1-12-2020

# Postpartum Depression! One IV and I am Back to Happy!

Gabrielle DuBruille
*Boca Raton Regional Hospital*, GDubruille@brrh.com

# Postpartum Depression! One IV and I am Back to Happy!

Gabrielle DuBruille, PharmD
PGY-1 Resident Pharmacist
Boca Raton Regional Hospital
Baptist Health South Florida

# Disclosures

The author of this presentation has no relevant financial or non-financial relationships in the products described and reviewed in this presentation

# Objectives

- Discuss the epidemiology, diagnostic criteria, and pathophysiology of postpartum depression (PPD)
- Review clinical evidence for the treatment options for women suffering with PPD
- Identify treatment regimens for women suffering with PPD
- Evaluate the implication of new drug therapies on the management of PPD
- Recognize side effects and monitoring parameters associated with drugs used in the treatment of PPD

# PPD Introduction

Courtesy of parents.com

More intense than “baby blues”

“Baby blues” symptoms: crying spells, mood swings, anxiety, difficulty sleeping

“Baby blues” time frame: resolves around 2 weeks post delivery

# What is PPD?

A depressive episode that can occur **during** pregnancy as well as **after** delivery

Courtesy of PBS

*Postpartum Support International.* 2013; 1-6.

# Definitions

Postpartum depression differs according to different resources:

- DSM-V: onset within 4 weeks
- ICD-10: onset within 6 weeks
- Clinical research and practice: onset within 1 year

Courtesy of Harvard Health

*CNS Spectr.* 2015;20(1):48-59. *N Engl J Med.* 2016;375(22):2177-2186.

# Diagnostic Criteria

- Diagnostic and statistical manual for mental disorders (DSM)
- Latest edition: DSM-5 (2013)


Courtesy of American Psychiatric Association

American Psychiatric Association (APA). Diagnostic and statistical manual of mental disorders. APA; 2013.

# Major Depressive Disorder (MDD) Diagnostic Criteria

One or more major depressive episodes, no history of mania

≥ 5 symptoms for at least 2 weeks

Must have depressed mood or loss of interest

American Psychiatric Association (APA). Diagnostic and statistical manual of mental disorders. APA; 2013.

# DSM-5 Criteria

**Must have at least 5 symptoms, with one being (1) or (2)**

1. Depressed mood
2. Loss of interest
3. Weight loss or weight gain
4. Insomnia or hypersomnia
5. Psychomotor agitation or retardation
6. Fatigue
7. Feelings of worthlessness
8. Diminished ability to think or concentrate
9. Recurrent thoughts of death, suicidal ideation, suicide attempt

American Psychiatric Association (APA). Diagnostic and statistical manual of mental disorders. APA; 2013.

# PPD Diagnostic Criteria

- Same DSM-5 criteria as MDD, but a specifier was created:

**Postpartum and antepartum depression**

- With peripartum onset
- Onset of depressive episode during pregnancy or within 4 weeks postpartum

American Psychiatric Association (APA). Diagnostic and statistical manual of mental disorders. APA; 2013.

# Prevalence

| Postpartum depression | Major depressive disorder in women |
| --- | --- |
| 9% | 10% |

*J Womens Health.* 2019;28(8):1068-1076.

# PPD Onset

| Antepartum | Postpartum |
| --- | --- |
| 38% | 42% |

Highest incidence of postpartum depression occurs in the first 6 weeks after delivery

*J Affect Disord.* 2016;203:111. *Am J Obstet Gynecol.* 2005;192(2):522-6.

