Clinical Updates in Postpartum DEPRESSION MANAGEMENT:

Integrating Novel Therapeutics Targeting GABA-A in Practice

FACULTY

Anita Clayton, MD
Chair of Psychiatry and
Neurobehavioral Sciences
Wilford W. Spradlin Professor
University of Virginia School of Medicine
Charlottesville, Virginia

Jennifer Payne, MD
Professor and Vice Chair of Research
Department of Psychiatry and
Neurobehavioral Sciences
University of Virginia School of Medicine
Charlottesville, Virginia

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PROGRAM OVERVIEW

The goal of this CME program is to enhance healthcare practitioner awareness of the burden of postpartum depression, as well as the need for novel mechanism in the management of postpartum depression; clinical data concerning therapeutic agents for postpartum depression targeting GABA-A receptors; as well as evolving management approaches in postpartum depression, including best practices for integration in current treatment paradigms.

TARGET AUDIENCE

This activity is designed to meet the educational needs of US-based obstetrician-gynecologists, community-based practitioners, nurse practitioners, midwives, and psychiatrists concerning the identification and management of postpartum depression.

LEARNING OBJECTIVES

Upon the completion of this program, attendees should be able to:

- Evaluate the burdens of postpartum depression in consideration of gaps in management and opportunities to address gaps through novel mechanisms
- Summarize the clinical efficacy and safety data informing the use of extrasynaptic GABA-A receptor allosteric modulators in the management of postpartum depression
- Describe best practices and practical considerations in integrating GABA-A receptor allosteric modulators for the management of postpartum depression

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Agenda

The Burden of Postpartum Depression

- Maternal mortality rate
- Effects of PPD on the mother and infant
- Video: PPD background and the role of GABA

Identifying Postpartum Depression

- Definition of PPD
- Criteria for a major depressive episode
- Screening tools

Conventional Treatments for PPD

- Treatment for PPD/MDD: background
- Limitations of anti-depressants
- Adverse effects

Pathophysiology of Stress, Depression and Postpartum Depression

- Allopregnanolone: variations across pregnancy and the postpartum period
- Neurosteroids and PPD
- Introduction to the role of GABA

Interpreting Current Clinical Data With GABA-A Receptor Allosteric Modulators

- Video: the role of GABA in PPD

- The GABAergic hypothesis of depression
    - GABA and the stress response
    - Role of neuroactive steroids on stress in PPD/MDD
    - GABA-A receptors
    - NAS binding sites on GABA-A receptors

- Positive GABA allosteric modulators for PPD
    - Brexanolone
    - Zuranolone
    - How are NAS GABA-A PAMs different?
    - Practical considerations for use

Patient case

Conclusions and Q/A

Clinical Updates in PPD Management

Integrating Novel Therapeutics

Targeting GABA-A Receptors in Practice

Anita H. Clayton, MD
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Pre-Test Question 1

Which of the following is one of the criteria for defining postpartum depression?

1. Symptoms meet criteria for a major depressive episode
2. Onset of symptoms must be post-delivery
3. Symptoms must begin within one week of delivery
4. Symptoms must include change in weight, change in sleep, and decreased energy

Pre-Test Question 2

Brenda is a 34-year-old woman who gave birth to a baby girl 2 weeks ago. She reports to you with depressed mood, low energy, inability to concentrate, insomnia, and increased agitation. After further evaluation you diagnose her with postpartum depression, and she asks about what to expect if she starts a selective serotonin reuptake inhibitor (SSRI). What do you tell her?

1. If started she should see noticeable differences within 2 to 3 days.
2. They are a good starting point, but inadequate response or lack of efficacy may warrant a medication change.
3. She will likely see improvement in function and quality of life before symptomatic relief.
4. She likely won't experience any side effects, as <10% of patients experience 1 or more.

Pre-Test Question 3

After delivery hormones rapidly return to pre-pregnancy levels, but _____ receptors may take time to recover in women susceptible to postpartum depression

1. Histaminergic
2. Cholinergic
3. GABAergic
4. Dopaminergic

Pre-Test Question 4

A 28-year-old woman experiences depression midway through her third trimester and is placed on a monoamine oral antidepressant, with inadequate response over the next several weeks. This is her first episode of PPD, and she does not have a history of significant recurrent major depression. A week after delivery she is still experiencing moderate depression. Which of the following GABA-A targeting agents would be a good choice at this time?

1. Zuranolone
2. Brexanolone
3. Tranexamic acid
4. Flumazenil

Pre-Test Question 5

Compared to conventional antidepressants, positive GABA allosteric modulators for PPD (brexanolone and zuranolone) are associated with which of the following?

1. Shorter duration of effect
2. Faster onset of efficacy
3. Longer course of active treatment

Learning Objectives

Upon completion of this activity, participants will be able to:

- Evaluate the burdens of postpartum depression (PPD), identify gaps in management of PPD, and explore opportunities to address gaps through novel mechanisms
- Summarize the clinical efficacy and safety data informing the use of extrasynaptic GABA-A receptor allosteric modulators in the management of PPD
- Describe best practices and practical considerations in integrating GABA-A receptor allosteric modulators for the management of PPD

Symposium Outline

- Burden of Postpartum Depression
- Conventional Treatments and Opportunities for Improvement
- Pathophysiological Basis for Neurosteroid Involvement in Stress and Postpartum Depression
- Novel Mechanism of Action of Positive Allosteric Modulators of the GABA-A Receptor
- Brexanolone Clinical Data
- Zuranolone Clinical Data
- Practical Considerations
- Case Discussion

The Burden of Postpartum Depression

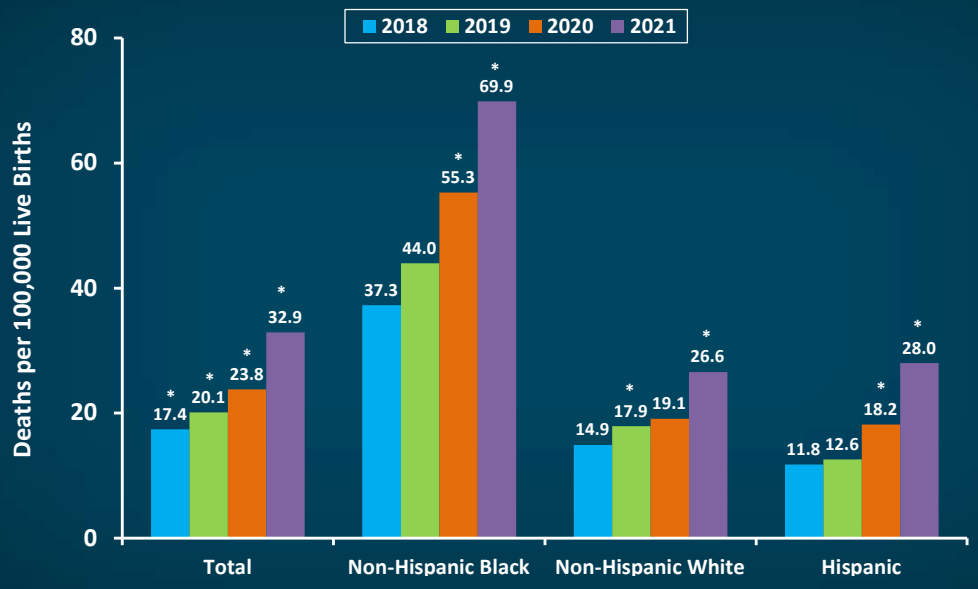
Jennifer L. Payne, MD

US Maternal Mortality Rate

Maternal deaths per 100,000 live births in select countries for 2018

Roper W. Stista.com. High U.S. Maternal Mortality Rate. November 19, 2020. Accessed March 29, 2024. https://www.statista.com/chart/23541/maternal-mortality-developed-countries/

US Maternal Mortality Rate is Increasing



*Statistically significant increase from previous year ($P < .05$)
NOTE: Race groups are single race.

Hoyert DL. Maternal mortality rates in the United States, 2021. NCHS Health E-Stats. MARCH 16, 2023. Accessed April 1, 2024. https://stacks.cdc.gov/view/cdc/124678

Audience Response Question

Which of the following is the leading cause of maternal mortality?

1. Hemorrhage
2. Cardiac/coronary conditions
3. Mental health conditions
4. Hypertensive disorders of pregnancy

Mental Health Conditions: Leading Cause of Maternal Mortality*

Condition	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

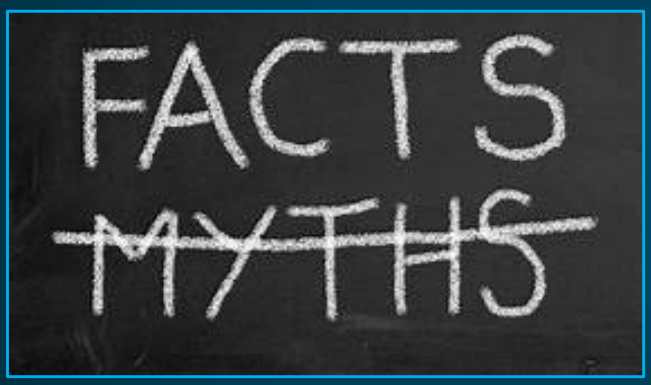
*Data includes 1,018 pregnancy-related deaths among residents of 36 states from 2017-2019 provided to Maternal Mortality Review Committee. Table includes underlying causes of pregnancy-related deaths overall and by race-ethnicity.

Trost S, et al. CDC, US Dept of Health and Human Services. Available at: https://www.cdc.gov/reproductivehealth/maternal-mortality/erase-mm/data-mmrc.html. Wisner KL, et al. *JAMA Psychiatry*. Published online February 21, 2024. doi:10.1001/jamapsychiatry.2023.5648.

