Perinatal psychopathology and pharmacological intervention

Learning objectives

- Discuss specific applications and considerations of psychopharmacological interventions with perinatal patients
- Discuss common challenges for psychiatric consultants in perinatal CoCM

Challenges for psychiatric consultants using the Collaborative Care Model

- Don’t get to ask patients questions yourself
- Don’t get to see or speak with patients yourself to gather or give information
- Managing higher risk patients may feel less comfortable
- Need to set limits around role, responsibilities and availability
- Providers may have different comfort levels regarding prescribing certain medications

Unclear diagnosis

- Can always have BHCM go back and collect more information; don’t have to decide about diagnosis or treatment on the spot
- Exact diagnosis may not be as essential if low concern for bipolar disorder (i.e., first line medication for depression or anxiety is SSRI)
- If there is confusion about bipolar disorder vs Cluster B traits or personality disorder, can choose diagnosis of mood disorder NOS and treat with mood stabilizer/SGA that could be helpful to both diagnoses

Unclear which medication to choose from a given class

- If there is not enough information in initial case presentation, can ask BHCM to ask further questions that would help decide (e.g., is patient sleeping well? Are they struggling with energy?)
- May have to ask BHCM to gather more information about previous medication trials (names, doses, length of time)
- May give referring provider a couple of options, while giving information about how one agent differs from the other, and let patient decide

High-risk patients

- Can recommend referral to higher levels of care while in the program
  - Local psychiatrist
  - Health provider
  - Inpatient admission
- Can have BHCM complete a safety plan with the patient and regularly call patient to check-in regarding safety

Setting limits

- Various requests may come up
  - Disability paperwork
  - Patient questions or concerns outside of allocated panel review time
  - Providers wanting you to prescribe a medication for various reasons (don’t feel comfortable with certain medication, patient no longer under their care)

- Anticipate these requests and decide as a group what your policy will be on handling these issues
  - There may be some flexibility involved based on the specifics of the case

Differing prescriber comfort levels

- There is sometimes an element of “liaison” work involved in collaborative care which can be uncomfortable for providers
- Some providers may be less comfortable prescribing medications
- Further conversation is recommended to address this issue
  - Phone calls are helpful if possible
  - Great opportunity for educating providers

Treatment guidelines

Mild-moderate illness or symptoms

- Psychotherapy + Complementary Alternative Approaches (CAM)
    - Brief supportive therapy including CBT, IPT, DBT and psychodynamic; support groups; insomnia treatment; assistance with sleep or breastfeeding

Moderate-severe illness or symptoms

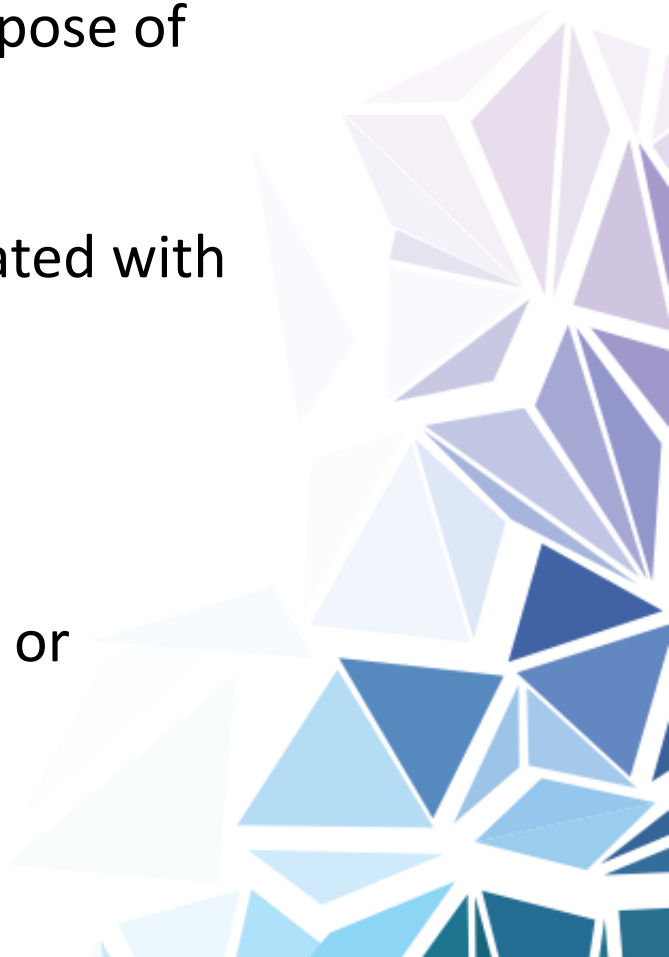
- Psychotherapy + antidepressant therapy; CAM as add-on treatment
    - Recurrent depressive disorder may require long-term antidepressant therapy, and given the high relapse rate (~70%), this should only be discontinued for next pregnancy after a full risk-benefit analysis

