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New Approaches to Postpartum Depression

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- ***Consultant:*** Fabre-Kramer Pharmaceuticals, Inc.; Palatin Technologies, Inc.; S1 Biopharma, Inc.; Sprout Pharmaceuticals, Inc. (a division of Valeant Pharmaceuticals); Fee to UVA – Takeda Pharmaceuticals U.S.A., Inc.
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- **Royalties/Copyright:** Balantine Books**;** Guildford Pub; CSFQ (Changes in Sexual Functioning Questionnaire)

Learning Objective 1

Increase screening by 50% for postpartum depression (PPD) in at-risk patients.

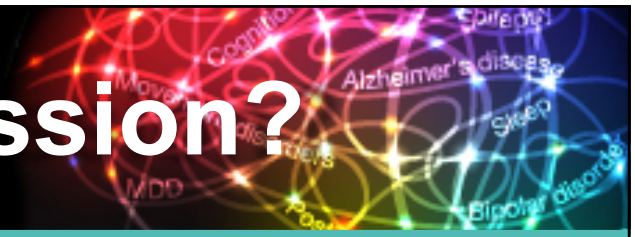
Learning Objective 2

Examine current strategies to improve clinical outcomes in PPD.

Learning Objective 3

Evaluate the benefits and risks of emerging therapies in improving treatment response and remission in PPD.

What is Postpartum Depression?



- The Baby Blues may affect up to 80% of new mothers and is manifested by brief (1-2 weeks) of mild worry, unhappiness, emotional lability, crying, fatigue
- Postpartum depression is major depressive episode beginning within 4 weeks of childbirth (may start later after weaning in breastfeeding women)
  - Appears to be related to rapid (in first 3-5 days after delivery) drop from extremely high levels of estrogen and progesterone during pregnancy to pre-pregnancy levels
  - Some women are particularly sensitive to normal hormonal changes (e.g. PMDD, perimenopausal depression, etc.)

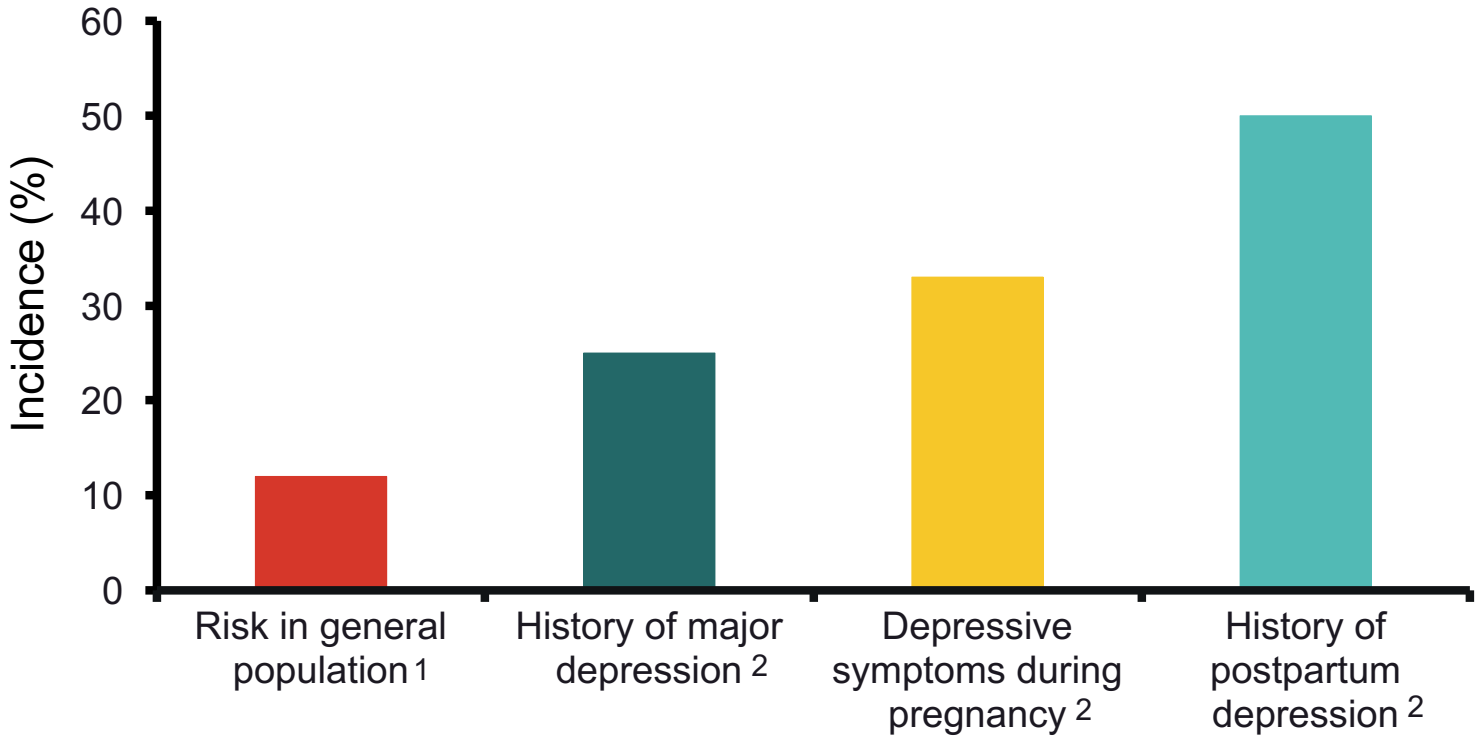
NIMH website. Available at https://www.nimh.nih.gov/health/publications/postpartum-depression-facts/index.shtml. Accessed October 24, 2017.

