



Project TEACH

FAMILIES THRIVE WITH GOOD MENTAL HEALTH

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Child/Adolescent & Perinatal Psychiatry Access Program**

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**Office of
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**Treating Bipolar Disorder in Perinatal Patients:
Psychopharmacological Approaches for Prescribers**



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Disclosures

No relevant disclosures

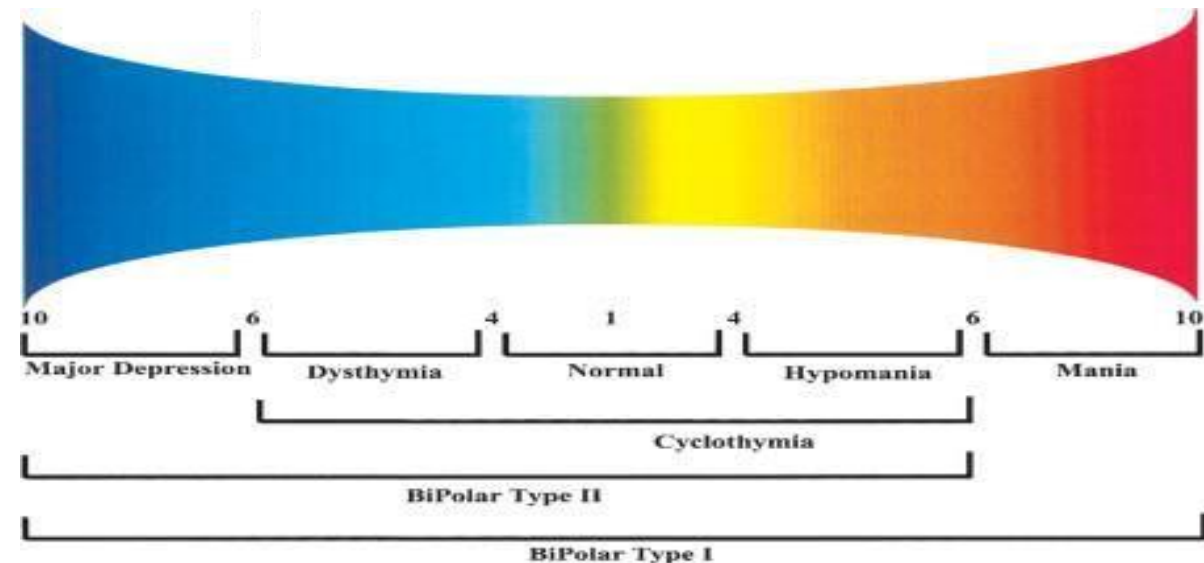
Learning objectives

- Recognize the clinical features and screening approaches for bipolar disorder in reproductive-age women.
- Evaluate medication interactions and teratogenic risks associated with mood stabilizers (lithium, lamotrigine, valproate, antipsychotics) in the preconception and perinatal periods.
- Apply evidence-based management strategies for pregnant and postpartum patients with bipolar disorder, including mood stabilizer dose adjustments across trimesters, sleep regulation, breastfeeding counseling, postpartum relapse prevention, and timely psychiatric consultation to optimize maternal and neonatal outcomes.

