopregnanolone/Neurosteroids

- FDA approval in 2019
- IV delivered analogue of allopregnanolone
- Allosteric modulator of GABA receptors
- Two positive, controlled trials in postpartum depression (onset during late pregnancy or postpartum, presented within six months postpartum with MDD)
- Rapid onset of benefit, durable efficacy to 30 days
- Implementation challenges: cost, in hospital
- Not currently available

Meltzer-Brody et al., Lancet 2018

Zuranolone: FDA approved for PPD

- Oral neurosteroid GABA allosteric modulator
- Studies have demonstrated benefit in placebo-controlled trials
- Administered orally for 2 weeks
- Significant improvement on HAM-D observed from day 3, at primary endpoint (day 15), through day 45
- Improvements on sleep, anxiety also demonstrated
- Studies for MDD in men and women
- Most common TEAEs with zuranolone: somnolence, dizziness, sedation
- Available through specialty pharmacies
- Scheduled
- Taken with fat containing food
- No clear guidance yet on breastfeeding
- Safety considerations with other CNS depressants (benzodiazepines)
- Current lack of longer term data or guidance on use after relapse and for other disorders such as postpartum anxiety, OCD, bipolar disorder, prevention of PPD
- Variable ease of obtaining and financial coverage

Deligiannidis et al., AJP 2023; Deligiannidis et al., JCP 2023;

Perinatal Depression: Non-medication treatments

- **Psychotherapy**
 - Evidence based therapies (Interpersonal Therapy, Cognitive Behavioral Therapy, Behavioral Activation); individual and groups; support; range of delivery options being explored: telehealth, phone, peer delivered, apps
- Psychoeducation, support groups
- Electroconvulsive Therapy (ECT)
- Transcranial Magnetic Stimulation (TMS)
- Complementary and Alternative Medicine (Integrative Medicine)

Spinelli MG. *Am J Psychiatry*. 1997;154(7):1028-1030; Dennis CL. *J Clin Psychiatry*. 2004;65(9):1252-1265; Yonkers KA et al. *Obstet Gynecol*. 2009; 114(3):703-713; Miller LJ. *Hosp Community Psychiatry*. 1994;45(5):444-450; Goodman and Santangelo, *Arch Women's MH*, 2011; Miniati et al., *Arch Women's Mental Health* 2014; O'Hara and Engeldinger, *Clin Obstet Gynecol* 2018; Deligiannidis and Freeman, 2014; Liu et al., *Worldviews Evid Based Nurs* 2022; Cohen et al. *Psychiatr Clin North Am*. 2010; Perlstein et al. *Am J Obstet Gynecol* 2009; Appleby et al., 1997; Branquinho et al., *J Affect Disorders* 2021.

Prevention: When? With What?

Leverage pregnancy: Assess for risk factors;
subsyndromal disorder(s); formulate plans

Implement plan, monitoring and actions



Pregnancy

Postpartum

Screening, assessments

Prevention before PPD onset: **Pre-pregnancy?** **During pregnancy?** **Immediately after delivery?**
Psychotherapies? Medications?

PPD Prevention

- Psychotherapies endorsed by the US
- Interpersonal Psychotherapy
- Cognitive behavioral therapy
- Groups and individual psychotherapies
- Few small randomized controlled trials of relapse prevention with medication for PPD
- Relapse pharmacologic prevention data robust for bipolar disorder

US Preventative Task Force, JAMA 2019
Zlotnick et al., 2016, Werner et al., 2014; Kozinsky et al., 2012
Wisner et al., 1994, 2001, 2003

Postpartum Bipolar Disorder and Postpartum Psychosis

Pregnancy & Postpartum: Risks of Discontinuing Medication

Viguera, et al. 2000:

- Retrospective comparison of recurrence rates, pregnant (N=42) vs. nonpregnant women (N=59) with bipolar disorder
- Rates of recurrence after discontinuation of medication
 - Similar for pregnant and nonpregnant women, except more depressive episodes in pregnant women (**overall recurrence rate = 55%**)
 - **Women at increased risk of recurrence postpartum (70% vs. 24%; 2.9 x more likely to have recurrence than nonpregnant women after same time course)**
 - **Recurrence risk greater after rapid discontinuation (≤ 2 wks) than gradual (2-4 wks)**

