Women's Health 2024 | Beyond the Annual Visit

Optimizing PPD Diagnosis and Treatment: The Role of Neuroactive Steroids and Multidisciplinary Care

Faculty

Kristina M. Deligiannidis, MD

- Director, Women's Behavioral Health, Zucker Hillside Hospital, Northwell Health
- Professor of Psychiatry, Molecular Medicine and Obstetrics & Gynecology, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell

Jennifer L. Payne, MD

- Professor and Vice Chair of Research
- UVA Vivian Pinn Scholar
- Department of Psychiatry and Neurobehavioral Sciences
- University of Virginia

Disclosures

Kristina M. Deligiannidis, MD

- Research: Gerbera Therapeutics, Premier Healthcare, Sage Therapeutics, Woebot Health
- Consulting Fees: Biogen, Brii Biosciences, Gerbera Therapeutics, GH Research, Reunion Neuroscience, Sage Therapeutics

Jennifer L. Payne, MD

- Research: Janssen, Myriad Genetics
- Consulting Fees: Biogen, Brii Biosciences, Flo Health, Sage Therapeutics
- Founder's Stock: Dionysus Health
- Patents: Epigenetic Biomarkers of Postpartum Depression and Premenstrual Dysphoric Disorder

Learning Objectives

- Utilize clinical screening tools effectively to diagnose postpartum depression (PPD)
- Integrate these tools into clinical workflows to enhance the early identification of PPD
- Educate on the role of neuroactive steroids (NAS) in the clinical practice of PPD disease management
- Apply evidence-based NAS utilization strategies to improve patient outcomes
- Develop strategies for enhancing multidisciplinary team collaboration in managing PPD and implementing coordinated care approaches to improve patient outcomes

Women's Health 2024 | Beyond the Annual Visit

From Delayed Diagnosis to Early Detection: Improving PPD Screening Practices

Jennifer L. Payne, MD

Professor and Vice Chair of Research

UVA Vivian Pinn Scholar

Department of Psychiatry and Neurobehavioral Sciences

University of Virginia

How Do We Define Postpartum Depression?

Postpartum Psychiatric Illness

- Postpartum Blues
- Postpartum Depression
- Postpartum Psychosis
- Postpartum Anxiety
- Postpartum Obsessive-Compulsive Disorder
- Postpartum Post-Traumatic Stress Disorder

Postpartum "Blues"

- Mood lability
- Crying spells
- Anxiety
- Trouble sleeping
- Usually start within 2-3 days of delivery
- "Blues" typically last a few days, less than 2 weeks
- There is no significant impact on functioning, no suicidal thoughts
- 80% of women experience the "Blues"

Postpartum Depression Definition

- Symptoms meet DSM criteria for a Major Depressive Episode
- Symptoms are present for most of the day, every day for 2 weeks or longer
- Functional impairment
- Can include severe symptoms such as suicidal ideation or thoughts of infanticide
- Can include anhedonia and anxiety
- May start during pregnancy and continue postpartum
- DSM-IV criteria: Symptoms begin within ONE month
- DSM-5 now uses "peripartum" – 50% of PPD began in pregnancy

How Common Is Postpartum Depression?

- Depends on the population!
- Many “postpartum depressions” begin during pregnancy, so rates are not completely clear
  - General population: 13%-17% when assessed postpartum only (so includes cases that start during pregnancy)
    - Most go on to have recurrent Major Depression
  - In women with preexisting mood disorders:
    - Around 20%-30% with symptom onset postpartum
    - Around 50% when including symptoms during pregnancy and postpartum

Risk Factors for Postpartum Depression

Risk Factors for Postpartum Depression

- Family history of PPD
- Personal history of PPD
- History of Major Depression or Bipolar Disorder (especially off of medications)
- Depression during pregnancy *
- Psychosocial stress: financial, partner dissatisfaction
- Lack of social support
- History of or current abuse
- History of adverse childhood experiences
- History of premenstrual mood symptoms

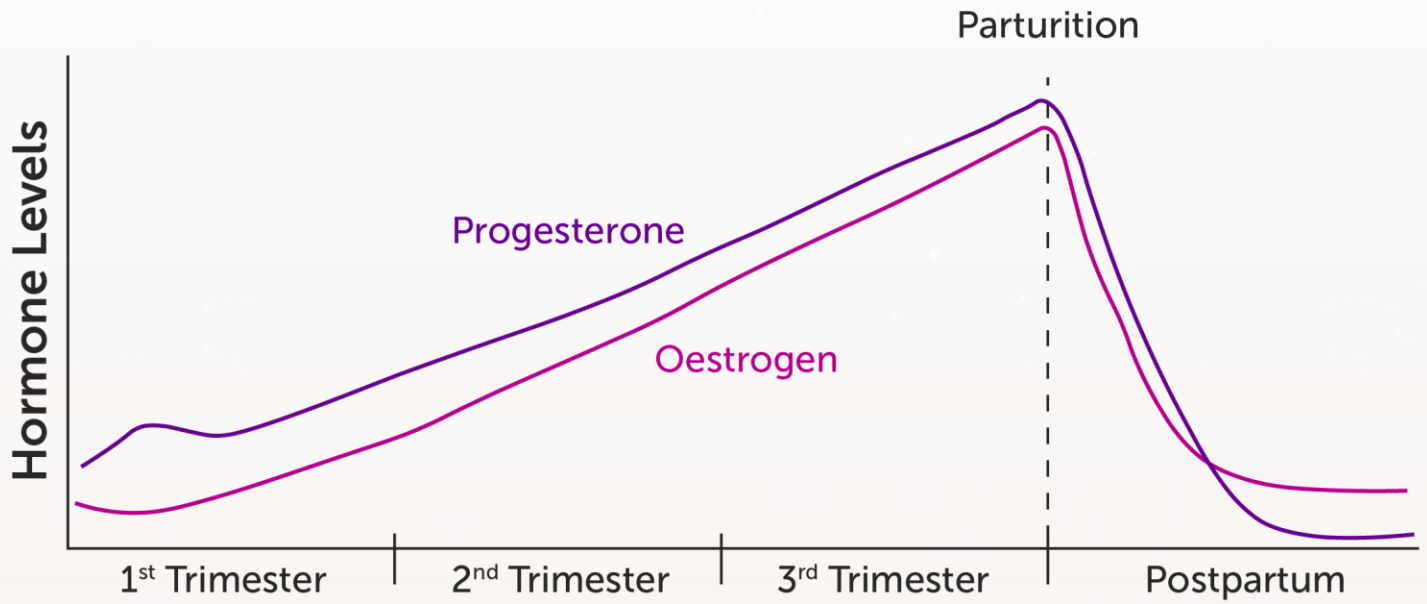
Increased Risk for Major Depression Postpartum

- There is **No Evidence** that the risk of Major Depression increases during pregnancy
- 2002 National Epidemiologic Survey on Alcohol and Related Conditions (Vesga-López O, et al. *Arch Gen Psychiatry*. 2008;65(7):805-815.)
- 14,549 women with a pregnancy in the past year
- No increased risk for Major Depression during pregnancy compared to nonpregnant female population
- Postpartum risk was elevated with an odds ratio of 1.52

Why Does the Postpartum Time-Period Increase the Risk for Psychiatric Illness?

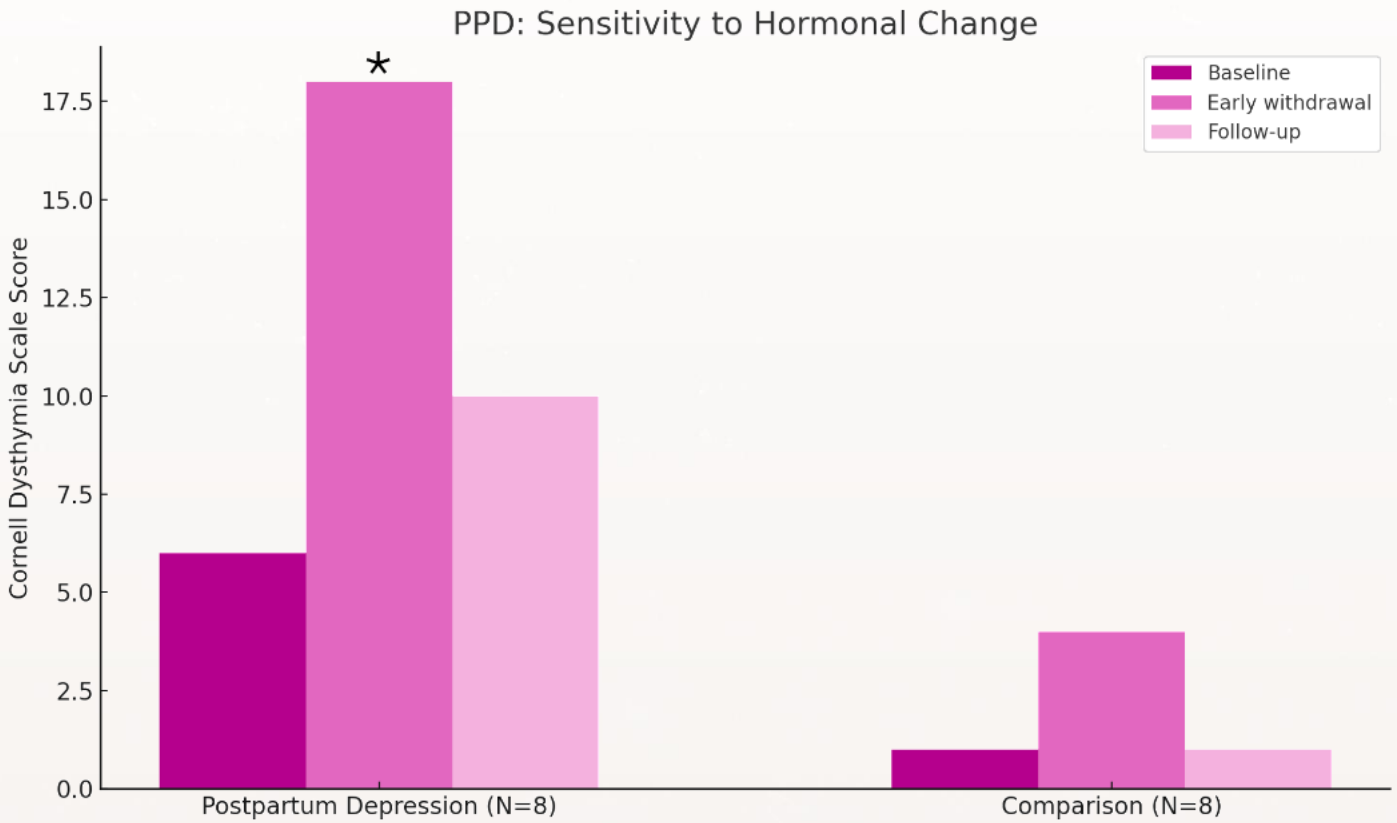
- Sleep deprivation
- Stress of becoming parents and caring for a newborn
- Discontinuation of medications for pregnancy

Hormonal Changes Associated With Pregnancy and Childbirth



Vink AS, et al. *Trends Cardiovasc Med.* 2018;28(1):64-75.