# Pathophysiology

1. Increased hormone sensitivity
2. Altered levels of neuropeptides
3. Altered levels of neurotransmitters
4. Genetics

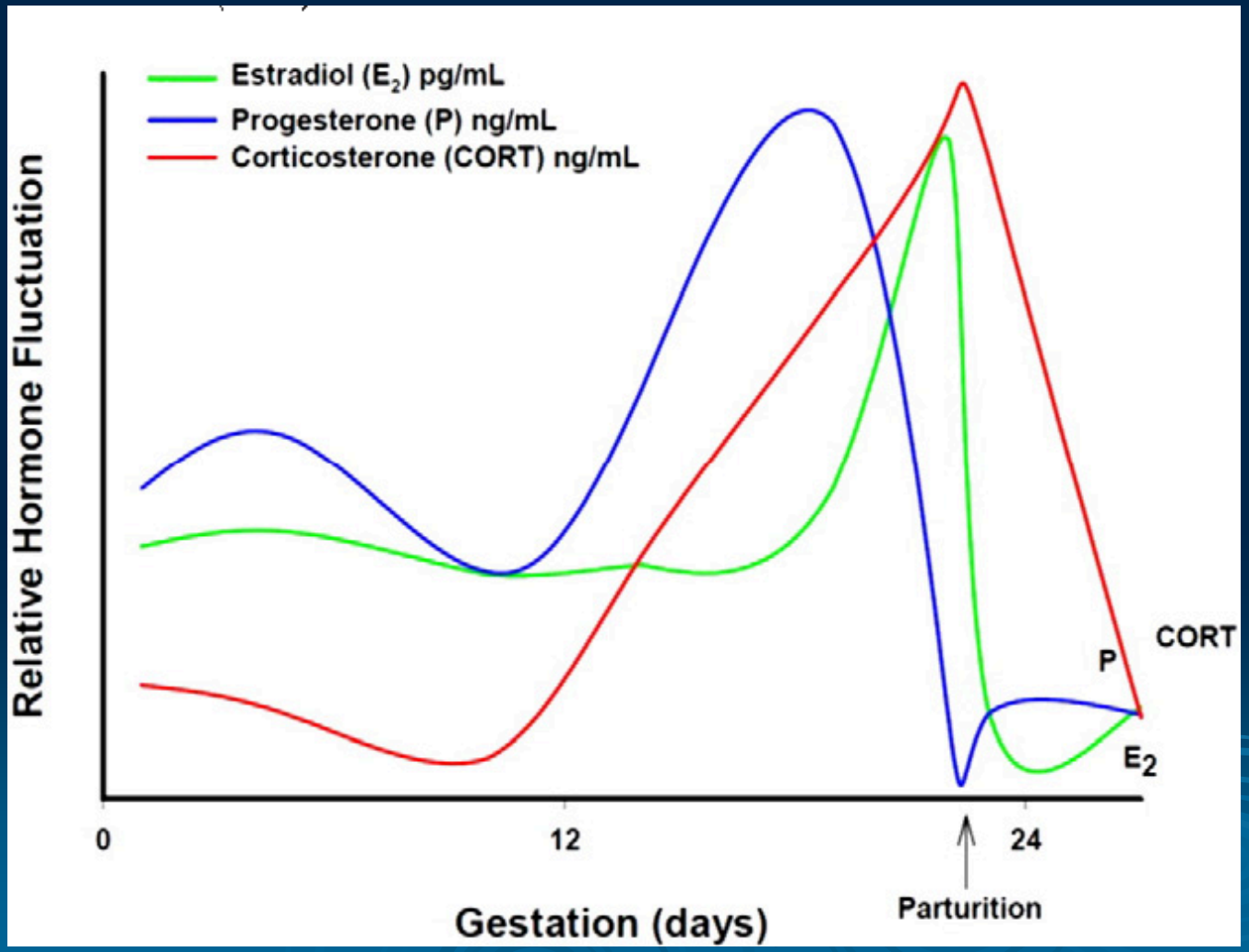
# Pathophysiology

## Increased hormone sensitivity

- Decrease in estrogen, progesterone, and cortisol
- Estrogen and progesterone are responsible for emotional processing, arousal, motivation, and cognition

*Front Neuroendocrinol.* 2019;52:165-180.

# Pathophysiology




Courtesy of Science Direct

# Pathophysiology

## Altered levels of neurotransmitters

- Elevated monoamine oxidase-A levels
- Metabolizes dopamine, norepinephrine, and serotonin

## Altered levels of neuropeptides

- Allopregnanolone increases during pregnancy, then decreases after childbirth
- Fluctuations linked to depression and anxiety

## Genetics

- Family history increases risk

*Front Neuroendocrinol.* 2019;52:165-180.

# Risk Factors

- Previous history of depression
- Family history of depression, mood disorders, or anxiety disorders
- Sexual abuse
- Negative attitude towards pregnancy
- Absence of breastfeeding
- Adolescent pregnancy
- Lack of social support
- Unhealthy lifestyle

*J Educ Health Promot*. 2017;6:60.

# Complications of PPD

- Prenatal onset associated with substance abuse, preeclampsia, and low birth weight
- Poor infant nutrition and health
- Weakened maternal-infant bonding time
- Delayed cognitive skills

*N Engl J Med.* 2016;375(22):2177-2186. *CNS Drugs.* 2019;33(3):265-282. *Neuroendocrinol.* 2019;52:165-180.

