

# Psychotropic Medications in Pregnancy

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Day in Psychiatry 2018

## **Declaration of Conflict of Interest:**

**I DO NOT** have any affiliation (financial or otherwise) with any for-profit or not-for-profit organizations.

I have received an honorarium for this presentation from Grand River Hospital Foundation.

**I DO NOT INTEND** to make therapeutic recommendations for medications that have not received regulatory approval

(e.g “off-label”use).

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This 2018 Day in Psychiatry educational event has received unrestricted educational grants from the following organizations:

Lundbeck

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The KW Pharmacy

HLS Therapeutics

# Conflicts of interest

Mitigating Potential Conflicts of Interest:

**Not applicable**

# Learning goals



- ▶ Review the prevalence of mental illness in the young female adult population
- ▶ Review current information on teratogenicity of common psychotropic medications including post partum exposure risk and risk of long term neurocognitive consequences
- ▶ Discuss current guidelines for the safe use of common psychotropic medications in pregnancy
- ▶ Highlight local and national resources about safe medication use in pregnancy

# Case

- ▶ 35 year old female, married, 2 stepchildren
- ▶ Referred by obstetrician/ gynecologist – history of depression and considering pregnancy
- ▶ History of depression since teenage years
- ▶ Multiple previous psychiatric admissions for depressive symptoms and SI
- ▶ Tried on numerous antidepressants and treatment with ECT
- ▶ Since April 2018, started on Fluoxetine with notable improvement, mood now stable
- ▶ Would like advice re: risk of depression during pregnancy and whether to continue medication

# How to treat?

- A. Advise re: risks and benefits and recommend to continue treating during pregnancy
- B. Advise re: risks and benefits and recommend discontinue medication prior to pregnancy with close follow up
- C. Advise re: risks and benefits and recommend to continue but to taper in third trimester
- D. Advise re: risks and benefits and discontinue in first trimester, restart in second trimester

# Depression/ Anxiety

- ▶ Women most likely to be diagnosed with depression or anxiety between ages 25-44
- ▶ 20% of women reproductive age affected by depression
- ▶ Depression 7-15% during pregnancy
- ▶ Anxiety 4-39%
- ▶ Relapse rate of up to 68% of women





# Things to consider

- ▶ The woman's previous response to treatments
- ▶ Stage of pregnancy
- ▶ Risk to mother/baby
- ▶ Current literature on different drugs and their reproductive safety

**Table 3.** Treatment of Mild to Moderate Major Depressive Disorder during Pregnancy.

Recommendation	Treatment	Level of Evidence
First line	CBT (individual or group)	Level 1
	IPT (individual or group)	Level 1
Second line	Citalopram, escitalopram, sertraline	Level 3
Third line	Structured exercise, acupuncture (depression specific), bright-light therapy	Level 2
	Bupropion, desvenlafaxine, duloxetine	Level 3
	fluoxetine, fluvoxamine, mirtazapine, TCAs (caution with clomipramine), venlafaxine	or Level 4
	ECT (for severe, psychotic, or treatment-resistant depression)	Level 3
	Therapist-assisted Internet CBT, mindfulness-based CBT, supportive psychotherapy, couples therapy, psychodynamic psychotherapy, rTMS	Level 4
	Combination SSRI + CBT or IPT	Level 4

**Table 4.** Treatment of Mild to Moderate Postpartum Depression during Breastfeeding.

Recommendation	Treatment	Level of Evidence
First line	CBT (individual or group)	Level 1
	IPT (individual or group)	Level 1
Second line	Citalopram, escitalopram, sertraline	Level 2
	Combination SSRI + CBT or IPT	Level 2
Third line	Structured exercise, acupuncture (depression specific), therapist-assisted Internet CBT, or behavioural activation	Level 2
	Fluoxetine, fluvoxamine, paroxetine TCAs (except doxepin)	Level 2
	Bupropion, desvenlafaxine, duloxetine, mirtazapine, venlafaxine, TMS, bright-light therapy	Level 3
	ECT (for severe, psychotic, or treatment-resistant depression)	Level 3
	Mindfulness-based CBT, supportive psychotherapy, couples therapy, psychodynamic psychotherapy	Level 4