Is Postpartum Depression Associated With Changes in Hormones?

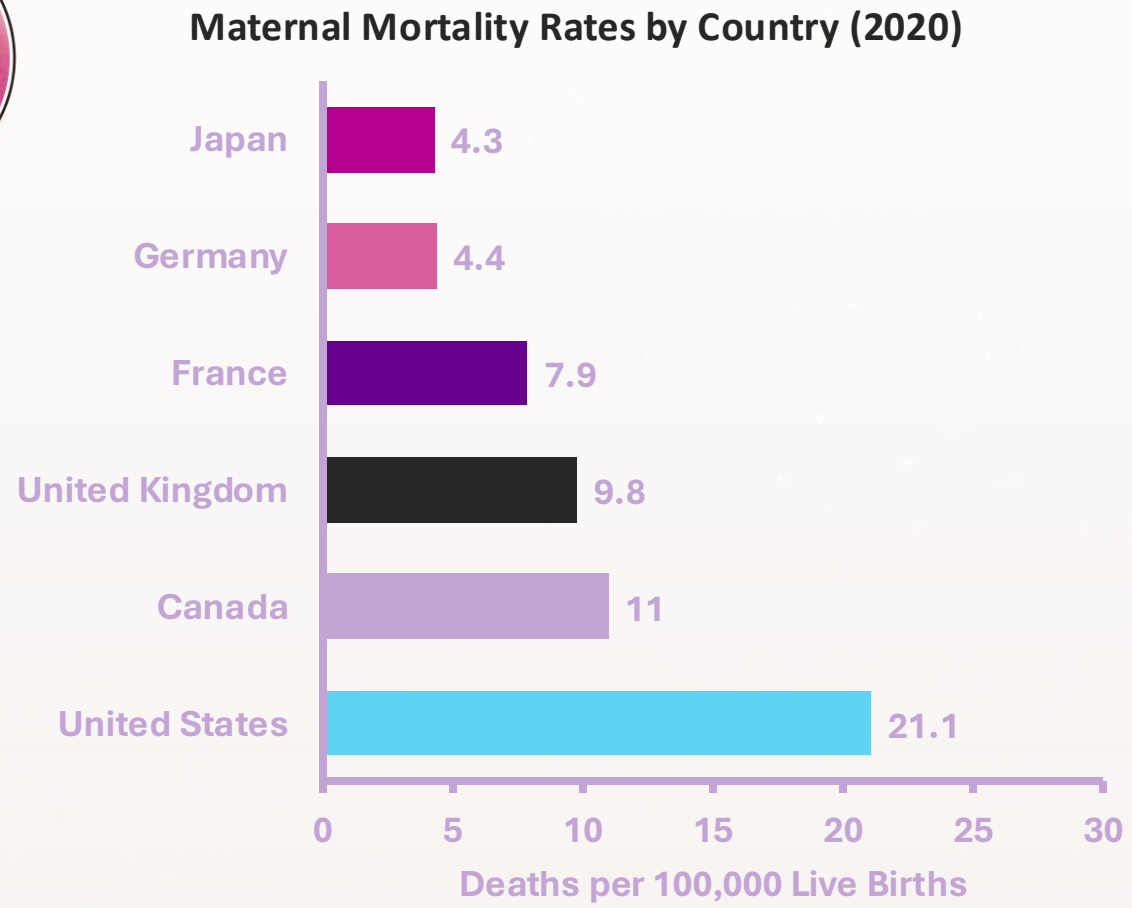


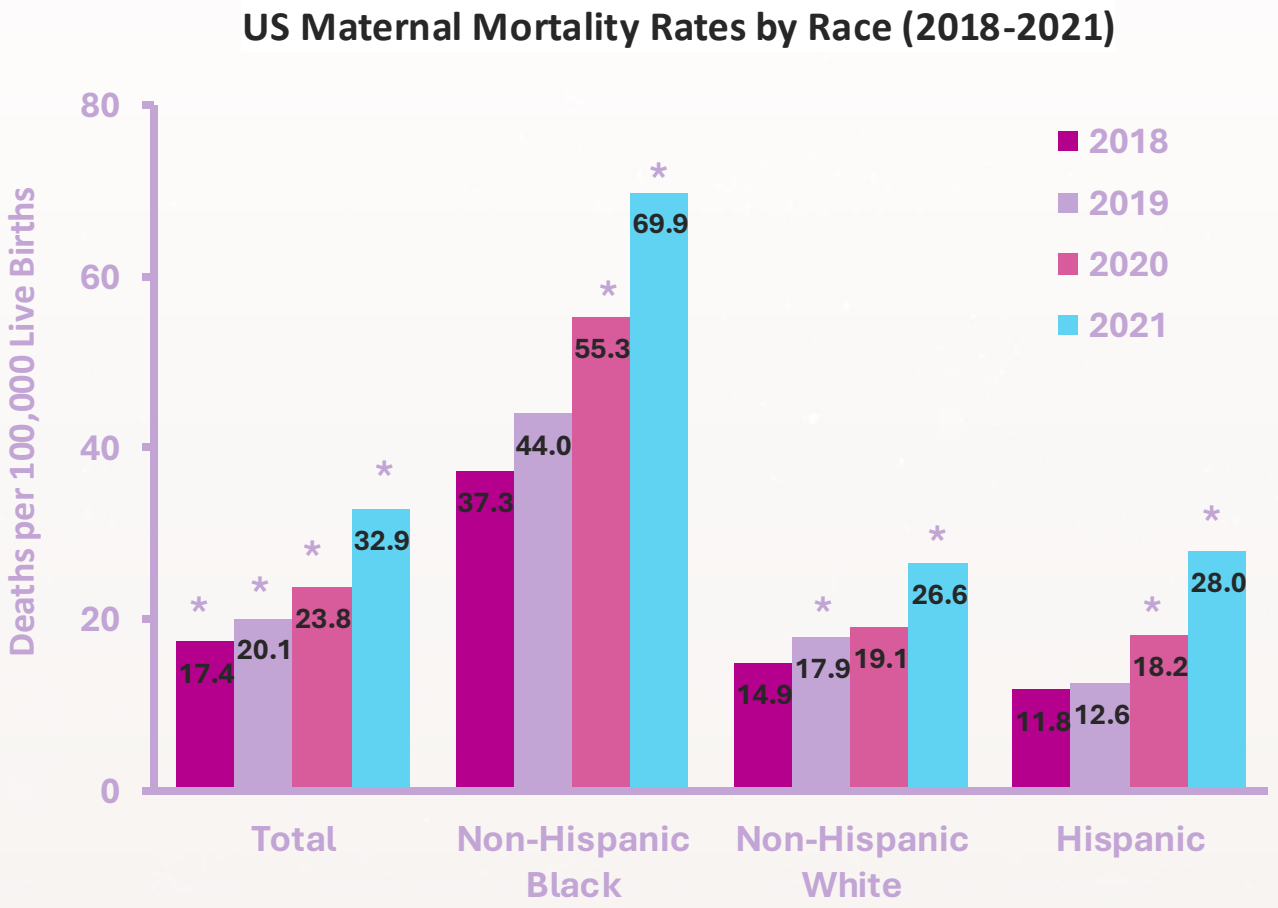
*Significant difference between baseline and withdrawal periods in the group with a history of postpartum depression (Bonferroni post hoc t test, $P < 0.01$)

Bloch M, et al. *Am J Psychiatry*. 2000;157(6):924-930.

Impact of Postpartum Depression

US Maternal Mortality Rate Is High and Rising





*Statistically significant increase from previous year ($P < 0.05$).

Richter F. Statista, June 24, 2024. https://www.statista.com/chart/23541/maternal-mortality-developed-countries
Hoyert DL. CDC, March 16, 2023. https://stacks.cdc.gov/view/cdc/124678

Mental Health Conditions: Leading Cause of Maternal Mortality

Underlying Cause of Pregnancy-Related Deaths (2017-2019)

	Total		Hispanic		Non-Hispanic									
					AIAN		Asian		Black		NHOPI		White	
	N	%	n	%	n	%	n	%	n	%	n	%	n	%
Mental health conditions	224	22.7	34	24.1	2	—	1	3.1	21	7.0	0	—	159	34.8
Hemorrhage	135	13.7	30	21.3	2	—	10	31.3	33	10.9	1	—	53	11.6
Cardiac and coronary conditions	126	12.8	15	10.6	1	—	7	21.9	48	15.9	0	—	49	10.7
Infection	91	9.2	15	10.6	1	—	0	0.0	23	7.6	0	—	49	10.7
Embolism-thrombotic	86	8.7	9	6.4	0	—	2	6.3	36	11.9	0	—	34	7.4
Cardiomyopathy	84	8.5	5	3.6	0	—	2	6.3	42	13.9	0	—	33	7.2
Hypertensive disorders of pregnancy	64	6.5	7	5.0	0	—	1	3.1	30	9.9	1	—	22	4.8
Amniotic fluid embolism	37	3.8	6	4.3	1	—	7	21.9	10	3.3	2	—	9	2.0
Injury	35	3.6	5	3.6	1	—	1	3.1	15	5.0	0	—	10	2.2
Cerebrovascular accident	25	2.5	2	1.4	0	—	0	0.0	10	3.3	0	—	13	2.8
Cancer	19	1.9	3	2.1	0	—	1	3.1	7	2.3	0	—	7	1.5
Metabolic/endocrine conditions	12	1.2	2	1.4	0	—	0	0.0	6	2.0	0	—	3	0.7
Pulmonary conditions	12	1.2	1	0.7	0	—	0	0.0	4	1.3	1	—	5	1.1

- Maternal suicide is a major cause of death in pregnancy and accounts for ≤20% of all postpartum deaths
- Psychiatric disorders are the leading cause of indirect maternal deaths
- However, suicide is a rare event during pregnancy and is lower than the rate in the general population

Wisner KL. *JAMA Psychiatry.* 2024;81(5):521-526. Chin K. *Curr Psychiatry Rep.* 2022;24(4):239-275.
Trost SL. CDC, 2022. https://www.cdc.gov/maternal-mortality/php/data-research/mmrc-2017-2019.html

Myth:
Women should tolerate being depressed during pregnancy and postpartum for the sake of the baby

Truth:
Depression during and after pregnancy leads to poor outcomes for mom AND baby

Economic cost in the US in 2017 =
$14 Billion!