# Treatment Options for PPD

Psychosocial and psychological methods: Mild to moderate PPD

Antidepressants: Moderate to severe PPD

Hormonal therapy: Estrogen, brexanolone (Zulresso®)

# When to Consider Antidepressants

- Refractory symptoms not responding to psychological treatment
- Severe symptoms requiring rapid treatment
- Patient preference

*N Engl J Med.* 2016;375(22):2177-2186.

# Pharmacotherapy

- May improve symptoms better than non-pharmacological care
- Continue treatment for at least 6 months after effective dose determined
- Side effects may be increased in the postpartum period
- Antidepressants may take up to 4-6 weeks for maximum effects

# Pharmacotherapy

**Selection based upon:**

- Prior response to antidepressants
- Side effect profile
- Pregnancy category
- Infant exposure
- Patient preference

https://www.drugs.com/slideshow/save-money-medication-costs-1027

# Antidepressant Options

- Selective serotonin reuptake inhibitors (SSRIs)
- Serotonin norepinephrine reuptake inhibitors (SNRIs)
- Monoamine oxidase inhibitors (MAOIs)
- Tricyclic antidepressants (TCAs)

# Question #1

Select the antidepressant(s) that are considered SNRIs:

a) Citalopram (Celexa®)

b) Venlafaxine (Effexor®)

c) Paroxetine (Paxil®)

d) Duloxetine (Cymbalta®)

# Quick Review

## SSRI

- Citalopram (Celexa®)
- Escitalopram (Lexapro®)
- Fluoxetine (Prozac®)
- Paroxetine (Paxil®)
- Sertraline (Zoloft®)

## SNRI

- Desvenlafaxine (Pristiq®)
- Duloxetine (Cymbalta®)
- Levomilnacipran (Fetzima®)
- Venlafaxine (Effexor®)

## TCA

- Amitriptyline (Elavil®)
- Desipramine (Norpramin®)
- Nortriptyline (Pamelor®)

## MAOI

- Phenelzine (Nardil®)
- Tranylcypromine (Parnate®)

# Treatment

**First line:** SSRIs

- Citalopram (Celexa®), escitalopram (Lexapro®), sertraline (Zoloft®)

**Second line:** Switch agents instead of augmentation

- Different SSRI, SNRI, bupropion (Wellbutrin®), mirtazapine (Remeron®)

**Additional options:**

- Trazodone (Desyrel®), Nefazodone (Serzone®)
- TCAs

*The Canadian Journal of Psyhiatry*. 2016;61(9):502-603.

# Antidepressants to Avoid

## Pregnancy

- **Paroxetine (Paxil®)**: Risk of congenital cardiovascular malformations
- **Clomipramine (Anafranil®)**: Risk of congenital cardiovascular malformations
- **MAOIs**: Interaction with medications and foods

## Breastfeeding

- **Doxepin (Silenor®)**: High passage into breastmilk resulting in possible irritability, convulsions, and respiratory depression in the neonate
- **MAOIs**: Lack of breastfeeding data, interaction with medications and foods

*The Canadian Journal of Psyhiatry*. 2016;61(9):502-603.

# Risk Factors

- Assess benefit of breastfeeding versus risk of neonatal exposure to medication

| Low lactation risk | Moderately safe lactation risk | Hazardous lactation risk |
|---|---|---|
| • Sertraline (Zoloft®)* | • Fluoxetine (Prozac®) | • Lithium |
| • Paroxetine (Paxil®) | • Citalopram (Celexa®) | |
| • Nortriptyline (Pamelor®) | • Venlafaxine (Effexor®) | |
| | • Escitalopram (Lexapro®) | |

* Preferred

*ACOG Practice Bulletin. 2008;92:1-20.*

# Side Effects

## SSRIs

- Nausea, vomiting, diarrhea
- Headache
- Hyponatremia
- Sexual dysfunction
- QTc prolongation (citalopram (Celexa®))

## SNRIs

- Similar to SSRIs
- Seizures
- Hypertension

# Side Effects

## TCAs

- Anticholinergic side effects
- Orthostatic hypotension
- Possible fatal overdose
- Sedation

## MAOIs

- Hypertensive crisis
- Headache
- Dizziness
- Insomnia

# Hormonal Therapy

# Estrogen Therapy

- Limited evidence supporting use
- Clinical review indicates reduction in symptoms of major depression after 12 weeks in patients with severe PPD
- Place in therapy: Severe PPD, not first line therapy

*Cochrane Database Syst Rev.* 2008;4:CD001690.

