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

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

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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

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

Courtesy of parents.com
What is PPD?

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

Courtesy of PBS
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
Diagnostic Criteria

- Diagnostic and statistical manual for mental disorders (DSM)

Courtesy of American Psychiatric Association
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

**DSM-5 Criteria**

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

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Depressed mood</td>
</tr>
<tr>
<td>2.</td>
<td>Loss of interest</td>
</tr>
<tr>
<td>3.</td>
<td>Weight loss or weight gain</td>
</tr>
<tr>
<td>4.</td>
<td>Insomnia or hypersomnia</td>
</tr>
<tr>
<td>5.</td>
<td>Psychomotor agitation or retardation</td>
</tr>
<tr>
<td>6.</td>
<td>Fatigue</td>
</tr>
<tr>
<td>7.</td>
<td>Feelings of worthlessness</td>
</tr>
<tr>
<td>8.</td>
<td>Diminished ability to think or concentrate</td>
</tr>
<tr>
<td>9.</td>
<td>Recurrent thoughts of death, suicidal ideation, suicide attempt</td>
</tr>
</tbody>
</table>

PPD Diagnostic Criteria

- Same DSM-5 criteria as MDD, but a specifier was created:
  - With peripartum onset
  - Onset of depressive episode during pregnancy or within 4 weeks postpartum

Prevalence

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

(J Womens Health. 2019;28(8):1068-1076.)
High incidence of postpartum depression occurs in the first 6 weeks after delivery.
Pathophysiology

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

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

Pathophysiology
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
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
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

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

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)
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®)

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

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

#### MAOI
- Phenelzine (Nardil®)
- Tranylcypromine (Parnate®)
Treatment

First line: SSRI's
- 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

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

Risk Factors

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

Low lactation risk

• Sertraline (Zoloft®)*
• Paroxetine (Paxil®)
• Nortriptyline (Pamelor®)

Moderately safe lactation risk

• Fluoxetine (Prozac®)
• Citalopram (Celexa®)
• Venlafaxine (Effexor®)
• Escitalopram (Lexapro®)

* Preferred

Hazardous lactation risk

• Lithium

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

Brexanololone (Zulresso®)

Courtesy of Drug Topics
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
Question #3

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

a) True

b) False
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
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
### Adverse Reactions

#### Black Box Warnings (BBW)
- Excessive sedation
- Loss of consciousness

#### Adverse Drug Reactions
- Suicidal thoughts and behaviors
- Presyncope
- Xerostomia

Adverse Reactions

Terminate infusion if:

- Excessive sedation
- Loss of consciousness
- Hypoxic

Resume infusion at the same dose or lower dose

Do NOT resume infusion

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

<table>
<thead>
<tr>
<th>Time</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 4 hours</td>
<td>30 mcg/kg/hour</td>
</tr>
<tr>
<td>4 to 24 hours</td>
<td>60 mcg/kg/hour</td>
</tr>
<tr>
<td>24 to 52 hours</td>
<td>90 mcg/kg/hour</td>
</tr>
<tr>
<td>52 to 56 hours</td>
<td>60 mcg/kg/hour</td>
</tr>
<tr>
<td>56 to 60 hours</td>
<td>30 mcg/kg/hour</td>
</tr>
</tbody>
</table>

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

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

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

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
Baseline Demographics

Average age: 28 YO

History of depression:
Study 1: 43%
Study 2: 29%

62% white population

Baseline antidepressant use:
Study 1: 25%
Study 2: 18%

Average HAM-D score: 26

Concomitant antidepressant use:
Study 1: 30%
Study 2: 25%

Study 1 Methods

138 patients with PPD ≤ 6 mo post delivery

- Brexanolone 90 mcg/kg/hr titration (n=45)
- Brexanolone 60 mcg/kg/hr titration (n=47)
- Placebo (n=46)
Study 2 Methods

108 patients with PPD ≤ 6 mo post delivery

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

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

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)

Primary Outcome

Results

## Secondary Outcome Results

<table>
<thead>
<tr>
<th>Study 1</th>
<th>Placebo (n=43)</th>
<th>BRX60 (n=38)</th>
<th>BRX90 (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LS mean change from baseline (SE)</td>
<td>LS mean change from baseline (SE)</td>
<td>LS means difference* (SE)</td>
</tr>
<tr>
<td>2 h</td>
<td>-5.0 (0.7)</td>
<td>-5.0 (0.7)</td>
<td>0.1 (1.0)</td>
</tr>
<tr>
<td>4 h</td>
<td>-6.9 (0.8)</td>
<td>-9.0 (0.9)</td>
<td>-2.1 (1.2)</td>
</tr>
<tr>
<td>8 h</td>
<td>-8.1 (0.9)</td>
<td>-10.2 (1.0)</td>
<td>-2.0 (1.3)</td>
</tr>
<tr>
<td>24 h</td>
<td><strong>-10.7 (1.1)</strong></td>
<td><strong>-15.0 (1.2)</strong></td>
<td><strong>-4.3 (1.6)</strong></td>
</tr>
<tr>
<td>36 h</td>
<td>-12.6 (1.1)</td>
<td>-17.7 (1.2)</td>
<td>-5.1 (1.6)</td>
</tr>
<tr>
<td>48 h</td>
<td>-18.6 (1.2)</td>
<td>-23.1 (1.4)</td>
<td>-4.5 (1.7)</td>
</tr>
<tr>
<td>60 h</td>
<td><strong>-17.7 (1.2)</strong></td>
<td><strong>-3.7 (1.6)</strong></td>
<td><strong>-6.9 to -0.5</strong></td>
</tr>
<tr>
<td>72 h</td>
<td>-14.7 (1.2)</td>
<td>-19.7 (1.3)</td>
<td>-5.0 (1.7)</td>
</tr>
<tr>
<td>7 days</td>
<td>-13.3 (1.3)</td>
<td>-17.4 (1.4)</td>
<td>-4.1 (1.8)</td>
</tr>
<tr>
<td>30 days</td>
<td>-13.8 (1.3)</td>
<td>-19.5 (1.4)</td>
<td>-5.6 (1.9)</td>
</tr>
</tbody>
</table>

Secondary Outcome

Results

- **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)  
  \[p=0.6710\]
Adverse Drug Reactions

Study 1
- Treatment: 41 patients
- Placebo: 22 patients

Study 2
- Treatment: 25 patients
- Placebo: 24 patients
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
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.
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
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.
Thank you!
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References

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