Psychiatric Medications:
Perinatal and Lactation Considerations

Approaching Risk/Risk Discussions around Lithium and Anticonvulsants, SGAs, and Benzos

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Counseling women on whether to continue medication during pregnancy includes assessing the risks and benefits of the medication as well as the risks related to the illness.

Consider…

Medication = an Exposure

Illness = an Exposure

…and try to decrease maternal exposures associated with adverse outcomes.

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Lithium and anticonvulsants (i.e., lamotrigine, oxcarbazepine), Second Generation Antipsychotics, and benzodiazepines (i.e. lorazepam) can be continued in pregnancy with appropriate risk and benefit assessment, providing the patient and her partner psychoeducation, monitoring symptoms, and adjusting the dose of medication due to symptom worsening or changing medication concentration.

Mood Stabilizers

Perinatal and Lactation Considerations

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Objectives

- To understand how to approach a risk/benefit analysis of the use of the following mood stabilizing medications in pregnancy:
  - lithium, lamotrigine, valproic acid, carbamazepine/oxcarbamazepine, topiramate and gabapentin

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Risks of Untreated Bipolar Illness for Mother

- Increased risk of mood episodes (~85% if medications stopped)
- Increased rate of c-section
- Placental abnormalities
- Antepartum hemorrhage
- Pre-eclampsia

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Vigeura et. al., *American Journal of Psychiatry*, 2007, 1817-1824; Boden et al., *BMJ*, 2012, 1-10

Risks of Untreated Bipolar Illness for Baby

- Pre-term birth
- Small for Gestational Age
- Low birth weight
- Poor developmental outcomes

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Epstein et al., *Drug, Healthcare and Patient Safety* 2015, 7-29; Jablensky, et al. *American Journal of Psychiatry*, 2005. 162(1): p. 79-91

Lithium

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Lithium and Risks of in Utero Exposure to the Fetus

- Limited data derived from case reports suggest the following adverse outcomes, however the prevalence is unknown:
  - Diabetes insipidus
  - Respiratory problems
  - Tachycardia
  - Transient neonatal hypothyroidism
  - Tremor
  - Neuromuscular complications

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Ebstein's Anomaly

- Is a right ventricular outflow tract obstruction defect. It is also described as a downward displacement of the tricuspid valve. Severity of the defect varies.

- The defect occurs in approximately 1 out of every 20,000 infants in the general population

Lithium and Risks of Ebstein's Anomaly

- In 1974 the risk of Ebstein's anomaly attributed to lithium exposure was estimated to be 400 times that in the general population according to the International Register of Lithium Babies.
- More recently, in studies with a more systematic research approach, investigators determined that the risk of Ebstein's anomaly due to lithium exposure is significantly less than previously suggested.
  - In 1994 Cohen et al. 0.1 – 0.2 infants per 100 exposures.
  - In 2017 Patorno et al. 0.60 per 100 births among infants exposed to first trimester compared to 0.18 per 100 unexposed infants.
  - In 2018 Munk-Olsen et al. increase in overall malformations (7.4% vs but no increase in cardiac malformations.

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Cohen et al. *JAMA*. 1994 Jan 12;271(2):146-50. Patorno et al. N Engl J Med 2017; 376:2245-54
Munk-Olsen et al. *The Lancet Psychiatry* 2018.

Lithium, Risks of Cardiac Malformations, and Monitoring

- The overall estimated risk of a non-Ebstein's cardiac malformation due to first trimester lithium exposure is 1.67 to 1.80 which translates into 1 to 2 additional cases per 100 exposures.
- A fetal echocardiogram should be obtained at 20 – 22 weeks gestation

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Patorno et al. N Engl J Med 2017; 376:2245-54

