Zuranolone for Postpartum Depression

Marissa Beal, DO
Assistant Professor
Department Of Psychiatry and Behavioral Health

Disclosures

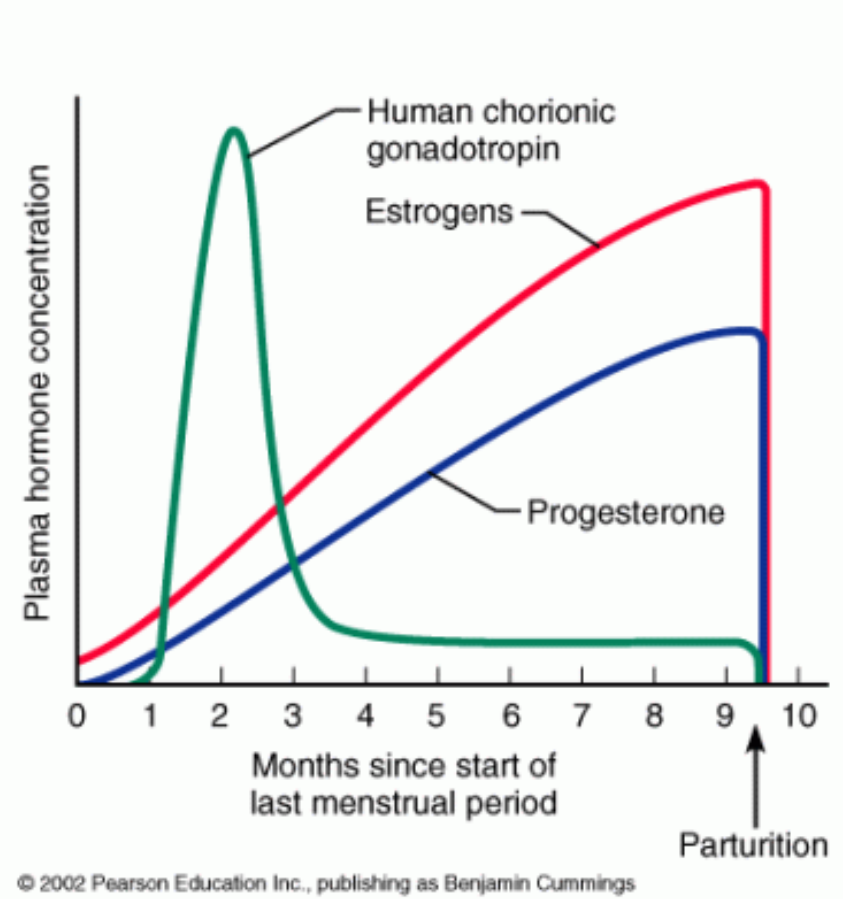
- No conflicts of interest

Zuranolone

- Synthetic neurosteroid
- Allopregnanolone analogue
- Orally bioavailable form of brexanolone (60hr IV infusion)
- FDA indication: postpartum depression
- DEA Schedule IV

Pathophysiology

- Allopregnanolone
  - Neuroactive steroid metabolite of progesterone
  - Positive allosteric modulator of GABA-A receptor
  - May increase GABAergic function
- Role of GABA
  - Inhibitory signaling pathway of the CNS
  - Hypofunction has been associated with PPD
  - Down regulation of receptors during pregnancy



Key studies: Methods

- Deligiannidis et al., 2021; 2023
- Double-blind, randomized, placebo-controlled trial
- Inclusion:
  - Adult female patients
  - 6 months or less postpartum (2021) or 12 months or less (2023)
  - Dx of MDD without psychosis which started no earlier than third trimester and no later than 4 weeks after delivery
  - Agree to use contraception
- Exclusion:
  - Breastfeeding or must agree to cease giving milk to infant
  - Psychosis, bipolar disorder, schizophrenia, schizoaffective disorder, substance use disorder

