November 11, 2023

Current Bipolar Disorders Treatment Recommendations in Patients who are Pregnant

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Relevant Financial Relationship Disclosures

Stephanie Nichols has no relevant financial relationships with ineligible companies to disclose.

Learning Objectives

1. Analyze the efficacy, risks, and benefits of withholding or utilizing psychiatric medications for bipolar disorder during the prenatal and peripartum periods.
2. Evaluate current guideline recommendations and recent literature describing the use of psychiatric medications in pregnant patients living with a bipolar disorder.

r/bipolar

Were you on meds during your pregnancies? I'm terrified of getting pregnant and having to either stop getting my meds or switch kinds

There are plenty of meds available during pregnancy. **You do not have to cold turkey your meds**.

I have a 2 year old right now and it's the best thing that ever happened to me. **I stayed on my meds through pregnancy**…and I live a totally stable and happy life. I used to be suicidal and he gave me something to live for.

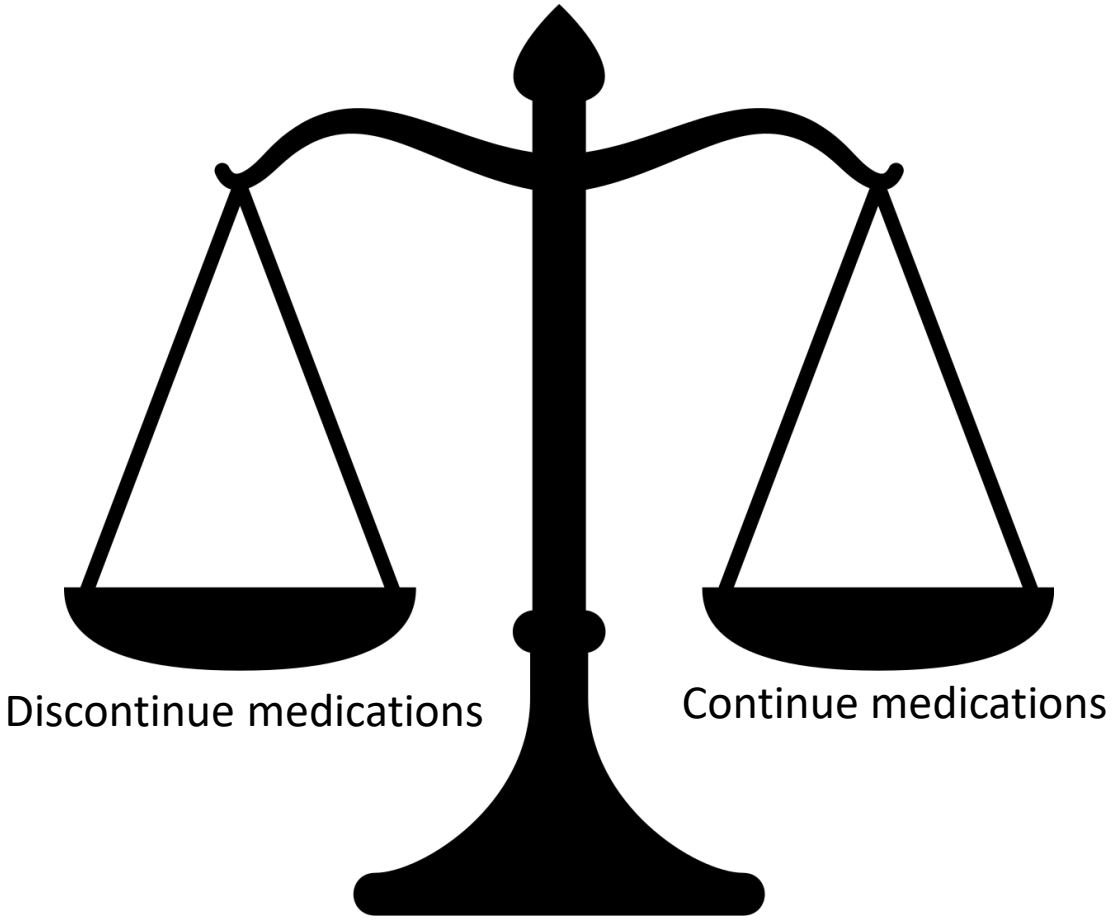
My doctor **put me on lamictal** bc it's neutral for pregnancy. Not pregnant *yet* but hopeful.

Yes, it's possible! :-) planning ahead definitely helps. I worked with a psychiatrist... I **switched all my meds to pregnancy and breastfeeding safe meds 3-4 months before I actively started trying**. I had no hypomanic or depressive episodes during my pregnancy and… postpartum.