Lithium and Labor

- **Placental Transfer -** Lithium crosses the placenta and lithium maternal serum-to-umbilical cord concentration are approximately equal regardless of dose; maternal serum-to-umbilical cord ratio is estimated to be 1.05
- **Concentration at Birth** - High lithium concentrations (>0.64 mEq/liter) at birth have been associated with significantly higher rates of central nervous system (i.e., lethargy and depression) and neuromuscular (hypotonia, flaccidity, decreased tendon reflexes, poor suck and poor Moro reflex) complications at birth.
- **Reduction of Risk of Perinatal Complications** - Suspension of lithium at the onset of labor or 24-48 hours prior to a scheduled caesarean section or an indication of labor has been shown to reduce the risk of neonatal complications

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Newport D.J. *Am J Psychiatry* 2005.162;2162 -2107

Risks for Lithium Toxicity

- The following will increase the risk for lithium toxicity in pregnancy and warrant extra monitoring of blood concentration and adverse symptoms
  - Vomiting and fluid loss
  - Use of non-steroidal anti-inflammatory agents (not recommended third trimester)
  - Use of diuretics

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Lithium and Breastfeeding

- Exposure to lithium through breastmilk is substantially less than in utero exposure
- Excretion of lithium in breast milk:
  - Bogen et al. (2012) - Breastfed infants (n=3) have levels 10 -17% of the maternal serum concentration.
  - Viguera et al. (2007) – For maternal-infant pairs (n=10), maternal serum, breast milk, and infant serum daily trough concentrations of lithium 0.76, 0.35, and 0.16. It was estimated that lithium in breast milk was half of the maternal serum and infant serum was half of the lithium concentration in breast milk. "Rule of Halves".
  - Schou et al. (1973) – Infant serum concentrations (n=10) were 1/3rd c maternal serum level

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Bogen, DL. *Arch Womens Ment Health.* 2012; 15(1): 69-72;
Viguera, AC. *Am J Psychiatry*. 2007; 164(2):342-5. Schou, M. *Br Med J*. 1973;2:138

Breastmilk Exposure to Lithium and Outcomes

- Elevations of thyroid-stimulating hormone, blood urea nitrogen, and creatinine have been reported and were transient
- No adverse developmental effects
- No cases of hypotonia (“floppy baby”) associated with lithium exposure through breastmilk. Although case reports have suggested this outcome due to breast milk exposure, these cases have included babies with in utero exposure and medical comorbidities. As a result it is difficult to attribute the outcome exclusively to lithium exposure through breastmilk or to discern which outcomes are attributable to in utero exposure or infant comorbidities.

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Viguera, AC. *Am J Psychiatry*. 2007; 164(2):342-5.

Risks and Benefits of Breastfeeding

Aside from medication exposure, the benefits of breastfeeding for women with Bipolar Disorder must be weighed against the risks.

- Sleep deprivation is a significant risk factor to Bipolar Disorder independent of medication compliance
- Additional risk factors:
  - Polytherapy
  - Infant with medical problems (i.e., respiratory infection, kidney deformity, fever, GI issues, fluid loss)
  - Mother with active illness

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Lithium Concentration Monitoring in Infants

- Obtain serum lithium, TSH, blood urea nitrogen, and creatinine in the immediate postpartum period
  - Repeat at 4-6 weeks
- No further regular monitoring recommended.
- Signs of toxicity include lethargy, poor feeding, and hypotonia.
- Toxic symptoms may be reversed with intravenous hydration
- Any infant with these symptoms should see a doctor, have labs checked, and receive treatment if needed.

Anti-Epileptics

Perinatal and Lactation Considerations

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Anti-Epileptics (AEDs)

- Most safety knowledge about the use of AEDs in pregnancy comes from epilepsy registries
- Dosing and monitoring can vary depending on the indication and the individual (often higher doses required for management of epilepsy compared to bipolar disorder)
- Polypharmacy is associated with increased risk of major malformations and other adverse outcomes

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Tomson and Battino, *Lancet Neurology,* 2012, 810-813

Risk of In-Utero Exposure: Lamotrigine

- Considered first-line among AEDs for the treatment of both bipolar disorder and epilepsy during pregnancy given it's favorable risk/benefit profile
- ~2.7% risk for major malformations (equivalent to the baseline 3-5% risk in the general population)
- Potential increased rate of cleft palate
  - found in only 1 study, not replicated in 5 others

