Brexanolone: Clinical Considerations and Future Research Directions

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Disclosures

None

"What conflict of interest?!
I work here in my spare time."

Objectives

Participants will be able to:

- Epidemiology of perinatal depression
- Understand current scientific literature on prescribing antidepressants in pregnancy.
- Understand biological background that fueled interest in Brexanolone
- Critically review scientific literature on Brexanolone and strength of findings.
- Clinical challenges in Brexanolone administration.
- Discuss future Clinical and Research directions.

Talk Overview

- How common is perinatal depression?
- Why treat perinatal depression during pregnancy?
- How to treat perinatal depression in pregnancy? When it doesn't work….
- What are neurosteroids? What is the role of Neurosteroids (Allopregnanolone) in perinatal depression?
- Scientific investigation of Allopregnanolone?
- Scientific literature supporting the use of Brexanolone for postpartum depression.
- Clinical application and utility of Brexanolone

How Common is Perinatal Depression?

Depression During Pregnancy

There is **No Evidence** that the risk of Major Depression increases during pregnancy!

- *No increased risk* for MDD *during pregnancy* compared to nonpregnant female population
- *Postpartum risk was elevated among women with MDD* with an odds ratio of 1.52
- *Postpartum risk was elevated among women with BPAD* with odds ration of 2.9
- 23X more likely to be admitted in the first year postpartum than any other time in their lives.

Approximately 10% of all pregnant women meet criteria for major depression.

Rate is higher in women from lower SES and in women with pre-existing mood disorders (20-40%)

Pregnancy and Relapse of Mood Disorders

- The rate of relapse in women with mood disorders who stop their medications for pregnancy is very high
  - 70% in Major Depression
  - 85% or more in Bipolar Disorder
- The rate of relapse in women with mood disorders who continue their medications for pregnancy is also high
  - 26% in Major Depression
  - 33% in Bipolar Disorder

Postpartum Depression: Who is at Risk?

25-50% of women with a *pre-existing* mood disorder

70-90% of women with a pre-existing mood disorder *who stop* their meds for pregnancy

ENVIRONMENT plays a role

GENETICS play a role

Why Treat Perinatal Depression?

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.

Adverse Pregnancy Outcomes Associated with Antenatal Depression

- Preterm delivery (OR ~ 1.5)
- Low birth weight (OR ~ 2)
- Decreased motor tone and activity in the baby
- Higher cortisol levels in the baby
- Poor reflexes in the baby
- ADHD and behavioral problems, particularly in boys

Postpartum Depression Effects on the Infant

- Depression during pregnancy increases the risk of PPD
- PPD is associated with the following in exposed children:
  - Lower IQ
  - Slower language development
  - ADHD
  - Behavioral problems
  - Psychiatric illness

You Have Two Patients

Treatment potentially benefits both the mom ***and*** fetus.

Failure to treat poses potential risks to both the mom ***and*** fetus.

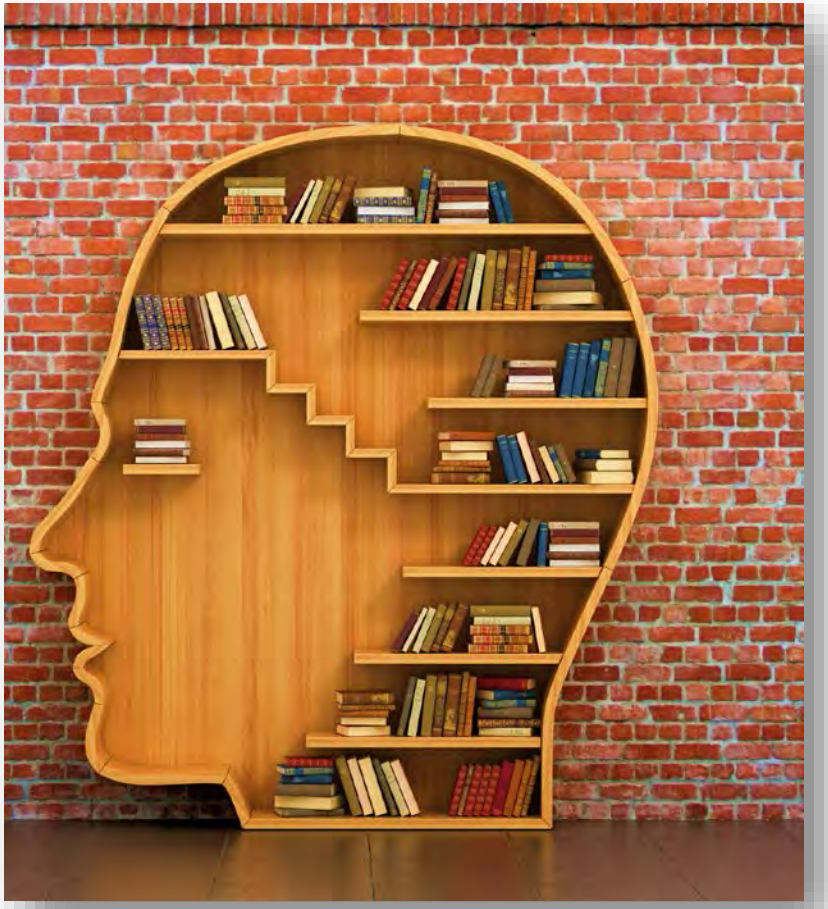
The Discussion

- **Not truly a Risk-Benefit Discussion**
- **Risk-Risk Discussion**
- **Risks associated with medication exposure**
- **Risks associated with untreated psychiatric illness for mom and exposure to illness for baby**

Problems with the Literature

Most studies don't control for:

- Underlying psychiatric illness
- Severity of psychiatric illness
- Risk factors that are found in a higher rate in the psychiatric population (Diabetes, Smoking, Substance Use, Obesity etc)
- Whether or not the mother was psychiatrically ill during pregnancy
- Multiple medications



Apples to Apples

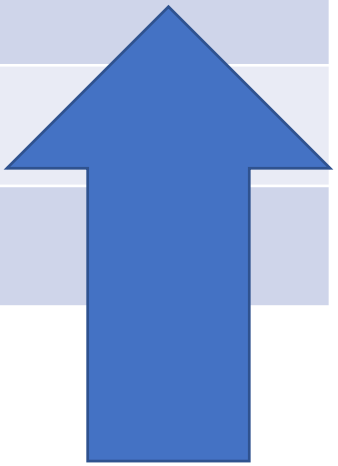
- Studies which compare
  - pregnant women with depression taking meds
  - pregnant women with depression NOT taking meds

Generally, do NOT find associations between antidepressants and

- Heart Defects
- Persistent Pulmonary Hypertension
- Autism

Studies on Antidepressants that have Adjusted for Psychiatric Illness and Severity

Outcome of Interest	Unadjusted Odds Ratio for Exposure to SSRI's	Adjusted for Psychiatric Illness	Adjusted for Severity of Illness and/or Other Confounds
Cardiac Defects	1.25 (1.13-1.38)	1.12 (1.00-1.26)	1.06 (0.93-1.22)
Preterm Birth	1.44 (1.34-1.56)	1.61 (1.26-2.05)	1.53 (1.40-1.66)
Persistent Pulmonary Hypertension	1.51 (1.35-1.69)	1.36 (1.18-1.57)	1.10 (0.94-1.29)
Autism-Pooled Case Control	1.7 (1.3-2.3)	1.4 (1.0-2.0)	
Autism-Pooled Cohort	1.8 (1.3-2.6)	1.5 (0.9-2.7)	



What About Other Psychiatric Medication Categories?