# Brexanolone (Zulresso®)


Courtesy of Drug Topics

# Question #2

The mechanism of action of brexanolone (Zulresso®) is related to its direct, rapid increase of serotonin and norepinephrine in the brain

a) True

b) False

Zulresso (brexanolone) [prescribing information]. Cambridge, MA: Sage Therapeutics, Inc; June 2019.

# Question #3

Brexanolone (Zulresso®) is administered over 60 hours as a continuous infusion

a) True

b) False

Zulresso (brexanolone) [prescribing information]. Cambridge, MA: Sage Therapeutics, Inc; June 2019.

# Hormonal Therapy

Brexanolone (Zulresso®)

Endogenous hormone: positive allosteric modulator of GABA-A receptors

Only FDA approved treatment for postpartum depression in adults

Schedule IV controlled substance

Zulresso (brexanolone) [prescribing information]. Cambridge, MA: Sage Therapeutics, Inc; June 2019.

# Administration

Single continuous IV infusion over 60 hours

Approved as a risk evaluation and mitigation strategy (REMS) drug due to serious adverse reactions


Courtesy of Drug Topics

Zulresso (brexanolone) [prescribing information]. Cambridge, MA: Sage Therapeutics, Inc; June 2019.

# Adverse Reactions

| Black Box Warnings (BBW) | Adverse Drug Reactions |
| --- | --- |
| • Excessive sedation<br>• Loss of consciousness | • Suicidal thoughts and behaviors<br>• Presyncope<br>• Xerostomia |

Zulresso (brexanolone) [prescribing information]. Cambridge, MA: Sage Therapeutics, Inc; June 2019.

# Adverse Reactions

**Terminate infusion if:**

- Excessive sedation
- Loss of consciousness

→ Resume infusion at the same dose or lower dose

- Hypoxic

→ Do NOT resume infusion

Zulresso (brexanolone) [prescribing information]. Cambridge, MA: Sage Therapeutics, Inc; June 2019.

# REMS Program

| | |
|---|---|
| Healthcare settings | • Healthcare settings must be certified in the ZULRESSO REMS to administer the drug |
| Patients | • Patients must be enrolled in the ZULRESSO REMS to be able to start treatment |
| Pharmacies | • Pharmacies **outside** the healthcare setting that are preparing the drug for administration must enroll in the ZULRESSO REMS |

# Dosing

| Time | Dose |
|---|---|
| 0 to 4 hours | 30 mcg/kg/hour |
| 4 to 24 hours | 60 mcg/kg/hour |
| 24 to 52 hours | 90 mcg/kg/hour |
| 52 to 56 hours | 60 mcg/kg/hour |
| 56 to 60 hours | 30 mcg/kg/hour |

- No renal impairment dose adjustment
- No hepatic impairment dose adjustment

Zulresso (brexanolone) [prescribing information]. Cambridge, MA: Sage Therapeutics, Inc; June 2019.

# Primary Literature

**Brexanolone injection in postpartum depression: two multicenter, double-blind, randomized, placebo controlled, phase 3 trials**

*Lancet.* 2018;392(10152):1058-1070.

# Methods

**Objective**

- Assess the efficacy of brexanolone (Zulresso®) in the treatment of moderate to severe postpartum depression

**Design**

- Double-blind, randomized, placebo-controlled, phase 3 clinical trials

*Lancet.* 2018;392(10152):1058-1070.

# Methods

**Inclusion criteria**

- 18-45 YO
- ≤ 6 mo postpartum
- Qualifying HAM-D score
  - Study 1: ≥26
  - Study 2: 20-25
- Depressive episode that met DSM-IV criteria
- Negative pregnancy test

**Exclusion criteria**

- Renal failure requiring dialysis
- Anemia
- Known allergy to allopregnanolone or progesterone
- History of schizophrenia or bipolar disorder