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Meador et al. *Epilepsy Res* 2008; 81:1–13; Pariente et al. *CNS Drugs.* 2017 Jun;31(6):439-450; Wilson et al. *J Obstet Gynaecol Can* 2015;37(6):534–549

Risk of In-Utero Exposure: Valproic Acid

- Highest risk for all major malformations among AEDs (~10%)
    - Neural tube and cardiac defects are the main concern
- Associated with neurodevelopmental impairment, reduction in IQ
- Risk of major malformations and cognitive impairment is dose dependent (doses>1g substantial increased risk)
- Frequently avoided in pregnancy, requires careful discussion with OB
- If must be used in pregnancy, high dose folic acid (4 mg) is recommended as supplementation

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Meador et al. Epi*lepsy Res* 2008; 81:1–13; Haskey and Galbally, *Aust N Z J Psychiatry,* 2017 Nov;51(11):1087-1097

Risk of In-Utero Exposure: Carbamazepine and Oxcarbamazepine

Carbamazepine:

- Some studies have shown an increased overall risk in congenital malformations, others have shown rates consistent with the general population
- Likely higher rates of orofacial clefts, neural tube defects (6.3%) compared to other AEDs

Oxcarbamazepine:

- Data are limited
- Rates of congenital malformations appear similar to that in the general population

If must be used in pregnancy, high dose folic acid (4 mg) is recommended as supplementation

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Hill et al. *Expert Rev Neurother.* 2010 June ; 10(6): 943–959; Wilson et al. *J Obstet Gynaecol Can* 2015;37(6):534–549

AEDs and Breastfeeding

- AEDs passed in different amounts in maternal breast milk
- Monitor the infant for sedation, difficulty with feeding, weight gain/loss and developmental milestones
- Often potential benefits of breastfeeding outweigh risks of medication, but should consider both medication specific and non-medication factors (frequency of feedings, impact on sleep) when discussing lactation in patients with bipolar disorder

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Lamotrigine and Breastfeeding

- Variable passage into breast milk
- Infants can have higher levels due to limited ability to metabolize lamotrigine early after birth
- 1 case of apnea in a mother who was had lamotrigine toxicity, dose>500 mg; monitor for sedation, rash, poor sucking
- Breastfeeding encouraged by the American Academy of Neurology and Epilepsy

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Newport et al. *Pediatrics* 2008; 122:223–231

Valproic Acid and Breastfeeding

- In general low levels passed in breastmilk (<10% across all studies and on average between 1-7%)
- No major adverse reactions known, but watch for theoretical signs of liver toxicity (jaundice, bruising)
- No known impact on cognitive development or IQ when used as monotherapy

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Meador et al. *JAMA Pediatrics*, 2014; 168: 729-36; Stowe, *J Clin Psychiary*, 2007, 22-28; Piontek et al. *J Clin Psychiatry*, 2000;61:170-172

Carbamazepine and Oxcarbamazepine and Breastfeeding

Carbamazepine:

- Passed in higher levels in breastmilk
- Adverse reactions are infrequent but have included sedation, difficulty feeding, hepatic dysfunction
- No known impact on growth and development from exposure to carbamazepine in breastmilk

Oxcarbamazepine:

- limited data, but no known adverse outcomes
- It is recommended to monitor for sedation, weight gain and developmental milestones

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Meador et al. *JAMA Pediatrics*, 2014; 168: 729-36; Stowe, *J Clin Psychiary*, 2007, 22-28

Other AEDs: Topiramate and Gabapentin

- Topiramate and gabapentin are not first-line mood stabilizers; however, there may be other indications for use in pregnancy (e.g. epilepsy, anxiety)
- When prescribing these medications consider risks of in-utero exposure, pharmacokinetics during pregnancy, medication monitoring plan, and knowledge known about their use in lactation

Second Generation Antipsychotics

Perinatal and Lactation Considerations

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Objectives

- Develop an approach to risk/benefit discussion around SGAs in peripartum
- For SGAs, be aware of :
  - Preconception considerations
  - Morphologic teratogenicity; Neurodevelopmental teratogenicity; Other neonatal outcomes; Placental Passage of SGAs; Pharmacokinetic changes in pregnancy
  - Literature on safety in Lactation