My wife absolutely did not want to carry, so after **consulting with my psychiatrist**, **we agreed that it was best for me to continue…on a safe dosage of meds that would not harm the fetus**. I was actually the most stable I had been in years most likely due to the hormones, medications, and self care I was so adamant on providing myself during that time!

Balancing risk versus benefit of treating bipolar disorder throughout pregnancy

- Concerns about ongoing medication use and fetal safety
- Misconceptions that pregnancy is emotionally protective

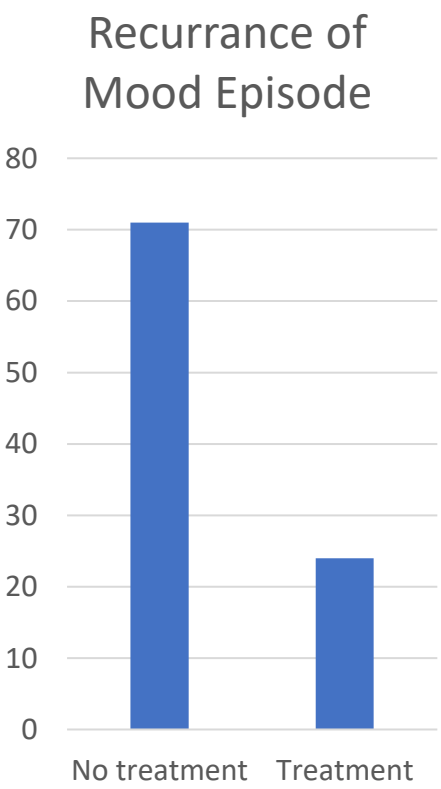


- Concerns about untreated bipolar disorder and maternal safety
- Consideration of holistic risk versus benefit to the dyad

Untreated bipolar disorder in people who are pregnant

- Up to 85% have a mood episode with discontinuation of mood stabilizer (vs 37% with continuation)
- First delivery is twice as likely to be associated with mood episode than subsequent ones (OR 2.0, 95% CI 1.64–2.56)
- People who had a birth-related mood episode were twice as likely to not have more children vs those who did not
- **Treatment reduces episode recurrence rate by 66%**

	Bipolar 1 (% developed episode)	Bipolar 2 (% developed episode)
First pregnancy	35	46
Second pregnancy	21	33
Subsequent pregnancies	15	-



Rusner M, Berg M, Begley C.. BMC Pregnancy Childbirth. 2016;16(1):331. Published 2016 Oct 28. doi:10.1186/s12884-016-1127-1;
Singh S, Deep R. Indian J Pharmacol. 2022;54(6):443-451. doi:10.4103/ijp.ijp_407_21

Impact of Perinatal Depression on the Dyad

Increased risk of pre-eclampsia and surgical delivery

Higher substance use during pregnancy

Increased risk of preterm birth (OR 1.39), low birth weight (OR 1.49), and intrauterine growth restriction (OR 1.45)

Maternal Impact

Fetal/Infant/Child Impact

Maternal suicide deaths outnumber mortality from hemorrhage and hypertensive disorders

Reduced prenatal care and inadequate maternal weight gain

Developmental delay at 18 months (OR 1.34)

Grote NK, et al. Arch Gen Psychiatry. 2010;67(10):1012–1024.;
Yonkers KA, et al. Obstet Gynecol. 2009;114(3):703-713.;
American College of Obstetricians and Gynecologists. Obstet Gynecol. 2018;132:e208-12.;
Byatt N, et al. Acta Psychiatr Scand. 2013:127:94–114.

Epidemiology of Postpartum Psychosis (PP)

- Overall estimated up to 0.1-0.2% incidence (0.25 to 0.6 per 1,000 births)
  - Risk increases to 1 in 7 with PP history
  - >50% in those with bipolar disorder or schizophrenia and history of PP
- Risk ↑ 2.5-fold in patients with bipolar disorder and a 1st degree relative with PP vs those with bipolar disorder and no relative with PP history (74% vs 30%)
- **Risk is almost 3-fold higher with perinatal discontinuation of mood stabilizer**

	Postpartum Psychosis
Incidence, no history of psychiatric hospitalization, 1st birth	0.04%
Incidence, any history of psychiatric hospitalization, 1st birth	9.24%
Cumulative Incidence, adjusted for age at 1st birth	0.07%