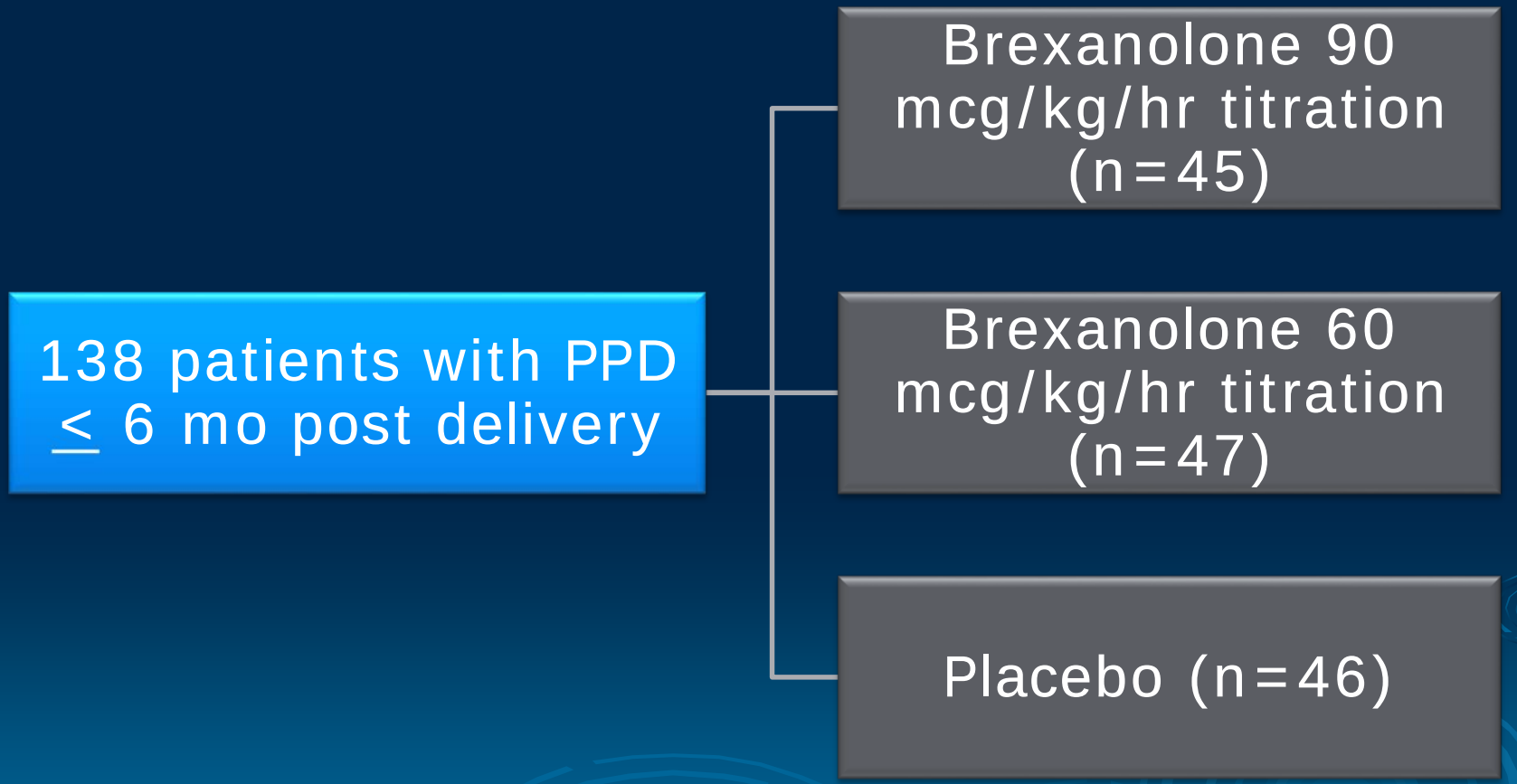
*Lancet.* 2018;392(10152):1058-1070.

# Baseline Demographics

| | | |
|---|---|---|
| Average age: 28 YO | 62% white population | Average HAM-D score: 26 |
| History of depression: Study 1: 43% Study 2: 29% | Baseline antidepressant use: Study 1: 25% Study 2: 18% | Concomitant antidepressant use: Study 1: 30% Study 2: 25% |

*Lancet.* 2018;392(10152):1058-1070.

# Study 1 Methods




*Lancet.* 2018;392(10152):1058-1070.

# Study 2 Methods

108 patients with PPD ≤ 6 mo post delivery

- Brexanolone 60 mcg/kg/hr titration (n=54)
- Placebo (n=54)

*Lancet.* 2018;392(10152):1058-1070.

# Primary Outcome

**1° Outcome:** Change from baseline in the Hamilton Depression Rating Scale (HAM-D) at 60 hours

- HAM-D determines level of depression
  - 17 item scored questionnaire
    - Mild depression: 10-13 points
    - Mild to moderate depression: 14-17 points
    - Moderate to severe depression: >17 points

*Lancet.* 2018;392(10152):1058-1070.