Key studies: Methods

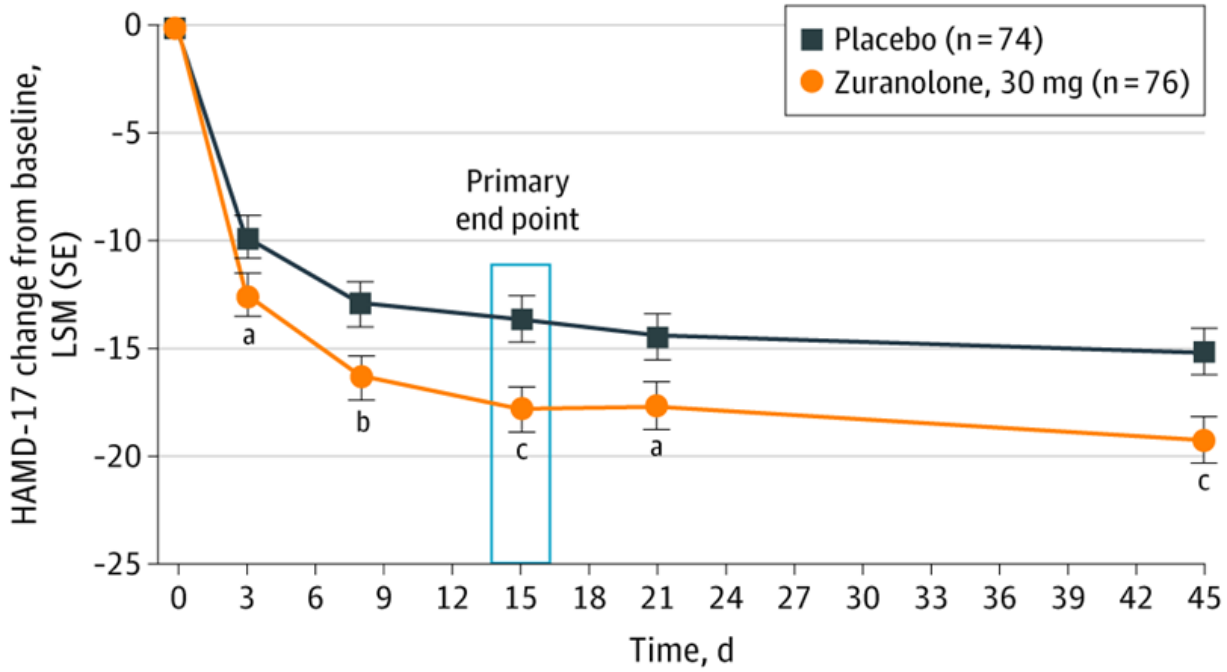
- Placebo vs zuranolone 30mg or 50mg each evening with food for 14 days
- Primary end point
  - HAM-D change from baseline at day 15
- Secondary end point
  - HAM-D at days 3, 8, 21, and 45
    - Remission (score ≤7) and reduction (≥50% reduction in score from BL)
  - HAM-A

(Deligiannidis et al., 2021; 2023)