Severe or treatment-resistant depression, bipolar depression, mania, or psychosis

- Combination of antidepressants, antipsychotics, mood stabilizers, hypnotics, anti-anxiety medication and ECT can be considered; psychotherapy + CAM as add-on treatments

Broad strokes

- Patients who are successfully treated with safe medications during pregnancy should generally not change medications for the purpose of breastfeeding
- Postpartum patients who start pharmacotherapy should be treated with medications that were efficacious in the past
- Psychotropic polypharmacy should be avoided if possible
- There is little evidence to support timing of drug administration or discarding breastmilk (“pump and dump”)



Antidepressants and autism

Headlines are scary, but

- Only 0.72% prevalence in general population vs. 1–1.2% in exposed population
- These studies frequently have significant limitations, including not comparing women taking antidepressants with women who have similarly severe depression and are not taking medication

Reality: it's complicated!

- Literature shows that infants born to moms with health problems face higher risks than infants born to moms that are well
- Evidence from well-designed studies shows that when women taking antidepressants are compared with women who share the same risk profile, antidepressants are no longer linked with poor outcomes
- Risk may run with the disease and not its treatment

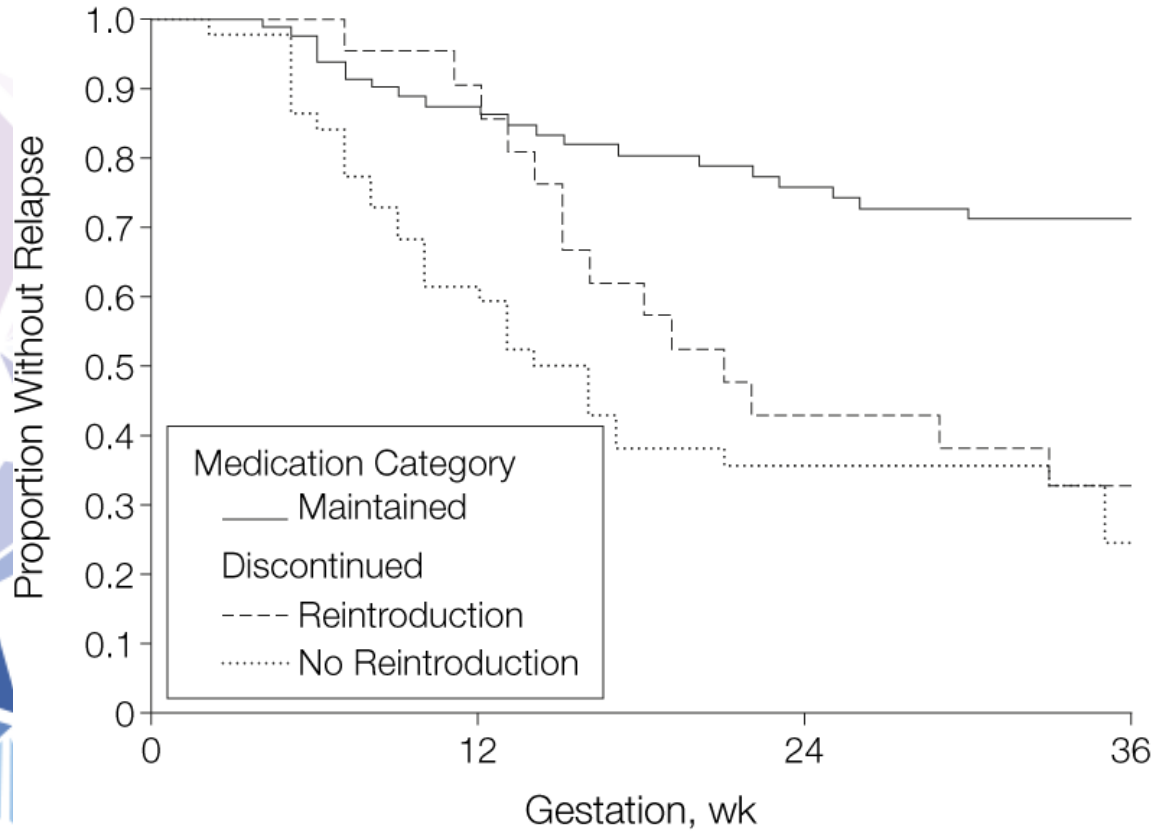
Risk-risk discussion

Risk of untreated illness

Risk of treatment

There is no risk-free zone.

Time to depression relapse during pregnancy among euthymic women on/off medications[1]



N= 201

Recurrence of depressive symptoms:

- 26% when medicine continued
- 68% when medicine is discontinued

Acute depression

- Any SSRI is first line treatment
  - However, it can take a while to become effective
- For patients with significant fatigue or low motivation and minimal to no anxiety symptoms:
  - May consider Wellbutrin due to pseudo-stimulant properties
- For patients with significant insomnia and poor appetite:
  - May consider Remeron as it helps quickly with sleep and appetite

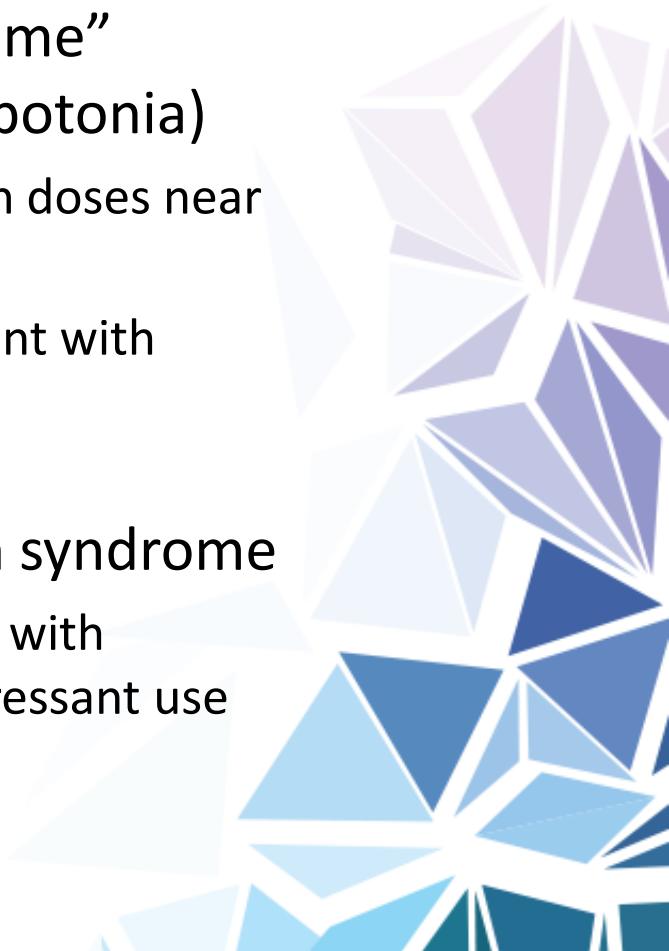
Benzodiazepines

Risks in pregnancy

- Formerly category D (positive evidence of risk)
  - However, no evidence of congenital malformation; initial concern for cleft lip/palate disproven
- Lorazepam and clonazepam preferred
  - Less likely to accumulate in fetus/neonate
  - Alprazolam rapid on/off = unknown fetal effects

