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
- To develop a basic knowledge of these medications during the perinatal period including:
  - Risk of major malformations
  - Pharmacokinetics during pregnancy
  - Monitoring during pregnancy
  - Considerations with lactation

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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.

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

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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

Perinatal and Lactation Considerations

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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

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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 lithium in first trimester compared to 0.18 per 100 unexposed infants.
  - In 2018 Munk-Olsen et al. increase in overall malformations (7.4% vs. 4.3 but no increase in cardiac malformations.

NATIONAL CURRICULUM IN REPRODUCTIVE – PSYCHIATRY –

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 br "Rule of Halves".
  - Schou et al. (1973) – Infant serum concentrations (n=10) were 1/3r maternal serum level

NATIONAL CURRICULUM IN REPRODUCTIVE – PSYCHIATRY –

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.

NATIONAL CURRICULUM IN REPRODUCTIVE – PSYCHIATRY –

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.

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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
- High dose folic acid (4 mg) is frequently recommended as supplementation

NATIONAL CURRICULUM IN REPRODUCTIVE – PSYCHIATRY –

Meador et al. *Epilepsy Res* 2008; 81:1–13; Pariente et al. *CNS Drugs.* 2017 Jun;31(6):439-450

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

NATIONAL CURRICULUM IN REPRODUCTIVE – PSYCHIATRY –

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

NATIONAL CURRICULUM IN REPRODUCTIVE – PSYCHIATRY –

Hill et al. *Expert Rev Neurother.* 2010 June ; 10(6): 943–959

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

NATIONAL CURRICULUM IN REPRODUCTIVE – PSYCHIATRY –

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

NATIONAL CURRICULUM IN REPRODUCTIVE – PSYCHIATRY –

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 developr milestones

NATIONAL CURRICULUM IN REPRODUCTIVE – PSYCHIATRY –

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

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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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Mood Stabilizer and Perinatal Dosing

Pharmacokinetic Considerations

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General Considerations of Dosing During Pregnancy and Post-Partum

- Pharmacokinetics of medications may change because of physiological changes during pregnancy (increased renal clearance, increased metabolic enzyme activity with resultant increase in medication clearance (i.e., glucuronidation)
- Dosing adjustments may be necessary both during pregnancy and early in the post-partum
- A medication monitoring plan is often required
- It is important to collaborate with both the OB and pediatrician

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Lithium Pharmacokinetics in Pregnancy

- Lithium is exclusively eliminated by the kidney
- Glomerular filtration rate (GFR) increases during the first trimester by 50% and remains elevated throughout pregnancy.
- Lithium concentrations decrease across pregnancy and this is attributed to declines in increase in GFR.
- Declining concentrations of lithium over the course of p is a risk factor for symptom worsening due to the narro therapeutic window of lithium (0.6-1.0 mEq/L)

NATIONAL CURRICULUM IN REPRODUCTIVE – PSYCHIATRY –

Schou et al. *Br Med J* 1973;2:137; Westin et al. *BMJ Open* 2017;7:e015738;
Wesseloo et al. *Br J Psychiatry* 2017 Jul 2; 211(1):31-36

Lamotrigine Pharmacokinetics in Pregnancy

Lamotrigine:

- Metabolized primarily by glucuronidation in the liver and renally excreted
- Rising estradiol levels in pregnancy are associated with increased glucuronidation→faster metabolism of lamotrigine
- Lamotrigine metabolism increases as early as 8-10 weeks and continues to progressively increase through 32 weeks gestation
- Although most women women will experience increased lamotrigine clearance during pregnancy, the magnitude of the increase var

Faster clearance often necessitates dose increases of lamotrig pregnancy!

