BACK TO BASICS: PERINATAL PSYCHOPHARMACOLOGY

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This discussion focuses primarily on the medical treatment of patients; however, nonpharmacological treatments of these symptoms (e.g., psychotherapy, etc.) are often helpful as alternative or adjunctive approaches.
GETTING WARMED UP...
27YO single woman, currently 25 weeks pregnant with her third child. Patient has a history of depression in the past, with recurrences, with one psychiatric hospitalization after a suicide attempt in her late teens. Multiple previous medication trials for depression. She had been relatively well-controlled on Vortioxetine (Trintellix) prior to pregnancy, but self-discontinued when she learned of her pregnancy. She now complains of depressed mood, poor sleep, and lethargy all the time, anxiety and sadness. Admits to having some difficulty in functioning, including caring for children and getting to work daily.

What is your next step in the management of this patient’s depressive symptoms?
WHAT IS YOUR NEXT STEP IN THE MANAGEMENT OF THIS PATIENT’S DEPRESSION?

1) Start an older SSRI, like sertraline.
2) Hold off on all medications for now, symptoms are not concerning at this time.
3) Re-start vortioxetine, as pt recently had success with the medication.
4) Refer to Psychiatry.
DEPRESSION

- DSM-5 criteria: 5 or more symptoms present during the same 2-week period, representing a change from previous functioning.
  - Either depressed mood or anhedonia must be present
  - Peripartum onset: onset during pregnancy or up to 1 year postpartum
DEPRESSION

- Risk Factors:
  - Personal history of affective illness
  - Marital/relational discord
  - Inadequate social supports
  - Recent adverse life events
  - Lower SES
  - Unwanted pregnancy

DEPRESSION

- Often overlooked in pregnancy...
  - Poor sleep
  - Appetite changes
  - Decreased energy
  - Decreased libido

DEPRESSION

- Symptoms to guide diagnosis...
  - Lack of interest in pregnancy
  - Profound anhedonia
  - Guilty ruminations
  - Suicidal ideation

DEPRESSION

- Be sure to screen for...
  - Anemia
  - Gestational diabetes
  - Thyroid dysfunction

All can present with depressive symptoms and may complicate the diagnosis of depression.
MOOD SYMPTOMS IN THE POSTPARTUM PERIOD

Baby Blues

- Affects 70-85% of women (considered normal!)
- Duration of symptoms < 2 weeks
- Mild
- Self-limited
- Little to no intervention needed

Postpartum Depression

- Affects 10-15% of women
- Criteria met for MDE
- Tends to have a later onset (2-4 weeks PP)
- Severe/impairing symptoms usually present
  (anhedonia, sense of failure, suicidality, psychosis)
SUICIDALITY (OR IMMINENT RISK)

- History of suicide attempt
- High lethality of prior attempts
- Current plan
- Current attempt
- AODA
- Lack of protective factors (including social support)

No prior attempts
No plan
No intent
No AODA
Protective factors ("what prevents you from acting?")
PERINATAL ANXIETY

- Spectrum of anxiety symptoms occurring during pregnancy and/or the postpartum period
- Prevalence: as common as perinatal depression, 8.5-13% of women
- Symptoms:
  - Persistent and excessive worries
  - Inability to relax
  - Physiological arousal
  - Intrusive thoughts = COMMON
THOUGHTS OF HARMING INFANT

Secondary to Anxiety/OCD
• Good insight
• Thoughts are intrusive and scary
• No psychotic symptoms
• Thoughts cause anxiety

Secondary to Psychosis
• Poor insight
• Delusional beliefs with distortion of reality present
• Other psychotic symptoms
SCREENING

“Clinicians screen patient at least once during the perinatal period for depression and anxiety symptoms using a standard, validated tool.”

“All obstetrician-gynecologists and other obstetric care providers should complete a full assessment of mood and emotional well-being during the comprehensive postpartum visit for each patient.”

“Coupled with appropriate follow-up and treatment.”

“Systems should be in place for ensuring follow-up for diagnosis and treatment.”

“Recommends screening for depression in the general adult population, including pregnant and postpartum women. Screening should be implemented with adequate systems in place to ensure accurate diagnosis, effective treatment, and appropriate follow-up.”

Other issues: Providers need to be cautious regarding misdiagnosis of bipolar disorder (e.g., need to screen for symptoms of mania), and screen for anxiety disorders.

Siu AL, 2016.
The primary care pediatrician has a unique opportunity to identify maternal depression and help to prevent adverse developmental and mental health outcomes for the infant and family.

Screening can be integrated into the well-child care schedule and included in the prenatal visit.

Intervention and referral are optimized via collaborative relationships with community resources.

