MOOD STABILIZERS AND SECOND-GENERATION ANTIPSYCHOTICS IN THE PERINATAL PERIOD

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OBJECTIVES:

- Review key considerations for use of mood stabilizers/antipsychotics in pregnancy/postpartum

- Improve knowledge of dosing recommendations for mood stabilizers during pregnancy/postpartum

- Improve knowledge re: risks and benefits of different mood stabilizers and antipsychotics for mood stabilization, during pregnancy/postpartum

OUTLINE:

Review of Mood Stabilizers:

- Lamotrigine
- Lithium
- Carbamazepine
- Valproate/Valproic Acid/Depakote
- Others with some data

Review of Second-Generation (Atypical) Antipsychotics:

- Known/Unknown Risks
- Gestational Diabetes
- Others without data

A FEW LEARNING POINTS:

- "Safety" is a relative term
  - Risk of congenital malformations is ~3% in baseline population
  - Pregnancy is a state of inherently increased risk for many mood disorders, including bipolar
- Risks vs benefits includes:
  - Risks of psychiatric decompensation/mood episode recurrence vs medication exposure
    - Mood episodes increase risk for decreased prenatal care, increased rates of postpartum depression, difficulty with breastfeeding, potential for impaired infant bonding
    - Medication exposure *in utero* is not quantified in studies, limited/absent data re: placental passage
    - **Recommendation**: shared decision-making is key!
  - Risks of tolerated, "less safe" medication vs new medication during time-limited trial
    - **Recommendation**: Medications that work prior to pregnancy should be continued during pregnancy
      - Exceptions: Valproic acid, carbamazepine
    - **Recommendation**: DO NOT SWITCH during pregnancy, if possible
    - Ideally, trial of new medications are initiated prior to pregnancy and allow for mood surveillance/demonstrated stability >6 months

A FEW LEARNING POINTS:

- Inadequate treatment leads to potential *in utero* medication exposure, while leaving patients exposed to psychiatric illness
  - Dose for adequate symptom control
  - Monotherapy > polypharmacy

- "What's best for mom is best for baby"

- Expect dosing changes due to metabolism in pregnancy

RISKS OF BIPOLAR DISORDER IN PREGNANCY:

Mother:

- Increased risk of mood episodes (85% recurrence rate if medications are stopped)
- 5x increased risk for postpartum depression