Perinatal Depression is Common

- The highest rates for depression occur in women ages 25 to 44
- Postpartum depression is seen in 10% – 15% of women.[4] Postpartum PTSD in 4%[2], up to 18% with severe complications at birth.[5]
- OCD rates of 2.4%.[3]
- Depression may also follow pregnancy loss, with severity proportional to gestational age at miscarriage

1. Wisner KL, et al. *JAMA Psychiatry* 2013;70(5):490-498; 2. Grekin R, O'Hara MW. *Clinical Psychology Review* 2014;34:389-401; 3. Russell EJ, et al. *J Clin Psychiatry* 2013;74(4):377-385.

Psychiatric History Predicts Risk of Depression in the Postpartum Period



1. O'Hara MW, et al. *J Abnorm Psychol*. 1984;93:158-171.
2. O'Hara MW, et al. *Postpartum Depression: Causes and Consequences*. 1995.

Screening Tool: Edinburgh Postnatal Depression Scale (EPDS)

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

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

***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

4. I have been anxious of worried for no good reason

- ❑ No, not at all
- ❑ Hardly ever
- ❑ Yes, sometimes
- ❑ Yes, very often

***5. I have felt scared of panicky for no very good reason**

- ❑ Yes, quite a lot
- ❑ Yes, sometimes
- ❑ No, not much
- ❑ No, not at all

***6. Things have been getting on top of me**

- ❑ Yes, most of the time I haven't been able to cope well
- ❑ 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

***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

***8. I have felt sad or miserable**

- ❑ Yes, most of the time
- ❑ Yes, quite often
- ❑ Not very often
- ❑ No, not at all

***9. I have been so unhappy that I have been crying**

- ❑ Yes, most of the time
- ❑ Yes, quite often
- ❑ Only occasionally
- ❑ No, never

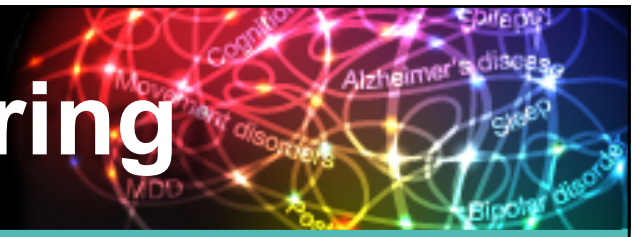
***10. the thought of harming myself has occurred to me**

- ❑ Yes, quite often
- ❑ Sometimes
- ❑ Hardly ever
- ❑ Never

*questions are reverse scored

Cox JL, et al. *Br J Psychiatry.* 1987;150:782-786.