NATIONAL CURRICULUM IN REPRODUCTIVE – PSYCHIATRY –

Chen et al. *Drug Metab Dispos* 2009; 37:1841 – 1847; Pennell et al. *Epilepsy Behav* 2007; 11:263–269

Valproic Acid, Carbamazepine, and Oxcarbazepine Pharmacokinetics in Pregnancy

Valproic Acid:

- Metabolized by glururonidation and oxidation→ may lead to decreased levels in pregnancy

Carbamazepine:

- Metabolized by CYP system (3A4) and glucuronidation→ reduction vs unchanged levels in pregnancy

Oxcarbamazepine:

- Metabolized by glucuronidation→increased clearance

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General Medication Monitoring Principles

- Optimize dose in order to achieve symptom remission pre-pregnancy (when able) and check trough level that corresponds with affective remission for the individual patient
- Educate the patient about the potential of symptom worsening and the likely need to increase the dose during pregnancy
- Monitor symptoms monthly (lamotrigine/oxcarbazepin every trimester (lithium/carbamazepine)

NATIONAL CURRICULUM IN REPRODUCTIVE – PSYCHIATRY –

Clark et al. *Am J Psychiatry*. 2013 Nov;170(11):1240-7

General Medication Monitoring Principles

- Check monthly trough levels (lamotrigine/oxcarbazepine) or 12-hour levels each trimester (lithium/carbamazepine)
  - If patient is asymptomatic and the concentration is less than pre-pregnancy therapeutic concentration, consider increasing the dose to prevent symptom worsening.
  - If symptoms are present and concentration is less than pre-pregnancy therapeutic concentration, increase dose.
- Consider dosing twice daily or using long-acting form to avoid peaks in medication
- Collaborate with OB, consider 2nd trimester level 2 ultrasound

NATIONAL CURRICULUM IN REPRODUCTIVE – PSYCHIATRY –

Clark et al. *Am J Psychiatry*. 2013 Nov;170(11):1240-7

Special Consideration for Lamotrigine Medication Monitoring

- For many, the lamotrigine dose will require a dose increase of ≥ 25% over the course of pregnancy. Some patients require double their therapeutic pre-pregnancy dose.
- Taper quickly to pre-pregnancy dose post-partum! If lamotrigine dose is increased in pregnancy, lamotrigine dose should be decreased by 25% of the dose increased on the first day postpartum.
- Monitor for signs/symptoms of lamotrigine toxicity (dizziness, blurred vision, nausea/vomiting, drowsiness, loss of coordination).
- Check trough level if patient complains of any adverse effects (i.e., dizziness, ataxia, blurred vision) which may indicate lamotrigine toxicity.

NATIONAL CURRICULUM IN REPRODUCTIVE – PSYCHIATRY –

Sabers et al. N*eurologica,* July 2012; 126:e1 – e4

Sheila is a 32 y/o female who has been taking lithium for 10 years with good response. She had her first child 5 years ago and discontinued lithium prior to pregnancy due to concerns of exposure to her baby. She did not resume in postpartum and had an onset of postpartum psychosis. She is planning to have a second child and is considering continuing lithium in pregnancy.

What should you inform her about continuing lithium during the first trimester?

1. Lithium is associated with an increased risk for all cardiac malformations which occurs at a rate of 1 to 2/100 cases.
2. Lithium increases the risk for Ebstein's anomaly which occurs commonly in 10 to 20 per 200 cases.
3. The most concerning malformation of the heart is teratology of fallot which can be avoided with holding lithium until the second trimester.
4. The dose of lithium should be decreased to prevent risk of congenital malformations.

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Sheila's psychiatrist recently checked her lithium level and it was 0.8 mEq/L. What is her infant's concentration?

1. 0.3 mEq/L to 0.4 mEq/L
2. 0.6 mEq/L to 0.7 mEq/L
3. 0.1 mEq/L to 0.2 mEq/L
4. 0.04 mEq/L to 0.05 mEq/L

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Mrs. J is a 36 married, employed female who presents with a history of Bipolar Disorder I. She has a history of three suicide attempts associated with mixed episodes. She was hospitalized for each episode. Her symptoms have been in remission with lithium 1200 mg hs and a lithium concentration of 0.9 in addition to olanzapine 5 mg hs. She is pregnant with her first child. She is 16 weeks pregnant and presents with complaints of increasing irritability and anxiety which she attributes to all that she has to do to prepare for the baby's arrival.