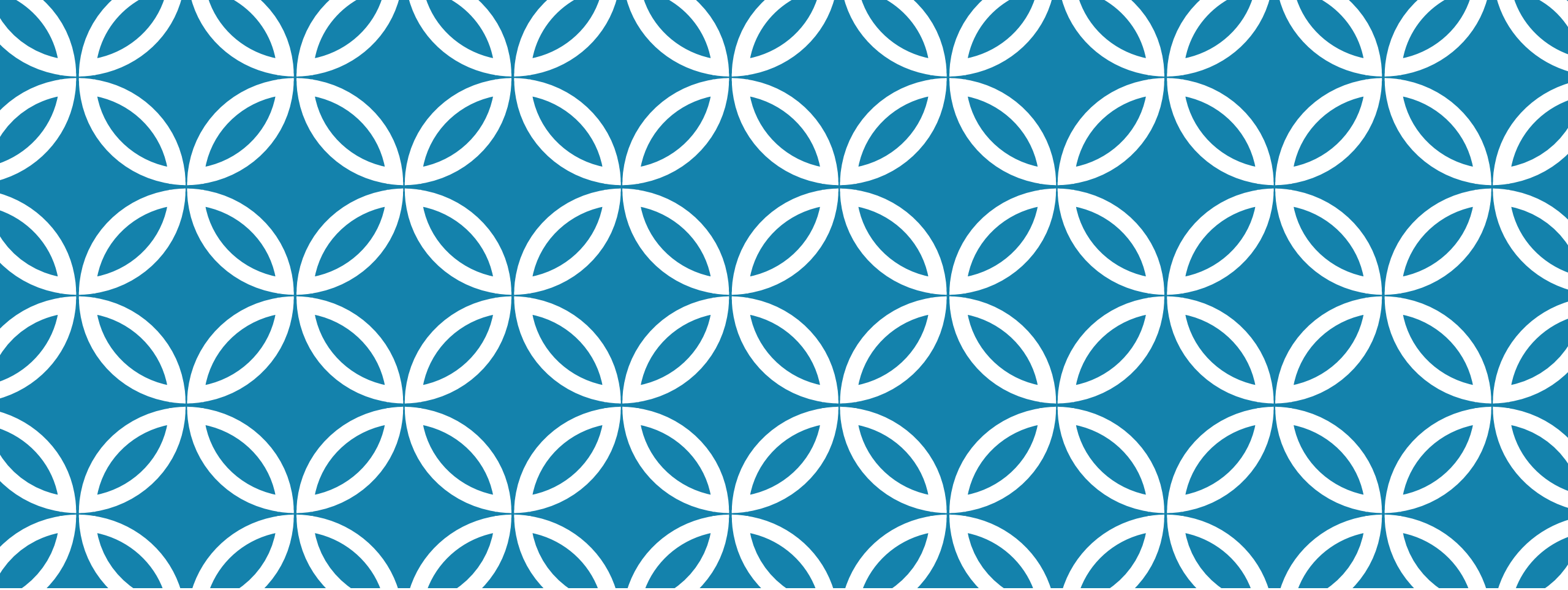
Pregnancy outcomes carry increased risk for:

- C-section
- Placental abnormalities
- Pre-eclampsia
- Antepartum hemorrhage

Infant outcomes carry increased risk for:

- Pre-term birth
- Small for gestational age (SGA) and/or low birth weight
- Poorer developmental outcomes

Maintaining euthymia peripartum, maximizes well-being for patients and families



MOOD STABILIZERS

Lithium, Lamotrigine, and others

LAMOTRIGINE

- INDICATIONS: bipolar disorder **maintenance**

- Well studied in pregnancy

- SAFETY:

- NOT associated with: miscarriage, preeclampsia, placental abruption, preterm birth, SGA or LBW, negative neurodevelopmental outcomes
- Multiple large studies show no increase in congenital malformations
  - One small study showed increase risk for cleft lip/palate by 1%, not replicated in other studies

- DOSING:

- Expect lamotrigine metabolism to increase during pregnancy… clearance increases up to 300%!
  - Limited clinical utility in monitoring serum levels for mood (better data for antiepileptic activity)
  - Can reasonably expect need for increased dose, if mood symptoms recur
- Prescribe BID for more stable plasma levels

LITHIUM

- INDICATIONS: Acute mania; acute episodes with mixed features; bipolar disorder maintenance. Also used off-label for bipolar depression

- SAFETY:

- NOT associated with:
  - Miscarriage, preterm birth, low birth weight, neurodevelopmental outcomes (children studied to 14 yo)
- "Notorious" for increased risk of cardiac malformations
  - Ebstein's Anomaly: in general pop, 0.005%. With lithium: 0.1-0.2%.
  - Other cardiac anomalies: 1.2% in general population; with lithium 1.9%
  - In a single study, risk of cardiac malformations appeared to triple with doses >900 mg/day. The risk of neonatal complications was higher in women with a median Li level of >0.64 mEq/L.
- Case reports, unknown prevalence: diabetes insipidus, transient neonatal hypothyroidism, goiter (increased risk w/ maternal hypothyroidism), tachycardia, respiratory problems, tremor, neuromuscular effects

LITHIUM

- Infant outcomes:
  - Higher incidence of: lethargy, depression, respiratory depression, hypotonia, poor suck
    - Effects resolved in 2 days to 2 weeks
  - In some studies, the effects were not actually statistically significant when compared to non-lithium mothers with bipolar disorder

