Moms' Access Project ECHO

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Project ECHO®

Brexanolone (Zulresso)

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Speaker Disclosures

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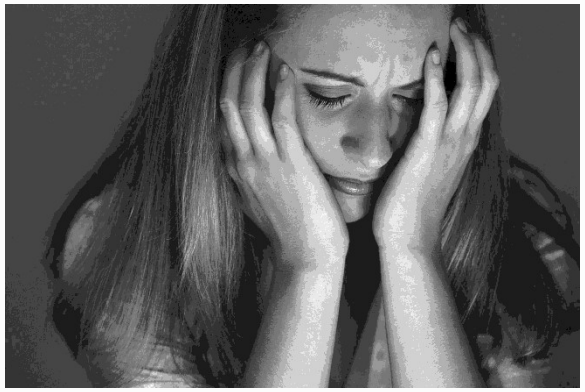
Learning Objectives

- Review risk of postpartum depression and consequences for mother and baby
- Review current pharmacologic treatment options
- Describe basic pharmacology of Brexanolone, clinical studies and indication
- Summarize side effects, administration parameters, breastfeeding and cost

Background



- Postpartum depression affects up to 20% women after childbirth
- Serious consequences for mother and baby

"Every year, more than 400,000 infants are born to mothers who are depressed, which makes perinatal depression the most under diagnosed obstetric complication in America. Postpartum depression leads to increased costs of medical care, inappropriate medical care, child abuse and neglect, discontinuation of breastfeeding, and family dysfunction and adversely affects early brain development."

Pediatrics, 2010; 126; 1032-1039

Psychopharmacologic Treatment

- Selective serotonin re-uptake inhibitors (SSRIs) generally used for initial treatment of moderate to severe PPD
- Data on efficacy mixed and maximal effects achieved after several weeks
- Serotonin norepinephreine reuptake inhibitors (SNRIs) and Tricyclic antidepressants (TCAs) also used; data on efficacy limited
- ECT rapid and effective

Progesterone in the Perinatal Period

- Levels of progesterone rise throughout pregnancy; drop precipitously after delivery
- Allopregnanolone is a metabolite of progesterone and a GABAA modulator
- Allopregnanolone levels change in parallel with progesterone
- Animal models showed significant effect of allopregnanalone on anxiety and depression

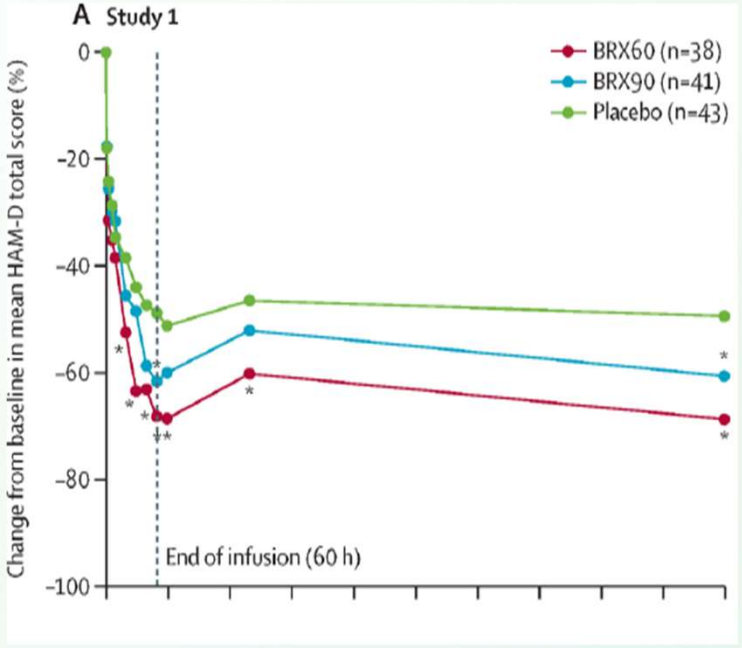
Brexanolone Basics

- First drug approved by FDA for treatment of postpartum depression
- Chemically identical to allopregnanolone
- GABA-A receptor modulator (these receptors may not adapt to rapid changes in the PP period)
- Five vials of Brexanolone (amount for treatment of woman <90 kg) cost $ 34,000