SCREENING: TIMELINE

- Initial prenatal visit
- 28 weeks gestation
- 2-4 weeks postpartum
- 12 weeks postpartum
- Consider another screening at 9-12 months PP
SCREENING: PRINCIPLES

- Validated tool
- Protocols
- Normalize
- Document
PREGNANCY AND LACTATION LABELING RULE (PLLIR)

Published in 2014, implementation over 3 years

Replaces the “RISK” categories (A, B, C, D, X)

Narrative model of drug labeling
TREATING DEPRESSION (AND ANXIETY)

- Sertraline: 19%
- Bupropion: 16%
- Citalopram: 15%
- Escitalopram: 14%
- Fluoxetine: 13%
- Venlafaxine: 9%
- Paroxetine: 6%
- Duloxetine: 8%

THE RISK OF UNTREATED PSYCHIATRIC SYMPTOMS

- Untreated psychiatric illness is not benign!
  - Spontaneous abortion
  - Increased risk for congenital abnormalities (especially in cranial-neural crest derived structures—e.g., cleft lip/palate)
  - Preterm labor/preterm delivery
  - Low birth weight/fetal growth restriction
  - Preeclampsia
  - Behavioral concerns in children

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)

- Represent 60-70% of new prescriptions for depression/anxiety
- Easy to use, to dose
- High therapeutic index
- Generally well-tolerated...
  - Headaches
  - GI upset
  - Weight gain (*thought to be dependent on anticholinergic activity*)
  - Sexual dysfunction
  - Withdrawal syndrome

Fluoxetine (Prozac)
Sertraline (Zoloft)
Paroxetine (Paxil)
Citalopram (Celexa)
Escitalopram (Lexapro)
Fluvoxamine (Luvox)
SSRIs: WHAT ARE THE RISKS?

- Congenital anomalies
- Poor neonatal adaptation
- Persistent pulmonary hypertension of the newborn (PPHN)
- Autism spectrum disorder
SSRIs: CONGENITAL ANOMALIES

- No associations in prospective, controlled studies
- Some retrospective case-control studies have demonstrated increased risk
- Retrospective database reviews = controversial (increased risk of septal heart defects)

Reports consistently indicate that ~25-30% of infants exposed to SSRIs in late pregnancy manifest symptoms of PNA. Comments:
- Jitteriness, restlessness, irritability, increased muscle tone, rapid breathing
- Symptoms are transient
- Resolve spontaneously
- No specific medical intervention required
- "Washout period" does NOT prevent this syndrome

2014 meta-analysis of 7 cohort and case-control studies:
- Exposure to SSRIs in early pregnancy was not associated with PPHN.
- Exposure in late pregnancy (after 20 weeks) was associated with an increased risk of PPHN (OR = 2.50, CI 1.32-4.73, P = 0.005).

Things to consider:
- Absolute risk of PPHN is low.
- OTHER risk factors.
- Studies included in the meta-analysis did not control for significant confounding factors.

FDA amended labeling in 2011 to reflect that a definitive link cannot be established.

SSRIs: AUTISM SPECTRUM D/O

Several epidemiologic studies demonstrated an association with prenatal exposure of SSRIs and ASD

**Beware confounding factors!**
- Drug exposure vs. symptom exposure??
- Controlling for maternal mental illness...reliable measures of severity??

- Data at face value: 87% increased risk
  - Average child = 1% risk (SSRI exposure = 1.87%)

SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIs)

- Risk of major congenital malformations after first-trimester exposure?
- Possible increase in miscarriage
- Possible increased risk of gestational hypertension
- No longer-term behavioral studies

Venlafaxine (Effexor)
Desvenlafaxine (Pristiq)
Duloxetine (Cymbalta)

OTHER ANTIDEPRESSANT MEDICATIONS

- **Mirtazapine**
  - No known risk of major malformations
  - Side effect considerations:
    - Nausea is less likely than with SSRIs; *may be used with hyperemesis gravidarum*
    - Weight gain can increase obstetric complications
    - Sedation may be difficult to tolerate in pregnancy/postpartum, but can be useful in patients struggling with insomnia

- **Bupropion**
  - No increased risk of congenital abnormalities
  - Decreased birth weight at higher doses
  - Elevated rate of spontaneous miscarriage (p = 0.009)
  - *Lowers seizure threshold*—possible risk in women with preeclampsia

Chun-Fai-Chan B et al, 2005.
ANXIOLYTICS: BENZODIAZEPINES

- Early reports suggested an increase risk of cleft lip/palate
  - Not confirmed by more recent studies!
- Toxicity in newborns
  - Sedation, floppy baby syndrome, respiratory depression
- Concern for potential of physiological dependence and withdrawal for infant with *chronic, frequent use* throughout pregnancy

ANXIOLYTICS: OTHER

- Buspirone
- Hydroxyzine
- Gabapentin
March 20: News of FDA approval for first-ever medication with a specific indication/approval for post partum depression

- Analogue of the endogenous human hormone allopregnanolone (neurosteroid)
- Mechanism of action is unknown (GABA<sub>A</sub> receptor activity?)
- 3 studies provided evidence of efficacy, with primary outcome change in baseline on HAM-D at 60 hours post-infusion