Luca DL. *Am J Public Health.* 2020;110(6):888-896.

Consequences for Mother and Infant

Antenatal depression

- Preterm birth
- Low birth weight
- Gestational diabetes
- Preeclampsia
- C-section

Children exposed to PPD

- Lower IQ
- Slower language development
- ADHD
- Behavioral problems
- Psychiatric illness

Mothers with PPD

- Increased smoking and substance use
- Increased ER utilization
- Talk to their babies less
- Reduced car seat use
- Reduced pediatric healthcare adherence (vaccinations, checkups)

Paediatr Child Health. 2004;9(8):575-598. Slomian J, et al. *Womens Health (Lond)*. 2019;15:1745506519844044. Robertson E, et al. *Gen Hosp Psychiatry*. 2004;26(4):289-295. Jahan N, et al. *Cureus*. 2021;13(8):e17251.

How Do We Identify Postpartum Depression?

Diagnostic Criteria for PPD

- Symptoms meeting criteria for a major depressive episode
  - May start during pregnancy and continue postpartum
  - DSM-IV: Symptoms begin within ONE month of delivery
  - DSM-5: Now uses "peripartum" specifier

Must have ≥5 of 9 symptoms (including ≥1 *):
(within 2-wk period and change from previous functioning)

- *Depressed mood
- *Decreased interest or pleasure (anhedonia)
- Change in weight
- Change in sleep
- Psychomotor retardation or agitation
- Decreased energy
- Feeling worthless or guilt
- Decreased concentration
- Thoughts of death or suicide

AND all 4 criteria:

- Distress or impairment
- Not due to a substance use disorder, other medical conditions
- No history of mania
- Not explained by other psychiatric disorders

Screening Tools

EPDS:

- Edinburgh Postnatal Depression Scale

PHQ-9:

- Patient Health Questionnaire-9 for major depression

MDQ:

- Mood Disorder Questionnaire to assess for bipolar disorder

EPDS: Specific to Pregnant and Postpartum Women

In the past 7 days...			
1. I have been able to laugh and see the funny side of things:		6. Things have been getting on top of me	
• As much as I always could	0	• Yes, most of the time I haven't been able to cope at all	3
• Not quite so much now	1	• Yes, sometimes I haven't been coping as well as usual	2
• Definitely not so much now	2	• No, most of the time I have coped quite well	1
• Not at all	3	• No, I have been coping as well as ever	0
2. I have looked forward with enjoyment to things:		7. I have been so unhappy that I have had difficulty sleeping:	
• As much as I ever did	0	• Yes, most of the time	3
• Rather less than I used to	1	• Yes, sometimes	2
• Definitely less than I used to	2	• No, not very often	1
• Hardly at all	3	• No, not at all	0
3. I have blamed myself unnecessarily when things went wrong:		8. I have felt sad or miserable:	
• Yes, most of the time	3	• Yes, most of the time	3
• Yes, some of the time	2	• Yes, quite often	2
• Not very often	1	• Not very often	1
• No, never	0	• No, not at all	0
4. I have been anxious or worried for no good reason:		9. I have been so unhappy that I have been crying:	
• No, not at all	0	• Yes, most of the time	3
• Hardly ever	1	• Yes, quite often	2
• Yes, sometimes	2	• Only occasionally	1
• Yes, very often	3	• No, never	0
5. I have felt scared or panicky for no very good reason:		10. The thought of harming myself has occurred to me:	
• Yes, quite a lot	3	• Yes, quite often	3
• Yes, sometimes	2	• Sometimes	2
• No, not much	1	• Hardly ever	1
• No, not at all	0	• Never	0

- Score of >10: 90% sensitive
- Score of ≥13: Strongly correlates with meeting criteria for an MDE

Cox JL, et al. *Br J Psychiatry*. 1987;150:782-786.

PHQ-9 for Major Depressive Disorder

Over the previous 2 wk, how often have you been bothered by the following issues?	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed – or the opposite, being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3
If you checked off any of these problems, how difficult have these issues made it for you to work, take care of things at home, or get along with other people?	**Not difficult at all**	**Somewhat difficult**	**Very difficult**	**Extremely difficult**

- Interpretation of total score
  - 1-4: Minimal depression
  - 5-9: Mild depression
  - 10-14: Moderate depression
  - 15-19: Moderately severe depression
  - 20-27: Severe depression

Kroenke K, et al. *J Gen Intern Med*. 2001;16(9):606-613.

MDQ for Bipolar Disorder

1. Has there ever been a period of time when you were not your usual self and....
- ...you felt so good or so hyper that other people thought you were not your normal self or you were so hyper that you got into trouble?
- ...you were so irritable that you shouted at people or started fights or arguments?
- ...you felt much more self-confident than usual?
- ...you got much less sleep than usual and found you didn't really miss it?
- ...you were much more talkative or spoke faster than usual?
- ...thoughts raced through your head or you couldn't slow your mind down?
- ...you were so easily distracted by things around you that you had trouble concentrating or staying on track?
- ...you had much more energy than usual?
- ...you were much more active or did many more things than usual?
- ...you were much more social or outgoing than usual, for example, you telephoned friends in the middle of the night?
- ...you were much more interested in sex than usual?
- ...you did things that were unusual for you or that other people might have thought were excessive, foolish, or risky?
- ...spending money got you or your family in trouble?

2. If you checked YES to more than one of the above, have several of these ever happened during the same period of time?

3. How much of a problem did any of these cause you — like being able to work; having family, money, or legal troubles; getting into arguments or fights?
No problem, minor problem, moderate problem, serious problem

4. Have any of your blood relatives (ie, children, siblings, parents, grandparents, aunts, uncles) had manic-depressive illness or bipolar disorder?

5. Has a health professional ever told you that you have manic-depressive illness or bipolar disorder?

- Item 1 lists manic symptoms
- Items 2-5 address symptom overlap, level of problems caused, family history, and prior diagnosis
- Positive screen:
  - "Yes" to ≥7 for 13 items in question 1 breakouts
  - "Yes" to question 2
  - Answering "moderate" or "serious problem" to 3
- Next step is comprehensive evaluation for bipolar spectrum disorder

Hirschfeld RM, et al. *Am J Psychiatry*. 2000;157(11):1873-1875. Isometsä E, et al. *BMC Psychiatry*. 2003;3:8. Wang HR, et al. *Depress Anxiety*. 2015;32(7):527-538. https://www.ohsu.edu/sites/default/files/2019-06/cms-quality-bipolar_disorder_mdq_screener.pdf

Conventional Treatments for PPD

Room for Improvement?

Standard Treatment Options for PPD

Treatment for PPD = Treatment for MDD

Standard of Care Therapies

- Recommend psychotherapy (cognitive behavioral therapy, interpersonal therapy) ***if at all possible***
- Antidepressant medication
- Light box therapy
- Transcranial magnetic stimulation
- Electroconvulsive therapy

Antidepressant Therapy for PPD

- In patients with previous MDE(s) successfully treated with a particular antidepressant, use ***that*** antidepressant
- If no previous MDE, start with SSRI
- If patients have tried and failed several different antidepressants, use a different class
- An adequate trial is defined as 8 wk at the therapeutic dosage (ATRQ uses at least 6 weeks)

Fitelson E, et al. *Int J Womens Health*. 2010;3:1-14. Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/postpartum-depression/diagnosis-treatment/drc-20376623

Limitations of Current Standard of Care Antidepressant Therapy

Onset of Action

With current oral antidepressants, it takes, on average, 6 to 8 weeks for patients to achieve remission

Efficacy

Inadequate response/lack of efficacy, low rates of remission, and substantial relapse rates remain challenges in managing MDD and PPD

Functioning and QoL

Improvements in functioning and quality of life tend to lag behind symptomatic relief