Screening Tool: EPDS Scoring



- Questions 1, 2, & 4
  - Are scored 0, 1, 2 or 3 with top box scored as 0 and the bottom box scored as 3
- Questions 3, 5-10
  - Are reverse scored, with the top box scored as a 3 and the bottom box scored as 0
- Maximum score: 30
  - Positive depression: 10 or greater
  - Always look at item 10 (suicidal thoughts)

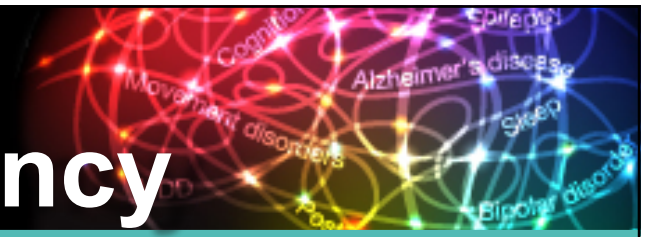
Cox JL, et al. *Br J Psychiatry.* 1987;150:782-786.

Postpartum Depression Screening

- 10,000 women 4-6 weeks postpartum completed the Edinburgh Postnatal Depression Scale (EPDS)
- 14% were screen-positive with score ≥10; these women more likely to be younger, black, publically insured, single and less well educated
- 40% of episodes began postpartum, 33% during pregnancy, 27% before pregnancy
- Almost 20% had self-harm ideation
- 69% had MDD, 2/3 had comorbid anxiety disorders, and 23% had BPAD (assoc. with increased risk of postpartum psychosis)

Wisner KL, et al. *JAMA Psychiatry.* 2013;70(5):490-498.

Effects of Untreated Depression During Pregnancy



- Inadequate nutrition
- Sleep disturbance
- Non-compliance with prenatal care
- Substance abuse
- Poor maternal – child bonding
- Spontaneous abortion
- Low birth-weight infants and slow weight gain
- Delayed developmental milestones
- Cognitive and psychological problems in the child
- Postpartum depression

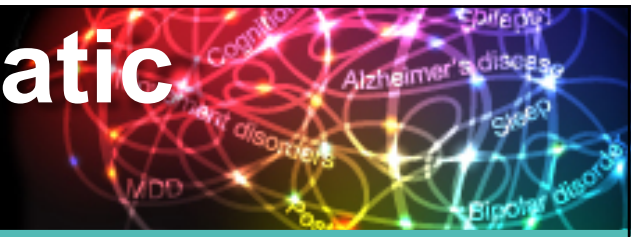
ACOG Committee. *Obstetrics & Gynecology*. 2008;111(4):1001-1020.

Current Management of MDD in Pregnancy

- Psychotherapy: Interpersonal therapy (IPT),[1] cognitive behavioral therapy (CBT)[2]
- Antidepressants
  - No well-controlled studies in pregnancy,[2,3] but no generalized increased risk of teratogenesis or neurobehavioral sequelae[4]
  - Possible bupropion, buspirone, estradiol,[5] antipsychotic (quetiapine) or thyroid augmentation
  - Avoid paroxetine, benzodiazepines, valproate, lithium, carbamazepine, TCAs
- Other: electroconvulsive therapy,[6] support groups[7]
- Potential risks of treatment must be weighed against known risks of untreated illness to mother and fetus[1-3]

1. Spinelli MG, et al. *J Clin Psychiatry.* 2013;74(4):393-399. 2. Nonacs R, et al.. *Psychiatr Clin NA.* 2003;26:547-562; 3. Stowe ZN, et al. *CNS Spectrums.* 2001;6:150-166; 4. Byatt N, et al. *Acta Psychiatr Scand.* 2013;127:94-114. 5. Moses-Kolko EL, et al. *Clinical Obstet & Gynecol.* 2009;52(3):516-529; 6. Leiknes KA, et al. *Arch Womens Ment Health*. 2015;18:1-39. 7. Tripathy P, et al. *Lancet*. 2010;375(9721):1182-1192.