# HAM-D Questionnaire

## HAM-D Items

- Depressed mood
- Feelings of guilt
- Suicide
- Initial insomnia
- Insomnia during the night
- Delayed insomnia
- Work and interests
- Retardation
- Agitation

**Points:**

0- Absent
1- Sadness
2- Occasional weeping
3- Frequent weeping
4- Extreme symptoms

- Hypochondriasis
- Weight loss
- Insight

# Secondary Outcome

HAM-D score reduction at

- 0, 2, 4, 8, 12, 24, 48, 60 and 72 hours after infusion
- Follow-up days 7 and 30

# Primary Outcome Results

## Study 1

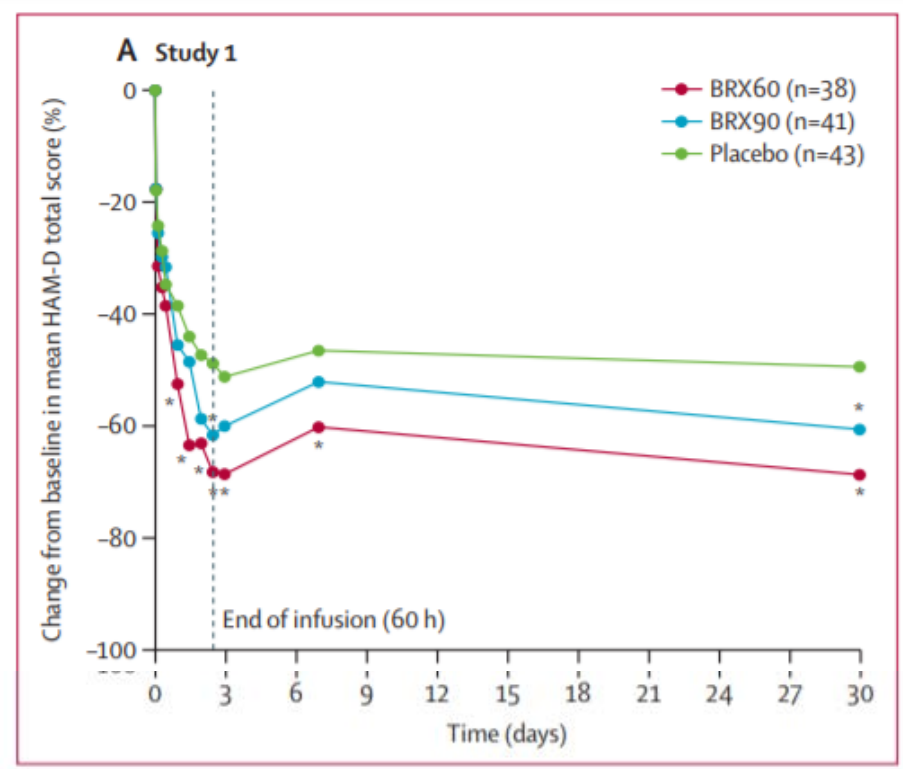
- **Brex 60:** 19.5 point reduction
  - (95% CI -8.8 to -2.2)
- **Brex 90:** 17.7 point reduction
  - (95% CI -6.9 to -0.5)

