

Mental Health Throughout the Reproductive Life Cycle

Julia N. Riddle, MD
Assistant Professor
Center for Women's Mood Disorders
UNC School of Medicine
Department of Psychiatry
Chapel Hill, NC

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Disclosure

Advisory Board: Cercle.ai

Ownership Interest: Cercle.ai

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Additional Disclosure

Some slides have been adopted from many collaborative efforts with colleagues including Lindsay Standeven, MD, Liisa Hantsoo, MD, and Lauren M. Osborne, MD.

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Learning Objectives

1. Understand the contribution of reproductive transition in psychiatric symptoms.
2. Appreciate assessment and screening options for premenstrual dysphoric disorder, and anxiety and depression in perimenopause and pregnancy.
3. List the treatment options for premenstrual dysphoric disorder, perimenopause mood/anxiety symptoms, and perinatal depression/anxiety.

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The Reproductive Lifecycle

- Reproductive age: Menarche – Menopause (~12 – 51 yo)
- Important hormonal transitions:
 - Menstrual cycles (average age of menarche: 12.4 years)
 - Pregnancy
 - Parturition and Postpartum
 - Perimenopause



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Reproductive Transitions - Punchline

Current Wisdom

- It is the **change in hormone levels**, rather than the levels themselves that are the culprits of psychiatric symptoms during reproductive transitions

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Hormonal Transitions

Disorder/Syndrome	Prevalence *	Timing of Onset
Perinatal Depression	15-20%	During pregnancy – 12 months postpartum
Perinatal Anxiety Disorders	12 -20%	During pregnancy – 12 months postpartum
Postpartum OCD	2-4%**	Up to 12 months postpartum
Postpartum Psychosis	0.2%	Usually with first weeks postpartum
Premenstrual Dysphoric Disorder	4-8%	Reproductive Years***
Premenstrual Exacerbation of Illness (PME)	60%+	Reproductive Years***
Perimenopausal Mood Symptoms	45-68%	4 th and 5 th decade of life

*Prevalence rates vary across different studies.

**Up to 9% in some studies

***Reproductive years are defined at menarche to menopause. Not perinatal/postpartum prevalence are a report of percentage with illness of those pregnant or after a life birth.

Font: Hutner et al¹⁴.

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Menstrual Cycle Related Disorders

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Menstrual Cycles

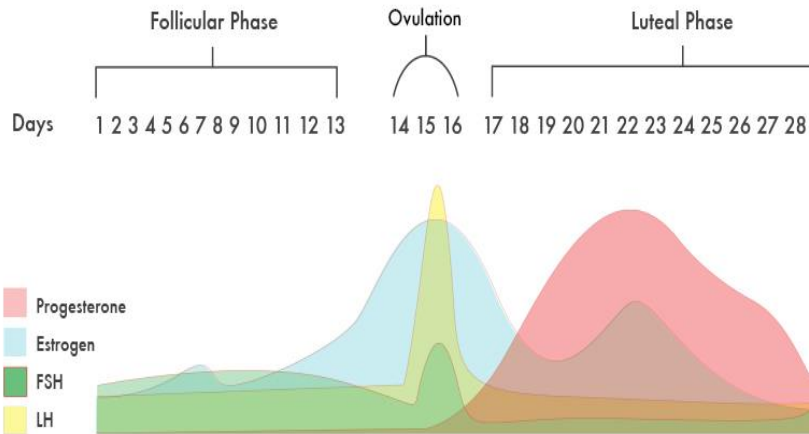


Image: International Association of Premenstrual Mood Disorders (IAPMD)

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Premenstrual Syndrome (PMS)

- Premenstrual syndrome (PMS) is **not a psychiatric disorder**.
- Estimated 75% of women experience some premenstrual symptoms.
- May include *only* physical symptoms.
- American College of Ob-Gyn (ACOG) Definition:
 - At least 1 symptom (mood or physical), causes interference
 - Present in 5 days pre-menses
 - Remit within 4 days of menses onset
 - At least 3 menstrual cycles in a row

Criteria from American College of Obstetrics and Gynecology (ACOG)

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Premenstrual Exacerbation (PME)