Risks at birth

- “Floppy baby syndrome” (neonatal apnea, hypotonia)
  - Associated with high doses near delivery
  - Generally, not present with therapeutic doses
- Neonatal adaptation syndrome
  - Increased incidence with concurrent antidepressant use



Antidepressants and benzodiazepines: breastfeeding

- Generally, SSRIs, SNRIs, Wellbutrin, TCAs have good data
  - Infant levels 1–20% of mom's level depending on drug
  - Sertraline and paroxetine have lowest concentrations found in breast milk (however, this does not correlate with any different/improved clinical outcomes)

- Benzodiazepines are generally ok
  - Infant levels 2.5–8.5% of mom's level
  - Ativan, Klonopin are preferred
  - At prescription doses, generally do not see sedation in baby

Lithium: pregnancy

Risk[2]

- Relative risk of cardiac malformations calculated was 1.65
- If the risk of cardiovascular malformations is 1.15% in women with no exposure, the risk rises to about 1.9% in infants exposed to lithium
- Dose response effect (risk increased approximately threefold in doses above 900 mg per day)

Strategies

- Half-life is short (8–10hrs), causing peaks
  - Dose tid–qid or use extended release
- First trimester exposure: high-resolution US/fetal echo at 16–18 weeks gestation
- Risk of toxicity with pregnancy-related emesis
- Renal excretion of the drug changes throughout the trimesters so need to monitor blood levels frequently and adjust dose accordingly to maintain therapeutic level
- Do very frequent level-monitoring postpartum and return to pre-pregnancy dose immediately postpartum

Lithium: breastfeeding

- Excretion of lithium into breastmilk is highly variable
- Measured infant plasma levels: 30%–40% of maternal plasma levels
- Reports exist of breastfed infants who have shown signs/symptoms associated with lithium toxicity
    - May occur more frequently in infants with elimination impairments (e.g., dehydration) or in newborns/premature infants
- Lithium usually not recommended due to risk for neonatal dehydration and lithium toxicity but can be done if no other choice OR if patient is on relatively low dose, really wants to breastfeed, and physician following infant is comfortable with monitoring

Lamotrigine: pregnancy

- Teratogenicity:
  - 3 out of 4 registries report no more than baseline population risk for malformations (2–4%)
  - 1 out of the 4 registries suggested increase in relative risk for midline facial clefts with 1st trimester exposure, but absolute risk is very low (4:1,000)
- Neonatal Toxicity
  - Transient liver toxicity
  - Watch for skin rash
- Increased excretion in pregnancy; may need to increase dose in later gestation
- **Lamotrigine is the #1 mood stabilizer for bipolar depression in pregnancy—safe and effective**

Valproic acid: pregnancy

- **DO NOT PRESCRIBE** in women of childbearing age and **DEFINITELY NOT IN PREGNANCY**
- Teratogenicity: 10%, particularly if exposure in 1st trimester
  - Neural tube defects, dose related
  - Midface hypoplasia and other facial anomalies
  - Cardiac anomalies
  - Folate supplementation up to 5mg daily may reduce risk
- Intrauterine growth restriction (IUGR)
- Mental retardation
- Neonatal toxicity
  - Irritable, jittery, hypotonia, feeding difficulties, liver toxicity
  - Hypoglycemia

Carbamazepine: pregnancy

- Teratogenicity: 6%
  - Neural tube defects
  - Craniofacial and other facial anomalies
  - Worse when in combination with valproic acid
- Fetal vitamin K deficit, fetal bleeding
- Intrauterine growth restriction (IUGR)
- Neonatal toxicity
  - Transient liver toxicity
  - Neonatal bleeding, administer 1mg vitamin K to baby

Mood stabilizers: breastfeeding

Valproic acid

- Infant levels relatively low
- Theoretical risk of infant hepatotoxicity, thrombocytopenia
- Concern re: mom becoming pregnant again

Carbamazepine

- Infant levels relatively high
- Infant monitoring recommended (drug levels, liver enzymes, CBC)