Abbreviations: HAM-D = Hamilton Rating Scale for Depression; FU = follow-up; LS = least squares; SE = standard error
Note: * indicates time points when statistically significant improvement was achieved for SAGE-547 60 µg/kg/h as compared with placebo. † indicates time points when statistically significant improvement was achieved for both SAGE-547 groups as compared with placebo. * for Day 14 and Day 21 are lower than surrounding time points as these visits were added with Amendment 3. An unstructured covariance structure was used to model the within-subject errors.
BREXANOLONE: CLINICAL UTILITY

- Most common adverse effects in clinical trials: dizziness, drowsiness
  - More concerning effects: suicidal ideation and syncope/altered consciousness ➔ REMS, will only be available at certified health care facilities
- 60-hour infusion must then be administered in an inpatient setting
- NO DATA on safety of brexanolone while breastfeeding
- COST: 25K-34K per infusion
PRECONCEPTION PLANNING

50% of pregnancies are unplanned

ONE KEY QUESTION: "Would you like to become pregnant in the next year?"

The National Campaign to Prevent Teen and Unplanned Pregnancy.
## KEY PRINCIPLES OF PSYCHOPHARMACOLOGY

### During Pregnancy
- Return to a **previously effective medication**, if possible/appropriate.
- **Monotherapy** is the goal (but remission of symptoms trumps monotherapy).
- Utilize lowest **effective** dose of medication.
  - Majority of risks are not dose dependent.
  - Avoid exposure of patient/fetus to both symptoms + medications.
- Appropriate **monitoring** based upon drug regimen utilized.

### During Lactation
- All psychotropic medications are secreted into breastmilk, but concentrations may vary considerably.
- AAP: “safe” breastfeeding ratio of infant dose exposure to maternal dose is <10%.
  - All antidepressant meds fall below the 10% cutoff.
  - MOST psychotropic medications are compatible with breastfeeding.
- If taking antidepressants in pregnancy, continue the same medication during lactation to limit the infant’s exposure to a single medication (if possible).
Diagnosis

Period of stability

Risk of relapse

Current symptom burden

RISKS

Educational resources provided

Non pharmacological treatment options

Collaboration

DOCUMENTATION
RESOURCES

- Websites:
  - https://womensmentalhealth.org/
  - https://nichd.nih.gov/ncmhep/initiatives/moms-mental-health-matters/

- Apps:
  - InfantRisk *(free!)*
  - Reprotox *(free for trainees!)*
  - MGH-PDS *(free!)*
Case Discussions…
CASE VIGNETTE #1

- 27YO single woman, currently 25 weeks pregnant with her third child. Patient has a history of depression in the past, with recurrences, with one psychiatric hospitalization after a suicide attempt in her late teens. Multiple previous medication trials for depression. She had been relatively well-controlled on Vortioxetine (Trintellix) prior to pregnancy, but self-discontinued when she learned of her pregnancy. She now complains of depressed mood, poor sleep, and lethargy all the time, anxiety and sadness. Admits to having some difficulty in functioning, including caring for children and getting to work daily.
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CASE VIGNETTE #2

- 22YO single woman, in final year of college, currently 26 weeks pregnant. Pregnancy was unplanned. History of sexual assault as a teenager. Limited social support from FOB or family. Struggling primarily with anxiety symptoms surrounding life changes, worry about caring for infant independently, both financially and emotionally. Panic symptoms occurring several times weekly; she has started to miss classes/assignments in the past month. As pregnancy has progressed, there has been increased concern about delivery, likely stemming from trauma history. No previous psychotropic medication trials.
WHAT WOULD BE YOUR NEXT STEP(S) IN THE MANAGEMENT OF THIS PATIENT?

1) Start alprazolam 2 mg TID to address anxiety/panic symptoms.
2) Refer to Psychiatry.
3) Consider an SSRI in conjunction with trauma-focused psychotherapy.
4) No treatment now, monitor symptoms at every visit.
CASE VIGNETTE #3

- 34 YO married woman, no previous pregnancies, attorney, anticipating conception in the upcoming several months. Has struggled with insomnia for several years, currently managed on zolpidem 10 mg nightly. Questioning safety profile of utilization of zolpidem in pregnancy and would like to know her options prior to conception.
WHAT WOULD BE YOUR NEXT STEP(S) IN THE MANAGEMENT OF THIS PATIENT?

1) Continue zolpidem.
2) Recommend melatonin, as it is a natural OTC sleep aid.
3) Encourage PRN dosing of lorazepam or clonazepam at night as needed for sleep.
4) Refer to Sleep Medicine or Psychiatry.
SLEEP AIDs

More Data
- Sleep hygiene, CBT-i
- Benzodiazepines
- Mirtazapine
- Zolpidem
- TCAs

Limited/No Data
- Melatonin
- Trazodone

Tomfohr LM. Sleep. 2015 Feb 18.
REFERENCES


REFERENCES (CONTINUED)


“Attention is the rarest and purest form of generosity.”
~Simone Weil

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