Harlow BL, et al. Arch Gen Psychiatry. 2007;64(1):42-8.
Sit D, et al. J Womens Health (Larchmt). 2006;15(4):352–368.
Bergink V, et al. Am J Psychiatry. 2016;173(12):1179-1188.
Jones I, et al. Am J Psychiatry. 2001;158(6):913

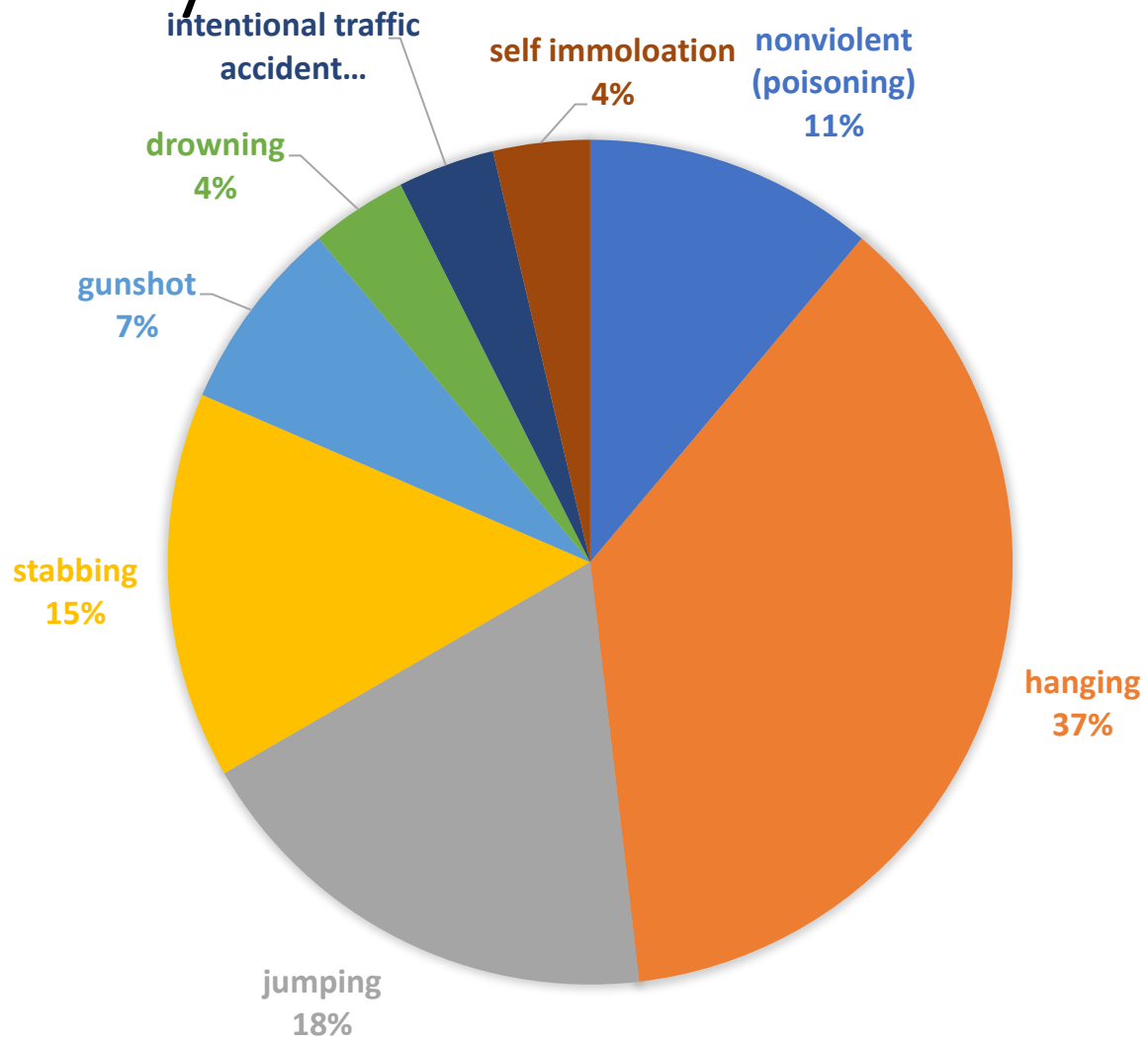
Clinical Features of Postpartum Psychosis

- Women experience 22 times more psychotic or manic episodes during the postpartum period than in any other period of their lives
- The mean age of onset is 26.3 years
- Usual onset between 2-14 days post delivery, 90% occur in first 4 weeks
- Initial signs and symptoms include: restlessness, irritability, insomnia
- Paranoid, grandiose, or bizarre delusions, rapidly shifting mood, confused thinking, and grossly disorganized and withdrawn behavior are common
  - Delusions often revolve around the infant → including altered infant identity or a sense of persecution from the baby
  - Auditory hallucinations instructing self-harm or infant harm may occur