Lamotrigine

- Infant levels 30% mom dose; theoretical concerns about risk for Stevens-Johnson syndrome though no infant cases of this have been reported
- Generally safe

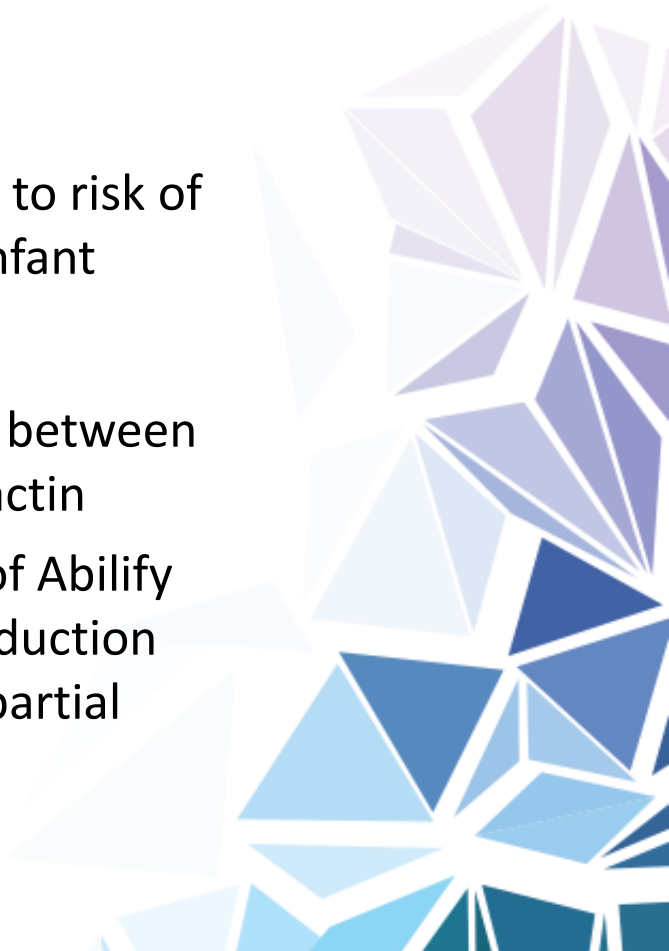
Antipsychotics: pregnancy and breastfeeding

Pregnancy

- Generally safe
- Overall, studies point to a very small increased rate of congenital anomalies (as with essentially all the psychotropic drugs we use in pregnancy)
- Second generation antipsychotics (SGAs) have better safety data than first generation
- Olanzapine, quetiapine have the best safety data of the SGAs
- Abilify is likely safe
- Some concern that Risperdal may increase risk of cardiac malformations

Breastfeeding

- Safety
  - Generally ok
  - Avoid clozapine due to risk of agranulocytosis in infant
- Milk production
  - Inverse relationship between dopamine and prolactin
  - Some case reports of Abilify decreasing milk production (potentially due to partial dopamine agonism)



Stimulants: pregnancy

- Most effective treatment for ADHD
- ADHD is comorbid with mood, anxiety and substance use disorders
- Contraindications and concerns
  - High blood pressure
  - Cardiac disease
  - Underweight/eating disorder (appetite suppressant)
  - Substance use disorder (controversial)

Potential risks of stimulants in pregnancy (1 of 2)

1st Trimester

- Congenital malformations: Data reassuring
- Miscarriage: higher rate of miscarriage in methylphenidate group. However, associated with a history of miscarriages and might also be related to the mother's underlying disorder or indication of a comorbid condition.