**Table 2—FDA Pregnancy Risk Factors**

Category A	In controlled human studies, drug does not demonstrate risk to fetus in any trimester.
Category B	In animal studies, drug does not demonstrate risk to fetus, and there are no controlled human studies. <i>or</i> In animal studies, drug is associated with adverse effect, and in controlled human studies, drug does not demonstrate risk to fetus in any trimester.
Category C Drug should be used only if potential benefit outweighs potential risk to fetus.	In animal studies, drug is associated with adverse effect, and there are no controlled human studies. <i>or</i> There are no animal or human studies.
Category D Drug should only be used in a serious or life-threatening situation when alternatives are unavailable or ineffective.	Use of drug in pregnant women demonstrates risk to human fetus, but potential benefit to mother may outweigh risk to fetus.
Category X Drug is contraindicated in women who are pregnant or may become pregnant.	In animal studies, drug demonstrates fetal abnormalities, and potential risk to fetus outweighs benefit to mother. <i>or</i> In human studies or experience, drug demonstrates fetal abnormalities, and potential risk to fetus outweighs benefit to mother.

Adapted from reference 1.

# Question

▶ SSRI/ SNRI medication is in what FDA category

A. A

B. B

C. C

D. D

# Answer

- ▶ Category C with exception of Paroxetine

# Pregnancy and lactation labeling rule (PLLR)

- ▶ Four headings:
  - ▶ Pregnancy Exposure Registry
  - ▶ Risk Summary\*
  - ▶ Clinical Considerations
  - ▶ Data
- ▶ Started in June 30 2015
- ▶ Prescription drugs to remove pregnancy letter categories by June 2020, gradual process



# Question

- ▶ Which of the following are known risks with antidepressant medication during pregnancy?
  - A. Congenital anomalies
  - B. Persistent pulmonary hypertension of the newborn
  - C. Postnatal adaptation syndrome
  - D. Diabetes
  - E. Autism



# SSRI/SNRI - teratogenicity

- ▶ Teratogenic risk ~general population risk (2-4%)
- ▶ Exception – paroxetine (Increased risk of heart malformation)
- ▶ The US FDA issued a warning in 2005 that paroxetine exposure during the first trimester may increase the risk of cardiac malformations, changed to pregnancy category D
- ▶ Fetal echocardiography with first trimester paroxetine exposure has been suggested

# SSRI/SNRI – Persistent pulmonary hypertension of the newborn

- ▶ Failure of the normal circulatory transition that occurs after birth
- ▶ General population risk - 1–2 infants per 1000 live births with a 10–20% mortality risk that can vary with etiology
- ▶ The absolute risk is approximately 0.3% with SSRI use after week 20 of pregnancy

# SSRI/SNRI Neonatal adaption syndrome

- ▶ sleeping diff., feeding diff., temperature instability, tremors, convulsions, hypoglycemia, vomiting, excessive cries
- ▶ • Onset at birth to 4 days after (depending at 1/2-life of rx taken) and last up to 2 weeks (benign, no long-term consequences)
- ▶ • **30% of exposed BBs are affected, dose-dependant effect**
- ▶ • **What causes NAS?** Not fully understood but studies demonstrate that multiple factors including transient dysregulation of the serotonergic system and ↑ reactivity of the HPA axis (Kievet N. et al 2015, Kievet N. et al 2016)

# SSRI/SNRI Neonatal adaption syndrome

- ▶ **Newest data does not support to taper 14 days before** (Warburton et al, 2010, retrospective study with n= 119 547)
- ▶ Product label for the SSRIs has been changed and no longer recommends tapering the SSRI

# SSRI Other risks

- ▶ Higher numbers of spontaneous abortion (unclear if statistically significant)
  - ▶ Risk higher with Paroxetine and Venlafaxine
  - ▶ Most studies do not control for maternal depression
- ▶ Low birth weight
- ▶ Preterm birth
  - ▶ Eke et al 2016 meta-analysis (8 studies) – slight increase risk of preterm birth OR 1.24

# Autism?

- ▶ Gentile et al (2015, systematic review of 8 studies):
- ▶ 6 of 8 studies showed possible link,
- ▶ Studies contained multiples limitations and confounding factors not studied
- ▶ Conclusion: Not enough evidence to link antidepressants with autism; further research is needed

