Updates in Postpartum Depression – February 2024

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"*Postpartum* Depression" is not an accurate description of depressive symptoms throughout the peripartum period. More recent data increasingly shows that, for many, depressive symptoms begin in early pregnancy, continue through pregnancy, and persist into the postpartum period.

Some studies have suggested several distinct phenotypes of depressive symptoms in the peripartum period. In one dataset review, patients with the most elevated depressive screening scores at 4-5 months postpartum fell into distinct categories: one group had onset of severe anxious depression (and anxious anhedonia) in the 1st or 2nd trimester, and another group had onset of severe symptoms >8 weeks postpartum. About half of women who developed depressive symptoms in the first 8 weeks postpartum continued to endorse severe symptoms at 4-5months postpartum. Women who developed depressive symptoms in the later 2nd trimester or 3rd trimester largely reported resolution of these symptoms by 4-5 months postpartum. Patients who reported suicidal ideation on screening tests were more likely to be described as having "*anxious* depression" or "*anxious* anhedonia", rather than "depression" alone.

Anxiety and anhedonia are associated with pregnancy and obstetric concerns and may increase the risk of progression into major depressive disorder.

Overall, the literature is supporting a movement towards early screening (1st and 2nd trimester), targeted intervention, and an emphasis on assessment of co-morbid anxiety and not just mood.

During pregnancy, assessment of MDD symptoms can be more nuanced. Poor sleep, changes in appetite, decreased energy, and decreased libido are all "expected" to some extent.

Symptoms that can help us guide diagnosis of MDD in pregnancy:

- Lack of interest in pregnancy
- Anxious and guilty ruminations
- Profound anhedonia
- Suicidal ideation

UPDATES IN TREATMENT: USE OF NEUROACTIVE STEROIDS

Allopregnanolone (ALLO) is

- a metabolite of progesterone
- allosteric modulator at the GABA-A receptor → → modulates HPA axis through CRH
- classified as a neuroactive steroid

Over the last 2 decades there is an increasing body of evidence that shows:

1. an anxiolytic response to allopregnanolone (animal studies)
2. low levels of allopregnanolone in humans is associated with depressed mood symptoms (hit or miss)
3. antidepressant treatment raises levels of allopregnanolone
4. in individuals, relative changes in the balance of allopregnanolone is positively associated with mood symptoms in women

5. basic science studies, however, are conflicting between the association between ALLO levels and postpartum depressive symptoms

HPA axis controls neuroendocrine response to STRESS. The HPA axis is heavily regulated by GABAergic signaling. During pregnancy, ALLO levels steadily increase, peaking in 3rd trimester, followed by a precipitous decline before delivery. Some research suggests that rising levels of ALLO result in down regulation of GABA-A receptors (and/or change GABA-A receptor subunit expression). A subtype of PPD may be related to this change in receptor function.