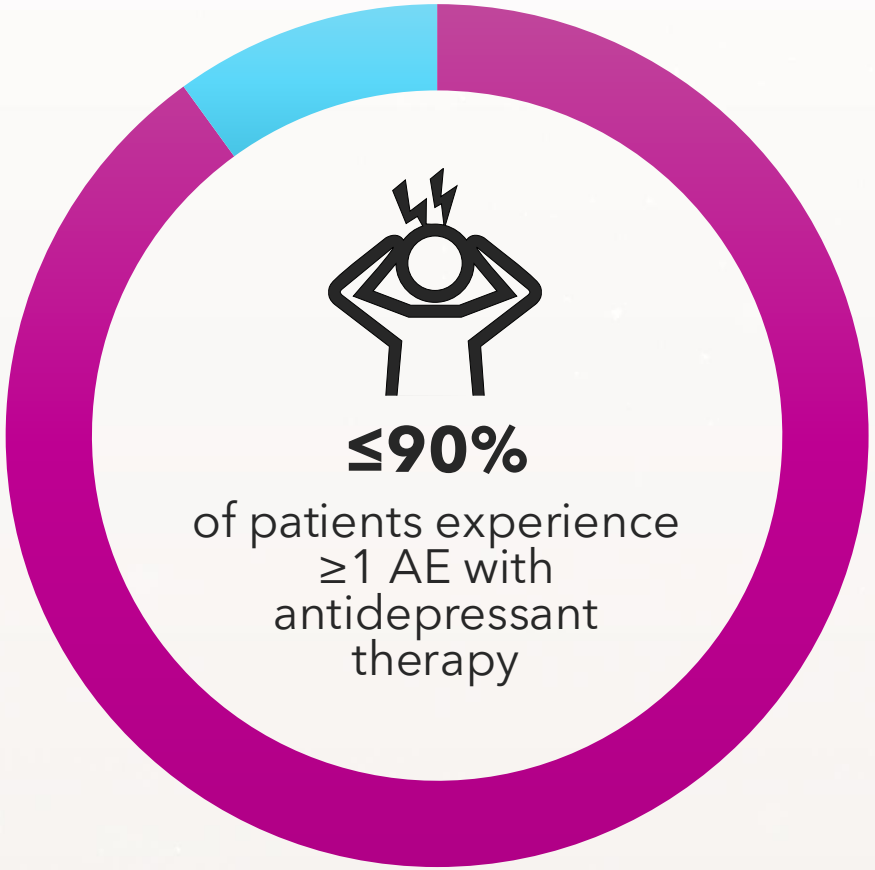
Safety and Tolerability

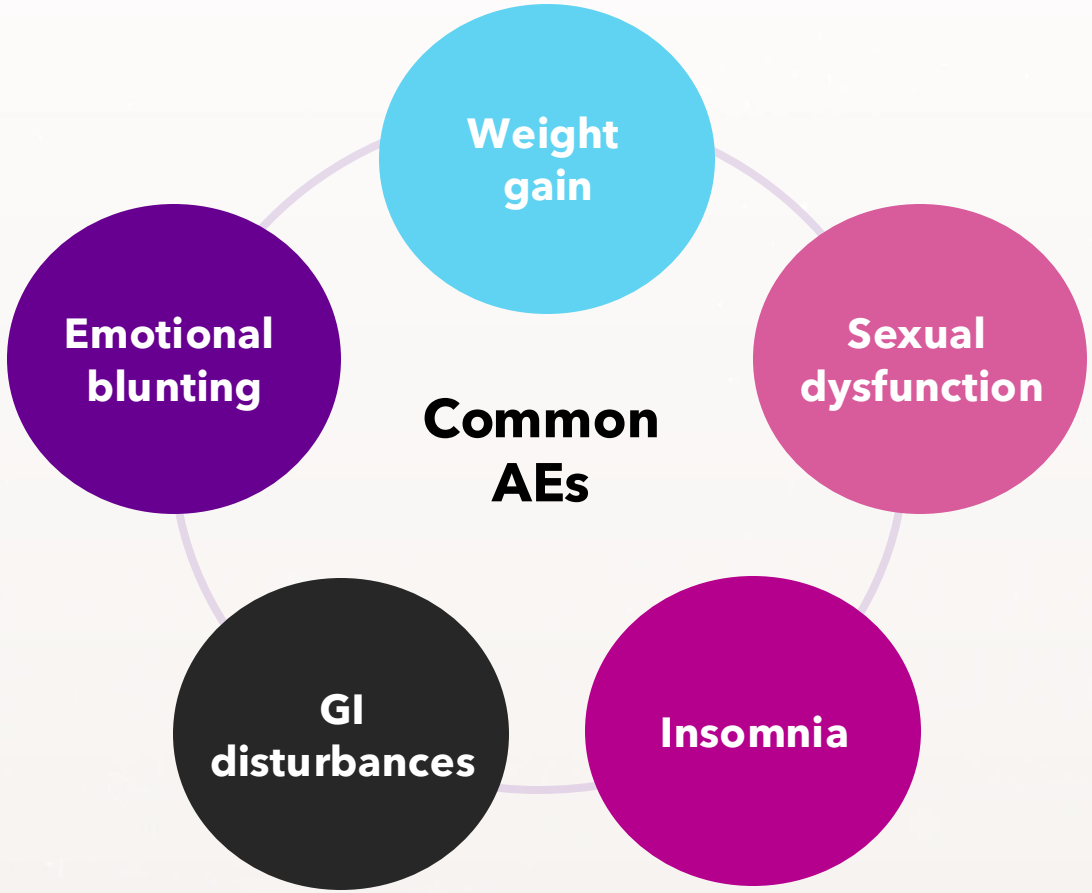
Current therapies are associated with significant side effects, which can interfere with adherence

Kaufman Y, et al. *Ther Adv Psychopharmacol*. 2022;12:20451253211065859.

Current Antidepressants: Distinct Tolerability Profiles

- AEs are greatest with SSRIs > SNRIs > atypical antidepressants





Solmi M, et al. *Braz J Psychiatry*. 2021;43(2):189-202. Ferguson JM. *Prim Care Companion J Clin Psychiatry*. 2001;3(1):22-27. Santarsieri D, et al. *Drugs Context*. 2015;4:212290.

Conclusions

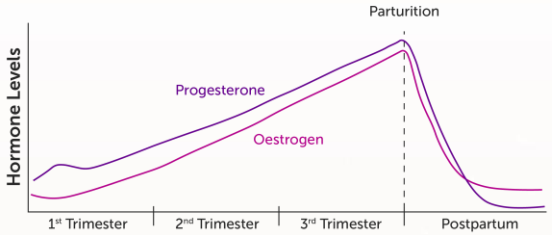
- PPD is common, serious, and has deleterious effects on maternal, pregnancy, and child outcomes.
- The increased risk of psychiatric illness postpartum is likely due to a combination of factors including genetics, hormonal change, stress, and sleep deprivation.
- Standardized screening for PPD is easy and inexpensive with self-rating scales.
- Conventional antidepressants such as SSRIs can be used to treat PPD but take weeks to work and have several common side effects.

Women's Health 2024 | Beyond the Annual Visit

Advancing PPD Treatment: Pathophysiology of PPD, Current PPD Therapeutic Strategies, and Clinical Implementation of NAS

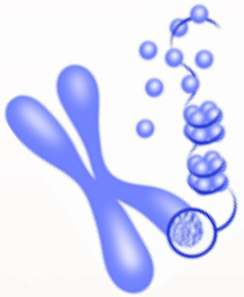
Kristina M. Deligiannidis, MD
Director, Women's Behavioral Health
Zucker Hillside Hospital, Northwell Health
New York, NY

The Pathophysiology of Perinatal Depression (PND) Is Complex



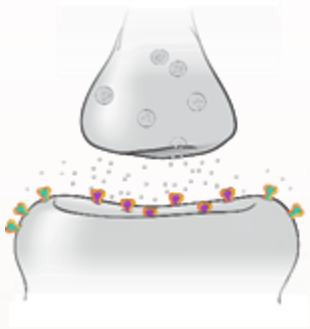
Endocrine Mechanisms

A subset of women with PPD are susceptible to fluctuating reproductive hormone levels during the peripartum period.[1]



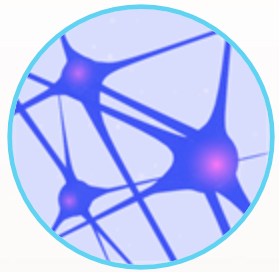
Epigenetic Mechanisms

Estradiol-mediated epigenetic mechanisms may be associated with PPD risk.[2]



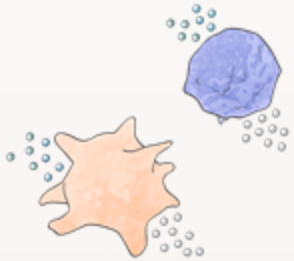
Synaptic Transmission Mechanisms

Alterations in monoamines (serotonin receptors) and neurotransmitters (GABA receptors and glutamate) have been implicated in PPD.[5-7]



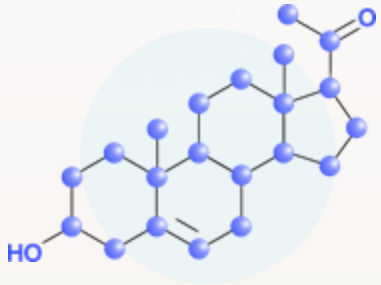
Neural Network Mechanisms

Imaging studies have demonstrated altered activity in the amygdala, prefrontal cortex, cingulate cortex, and insula in PPD.[10,11]



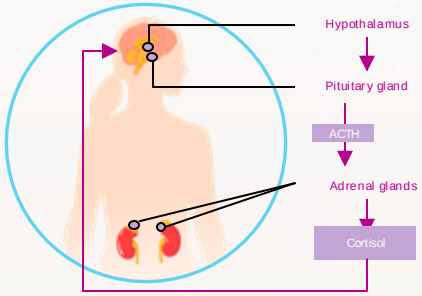
Inflammatory Mechanisms

Altered levels of immune system factors have been associated with PPD.[3]



Neurosteroid Mechanisms

Altered levels of allopregnanolone and dysfunction in NAS signaling have been observed in PPD.[4]



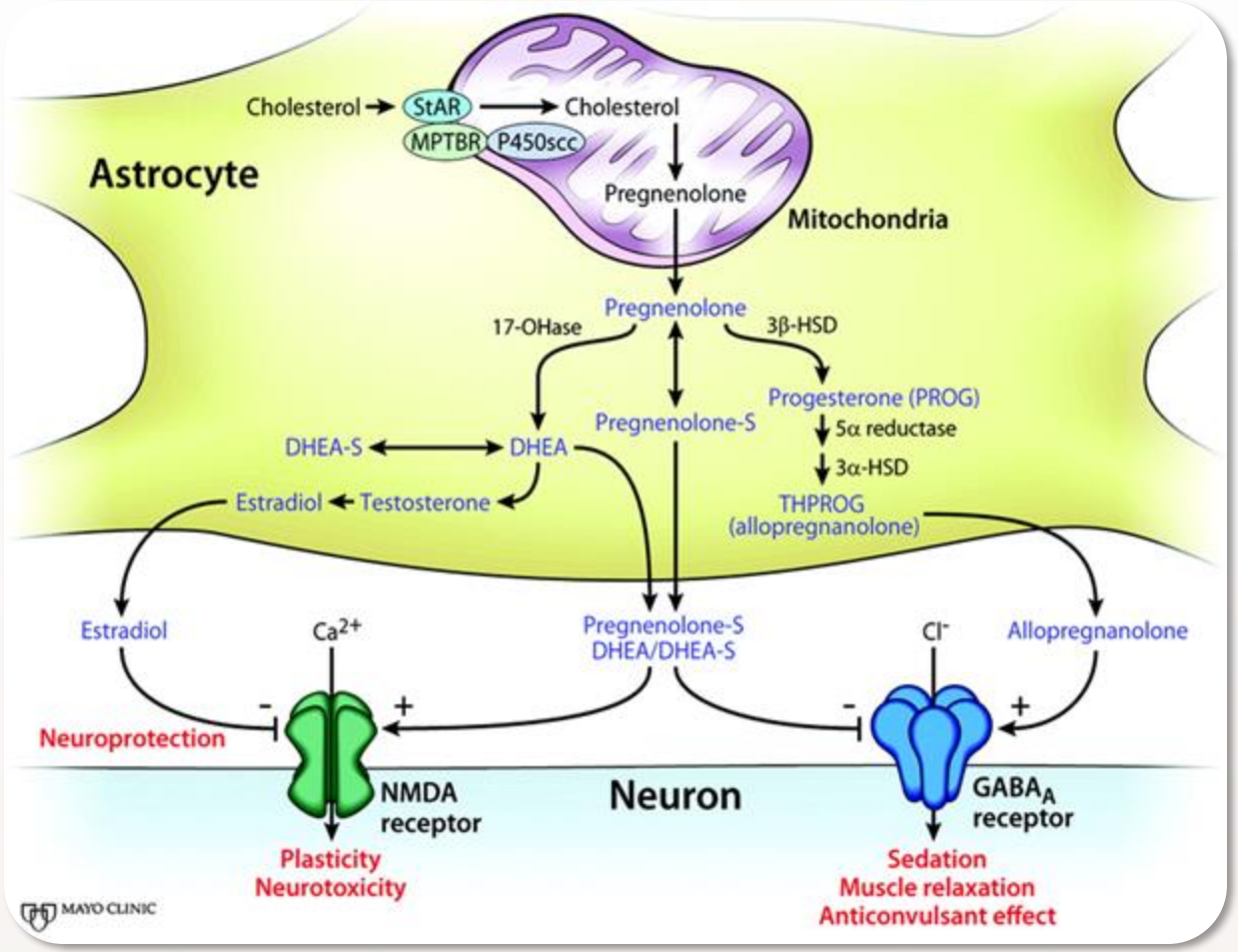
Stress Mechanisms

Dysfunction of the HPA axis has been implicated in women with PPD and animal models of PPD, particularly overactivity.[8,9]

Women's Health 2024 | Beyond the Annual Visit

1. Schiller CE, et al. *CNS Spectr*. 2015;20(1):48-59. 2. Guintivano J, et al. *Mol Psychiatry*. 2014;19(5):560-567. 3. Osborne LM, et al. *Psychoneuroendocrinology*. 2013;38(10):1929-1952. 4. Schüle C, et al. *Prog Neurobiol*. 2014;113:79-87. 5. Licheri V, et al. *Neural Plast*. 2015;2015:170435. 6. Jun C, et al. *Exp Neurobiol*. 2014;23(1):28-35. 7. Moses-Kolko EL, et al. *Fertil Steril*. 2008;89(3):685-692. 8. Bloch M, et al. *Compr Psychiatry*. 2003;44(3):234-246. 9. Melón LC, et al. *Psychoneuroendocrinology*. 2018;90:182-193. 10. Duan C, et al. *Curr Psychiatry Rep*. 2017;19(10):70. 11. Fiorelli M, et al. *Behav Neurol*. 2015;2015:913843.