Generally avoid valproic acid and carbamazepine

Lithium has a <1% chance of Ebstein's anomaly. AR is 1/1000.

Lamotrigine and gabapentin are generally considered safe

Avoid the use of large amounts of benzodiazepines

Atypical antipsychotics associated with mild developmental delay at 6 months that resolves by 1 year

Little evidence for stimulants

General Rules for Medication Plans During Pregnancy

Rule Number 1

- Assume all women of reproductive age will get pregnant!
- Discuss potential complications for the baby with the medication that you're prescribing
- Discuss what form of birth control they are using or will in the future
- Emphasize the need for a planned pregnancy regarding psychiatric medications

Rule Number 2

Limit the number of exposures for the baby

- Exposure to psychiatric illness counts
  - goal to keep Mom **well** during pregnancy to eliminate this exposure
- Maintain Mom on as **few** medications as possible
- Try to make medications changes before pregnancy
  - make sure that Mom is **stable** before getting pregnant

Rule Number 3: Older is better

Use medications that we know more about

- Older=Better (generally)
- Epilepsy literature increases samples sizes
- FDA categories not very useful- phasing out
- Source: Reprotox

Rule 4

- Monitor blood levels when possible
- Consider prophylactic increases (or decreases) to maintain blood level
- **Don’t undertreat!**
- If you increase during pregnancy consider decreasing postpartum

Unplanned Pregnancy-Oops!

Don’t Panic!

- Taper medications that you want to try to discontinue
- Don’t switch to an older medication- baby is already exposed

Breastfeeding

- **Most psychiatric medications can be used during breastfeeding**
- Possible exceptions: lithium, clozapine
- **Do not switch** to a different medication from one used in pregnancy unless mom is ill
- **Do not switch** to a different medication from one used in pregnancy because it has lower levels in breast milk
- Resource: Drugs and Lactation Database (LactMed)