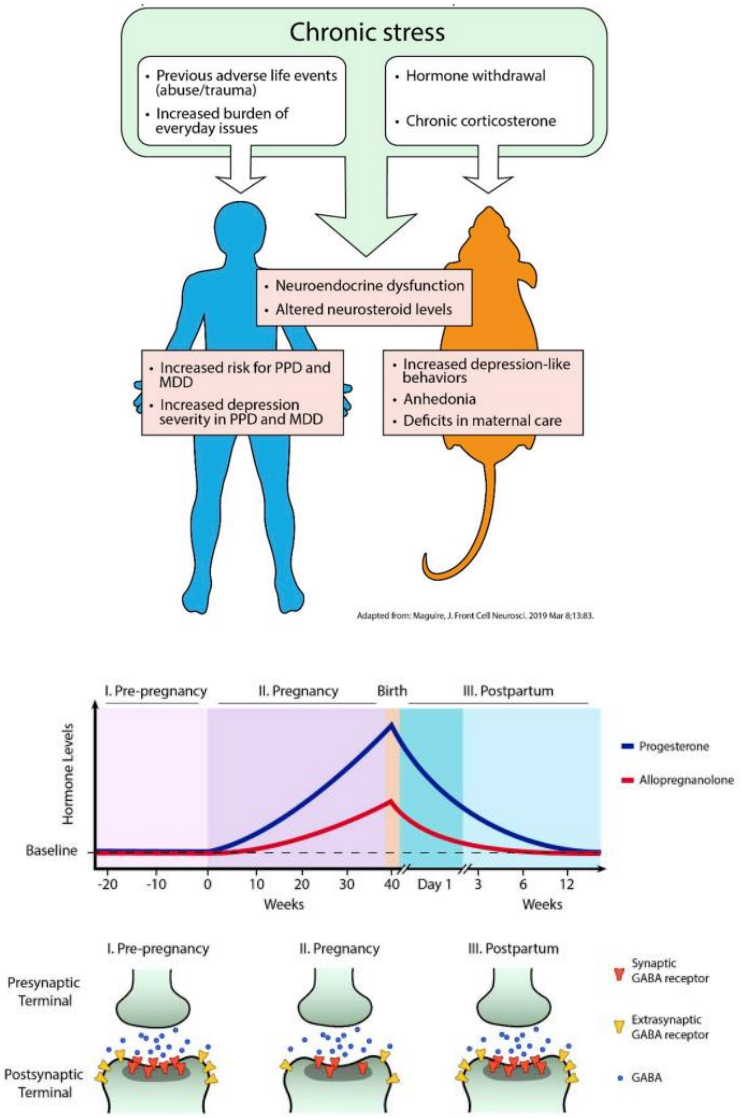


Fig. 2. GABAergic signaling in the perinatal period may be altered by fluctuations in neuroactive steroid levels and changes in the expression of $GABA_AR$ subunits. Altered expression of $GABA_AR$ subunits could alter both the number and localization of $GABA_ARs$.

(pictures from Meltzer-Brody, 2020)

- ALLO may not *directly* correlate with depressive symptoms, but function of the ***GABA-A receptor (specifically, the delta and gamma-2 subunits)*** may be more closely related to symptom

development. ALLO may also affect expression of the different subunits. Increasing ALLO levels back to the levels during pregnancy may help restore subunit expression and function

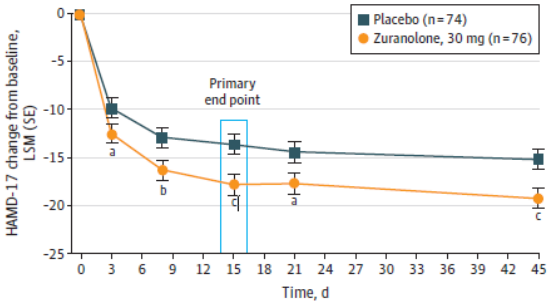
- Dysregulated GABA signaling likely affects response to stress and increases the risk of depressive symptoms
- For this reason, it has been suggested that we try to normalize the HPA axis (stress response) via GABA signaling to address certain subtypes of postpartum depression
- ALLO is one of the most potent neuroendocrine modulators of GABA signaling (that we know of so far), and its levels change throughout pregnancy and immediately postpartum

ZURANOLONE

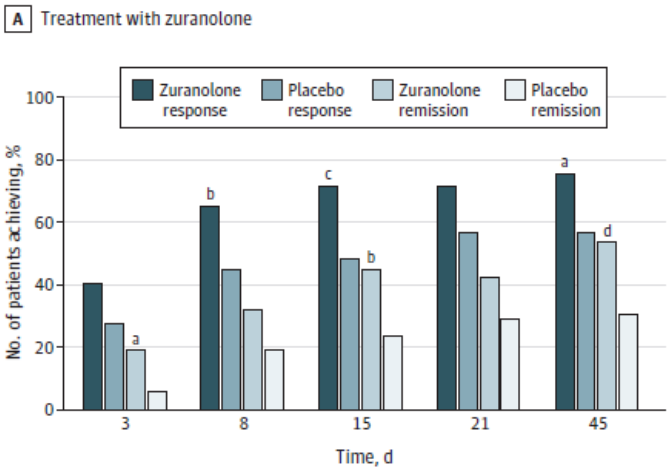
ROBIN trial (2021)

- Double-blind RCT. Industry-funded
- Patients: no more than 6 months postpartum. Symptoms must have started in 3rd trimester or within first 4 weeks after delivery. Excluded if **lactating**, history of psychotic or bipolar disorders
- 30mg nightly with food for 14 days (option to reduce to 20mg dose if side effects). Participants continued on a stable dose of an antidepressant
- Treatment arm separated from placebo by day 3. Placebo response also quite high. Anxiety symptoms improved, as well
- No data after day 45
- Very well-tolerated. Somnolence, dizziness, and headache were most common complaints (rates of these complaints were same as placebo arm). One patient in treatment arm experienced a confusional state that improved with dose reduction

Figure 2. Least-Squares Mean (LSM) Change From Baseline in the 17-Item Hamilton Rating Scale for Depression (HAMD-17) Score



Treatment with zuranolone, 30 mg, achieved the primary end point of a significant change from baseline HAMD-17 total score at day 15 compared with placebo using mixed-effects model for repeated measures. HAMD-17 total score at time points other than day 15 were secondary end points, not adjusted for multiplicity and therefore reported as point estimates, which also showed sustained improvements for the zuranolone group compared with the placebo group.