Neuroactive Steroids Are Pregnenolone Metabolites That Modulate GABAergic and Glutamatergic Neurotransmission



Benarroch EE. *Neurology.* 2007;68(12):945-947.

Neuroactive steroids (NAS)

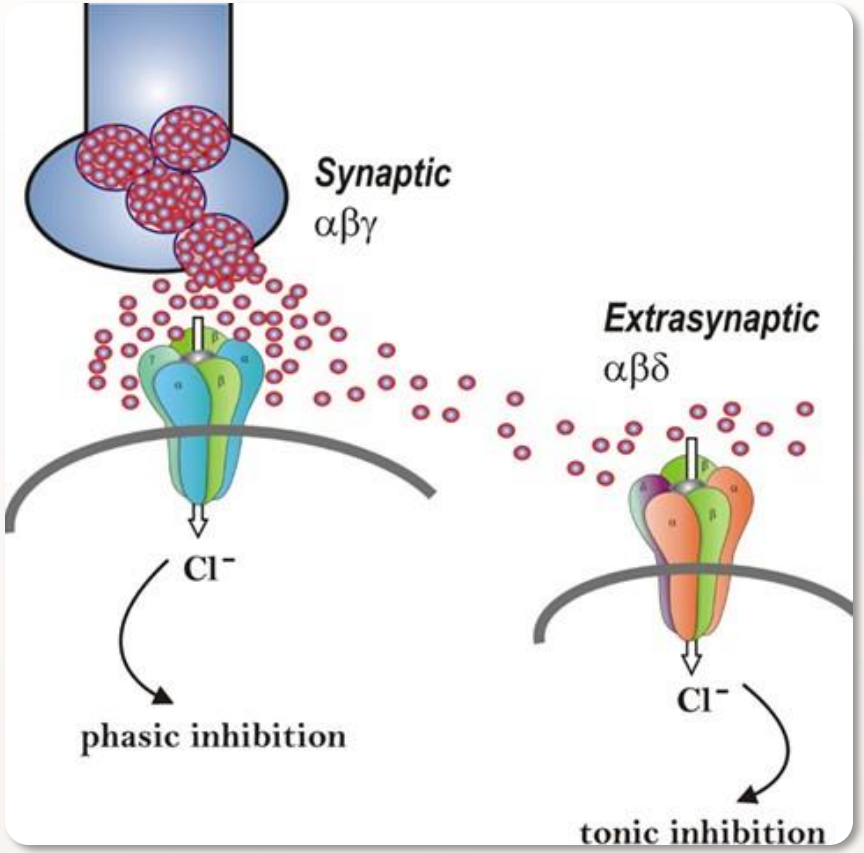
Natural or synthetic steroids which act on the brain by serving as transcription factors in the regulation of gene expression or by interacting with membrane-bound NT receptors[1]

Many NAS are positive allosteric modulators (PAMs) of the GABAA receptor, enhancing tonic or phasic GABAergic inhibition via facilitating negatively charged Cl- ion flow[2]

CNS NAS have important roles in acute and chronic stress conditions[3,4]

1. Paul SM, et al. *FASEB J.* 1992;6(6):2311-2322. 2. Callachan H, et al. *Proc R Soc Lond B Biol Sci.* 1987;231(1264):359-369. 3. Maguire J. *Front Cell Neurosci.* 2019;13:83. 4. Crowley SK, et al. *Psychopharmacology (Berl).* 2016;233(7):1299-1310.

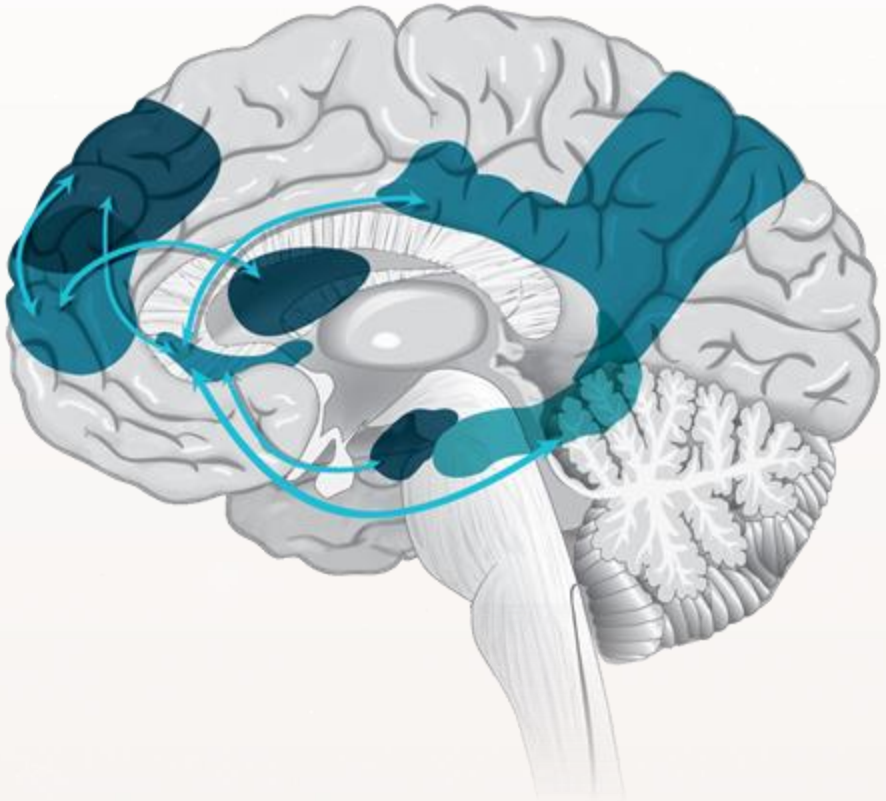
NAS Enhance Tonic and Phasic Inhibition Through Synaptic and Extrasynaptic $GABA_AR$



Postsynaptic GABA-A receptors, which are pentameric chloride channels composed of 2α2βγ subunits, mediate the phasic portion of GABAergic inhibition, while extrasynaptic GABA-A receptors, pentamers composed of 2α2βδ subunits, primarily contribute to tonic inhibition

Reddy DS. *Front Endocrinol (Lausanne).* 2011;5:2:38. doi:10.3389/fendo.2011.00038

Perinatal Depression (PND) Is Associated with Neural Network Dysregulation



Neuroactive steroids (NAS), through their modulation of $GABA_A$ receptors, regulate inhibition-excitation balance within neural networks.[1,2]

PND has been associated with altered functional connectivity of the default mode network, salience, and central executive networks.[1,3-5]

Women with PND have altered postpartum resting-state connectivity that is associated with plasma allopregnanolone concentrations and depression severity.[1]

1. Deligiannidis KM, et al. *Neuropsychopharmacology*. 2019;44(3):546-554. 2. Sripada RK, et al. *Hum Brain Mapp*. 2014;35(7):3249-3261. 3. Pawluski JL, et al. *Trends Neurosci*. 2017;40(2):106-120. 4. Deligiannidis K, et al. *J Psychiatr Res*. 2013;47(6):816-828. 5. Chase HW, et al. *Soc Cogn Affect Neurosci*. 2014;9(8):1069-1075.

Mechanisms Implicated in Perinatal Depression (PND) Pathophysiology in Relation to Potential MOA Mediating Antidepressant Effects of Allopregnanolone (ALLO)

Mechanism of action of ALLO	Implicated in PND pathophysiology	Potential mechanisms mediating ALLO antidepressant effects
GABAergic dysfunction	+	+
HPA axis dysfunction	+	+
NAS deficits	+	+
Altered network communication	+	+
Neuroinflammation	+	+
Genetic predisposition	+	?

+, strong relationship; ?, relationship is currently undetermined.

Table adapted from Walton N, et al. *Neurobiol Stress.* 2019;11:100198.

There Is a Strong Evidence Base for Psychotherapies in Perinatal Depression

- Psychotherapies are recommended as monotherapy for mild-moderate unipolar perinatal depression
- Interpersonal psychotherapy (IPT)[1-5]
- Cognitive behavioral therapy (CBT)[6-10]
- Mindfulness-based CBT[11-13]
- Peer support and group psychotherapies[14-18]

1. Reay R, et al. *Int J Group Psychother.* 2012;62(2):221-251; 2. Grote NK, et al. *Psychiatr Serv.* 2009;60(3):313-321; 3. Spinelli MG, et al. *Am J Psychiatry.* 2003;160(3):555-562; 4. 5. O'Hara MW, et al. *Arch Gen Psychiatry.* 2000;57(11):1039-1045; Klier CM, et al. *J Psychother Pract Res.* 2001;10(2):124-131; Stuart S, et al. *J Psychother Pract Res.* 1995;4(1):18-29); 6. Milgrom J, et al. *J Med Internet Res.* 2016;18(3):e54; 7. Milgrom J, et al. *Aust N Z J Psychiatry.* 2015;49(3):236-245; 8. Ammerman RT, et al. *Behav Ther.* 2013;44(3):359-372; 9. Le HN, et al. *J Consult Clin Psych.* 2011;79(2):135; 10. Chabrol H, et al. *Psychol Med.* 2002;32(6):1039-1047; 11. Dimidijian S, et al. *J Consult Clin Psychol.* 2016;84(2):134-145; 12. Dimidijian S, et al. *Behav Res Ther.* 2014;63:83-89; 13. Goodman JH, et al. *Arch Womens Ment Health.* 2014;17(5):373-387; 14. Dennis CL, et al. *BMJ.* 2009;338:a3064; 15. Dennis CL. *Can J Psychiatry.* 2003;48(2):115-124.; 16. Chen CH, et al. *J Psychosom Res.* 2000;49(6):395-399; 17. Honey KL, et al. *Br J Clin Psychol.* 2002;41(Pt 4):405-409; 18. Milgrom, et al. *Br J Clin Psychol.* 2005;44(Pt 4):529-542.