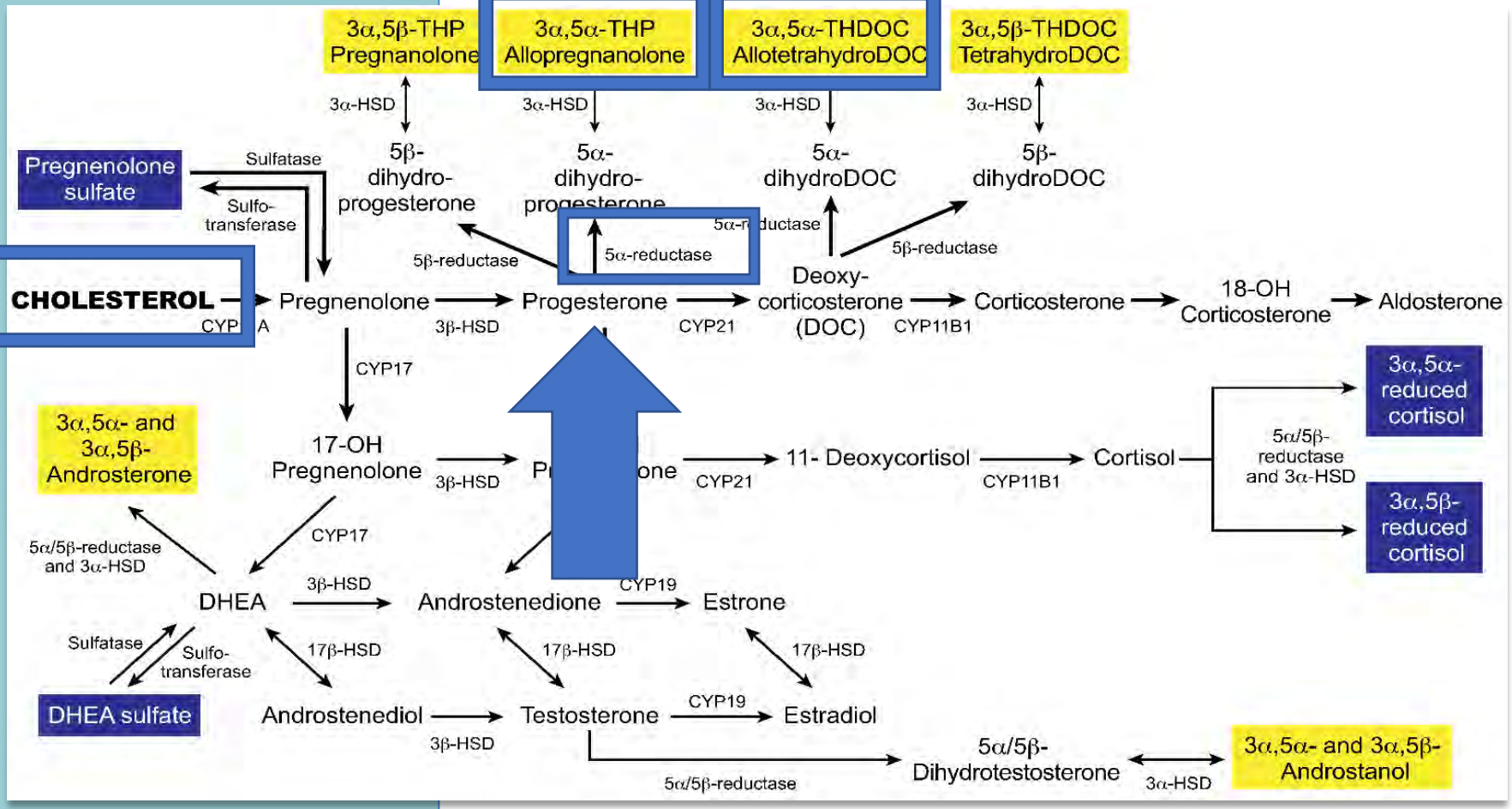
Take Home Points

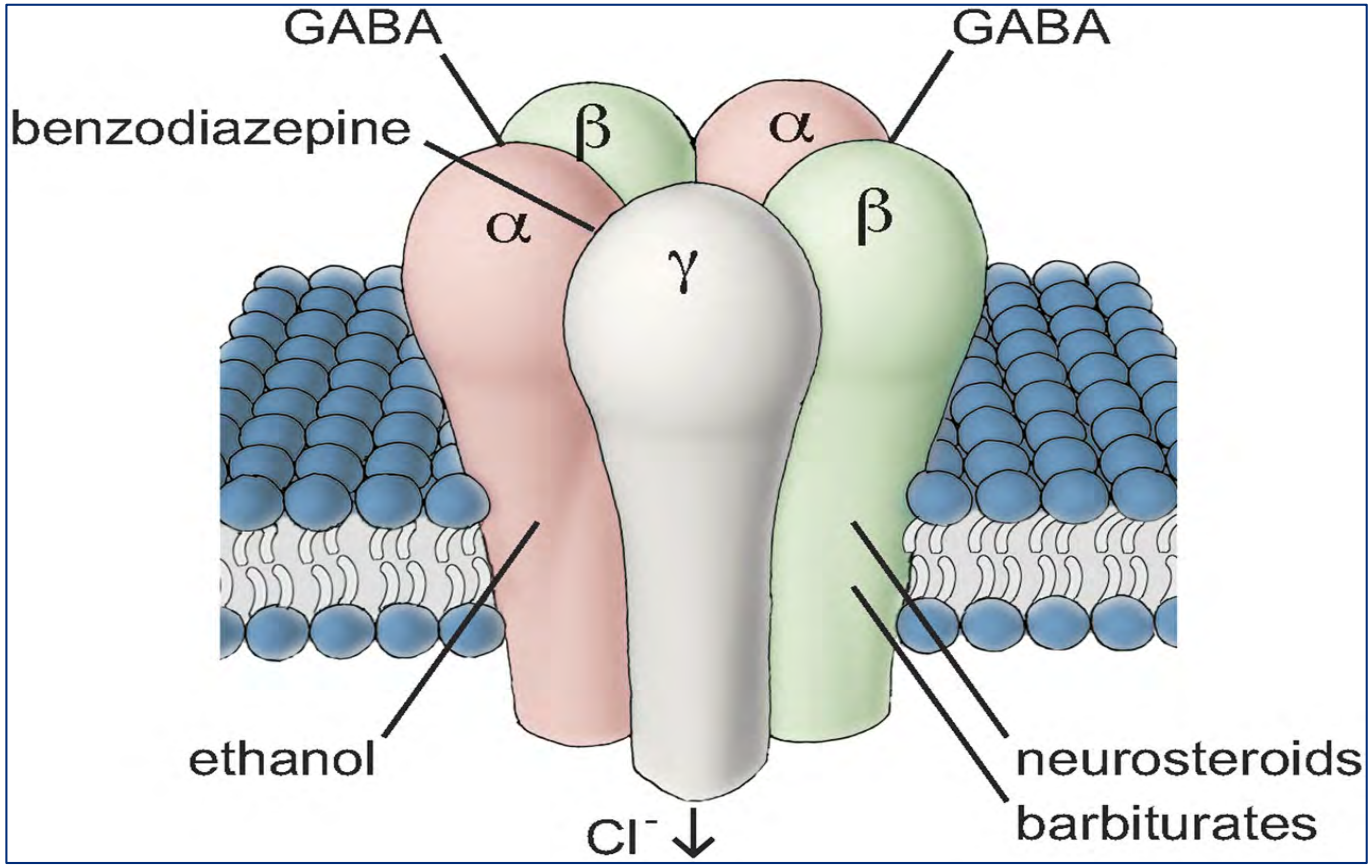
- Active psychiatric illness during pregnancy and postpartum is associated with poor outcomes for the infant
- Literature on the safety of psychiatric medications during pregnancy is frequently poorly controlled and "confounded by indication."
- One needs to look at the literature *as a whole* to determine safety of medications during pregnancy
- With a few exceptions most psychiatric medications can be used safely during pregnancy
- We are probably undertreating psychiatric illness during pregnancy! Risk of PPD increases...

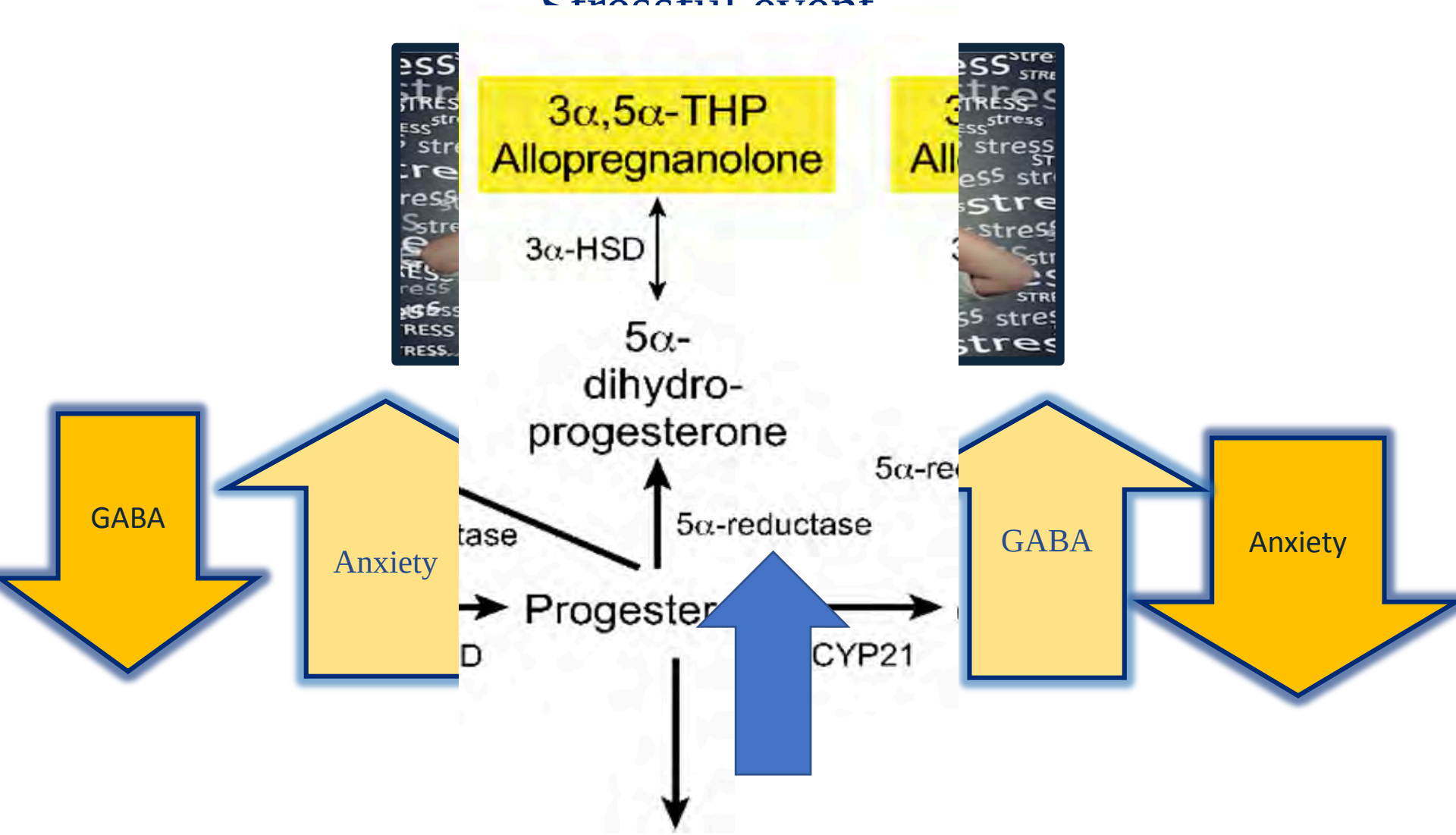
When medicines don’t work OR PPD develops de novo…

- What are Neuroactive steroids? What is the role of Neuroactive steroids (Allopregnanolone) in perinatal depression?
- Scientific investigation of Allopregnanolone?
- Scientific literature supporting the use of Brexanolone. for postpartum depression.
- Clinical application and utility of Brexanolone.