- Continuous symptoms that worsen in second half of menses (luteal phase)
- 60-65% of women w/ MDD experience premenstrual worsening (Haley et al 2013, Hartlage et al 2004).
- PMDD should not be diagnosed when patient experiences premenstrual exacerbation of another psychiatric disorder
- PMDD can be considered if symptoms and changes in function are characteristic of PMDD and markedly different from symptoms of the ongoing disorder

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Premenstrual Dysphoric Disorder (PMDD)

- Occurs in 3-8% of women
- A mood disorder
- Cumulative symptomatic time: 4-8 years
- Associated with risk of PPD and Perimenopausal mood symptoms
- Change in hormones during the luteal phase that seem to be key to etiology

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PMDD – DSM-5 Criteria

Criterion B: Must have 1 core mood symptom.

1. **Affective lability** (tearful, sensitive to rejection)
2. **Irritability** / anger / interpersonal conflicts
3. **Low mood** / hopeless / self-deprecating thoughts
4. **Anxiety** / tension

Criterion C: Must have 1.

1. **Decreased interest**
2. **Difficulty concentrating**
3. **Low energy**
4. **Appetite** changes / food cravings
5. **Sleep disturbance** (hypersomnia / insomnia)
6. **Overwhelmed** / out of control
7. **Physical sx** (headaches, breast tenderness)

Criterion A: Must have ≥5 symptoms present in luteal week, remit after menses, majority of cycles in past 1y.

Criterion D: Distress / impairment

Criterion E: Not exacerbation of other disorder

Criterion F: Prospective daily ratings for ≥2 symptomatic cycles

Criterion G: Not due to substances / medical condition

PMDD/PME – Diagnosis

Clinical Interview

- Assess for symptoms report and course
- Assess for other, unremitting illness
- Rule out other cyclical disorders
- Daily Record of Severity of Problems (DSRP)
 - Available online free

DAILY RECORD OF SEVERITY OF PROBLEMS

Name or Initials _____
Month/Year _____

Please print and use as many sheets as you need for at least two FULL months of ratings.

Each evening rate 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 (Monday="M", Tuesday="T", etc.)	Note spotting by entering "S"	Note menses by entering "M"	Begin rating on correct calendar day	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	
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PMDD – Treatment

1. Nonpharmacologic
 - Lifestyle modifications: sleep, exercise, diet
 - Calcium carbonate (600 – 1000 mg)
 - Cognitive Behavioral Therapy (CBT)
2. SSRI
 - Intermittent vs. continuous dosing
3. Monophasic oral contraceptive
4. GnRH Medication
5. Oophorectomy (rare)

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PMDD – Treatment - SSRIs

Selective Serotonin Reuptake Inhibitors

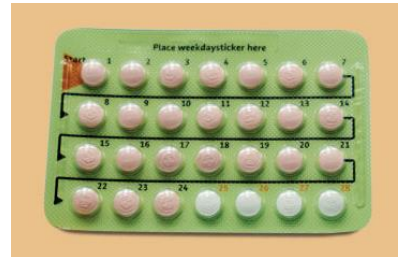
- Unlike in MDD, there is rapid onset
- Lower doses
 - 25 to 50 mg sertraline (Kornstein et al 2006)
 - 20 mg fluoxetine (Steiner et al 2005)
 - 10 mg to 20 mg paroxetine (Steiner et al 2008)
 - 12.5 to 25 mg paroxetine CR (Steiner et al 2005)
- Different regimens
 - Continuous
 - Intermittent (timed start and stop in each cycle)
 - Symptom onset

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PMDD – Treatment - OCPS

Oral Contraceptive Pills

- Mixed evidence for efficacy of oral contraceptives for PMDD (Cunningham et al 2009).
- Yaz (Drospirenone + ethinyl estradiol 24/4) is the only COC that is FDA-approved to treat PMDD.
- Meta-analysis: Yaz reduced PMDD symptoms, but large placebo effect (Lopez et al 2012.)