Postpartum Psychosis

1 to 2 per 1000 pregnancies

Rapid, dramatic onset usually within first 2 weeks

Suspect Bipolar disorder, but may be index episode or circumscribed episode of psychotic disorder:

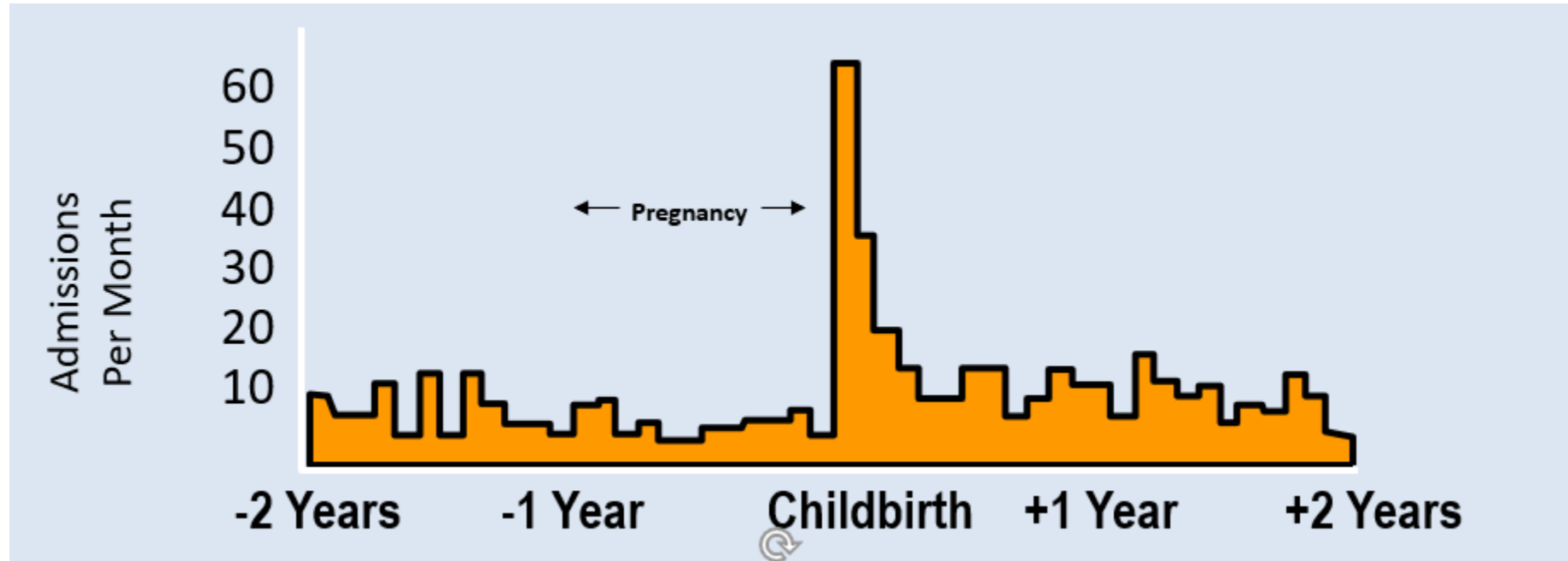
- Underlying diagnosis: affective psychosis (bipolar disorder or schizoaffective disorder)
- Family and genetic studies, index episode follow-up

High risk of harm to self and infant

- Psychiatric emergency
- Estimated that 4% of women with postpartum psychosis commit infanticide

Nonacs and Cohen, 1998; Jones & Craddock, 2001;
Spinelli, AJP, April 2009; Osborne 2018; Spinelli, AJP 2004; Spinelli, AJP 2009

Risk of Psychiatric Hospitalization During Pregnancy and Postpartum



Highest risk of hospitalization for new mothers is 10 to 19 days postpartum, increased outpatient contacts first three months

Kendell et al. *Br J Psychiatry*. 1987;150:662; Munk-Olsen et al., *JAMA*. 2006;296(21):2582-2589.