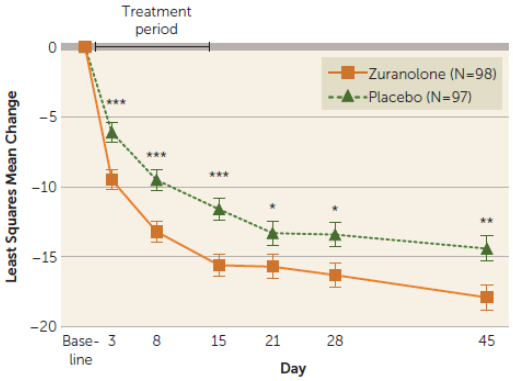


SKYLARK TRIAL (2023)

- Same general structure as ROBIN (also industry-funded by Sage)

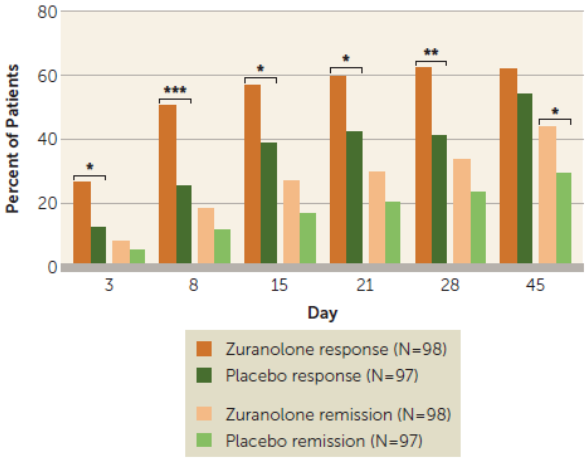
- Test dose of 50mg nightly with food (or 40mg if side effects)
- Same trend in response as seen in ROBIN
- Degree in change on rating scales is not different from ROBIN (30mg dose), although not directly compared.

FIGURE 2. Change from baseline in HAM-D score in a placebo-controlled trial of zuranolone 50 mg/day for postpartum depression (full analysis set)[a]



[a]The primary endpoint was change from baseline in score on the 17-item Hamilton Depression Rating Scale (HAM-D) at day 15, and the key secondary endpoints included change from baseline in HAM-D score at days 3, 28, and 45. Multiplicity was accounted for when analyzing primary and key secondary endpoints. All other secondary endpoints were not adjusted for multiplicity and are to be interpreted with nominal p values. Error bars indicate standard error. *p<0.05. **p<0.01. ***p<0.001.

FIGURE 3. HAM-D response and remission (full analysis set) in a trial of zuranolone 50 mg/day for postpartum depression[a]



[a]Response was defined as a reduction ≥50% from baseline in score on the 17-item Hamilton Depression Rating Scale (HAM-D), and remission was defined as a HAM-D score ≤7. Secondary endpoints were not adjusted for multiplicity and are to be interpreted with nominal p values. *p<0.05. **p<0.01. ***p<0.001.

WHAT ARE THE RECOMMENDATIONS?

The appropriate patient is someone who:

- Had onset of depressive symptoms in very late 3rd trimester or in the first 4 weeks after delivery
    - Experts advise only for patients with symptom onset after delivery, due to mechanism of action
    - Symptoms were not present earlier in pregnancy
- Can take a medication once daily with foo. Instructions are to take for 14 days with a fatty meal. Recommended dose is 50mg, but 30mg is assumed to be equally effective
- May be okay with not breastfeeding for several weeks. Not studied in lactation very well, although preliminary data suggests it is safe. Official recommendation is not offer breastmilk to the baby
- Does not need to drive daily. Box warning to not drive or operate heavy machinery for 12 hours after a dose

Zuranolone was only studied in conjunction with a stable dose of an antidepressant. Should you start an antidepressant at the same time as zuranolone, or attempt monotherapy?

- Jury is out on this one

- Since response to treatment with zuranolone is so rapid (whereas response is less so with standard antidepressants), a reasonable approach would be to follow up at 1-2 weeks. If responding well, can hold off on adding an antidepressant. If not responding well, will likely want to a traditional treatment
- Follow-up again 4-6 weeks after starting treatment. If remission has been achieved, continue to monitor. If depressive symptoms continue, consider adding additional treatment (medication and/or psychotherapy)

No data for women who deliver prematurely via C-section due to complications. We do not know what allopregnanolone is doing in those cases, and it is theorized that we would not see the precipitous decline in levels in this type of birth. At this point, we don't think zuranolone would, mechanistically, be effective in these cases.

Not recommended for postpartum anxiety alone, people with a history of psychotic or bipolar disorders, or other psychiatric disorders with a postpartum onset.

Zuranolone is only approved for 18 years old and older (Brexanolone is 15 years older and older)

References

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