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PME – Treatment

- Treat the underlying illness
 - For example, more aggressively treat the depression, anxiety, or bipolar illness
- Consider OCP, LARC, or other form of birth control
- Can consider intermittent increases in medications during luteal phase or targeted treatment for symptoms



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Comment About Hormone Treatment

- Hormone “imbalance” is not thought to be a primary driver
- Single timepoint hormone test are mostly useless because estrogen and progesterone *should* fluctuate throughout a cycle
- Oral progesterone can have a lot of mood and functional side effects

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Perimenopause

- Mean age: 51
- Post-menopausal: One year after last menstrual period
- Perimenopause begins up to **10 years prior to menopause**
- Average duration of perimenopausal/menopause symptoms: **4-8 years**
- Hormonal transition

Women Have Been Misled About Menopause

Hot flashes, sleeplessness, pain during sex: For some of menopause's worst symptoms, there's an established treatment. Why aren't more women offered it?

Study Shows the Staggering Cost of Menopause for Women in the Work Force

Some are taking sick days. Others are cutting back their hours. Still others end up quitting altogether.



Menopause Is Having a Moment

Our writer explains why menopause has been misunderstood by both doctors and society, and what happened after she wrote about it.

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Perimenopause – Symptoms

Physical

- Hot flashes (Vasomotor Symptoms)
- Menometrorrhagia
- Incontinence
- Headache
- Palpitations
- Breast tenderness
- Musculoskeletal pain
- Restless legs
- Vaginal dryness
- Dyspareunia

Mood/Behavior

- Insomnia
- Fatigue
- Low mood
- Irritability
- Impaired concentration
- Memory problems

Perimenopause – Screening

Menopause Rating Scale (MRS)

Which of the following symptoms apply to you at this time?
 (X ONE Box For EACH Symptom) For Symptoms That Do Not Apply, Please Mark "None".

Symptoms:	Score = 0 1 2 3 4				
	none	mild	moderate	severe	extremely severe
1. Hot flashes, sweating (episodes of sweating).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Heart discomfort (unusual awareness of heart beat, heart skipping, heart racing, tightness).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Sleep problems (difficulty falling asleep, difficulty in sleeping through the night, waking up early).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Depressive mood (feeling down, sad, on the verge of tears, lack of drive, mood swings).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Irritability (feeling nervous, inner tension, feeling aggressive).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Anxiety (inner restlessness, feeling panicky).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Physical and mental exhaustion (general decrease in performance, impaired memory, decrease in concentration, forgetfulness).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. Sexual problems (change in sexual desire, in sexual activity and satisfaction).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. Bladder problems (difficulty in urinating, increased need to urinate, bladder incontinence).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. Dryness of vagina (sensation of dryness or burning in the vagina, difficulty with sexual intercourse).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11. Joint and muscular discomfort (pain in the joints, rheumatoid complaints).....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Greene Climacteric Scale

The Greene Scale provides a brief measure of menopause symptoms. It can be used to assess changes in different symptoms, before and after menopause treatment. Three main areas are measured: 1. Psychological (items 1-11), 2. Physical (items 12-18), 3. Vasomotor (items 19, 20).

Please indicate the extent to which you are bothered at the moment by any of these symptoms by placing a tick in the appropriate box.

SYMPTOMS	Not at all 0	A little 1	Quite a bit 2	Extremely 3	
1. Heart beating quickly or strongly					
2. Feeling tense or nervous					
3. Difficulty in sleeping					
4. Excitable					
5. Attacks of anxiety, panic					
6. Difficulty in concentrating					
7. Feeling tired or lacking in energy					
8. Loss of interest in most things					
9. Feeling unhappy or depressed					
10. Crying spells					
11. Irritability					
12. Feeling dizzy or faint					
13. Pressure or tightness in head					
14. Parts of body feel numb					
15. Headaches					
16. Muscle and joint pains					
17. Loss of feeling in hands or feet					
18. Breathing difficulties					
19. Hot flushes					
20. Sweating at night					
21. Loss of interest in sex					
Score					Total

Greene, J. A factor analytic study of climacteric symptoms *Journal of Psychosomatic Research* (1976), 20, 425-430.