Table 2. Psychiatric Diagnoses Prior to and at Index PP Episode per the Mini-International Neuropsychiatric Interview for Psychotic Disorder Studies (MINI-PDS) (N = 248).

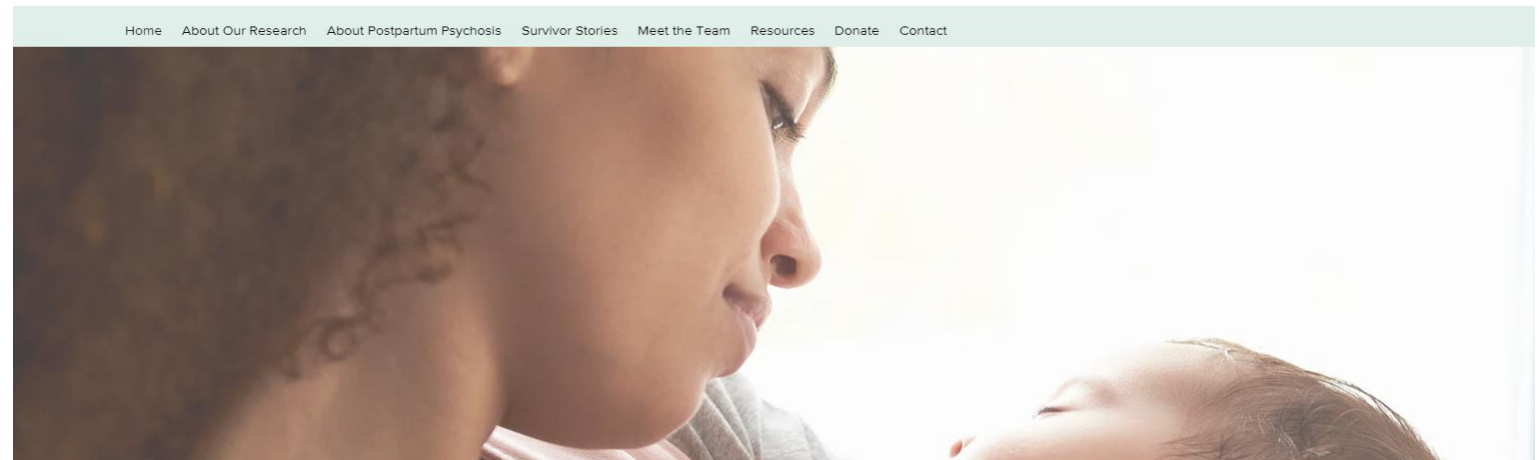
Psychiatric Diagnosis	n (%)
Prior to Index PP Episode	
Major Depressive Disorder (MDD)	94 (37.90)
Generalized Anxiety Disorder (GAD)	55 (22.18)
Bipolar Disorder	54 (21.77)
Eating Disorder (Anorexia Nervosa, Bulimia Nervosa, or Binge Eating Disorder)	40 (16.13)
Post Traumatic Stress Disorder (PTSD)	38 (15.32)
Alcohol Use Disorder (AUD)	34 (13.71)
Panic Disorder	28 (11.29)
Substance Use Disorder (SUD)	22 (8.87)
Obsessive Compulsive Disorder (OCD)	21 (8.47)
None	95 (38.31)
Index PP Episode per MINI-PDS*	
Bipolar I Disorder with Psychotic Features	178 (71.77)
Major Depressive Disorder (MDD) with Psychotic Features	36 (14.52)
Brief Psychotic Disorder	22 (8.87)
Other†	12 (4.84)

*Time periods assessed: 1) pre-pregnancy, 2) pregnancy, 3) postpartum up to 6 months, 4) 6 months postpartum up to time of interview.

†Schizoaffective Disorder (n = 6), Schizophreniform Disorder (n = 4), Unspecified Psychotic Disorder (n = 1), Schizophrenia (n = 1).