Meta-analyses and Systematic Reviews



- Data from 20 epidemiologic studies
- Conflicting conclusions regarding the safety of antidepressant use during pregnancy
- Studies have methodological limitations:
  - Data from retrospective studies
  - Incomplete information on timing of exposure and dosages

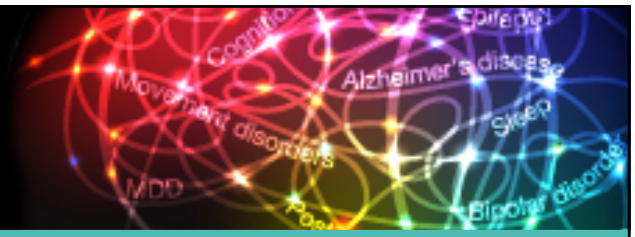
Gentile S. *Acta Psychiatr Scand.* 2011;123:266-275; Wurst KE, et al. *Birth Defects Res A Clin Mol Teratol*. 2010;88:159-170; de Crescenzo F, et al. *J Affect Disord.* 2014;154:39-44.

Risk of Psychotropic Exposure

- During pregnancy (across the placenta)
  - Somatic teratogenicity
  - Neonatal toxicity
  - Long-term neurobehavioral effects
- With lactation (in breast milk), exposure determined by:
  - The rate of absorption into maternal circulation
  - Diffusion from maternal circulation to breast milk
  - Absorption/metabolism of the agent by the infant

FDA Pregnancy and Lactation Labeling Final Rule (PLLR) went into effect 6/30/15.
Requires narrative of risk summary, clinical considerations, and data.

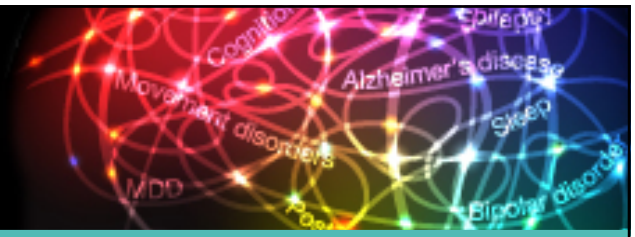
SSRI Antidepressants



- In pregnancy, all have risks similar to general population except paroxetine due to heart malformations.
- Most data available for fluoxetine. May need to maximize dose for depression remission (increased volume of distribution, increased metabolism).
- Lactation: recommend sertraline due to short half-life and undetectable levels in breast milk, especially at doses <100 mg/d

ACOG Committee. *Obstetrics & Gynecology*. 2008;111(4):1001-1020.

Other Antidepressants



- No increase in congenital malformations with bupropion; SNRIs (venlafaxine, duloxetine) but data limited; trazodone; mirtazapine
- TCAs: Not recommended in pregnancy (orthostatic hypotension at delivery); avoid doxepin with lactation

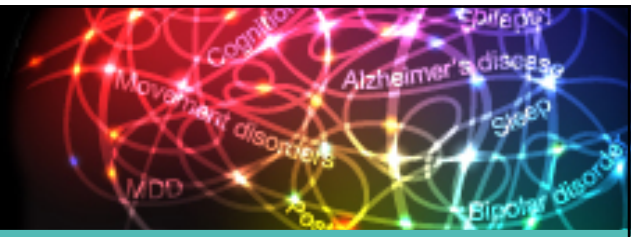
ACOG Committee. *Obstetrics & Gynecology*. 2008;111(4):1001-1020.