Perimenopause & Depression

- Often sub-syndromal
- High risk with a prior episode of depression and/or history of PMDD/PPD
- Uncommon to have first lifetime episode
- Risk factors: Younger age onset, Black, Hispanic, low SES, adverse childhood events, smoking, elevated BMI, chronic medical conditions

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Perimenopause & Depression – Treatment

- Note: No FDA approved medications for perimenopausal mood symptoms, but many open trials
- Can consider mood and vasomotor symptoms together if present.
- If no VMS, would treat like depression
- If depression and VMS....

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Perimenopause & Depression – Treatment

- If depression and VMS, consider:
 - Venlafaxine/desvenlafaxine
 - Duloxetine
 - Paroxetine
 - Fluoxetine
 - Gabapentin
 - Clonidine
- Can use low doses if using for VMS alone and HRT contraindicated/not wanted

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Perimenopause – Treatment – HRT

- Hormone Replacement Therapy (HRT) and Menopause Hormone Therapy (MHT) are estrogen (with progesterone) derived products.
- Gained popularity in the 1970s.
- Fell out of favor following World Health Initiative (WHI) Study (2002) showing increased risk (small AR) of CAD, Stroke, PEs and invasive breast cancers.
 - Has since been re-evaluated for relative risk
- HRT is the most effective treatment for the vasomotor symptoms...**75% reduction in weekly hot flush** frequency compared with placebo (2004 Cochrane meta-analysis)

“For women aged younger than 60 years or who are within 10 years of menopause onset and have no contraindications, the benefit-risk ratio is most favorable for treatment of bothersome [vasomotor symptoms]...”
North American Menopause Society (2017)

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Taking a Reproductive History to Include Psychiatric Symptoms

- Age of menarche
- Characterize cycle
- Any physical symptoms prior to menses
- Any physical symptoms
- Prior hormonal contraception & any mood respond (+/-)
- Number of pregnancies and outcomes
- Mood in pregnancy and postpartum + any treatment

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Perinatal Mental Illness



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The Myth



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The Truth

- Postpartum Depression is the #1 complication of delivery
- Prevalence of postpartum depression (PPD) estimated at 10-15%+ (Moses-Kolko & Roth, 2003)

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The Truth

Disorder/Syndrome	Prevalence*	Timing of Onset
Perinatal Depression	15-20%	During pregnancy – 12 months postpartum
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*Prevalence rates vary across different studies.

**Up to 9% in some studies

***Reproductive years are defined at menarche to menopause. Not perinatal/postpartum prevalence are a report of percentage with illness of those pregnant or after a life birth.

Font: Hutner et al^[1].

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Why We Care

In pregnancy

- Increased use of substances
- Less healthy nutrition
- Higher BMI
- Less perinatal care
- Increase risks of obstetrical complications
- Low birth weight
- Preterm labor

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Why We Care

After delivery

- Reduced breast feeding
- Reduced bonding
- Infant outcomes: IQ, behavioral issues, social-emotional development
- Suicide: 20% of all postpartum deaths (Shadigian & Bauer, 2005)
- Psychiatric disorders in general are the leading cause of indirect maternal deaths (Oates, 2003)

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Screening

- Ideally preconception planning for risk factors
 - If concerned, please consider a consultation with a reproductive psychiatrist
- Edinburgh Perinatal Depression Screen Scale (EPDS)
- Perinatal Anxiety Screening Scale (PASS)
- General Anxiety Disorder-7 (GAD-7)
- Screen multiple times, risks changes throughout the process

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Perinatal Depression - Overview

WHEN: During Pregnancy and up to a year postpartum, most common in first 3 months postpartum

WHO: 10-15% of women

SYMPTOMS

- Feelings of anger or irritability
- Lack of interest in the baby
- Appetite and sleep disturbance
- Crying and sadness
- Feelings of guilt, shame or hopelessness
- Loss of interest, joy or pleasure in things you used to enjoy
- Possible thoughts of harming the baby or yourself

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Perinatal Depression - Treatment

- Therapy
- Medication: SSRIs, augmentation
- Brexanolone/Zuranolone – only FDA approved medications
- ECT
- TMS
- Self-care: Sleep!