# Long term neurodevelopmental problems?

- ▶ Observational study at 6 years old: **NO signif. =/ on temperament, IQ, behaviors, cognitive functions** (Gentile S. et Galbally M. 2011)
- ▶ • Giovanni P. et al (2014, systematic review of 22 studies):
  - minor neurodevelopmental also observed in BBs non-exposed but whose mothers had untreated antenatal depression!!
  - Contradictory results between studies regarding motor development
  - Conclusion: need further studies, lots of confounding factors unstudied, overall cannot exclude that negative effects are due to depression itself...
- ▶ • Handal et al (2016, large population-based pregnancy cohort study, n= 51 404 pregnancies): prolonged exposure of SSRIs during pregnancy is associated with a delay in fine motor development at OR 1.42 VS no exposure, weakened association after adjusting for anxiety and depression
- ▶ = **Weak association, not to the extent of clinical importance...**

	Prenatal effects	Perinatal Outcome	Malformations – GI, neuro	Cardiac malformations	PNAS*	PPHN	Autism	ADHD	Neurological development/fine motor skills	SUMMARY
line	No increased risk for miscarriage	<i>Mixed evidence for Low birth weight, preterm birth and small for gestational age</i>	No	No	Yes	Yes	Mixed	Mixed	Mixed	Mixed evidence - insignificant association with negative outcomes. Also very low concentrations in breast milk
ram	No increased risk for miscarriage	<i>Mixed evidence for Low birth weight, preterm birth and small for gestational age</i>	No	No	Yes	Yes	Mixed	Mixed	Mixed	Mixed evidence - insignificant association with negative outcomes
ram**	No increased risk for miscarriage	<i>Mixed evidence for Low birth weight, preterm birth and small for gestational age</i>	No	No	Yes	Yes	Mixed	Mixed	Mixed	Mixed evidence – insignificant association with negative outcomes; also lack of studies
ctine	No increased risk for miscarriage	<i>Mixed evidence for Low birth weight, preterm birth and small for gestational age</i>	Neural tube defects - Anencephaly Gastrochisis Omphalocele	Septal defects RV outflow obstruction	Yes	Yes	Mixed	Mixed	Mixed	Repeated associations with significant malformations, particularly cardiac defects
amine	No increased risk for miscarriage	<i>Mixed evidence for Low birth weight, preterm birth and small for gestational age</i>	Limited evidence	Limited evidence	Yes	Yes	Mixed	Mixed	Mixed	Not enough data to inform decision-making
ctine	No increased risk for miscarriage	<i>Mixed evidence for Low birth weight, preterm birth and small for gestational age</i>	Craniosynostosis	RV outflow obstruction VSDs	Yes	Yes	Mixed	Mixed	Mixed	Repeated associations with significant malformations



# Others

- ▶ Bupropion -category C, no increased risk malformation, slight increase risk of spontaneous abortion
- ▶ Mirtazapine - category C
- ▶ Trazadone – category C
- ▶ Vortioxetine –category C

# Benzodiazepines

- ▶ Cleft palate
- ▶ Neonatal withdrawal
- ▶ Preterm birth
- ▶ Low birth weight

# Risks of untreated depression/ anxiety

- ▶ Insufficient maternal weight gain
- ▶ Decisions to terminate the pregnancy
- ▶ Increased risk of substance/alcohol use
- ▶ Preeclampsia
- ▶ Preterm birth
- ▶ Intra-uterine growth restriction
- ▶ low birth weight
- ▶ Increased rate of C-section
- ▶ NICU admission
- ▶ Anxiety and postpartum depression
- ▶ Suicide
- ▶ Infant cognitive and emotional complications postnatally

# Back to case

- ▶ Discussed risks and benefits
- ▶ Recommended to continue antidepressant
- ▶ Close follow up

# Case – Bipolar disorder

- ▶ 28 year old female with history of bipolar disorder
- ▶ Currently stable for past 2 years
- ▶ Previous history of manic episode requiring psychiatric admission
- ▶ Was on lithium 1200 mg po qhs, therapeutic level 0.78 on last blood work
- ▶ Unplanned pregnancy – 6 weeks pregnant



# Bipolar disorder

- ▶ % pregnancy
- ▶ Recurrence of mood episode in 80-85% of women who discontinued their mood stabilizer in first trimester, compared to 30% who did not (Viguera et al. 2007)
- ▶ Increased risk of postpartum psychosis (20-30%)