Clinical Considerations in Breastfeeding Women

- Treatment of breastfeeding mothers requires careful risk-benefit assessment
- Must weigh risk of treatment against risk of untreated illness to mother and infant
  - Maternal depression has adverse effects on infants
  - All antidepressants are excreted into human breast milk
- Additional factors to consider:
  - Severity of depressive illness, past psychiatric history, history of previous treatment response, available safety data in lactation

Newport J, et al. *Semin Perinatol*. 2001;25:177-190; Stowe ZN, et al. *CNS Spectrums*. 2001;6:150-166; Newport J, et al. *Psychopharmacol Bulletin*. 2003; 37:148-166; Nonacs R, et al. *J Clin Psychiatry*. 1998;59(suppl 2):34-40.

Medications in Lactation

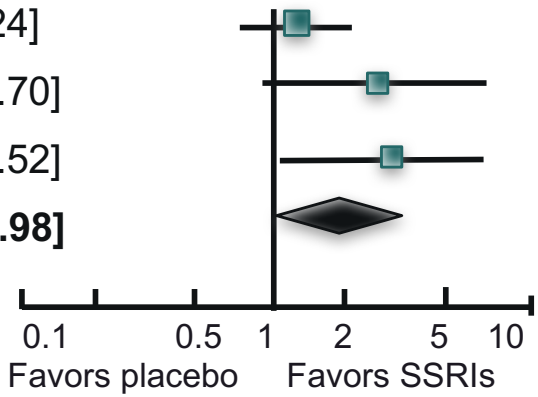


- Drugs taken by mother pass to infant:
  - Avoid lamotrigine (monitor for rash in infant), lithium (levels in breast milk similar to maternal serum), valproate and carbamazepine (potential hepatotoxicity requires monitoring of liver function tests, bilirubin, white blood cells), benzodiazepines (CNS depression), doxepin, TCAs (constipation in baby)
- Relatively safe: newer antidepressants (sertraline and bupropion have lowest levels in breast milk), z-drug hypnotics, buspirone, newer antipsychotics

ACOG Committee. *Obstetrics & Gynecology*. 2008;111(4):1001-1020.

Remission Rate of SSRIs in Postpartum Depression

Study or Subgroup	SSRIs Events	SSRIs Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Bloch 2012 (1)	13	20	10	20	52.7%	1.3 [0.75, 2.24]
Hantsoo 2013 (2)	9	17	4	19	22.4%	2.51 [0.94, 6.70]
Yonkers 2008 (3)	13	35	5	35	24.9%	2.60 [1.04, 6.52]
Total (95% CI)		**72**		**74**	**100%**	**1.79 [1.08, 2.98]**
Total events	35		19			



Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 2.61$, df = 2 ($p = .27$); $I^2 = 23\%$

Test for overall effect: $Z = 2.25$ ($p = .02$)

(1) Sertraline + psychological therapy (brief dynamic psychotherapy) vs. placebo + psychological therapy (brief dynamic psychotherapy)

(2) Sertraline vs. placebo

(3) Paroxetine vs. placebo

Molyneaux E, et al. *Cochrane Database Syst Rev*. 2014;(9):CD002018.

Summary of Randomized Controlled Trials (RCT) of Postpartum Antidepressant Efficacy

Study Design	Sample Size (N)	Treatment Duration	Intervention	Remission Rate	Comments
Double-blind RCT	87	12 weeks	Fluoxetine + 1 or 6 CBT sessions vs. placebo + 1 or 6 CBT sessions	Not reported	No advantage of combining both fluoxetine and CBT
RCT	35	12 weeks	Paroxetine vs. paroxetine + CBT	87.5% (paroxetine) vs 78.9% (paroxetine + CBT)	Both groups had significant improvement in mood ($p < .01$)
RCT	109	8 weeks + 16 weeks follow-up	Sertraline vs. nortriptyline	46% (sertraline) vs. 56% (nortriptyline)	No differences at 4, 8, and 24 weeks

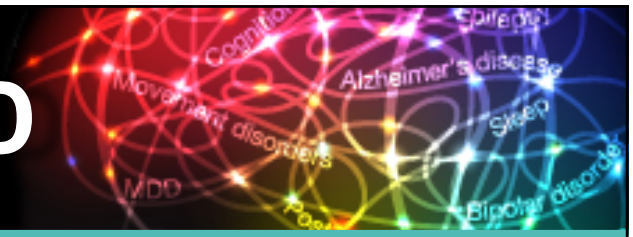
Sharma V, et al. *Prim Care Companion CNS Disord*. 2013;15(6):PMC3977774.