2nd Trimester

- Growth concerns: methamphetamine exposure during pregnancy associated with shorter gestational ages and low birth weight
- Contradicted by finding of LGA babies

Bottom line: Possibly increased risk of preterm birth, gestational hypertension, SGA/growth restriction

Potential risks of stimulants in pregnancy (2 of 2)

3rd Trimester

- Preterm delivery: moderate risk for preterm birth (aOR 1.3; 95% CI 1.1-1.6)
- Large for gestational age (aOR 1.3; 95% CI 1.0-1.7)
- Low Apgar scores with methylphenidate exposure
- Adverse placental-associated outcomes (preeclampsia, placental abruption, growth restriction and preterm birth)

Peripartum

- No significant differences in median gestational age at delivery; rate of preterm delivery; median birth weight
- Increased risk of NICU admissions
- Increased risk of CNS Disorders (seizure, NOS)

Bottom line: Possibly increased risk of preterm birth, gestational hypertension, SGA/growth restriction

When to continue stimulants in pregnancy: a question of functioning

Table 2
Adjustment and recurrence strategy for attention deficit hyperactivity disorder during pregnancy

Mild ADHD (Minimal Functional Impairment off Medication)	Moderate ADHD (Some Functional Impairment off Medication)	Severe ADHD (Significant Functional Impairment, Including Driving Safety)
Optimize sufficient nonpharmacologic management strategies and ensure self-management strategies in place (with history of success in supporting functionality of woman in domestic and occupational roles)	Optimize nonpharmacologic strategies; consider when necessary use of stimulant	Maintain medication, consider closer obstetric monitoring for fetal growth and hypertensive disorders of pregnancy

Treatment of ADHD with non-stimulants in pregnancy and breastfeeding

- Bupropion (Wellbutrin)
  - Safe in pregnancy and breastfeeding
- SNRIs (Effexor, venlafaxine)
  - Safe in pregnancy and breastfeeding
- Atomoxetine (Strattera)
  - Very little data in pregnancy or breastfeeding, but so far, nothing negative

Stimulants: breastfeeding

- Are secreted into breastmilk in low levels
- So far, no evidence of harm in infants (short term)
- May decrease breast milk supply in women without established supply

Prescribing wisdom (1 of 2)

- Perinatal patients are generally in more distress than non-perinatal patients
  - Especially postpartum due to compounding factors of sleep deprivation, drastic hormonal shifts and significant life change
  - May **titrate antidepressants every two weeks** until reach sufficient symptom relief
  - Remember: **start low**, you may **go slow** if needed for tolerability (i.e., increase dosage by small amounts each time), aim for a target therapeutic dose
  - For patients with moderate to severe symptoms, consider prescribing **PRN for a short time before other medications kick in**. Short term Ativan and Klonopin can be extremely helpful (in patients without risk factors for substance abuse and significant functional impairment/distress)

Prescribing wisdom (2 of 2)

- Sertraline has the least transfer to breast milk but is not necessarily the best “first-line” medication due to high rate of side effects (GI, sedation, activation, emotional “numbing”)
  - Also, the fact that it has minimal excretion into breastmilk is not necessarily correlated with better or different outcomes

- Remeron can be very useful during this time, particularly with patients who have significant insomnia and poor appetite (+/- nausea)

Acute anxiety or panic attacks

- May prescribe PRN medication as appropriate based on pregnant vs. postpartum status (benzodiazepine, gabapentin, hydroxyzine, quetiapine, etc.)
  - Not ideal for panic attacks given that may reinforce idea that panic attack must be stopped/patient can't tolerate it
    - Discuss with patient that PRN will likely be short term
  - However, therapy can take a while (time to connect, engage, see improvement)

PRN medications for sleep or anxiety (1 of 2)

Benzodiazepines

- Helpful for anxiety, insomnia due to anxiety
- Screen for history of SUD/chronic poor coping
- Can be habit forming
- Plan for a time-limited course
- Ativan and Klonopin most used (do not prescribe Xanax)

Gabapentin

- Newer drug, but data reassuring so far
- Can be helpful for people trying to discontinue MJ
- More anxiolytic than sedating (as opposed to next slide)
- Generally, well tolerated
- Wide dose range
- Much less risk of dependence or abuse (as opposed to benzos)

PRN medications for sleep or anxiety (2 of 2)

Benadryl/hydroxyzine

- Benadryl—OTC; may lose efficacy if used regularly
- Hydroxyzine—avoid in pregnancy, limited data
- Antihistamine properties can decrease breastmilk supply

Unisom

- OTC
- Used frequently in pregnancy (especially for nausea)
- In breastfeeding, avoid prolonged use