Maternal Suicide

- Major cause of maternal death in pregnancy
- Accounts for up to 20% of all postpartum deaths
- In general, psychiatric disorders are the leading cause of indirect maternal deaths
- Overall, though, suicide is a rare event during pregnancy and is lower than the rate in the general population

Chin K, et al. *Curr Psychiatry Rep*. 2022;24:239-275. doi:10.1007/s11920-022-01334-3



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

Adverse Pregnancy Outcomes Associated with Antenatal Depression

- Preterm birth
- Low birth weight
- Gestational diabetes
- Pre-eclampsia
- C-section

Postpartum Depression: Effects on the Infant

- Postpartum Depression is the most common complication of having a baby
- Depression during pregnancy increases the risk of Postpartum Depression
  - PPD is associated with the following in exposed children:
    - Lower IQ
    - Slower language development
    - ADHD
    - Behavioral problems
    - Psychiatric illness

Maternal depression and child development. *Paediatr Child Health*. 2004;9:575-598. doi:10.1093/pch/9.8.575

(Postpartum) Depressed Moms are…

- More likely to smoke, use substances
- More likely to use ER for health care
- Less likely to talk to their babies
- Less likely to give their kids vitamins
- Less likely to put their kids in car seats
- Less likely to get their kids vaccinated or go to checkups

Slomian J, et al. *Womens Health (Lond).* 2019;15:1745506519844044. doi:10.1177/1745506519844044

Economic Costs of Perinatal Mood and Anxiety Disorders

Am J Public Health. 2020 June; 110(6): 888–896. PMCID: PMC7204436
Published online 2020 June. doi: 10.2105/AJPH.2020.305619 PMID: 32298167

Financial Toll of Untreated Perinatal Mood and Anxiety Disorders Among 2017 Births in the United States

Dara Lee Luca, PhD, Caroline Margiotta, MA, Colleen Staatz, MPH, Eleanor Garlow, BA, Anna Christensen, PhD, and Kara Zivin, PhD, MS, MA✉

$14 Billion Dollars in the US in 2017!

How do We Identify Postpartum Depression?

Audience Response Question

Which of the following is one of the criteria for defining postpartum depression?

1. Symptoms meet criteria for a major depressive episode
2. Onset of symptoms must be post-delivery
3. Symptoms must begin within one week of delivery
4. Symptoms must include change in weight, change in sleep, and decreased energy

Postpartum Depression Definition

- Symptoms meet criteria for a Major Depressive Episode
- May start during pregnancy and continue postpartum
- DSM-IV criteria: Symptoms begin within ONE month of delivery
- DSM-5: Now uses “Peripartum”

Mughal S, et al. *StatPearls*. StatPearls Publishing; January 2024. https://www.ncbi.nlm.nih.gov/books/NBK519070/

Criteria for a Major Depressive Episode

5 of 9 depression symptoms:

≥5 symptoms during the same two-week period that are a 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

Additional required criteria:

Must have all 4, plus ≥5 depressive symptoms at left

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

* One of these 2 symptoms is required – DSM-5

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Accessed April 1, 2024. https://dsm.psychiatryonline.org/doi/epdf/10.1176/appi.books.9780890425596

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

OCD = obsessive compulsive disorder

American College of Obstetricians and Gynecologists. Patient Screening. Accessed April 1, 2024. https://www.acog.org/programs/perinatal-mental-health/patient-screening

EPDS- Specific to Pregnant and Postpartum Women

Past 7 Days …

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

Score of >10
90% Sensitive

Score of ≥13 strongly correlates with meeting criteria for a MDE

Q#10 asks about self-harm

Cox JL, et al. *Br J Psychiatry*. 1987;150:782-786. doi:10.1192/bjp.150.6.782

PHQ-9 for MDD

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✓" to indicate your answer)*	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

FOR OFFICE CODING 0 + _____ + _____ + _____
=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all ☐ | Somewhat difficult ☐ | Very difficult ☐ | Extremely difficult ☐

- Review period is over the past 2 weeks
- 9 items, including self-harm/suicidal thoughts; Item 10 rates difficulty associated with symptoms
- Responses
  - 0: Not at all
  - 1: Several days
  - 2: More than half the days
  - 3: Nearly every day
- Interpretation of total score
  - 1 to 4: Minimal depression
  - 5 to 9: Mild depression
  - 10 to 14: Moderate depression
  - 15 to 19: Moderately severe depression
  - 20 to 27: Severe depression

Kroenke K, et al. *J Gen Intern Med*. 2001;16:606-613. doi: 10.1046/j.1525-1497.2001.016009606.x

MDQ for Bipolar Disorder

Mood Disorder Questionnaire (MDQ)

Name: _____ Date: _____

Instructions: Check [✓] the answer that best applies to you. Please answer each question as best you can.

	Yes	No
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? *Please check 1 response only.*	○	○
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? *Please check 1 response only.* ○ 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?	○	○

Adapted from: Hirschfeld R, et al. *Am J Psychiatry*. 2000;157:1873-1875. doi: 10.1176/appi.ajp.157.11.1873
Isometsä E, et al. *BMC Psychiatry*. 2003;3:8. doi: 10.1186/1471-244X-3-8
Wang HR, et al. *Depress Anxiety*. 2015;32:527-538. doi: 10.1002/da.22374
https://www.ohsu.edu/sites/default/files/2019-06/cms-quality-bipolar_disorder_mdq_screener.pdf
Accessed April 1, 2024.

MDQ for Bipolar Disorder

- 5 items: #1 lists 13 manic symptoms; Items #2 through #5 address symptom overlap, level of problems caused, family history, and prior diagnosis
- Responses
  - Yes/No
- Positive screen
  - Yes to ≥7 of the 13 items in #1, and
  - Yes to #2, and
  - Moderate or serious to #3
- Next step is comprehensive evaluation for bipolar spectrum disorder

Hirschfeld RM, et al. *Am J Psychiatry*. 2000;157:1873-1875. doi: 10.1176/appi.ajp.157.11.1873

Conventional Treatments for PPD

Room for Improvement?

Treatment for Postpartum Depression = Treatment for Major Depression

These Include:

- Psychotherapy (Cognitive Behavioral Therapy, Interpersonal Therapy)
- Antidepressant Medications (Selective Serotonin Reuptake Inhibitors)
- Phototherapy
- Transcranial Magnetic Stimulation, Electroconvulsive Therapy (Treatment Resistant Depression only)

Mayo Clinic. Postpartum depression. Accessed April 1, 2024. https://www.mayoclinic.org/diseases-conditions/postpartum-depression/diagnosis-treatment/drc-20376623

Treatment for Postpartum Depression

- In the patient has had a previous major depressive episode successfully treated with a particular antidepressant - use THAT antidepressant
- If no previous history start with selective serotonin reuptake inhibitors (SSRI)
- If the patient has tried and failed several different antidepressants AT AN ADEQUATE DOSE, use a different class of antidepressants
- An adequate trial is defined as: 8 weeks at a therapeutic dosage (ATRQ uses at least 6 weeks)
- Recommend psychotherapy if at all possible

ATRQ = Antidepressant Treatment Response Questionnaire

Fitelson E, et al. *Int J Womens Health*. 2010;3:1-14. doi:10.2147/IJWH.S6938

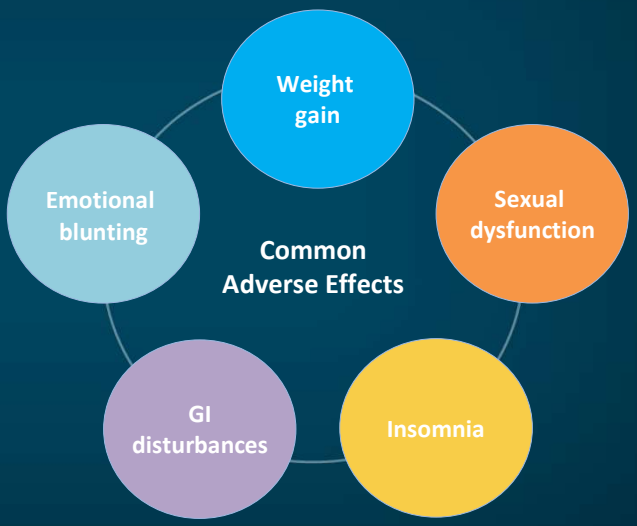
Limitations With Current Standard-of-Care Antidepressant Therapies

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 Major Depression
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. doi:10.1177/20451253211065859

Current Antidepressants: Distinct Tolerability Profiles

Side effects are greatest with SSRIs > SNRIs > Atypical antidepressants



GI, gastrointestinal; SOC, standard of care

Solmi M, et al. *Braz J Psychiatry*. 2021;43:189-202 doi: 10.1590/1516-4446-2020-0935; Ferguson JM. *Prim Care Companion J Clin Psychiatry*. 2001;3:22-27. doi:10.4088/pcc.v03n0105
Cartwright C, et al. *Patient Prefer Adherence*. 2016;10:1401-1407 doi:10.2147/PPA.S110632