What are Neuroactive Steroids?

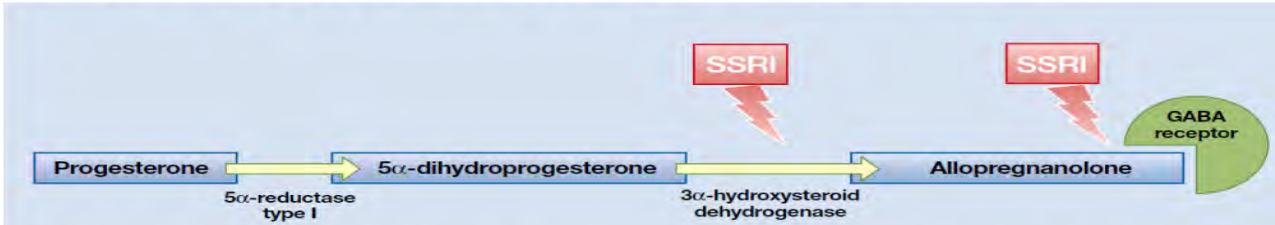



GABA
GABA
benzodiazepine
β
α
α
β
γ
ethanol
neurosteroids
barbiturates
Cl⁻


3α,5α-THP
Allopregnanolone
3α-HSD
5α-
dihydro-
progesterone
5α-reductase
GABA
Anxiety
GABA
Anxiety

- **Inhibitory NASs down in chronic mental illness**
- **SSRIs reverse**

Conversion of progesterone to ALLO and the SSRI influence



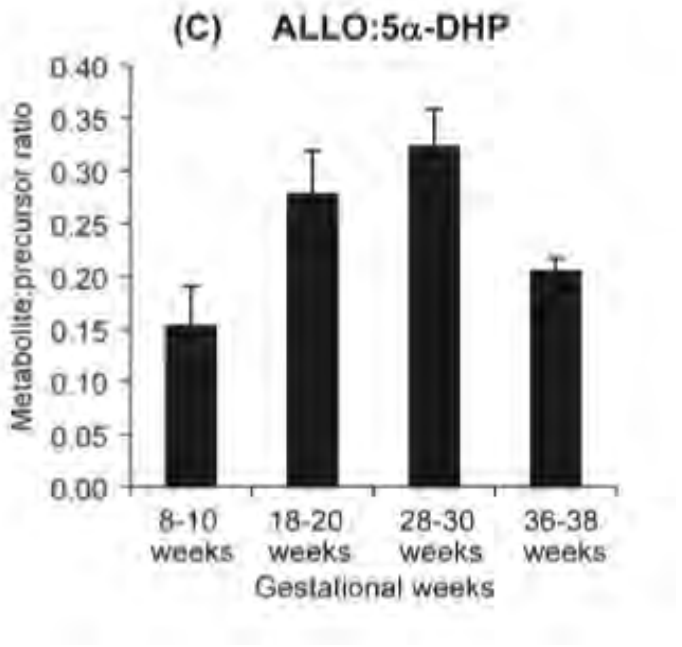
SSRIs enhance the sensitivity of $GABA_A$ receptors or promote the formation of more ALLO as shown here. This is one possible mechanism by which they could be helping to alleviate PMDD symptoms.

ALLO: allopregnanolone; GABA: γ-aminobutyric acid; PMDD: premenstrual dysphoric disorder; SSRI: selective serotonin reuptake inhibitor

Neuroactive Steroids in Pregnancy — like MDD or PMDD ?

Allopregnanolone in Normal Pregnancy

- Levels 7-9x ↑
- Ratio to precursor may ↓ before delivery
- ↓ expression GABA-A receptor subunit & binding capacity
- ↑ within 48 hours after delivery
- Return to normal by 6 weeks PP



Gilbert Evans et al., Gynecological Endocrinology, November 2005; 21(5): 268–279

Peripheral ALLO

Journal of Psychiatric Research 47 (2013) 816–828

Contents lists available at SciVerse ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

GABAergic neuroactive steroids and resting-state functional connectivity in postpartum depression: A preliminary study

Kristina M. Deligiannidis [a,*], Elif M. Sikoglu [b], Scott A. Shaffer [c], Blaise Frederick [d,e], Abby E. Svenson [a], Andre Kopoyan [c], Chelsea A. Kosma [a], Anthony J. Rothschild [a,1], Constance M. Moore [b,1]

Neuropsychobiology

Neuropsychobiology 2014;69:147–153
DOI: 10.1159/000358838

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Published online: April 26, 2014

Low Serum Allopregnanolone Is Associated with Symptoms of Depression in Late Pregnancy

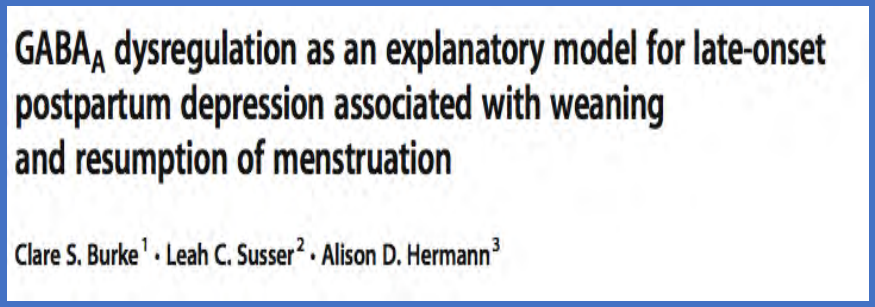
Charlotte Hellgren [a] Helena Åkerud [a] Alkistis Skalkidou [a] Torbjörn Bäckström [b]
Inger Sundström-Poromaa [a]

Psychopharmacology (2016) 233:1299–1310
DOI 10.1007/s00213-016-4217-x

ORIGINAL INVESTIGATION

Blunted neuroactive steroid and HPA axis responses to stress are associated with reduced sleep quality and negative affect in pregnancy: a pilot study

Shannon K. Crowley [1] · Todd K. O'Buckley [2] · Crystal E. Schiller [1] · Alison Stuebe [3,4] · A. Leslie Morrow [1,2,5] · Susan S. Girdler [1]