Massachusetts General Hospital Postpartum Psychosis Project (MGHP3)



Cohen LS, Arakelian M, Church TR, Dunk MM, Gaw ML, Yoon HE, Kobylski LA, Vanderkruik R, Freeman MP. The phenomenology of postpartum psychosis: preliminary findings from the Massachusetts General Hospital Postpartum Psychosis Project. *Mol Psychiatry*. 2025 Jun;30(6):2537-2544.

Who is at greatest risk for postpartum psychosis?

Risk Factor	% that developed postpartum psychosis
Hospitalization for psychotic episode during the pregnancy	44%
Hospitalization for a past psychotic episode prior to the pregnancy	14.5%
Any previous psychiatric hospitalization	9.2%
Previous hospitalization for bipolar mood episode	2.0%
Baseline population risk	0.07%

Harlow et al, Arch Gen Psychiatry 2007

Treatments

Mood stabilizers –
especially lithium,
atypicals

lamotrigine (only for depressive polarity)

Sleep medications
when needed

Regimens with multiple
medications are
common – consider
risks/benefits of each
as treatment evolves

ECT is an option for
severe illness during
pregnancy and the
postpartum

Postpartum Psychosis: Acute Treatment

- Inpatient psychiatric hospitalization
- Rule out medical conditions
- Length of stay depends on clinical condition
- Many women will need to stop breastfeeding
- Primary pharmacotherapy: mood stabilizer and an antipsychotic, with medications for anxiety, insomnia, and agitation as needed
 - Sequential study of benzodiazepines, antipsychotics, lithium and ECT found majority of response with lithium
 - Mainstay treatment – **lithium**, antipsychotics, ECT

Sit et al., J Women's Health, 2006; Bergink et al., AJP 2015; Jairaj et al., 2023

Postpartum Psychosis or Mania: Treatment After Discharge

- For women with bipolar disorder, maintenance is crucial to prevent relapse
- Treatment planning for adequate sleep, support, help in meeting the needs of caring for a baby
- Close monitoring is required for safety
 - Psychoeducation of family and friends
- Isolated postpartum psychosis: Little data to inform length of care
- Need to monitor in case index episode of bipolar disorder
 - Psychotherapy and close monitoring
 - Treatment 6-12 mo with pharmacotherapy

Bipolar Disorder and Postpartum Psychosis

Postpartum Psychosis

- 1-2 per 1000 deliveries
- Most commonly associated with bipolar disorder
- Can occur circumscribed to the postpartum
- High risk of harm to infant, mother, other children in household

Nonacs and Cohen, 1998; Jones & Craddock, 2001; Spinelli, AJP, April 2009; Osborne 2018; Spinelli, AJP 2004; Spinelli, AJP 2009; Wesseloo et al. Am J Psychiatry. 2016

Prevention of severe postpartum illness

- **History of isolated postpartum psychosis**
 - High risk for recurrence **postpartum**
 - Prophylaxis may be deferred to immediately postpartum
- **Bipolar disorder**
 - **High risk for recurrence throughout pregnancy and the postpartum**
 - High risk postpartum relapse, postpartum prophylaxis decreases risk
 - Clinical picture during pregnancy greatly factors into postpartum prognosis – recommendation not to delay treatment

Postpartum Treatment

- **Prescribe Sleep**
 - Sleep deprivation increases the risk of relapse to mood episodes – similar to antidepressants regarding risk of induction of mania/hypomania (10%)
- **Prescribe Support**
 - Good social support associated with quicker recovery, less symptomatic; better prophylaxis against episodes
- **Psychoeducation**
 - Education during pregnancy (and preconception) about risk of postpartum mood episodes and postpartum psychosis
 - Include partners/families in conversations about postpartum illness and risks during pregnancy

Colombo, et al. 1999; Johnson, et al. 1999; Stefos, et al. 1996

Mood Stabilizers & Breastfeeding

Lithium – historically not recommended in breastfeeding

- Toxicity in infants reported in a notable number of cases; Contraindicated at one time by the American Academy of Pediatrics
- Modest study has shown that with careful monitoring may be reasonable with low infant lithium blood levels (careful monitoring required)