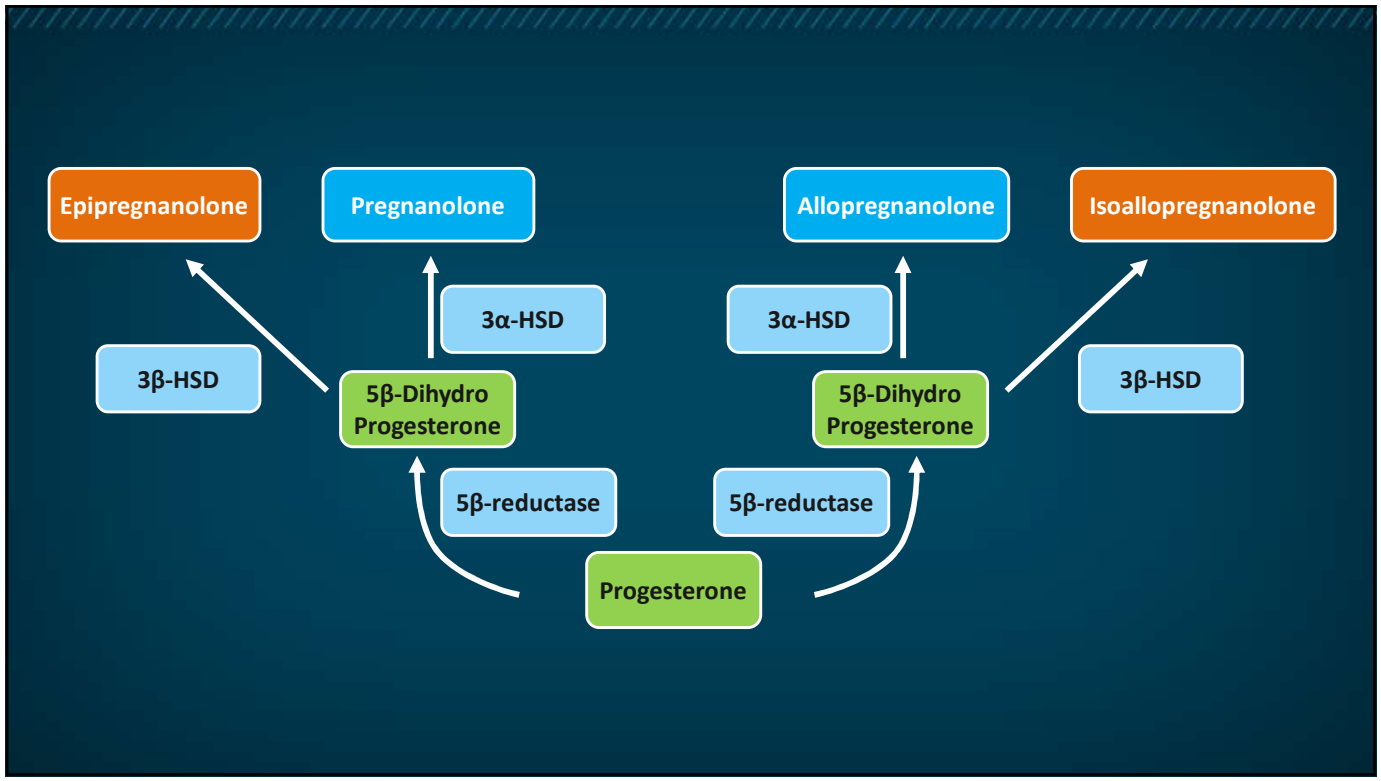
Monoamine Hypothesis of Depression-Limitations

- All antidepressants increase one or more monoamines in the brain
- But to date not all depressed patients respond to antidepressants
- Around 50% respond to the first antidepressant they take and fewer and fewer respond to the next series of trials
- Antidepressants increase monoamines immediately in the brain yet patients take weeks to respond.
- So the monoamine hypothesis does not completely fit the clinical picture….

Massart R, et al. *Philos Trans R Soc Lond B Biol Sci*. 2012;367:2485-2494. doi:10.1098/rstb.2012.0212

Pathophysiology of Stress, Depression and Postpartum Depression

The Role of the GABAergic System



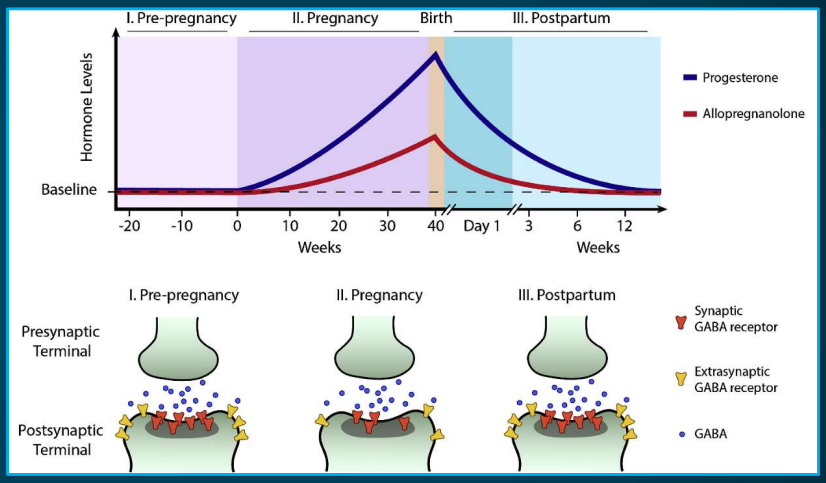
Audience Response Question

Postpartum depression appears to be related to sensitivity to a rapid _____ of estrogen, progesterone, and allopregnanolone in the first few days after delivery.

1. Spike
2. Drop

Allopregnanolone Variations Across Pregnancy and Postpartum Period

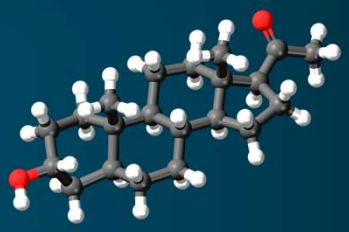
- PPD appears to be related to sensitivity to the normal rapid drop (in first 3 days after delivery) from extremely high levels of estrogen, progesterone and its metabolite, allopregnanolone during pregnancy to pre-pregnancy levels
- Often associated with prior history of reproductive-related mood disorders (eg, PMDD)



Meltzer-Brody. *Neurobiol Stress*. 2020;12:100212. doi:10.1016/j.ynstr.2020.100212

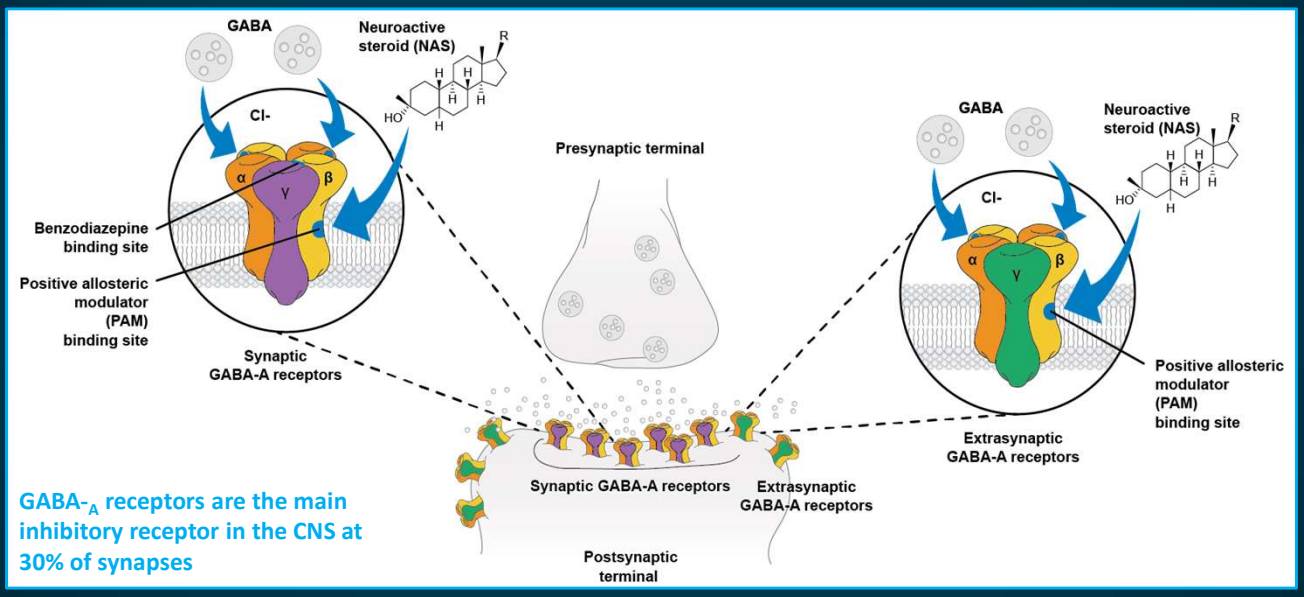
Neurosteroids and Postpartum Depression

- Progesterone and allopregnanolone rise steadily through pregnancy before a sudden drop in the postpartum
- Neurosteroids are potent modulators of the GABA-A receptor
- The rising levels of allopregnanolone in pregnancy are thought to down-regulate GABA-A receptors in the brain and change what subunits of the receptor are prominent
- After delivery, hormones rapidly return to pre-pregnancy levels, but GABA-A receptors may take time to recover in women susceptible to postpartum depression



Wang M. *Front Endocrinol (Lausanne)*. 2011;2:44. doi:10.3389/fendo.2011.00044; Pinna G, et al. *Front Glob Womens Health*. 2022;3:823616. doi:10.3389/fgwh.2022.823616

Neuroactive Steroid Binding Sites on GABA-A Receptor



GABA-$_A$ receptors are the main inhibitory receptor in the CNS at 30% of synapses

Jacob TC, et al. *Nat Rev Neurosci*. 2008;9:331-343. doi:10.1038/nrn2370; Reddy DS, Estes WA. *Trends Pharmacol Sci*. 2016;37:543-561. doi:10.1016/j.tips.2016.04.003