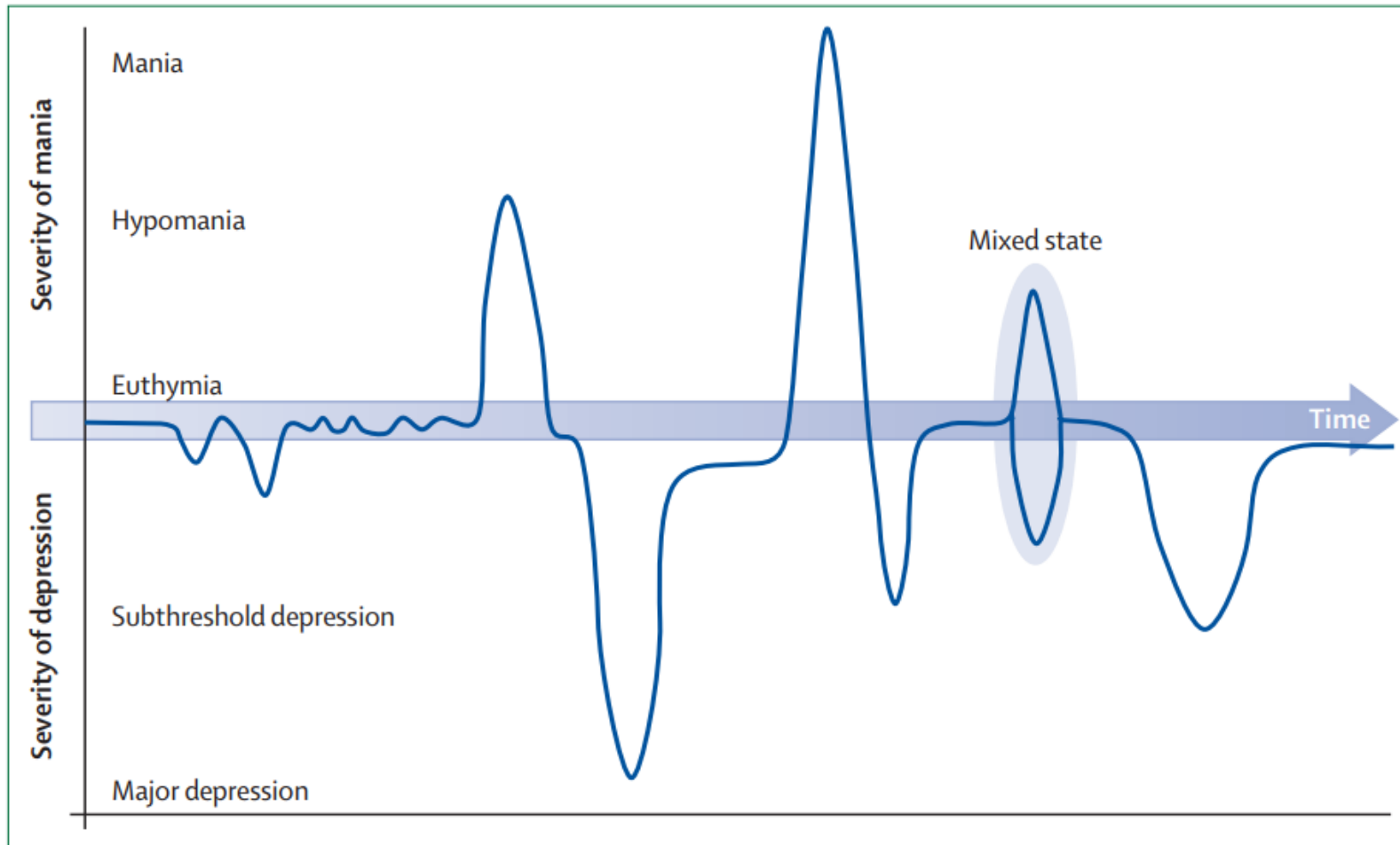
Bipolar Disorder

- Bipolar disorder is a lifelong, complex illness with a spectrum of subtypes that vary in severity and presentation.
- BD requires active management in different stages of the disease.
- BD imposes significant morbidity on the lives of those affected.
- Medication management in women of reproductive age is challenging, given that previously stable regimens may need to be adjusted for pregnancy, and the postpartum period is an extremely high-risk period for relapse.