Sit D, et al. J Womens Health (Larchmt). 2006;15(4):352–368.
Isik M. Eastern J Med. 2018;23(1):60-63.
Meltzer-Brody S et al, Psychol Med. 2017 Jun;47(8):1427-1441

Suicide in the Year after Delivery

- Psychosis combined with lack of insight and judgment can lead to death by suicide
- Mental illness has contributed to 12% of maternal deaths (83% suicide)
- Suicide ↑ 70-fold in the year after childbirth & is the leading cause of maternal death
- Nonviolent suicide occurs in 48% of women but accounts for only 11% of suicide deaths in those up to 1yr postpartum



METHOD OF MATERNAL SUICIDE DEATH (FIRST YEAR POSTPARTUM)

Brockington I. Arch Womens Ment Health. 2017;20(1):63–69.; Kumar R, et al. J Affect Disord. 1995;33(1):11-22.; Tsirigotis K, et al. Med Sci Monit. 2011;17(8):PH65–PH70.; Sit D, et al. J Womens Health (Larchmt). 2006;15(4):352–368.; CEMD. Confidential enquiries into maternal deaths: Why mothers die, 1997–99. London: Royal College of Obstetricians and Gynaecologists; 2001.

Infanticide and Neonaticide

- 28-35% of patients with postpartum psychosis have delusions about their infant, but only 9% have thoughts of causing harm
- 4.5% rate of infanticide with postpartum depressive psychosis vs <1% in psychosis without overt depression
- Neonaticide
  - occurs within 24 hours of birth
  - associated with maternal denial of pregnancy
  - characterized by dissociative hallucinations, brief amnesia, and depersonalization

In 1756 an unmarried woman called for help with her delivery but a week later became strange in speech and behavior and strangled the child. She kept it beside her on the bed, and, when visitors came, said 'the Devil had tempted her'.

Brockington I. Arch Womens Ment Health. 2017;20(1):63–69.
Sit D, et al. J Womens Health (Larchmt). 2006;15(4):352–368.
Kumar R, et al. J Affect Disord. 1995;33(1):11-22.

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Screening for Postpartum Psychosis

- Especially prudent in high risk patients
- Educate patient and family to contact provider urgently if mood swings, confusion, strange beliefs, and hallucinations occur in the first 2–4 weeks post childbirth

Mood Disorder Questionnaire

- Past and current symptoms of high, hyper/irritable mood, excess energy, racing thoughts, pressured speech
- Not specific to the perinatal period

13 item questionnaire

"Has there ever been a period of time when you were not your usual self and…"

- …you felt so good or so hyper that you got into trouble?
- …you were so irritable that you shouted at people or started arguments?
- …you got much less sleep than usual and didn't miss it?
- …thoughts raced through your head?
- …you had more energy than usual?

Available here: https://www.integration.samhsa.gov/images/res/MDQ.pdf

Cox JL, et al. Br J Psychiatry. 1987;150:782-786
https://www.integration.samhsa.gov/images/res/MDQ.pdf

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Linking Postpartum Psychosis and Bipolar Disorder

- Symptom presentation overlaps but varies
  - Thought broadcasting, thought control, “experiences of influence”, auditory hallucinations, and primary delusions more common with postpartum onset (62% vs 28%, $p<0.05$)
  - More “perplexity”, delusions of control, blunted affect, and emotional turmoil, but less grandiosity and decreased need for sleep with postpartum onset
- 86% (n=110) with postpartum psychosis subsequently met criteria for bipolar disorder
- Bipolar disorder plus a family history of postpartum psychosis is associated with 2-fold more postpartum episodes vs no family history
- Postpartum psychosis in 260 per 1000 deliveries in patients with bipolar disorder versus 1-2 per 1000 in general population

Chaudron LH, et al. J Clin Psychiatry. 2003;64:1284-92.