Summary of Randomized Controlled Trials (RCT) of Postpartum Antidepressant Efficacy

Study Design	Sample Size (N)	Treatment Duration	Intervention	Remission Rate	Comments
Double-blind RCT	60	8 weeks	Paroxetine vs. placebo	43% (paroxetine) vs. 32% (placebo)	No statistically significant difference
RCT	254	18 weeks	Antidepressants vs. nondirective counseling	45% (antidepressant) vs. 20% (nondirective counseling) at 4 weeks	Antidepressants were significantly better at 4 weeks, but no statistically significant difference at 18 weeks
Double-blind RCT	44	8 weeks	Sertraline + psychotherapy vs. placebo + psychotherapy	65% (sertraline + psychotherapy) vs. 50% (placebo + psychotherapy)	No significant difference

Sharma V, et al. *Prim Care Companion CNS Disord*. 2013;15(6):PMC3977774.

Emerging Therapies in PPD

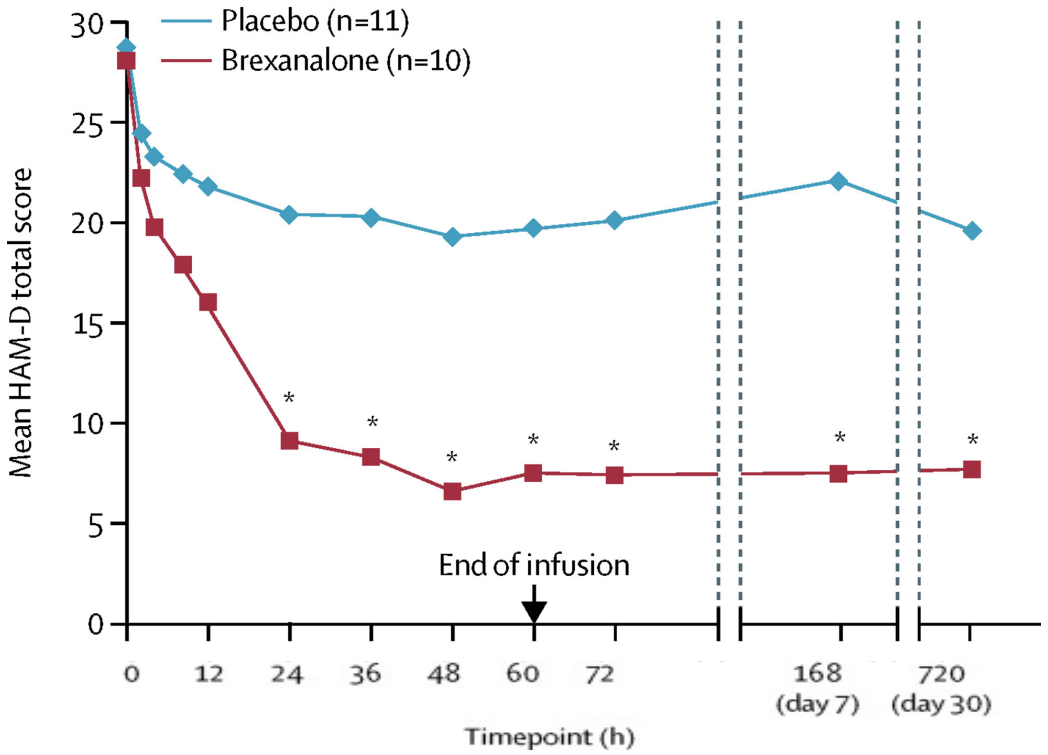


- Brexanolone,* IV form of allopregnanolone, positive allosteric modulator of synaptic and extrasynaptic $GABA_A$ receptors
- RCT of 21 women 18 - 45 years old, $\leq$ 6 months postpartum with severe PPD (HAM-D score $\geq$ 26) that began between 3rd trimester and 4 weeks postpartum
- Could continue on stable antidepressants/no change (27% - 30%)
- Breastfeeding held from screening through Day 12
- Randomized to 60 hour infusion of brexanolone or placebo as inpatient; follow-up to day 30

*Brexanolone is under investigation for the specific treatment of PPD.

Kanes S, et al. Lancet. 2017;390:480-489.

Brexanolone* vs. Placebo in Reducing HAM-D Scores



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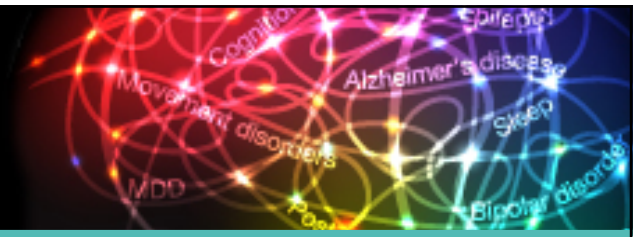
Kanes S, et al. *Lancet* 2017;390:480-489.

Efficacy Results



- At 60 hours, mean reduction HAM-D total score was 21.0 pts in brexanolone* vs. 8.8 pts in placebo with mean difference of -12.2 pts. Effect size = 1.2. MADRS results similar.