# Bipolar disorder

- ▶ Mood stabilizers
- ▶ Antipsychotic medication

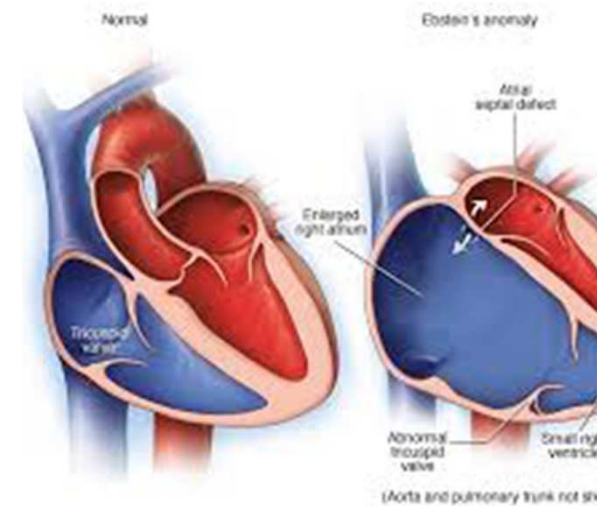
# Question

- ▶ Which mood stabilizer has highest risk of congenital malformation?
  - A. Lithium
  - B. Valproic acid
  - C. Lamotrigine
  - D. Carbamazepine



# Lithium

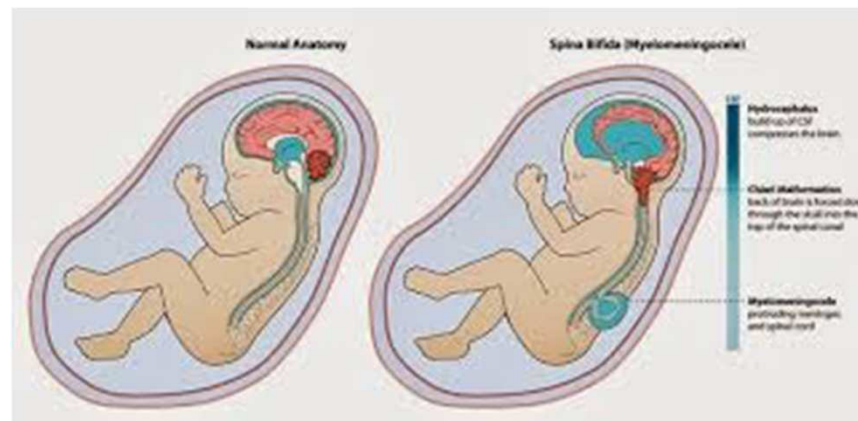
- ▶ Epstein anomaly 0.1% risk
- ▶ Neonatal complications have included 'floppy baby syndrome', nephrogenic diabetes insipidus, hypothyroidism, low muscle tone, lethargy, tachycardia, cyanosis and respiratory difficulties
- ▶ Lithium levels and renal function monitoring
- ▶ May need higher doses in 3<sup>rd</sup> trimester
- ▶ Reduce levels 24-48 hours prior to delivery
- ▶ Recommend 2<sup>nd</sup> trimester U/S, fetal echocardiogram



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# Valproic acid

- ▶ Increased risk of congenital malformation (~10%) neural tube defects, craniofacial anomalies, cardiac defects, hypospadias, oral cleft
- ▶ Newborns exposed to valproate may have lower Apgar scores, irritability, feeding difficulties and hypertonia
- ▶ leads to lower IQ and delayed neurocognitive development in children up to 6 years of age



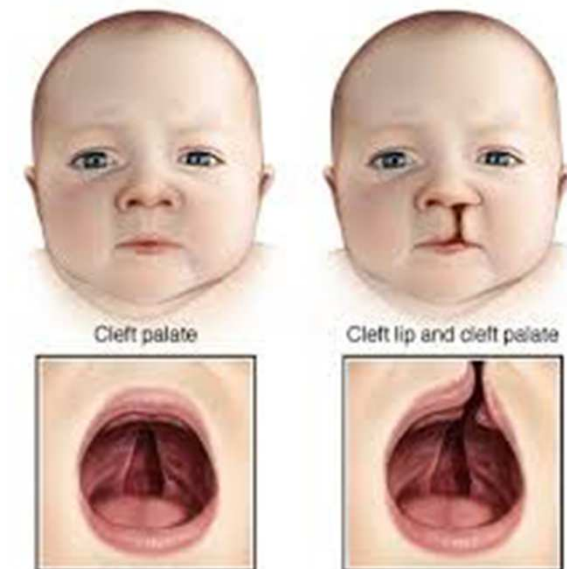
# Carbemazepine

- ▶ Increased risk of spina bifida (26 cases per 10,000 vs 10 cases per 10,000 with no exposure)
- ▶ neural tube defects, anomalous pulmonary venous return, facial dysmorphism, cleft palate, diaphragmatic hernia, skeletal abnormalities and hypospadias in some studies
- ▶ Some studies have shown developmental delays