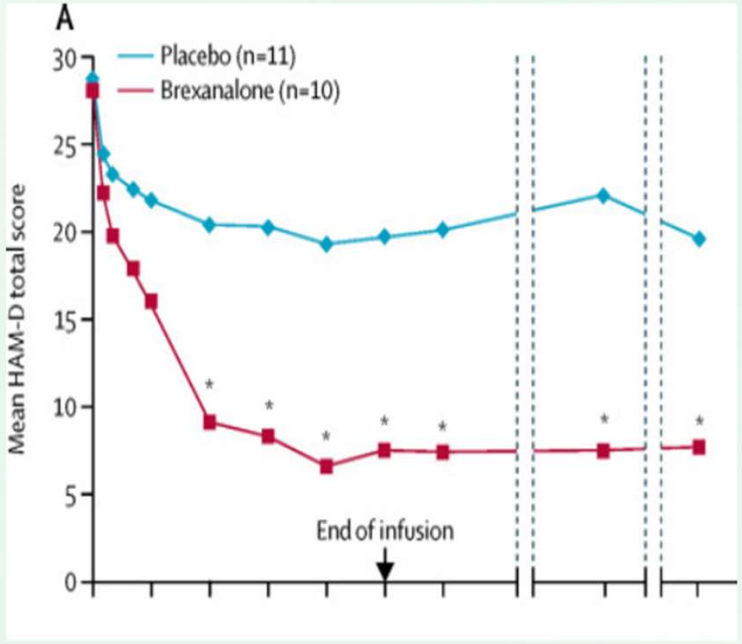
Clinical Studies

- Approval based on results of 2 randomized, double-blind, placebo-controlled trials
- Included 246 women who were < 6 months PP
- Inclusion criteria; onset of MDD in 3rd trimester or within 4 weeks postpartum
- Women in study 1: HAM-D scores > 26 (severe)
  Study 2: HAM-D scores 20-25 (moderate)
- In both trials HAM-D scores were significantly lower at end of infusion
- After 30 days, HAM-D scores remained lower in women in study 1, but not 2

Clinical Studies



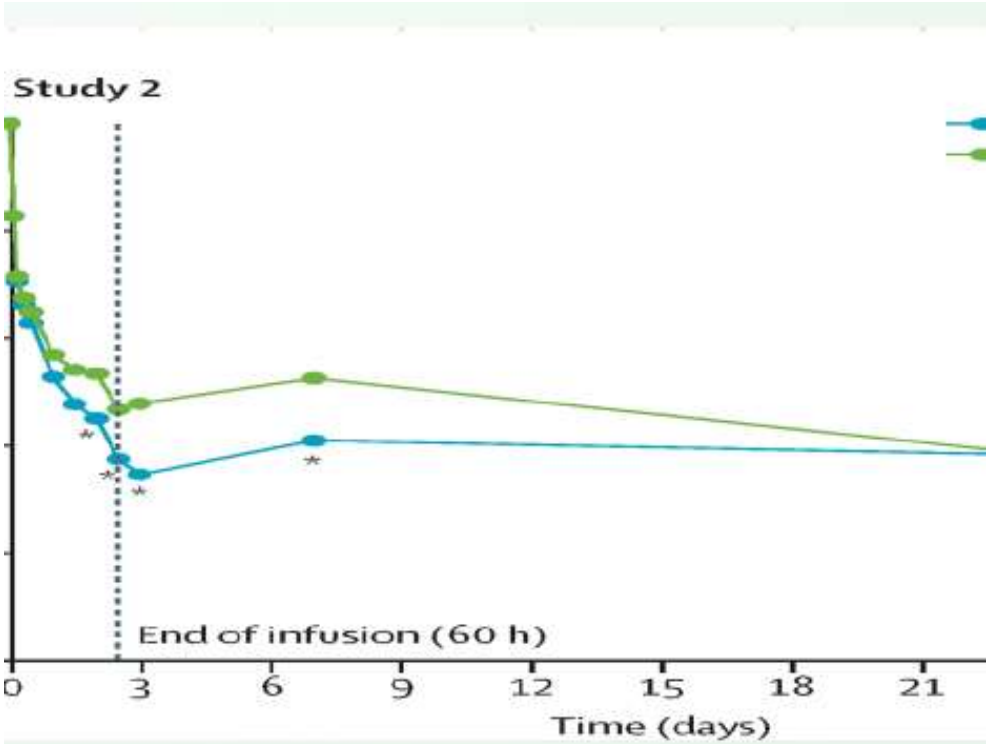
(FIGURE 2; MELTZER-BRODY ET AL, 2018)



(FIGURE 2; KANES ET AL, 2017)

Clinical Studies

- Brx group lost advantage at day 30
- May be due to high placebo response rate
- Women with moderate (HAM-D 20 to 25) rather than severe (HAMD > 26) depression



(Figure 2; Meltzer-Brody et al, 2018)

Meta analysis of all trials

- Statistically significant advantage of brexanolone over placebo started at 24 hours, peaked at 36 hours and lasted at least 7 days
- Large effect sizes:
  - **Response NNT 4 to 7**
  - **Remission NNT 3 to 8**

Zheng et al, 2019

Administration and side effects

- Administered as IV infusion over 60 hours
- Side effects based on initial clinical trials:
  - Sedation/somnolence
  - Headaches
  - Dizziness
  - Pre-syncope/vertigo
  - Dry mouth
  - Hot flash
  - Loss of consciousness

REMS

- FDA instituted a Risk Evaluation and Mitigation Strategy (REMS) program 2/2 risk of loss of consciousness
- Requires that pharmacies/healthcare facilities purchasing and dispensing medication are certified
- Continuous supervision during administration is required
  - Continuous pulse oximetry
  - Monitoring q 2 hours for excessive sedation (non-sleep hours)
  - Stop treatment for hypoxemia; for excessive sedation, stop infusion and resume when sx resolve

Pregnancy and Lactation

- Not approved for use in pregnant women
  - Developmental toxicities in animals given higher than recommended human dose
- Drug has low bioavailability, not expected to adversely affect breastfeed infants
- No women breastfeed during study

Practical considerations

- No formal policy for CMS
- Other policies mirror inclusion criteria from the RCTs
- Might require prior authorization or letter of medical necessity
- Some plans require evidence of treatment resistance
- Implementation: Who is the primary team?

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- Zheng, W., Cai, D. B., Sim, K., Ungvari, G. S., Peng, X. J., Ning, Y. P., ... & Xiang, Y. T. (2019). Brexanolone for postpartum depression: a meta-analysis of randomized controlled studies. *Psychiatry research*.

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