Key Studies 2021: Results

a P = .03
b P = .01
c P = .003

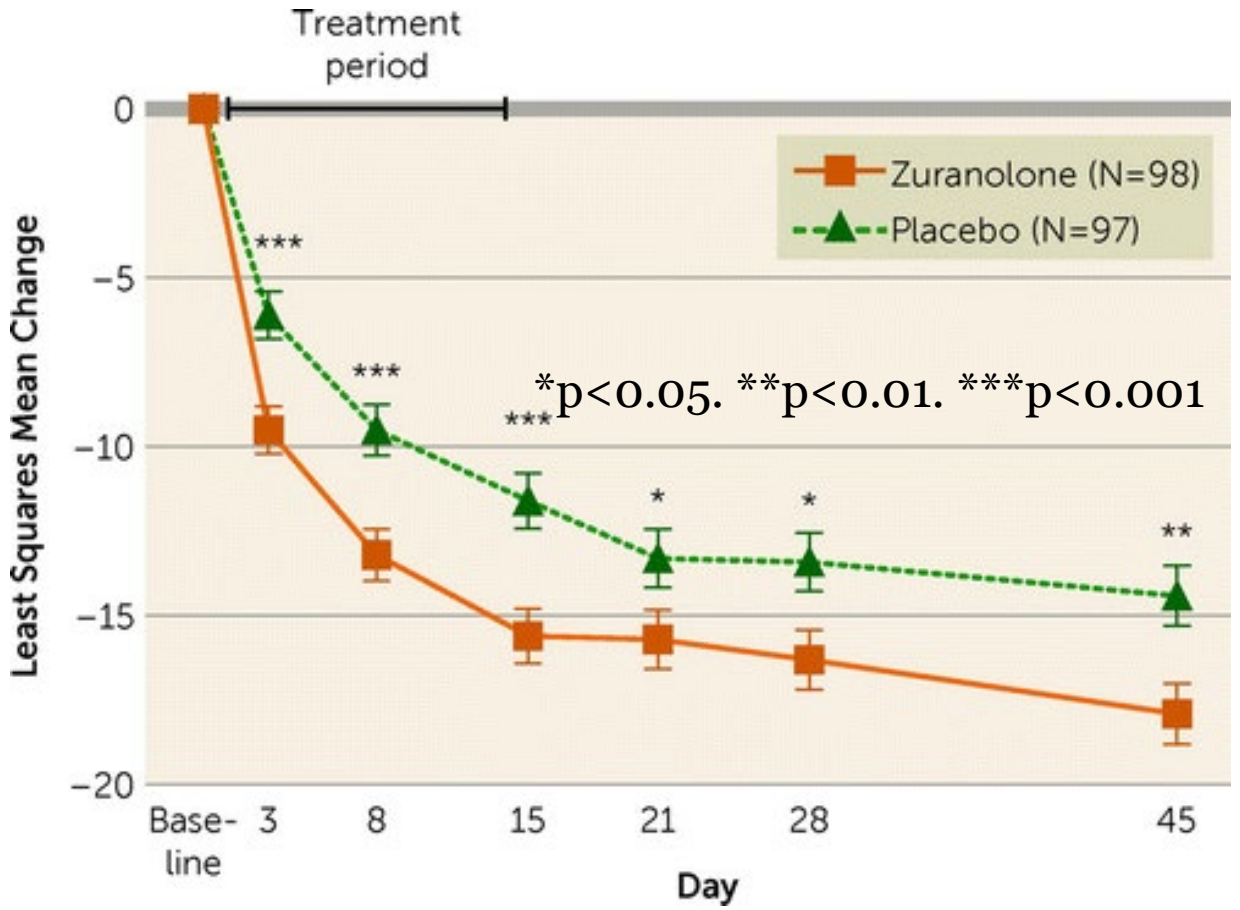
- Reduction from baseline in total HAM-D scores compared to placebo at day 15
- Also significant as soon as day 3 and lasting until day 45



(Deligiannidis et al., 2021)

Key Studies 2023: Results

- Reduction in HAM-D scores at day 3
- Difference from placebo continued to increase up to day 15 and remained significant up to day 45



(Deligiannidis et al., 2023)

Key Studies: Side effects

- Well tolerated
  - Somnolence
  - Sedation
  - Headache
  - Dizziness
  - URI
  - Diarrhea
  - Nausea

(Deligiannidis et al., 2021; 2023)

Limitations

- Mostly patients in the US
- Only severe PPD
- Bipolar disorder/psychosis/substance use was excluded
- High placebo response
- Unknown response after 45 days
- Unknown effect on lactation

(Deligiannidis et al., 2021; 2023)

Lactation

- Brexanolone:
  - 12 healthy volunteers – estimated RID of 1.342
- Zuranolone
  - 14 women with daily oral administration of zuranolone 30mg for 5 days
  - At steady state (day 5), RID was 0.357%

(Wald et al., 2022)

Pharmacokinetics

- Half life of 19-24 hours
- Steady state is 3-5 days
- Tmax: 5-6 hours
- Substrate of CYP3A4, primarily hepatically metabolized with no active metabolites
- Administer with fat containing food from 400-1,000 calories, 25% - 50%
- Lower dose to 30mg if Child-Pugh Class C or moderate or severe renal impairment

Pharmacology

- Capsules: 20, 25, 30mg
  - Blister pack for 25mg capsules
- Administered for 14 days
- Interactions
  - Other CNS depressants
  - CYP3A4 inhibitors – may increase risk of SE, reduce dose
  - CYP3A4 inducers – may decrease efficacy
- Dose dependent sedation
  - Black box warning: CNS depressant effect – “do not drive or engage in other hazardous activities 12 hours after administration for the duration of the 14 day course”

Discussion

- New oral option for patients with onset of depressive symptoms in third trimester and <4 weeks postpartum
- Rapid acting with antidepressant effect starting within 3 days and sustained effect at day 45
- Limited information about effect after day 45
- Side effects include sedation, dizziness, headache
- Limited data regarding breastfeeding
- Unclear regarding abuse potential

References

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