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Clinical Features – Perinatal Anxiety

WHEN: Most common in first 3 months postpartum, can also occur after weaning breastfeeding

WHO: 6-10% of moms in the postpartum

SYMPTOMS :

- Constant worry
- Feeling that something bad is going to happen
- Racing thoughts
- Disturbances of sleep and appetite
- Inability to sit still
- Physical symptoms like shortness of breath, dizziness, hot flashes, and nausea

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Treatment – Perinatal Anxiety

- No comprehensive algorithm yet
- Cognitive Behavioral Therapy (CBT)
- SSRI/SNRI (higher doses!)
- Benzodiazepines
- Neuroleptics/antipsychotics for augmentations
- Sleep
- Yoga

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Clinical Features – Perinatal OCD

WHEN: 1 week to 3 months postpartum

WHO: 4% of women, 25% have impairing symptoms though may not meet full criteria

SYMPTOMS

- Obsessions are persistent, disturbing, repetitive thoughts which are often related to the baby
- Compulsions, where the mom may do certain things over and over again to reduce her fears and obsessions. This may include things like needing to clean constantly, check things many times, count or reorder things.
- A sense of horror about the obsessions
- Fear of being left alone with the infant
- Hypervigilance in protecting the infant
- Moms with postpartum OCD know that their thoughts are bizarre and are very unlikely to ever act on them.

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GAD vs. OCD

The Nature of the Thoughts

GAD	OCD
Anxious thoughts are worries related to real-life, routine matters that bring about apprehension and thought distortions. Thought content tends to shift over time.	Intrusive, repetitive thoughts and/or ritualistic behaviors that are experienced as unwanted.

“what if I have to have a C-section and I have a complication and then I can’t work again and am a bad mother?”

“I keep seeing an image that I’m going to drop the baby down the stairs, so now I sit when I go down the stairs or I don’t hold the baby at all”

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A Word About Intrusive Thoughts/Images

- 100% of new moms (and many dads) will experience intrusive thoughts and/or images of harm coming to the baby. Most of them do not have OCD.
- These only become problematic if they change how a mother acts
 - Ie. If you no longer feel like you can care for your baby
 - Ie. You cannot sleep
- These are NOT psychotic symptoms!!!
 - Psychotic delusions of harm coming to the baby do not cause distress – due to illness, they seem like a good idea

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Treatment – Non-Pharm

- Therapy, especially interpersonal
- Sleep
- Yoga
- Exercise
- Light Box
- Mindfulness practices

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Treatment - Sleep

- Intentional conversation/strategy
- Finding a space
- Recruiting support
- Breastfeeding
- 3-4 uninterrupted hours



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Treatment – Medication Pitfalls

- Stopping treatment abruptly when patients becomes pregnant due exclusively to concerns about medications (and not risk of untreated illness)
- Not optimizing SSRI/SNRIs to target symptoms
- Switching a patient's medication after she is pregnant to go to a "safer" one
- Not monitoring/increasing medications in third trimester

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Treatment – Brexanolone

- FDA approved in March 2019
- 60-hour infusion
- Inpatient
- Progesterone metabolite (allopregnanolone)
- Positive allosteric modulator of GABA-A receptors
- SE: Sedation, dizziness
- Cost: \$34,000

F.D.A. Approves First Drug for Postpartum Depression

The medication works quickly, within 48 hours. But it's an expensive infusion and requires a stay in a medical center.



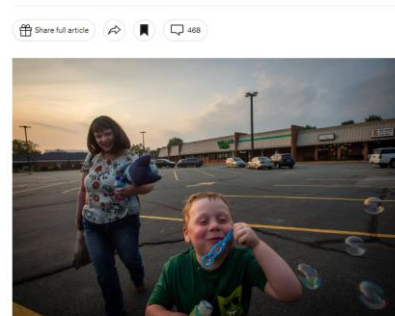
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Treatment – Zuranolone

- Approved August 2023, available Nov 2023
- Two weeks
- Slightly different formulation than Brex
- SE: Sedation
- Breastfeeding? Low concern so far

For the First Time, There's a Pill for Postpartum Depression

Because the pill works faster than other antidepressants and is taken for only two weeks, it may encourage more treatment of the debilitating condition.