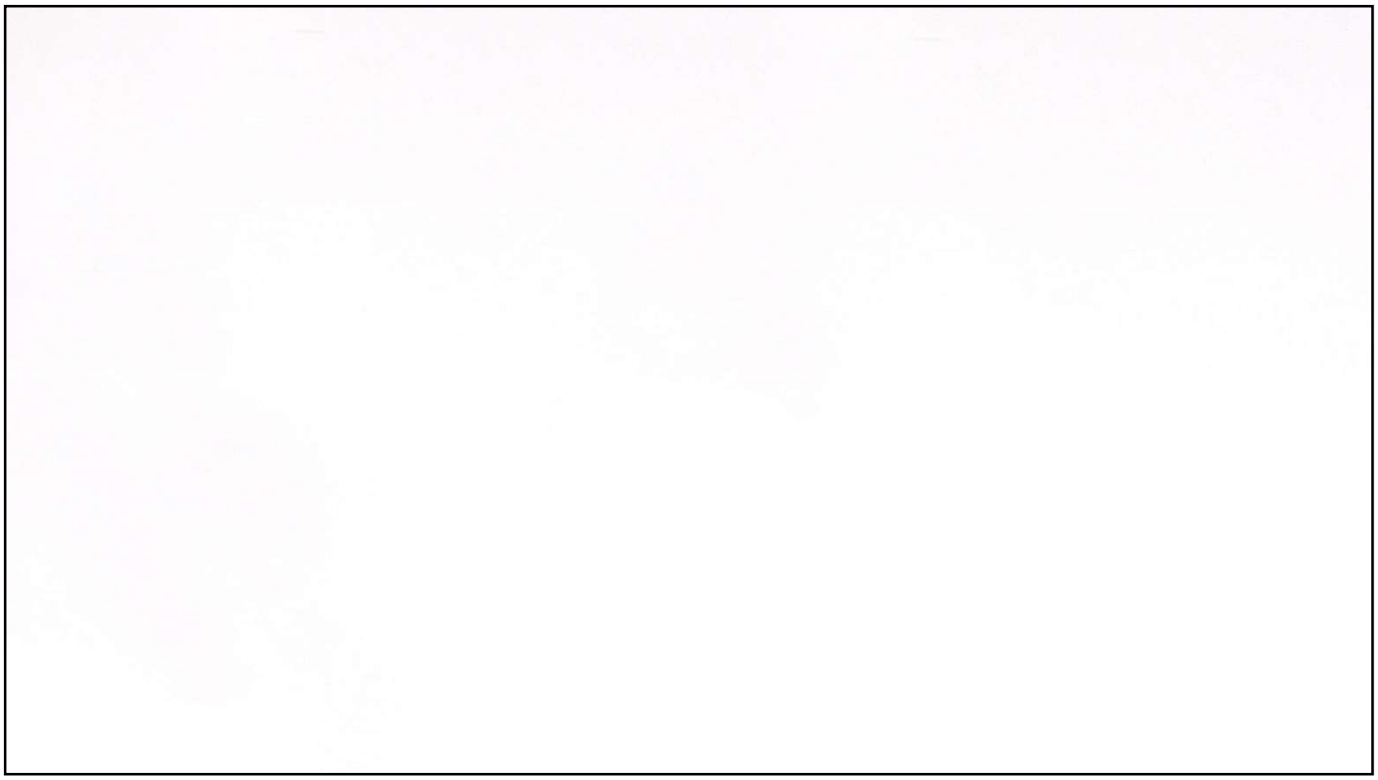
Postpartum Depression — A Biologically Vulnerable Period for the GABAergic System

- Stress also plays a role in PPD and can result in changes in allopregnanolone levels and in the GABA-A receptor.
- Pregnancy is accompanied by significant changes in gonadal steroid and NAS levels that then precipitously decrease with delivery. Thus, levels of allopregnanolone are dramatically lower postpartum compared to pregnancy.
- Women who develop PPD may have specific vulnerabilities in the GABAergic system (lower levels of Allopregnanolone in the 2nd trimester, GABA receptor subunit differences) that make them particularly vulnerable to developing depression in the perinatal period.
- We can think of PPD as a special case of vulnerability in the GABAergic system that gets triggered likely due to the stress surrounding becoming a parent and the hormonal changes that occur during pregnancy and delivery that expose vulnerabilities in the GABAergic system.

Feng YF, et al. *Mol Neurobiol*. 2024;61:385-396. doi:10.1007/s12035-023-03574-7; Wang M. *Front Endocrinol (Lausanne)*. 2011;2:44. doi:10.3389/fendo.2011.00044;
Pinna G, et al. *Front Glob Womens Health*. 2022;3:823616. doi:10.3389/fgwh.2022.823616

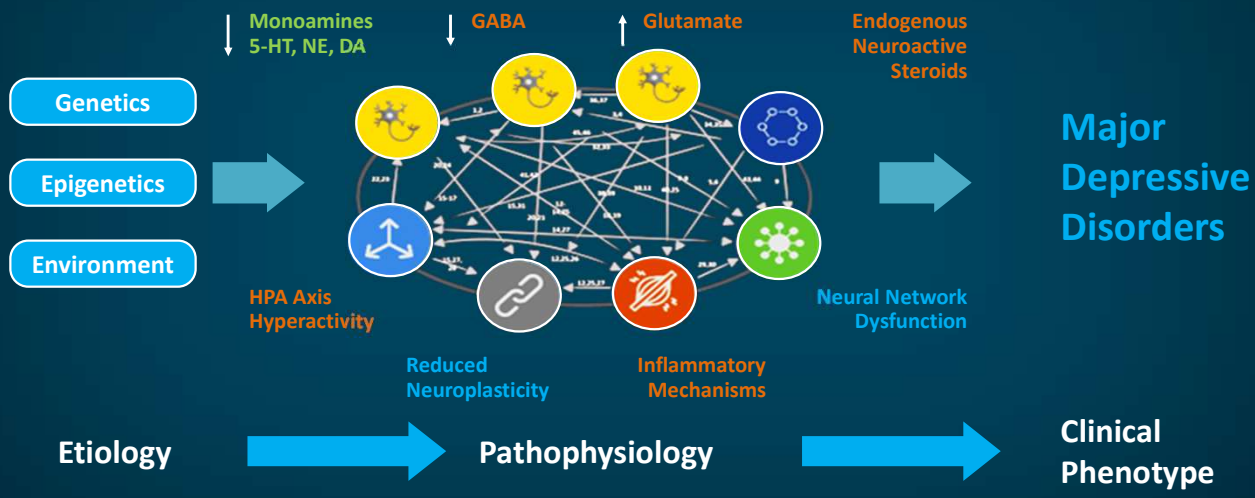
Interpreting Current Clinical Data with GABA-A Receptor Allosteric Modulators in Postpartum Depression

Anita H. Clayton, MD



United Theory of Depression

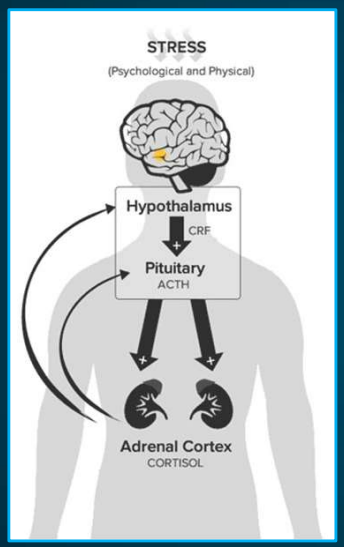
Synaptic Dysfunction Mechanisms



5-HT = serotonin; DA = dopamine; GABA = gamma-aminobutyric acid; HPA = hypothalamic-pituitary-adrenal; NE = norepinephrine

Adapted from: Dean J, Keshavan M. *Asian J Psychiatr*. 2017;27:101-111. doi:10.1016/j.ajp.2017.01.025

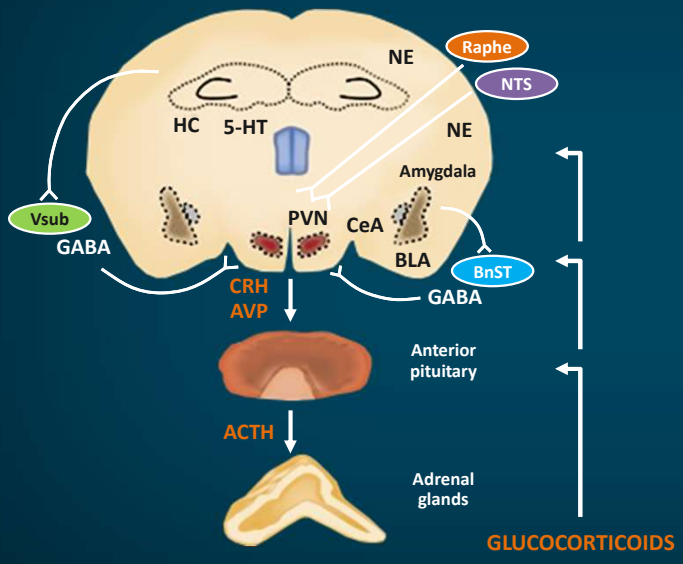
The GABAergic Hypothesis of Depression

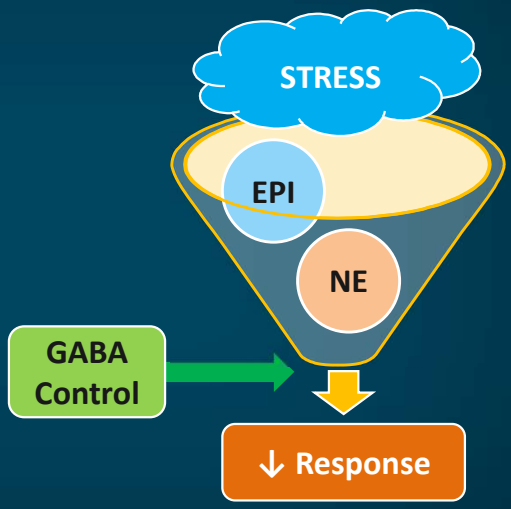


- Idea is that depressive disorders are actually stress disorders
- GABA is the major inhibitory neurotransmitter in the brain
- GABA mediates the effects of stress on the brain
- GABA balances and fine-tunes excitatory neurotransmission of various neuronal systems including the monoaminergic and cholinergic projections to the forebrain
- Accumulating evidence in both humans and animal models implicates alterations in the GABAergic system, including at the GABA receptor level, underlying depression and anxiety disorders

Luscher B, et al. *Mol Psychiatry*. 2011;16:383-406. doi:10.1038/mp.2010.120.