What should be the next step(s) to address Mrs. J's complaints?

1. Weekly therapy to address her worsening anxiety and catastrophizing of her to do list.
2. Check a lithium level.
3. Split her dose into twice daily instead of once daily dosing.
4. Have return for follow-up in four weeks to reassess.
5. a, b, and c
6. All of the above

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Ms. K is a 31 yo married female with a history of bipolar disorder type I who presents for a pre-conception planning visit. Over the course of the interview she tells you she has had multiple mood episodes in the setting of tapering lithium, two of which resulted in inpatient psychiatric hospitalization. She tells you she wants to taper lithium again in anticipation of pregnancy as she wants the risk for the baby to be "0."

What do you advise her about the risks of untreated illness during pregnancy?

A. Pregnancy is protective so she will likely do well during pregnancy

B. Untreated bipolar illness during pregnancy is associated with obstetrical complications such as pre-eclampsia, increased risk of c-section, placental abnormalities

C. Women with bipolar disorder have a high risk of recurrent affective episodes during pregnancy, and this risk if increased if medications are stopped

D. Untreated bipolar illness is associated with risks for the baby including low birth weight, pre-term birth, developmental abnormalities, among others

E. B, C, and D should all be discussed with the patient

NATIONAL CURRICULUM IN REPRODUCTIVE – PSYCHIATRY –

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NATIONAL CURRICULUM IN REPRODUCTIVE – PSYCHIATRY –

Ms. L is a 30 yo female with a history of bipolar II disorder who currently takes lamotrigine 200 mg at bedtime as monotherapy. She is thinking of trying to conceive in the next year and after a thorough discussion of the risks and benefits of lamotrigine use in pregnancy with her psychiatrist has decided to remain on medication during pregnancy. She asks what, if anything, she should do prior to conception.

A. Nothing, she is doing well and has already gone thorough pre-conception counseling with her psychiatrist.

B. Add a low-dose atypical antipsychotic for added protection during pregnancy.

C. Check a trough (before next dose) level of lamotrigine to keep to use for comparison in pregnancy.

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Ms. L is a 30 yo female with a history of bipolar II disorder who currently takes lamotrigine 200 mg at bedtime as monotherapy. She is thinking of trying to conceive in the next year and after a thorough discussion of the risks and benefits of lamotrigine use in pregnancy with her psychiatrist has decided to remain on medication during pregnancy. She asks what, if anything, she should do prior to conception.

A. Nothing, she is doing well and has already gone thorough pre-conception counseling with her psychiatrist.

B. Add a low-dose atypical antipsychotic to provide additional protection against episode recurrence during pregnancy.

C. Check a trough (before next dose) level of lamotrigine to keep to use for comparison when monitoring lamotrigine concentration during pregnancy.

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Ms. L returns for a follow-up visit at 16 weeks gestation and describes worsening mood, more irritability, lower energy and reduced interest. She says she has been taking her medication nightly and therefore does not understand why she is having symptoms. What do you tell her?

A. Lamotrigine has suddenly become ineffective and she should switch to an atypical neuroleptic

B. Ask her if she is sure she is taking her medication every night

C. Rising estradiol levels are causing lamotrigine to be metabolized faster. You explain that this is expected and she likely needs a dose increase at this time

NATIONAL CURRICULUM IN REPRODUCTIVE – PSYCHIATRY –

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Which of the following statements about valproic acid use in pregnancy and lactation are true?

A. Valproic acid use during pregnancy is associated with both neural tube defects and cardiac defects
B. The risks associated with valproic acid use in pregnancy are dose dependent
C. Valproic acid use during lactation is associated with substantial risks and should be avoided
D. A, B, and C are all true
E. A and B are true

NATIONAL CURRICULUM IN REPRODUCTIVE – PSYCHIATRY –

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