# Lamotrigine

- ▶ Early reports had suggested an increased risk of oral clefts, but recent reports from multiple international registries fail to demonstrate an increased risk of congenital malformations with lamotrigine
- ▶ Lamotrigine doses may need to be adjusted closer to delivery or after delivery, owing to changes in its clearance



# Answer

- ▶ Valproic acid 10% risk of congenital anomalies

# 1<sup>st</sup> generation antipsychotics

- ▶ Major congenital malformations have generally not been reported to be increased with use of FGAs during pregnancy, or minimally increased associated with an increased risk of PTB
- ▶ risk of transient neonatal complications with FGA use including extrapyramidal symptoms, motor restlessness, tremor, hypertonicity, dystonia and withdrawal symptoms.
- ▶ minimal study of long-term effects of FGA exposure on child neurocognitive development

# 2<sup>nd</sup> generation antipsychotics

- ▶ Major congenital malformations have not generally been reported to be increased with SGA use during pregnancy, or minimally increased
- ▶ SGAs have been associated with an increased risk of gestational diabetes, obesity, metabolic syndrome and hypertension
  - ▶ Should supplement with Folic acid 5 mg
- ▶ abnormal muscle movements and withdrawal symptoms in newborns whose mothers were treated with antipsychotics during the third trimester of pregnancy

# Back to case

- ▶ Patient had already discontinued Lithium
- ▶ Developed depressive symptoms
- ▶ Started on Lamotrigine
- ▶ Symptoms improved
- ▶ Plan to discuss treatment after delivery



# Summary

The image shows a decorative header for a presentation slide. It features a dark blue background with a white wavy line at the bottom. On the right side, there are two light blue circles of different sizes and a solid blue square. The word "Summary" is written in white, sans-serif font on the left side of the header.

**RULE 6****Be supportive if the patient goes against your recommendations**

There are many reasons why a woman might choose to go against her psychiatric treatment provider's advice, particularly regarding drug use during pregnancy.

It is important that the treatment provider continues to support the patient despite such disagreements.

Again, a team approach will often help avoid disagreements, and providing as much information as possible on the risks of untreated psychiatric disorders during pregnancy can also be helpful.

**RULE 1****All changes to drugs should be carried out before pregnancy if possible**

This minimizes the number of exposures to the baby and promotes mood stability for the mother.

**RULE 2****Ideally the patient should be stable psychiatrically for at least 3 months before trying to get pregnant**

This is not always practical but should provide some evidence and reassurance that the patient's mood is stable before pregnancy begins.

**RULE 3****Use drugs that we know something about: fewer data are available for recently approved drugs**

If a drug has been available for several years there is at least some evidence that it is unlikely to be associated with major organ malformations, for example.

**RULE 4****Minimize the number of exposures for the baby**

Try to minimize the number of drugs used but consider exposure to psychiatric illness an exposure.

Changing drugs once a woman is pregnant increases the number of exposures.

One common scenario is for a woman on a newer psychotropic drug to become pregnant and be switched to an older drug that has more evidence for safety. This plan increases the exposures for the baby—first to the newer drug and secondly to the older drug.

In addition, it is highly likely that the mother would relapse after switching, and exposure to the psychiatric disorder would constitute a third exposure for the child.

**RULE 5****Use a team approach**

This includes family and other doctors involved in the patient's care.

To provide good care for mother and child it is essential to educate the family about the risks and benefits of treatment and no treatment, as well as signs and symptoms of relapse.

Similarly, communicating directly with the obstetrician and the pediatrician will minimize miscommunication and differences of opinion, and maximize the patient's treatment outcomes.



# Local resources

- ▶ **Motherisk Helpline**  
1-877-439-2744 (Toll-free)  
416-813-6780 (Toronto and GTA)
- ▶ <https://womensmentalhealth.org>
- ▶ [Reprotox.org](https://reprotox.org)

Thank you!

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# References

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- ▶ <http://www.motherisk.org>