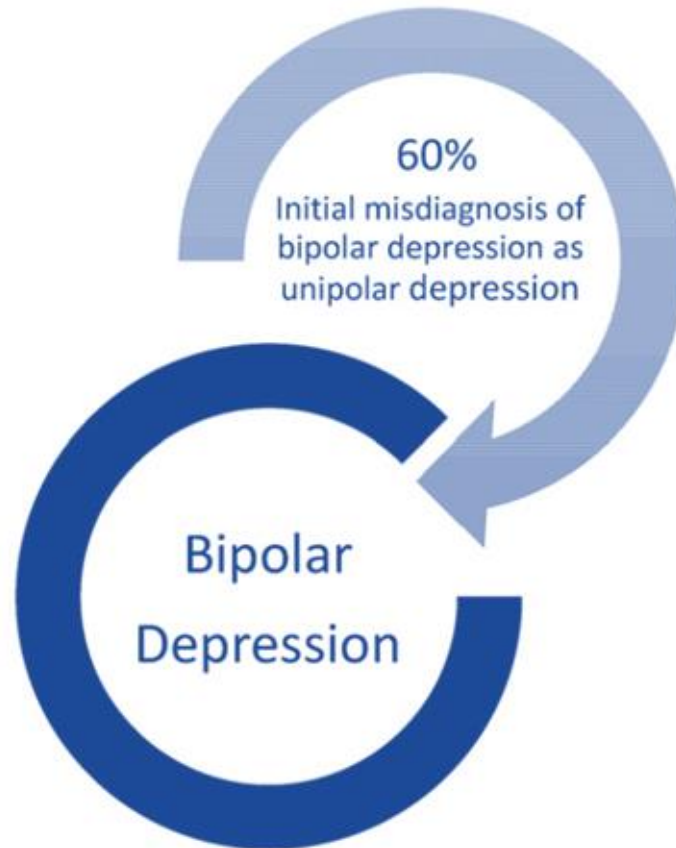
<https://www.bipolarpsychologist.com.au/understanding-bipolar/>



Life chart showing the progression of bipolar disorder



Importance of differentiating between unipolar and bipolar depression




Reasons for misdiagnosis:

- Incomplete understanding of bipolar disorder by healthcare professionals
- Overlooked or no history of mania
- Failure to differentiate symptoms that can help identify unipolar and bipolar depression

Consequences of misdiagnosis:

- Inappropriate use of antidepressant agents
- Increased acute risk of switch from depression to mania/hypomania with antidepressant use
- Delay of proper treatment

Bipolar Disorder vs MDD

Bipolar Disorder		MDD 
Earlier (< 25 y)	Age at onset	Later
More frequent	Family history of psychiatric disorders	Less frequent
Yes	Hypomania	No
More likely	Atypical depressive features	Less likely
Higher	Episode recurrence	Lower
More likely	Antidepressant treatment failure	Less likely

Bipolar Disorder in Perinatal Period

- Medication management of bipolar disorder in women of reproductive age is challenging.
- Previously stable regimens may need to be adjusted for pregnancy, and the postpartum period is an extremely high-risk period for relapse.
- Pharmacologic management is central to the care of patients with bipolar disorder, and medication decisions during pregnancy and the postpartum period require careful, individualized consideration.
- During pregnancy, the primary goal is maintaining maternal mood stability — reducing the substantial risks of untreated illness — while carefully minimizing medication-related harms, including teratogenicity, neurodevelopmental effects, and perinatal complications.

Bipolar Disorder and Risks in Perinatal Period

- Multifactorial risks for increased bipolar – spectrum mood episode occurrence:
 - Overlap between peak reproductive years and onset of bipolar disorder
 - Hormonal and physiological changes accompanying pregnancy
 - Stress related to childbirth and parenting
- Bipolar disorder is a risk factor for:
 - Perinatal suicide
 - Postpartum Psychosis
 - Infanticide

Risk of untreated bipolar disorder in perinatal period

- Higher risk of adverse pregnancy outcomes including:
 - Gestational hypertension,
 - Hemorrhage,
 - Cesarean delivery and
 - Small for gestational age infants
- Higher risk of recurrence of mood episodes
- Risk of severe psychiatric outcomes
- Risk for child protection concerns and parent –child relationship disruption due to psychiatric illness

Prevalence of Bipolar Disorder in Perinatal Women

- In women with no known psychiatric illness preceding the perinatal period, pooled prevalence of BD was 2.6% (95% CI, 1.2% - 4.5%) and prevalence of bipolar-spectrum mood episodes (including depressed, hypomanic/manic, mixed) during pregnancy and the postpartum period was 20.1% (95% CI, 16.0 – 24.5 %)
- In women with a prior BD diagnosis, 54.9% (95% CI, 39.2% - 70.2%) were found to have at least one bipolar-spectrum mood episode occurrence in the perinatal period.
- Perinatal period is associated with high rates of bipolar-spectrum mood episodes; pregnant and postpartum women represent a special risk population.