- Toxicity risks increased by:
  - NSAIDS
  - Antihypertensive added/dose change
  - Fluid loss (dehydration)

LITHIUM

DOSING, prior to pregnancy:

- Folic acid supplementation reduces risk for congenital heart defects, up to 20% in one meta-analysis
  - Data is more limited for the use of folate to prevent CHD (compared to neural tube defects), and therefore there are no standardized recommendations for folate supplementation for reducing CHD
  - For patients on lithium: 1mg daily, starting 1 mo prior to conception and throughout pregnancy

- If you choose to switch mood stabilizers: Beware rapid tapering off lithium!
  - Tapering rapidly increases risk for precipitating mood episode
  - Recommend tapering >1 mo

LITHIUM

DOSING, during pregnancy:

- Pre-pregnancy serum lithium level can be a helpful guide… BUT treat symptoms, not serum level
  - No good data for "goal range" for symptom stability, some patients more sensitive than others
- Lithium metabolism increases across all 3 trimesters
  - Increased renal clearance + increased plasma volume
  - If anything, anticipate (and warn patients of) the need to increase dose
  - Recheck serum level, 4-7 days following each dose change
- Consider BID dosing
  - Theoretical decrease in peak levels for fetus *in utero*

LITHIUM

DOSING, during delivery:

- No changes, don't "hold" the lithium!
- Multiple studies: no dramatic shift in serum level at time of delivery, no evidence to suggest holding lithium decreases the risk of perinatal and infant complications.

LITHIUM

MONITORING, during pregnancy:

- Pre-conception/first visit: BMP, Li level, TSH, urine specific gravity
- Fetal echo and Level II US in 2nd trimester (16-18 weeks vs 20-22 weeks gestation), defer to MFM
  - Clinical advantage of 16wks vs 20wks is unclear (variable recommendations across psych orgs)
- Check serum level monthly (?)
  - This is a theoretical recommendation based off a small, observational retrospective study of 113 women. Not primary outcome, it is extrapolated from observations of increased lithium metabolism and the fact that women with disease relapse had low serum levels
  - Should weigh patient burden vs benefit… if pt remains euthymic, could **check once per trimester at minimum**
  - **Always** check serum level if patient experiences recurrence of mood symptoms
- Check serum level at time of delivery, and 24 hours post-delivery

LITHIUM

DOSING, postpartum:

- Continue current lithium dose if patient remains euthymic
- Consider tapering back to pre-pregnancy dose over the following 4-8 weeks
- No clear guidelines here, so keep in mind:
  - Lithium levels do not become acutely toxic in the first week postpartum
  - Postpartum is an exquisitely high risk period for mood destabilization
- Advise patient to watch for symptom emergence (high risk period), as well as toxic effects (metabolism returning to pre-pregnancy levels)
  - n/v, diarrhea, abdominal cramping, restlessness, tremors, fasciculations/twitching

LITHIUM

MONITORING, postpartum:

- Twice weekly monitoring of serum levels, during the first 2 weeks
- Probably too burdensome (and no clear clinical basis), more realistically every 3-4 weeks for 2 mo
  - Goal serum level: >0.8
- Infant: serum lithium, TSH, BUN, CK
  - immediately postpartum, then repeat 4-6 weeks later.

CARBAMAZEPINE

- INDICATIONS: Acute mania; acute episodes with mixed features

- Less data than lamotrigine/lithium, but more information incoming

- SAFETY:
  - Increased teratogenicity: up to 2x (~7%), dose dependent
    - Neural tube (1%), craniofacial, cardiac, cleft lip/palate, minor birth defects
  - Mixed data re:
    - increased risk of miscarriage
    - Bleeding problems in newborn (low vitamin K)… see OB to discuss supplementation in 3rd trimester
    - Low birth weight
    - Neurodevelopmental outcomes of children
  - Not associated with: preeclampsia, placental abruption, preterm birth, low birth weight