Lamotrigine – substantial number of mother-baby pairs studied without adverse effects

Atypical antipsychotics – generally understudied or unstudied, depending on individual medication

American Academy of Pediatrics 2001; Viguera et al., 2007; Newport et al., 2009; Imaz et al., 2021; Heinonen et al., 2022

Mood Stabilizers and Breastfeeding

Lithium and Breastfeeding

- N=10 mother-baby pairs
- Mothers stable, lithium monotherapy 600 to 1,200 mg/day
- Babies' serum levels 0.09 to 0.3 meq/L (average 0.16)
- Transient increases in elevated infant TSH, BUN, Cr

Recommendations

Consider lithium when:

- Bipolar disorder in mother who is stable
- Lithium monotherapy (or simple regimen)
- Adherence to infant monitoring (lithium level, TSH, BUN, Cr immediately postpartum, 4 to 6 weeks of age, and then every 8 to 12 weeks)
- Healthy infant
- Collaborative pediatrician

BUN, blood urea nitrogen; Cr, creatinine; TSH, thyroid-stimulating hormone.

Viguera AC et al. *Am J Psychiatry*. 2007;164(2):342-345.

Approaching Barriers to Care

Multidisciplinary collaboration and education

Telehealth - when appropriate

Addressing shame and stigma

Prioritizing maternal mental health

Digital health – how to best integrate?

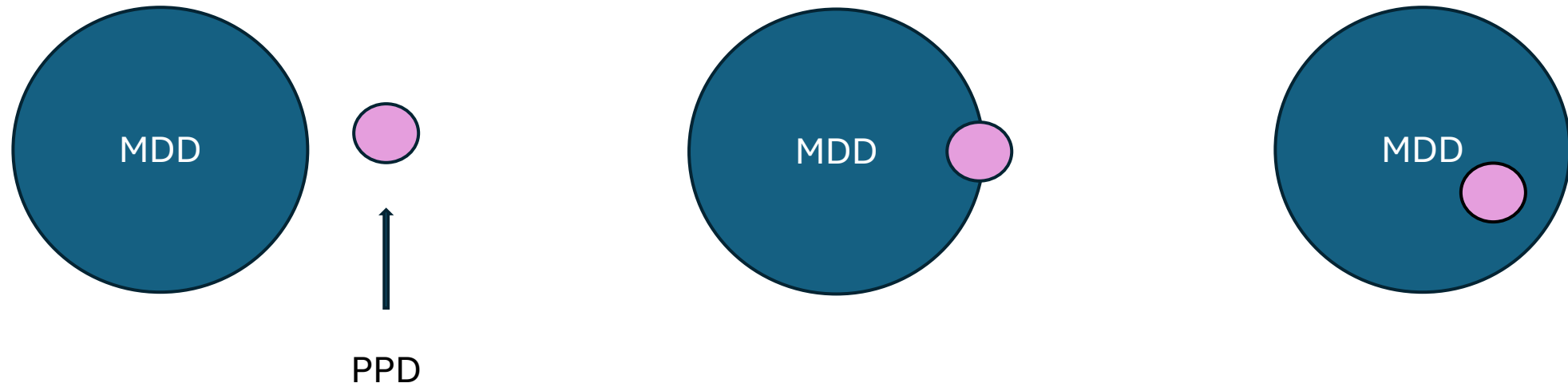
Collaborative care – best models?

Postpartum Depression:

Methodological Issues in Treatment Trials

Indication: Postpartum Depression (PPD)

- Specific? Specifically helpful for PPD?
- Efficacious for MDD, but PPD is an easier target?
- Easier? FDA requirements different for PPD vs. MDD - trial length, longer term data



Context of PPD – The Nuances

Context of having a
new baby

Breastfeeding or not

Comorbidity of other
disorders –
psychiatric and
obstetric/medical

Heterogeneity of
presentation

Stigma and shame

Will she get pregnant?