Clinical Pearls

- Perinatal mental health conditions, including bipolar disorder, are now among the leading obstetric complications in the US and represent a preventable cause of maternal mortality.
- In perinatal women — particularly those presenting with depressive symptoms — screening for bipolar disorder is warranted, given that rates of BD-spectrum mood episodes in this population may be higher than previously estimated and higher than in the general population.
- Bipolar disorder screening is essential before antidepressant pharmacotherapy is initiated, given the risk of mood destabilization in unrecognized cases.

Instrument 2: Steps Towards Diagnosis & Treatment Planning (continued) —

FIG 1: DECISION-MAKING ALGORITHM



Bipolar Disorder in Perinatal Period



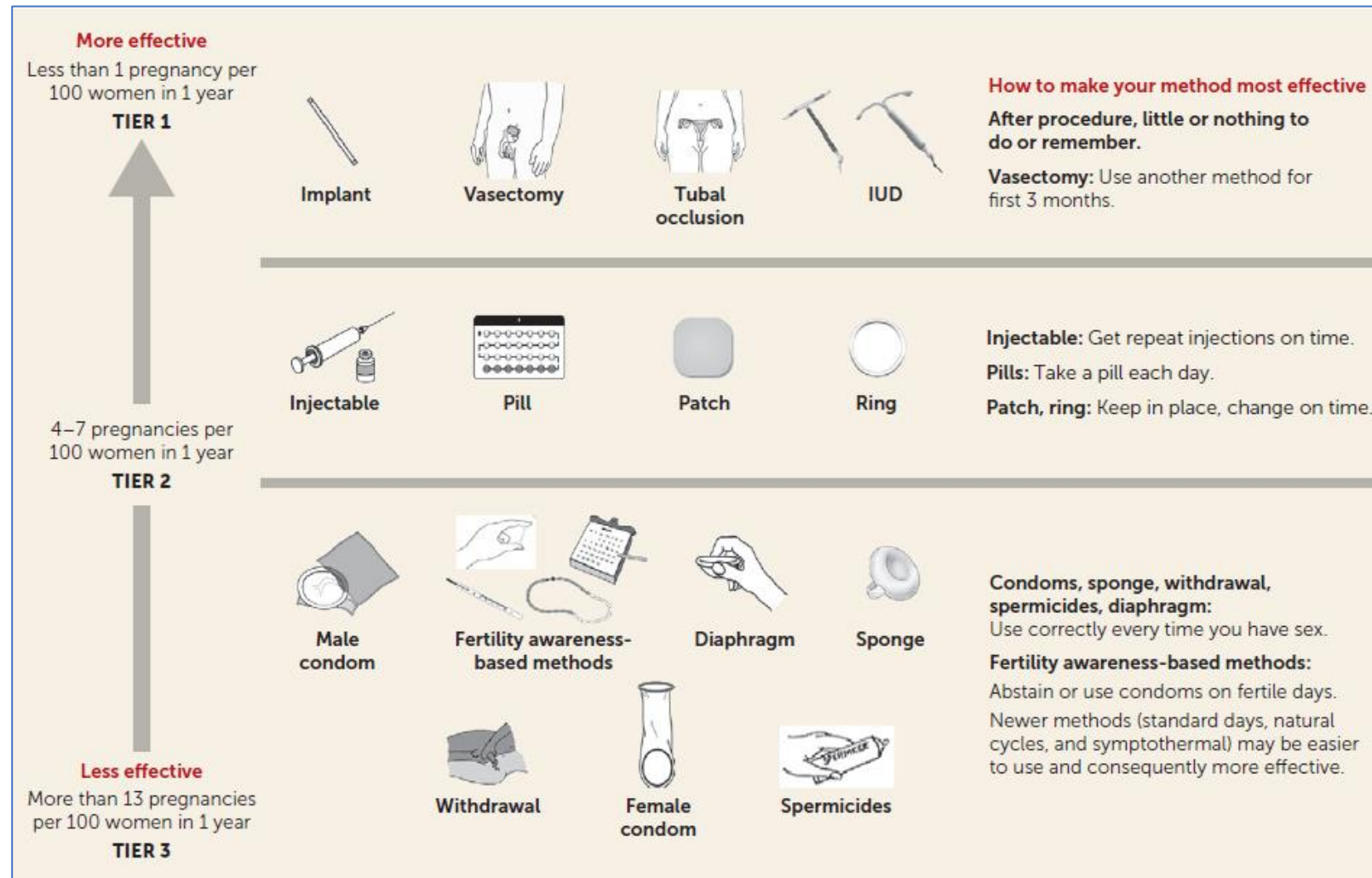
Bipolar Disorder – Preconception Considerations