$GABA_A$ dysregulation as an explanatory model for late-onset postpartum depression associated with weaning and resumption of menstruation

Clare S. Burke [1] · Leah C. Susser [2] · Alison D. Hermann [3]

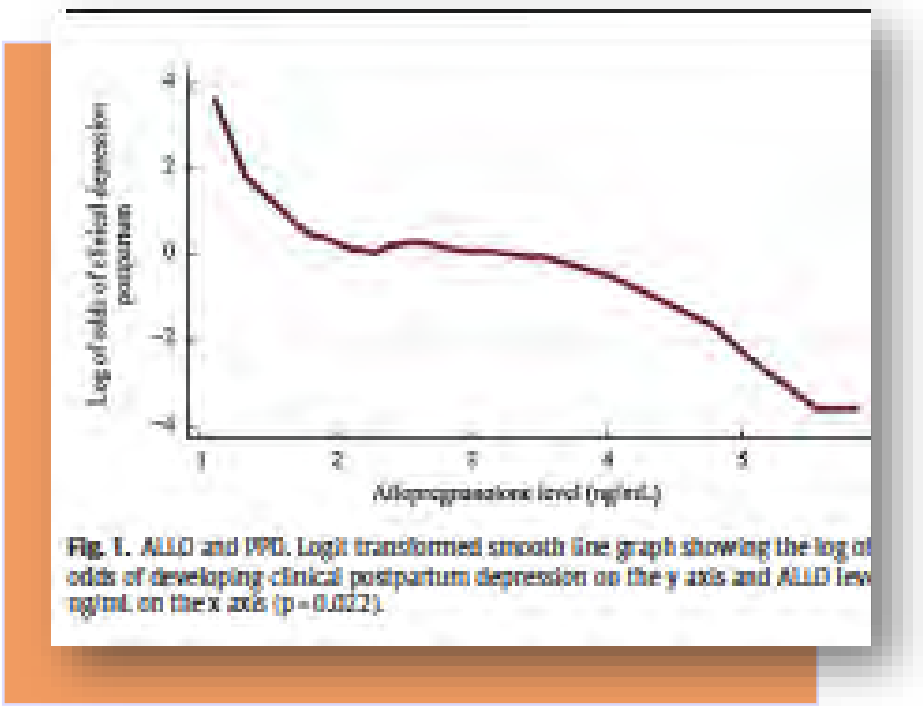


Fig. 1. ALLO and PPD. Logit transformed smooth line graph showing the log of odds of developing clinical postpartum depression on the y axis and ALLO level ng/mL on the x axis (p = 0.022).

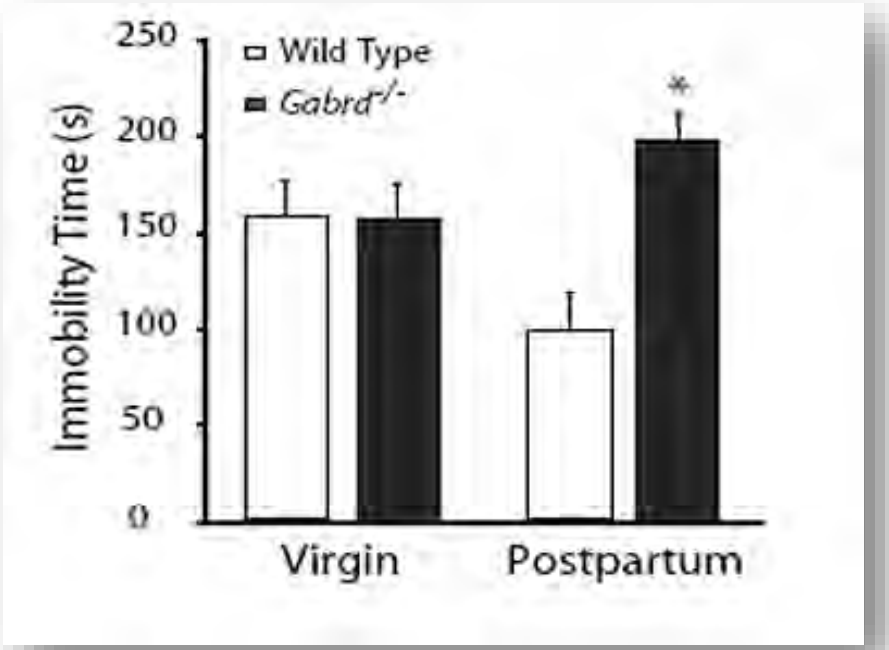
Allopregnanolone Blood Levels

- 60 pregnant women with history of mood disorder
- Measured 2nd and 3rd trimester progesterone and allopregnanolone
- 63% reduction in risk of developing PPD for every increase ng/mL of 2nd trimester allopregnanolone

GABA-A Receptor Knockout Mice

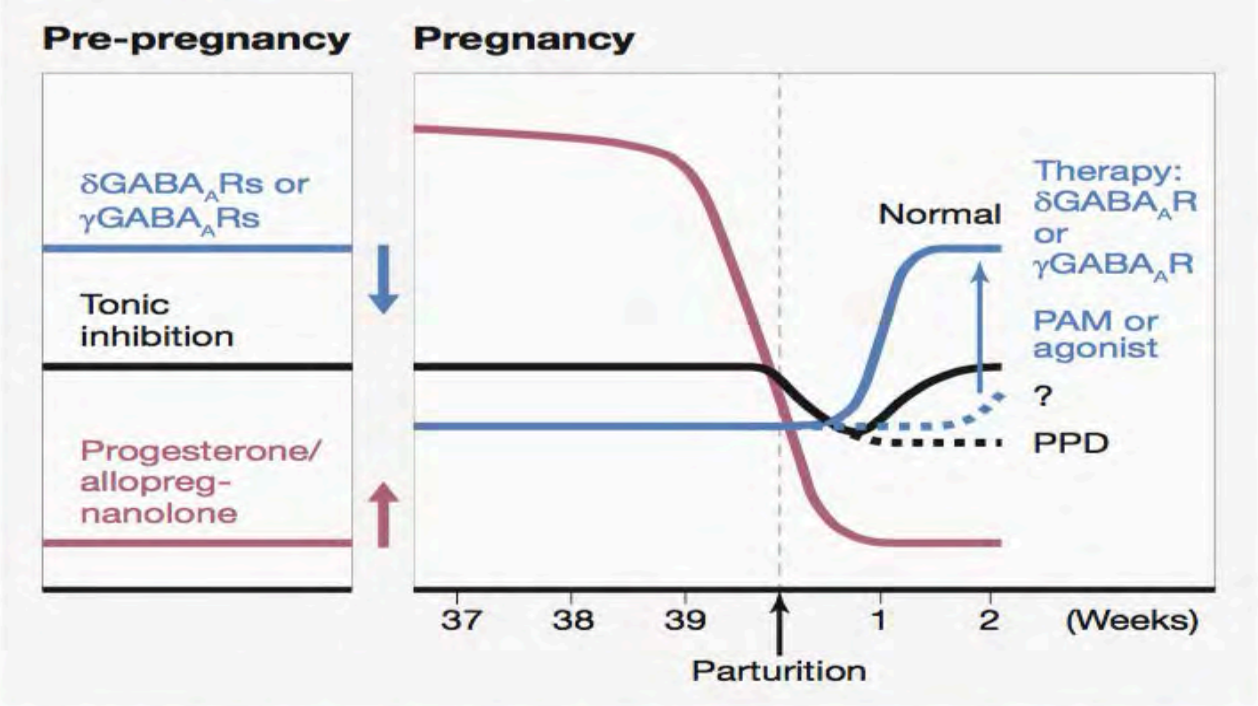
=

Increased Mood and Anxiety-like Behaviors Postpartum



Maguire & Mody, Neuron. 2008 July 31; 59(2): 207–213.