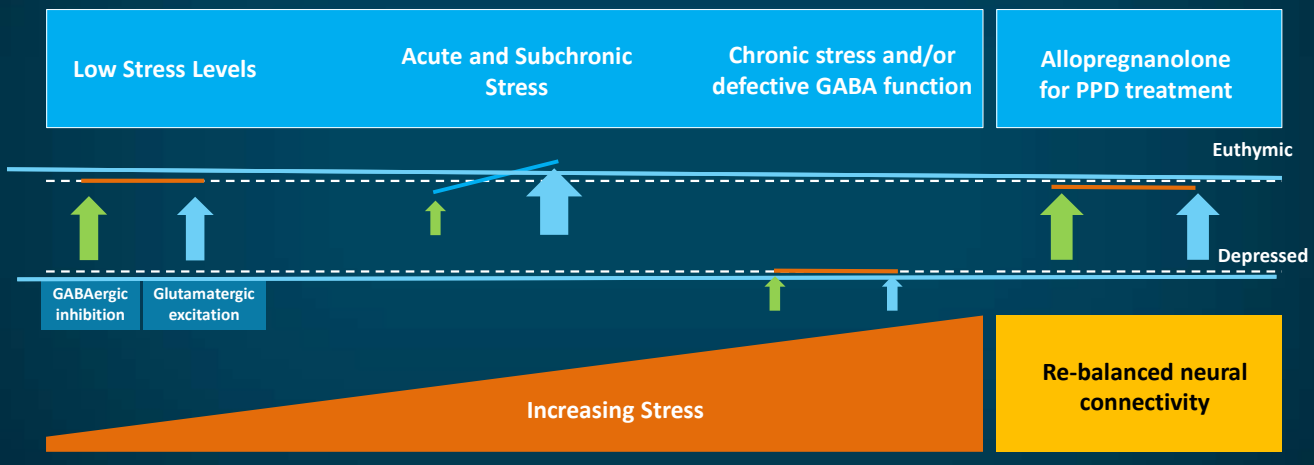
GABAergic System Controls the Stress Response





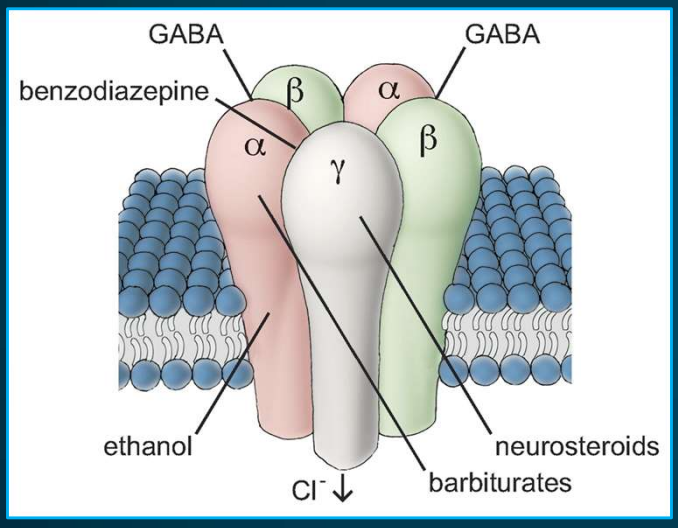
Arnett MG, et al. *Neuropsychopharmacology*. 2016;41:245-260. doi:10.1038/npp.2015.215

Potential Role of Neuroactive Steroids on Stress and HPA Hyperactivity in PPD/MDD



Meltzer-Brody S, Kanes SJ. *Neurobiol Stress*. 2020;12:100212. doi:10.1016/j.ynstr.2020.100212; Edinoff AN, et al. *Front Psychiatry*. 2021;12:699740. doi:10.3389/fpsyt.2021.699740; Antonoudiou P, et al. *Biol Psychiatry*. 2022;91:283-293. doi:10.1016/j.biopsych.2021.07.017

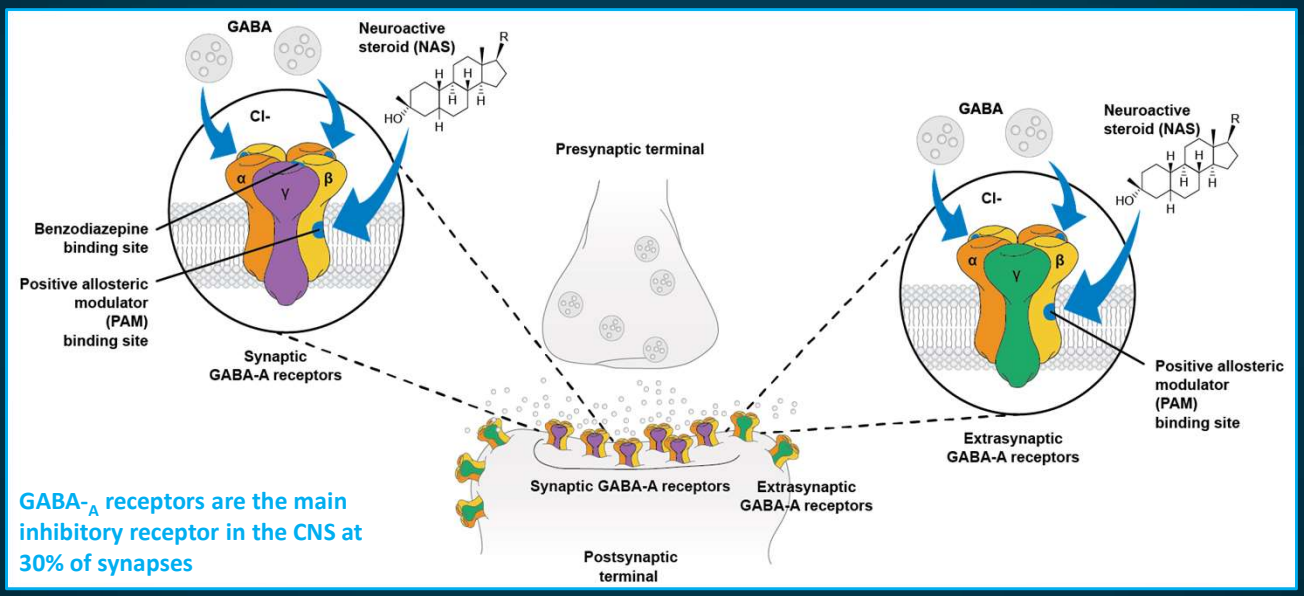
GABA-A Receptors



- Cl-ionophore complex composed of five subunits, most commonly two α's, two β's and one γ (α2β2γ)
- Ligand gated (ex. benzodiazepines, ETOH, neurosteroids)
- Ligand binding increases affinity for GABA neurotransmitter
- GABA is inhibitory, leading to sedation, calmness, anti-seizure
- Neurosteroids have their own binding site and modulate the activity of the GABA receptor

Chen X, et al. *Acta Pharmacol Sin*. 2019;40:571-582. doi:10.1038/s41401-018-0185-5

Neuroactive Steroid Binding Sites on GABA-A Receptor



GABA-$_A$ receptors are the main inhibitory receptor in the CNS at 30% of synapses

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Neuroactive Steroid Therapy: Positive GABA Allosteric Modulators for PPD

Shift in treatment paradigm:

- Short course of active treatment
- Rapid onset of efficacy
- Long duration of effect

	Brexanolone	Zuranolone
Molecule	Natural allopregnanolone formulated for solubility	Synthetic allopregnanolone analogue (added cyanopyrazole ring)
FDA Approval for PPD	2019	2023
Administration	Continuous IV infusion over 60 h (2.5 days) followed by12 hrs observation	Once daily (PM) oral x 14 days
Monitoring and supervision	Admission for HCP monitoring with pulse oximetry every 2 hrs during infusion; another caregiver must accompany patient if child is present	May be used at home
May use other antidepressants concurrently?	Yes; may increase risk of AE of sedation	Yes
Boxed Warning	Excessive sedation and sudden loss of consciousness	Concern for ability to drive <12 hrs after dose (mitigated with bedtime dosing)
REMS	Yes	No

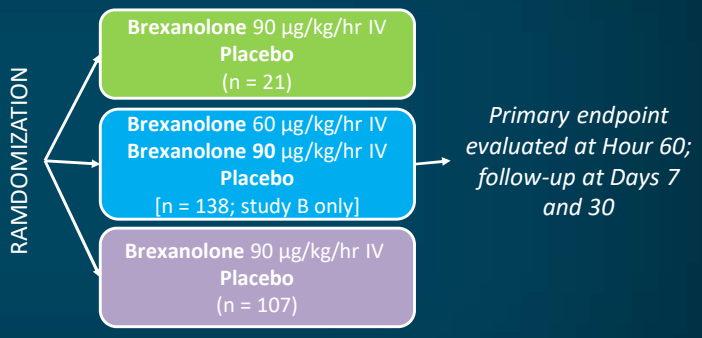
Reddy DS, et al. *Psychopharmacology*. 2023;240:1841-1863. doi:10.1007/s00213-023-06427-2; Althaus AL, et al. *Neuropharmacology*. 2020;181:108333. doi:10.1016/j.neuropharm.2020.108333;
Zulresso® (brexanolone). Prescribing information. Sage Therapeutics, Inc; 2022. https://assets.sagerx.com/zulresso/prescribing-information.pdf;
Zurzuvae™ (zuranolone). Prescribing information. Sage Therapeutics, Inc; 2023. https://documents.sage-biogen.com/us/zurzuvae/pi.pdf

3 Placebo-Controlled RCTs of IV Brexanolone in PPD

Women aged 18-45 yrs with MDE beginning between start of 3rd trimester and 4 wks postpartum; ≤6 mo postpartum at screening