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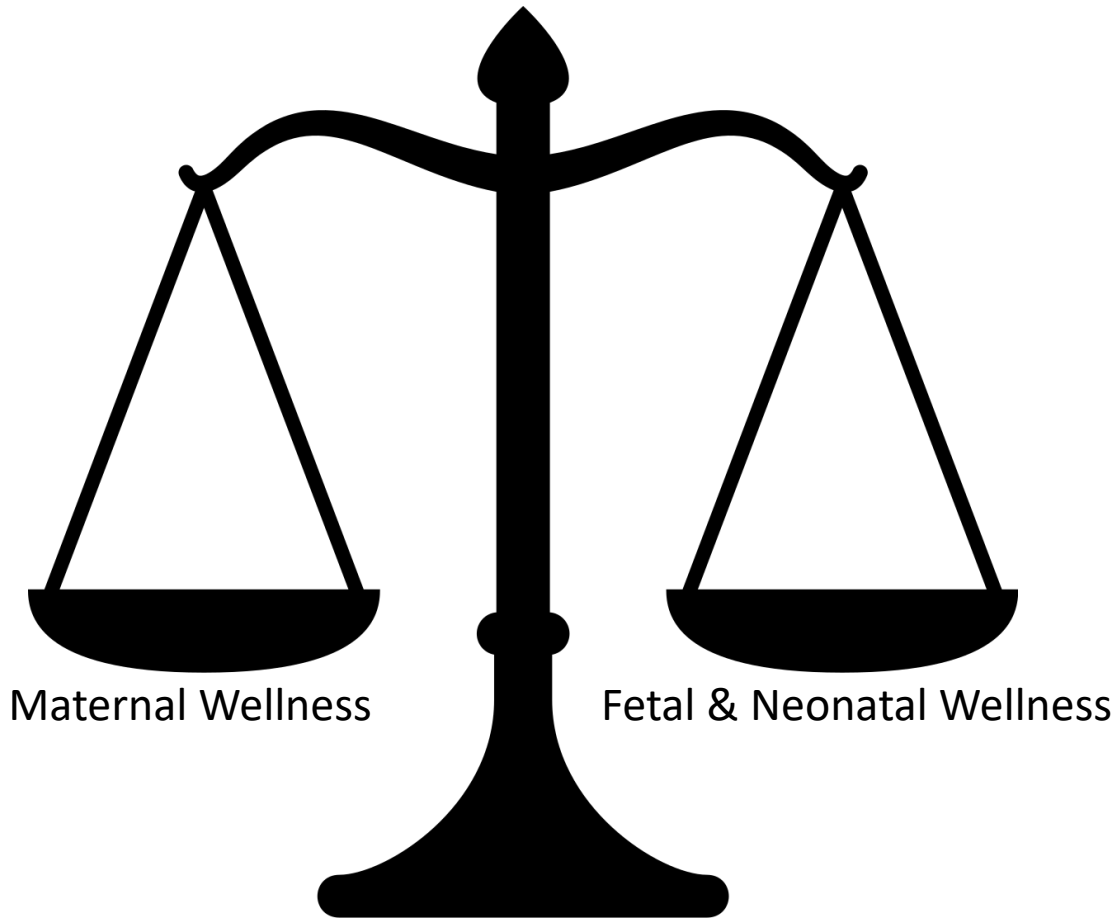
Balancing maternal and fetal wellness needs

Risk of postpartum depression

Risk of death by suicide

Risk of acute mania



Risk of postpartum psychosis

Risk of infanticide

Benefits of treating bipolar disorder during pregnancy

- Reduces the rate of childbirth-related mood episode including postpartum depression and postpartum psychosis
- For nearly half who discontinue mood stabilizer, recurrence of mood episode occurs in the first trimester
- Median onset of recurrence was 2 weeks for abrupt discontinuation vs 22 weeks for gradual taper

Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disord*. 2018;20(2):97-170. doi:10.1111/bdi.12609

Shared Decision Making: CANMAT 2018 Bipolar Disorder Guidelines Pregnancy Recommendations

- Use collaborative decision-making with the idea that medications can be continued, discontinued, or switched, and doses can be changed
- For medication-free pregnancy, in a patient clinically stable for 4-6+ months and low relapse risk, *it might be appropriate* to gradually taper off 1+ psychotropics prior to conception
- **Carefully analyze individualized risks-benefits prior to deciding to discontinue medication pre-conceptually**

Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disord*. 2018;20(2):97-170. doi:10.1111/bdi.12609

ACOG 2023 Guidelines

- 3-fold increased risk of bipolar destabilization with discontinuation of pharmacotherapy in pregnancy or postpartum

- Continuation of pharmacotherapy for pregnant individuals with bipolar disorder is **highly recommended**

Treatment and Management of Mental Health Conditions During Pregnancy and Postpartum: ACOG Clinical Practice Guideline No. 5. *Obstet Gynecol*. 2023;141(6):1262-1288. doi:10.1097/AOG.0000000000005202