BENCH to BEDSIDE….

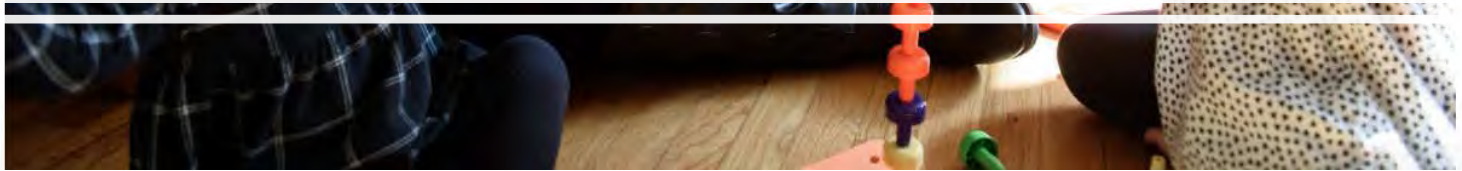


During the postpartum period, the brain's inhibitory GABA$_A$ receptors may not recover in time following their reduced numbers during pregnancy. This is likely the cause of postpartum depression prevalent in ~12% of childbearing women. A new therapy for this condition consists of administering a synthetic neurosteroid during the postpartum period to alleviate the mood disorder.

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

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

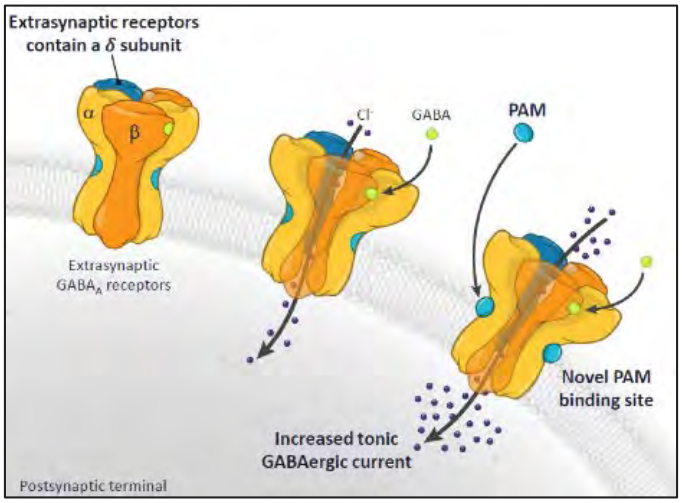
March 19, 2019



ZULRESSO™ (Brexanolone) Injection is Hypothesized to Work in PPD by Increasing GABA Function

Brexanolone Injection

- Proprietary iv formulation of allopregnanolone
- Positive allosteric modulator of $GABA_A$ receptors