Amy Bingham suffered from postpartum depression in 2018 after giving birth to her son, Benjamin. She received the new drug, zuranolone, in a clinical trial and said her symptoms gradually improved. Kate Medley for The New York Times

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Treatment – ECT & TMS

Electroconvulsive Therapy (ECT)

- Since the 1940s
- Most rigorous study (Anderson & Reti 2009):
 - Remission 78%
 - Very low rate of adverse effects for mother and fetus reviewed 339 cases, very effective, low rate of adverse effects
- Access is issue

Repetitive Transcranial Magnetic Stimulation

- Approved for MDD
- Open label studies show promise
- No adverse outcomes on fetus
- Long-term outcomes unknown

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Risk – Risk Conversations



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Risk – Risk Conversations

Untreated Perinatal Depression

- Lower quality of life
- Missed work
- Suicide attempts/completions
- Substance use
- HTN
- Preterm birth
- Small for gestational age
- Insecure attachment
- Developmental delay

Risk of SSRI

- ~~Congenital malformations~~
- ~~Preterm birth~~
- Persistent pulmonary hypertension of the newborn (PPHN)
- Neonatal adaptation syndrome
- ~~Developmental delays/autism~~

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Neonatal Adaptation Syndrome

- 20-30% of SSRI-exposed newborns
- May have symptoms of jitteriness, increased muscle tone, rapid breathing – but these are **transient, self limited, and not dangerous.**
- Risk is not related to dose
- Risk remains even if SSRI is stopped in third trimester

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Persistent Pulmonary Hypertension of Newborn

- Relative Risk very small
- 30 (exposure) vs. 20 (unexposed) out of 10,000 births

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Breastfeeding

- All psychiatric medications enter breastmilk
- Almost all safe to use
- Relative infant dose <10% per AAP
 - Sertraline = 0.05%
- Exceptions: Clozapine, high dose benzo, Lithium*
- LactMed



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Maternal Mental Health Hotline

Postpartum Support International:

1-833-943-5746 (1-833-9-HELP4MOMS)

Maternal Mental Health Hotlines

800-944-4773 (4PPD)

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Provider Hotlines

Local Maternal Mental Health Hotlines for Providers

- Massachusetts: MCPAP for Moms: <https://www.mcpapformoms.org/>
 - **Provider Line:** 855-Mom-MCPAP (855-666-6272)
- North Carolina: NCMATTERS: <https://www.med.unc.edu/ncmatters/>
 - **Provider line:** 919-681-2909
- Louisiana: LAMHPP: <https://medicine.tulane.edu/tulane-doctors/lamhpp>
 - **Provider line:** 504-988-9171
- Many others

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Resources

- Reprotox: Summary of literature on all meds in pregnancy, subscription service <https://reprotox.org/>
- Lactmed: Summary of literature on all meds in lactation, free services <http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm>
- MothertoBaby: Patient-friendly fact sheets on meds: <http://mothertobaby.org/>
- MGH Center for Women's Mental Health: Best informational website: https://womensmentalhealth.org?doing_wp_cron=1452175286.3503780364990234375000
- Motherrisk: Canadian helpline: <http://www.motherisk.org/>
- Postpartum Support International: Support group and help finding local resources <http://www.postpartum.net/>
- MCPAP FOR MOMS, <https://www.mcpapformoms.org/>

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Resources

- IAMPD.org
- WomensHealth.gov
- Menopause.org

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Average Number of Menstrual Cycles in a Woman's Reproductive Years?

- A. 100
- B. 200
- C. 450
- D. 600

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What Percentage Of Women Experience Premenstrual Exacerbation Of A Major Depression?

- A. 20%
- B. 30%
- C. 50%
- D. 60%+

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Do You Feel Like You Understand the Different Between Premenstrual Syndrome (PMS), Premenstrual Dysphoric Disorder (PMDD), and Premenstrual Exacerbation of Underlying Illness (PME)?

- A. Yes
- B. No
- C. Huh?



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What Is the Rate of Postpartum Depression?

- A. 1 in 3
- B. 1 in 7
- C. 1 in 10
- D. 1 in 15



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