- Study A (Phase II):
  HAMD-17 ≥26 (severe PPD); N = 21
- Study B (Phase III):
  HAMD-17 ≥26 (severe PPD); N = 138
- Study C (Phase III):
  HAMD-17 = 20-25 (moderate PPD); N = 108

Dose titrated from 30 µg/kg/hr x 1st 4 hrs to target dose and titrated down to 30 µg/kg/hr for last 4 hrs in 60 hr continuous infusion



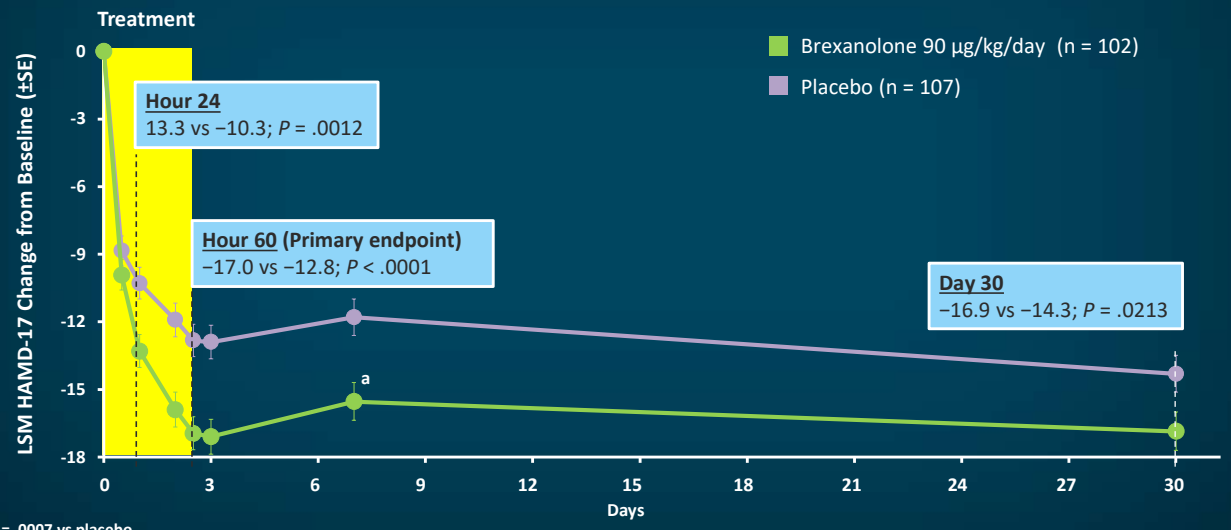
Primary endpoint: LSM change from baseline in HAMD-17 total score at Hour 60

Key secondary endpoint: LSM change from baseline in HAMD-17 total score at all other time points

Umbrella protocol allowed preplanned integrated study dataset analysis, efficacy of 90 µg/kg/hr dose, and safety of all doses

Meltzer-Brody S, et al. *Lancet*. 2018;392:1058-1070. doi:10.1016/S0140-6736(18)31551-4; Kanes S, et al. *Lancet*. 2017;390:480-489. doi:10.1016/S0140-6736(17)31264-3;
Zulresso® (brexanolone). Prescribing information. Sage Therapeutics, Inc; 2022. https://assets.sagerx.com/zulresso/prescribing-information.pdf

HAMD-17 Change From Baseline in Integrated Phase 3 Population at Brexanolone Recommended Dose



[a] *P* = .0007 vs placebo.

Meltzer-Brody S, et al. *Lancet*. 2018;392:1058-1070. doi:10.1016/S0140-6736(18)31551-4

AEs Across All Placebo-Controlled RCTs of Brexanolone

AEs in ≥2% of Patients and >Placebo, %	Brexanolone 90 µg/kg/hr (n = 102)	Brexanolone 60 µg/kg/hr (n = 38)	Placebo (n = 107)
Cardiac disorders			
• Tachycardia	3	—	—
Gastrointestinal disorders			
• Diarrhea	2	3	1
• Dry mouth	3	11	1
• Dyspepsia	2	—	—
• Oropharyngeal pain	2	3	—
Nervous system disorders			
• Dizziness, presyncope, vertigo	12	13	7
• Loss of consciousness	3	5	—
• Sedation, somnolence	13	21	6
Vascular disorders			
• Flushing, hot flush	2	5	—

Boxed Warning:
Excessive Sedation and Sudden Loss of Consciousness

- Brexanolone caused sedation and somnolence requiring dose interruption or reduction in 5% of patients compared with 0% for placebo
- Loss of or altered state of consciousness during brexanolone infusion occurred in 4% of patients compared with 0% for placebo
- All patients with loss of or altered state of consciousness recovered with dose interruption; fully recovered within 15-60 min
- Brexanolone can only be prescribed at certified facilities through a **Risk Evaluation and Mitigation Strategy (REMS)** safety program including monitoring for 12 hours after end of infusion

Zulresso® (brexanolone). Prescribing information. Sage Therapeutics, Inc; 2022. https://assets.sagerx.com/zulresso/prescribing-information.pdf

Safety and Side Effects

Treatment-emergent Adverse Events

	Study 1			Study 2	
	Placebo (n=43)	BRX60 (n=38)	BRX90 (n=41)	Placebo (n=53)	BRX90 (n=51)
Overall					
Any adverse event	22 (51%)	19 (50%)	22 (54%)	24 (45%)	25 (49%)
Severe adverse event	0	1 (3%)	0	1(2%)	2 (4%)
Serious adverse event	0	1 (3%)	0	0	1 (2%)
Adverse event leading to discontinuation of study treatment	1 (2%)	1 (3%)	0	0	2 (4%)
Deaths	0	0	0	0	0
Adverse events in three or more patients					
Headache	7 (16%)	7 (18%)	6 (15%)	6 (11%)	9 (18%)
Dizziness	1 (2%)	6 (16%)	6 (15%)	4 (8%)	5 (10%)
Somnolence	3 (7%)	7 (18%)	2 (5%)	2 (4%)	4 (8%)
Infusion site pain	1 (2%)	1 (3%)	4 (10%)	2 (4%)	5 (10%)
Nausea	3 (7%)	1 (3%)	0	2 (4%)	5 (10%)
Dry mouth	0	4 (11%)	0	1(2%)	2 (4%)
Fatigue	0	1 (3%)	1 (2%)	2 (4%)	3 (6%)

Data are n (%). Treatment-emergent adverse events were defined as an adverse event with onset after the start of study drug, or any worsening of a pre-existing medical condition or adverse event with onset after the start of study drug. Treatment-emergent adverse events were coded according to the Medical Dictionary for Regulatory Activities version 19.1 or later. BRX60=brexanolone injection 60 jug/kg per h. BRX90=brexanolone injection 90 g/kg per h.
Meltzer-Brody S, et al. *Lancet*. 2018;392:1058-1070. doi:10.1016/S0140-6736(18)31551-4

Safety and Tolerability

- Brexanolone is generally well-tolerated.
- Most frequent adverse events in trials: headache, dizziness, somnolence.
- Package insert cites most frequent adverse events: sleepiness, dry mouth, passing out and flushing of the skin or face.
- Approximately 5% of participants who received brexanolone had excessive sedation, including loss of consciousness, which was relieved by stopping the infusion immediately. May be restarted at lower dose.
- Participation in a Risk Evaluation and Mitigation Strategy (REMS) program is required.
- Label has a boxed warning for “Excessive Sedation and Sudden Loss of Consciousness.”
- Brexanolone is classified as a Class IV controlled substance.

Zulresso® (brexanolone). Prescribing information. Sage Therapeutics, Inc; 2022. https://assets.sagerx.com/zulresso/prescribing-information.pdf

Issues to Overcome for Use on Psychiatry Unit

- Administration of brexanolone requires constant pulse-ox monitoring with immediate nursing response (not standard on psychiatry units) and for 12 hours after infusion ends
- Assessments include using the Richmond Agitation and Sedation Scale (RASS) for excessive sedation every 2 hours during waking hours and every 4 during sleeping hours. This requires increased nursing staffing

ROBIN: Phase III Placebo-Controlled RCT of Zuranolone 30 mg in PPD

Women aged 18-45 yr with MDE beginning between start of third trimester and 4 weeks postpartum; ≤6 months postpartum at screening; HAMD-17 ≥26 (severe PPD); could continue stable dose of antidepressant
(N = 153)

RAMDOMIZATION

Zuranolone 30 mg PO x 14 days
Evening dose with food
(n = 77)

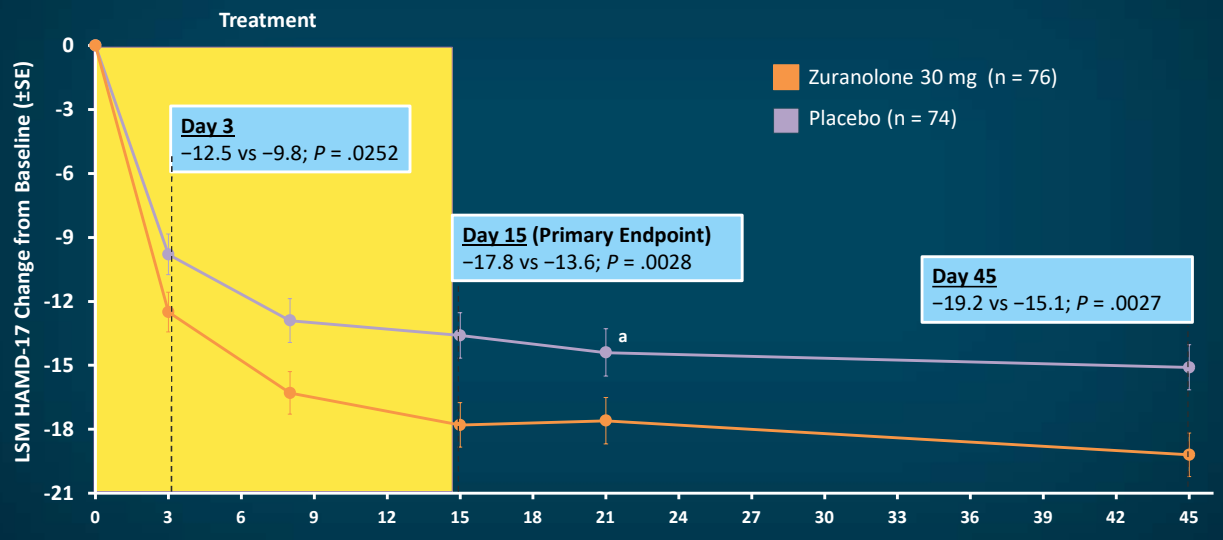
Placebo 14 days
Evening dose with food
(n = 76)

Primary endpoint evaluated at Day 15; follow-up through Day 45

- Primary endpoint: Least Squares Mean (LSM) change from baseline in HAMD-17 total score at Day 15
- Key secondary endpoint: LSM change from baseline in HAMD-17 total score at all other time points

Deligiannidis KM, eat al. *JAMA Psychiatry*. 2021;78:951-959. doi:10.1001/jamapsychiatry.2021.1559

ROBIN: HAMD-17 Change From Baseline with Zuranolone 30 mg



[a] Day 21 : *P* = .0321 vs placebo.