- DOSING:
  - As able, dose < 700mg TDD to reduce dose-dependent teratogenicity risk

VALPROATE/VALPROIC ACID/DEPAKOTE

- INDICATIONS: contraindicated in pregnancy (or reproductive-age females)

- SAFETY:
  - 3-5% risk of neural tube defects
  - 7-10% general teratogenicity risk (cleft palate, cardiac, other)
  - May also cause impaired cognitive function in children exposed *in utero:*
    - lower IQ in one small study, 6-9 points, with children at 3 yrs of agw
    - Poorer performance on language tests, in a very large cohort study, at 3rd & 6th & 8th grade levels
  - Increased risk (3-4x) for adverse neurodevelopmental outcomes, up to 25% of exposed children

- Up to 50% of pregnancies are unplanned, across sociodemographic lines

- Avoid in reproductive-age females with childbearing capacity, due to the above safety concerns.

- If valproic acid is necessary, patients should also take:
  - 4mg of folic acid supplementation daily, to reduce risk of birth defects in the setting of unplanned pregnancy
  - Durable form of contraception

MIXED/UNRELIABLE DATA

Gabapentin

- Not supported for management in bipolar disorder… BUT does get used in pregnancy
- Data overall reassuring re: no increased risk for neurodevelopmental outcomes
  - Risk increase for SGA, preterm birth … however, limited by confounding

Oxcarbazepine

- Limited data (two studies/reviews, ~300 exposures each), but no significant increase in congenital malformations

Topiramate

- Very limited data (< 200 exposures): 1.6-fold increase in risk of congenital malformations
- Reflected in other databases showing increased risk of cleft palate to 1.2%

SECOND GENERATION (ATYPICAL) ANTIPSYCHOTICS

Quetiapine, Olanzapine, Risperidone, Aripiprazole

ATYPICAL ANTIPSYCHOTICS (CLASS)

- No identified risk of miscarriage or stillbirth
  - Aripiprazole: one study yes, others no

- Congenital malformations: no increased risk
  - ~600 live birth exposures per National Pregnancy Registry for Atypical Antipsychotics (Mass. General Hospital)
  - Prospective study of ~300 self-reported exposures in Japan also did not demonstrate increased risk
  - No data: lurasidone, ziprasidone

- Mixed data for size, preterm birth

ATYPICAL ANTIPSYCHOTICS (CLASS)

Transient neonatal adaptation syndrome

- FDA warning 2011: potential risk for abnormal muscle movements (extrapyramidal signs or EPS) and withdrawal symptoms in newborns
- "…may include agitation, abnormally increased or decreased muscle tone, tremor, sleepiness, severe difficulty breathing, and difficulty in feeding. In some newborns, the symptoms subside within hours or days and do not require specific treatment; other newborns may require longer hospital stays."
- Frequency and degree of intervention need not well identified (many confounders)
- 69 cases through the FDA Adverse Events Reporting System

- Reassuring neurodevelopmental data: cohort study of >10,000 births demonstrated no increased risk of neurodevelopmental disorders
  - Children assessed beyond 8yrs of age
  - Exception: aripiprazole potentially associated with increased risk, with hazard ration 1.36. More studies required

ATYPICAL ANTIPSYCHOTICS (CLASS)

Gestational Diabetes:

- 2018 cohort study w/ Medicaid database: increased risk for quetiapine (RR 1.28) and olanzapine (RR 1.61)
- Swedish national register-based cohort study, N=1,307,487 singleton births
  - Small increased risk for women treated with quetiapine, olanzapine, and clozapine. (RR 1.6).
- Consider Fasting glucose tolerance test at 14wks & 28wks

- Other:

- Quetiapine has low placental passage

ATYPICAL ANTIPSYCHOTICS (OUTLIERS)