- Remission (HAM-D total score ≤7) reached in 7/10 brexanolone subjects vs. 1/11 in placebo group. Difference seen at 24 hr (6 vs.1 subject respectively, p = .056) and maintained at 60 hrs (p = .0364) and 30-day follow-up (p = .0499).
- CGI-I response also differed significantly between the treatment groups.

*Brexanolone is under investigation for the specific treatment of PPD.

Kanes S, et al. *Lancet* .2017;390:480-489.

Brexanolone* Safety in PPD

AE	Brexanolone	Placebo
Most common	4 of 10 subjects	8 of 11 subjects
Dizziness	2	3
Somnolence / sedation	3	0
Moderate TEAEs	2 of 10 subjects	2 of 11 subjects
Sinus tachycardia	1	0
Somnolence	1	0
Injection site pain	0	1
Tension headache	0	1
Severe TEAE / insomnia	0	1

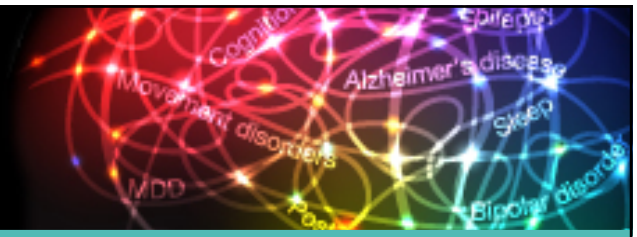
*Brexanolone is under investigation for the specific treatment of PPD.

Kanes S, et al. *Lancet* 2017;390:480-489

Conclusions

- There is no absolutely safe psychotropic drug for use during pregnancy or lactation. All psychotropic drugs pose some level of risk
- The provider (may be a multi-disciplinary team) and patient (may involve partner) must determine if the risks outweigh the benefits of treatment
- Newer classes of drugs have less risk, e.g. SSRIs, but caution should still be used in prescribing these medications to pregnant and/or nursing mothers
- Emerging therapies with new MOA and rapid onset are in development

Call to Action



- Utilize evidence-based tools to screen at-risk patients for postpartum depression
- Develop a safe, effective treatment plan for patients screening positive for postpartum depression, considering patient concerns and the risks/benefits of available therapies

Questions & Answers

Don’t forget to fill out your evaluations to collect your credit.