- In US, the 41.6% of pregnancies in general population are unintended.
- In patients with psychiatric vulnerability this risk is even higher at approximately 65%.
- Case-control data indicate that unplanned pregnancies are disproportionately common among women with bipolar disorder, who also report lower levels of pregnancy planning compared with healthy controls.
- Important part of the care is discussing the use of contraceptives and regularly exploring family planning.

Framework for conversation on contraception - PATH

- **P**regnancy **A**ttitudes: “Do you think you might like to have (more) children at some point?”
- **T**iming: “If considering future parenthood, when do you think that might be?”
- **H**ow important is prevention: “How important is it to you to prevent pregnancy (until then)?”

Comparison of contraceptive method effectiveness



Effects of mood stabilizers on hormonal contraceptives

Antiseizure mood stabilizer	Proposed mechanism of interaction	Clinical impact on oral contraceptives	Clinical recommendations
Carbamazepine	Dose-dependent induction of CYP3A4 Increase in sex hormone-binding globulin	Decreased effectiveness Reduced free plasma concentrations of progestins	Use alternatives: depot medroxyprogesterone acetate (possibly with a shorter dosing interval of every 10 weeks), or IUD (levonorgestrel or copper) Consider continuous (no hormone-free interval) use of high-dose estrogen combined oral contraceptives ^a Consider doubling the dose of levonorgestrel emergency contraceptive or using copper IUD as an alternative form of emergency contraceptive
Gabapentin ^b	NA	No effect	None
Lamotrigine ≥300 mg/d	Possible induction of glucuronidation, hydroxylation or sulfation of levonorgestrel	Modest reductions (approximately 20%) in levonorgestrel levels with oral contraceptives; clinical significance is unclear	Consider alternatives: depot medroxyprogesterone, etonogestrel subdermal implant, or IUD (levonorgestrel or copper)
Oxcarbazepine ^b	Induction of CYP3A4	Decreased effectiveness	Same as carbamazepine
Topiramate ^b >200 mg/d	Induction of CYP3A4	Decreased effectiveness	Same as carbamazepine ^c
Valproic acid/divalproex sodium ^d	NA	No effect	None