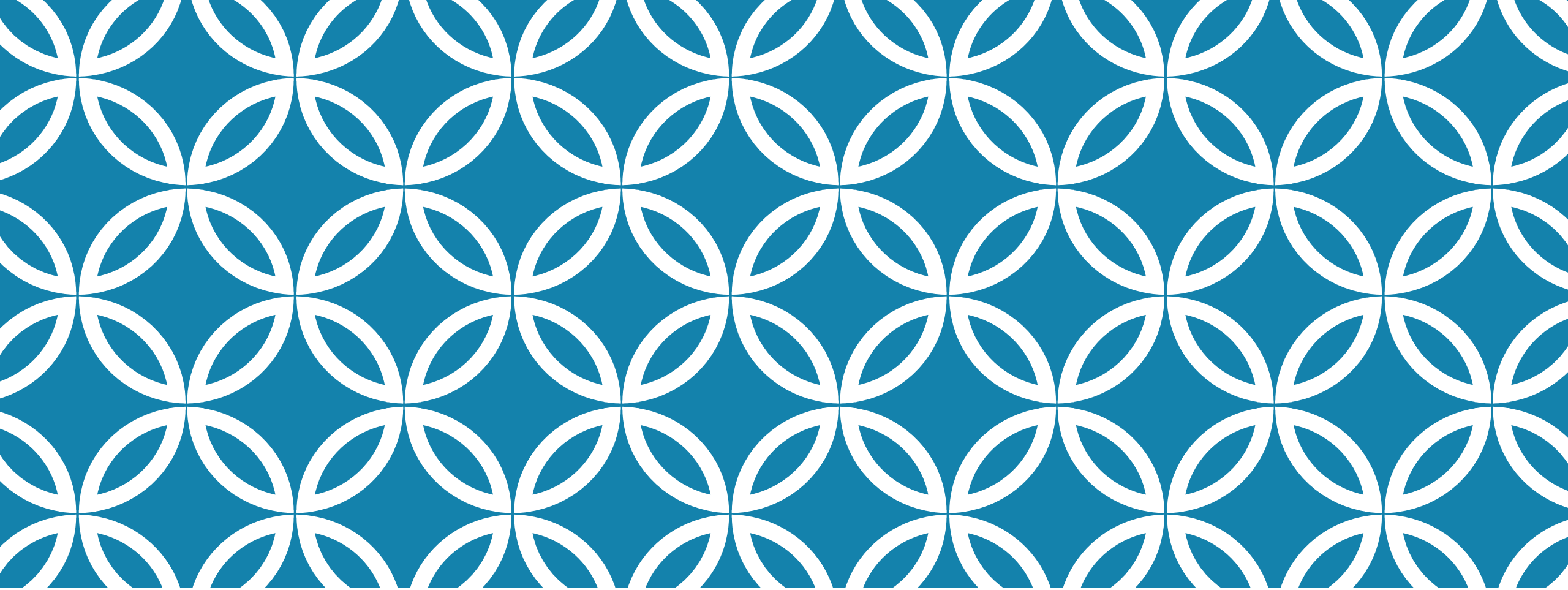
- Lurasidone
  - Almost no human data, single case report reassuring
  - Should be taken with food

- Ziprasidone
  - Animal studies concerning for increased risk of birth defects, but case reports without event
  - Also should be taken with food

METABOLISM IN PREGNANCY

- Metabolism increased across the majority of investigated metabolic enzymes
  - These include: CYP3A4, CYP2D6, CYP2C9, CYP2A6, UGT1A4 and UGT2B7 in observational studies
  - Physiologically-based pharmacokinetic models: Levels of quetiapine and aripiprazole both decreased in latter two trimesters
    - Recommended women during late pregnancy take at least 2.5x quetiapine dose, and 2x aripiprazole dose

- Metabolism decreased for CYP1A2
  - Observational studies
  - Olanzapine and clozapine
    - no studies of these drug levels in pregnancy
    - Extrapolating from caffeine metabolism (also CYP1A2)