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Schizophrenia in Pregnancy

- In contrast to affective disorders, little known about impact of schizophrenia pregnancy
- Higher vulnerability due to multiple factors:
  - reduced attendance at antenatal appointments
  - reduced use of prenatal vitamins, folate and thyroid hormone
  - increased rates of unplanned and unwanted pregnancy
  - limited social support and increased rates of domestic abuse, poverty, and disadvantage
  - Higher rates of unhealthy lifestyle (including smoking, alcohol and substance use)

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Breadon & Kulkarni ,*Expert Opinion on Pharmacotherapy*, 2019,
DOI: 10.1080/14656566.2019.1612876

Schizophrenia in Pregnancy

- High rate of discontinuation of antipsychotic medications in early and late pregnancy, and correspondingly high relapse rates

- High mental health care needs around pregnancy and childbirth:
  - Up to 41% of women with schizophrenia may actually require psychiatric admission during pregnancy

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Breadon & Kulkarni ,*Expert Opinion on Pharmacotherapy*, 2019, DOI: 10.1080/14656566.2019.1612876

Gentile & Fusco, *Psychiatry and Clinical Neurosciences*, 2019, http://onlinelibrary.wiley.com/doi/10.1111/pcn.12856/full

Schizophrenia in Pregnancy

- Confounding of illness and exposure to antipsychotics in available literature:
  - reports of higher rates of cardiovascular malformations, specifically septal defects, in babies of women with schizophrenia, and those taking atypical antipsychotics
  - prematurity, low birth weight, small for gestational age babies are all associated with the diagnosis of schizophrenia and with the use of antipsychotic medications

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Breadon & Kulkarni ,*Expert Opinion on Pharmacotherapy*, 2019,
DOI: 10.1080/14656566.2019.1612876

Schizophrenia in Postpartum

- Untreated psychosis associated with:
  - difficulties with bonding and attachment
  - separation from their baby
  - infant may be incorporated into its mother's delusions

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Gentile & Fusco, *Psychiatry and Clinical Neurosciences*, 2019, http://onlinelibrary.wiley.com/doi/10.1111/pcn.12856/full

Second Generation Antipsychotics

Perinatal and Lactation Considerations

SGAs: Preconception Considerations

Fertility

- Risperidone is known to cause hyperprolactinemia which reduces fertility. When this occurs, consider switching to an alternative SGA to facilitate conception.

Metabolic syndrome

- Several SGAs are associated with an increased risk of metabolic syndrome. Address modifiable risk factors (obesity) and optimize treatment of comorbid medical illnesses (dyslipidemia, diabetes).

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Morphologic Teratogenicity

Habermann et al:

- Increased risk of cardiovascular malformations (isolated ASDs and VSDs), (aOR 2.17; 95% CI 1.2-3.91)
    - Detection bias may account for the increase

*Lurasidone, Iloperidone, Paliperidone – no human data yet

Huybrechts et al:

- All SGAs, No increased risk, (aRR 1.05; 95% CI, 0.96 – 1.16)
- Small increased risk for one individual agent (Risperidone):

  Overall malformations (aRR 1.26; 95% CI, 1.02 – 1.56)

  Cardiac malformations (aRR 1.26; 95% CI, 0.88 – 1.81)

"Finding should be viewed as initial safety signal that requires further study."

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(Habermann et al Journal Clinical Psychopharmacology 2013, Huybrechts et al JAMA Psychiatry 2016,)

Morphologic Teratogenicity

Reassuring Data from the National Pregnancy Registry of Atypical Antipsychotics:

303 women completed the study and were eligible for inclusion in the analysis

The most commonly used second-generation antipsychotics in the exposed group were **quetiapine, aripiprazole, and olanzapine**.

Of 214 live births with first-trimester exposure to second-generation antipsychotics, three major malformations were confirmed.

In the control group (N=89), one major malformation was confirmed.

