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Case Studies: Lessons Learned from Drug Trials for Mood Disorders

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I have no conflicts of interest

Scope of the Problem: Perinatal Mood Disorder

- N=10,000 screened obstetrical population 4-6 weeks pp, 14% (1 of 7 individuals) had positive screen (≥10 Edinburgh Postnatal Depression Scale-EPDS)
  Wisner et al, JAMA Psychiatry 70(5): 490-8, 2013. PMID: 23487258
- Majority had major depression, recurrent, and a comorbid anxiety disorder; 20% had bipolar disorder
- The onset of the identified episodes for subjects was:
  - prior to pregnancy (26.5%)
  - during pregnancy (33.4%)
  - postpartum (4-6 weeks of birth) (40.1%)

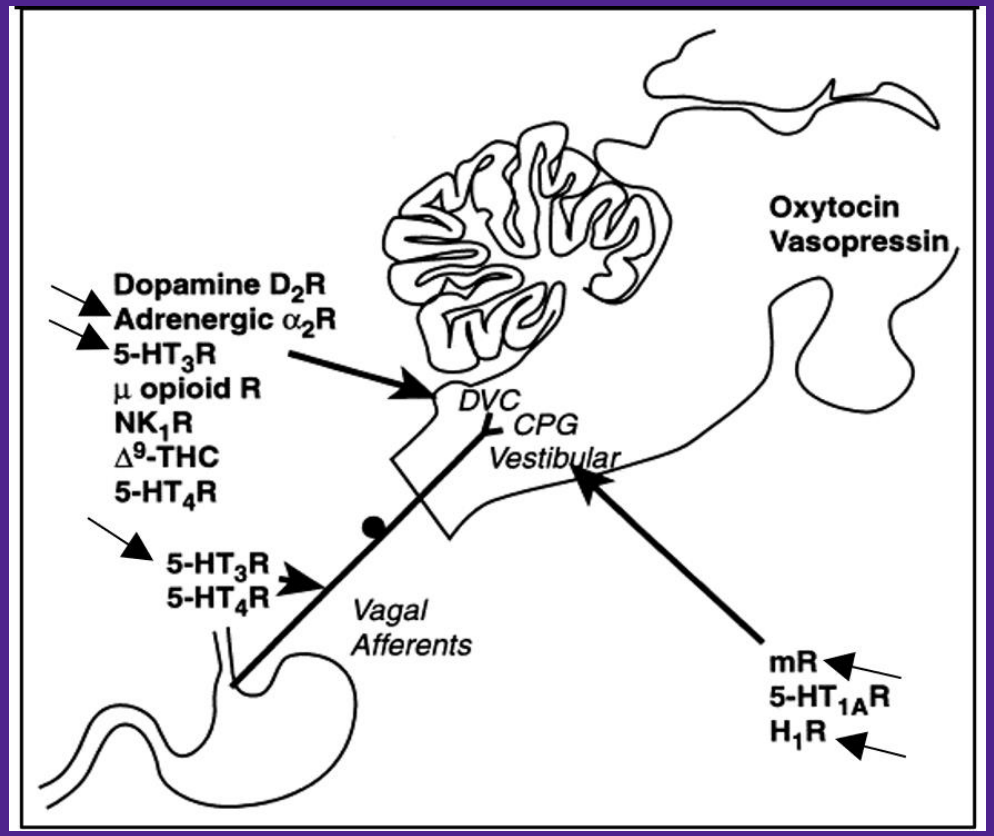
Maternal Mood/Anxiety Disorders

American College of Obstetrics and Gynecology (ACOG): "Perinatal Mood and Anxiety Disorders are associated with increased risks of maternal and infant mortality and morbidity and are recognized as a significant patient safety issue." *Obstetrics & Gynecology 2017;129:422–430*

- **Obstetric– Neonatal Complications**
  - Miscarriage, Hypertensive Disorders/ Preeclampsia, Preterm birth,
  - Cesarean delivery, Low birth weight
  - NICU admission
- **Early Social – Emotional Impact**
  - Poor infant self-regulation
  - Insecure attachment
- **Long Term Impairments**
  - Developmental and cognitive delays
  - Behavioral problems, psychopathology
- **Exposure to SSRI/ SNRI**
  - About 5% of pregnant patients, varying from 3-8%

Case 1: Silos and Stigma

- Repurposing mirtazapine (Remeron®) for severe nausea and vomiting in pregnancy (sNVP) NICHD R21 HD105101
- Antidepressant– FDA indication for major depressive disorder
- Used off-label for chemotherapy-induced NV, available ODT



Antagonize $5HT_3$ and 3 additional sites of action to impede emesis:

1) histamine (H1R)-has input directly to vomiting center;
2) muscarinic (mR)--input directly to vomiting center;
3) central presynaptic adrenergic α2 (adrenergic α2R), which activates emesis.