Antidepressants Are Indicated for Moderate/Severe Unipolar Postpartum Depression

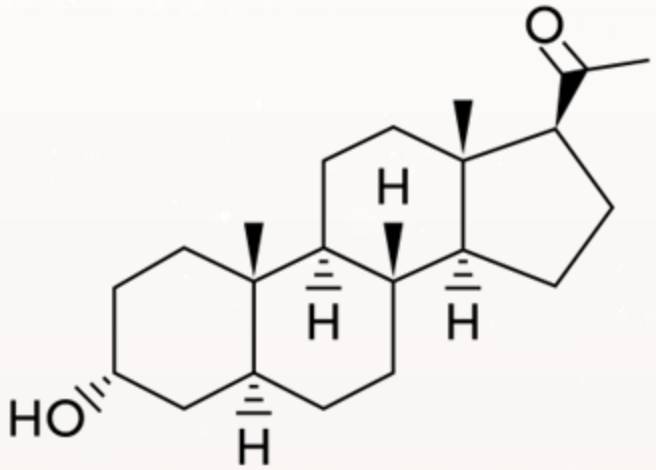
- Conventional antidepressants are indicated for moderate/severe postpartum depression, though are not FDA-approved for PPD[1-4]
- Meta-analysis of 11 RCTs showed that there may be a benefit of SSRIs over placebo in response (55% versus 43%; pooled risk ratio (RR) 1.27, 95% CI 0.97 to 1.66) and remission (42% versus 27%; RR 1.54, 95% CI 0.99 to 2.41) at 5 to 12 weeks' follow-up.[4]
- Treatment approach: titrate until efficacy/tolerability then treat acute episode at that dose -> once reach euthymia, continue treatment (continuation phase) to prevent relapse
- May have to try more than one conventional antidepressant (or augment) to achieve acceptable treatment response and tolerability; dosages are the same as those used outside of the postpartum period
- Most conventional antidepressants are compatible with breastfeeding.
    - Relative infant doses (RID) less than 10% of maternal dosage are acceptable per FDA; excellent clinical resource: Drugs and Lactation Database (LactMed). National Library of Medicine (US). https://www.ncbi.nlm.nih.gov/books/NBK501922/

1. Yonkers KA, et al. *Gen Hosp Psychiatry.* 2009;31(5):403-413. 2. Brown JVE, et al. *Cochrane Database Syst Rev.* 2021;2(2):CD013560. 3. Molenaar NM, et al. *Aust N Z J Psychiatry.* 2018;52(4):320-327. 4. Brown JVE, et al. *Cochrane Database Syst Rev.* 2021;2(2):CD013560.

Brexanolone Is FDA-Approved for the Treatment of PPD

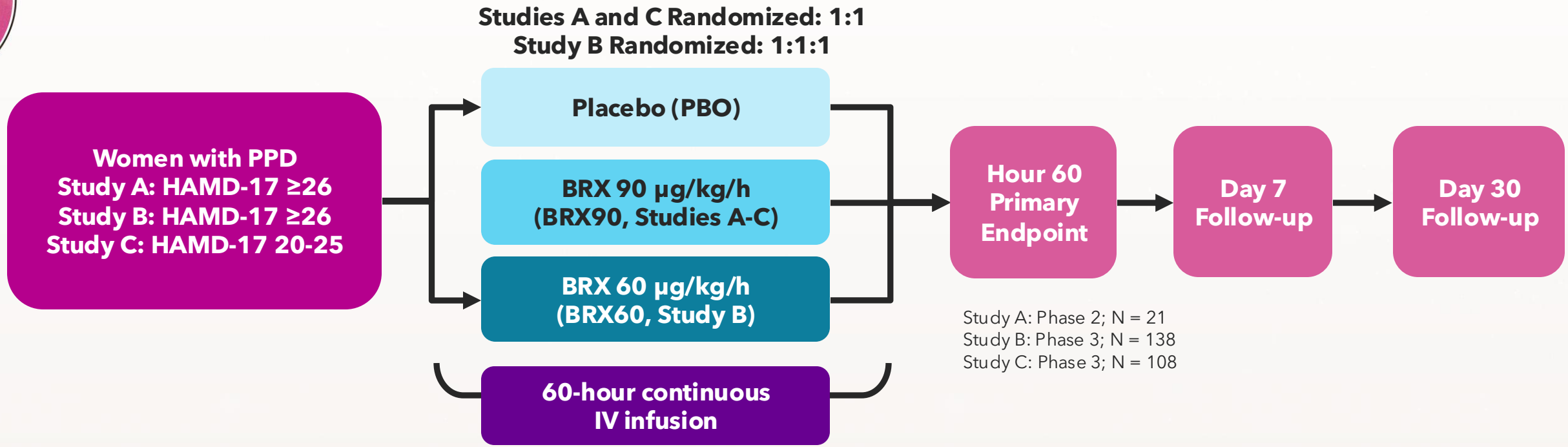
Brexanolone is an IV-administered, exogenous version of allopregnanolone, synaptic and extrasynaptic $GABA_A$ receptor PAM

- Per the US Prescribing Information, the dose regimen is administered as a continuous IV infusion over a total of 60 hours (step-wise up and down-titration)
- The recommended dosage is a titration up to 90 µg/kg/hour
- A reduction in dosage to 60 µg/kg/hour may be considered for patients who do not tolerate 90 µg/kg/hour
- Calculated maximum RID (relative infant dose) for brexanolone during infusion is 1.3%[1]
- Scheduling: Schedule IV, see package insert at https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=b40f3b2a-1859-4ed6-8551-444300806d13



1. Wald J, et al. *Clin Pharmacokinet*. 2022;61(9):1307-1319.

Brexanolone IV: 3 Placebo-Controlled RCTs (Hummingbird)

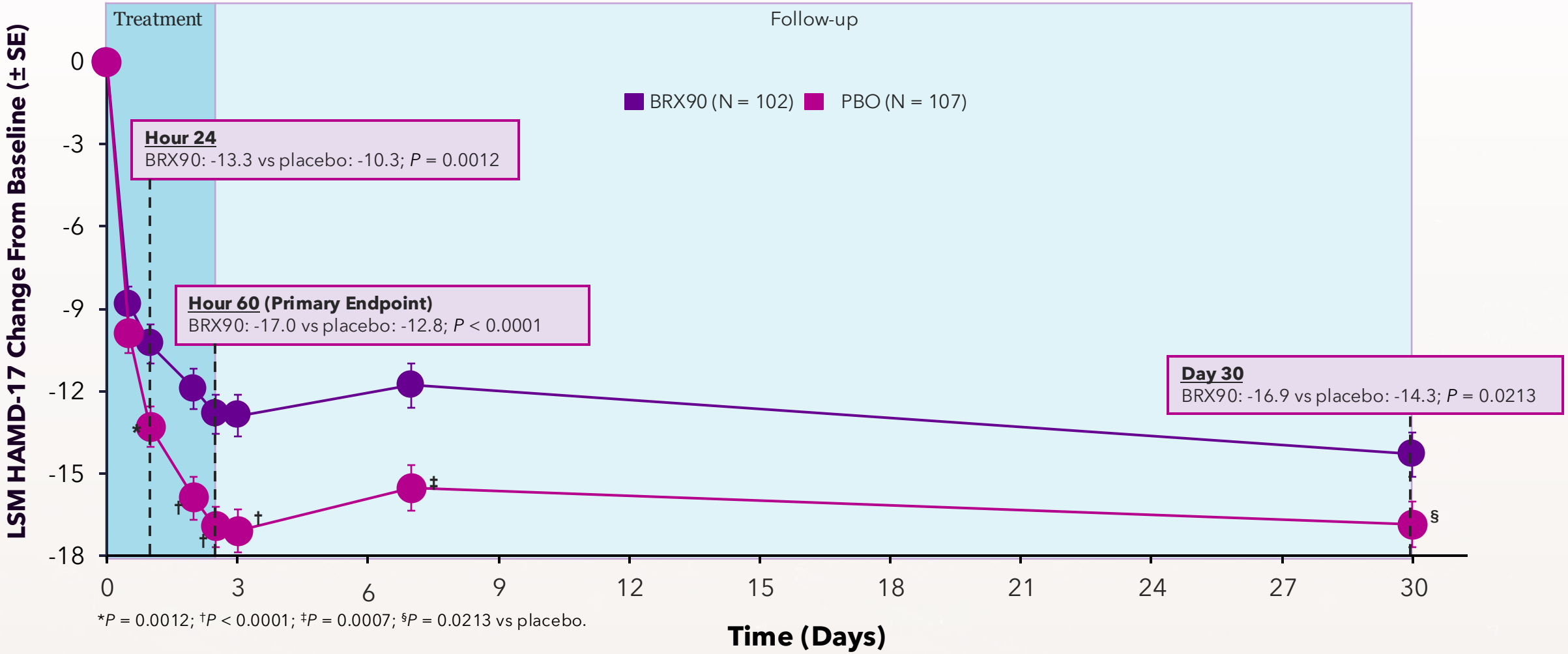


Study A: Phase 2; N = 21
Study B: Phase 3; N = 138
Study C: Phase 3; N = 108

Primary endpoint: least-squares mean (LSM) change from baseline in HAMD-17 total score at Hour 60
Secondary endpoints included LSM change from baseline in HAMD-17 total score at all other time points.
Secondary endpoints were not adjusted for multiplicity.
Umbrella protocol allowed pre-planned integrated study dataset analysis, efficacy BRX90 and safety all BRX.

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

Brexanolone: Integrated PPD Efficacy Analysis Change From Baseline in HAMD-17 Total Score



Meltzer-Brody S, et al. *Lancet*. 2018;392(10152):1058-1070.