Effects of hormonal contraceptives on mood stabilizers

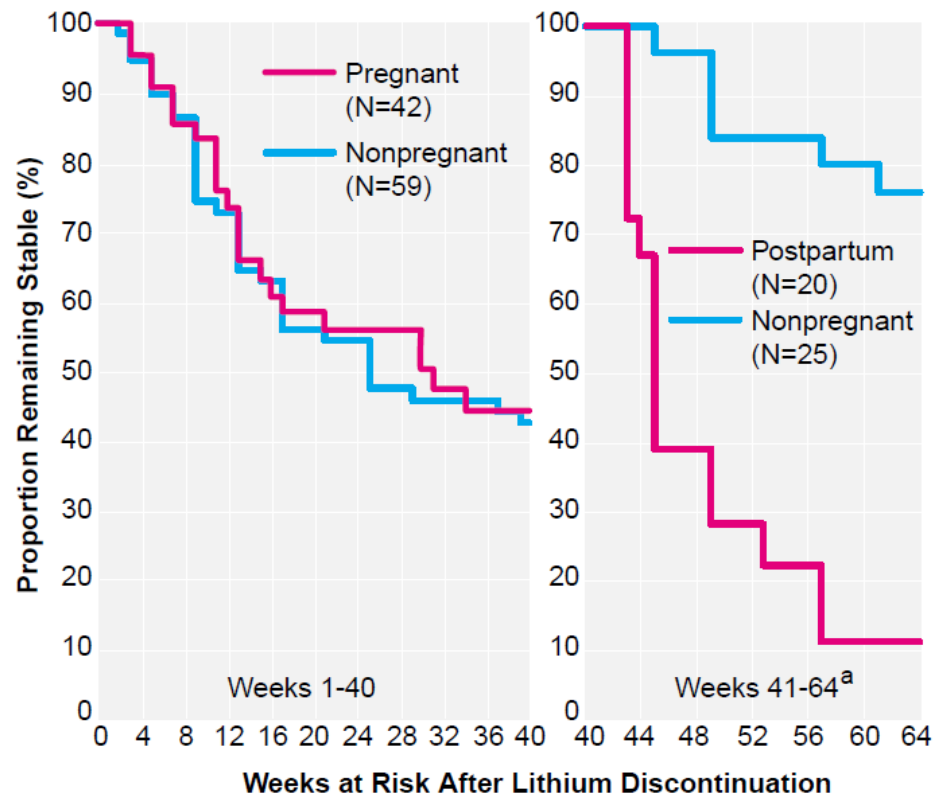
Antiseizure mood stabilizer	Proposed mechanism of interaction	Clinical impact on antiseizure medication	Clinical recommendations
Carbamazepine	NA	No effect	None
Gabapentin ^a	NA	No effect	None
Lamotrigine	Estrogen induces the metabolism of lamotrigine via induction of UGT1A4	May decrease lamotrigine plasma levels by 41% to 64%, resulting in potential breakthrough symptoms (unless also taking valproic acid)	Consider monitoring plasma levels Titrate lamotrigine dose by 50 to 100 mg/d weekly until efficacy is achieved, consider limiting hormone-free interval, and reduce dose if estrogen is discontinued
	Unknown	Certain progestins (drospirenone and levonorgestrel) may decrease lamotrigine levels	Consider alternatives: depot medroxyprogesterone, etonogestrel subdermal implant, or IUD (levonorgestrel or copper)
	Unknown	Desogestrel (progestin-only pill) may increase lamotrigine levels	Monitor for increased adverse effects with lamotrigine when used with progestin-only contraceptives
Oxcarbazepine ^a	NA	No effect	None
Topiramate ^a	NA	No effect	None
Valproic acid/divalproex sodium ^b	Estrogen may induce the metabolism of valproic acid via induction of UGT1A4	May decrease valproic acid levels by 21.5% to 23.4%	Consider monitoring valproic acid levels upon initiation, discontinuation, and during hormone-free intervals

Bipolar Disorder – Preconception Considerations

- Preconception care is a key opportunity to review and streamline pharmacologic regimens, weighing the risks of undertreated illness against potential fetal exposure.
- Reducing polypharmacy while preserving euthymia should be the guiding principle.
- Dose reduction is appropriate when a patient has documented stability at a lower dose or has never been exposed to one.
- Dose changes are contraindicated when they have previously precipitated relapse.
- Proactive education about physiological changes in drug metabolism during pregnancy and the high postpartum relapse risk is essential.