Deligiannidis KM, eat al. *JAMA Psychiatry*. 2021;78:951-959. doi:10.1001/jamapsychiatry.2021.1559

ROBIN: AEs with Zuranolone 30 mg in PPD

TEAE, n (%)	Zuranolone 30 mg (n = 78)	Placebo (n = 73)
Any AE	47 (60.3)	38 (52.1)
Severe AE	3 (3.8)	3 (4.1)
Serious AE	1 (1.3)	1 (1.4)
AE-drug discontinuation	1 (1.3)	0
Deaths	0	0
Most common TEAEs, ≥5% patients, n (%)		
Somnolence	12 (15.4)	8 (11)
Headache*	7 (9.0)	9 (12.3)
Dizziness	6 (7.7)	4 (5.5)
Upper respiratory tract infection	6 (7.7)	1 (1.4)
Diarrhea	5 (6.4)	2 (2.7)
Sedation	4 (5.1)	0
Nausea	3 (3.8)	6 (8.2)
Vomiting*	1 (1.3)	4 (5.5)
Abnormal dreams*	0	4 (5.5)
Hyperhidrosis*	0	4 (5.5)

* Greater in placebo vs zuranolone

- A similar proportion of patients reported TEAEs with zuranolone and placebo
- ~20% of subjects remained on oral ADs
- Somnolence, headache, dizziness, upper respiratory tract infection, diarrhea, and sedation were the most common AEs (≥5%) in the zuranolone group
- No episodes of loss of consciousness
- No signal for increased suicidal ideation or suicidal behavior compared with baseline, as measured by the Columbia-Suicide Severity Rating Scale

Deligiannidis KM, eat al. *JAMA Psychiatry*. 2021;78:951-959. doi:10.1001/jamapsychiatry.2021.1559

SKYLARK: Phase III Placebo-Controlled RCT of Zuranolone 50 mg in PPD

Women aged 18-45 yrs with MDE beginning between start of 3rd trimester and 4 wks postpartum; ≤12 mo postpartum at Day 1; HAMD-17 ≥26 (severe PPD); may continue stable dose of antidepressant
(N = 196)

RAMDOMIZATION

Zuranolone 50 mg PO x 14 days
Evening dose with food
(n = 98)

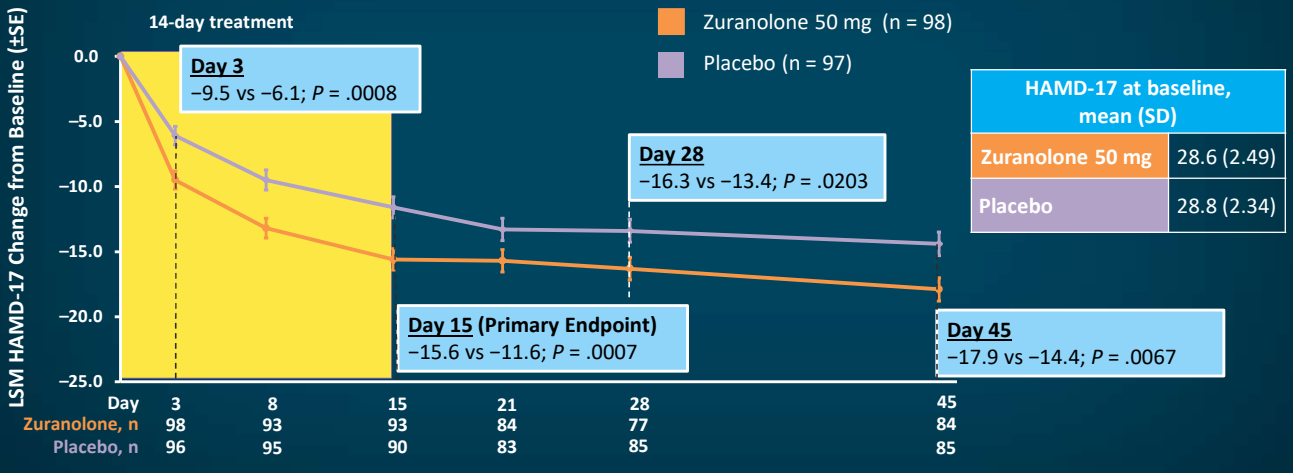
Placebo PO x 14 days
Evening dose with food
(n = 98)

Primary endpoint evaluated at Day 15; follow-up through Day 45

- **Primary endpoint:** LSM change from baseline in HAMD-17 total score at Day 15
- **Key secondary endpoint:** LSM change from baseline in HAMD-17 total score at Days 3, 28, and 45

Deligiannidis KM, et al. *Am J Psychiatry*. 2023;180:668-675. doi:10.1176/appi.ajp.20220785

SKYLARK: Change From Baseline in HAMD-17 Total Score with Zuranolone 50 mg



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

Deligiannidis KM, et al. *Am J Psychiatry*. 2023;180:668-675. doi:10.1176/appi.ajp.20220785

SKYLARK: AEs with Zuranolone 50 mg in PPD

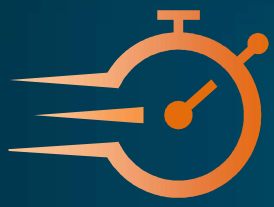
AE, n (%)	Zuranolone 50 mg (n = 98)	Placebo (n = 98)
TEAE	65 (66.3)	52 (53.1)
On treatment	59 (60.2)	41 (41.8)
Post-treatment	21 (21.4)	27 (27.6)
Mild	33 (33.7)	39 (39.8)
Moderate	29 (29.6)	12 (12.2)
Severe AE	3 (3.1)	1 (1.0)
Serious AE	2 (2.0)	0
AE leading to dose reduction	16 (16.3)	1 (1.0)
AE leading to discontinuation	4 (4.1)	2 (2.0)
AE leading to study withdrawal	1 (1.0)	1 (1.0)
Death	0	0

AE, n (%)	Zuranolone 50 mg (n = 98)	Placebo (n = 98)
TEAE ≥5%		
Somnolence	26 (26.5)	5 (5.1)
Dizziness	13 (13.3)	10 (10.2)
Sedation	11 (11.2)	1 (1.0)
Headache	9 (9.2)	13 (13.3)
Diarrhea	6 (6.1)	2 (2.0)
Nausea	5 (5.1)	6 (6.1)
Urinary tract infection	5 (5.1)	4 (4.1)
COVID-19	5 (5.1)	0

- No loss of consciousness, withdrawal symptoms or increased suicidal ideation/behavior were observed

Deligiannidis KM, et al. *Am J Psychiatry*. 2023;180:668-675. doi:10.1176/appi.ajp.20220785

How are NAS GABA-A PAMs Different?



Rapid action

Short course of treatment

Sustained effect

NAS = neuroactive steroid; PAM = positive allosteric modulator

When to Use NAS GABA-A Receptor PAM?

- Postpartum (who doesn't want a rapid antidepressant effect?)
- When a woman has been treated with appropriate doses of a common oral antidepressant during pregnancy with inadequate response at delivery
- Need for rapid response – depression is severe, significant functional impairment, thoughts of self-harm or harm to baby, lack of psychosocial support, poor response to standard treatment for prior PPD
- Others, eg, personalized medicine

Practical Considerations

General:

- Confirm patient meets criteria for moderate to severe PPD
- If taking standard oral antidepressant acting on monoamines, continue at same dose
- Use measurement-based monitoring (EPDS, PHQ-9) for baseline and outcomes through treatment and at endpoint

Brexanolone:

- REMS to monitor O2 and LOC and need for caregiver for infant when visiting, so requires a 72-hour inpatient stay
- Pause breastfeeding during infusion and for 3 days afterward
- Up-titrate from 30 µg/kg/d to 60 – 90 µg/kg/d and down-titrate to discontinue (either dose effective); may lower dose from 90 µg/kg/d to 60 µg/kg/d for AEs

Practical Considerations (continued)

Zuranolone:

- Utilize 50 mg/d dose in PM with food early enough so >12 hours until driving in AM due to potential somnolence/sedation. May lower dose if adverse effects are debilitating and persistent
- Recommend pausing breastfeeding during dosing, but levels in breastmilk are minimal
- Abstain from sex or use effective contraception during course of drug administration