ACOG 2023 Guidelines: Bipolar Disorder and Pregnant People

- Recommend against discontinuing mood stabilizers during pregnancy
  - For those on medications at time of pregnancy and stable, preferable to continue rather than switch
  - Switching requires cross-taper, exposing the fetus to additional medications and increasing the risk of destabilization
  - Divalproex is an exception and should be switched
- Recommend against valproate as first-line treatment for bipolar disorder
- Recommend that individuals using antipsychotics undergo screening for gestational diabetes
- Recommend that patients taking lithium receive an ultrasound exam in 2nd trimester; lithium levels must be monitored during pregnancy and postpartum

Treatment and Management of Mental Health Conditions During Pregnancy and Postpartum: ACOG Clinical Practice Guideline No. 5. *Obstet Gynecol*. 2023;141(6):1262-1288. doi:10.1097/AOG.0000000000005202

Shared Decision Making: CANMAT 2018 Bipolar Disorder Guidelines Pregnancy Recommendations

- Discuss and carefully consider potential teratogenic effects of different psychotropics and limitations of evidence
- With pharmacotherapy, use monotherapy at minimum effective dose
- Avoid divalproex due to elevated risk of neural tube defects and striking neurodevelopmental delay in children 3+ years, including loss of 9 IQ points

Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disord*. 2018;20(2):97-170. doi:10.1111/bdi.12609

CANMAT 2018 Guidelines for Acute Bipolar Depression: First Line for General Adult Patients

Order of Preference

	Treat acute depression	Prevent any mood episode	Prevent depression	Prevent mania	Treat acute mania	Acute safety / tolerability concerns	Chronic safety / tolerability concerns
	Level of Evidence: 1= highest; n.d. = no data Evidence is positive unless indicated "negative"					Impact on treatment selection: - = limited, + = minor, ++ = moderate, +++ = significant	
Quetiapine	1	1	1	1	1	+ / ++	++ / ++
Lurasidone + Li or DVP	1	3	3	4	n.d.	+ / ++	++ / ++ or +
Lithium	2	1	1	1	1	+ / +	++ / ++
Lamotrigine	2	1	1	2	1-negative	++ / -	- / -
Lurasidone	2	4	4	4	n.d.	- / +	- / +
Lamotrigine (adjunctive)	2	4	4	4	4-negative	++ / +	++ / ++

Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disord*. 2018;20(2):97-170. doi:10.1111/bdi.12609
Yatham LN, et al. Bipolar Disord. 2018;20(2):97-170.

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CANMAT 2018 Guidelines for Acute Mania: First Line Monotherapies for General Adult Patients

Order of preference

	Treat acute mania	Prevent any mood episode	Prevent mania	Prevent depression	Treat acute depression	Acute safety / tolerability concerns	Chronic safety / tolerability concerns
	Level of Evidence: 1= highest; n.d. = no data Evidence is positive unless indicated "negative"					Impact on treatment selection: - = limited, + = minor, ++ = moderate, +++ = significant	
Lithium	1	1	1	1	2	+ / ++	++ / ++
Quetiapine	1	1	1	1	1	+ / ++	++ / ++
Divalproex	1	1	3	2	2	- / +	++ / +
Asenapine	1	3	3	3	n.d.	- / +	- / +
Aripiprazole	1	2	2	n.d.	1-negative	- / +	- / +
Paliperidone	1	2	2	n.d.	n.d.	- / +	+ / ++
Risperidone	1	4	4	n.d.	n.d.	- / +	+ / ++
Cariprazine	1	n.d.	n.d.	n.d.	1	- / +	- / -

Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disord*. 2018;20(2):97-170. doi:10.1111/bdi.12609 Yatham LN, et al. Bipolar Disord. 2018;20(2):97-170.

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CANMAT 2018 Guidelines for Maintenance Therapy in Bipolar Disorder: First Line for General Adult Patients

Order of preference

	Prevent any mood episode	Prevent depression	Prevent mania	Treat acute depression	Treat acute mania	Acute safety / tolerability concerns	Chronic safety / tolerability concerns
	Level of Evidence: 1= highest; n.d. = no data Evidence is positive unless indicated "negative"					Impact on treatment selection: - = limited, + = minor, ++ = moderate, +++ = significant	
Lithium	1	1	1	2	1	+ / +	++ / ++
Quetiapine	1	1	1	1	1	+ / ++	++ / ++
Divalproex	1	2	3	2	1	- / +	++ / +
Lamotrigine	1	1	2	1	1-negative	++ / -	- / -
Asenapine	2	2	2	n.d.	1	- / +	- / +
Quetiapine + Li or DVP	2	1	1	2	1	+ / ++	+++ / ++
Aripiprazole + Li or DVP	2	n.d.	2	4	2	+ / +	++ / ++
Aripiprazole	2	n.d.	2	1-negative	1	- / +	- / +

atham LN, et al. Bipolar Disord. 2018;20(2):97-170.