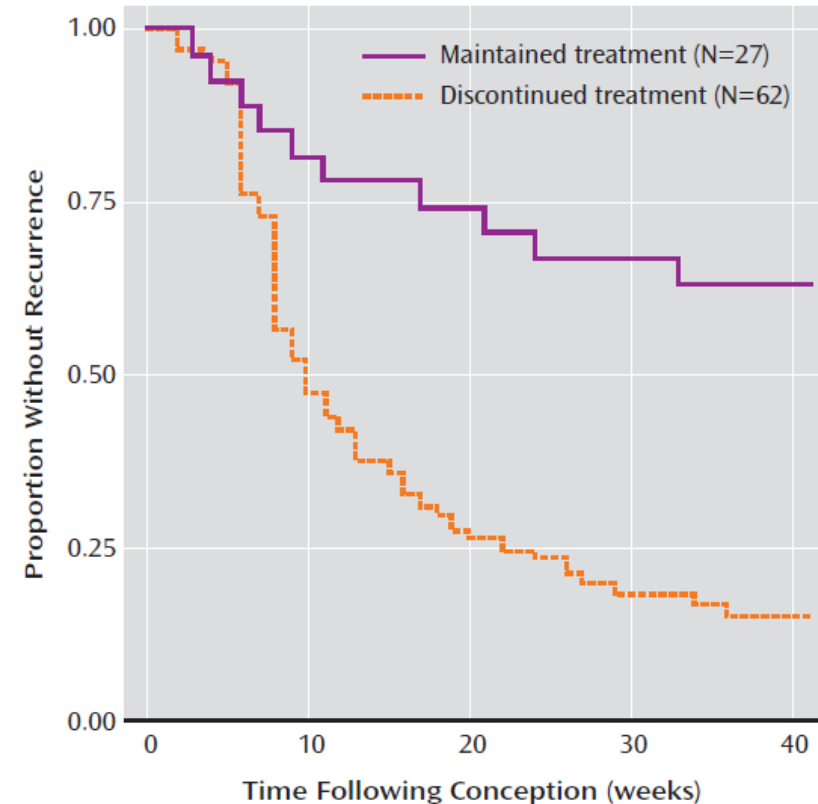
Bipolar Disorder in Pregnancy

FIGURE 1. Kaplan-Meier Survival Analysis of Bipolar Disorder Recurrence Risk After Lithium Discontinuation During Pregnancy and Postpartum and During Equivalent Time Periods in Nonpregnant Women



^a Subjects in this second analysis were those who had remained stable over the first 40 weeks after discontinuing lithium.

FIGURE 1. Kaplan-Meier Survival Functions for Pregnant Patients With Bipolar Disorder Who Maintained or Discontinued Treatment^a



^a Median time to first recurrence from the estimated date of conception was >41 weeks (95% CI=indeterminate) when mood stabilizer treatment was *maintained* (N=27) and only 9.0 weeks (95% CI=8.0–13.0) when treatment was *discontinued* (N=62; $\chi^2 \geq 17.9$, df=1, $p < 0.0001$), a 4.6-fold difference.

Clinical Pearls

- Lithium remains the mainstay treatment of bipolar disorder in the peripartum period.
- For patients with a known history of bipolar disorder who discontinued psychotropic medications during pregnancy, initiating prophylactic treatment immediately after delivery is advised.
- Adequate sleep protection in the postpartum period is a key non-pharmacologic strategy for reducing the risk of psychiatric decompensation in bipolar disorder.

Postpartum Psychosis – medical emergency!

- Women with BD have highest risk for PPP:
 - Baseline rate 1-2/1000
 - Bipolar women significantly higher risk (up to 20%)
 - 72-88% women with PPP have history of BD
- Typically presents fulminantly within days to weeks after giving birth.
- Symptoms include not only psychosis, but also confusion and dysphoric mania.
- Symptoms often wax and wane, that complicates or delay diagnosis.
- Psychiatric hospitalization is required to protect both mother and baby

Postpartum Psychosis

- Bergink et al., 2016: The authors reviewed the epidemiologic and genetic research and physiological postpartum triggers (endocrine, immunological, circadian) of psychosis.
- After an incipient episode, 20%- 50% of women have isolated postpartum psychosis.
- The remaining women have episodes outside the perinatal period, usually within the bipolar spectrum.
- The mechanism of onset is related to physiological changes after birth (e.g., hormonal, immunological, circadian), which precipitate disease in genetically vulnerable women.

Postpartum Psychosis

- Distinguish from pre-existing stable psychotic disorder
- Patient needs immediate psychiatric evaluation and cannot be alone with the infant (usually needs psych ER)
- If in doubt, call Project TEACH
- Medical workup: look for other causes of delirium, intoxication, immune dysfunction
 - CBC, LFTs, TFTs, BMP, B12, Folate, Utox
 - Consider imaging if focal findings

Postpartum Psychosis - Treatment

- The largest study (N=64) provided evidence that lithium is highly efficacious for both acute and maintenance treatment.
- Another report (N=34) described successful ECT treatment.
- Inpatient care is usually required to ensure safety, complete the diagnostic evaluation, and initiate treatment.
- The relapse risk after a subsequent pregnancy for women with isolated postpartum psychoses is 31% (95% CI=22–42).
- Strategies for prevention of postpartum psychosis include lithium prophylaxis immediately postpartum and proactive safety monitoring.