RESOURCES FOR YOU

Providers
and Patients

RESOURCES FOR YOU

PSI: postpartum support international

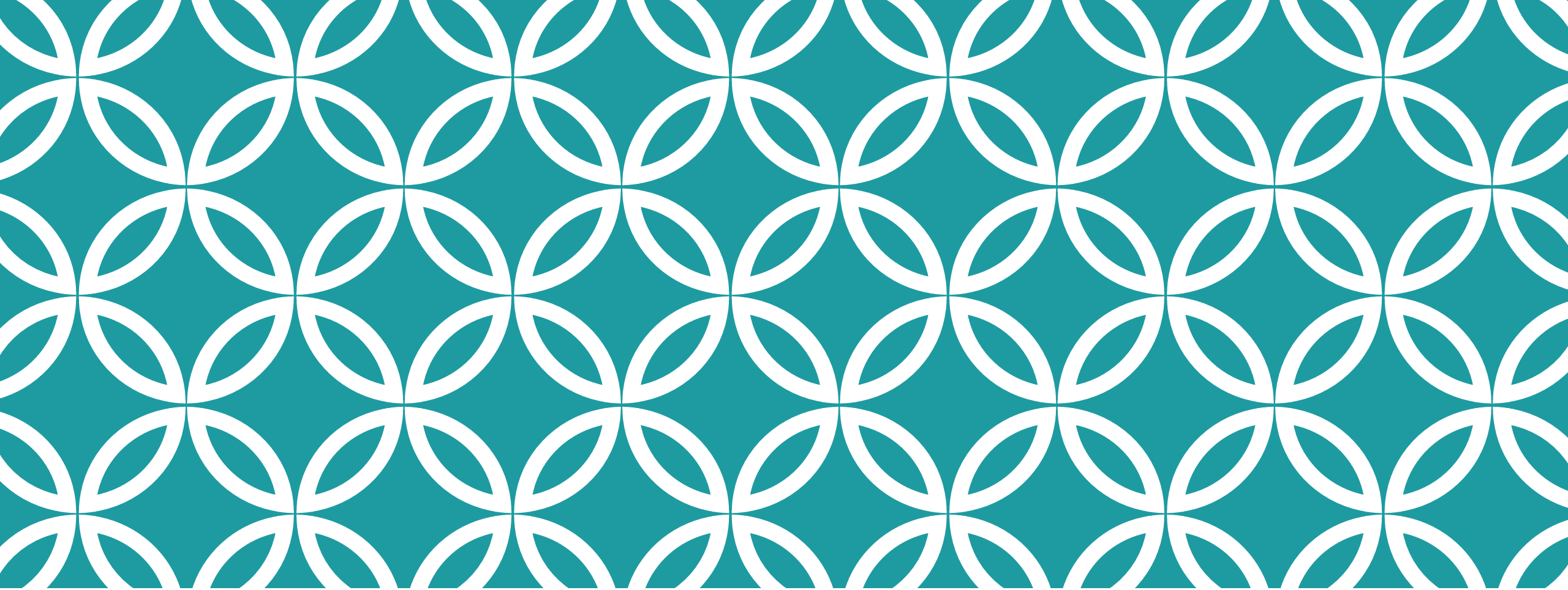
- www.postpartum.net
- National Maternal Mental Health Hotline: **1-833-943-5746 (1-833-9-HELP4MOMS)**
  - **Call or text!**
  - **Available in English or Spanish**
- Providers: can schedule phone consultation with perinatal MH professional
- Patients: list of providers (counselors, med providers) with perinatal training in their national database

Mother to Baby

- www.mothertobaby.org
- Drug "fact sheets" that are patient-friendly

MGH Center for Women's Mental Health:

- www.womensmentalhealth.org
- Searchable information for providers, as well as resource list



THANK YOU!

Questions?

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