Applying the CANMAT 2018 Guideline Recommendations to Pregnant Patients

	Prevent any mood episode (depression; mania)	Treat acute depression	Treat acute mania	Acute safety / tolerability concerns	Chronic safety / tolerability concerns
Level of Evidence: 1= highest; Evidence positive unless indicated "negative" * = 1st line therapy				Impact on treatment selection: - = limited, + = minor, ++ = moderate, +++ = significant	
Lithium	1 (1; 1) - 1st line	2 - 1st line	1 - 1st line	+ / +	++ / ++
Quetiapine	1 (1; 1) - 1st line	1 - 1st line	1 - 1st line	+ / ++	++ / ++
Lamotrigine	1 (1; 2) - 1st line	1 - 1st line	1-negative	++ / -	- / -
Asenapine	2 (2; 2) - 1st line		1 - 1st line	- / +	- / +
Aripiprazole	2 (n.d.; 2) -1st line	1-negative	1 - 1st line	- / +	- / +
Lurasidone	4 (4; 4) - 2nd line (with Li)	2 - 1st line		- / +	- / +
Paliperidone	2 (n.d.; 2) - 2nd line		1 - 1st line	- / +	+ / ++
Risperidone	4 (n.d.; 4) - 2nd line		1 - 1st line	- / +	+ / ++
Cariprazine		1 - 2nd line	1 - 1st line	- / +	- / -

Society for Bipolar Disorders (ISBD) 2018 guidelines for the r anagement of patients with bipolar disorder. *Bipolar Disord*. 2018;20(2):97-170. doi:10.1111/bdi.12609
Yatham LN, et al. Bipolar Disord. 2018;20(2):97-170.

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CANMAT 2018 Bipolar Disorder Guidelines: Pregnancy Considerations

- Prenatal vitamins are recommended before conception and continuously through pregnancy; should include 5 mg/day folic acid
- Each pregnancy should be closely monitored and appropriate screening tests (e.g., fetal ultrasound if lithium in first trimester) should be performed
- Because of physiologic and pharmacokinetic changes in second and third trimesters patients may require higher medication doses
  - increased plasma volume
  - Increased hepatic activity
  - Increased renal clearance

Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disord*. 2018;20(2):97-170. doi:10.1111/bdi.12609

Individual Medication Options

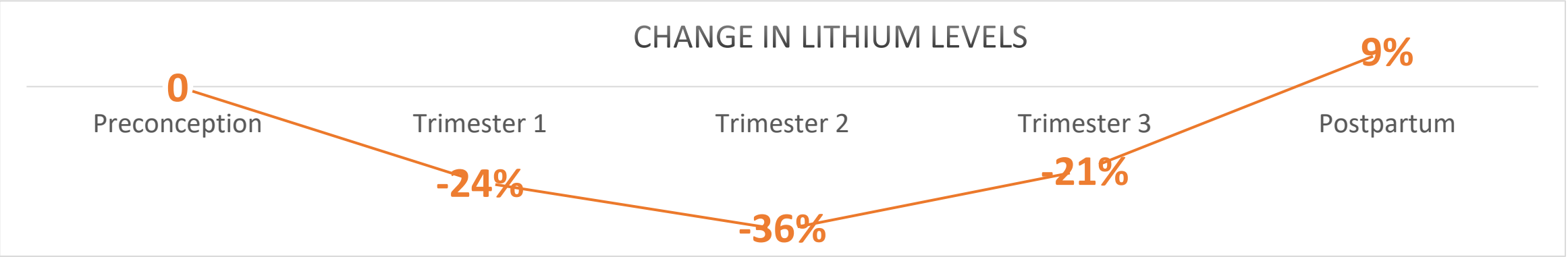
Lamotrigine

- Evidence suggests a lack of neurodevelopmental delays or chronic abnormalities
- Generally considered safe in pregnancy and a good option in patients with a history of recurrent depressive episodes, but a poor antimanic agent
- ACOG: lamotrigine is a preferred option for the treatment of bipolar II disorder for reproductive-aged females due to the low risk of teratogenicity
- Requires overlap with another agent for weeks to titrate up so it must be started ahead of time to avoid unnecessary exposure to two medications in utero
- Large pharmacokinetic changes in pregnancy
  - Requires up to 50% dose increase
  - Must reduce the dose quickly in the postpartum period as PK returns to baseline within days – failure to do so causes increased risk of SJS