The **absolute risk of major malformations was 1.4% for exposed infants and 1.1% for unexposed infants**. The odds ratio for major malformations comparing exposed infants with unexposed infants was 1.25 (95% CI=0.13–12.19).

Results suggest that it would be unlikely for second-generation antipsychotics to raise the risk of major malformations more than 10-fold beyond rates the general population or among control groups using other psychotropic medications

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Cohen et al., Am J Psychiatry 2015.

Neurodevelopment

Johnson et al:

- APs (FGA and SGA) exposure in utero lead to lower scores on a standard test of neuromotor performance(Infant Neurological International Battery) in infants at 6 months of age.

Peng et al:

- Infants exposed to SGAs had delayed development in cognitive, motor, social-emotional, and adaptive behavior as measured by the Bayley Scales of Infant and Toddler Development at 2 months of age but not at 12 months of age.
  - Limitations to studies include contribution of maternal illness
  - Neurodevelopmental effects may only cause short-term delay

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Johnson et al, Arch Gen Psychiatry 2012, Peng et al, Psychopharmacology 2013

Other Outcomes

- SGA use in utero is associated with inconsistent outcomes for the following:
  - Spontaneous abortion
  - Birth weight (low and high)
  - Preterm birth
- Neonatal complications: FDA issued warning (2011) for APs
  - EPS and Withdrawal/Toxicity signs (hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding problems)
  - Findings based on 69 case reports, majority of cases confounded by other factors (concomitant use of other drugs)
  - Habermann found an increased risk for neonatal adaption, but findings may also be a result of comedication and effects of maternal mental illness.

    SGA exposure 15.6% (n=37/237) compared to no exposure 4.2% (n=43/1014)

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Kulkarni et al Expert Op on Pharmacotherapy 2015, Habermann et al Journal of Clinical Psychopharmacology 2013, Sadowski et al BMJ 2013

Placental Passage

- Placental Passage – defined as the ratio of umbilical cord to maternal plasma concentrations:
  - Olanzapine 72.1 % (highest transfer)
  - Haloperidol 65.5 %
  - Risperidone 49.2 %
  - Quetiapine 23.8 % (lowest transfer)

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Boden et al Arch General Psychiatry 2012

Antipsychotic Metabolism in Pregnancy

- Increase in pregnancy:
    - CYP2A6
    - CYP2D6 (decreased serum levels of risperidone, aripiprazole, iloperidone)
    - CYP2C9
    - uridine 5’-diphosphate glucuronosyltransferase

- Decrease in pregnancy:
    - CYP1A2 (increased serum levels of clozapine, olanzapine)
    - CYP2C19

- Dosing may need to be adjusted if symptoms emerge

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Long Acting Injectable Antipsychotics

- LAIs
  - Data limited to case reports
  - Rely on oral AP risks to guide discussion on LAIs, more safety data needed
  - Weight should be given to continuing LAIs if patient stable prior to pregnancy, unknown risks associated with starting LAI during pregnancy
  - Bypass first pass hepatic metabolism – levels may stay more stable

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Lactation

- Drug excretion < 10% is generally considered negligible and compatible with breastfeeding, as it is unlikely to lead to dose related adverse events in the infant
- The 10% limit has been accepted by organizations such as the American Academy of Pediatrics

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Lactation

SGA	Relative Infant Dose (RID)	Special precautions
Clozapine	1.33 – 1.4%	Monitor for agranulocytosis
Olanzapine	0.3 – 2.2%	
Quetiapine	0.07 – 0.1%	
Risperidone	2.8 – 9.1%	
Ziprasidone	0.07 – 1.2%	
Aripirazole	1%	Can lower serum prolactin, which may affect milk supply

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Hale Medications and Mother's Milk

In Summary

- Consider indication and risks of exposure to maternal mental illness
- Preconception:
  - Optimize management of metabolic syndrome to reduce pregnancy complications.
  - Risperidone may impact fertility if associated with hyperprolactinemia.
- Morphologic teratogenicity:
  - No increased risk for SGAs except risperidone which was associated with small increase in risk for congenital malformations, including cardiac malformations.
  - Reassuring data from NPRAA unlikely for second-generation antipsychotics to raise the risk of major malformations.
- Neurodevelopmental teratogenicity:
  - SGAs associated with initial neurodevelopmental delay that resolved by 12 months of age. Need to control for severity of maternal illness in future studies.