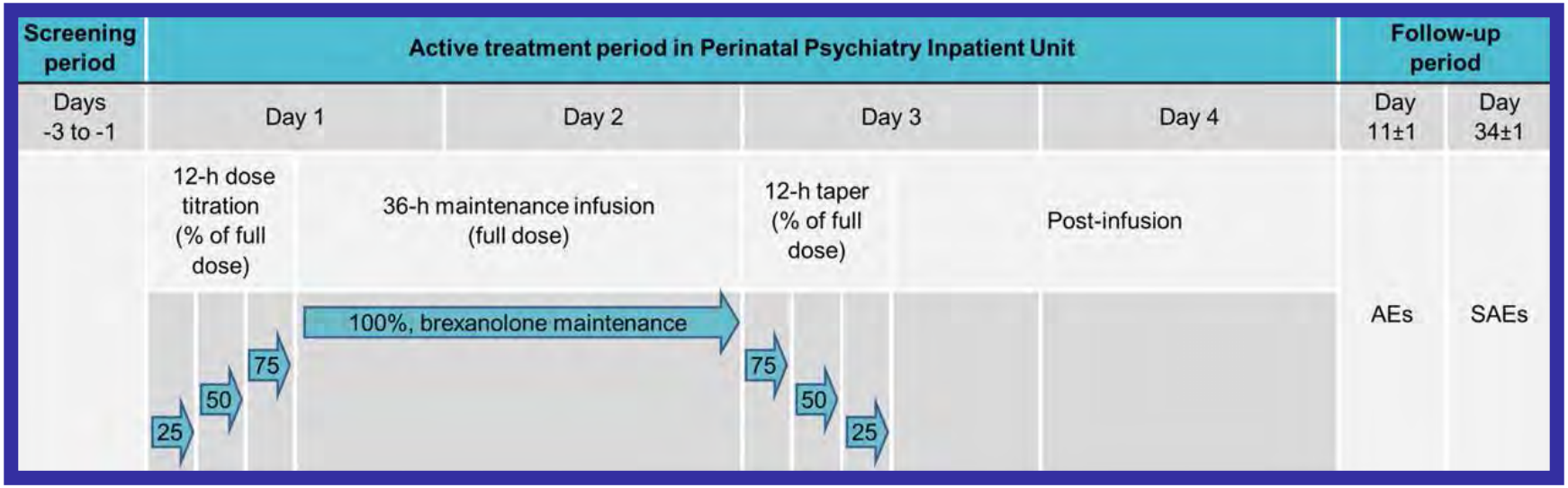


Therapeutic Rationale for Use of Brexanolone Injection

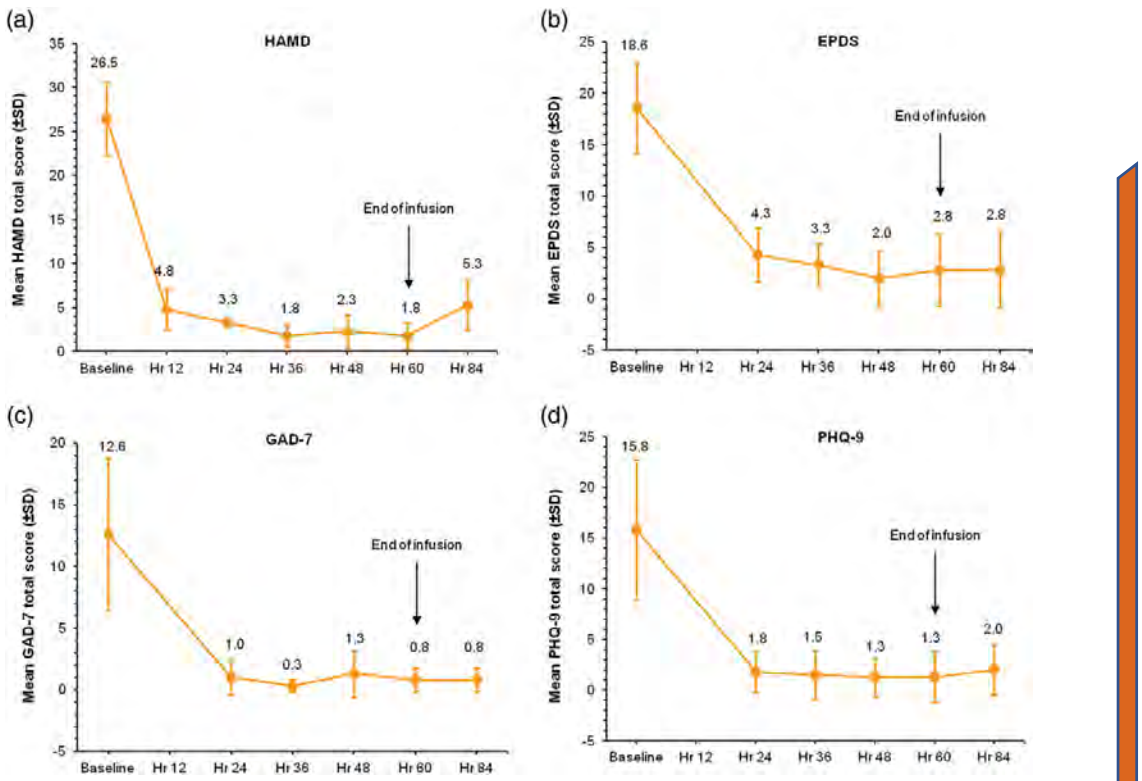
- GABAergic hypofunction has been associated with PPD[1,2,3]
- Brexanolone injection is a positive allosteric modulator of $GABA_A$ receptors[4,5]
- **Therefore, brexanolone injection may have therapeutic potential in PPD by increasing GABAergic function**

1. Luscher B, et al. *Molecular Psychiatry* 2011; 16(4): 383-406; 2. Deligiannidis KM, et al. *Psychoneuroendocrinology*. 2016;70:98-107; 3. Epperson CN et al *Psychopharmacology* 2006; 186(3): 425-433; 4. Maguire J and Mody I. *Psychoneuroendocrinology.* 2009 Dec;34 Suppl 1:S84-90; 5. Bialer M, et al. *Epilepsy Res* 2015; 11:85-141.

Infusion Plan – 60 HR IV INFUSION



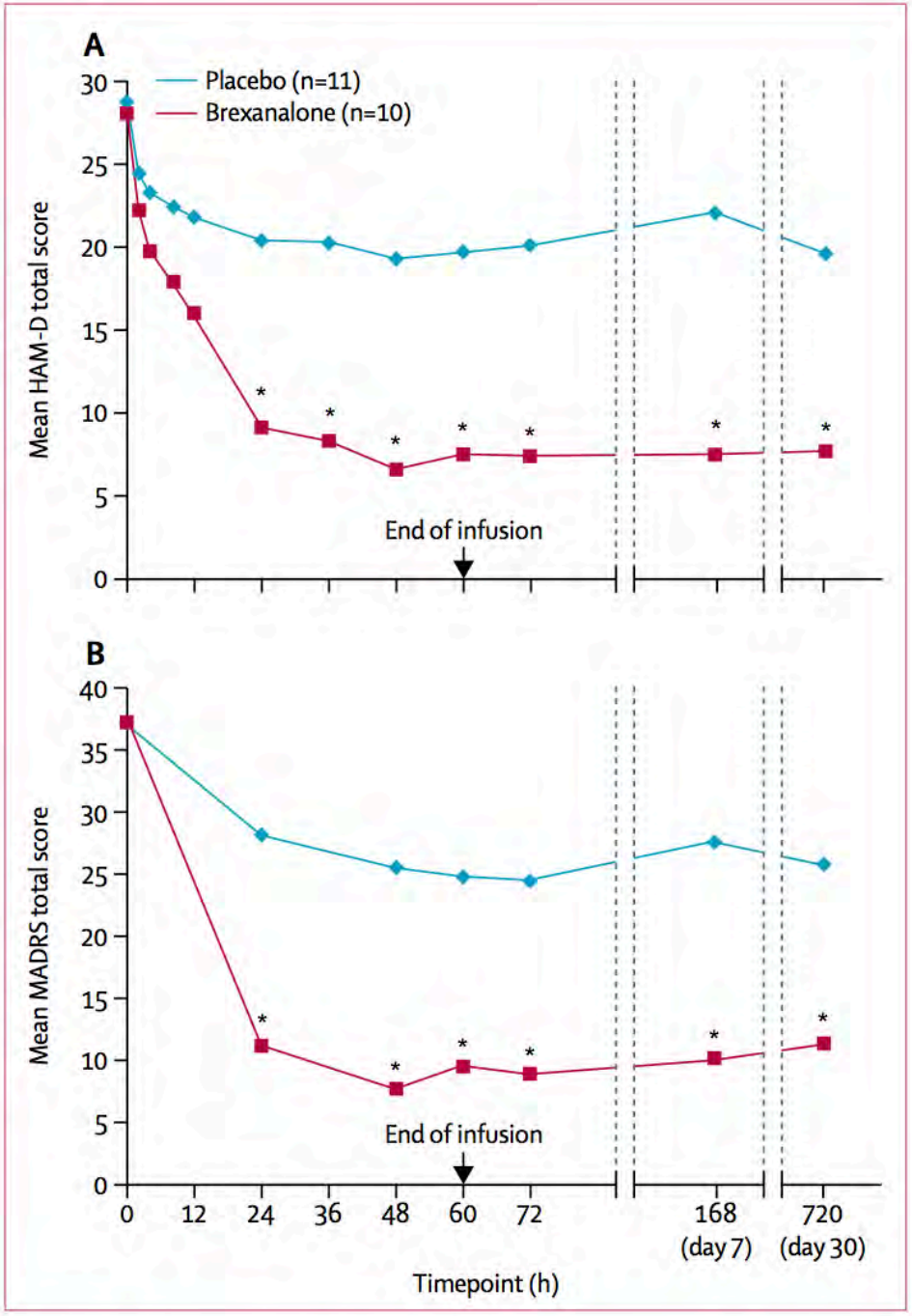
Brexanolone:
Open Label Study
N=4



All patients in clinical remission by 24 hours into the infusion, sustained throughout infusion.