(illustration from *Hornby PJ. Am J Medicine. 2001;111 Suppl 8A:106s-112s.):*

Case 1: Silos and Stigma

- Study section review: Why would mirtazapine be used rather than ondansetron-both antagonize the $5HT_3$ receptor? Reviewer quote: "psychotropics should not be used without an indication."
- The ACOG Practice Guideline for sNVP includes prochlorperazine (Compazine®) and chlorpromazine (Thorazine®).
- Both drugs have FDA indications for NV and schizophrenia
- "Value of study limited to women who have both depression and sNVP"
- Physiologic activity at differing receptor sites produce therapeutic effects of value for varying disease states.

Case 1: Silos and Stigma

- Study section reviewer commented that our team "has focused on mental health disorders of pregnancy and post-partum with less experience with this more 'medical' indication for mirtazapine"
- Drs. Wisner (psychiatry) and Stika (Ob/gyn) were co-PIs on the NICHD Obstetric-Fetal Pharmacology Center site at Northwestern.
- Member of scientific panels are affected by the same forces that result in stigma as the public.
- Psychiatrically ill and pregnant -doubly stigmatized

Case 2: IRB Hesitancy

- Many drugs are used chronically and continued in pregnancy (atypical antipsychotics- quetiapine, methadone, buprenorphine, antiretrovirals)
- CYP3A4 metabolizes >50% of drugs, activity increases across pregnancy
- PK studies of drugs largely limit sampling to second or third trimester
- How to dose? Conception → 40 wk → post-birth return to non-pregnant state
- **Probe drugs** assess activity of hepatic enzymes (www.fda.gov/media/82734/download).
- Selective probe for CYP3A4= midazolam (benzodiazepine)
- Goal: Develop drug dosing strategies to prevent early pregnancy relapse
- Perform probe studies at end of T1, T2, and T3 and postpartum in healthy pregnant women

Case 2: IRB Hesitancy

One of the following is true: **(Check box that is true)**

☐ The risk to the fetus[iii] is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus.

☐ There is no prospect of benefit to the fetus, the risk to the fetus is **NOT** greater than Minimal Risk, and the purpose of the research is the development of important biomedical[iv] knowledge which cannot be obtained by any other means.

Provide protocol specific findings justifying this determination:

Any risk is the least possible for achieving the objectives of the research.

Provide protocol specific findings justifying this determination:

- Hebert et.al (*Clin Pharmacol Ther. 2008;84(2):248-253, UW*) conducted midazolam probe studies (2 mg p.o.) at 28-32 weeks and postpartum

Parameter	Pregnancy	Postpartum	Percent difference	*P* value
$AUC_{0\rightarrow inf}$ (ng·h/ml)	9.5 ± 4.3	17.9 ± 6.0	–46 ± 26	<0.002
CL/F (l/min)	4.2 ± 1.8	2.0 ± 0.6	108 ± 62	0.002

- mean plasma Cmax was 6.4 ± 2.6 ng/mL - No adverse reactions, maternal sedation or changes in FHR detected.
- Cmax plasma for adult sedation was 90 ng/mL (14 X above)
- Midazolam syrup in adolescents at 0.5 mg/kg syrup, mean Cmax plasma =118±81.2 ng/mL
- Extrapolating to 65 kg (143 lb) female, 2 mg is 0.03 mg/kg

Case 2: IRB Hesitancy

- Not approved, but mixed vote
- Operational Definition:
- **"Minimal Risk** generally means that the probability and magnitude of physical or psychological harm anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life, or in routine medical, dental, or psychological examinations."
- Is there a dose that could qualify as having minimal risk?
- How does pregnancy affect the judgment of minimal risk?

Melancholy in Motherhood

You say that I'm depressed
I wonder if you understand
You've never lived, I think
In this God-forsaken land
I always fight to function
I'm fighting to survive
I'm trying desperately to remember
What it's like to feel alive
You say I'm carrying life inside
How can that really be?
How could life possibly survive
In a non-existent me?

Mental Health is **Fundamental** to Health