Trazodone

- No significant side effects in women other than grogginess
- Ideally, take at bedtime on nights where at least 6-8 hours of sleep can be achieved

Seroquel

- Very effective
- Can cause weight gain, other metabolic effects (usually at higher doses)
- Higher risk of side effects (restless leg, akathisia, over sedation)
- Has some anxiolytic effects
- Small potential to decrease breast milk supply due to antihistamine properties

Perinatal treatment developments: new evidence-based medications

Brexanolone

- Neurosteroid drug boasting depression remission in as little as 24–48 hours
- 60-hour continuous IV administration requiring 24-hour monitoring by a healthcare professional given that side effects can include excessive sedation and loss of consciousness
- This is not feasible or cost effective for many patients or healthcare settings

Zuranolone

- Neurosteroid
- Data from phase 3 SKYLARK study (randomized, double blind, placebo controlled); n=200, severe depression (Hamilton Depression Rating Scale (HAM-D)-17 score 26 or higher)
- Over 45-day trial, there was a consistent 3–4 point greater reduction on the HAMD-17 score as compared to placebo; at day 45 (-17.9 vs -14.4, P = 0.0067)
- Most common side effects were sedation, dizziness, headache, and GI effects

Case study 1

- 32-year-old woman who is 20 weeks pregnant with a history of anxiety
  - Used benzodiazepines as needed for anxiety prior to pregnancy
  - Experiencing depression and intense anxiety, which then leads to insomnia
    - Getting about 2 hours of sleep per night
    - Unisom, Benadryl have not been effective
  - Notes racing heart, crying spells, loss of motivation
  - Took Prozac previously, does not recall if it was helpful

Case study 2

- Patient is a 30-year-old woman who had **no previous mental health history**. She delivered her **second child 6 weeks ago** and has had **depression as well as intensifying anxiety and panic symptoms**, including derealization. Her OB started her on **Lexapro, she has titrated up to 10mg** and has been on this dose for 2 weeks. Since starting the medication, she states that she **feels numb and finds it hard to feel joy** and continues to have intense anxiety although it is somewhat improved.

- She texts her BHCM frequently throughout the week stating that she feels very anxious and wonders if her medication regimen is ideal

- She went to see her PCP about her anxiety who **instructed her to stop the Lexapro and start Zoloft 50mg**

Case study 2 continued

- You recommend that she **increase her dose of Lexapro to 20mg and start Ativan 0.25–0.5mg BID PRN**, and the BHCM relays this information to patient's OB and patient. BHCM also requests consent to reach out to this patient's primary care provider so that care can be coordinated, and one prescriber be identified for medication management to prevent confusion and negative outcome for patient.

- Patient is nervous about making these changes. **Agrees to increase Lexapro to 15mg but does not want to take Ativan**. Continues to frequently text BHCM that she is struggling and requests guidance and reassurance about treatment plan. She also **schedules and completes an evaluation with another psychiatric prescriber.**

Case study 3

Patient is a 21-year-old presenting with **“mood swings,” insomnia, and irritability two months after the birth of her first child**. Her pregnancy was unplanned. She states she was **diagnosed with bipolar disorder** when she was a teenager. Her **MDQ was positive**. Her father was physically abusive. She **used to cut herself as a teenager** but doesn’t do this anymore. She has struggled with passive suicidal ideation for a long time but has **never been psychiatrically hospitalized or had suicide attempts**. Her relationship with the father of the baby is rocky with a lot of conflict. She has **limited supports** and is currently taking care of the baby by herself. Her irritability and insomnia are making it **hard for her to function at work**. Finances are a stressor.

References

1. Cohen LS, Altshuler LL, Harlow BL, et al. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment [published correction appears in JAMA. 2006 Jul 12;296(2):170]. JAMA. 2006;295(5):499-507. doi:10.1001/jama.295.5.499

2. Patorno E, Huybrechts KF, Bateman BT, et al. Lithium Use in Pregnancy and the Risk of Cardiac Malformations. N Engl J Med. 2017;376(23):2245-2254. doi:10.1056/NEJMoa1612222