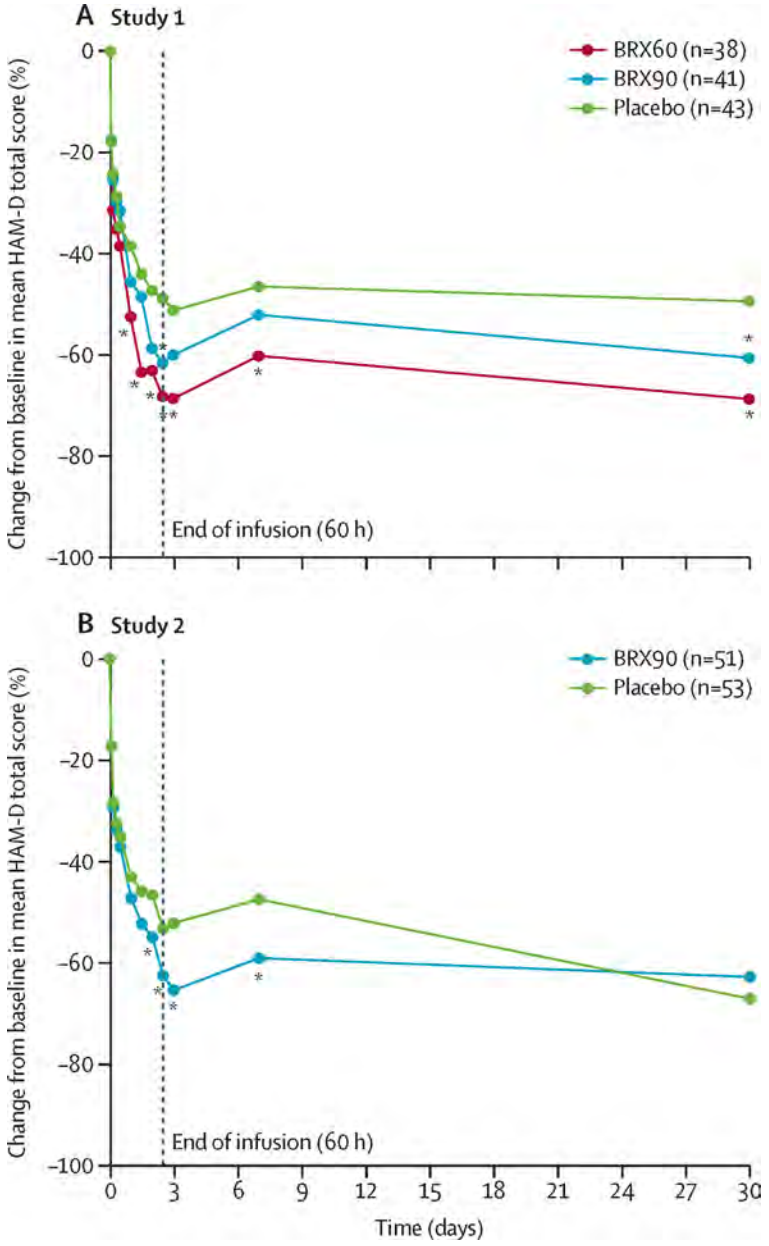
Brexanolone

Placebo Controlled Trials



Brexanolone

Placebo Controlled Trials



Adverse Effects of Brexanolone

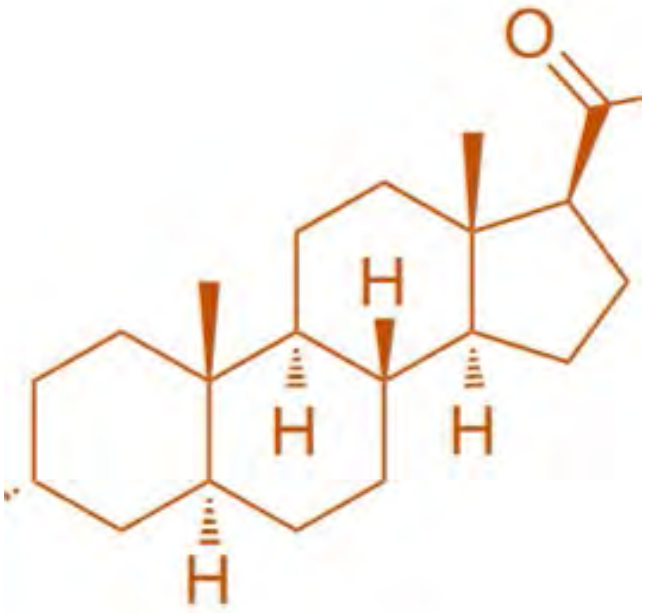
	Study 1			Study 2	
	Placebo (n=43)	BRX60 (n=38)	BRX90 (n=41)	Placebo (n=53)	BRX90 (n=51)
Overall					
Any adverse event	22 (51%)	19 (50%)	22 (54%)	24 (45%)	25 (49%)
Severe adverse event	0	1 (3%)	0	1 (2%)	2 (4%)
Serious adverse event	0	1 (3%)	0	0	1 (2%)
Adverse event leading to discontinuation of study 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 µg/kg per h. BRX90=brexanolone injection 90 µg/kg per h.

Meltzer-Brody et al., 2018

Use of Brexanolone

- Available now!
- Anticipated cost: $34,000
- Insurance coverage: Most major insurances are covering!
- MUST be administered inpatient with monitoring (continuous pulse ox, 1:1).
- Use: Inpatients for fast relief of suicidal ideation, severe symptoms, or treatment resistance.
- Likely does not change standard approaches to perinatal depression but stay tuned….



Goal: Healthy Mom, Healthy Baby!

Thank You!

The Johns Hopkins Women's Mood Disorders Center

- **Lauren Osborne**
- **Jennifer Payne**
- Samantha Meilman
- Courtney Erdly
- Meeta Pangtey
- Bridget Sundel
- Gina Grinstead
- Katherine McEvoy
- Allison Craig

- Our patients and research participants!!!

RESOURCES

- Women's Mood Disorders Center (East Baltimore): (410) 502-7449: Clinical and Research, one-time consults, MOST insurance http://www.hopkinsmedicine.org/psychiatry/specialty_areas/moods/patient_information/clinic_women.html
- Perinatal Mood Clinic (Bayview): (410) 550-0104: Clinical Only, BCBS http://www.hopkinsmedicine.org/psychiatry/bayview/medical_services/adult/perinatal_mood.html
- Reprotox: Summary of literature on all meds in pregnancy, subscription service https://reprotox.org/
- Lactmed: Summary of literature on all meds in lactation, free services http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm
- MothertoBaby: Patient-friendly fact sheets on meds: http://mothertobaby.org/
- MGH Center for Women's Mental Health: Best informational website: https://womensmentalhealth.org?doing_wp_cron=1452175286.3503780364990234375000
- Motherrisk: Canadian helpline: http://www.motherisk.org/
- Postpartum Support International: Support group and help finding local resources http://www.postpartum.net/
- MCPAP FOR MOMS, https://www.mcpapformoms.org/

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