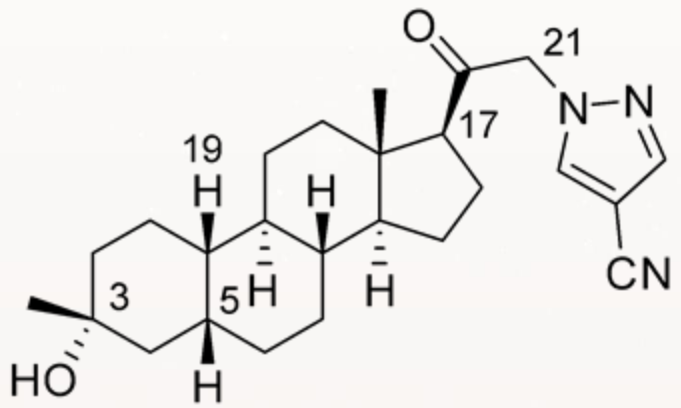
Adverse Events Associated With Brexanolone Treatment of PPD

- The most common AEs with brexanolone: sedation/somnolence (13%-21%), dizziness/presyncope/vertigo (12%-13%), LOC (3%-5%), dry mouth (3%-11%) and flushing/hot flush (2%-3%) [% across 60 ug/kg/hr and 90 ug/kg/hr dosing]
- Excessive sedation and sudden LOC boxed warning
  - Brexanolone caused sedation and somnolence that required dose interruption or reduction in 5% of brexanolone-treated patients compared to 0% in placebo
- LOC or altered state of consciousness during the brexanolone infusion occurred in 4% of the brexanolone-treated patients compared with 0% in placebo
- All patients with LOC or altered state of consciousness recovered with dose interruption; fully recovered within 15-60 minutes
- Brexanolone can only be prescribed at certified facilities through a Risk Evaluation and Mitigation Strategy (REMS) safety program
- Recent data report that rates of LOC are lower in clinical practice compared to those reported in the clinical trials as no LOC was reported in post-marketing surveillance[1]

Package insert available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=b40f3b2a-1859-4ed6-8551-444300806d13
FDA REMS website available at:
https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=387
1. Garafola S, et al. *Drugs Real World Outcomes*. 2023;10(3):351-356.

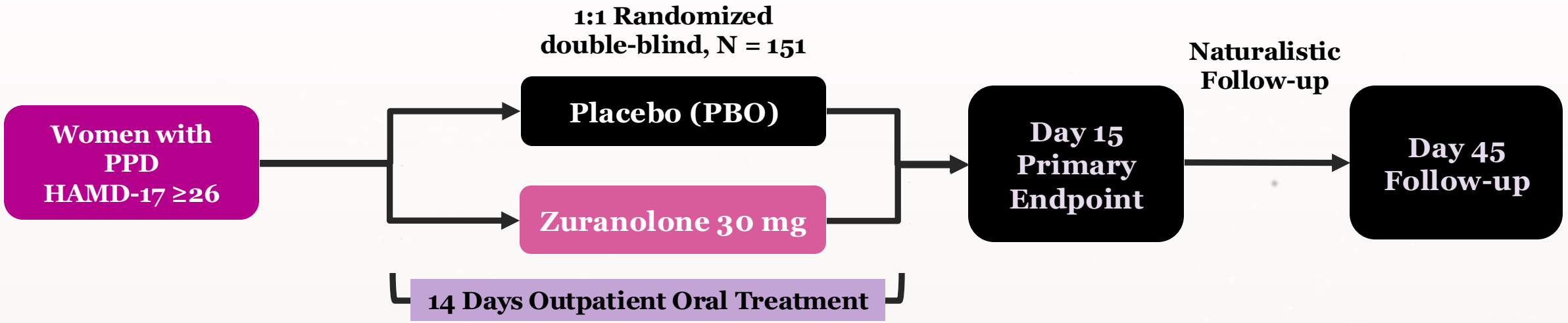
Zuranolone Is FDA-Approved for the Treatment of Postpartum Depression

- Zuranolone is a synthetic analog of allopregnanolone and is a PAM of synaptic and extrasynaptic GABA-A receptors[1]
- Difference between brexanolone and zuranolone is the addition of a cyanopyrazole ring to the structure of brexanolone[2,3]
- Approved by FDA for treatment of PPD on August 4, 2023
- Administered at home, 50 mg orally each evening x 14 days (no up or down titration)
- Mean RID is <1% (50 mg dosing, based on milk intake of 200 mL/kg/d)
- Schedule IV, see package insert: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=f18e53b0-d0bb-422d-8de7-ab64b7292b29



1. Althaus AL, et al. *Neuropharmacology*. 2020;181:108333.
2. Hoffmann E, et al. *Clin Pharmacokinet*. 2020;59(1):111-120.
3. Martinez Botella G, et al. *J Med Chem*. 2015;58(8):3500-3511.

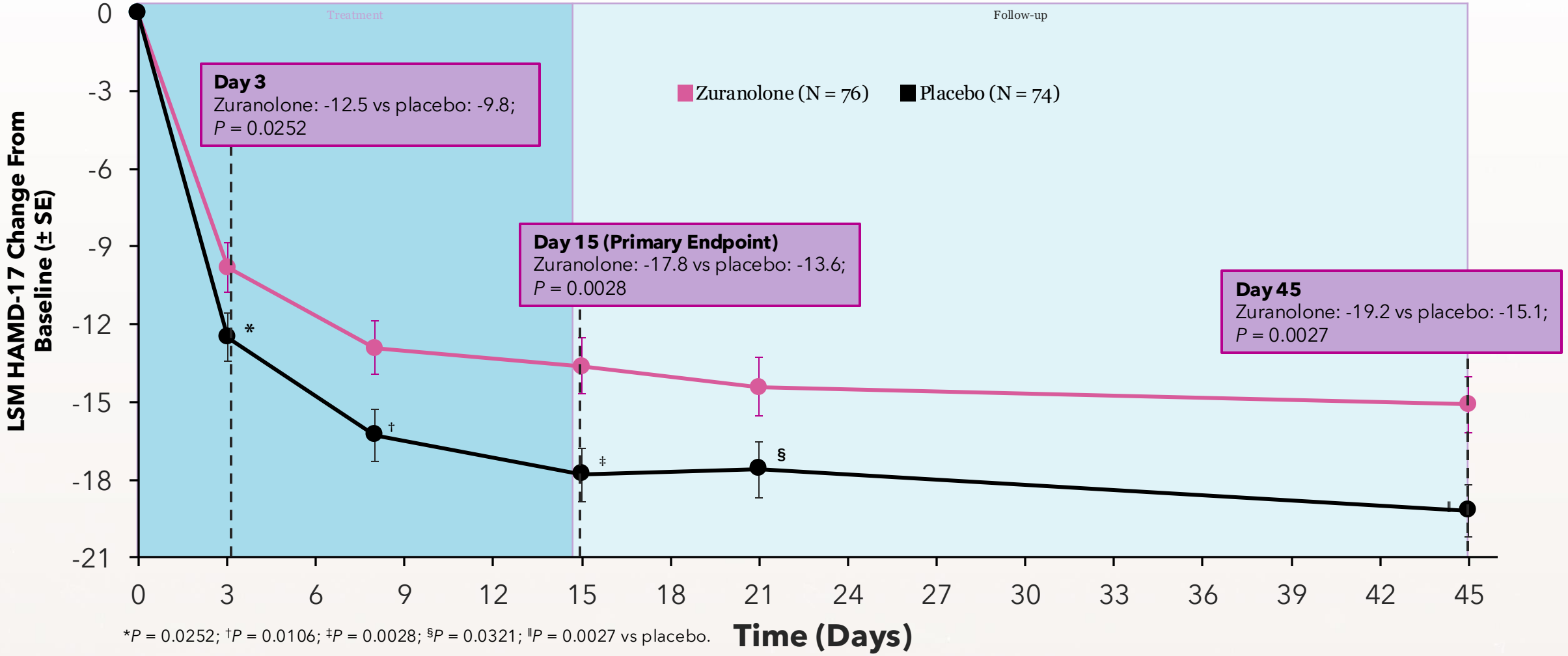
Zuranolone: Pivotal Placebo-Controlled RCT in PPD (ROBIN)



- Inclusion criteria: Women ages 18-45, ≤6 months postpartum, PPD (major depressive episode with onset in 3rd trimester or ≤4 weeks postpartum), and a HAMD-17 ≥26
- Primary endpoint: LSM change from baseline in HAMD-17 total score at Day 15
  - Secondary endpoints included HAMD-17 total score at all time points
  - Statistical analyses of secondary endpoints were not adjusted for multiplicity

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

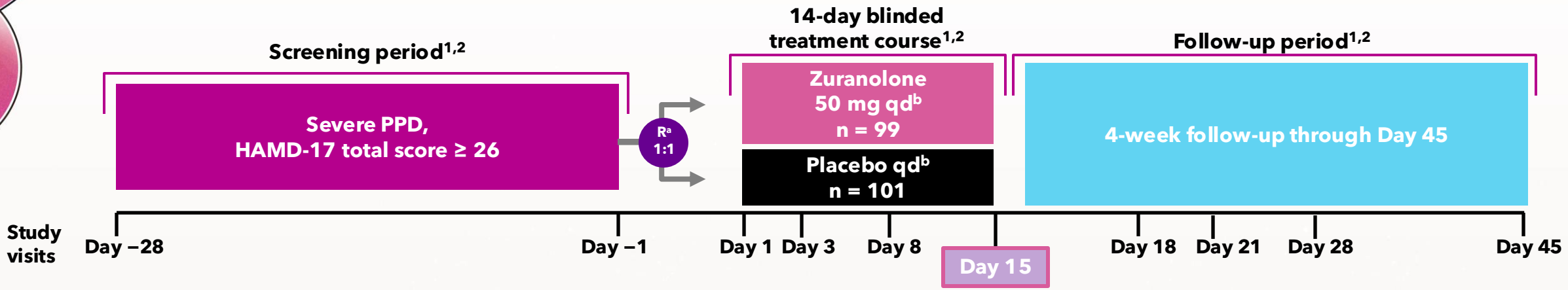
Zuranolone: Pivotal Placebo-Controlled RCT in PPD (ROBIN) Change From Baseline in HAMD-17 Total Score



*P = 0.0252; †P = 0.0106; ‡P = 0.0028; §P = 0.0321; ‖P = 0.0027 vs placebo.