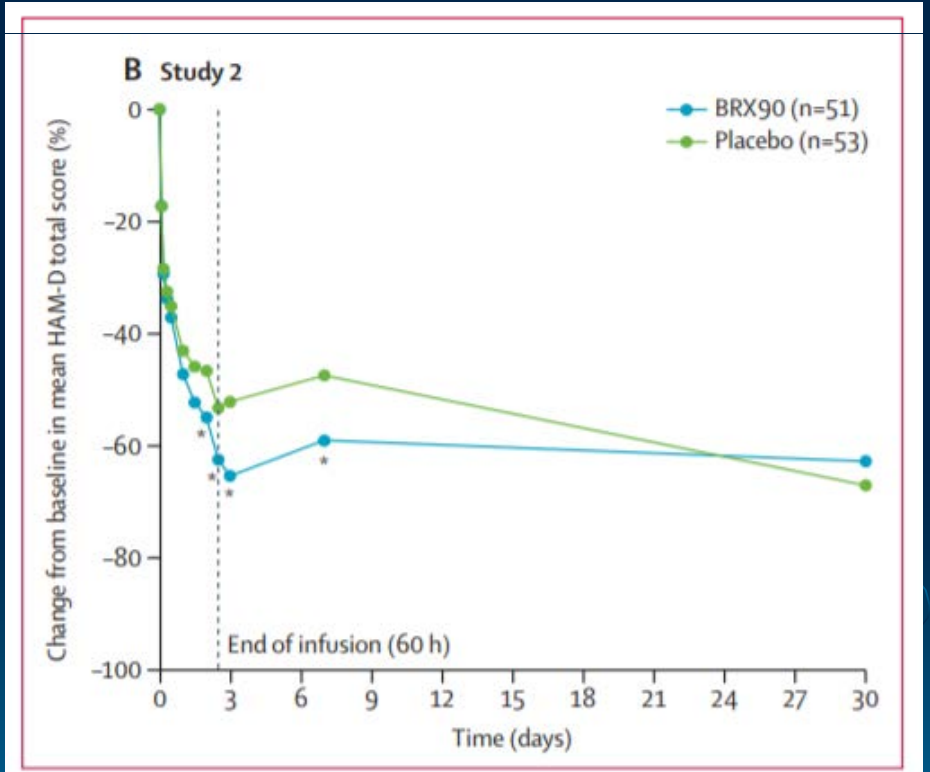
## Study 2

- **Brex 90:** 14.6 point reduction
  - (95% CI -4.5 to -0.5)

*Lancet.* 2018;392(10152):1058-1070.

# Primary Outcome Results




*Lancet.* 2018;392(10152):1058-1070.

# Secondary Outcome Results

| | Study 1 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Placebo (n=43) | BRX60 (n=38) | | | | BRX90 (n=41) | | | |
| | LS mean change from baseline (SE) | LS mean change from baseline (SE) | LS means difference* (SE) | 95% CI | p value* | LS mean change from baseline (SE) | LS means difference* (SE) | 95% CI | p value* |
| 2 h | −5·0 (0·7) | −5·0 (0·7) | 0·1 (1·0) | −1·8 to 1·9 | 0·9591 | −4·9 (0·7) | 0·2 (0·9) | −1·7 to 2·0 | 0·8677 |
| 4 h | −6·9 (0·8) | −9·0 (0·9) | −2·1 (1·2) | −4·5 to 0·3 | 0·0827 | −7·2 (0·9) | −0·3 (1·2) | −2·6 to 2·0 | 0·7968 |
| 8 h | −8·1 (0·9) | −10·2 (1·0) | −2·0 (1·3) | −4·7 to 0·6 | 0·1292 | −8·5 (1·0) | −0·4 (1·3) | −2·9 to 2·2 | 0·7801 |
| 24 h | −10·7 (1·1) | −15·0 (1·2) | −4·3 (1·6) | −7·5 to −1·1 | 0·0094 | | | | |
| 36 h | −12·6 (1·1) | −17·7 (1·2) | −5·1 (1·6) | −8·3 to −1·9 | 0·0020 | −13·9 (1·2) | −1·4 (1·6) | −4·5 to 1·8 | 0·3906 |
| 48 h | | | | | | | | | 0·0511 |
| 60 h | −17·7 (1·2) | | −3·7 (1·6) | −6·9 to −0·5 | 0·0252 | | | | 0·0252 |
| 72 h | | | | | | | | | 0·1389 |
| 7 days | −13·3 (1·3) | −17·4 (1·4) | −4·1 (1·8) | −7·7 to −0·4 | 0·0288 | −14·9 (1·3) | −1·6 (1·8) | −5·2 to 2·0 | 0·3799 |
| 30 days | −13·8 (1·3) | −19·5 (1·4) | −5·6 (1·9) | −9·5 to −1·8 | 0·0044 | −17·6 (1·4) | −3·8 (1·9) | −7·6 to 0·0 | 0·0481 |

*Lancet.* 2018;392(10152):1058-1070.

# Secondary Outcome Results

## HAM-D score reduction at 30 days

- **Study 1 BRX 60**: -13.8 vs -19.5 (95% CI -9.5 to -1.8) p=0.0044
- **Study 1 BRX 90**: -13.8 vs -17.6 (95% CI -7.6 to 0.0) p=0.0481
- **Study 2 BRX 90**: -15.2 vs -14.7 (95% -2.0 to 3.1) p=0.6710

*Lancet.* 2018;392(10152):1058-1070.

# Adverse Drug Reactions

**Study 1**

- Treatment: 41 patients
- Placebo: 22 patients

**Study 2**

- Treatment: 25 patients
- Placebo: 24 patients

*Lancet.* 2018;392(10152):1058-1070.

# Adverse Drug Reactions

## Most common

- Headache: 22 patients
- Dizziness: 17 patients
- Somnolence: 13 patients

## Serious

- Suicidal ideation: 1 patient
- Intentional overdose attempt during follow-up: 1 patient
- Altered state of consciousness: 1 patient
- Syncope: 1 patient

*Lancet.* 2018;392(10152):1058-1070.