Can a treatment be
used again if needed
for relapse or
recurrence

Level of support at
home

Sleep issues – can
someone else help for
restorative sleep,
night feedings, re:
sedating med

Impact of support
provided by contact in
study

Difficulty of getting to
appts and out of the
home

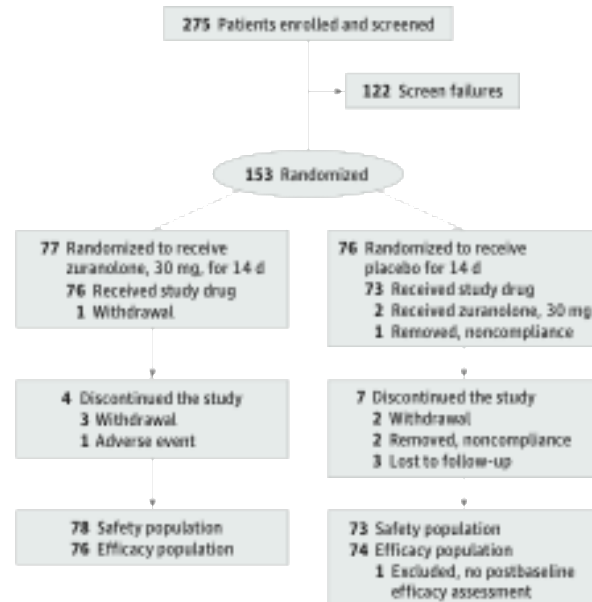
Risk of bipolar
disorder with index
episode being PPD

Recruitment
challenges

Recruitment Challenges and Generalizability

What happened before: phone screens?

Figure 1. CONSORT Diagram



JAMA Psychiatry | Original Investigation

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

Kristina M. Deligiannidis, MD; Samantha Meltzer-Brody, MD, MPH; Handan Gunduz-Bruce, MD, MBA; James Doherty, PhD; Jeffrey Jonas, MD; Sigui Li, MS; Abdul J. Sankoh, PhD; Christopher Silber, MD; Andrew D. Campbell, PhD; Brian Werneburg, PhD; Stephen J. Kanes, MD, PhD; Robert Lasser, MD, MBA

The result of short term studies for FDA approval:

Post-approval for PPD: What clinicians want to know about Zuranolone

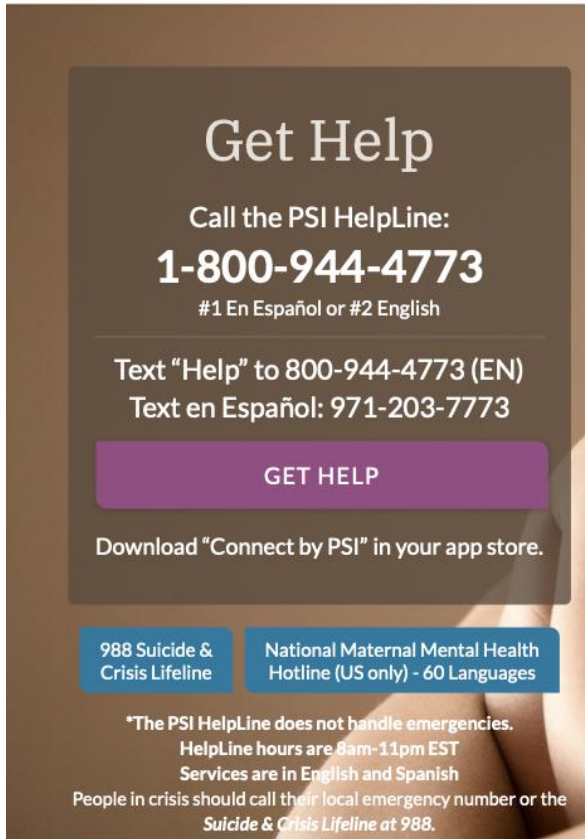
- Assuming a **brief course** approved, can it be used longer?
- If a patient responds, should they be started on an SSRI to maintain the response or continue to improve
- If they had been on an antidepressant prior to zuranolone, should they continue it
- If it works and pt relapses, can it be used again?
- PPD is recurrent – can use prophylactically after next pregnancy
- Other **postpartum** diagnoses –postpartum bipolar depressive episodes, postpartum anxiety, psychosis, OCD
- Outside of the postpartum?
 - Further out postpartum - 2 years? Any episode MDD? TRD?
 - Other hormonally related disorders- PMDD, perimenopause/menopause?
 - For men and women for MDD, bipolar depression
- Safety data unknown after 45 days
- For wider use, Phase 4 studies or build into earlier phases are needed