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

Zuranolone: Phase 3 Double-Blind, Placebo-Controlled RCT in PPD (SKYLARK)



Primary Endpoint[1]

- Change from baseline (CFB) in HAMD-17 total score at Day 15

Key Secondary Endpoints

- CFB in HAMD-17 total score at Days 3, 28, and 45

Inclusion

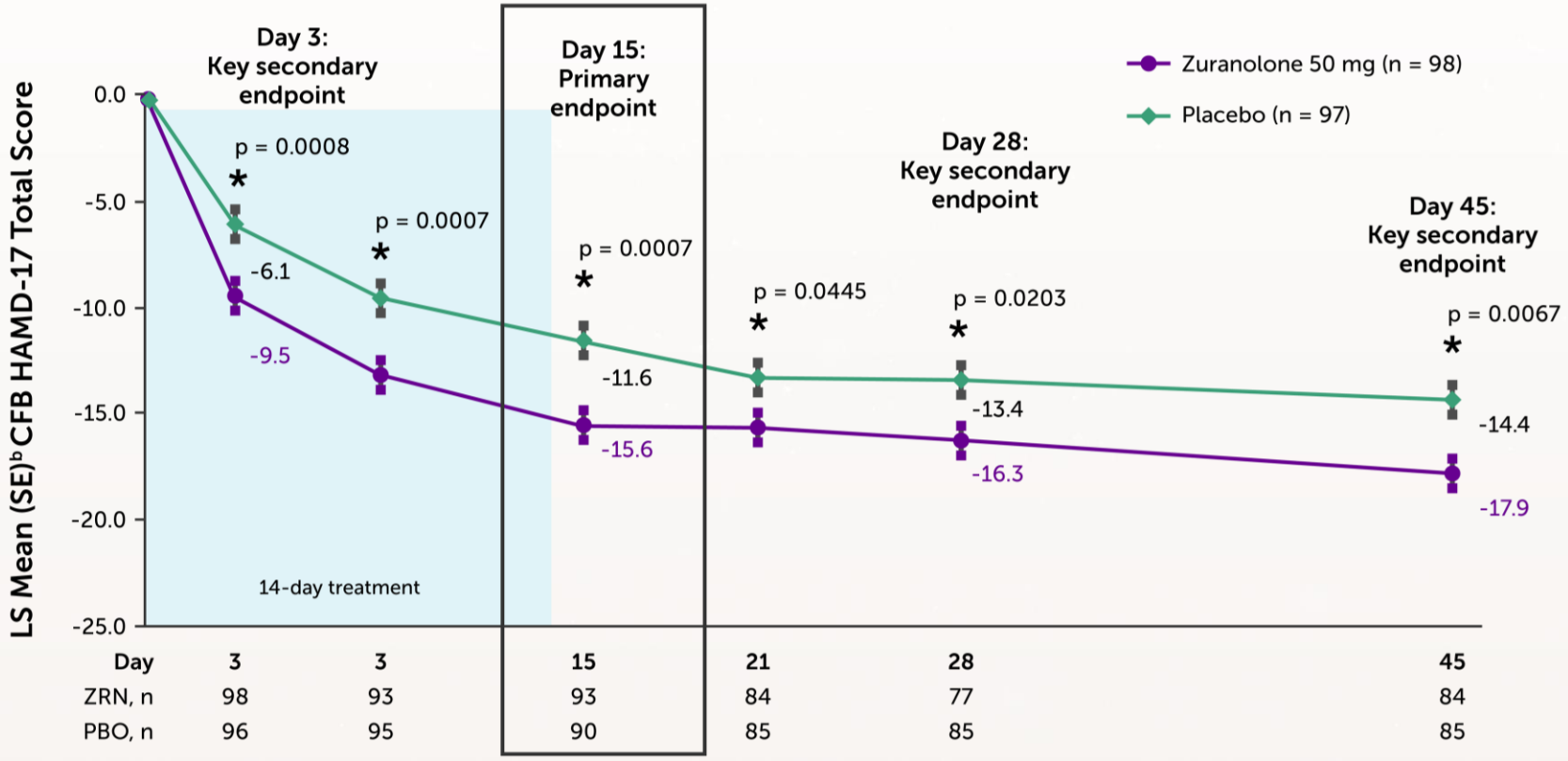
- Major depressive episode that began from third trimester to ≤4 weeks postpartum; ≤12 months postpartum at Day 1[1]
- Agreed not to provide breastmilk ≤7 days following the last dose
- Stable ADT use ≥30 days prior to Day 1 was continued throughout study[2]

Exclusion

- History of nonfebrile seizures, bipolar disorder, psychotic disorder, attempted suicide, or risk of suicide in the current episode[1]
- Use of benzodiazepines, barbiturates, $GABA_A$ receptor modulators, non-GABA anti-insomnia medications, and first- or second-generation antipsychotics

ADT, antidepressant therapy; CGI-S, Clinical Global Impression-Severity; EPDS, Edinburgh Postnatal Depression Scale; GABA, γ-aminobutyric acid; HAM-A, Hamilton Anxiety Rating Scale; HAMD-17, 17-Item Hamilton Rating Scale for Depression; PPD, postpartum depression; qd, once daily; R, randomisation; TEAE, treatment-emergent adverse event.
[a] Randomisation was stratified based on antidepressant treatment use at baseline. [b] Zuranolone 50 mg and placebo administered in the evening with fat-containing food.[2] Dose could be reduced to 40 mg as needed based on tolerability.[2]
1. A Study to Evaluate the Efficacy and Safety of SAGE-217 in Participants With Severe Postpartum Depression (PPD). ClinicalTrials.gov identifier:NCT04442503. Updated June 22, 2023. https://clinicaltrials.gov/ct2/show/NCT04442503. 2. Deligiannidis KM, et al. *Am J Psychiatry*. Published online July 26, 2023. doi:10.1176/appi.ajp.20220785

Change From Baseline (CFB) in HAMD-17 Total Score on Day 15 and Days 3, 28, and 45 Primary Endpoint and Key Secondary Endpoints



HAMD-17 at Baseline, Mean (SD)	
Zuranolone 50 mg	28.6 (2.49)
Placebo	28.8 (2.34)

FAS, full analysis set; HAMD-17, 17-Item Hamilton Rating Scale for Depression; LS, least squares; MMRM, mixed model of repeated measures; PBO, placebo.

***Statistically significant (per fixed hierarchal testing for key secondary endpoints). Data at Days 8 and 21 were not adjusted for multiplicity, and *P* values were considered nominal.**

[a] FAS was defined as all randomised participants who were administered zuranolone 50 mg or placebo with valid baseline and ≥ 1 postbaseline efficacy endpoint assessment. [b] LS mean and treatment difference along with CI and p-values were calculated using MMRM. The key secondary endpoints were tested in the following fixed sequence to control for multiplicity: CFB in HAMD-17 at Days 3, 28, and 45. If an endpoint was not significant at the 5% level, the following endpoints in the sequence were interpreted only with nominal p-value. Deligiannidis KM, et al. *Am J Psychiatry*. 2023;180(9):668-675.

Adverse Events Associated With Zuranolone Treatment of PPD

- The most common AEs that occurred in ≥2% of patients treated with zuranolone 50 mg included: somnolence (36%), dizziness (13%), diarrhea (6%), and fatigue (5%)
  - There were no episodes of LOC
- There was no signal for increased suicidal ideation or suicidal behavior compared with baseline, as measured by the Columbia-Suicide Severity Rating Scale
- There is a boxed warning for impaired ability to drive or engage in hazardous activities due to CNS depressant effects
  - Cautions people should not drive or operate heavy machinery for at least 12 hours after taking each dose of this medicine

Deligiannidis KM, et al. *JAMA Psychiatry*. 2021;78(9):951-959.
Deligiannidis KM, et al. *Am J Psychiatry*. 2023;180(9):668-675.

Clinical Pointers for Zuranolone Use in PPD

- Avoid concomitant EtOH use, benzodiazepines, opioids or other medication use that can increase impairment of psychomotor performance or CNS depressive effects such as somnolence and cognitive impairment
- Based on animal studies, ZRN may have adverse fetal effects, thus advise patients of reproductive potential to use effective contraception during ZRN treatment and for one week after the final dose; there is no data in pregnant individuals
- Can be taken as monotherapy or as an adjunct to another antidepressant medication
- Administer with a fat-containing food (eg, 400 to 1,000 calories, 25% to 50% fat)
- Recommended dosage is 50 mg PO in the evening x 14 days; may reduce to 40 mg dosing if CNS depressant effects; 30 mg dosing for severe hepatic impairment or moderate or severe renal impairment

Neuroactive Steroids Under Development for Postpartum Depression

- NORA520: an oral prodrug which is hydrolyzed to brexanolone (allopregnanolone)
  - Prodrug contains 2 pro-moieties, one to enhance oral absorption and one to prolong half-life
  - Phase 2 RCT in process: A Study to Assess the Efficacy, Safety, and Tolerability of Oral NORA520 in Adults With Severe Postpartum Depression (NuMom): NCT06285916

ClinicalTrials.gov identifier: NCT06285916.

Conclusions

- The pathophysiology of perinatal depression is multifactorial and includes neuroactive steroid and GABAergic dysfunction.
- Evidence-based treatments for perinatal depression include psychotherapies, conventional antidepressants and novel FDA-approved neuroactive steroid-based antidepressants (ie, brexanolone, zuranolone).
- Most conventional antidepressants and brexanolone and zuranolone are compatible with breastfeeding, as relative infant doses are low.

Women's Health 2024 | Beyond the Annual Visit

A Unified Approach: Coordinating Care for Effective PPD Treatment

Jennifer L. Payne, MD

Professor and Vice Chair of Research
UVA Vivian Pinn Scholar
Department of Psychiatry and Neurobehavioral Sciences
University of Virginia

It's a Team Sport!

Who Is Involved in a Multidisciplinary Team for Treating PPD?

Required

- Mental Health Provider/Team
- Ob-Gyn Provider/Team
- Pediatrics Provider/Team

If Appropriate

- Individual Therapist
- Lactation Consultant

Others

- Family Therapist
- Dyad Therapist/Psychologist
- Social Work
- Child Development Services
- Physical Therapist

How a Multidisciplinary Team Contributes to Effective Management of PPD

- It is essential that the mental health, ob-gyn, and pediatric providers/teams communicate and "be on the same page" regarding the plan of treatment in order to best support the patient and eliminate mixed messages.
- A multidisciplinary team provides comprehensive assessment, ideally of the entire family, leading to a holistic approach and customized treatment.
- A Team Approach also reduces stigma, provides support that increases compliance, and allows for early intervention when problems arise.
- Psychotherapy in addition to medication management has repeatedly been shown to be superior to psychotherapy or medication management alone in the treatment of depressive episodes.
- Psychotherapy increases insight into illness, thus reducing stigma and increasing long-term compliance with care.

The Family Is Part of the TEAM!

- Family can provide moral support.
- Family can provide physical support and help care for the baby and household.
- If the family understands the treatment plan and the reasons for the plan they can provide consistent messaging to the patient.
- Family understanding of the illness reduces stigma and increases compliance.

Effective Team Coordination Looks Like:

- **Communication, Communication, Communication!**
- Regular check-ins with the patient and family
- Regular check-ins with the team
- A holistic approach and evaluation
- Bringing in other professionals as needed

Conclusions

- Ideally the management of PPD is a Team Sport.
- A multidisciplinary team approach allows for consistent communication and messaging and a holistic approach that takes into account the entire family's functioning.
- A multidisciplinary team approach also allows for enhanced support and early intervention if and when there are problems.
- A multidisciplinary team approach also decreases stigma and increases compliance with care through education and consistent communication.