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In Summary

- EPS/neonatal adaptation:
  - Interpret FDA warning with caution. Studies have not adequately considered comedication and effects of maternal illness.
- Placental Passage of SGAs:
  - Highest rate of transfer for olanzapine, lowest for quetiapine.
- Pharmacokinetics:
  - Consider changes in hepatic metabolism in pregnancy and monitor symptoms closely.
- Lactation:
  - <10% relative infant dose for SGAs, which is considered acceptable or breast feeding.

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What about First Generation Antipsychotics?

- Most safety data for Haldol
- Earlier studies reported no significant increase in risk for major malformations with butyrophenones (mainly haloperidol) and phenothiazines (e.g. chlorpromazine)
- In more recent studies that adequately controlled for confounders, little risk of significant adverse maternal and neonatal outcomes for FGAs (and SGAs)

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McAllister-Williams et al. *Journal of Psychopharmacology* 2017, Vol. 31(5) 519–552

What about First Generation Antipsychotics?

- Many FGAs (haloperidol, perphenazine, trifluoperazine and chlorpromazine) are excreted in breast milk in small amounts, with an estimated RID of <10%

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McAllister-Williams et al. *Journal of Psychopharmacology* 2017, Vol. 31(5) 519–552

Benzodiazepines

Perinatal and Lactation Considerations

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Objectives

- Develop an approach to risk/benefit discussion around benzodiazepines

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Risks of Untreated Anxiety

- Possible increased risk for obstetrical complications: preterm birth, low birth weight, hypertensive disorders of pregnancy
- Anxiety during pregnancy is also an independent risk factor for postpartum depression
- Possible association with childhood anxiety, developmental, or behavioral problems in offspring

Insomnia

- Insomnia is one of the most consistent risk factors for postpartum psychiatric decompensation and must be treated aggressively
- CBT for insomnia is an evidence-based approach that should ALWAYS be the first choice in pregnancy as it is completely safe for baby
- Clinicians prescribing medications for insomnia should instruct women to get help with overnight infant care in order to avoid both disrupted sleep and the potential for unintentional infant harm from maternal sedation.

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Benzodiazepines

Perinatal and Lactation Considerations

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Benzodiazepines

- Aim to use minimum effective dose
- Aim to use medication with a shorter half-life (such as lorazepam) as opposed to a longer half-life (such as diazepam), to reduce level of exposure

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Lorazepam in Pregnancy

- Early reports suggested association between lorazepam use in the first trimester and cleft lip/palate (estimated risk: 0.7%)
- More recent studies have not demonstrated this association
- Upon delivery, signs of toxicity have been reported, including sedation, decreased muscle tone, and respiratory compromise (may be related to higher maternal dose)
- There have also been case reports of neonatal withdrawal, including irritability, sleep disruption, and (rarely) seizure

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Ban L, West J et al: First trimester exposure to anxiolytic and hypnotic drugs and the risks of major congenital anomalies: a United Kingdom population-based cohort study. PLoS One 2014: 9 (6); e100996.

Lorazepam while Breastfeeding

- Lorazepam is excreted in low levels in breastmilk
- It is generally administered safely even directly to infants
- Evidence from nursing mothers suggests that lorazepam is not associated with any adverse effects with the usual maternal doses

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Kelly LE, Poon S, Madadi P, et al: Neonatal benzodiazepine exposure during breastfeeding. J Pediatr 2012: 161 (3): 448-451.

Resources

- Reprotox (reprotox.org)
- Mother to Baby (mothertobaby.org)
- Massachusetts General Hospital Women's Mental Health Blog (womensmentalhealth.org)
- Lactmed (toxnet.nlm.nih.gov/newtoxnet/lactmed.htm)

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