Pipeline

- **Neurosteroids:** Rapid acting: in theory based on hormonal shifts during the postpartum, allopregnanolone drop within 24 hrs, mainly GABA_A receptor positive allosteric modulators (PAMs)
 - **Zuranolone, brexanolone – FDA Approved**
 - Short term studies
 - Zuranolone studied for MDD in men and women — longer studies
 - **Ganaxolone** did not differ significantly from placebo at 28 days – high placebo response rates
 - Outperformed placebo at 24-hour point – low placebo response at 24 hours, higher later endpoints
- **Rapid-Acting Psychedelic-Inspired Therapeutics:**
 - **Luvesilocin (formerly RE104):** Recent Phase 2 data (Reunion Neuroscience); subcutaneously administered prodrug targeting the serotonin 2A receptor.
 - **Inhaled Mebufotenin (GH001):** Developed as an ultra-rapid treatment administered via inhalation on a single-day individualized dosing regimen.
 - (Johnson M, Aceves Baldo P, Arbe E, Brennan B, Cohen SE, Doolin K, Gann W, Gregory D, Keady S, Kriger K, MacIsaac R, Ratcliffe S, Rubinow DR, Svendsen CB, Terwey TH, Tully D, Valcheva V, Zantvoord JB, Deligiannidis KM. Inhaled Mebufotenin (GH001) for Adult Patients With Postpartum Depression: A Phase 2a Open-Label Clinical Trial. J Clin Psychiatry. 2026 Jun 3;87(3):25m16284.)
- Accelerated Transcranial Magnetic Stimulation
- Mobile apps

[from AI, clinicaltrials.gov]

Important Resources

A vertical graphic with a brown background. At the top, it says "Get Help" in white. Below that, it says "Call the PSI HelpLine: 1-800-944-4773" in white, with "#1 En Español or #2 English" in smaller white text below the number. Then, it says "Text 'Help' to 800-944-4773 (EN)" and "Text en Español: 971-203-7773" in white. Below that is a purple button with "GET HELP" in white. Then, it says "Download 'Connect by PSI' in your app store." in white. At the bottom, there are two blue boxes: "988 Suicide & Crisis Lifeline" and "National Maternal Mental Health Hotline (US only) - 60 Languages". Below these boxes, it says "*The PSI HelpLine does not handle emergencies. HelpLine hours are 8am-11pm EST. Services are in English and Spanish. People in crisis should call their local emergency number or the Suicide & Crisis Lifeline at 988." in white.

Get Help

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1-800-944-4773
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GET HELP

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988 Suicide & Crisis Lifeline National Maternal Mental Health Hotline (US only) - 60 Languages

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Suicide & Crisis Lifeline at 988.

Postpartum Support International
www.postpartum.net

MGH Center for Women's Mental Health
www.womensmentalhealth.org

MGH Postpartum Psychosis Project
<https://www.mghp3.org>

MCPAP for Moms
<https://www.mcpapformoms.org>

National Maternal Mental Health Hotline
<https://mchb.hrsa.gov/national-maternal-mental-health-hotline>

Virtual Rounds at the Center for Women's Mental Health

 **Massachusetts General Hospital**
Founding Member, Mass General Brigham
Psychiatry Academy

- Started March 2020
- All health care providers welcome
- No cost to attend



Register here: <https://womensmentalhealth.org/educational-programs/virtual-rounds-at-the-cwmh/>

Thank you!

Marlene P. Freeman, MD

www.womensmentalhealth.org

WWW.MGHCME.ORG