Thoughts on Treatment of Postpartum Depression with GABA-A Receptor PAMs

- **Brexanolone:** use for inpatients, severe depression, suicidality and/or rapid relief when desired/needed
- **Classic Antidepressants:** use when there is a history of previous response, significant history of recurrent major depression (ie, probably needs long-term treatment). May be used in pregnancy and postpartum though not approved for PPD
- **Zuranolone:** use for first episode of PPD, when there is not a history of significant recurrent major depression, and when inadequate or partial response to monoamine oral antidepressant during pregnancy and after delivery
- Insurance coverage and cost will likely play a role in clinical decision making. Economic modelling suggests zuranolone is similarly cost-effective compared to SSRIs for treating PPD

O'Callaghan L, et al. *J Med Econ*. 2024;27:492-505. doi:10.1080/13696998.2024.2327946

Best Practices for use of NAS GABA-A PAM

Brexanolone

- Must be hospitalized for 72 hrs with monitoring for excessive sedation/LOC and have support caring for baby including when visiting mother (participation in REMS program)
- Pause breastfeeding, but exposure in breast milk low
- May lower dose from 90 µg/kg/d to 60 µg/kg/d for AEs
- Statistically significant separation from placebo at 24 hours sustained x 30 days in trials

Zuranolone

- Evening dosing with fatty meal in trials
- Recommend starting with 50 mg/d. Can lower to 40 or 30 mg/d for AEs
- Recommend driving only >12 hours after pm dose until know sedating effects in patient
- Do not use in pregnancy, but start after delivery if not responding to standard AD
- Suggest pausing breastfeeding, but exposure in lactation low
- Separates from placebo after 2 doses (Day 3). Sustained effects through 6 weeks (50% for 1 year after 14-day course 50 mg/d in MDD; additional 30% needed 2nd treatment course in 1-year F/U)

Both - use with severe MDD, thoughts of self-harm or harm to baby, significant functional impairment, poor response to standard treatment for prior PPD, patient preference, need or desire for rapid response. Avoid with benzodiazepines/opioids.

Patient Case

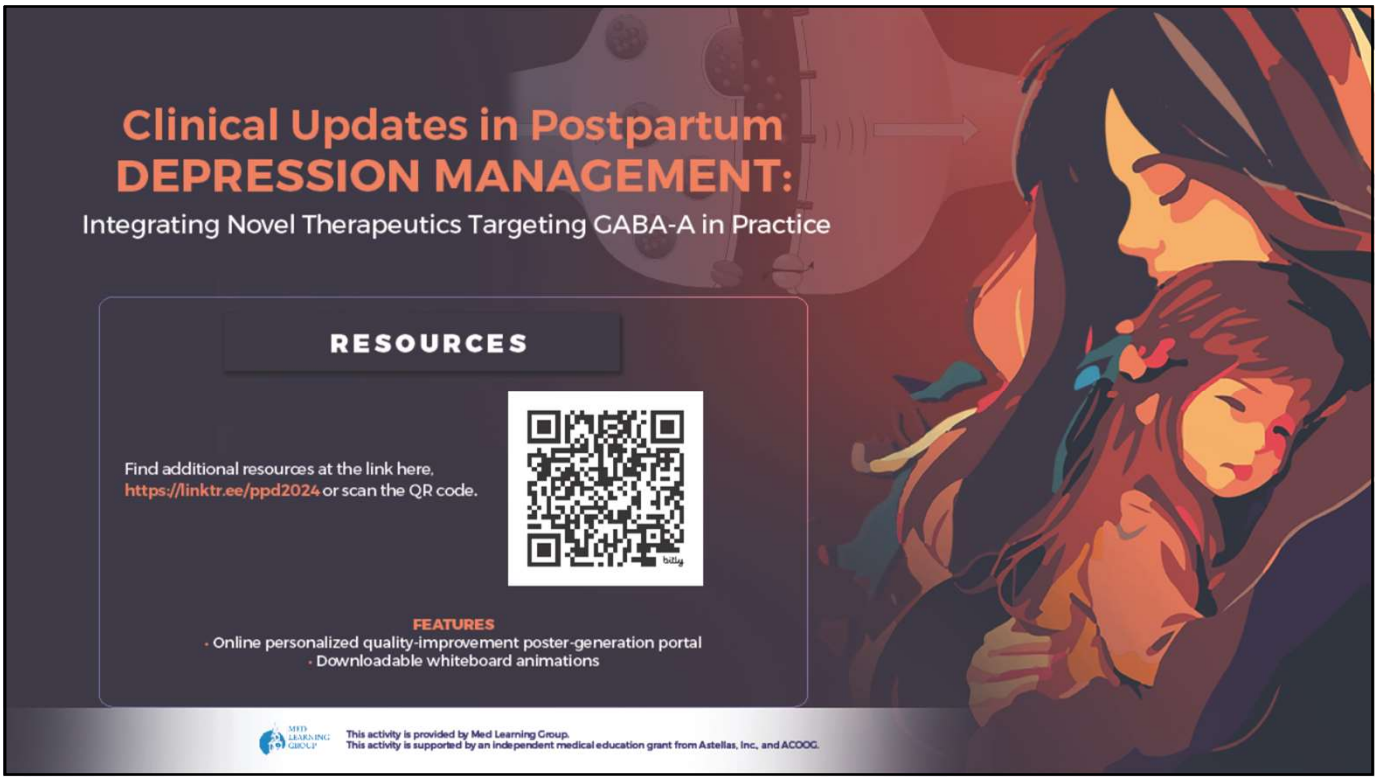
- 28-year-old, who contacts the Obstetrics clinic 3 weeks after delivery with complaints of worsening depression. Has not yet been to 1-month well-child check
- At age 25, she experienced a moderate MDE. She responded well to an SSRI which was discontinued after 1 year in remission
- Currently reports low mood in 3rd trimester with 3 weeks of severe depressive symptoms since delivery similar to previous MDE: loss of interest, sadness, sleep disturbance, low energy, slowed movements, severe difficulty concentrating, excessive and inappropriate guilt, and thoughts of death. Her EPDS score was 8 (#10=0) at week 24 of pregnancy. Today EPDS is 22 (#10=1). Functional impairment is significant for care of self, care of baby, social relationships, etc. She meets DSM-5-TR criteria for a MDE, peripartum.
- What would you advise?

Key Points

- Screen routinely for perinatal depression
- Individualize treatment per patient
- Assess and monitor treatment response using validated tools
- SSRIs/SNRIs appear safe and efficacious for mild, moderate, and severe perinatal depression during pregnancy and postpartum
- Neuroactive steroid (Allopregnanolone and analogues) GABA-A receptor PAMs recently FDA-approved for PPD are safe and efficacious for patients with moderate or severe perinatal depression

Thank You!

Questions and Answers


Clinical Updates in Postpartum
DEPRESSION MANAGEMENT:
Integrating Novel Therapeutics Targeting GABA-A in Practice
RESOURCES
Find additional resources at the link here,
https://linktr.ee/ppd2024 or scan the QR code.
FEATURES
• Online personalized quality-improvement poster-generation portal
• Downloadable whiteboard animations
This activity is provided by Med Learning Group.
This activity is supported by an independent medical education grant from Astellas, Inc., and ACOOG.

Clinical Updates in Postpartum Depression Management: Integrating Novel Therapeutics Targeting GABA-A in Practice

Postpartum Depression: Diagnosis and Management

Resource	Address
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Deligiannidis KM, Meltzer-Brody S, Gunduz-Bruce H, et al. Effect of zuranolone vs placebo in postpartum depression: a randomized clinical trial. *JAMA Psychiatry*. 2021;78(9):951-959.	https://pubmed.ncbi.nlm.nih.gov/34190962/
Edinoff AN, Odisho AS, Lewis K, et al. Brexanolone, a $GABA_A$ modulator, in the treatment of postpartum depression in adults: a comprehensive review. *Front Psychiatry*. 2021;12:699740.	https://pubmed.ncbi.nlm.nih.gov/34594247/
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Massart R, Mongeau R, Lanfumey L. Beyond the monoaminergic hypothesis: neuroplasticity and epigenetic changes in a transgenic mouse model of depression. *Philos Trans R Soc Lond B Biol Sci*. 2012;367(1601):2485-2494.	**https://pubmed.ncbi.nlm.nih.gov/22826347/**
Maternal depression and child development. *Paediatr Child Health*. 2004;9(8):575-598.	**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2724169/**
Meltzer-Brody S, Colquhoun H, Riesenberg R. Brexanolone injection in post-partum depression: two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet*. 2018;392(10152):1058-1070.	**https://pubmed.ncbi.nlm.nih.gov/30177236/**
Meltzer-Brody S, Kanes SJ. Allopregnanolone in postpartum depression: role in pathophysiology and treatment. *Neurobiol Stress*. 2020;12:100212.	**https://pubmed.ncbi.nlm.nih.gov/32435663/**
Mughal S, Azhar Y, Siddiqui W. Postpartum depression. *StatPearls*. 2024.	**https://pubmed.ncbi.nlm.nih.gov/30085612/**
Pinna G, Almeida FB, Davis JM. Allopregnanolone in postpartum depression. *Front Glob Womens Health*. 2022;3:823616.	**https://pubmed.ncbi.nlm.nih.gov/35558166/**
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Suryawanshi O, Pajai S. A comprehensive review on postpartum depression. *Cureus*. 2022;14(12):e32745.	**https://pubmed.ncbi.nlm.nih.gov/36686097/**

Resources and Societies

Resource	Address
American College of Obstetrics and Gynecology	https://www.acog.org/womens-health/faqs/postpartum-depression
American Psychological Association	https://www.apa.org/topics/women-girls/postpartum-depression
Anxiety and Depression Association of America	https://adaa.org/find-help-for/women/postpartum-disorders
Postpartum Depression Resources	https://www.postpartumdepression.org/resources/
Postpartum Support International	https://www.postpartum.net/
Substance Abuse and Mental Health Services Administration	https://www.samhsa.gov/find-help/national-helpline