# Study Conclusions

- Brexanolone (Zulresso®) administration resulted in significant and clinically meaningful reductions in HAM-D total score at 60 hours compared to placebo in women suffering with moderate to severe PPD
- Brexanolone (Zulresso®) is associated with rapid onset of action and durable treatment response
- Due to minimal concomitant antidepressant use, brexanolone (Zulresso®) should be utilized as primary therapy in PPD

*Lancet.* 2018;392(10152):1058-1070.

# Brexanolone (Zulresso®) Place in Therapy

Guidelines do not recommend use → Moderate to severe PPD → Adults ≤6 mo postpartum

# Hospital Logistics

- Sufficient budget to approve use
- Medication training for physicians, nurses, and pharmacists
- Stored in the pharmacy's controlled substance safe
- Must be administered in a hospital through a REMS program
- Increased nursing staff required for drug administration and continuous pulse oximetry monitoring

# Patient Logistics

- REMS enrollment
- Drug education prior to administration
- Minimum length of stay: 2.5 days
- Must be accompanied during interaction with children
- Insurance coverage

Courtesy of Women's Mental Health

# Question #4

Brexanolone (Zulresso®) has a BBW for suicidal thoughts and behaviors

a) True

b) False

Brexanolone has a warning for suicidal thoughts and behaviors, not a BBW. It has a BBW for excessive sedation and sudden loss of consciousness

Zulresso (brexanolone) [prescribing information]. Cambridge, MA: Sage Therapeutics, Inc; June 2019.

# Thank you!

# Postpartum Depression! One IV and I am Back to Happy!

Gabrielle DuBruille, PharmD
PGY-1 Resident Pharmacist
Boca Raton Regional Hospital
Baptist Health South Florida

# References


- American Psychiatric Association (APA). Diagnostic and statistical manual of mental disorders. APA; 2013.
- Dennis CL, Ross LE, Herxheimer A. Oestrogens and progestins from preventing and treatment postpartum. *Cochrane Database Syst Rev.* 2008;4:CD001690.
- Fisher SD, Wisner KL, Clark CT, et al. Factors associated with onset timing, symptoms, and severity of depression identified in the postpartum period. *J Affect Disord.* 2016;203:111.
- Frieder A, Fersh M, Hainline R, Deligiannidis. Pharmacotherapy of postpartum depression Current approaches and novel drug development. *CNS Drugs.* 2019;33(3):265-282.
- Ghaedrahmati M, Kazemi A, Kheirabadi G, Ebrahimi A, Bahrami M. Postpartum depression risk factors: A narrative review. *J Educ Health Promot*. 2017;6:60.
- McCurdy AP, Boule NG, Sivak A, Davenport MH. Effects of exercise on mild to moderate depressive symptoms in the postpartum period: a meta-analysis. *Obstet Gynecol.* 2017;129(6):1087-1097.
- Meltzer-Brody A, Colquhoun H, Riesenberg R, et al. Brexanolone injection in postpartum depression: two multicenter, double-blind, randomized, placebo-controlled, phase 3 trials. *Lancet.* 2018;392(10152):1058-1070.
- Patten SB. Updated CANMAT guidelines for treatment of major depressive disorder. *The Canadian Journal of Psyhiatry.* 2016;61(9):502-603.
- Payne JL, Maguire J. Pathophysiological mechanisms implicated in postpartum depression. *Front Neuroendocrinol.* 2019;52:165-180.
- Schiller CE, Meltzer-Brody S, Rubinow DR. The role of reproductive hormones in postpartum depression. *CNS Spectr.* 2015;20(1):48-59.
- Segre LS, Davis WN. Postpartum Depression and Perinatal Mood Disorders in the DSM. *Postpartum Support International.* 2013; 1-6.
- Stewart DE, Vigod S. Postpoartum Depression. *N Engl J Med.* 2016;375(22):2177-2186.
- Stowe ZN, Hostetter AL, Newport DJ. The onset of postpartum depression: implications for clinical screening in obstetrical and primary care. *Am J Obstet Gynecol.* 2005;192(2):522-6.
- Use of psychiatric medications during pregnancy and lactation. *ACOG Practice Bulletin. 2008;92:1-20.*
- Vesga-Lopez O, Blanco C, Keyes K, et al. Psychiatric disorders in pregnant and postpartum women in the United States. Arch Gen Psychiatry. 2008;65(7):805.
- Zhou J, Ko JY, Haight SC, Tong VT. Treatment of substance use disorders among women of reproductive age by depression and anxiety disorders status. *J Womens Health.* 2019;28(8):1068-1076.
- Zulresso (brexanolone) [prescribing information]. Cambridge, MA: Sage Therapeutics, Inc; June 2019.