Lithium and Ebstein's anomaly

- Once considered contraindicated, especially in the first trimester, but based on older reports with high rates of congenital anomalies (i.e., 400-fold increased risk) were susceptible to recall bias and other limitations
- Newer reports show much lower rates of abnormalities with lithium exposure
  - OR = 1.81 (95% CI 1.35–2.41) for congenital anomalies overall
  - OR = 1.86 (95% CI 1.16–2.96) for cardiac anomalies
- ACOG: new data shifts the risk/benefit ratio and renders lithium a reasonable treatment option, particularly for individuals with BP1 or a past lithium response
- ACOG: a detailed ultrasound examination to evaluate the fetal anatomy with a particular focus on cardiac anatomy is recommended, despite low absolute risk

Lithium dosing and monitoring during pregnancy and postpartum periods



- ACOG: MUST be managed during pregnancy and postpartum periods; should be a psychiatrist
- Monthly (or twice monthly) levels until week 34; Weekly levels until delivery; Twice weekly levels for 2 weeks postpartum
- Avoid underdosing: generally requires dose increase of 30 – 50% and twice daily administration by the 2nd trimester, then dose is reduced to preconception dose in the 2 weeks following delivery
- Risk of overdosing: Higher maternal lithium levels are associated with neonatal hypotonia, lethargy, and respiratory difficulties
- Some experts recommend holding lithium at labor onset or 24–48 hours before scheduled induction or delivery, then reinitiating postpartum at the pre-pregnancy dose

Deligiannidis KM, et al. J Clin Psychopharmacol. 2014;34(2):244–255.
Wesseloo R, et al. Br J Psychiatry. 2017 Jul; 211(1): 31–36.
Westin AA, et al. BMJ Open. 2017; 7(3): e015738.

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Antipsychotics

- Antipsychotics have a quicker onset of action, which is important with mania and/or postpartum psychosis
- Quetiapine: lowest placental passage, often a preferred first-line antipsychotic for bipolar disorder, but associated with metabolic risks and significant sedation
- Lurasidone (depression only): lower propensity for metabolic complications but limited data on safety and appropriate dosing during pregnancy; FDA category B
- Asenapine (acute mania or maintenance): must be taken sublingually
- Aripiprazole (acute mania or maintenance, not acute depression): reduced metabolic effects as well as lower risk of QTc prolongation and seizures; has a monthly injection
- ACOG: evidence of association between antipsychotics and gestational diabetes is conflicting, and should not inform clinical decision making regarding discontinuation of antipsychotic

Carbamazepine and oxcarbazepine

- Risk of teratogenicity with first trimester exposure
- ACOG: Before pregnancy, usually transition away from carbamazepine and oxcarbazepine, or if continuation, increase folate to 4mg/day
- ACOG: If already pregnant, decision to switch medications should balance location of teratogenic window and risk of destabilization

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Divalproex, sodium valproate, valproic acid

- Avoid in nearly all situations
- Situation where a switch is appropriate even during pregnancy
- Associated with neural tube defects and reduced IQ
- We also try to avoid use of this medication in people who have the potential to become pregnant (i.e., have a uterus) due to unique bipolar disorder risks such as mania-related hypersexuality

Key take aways

- Avoid divalproex in pregnant people and those who could become pregnant; switch if a patient on divalproex becomes pregnant
- Don’t discontinue or switch non divalproex mood stabilizers for pregnancy unless a patient is taking multiple mood stabilizes – then consider tapering off one
- Lamotrigine is an effective and safe option in pregnancy but not effective in acute mania
- Antipsychotics, especially quetiapine, are options in bipolar disorder but many are associated with metabolic syndrome and sedation
- Lithium is an effective option in people who are pregnant and highly effective in bipolar disorder but there is an increased risk of fetal anomalies so second trimester fetal ultrasound and close maternal level monitoring by a psychiatrist is recommended
- **Overall, we can safely use medications to treat our patients who are pregnant and have bipolar disorder**

Final consideration

- Since the co-morbidity rate of bipolar disorder and SUDs is very high, **please screen for and treat substance use disorders in all patients,** including those who are pregnant and have bipolar disorder!

- e.g., naltrexone with alcohol use disorder
- e.g., buprenorphine with opioid use disorder

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