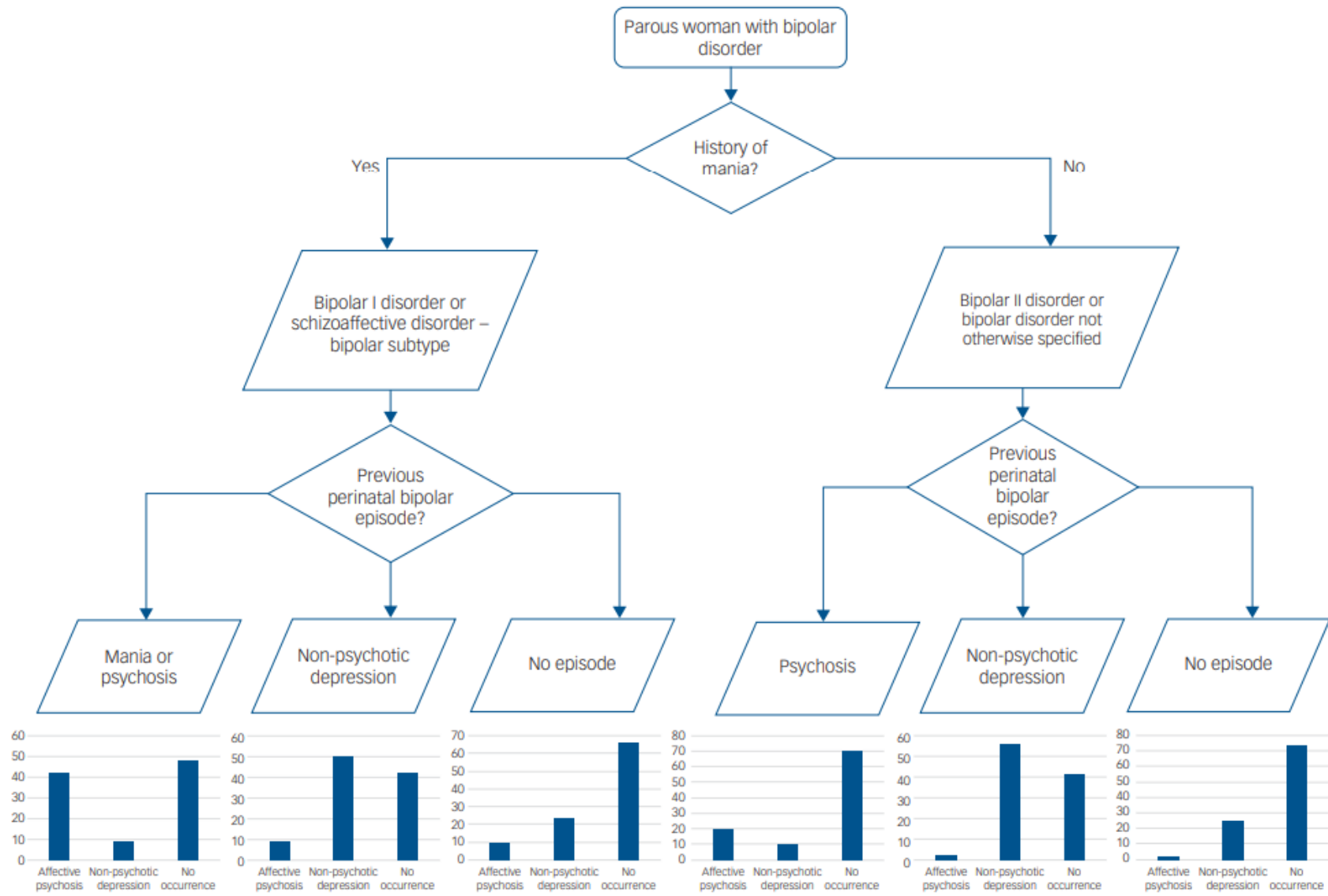
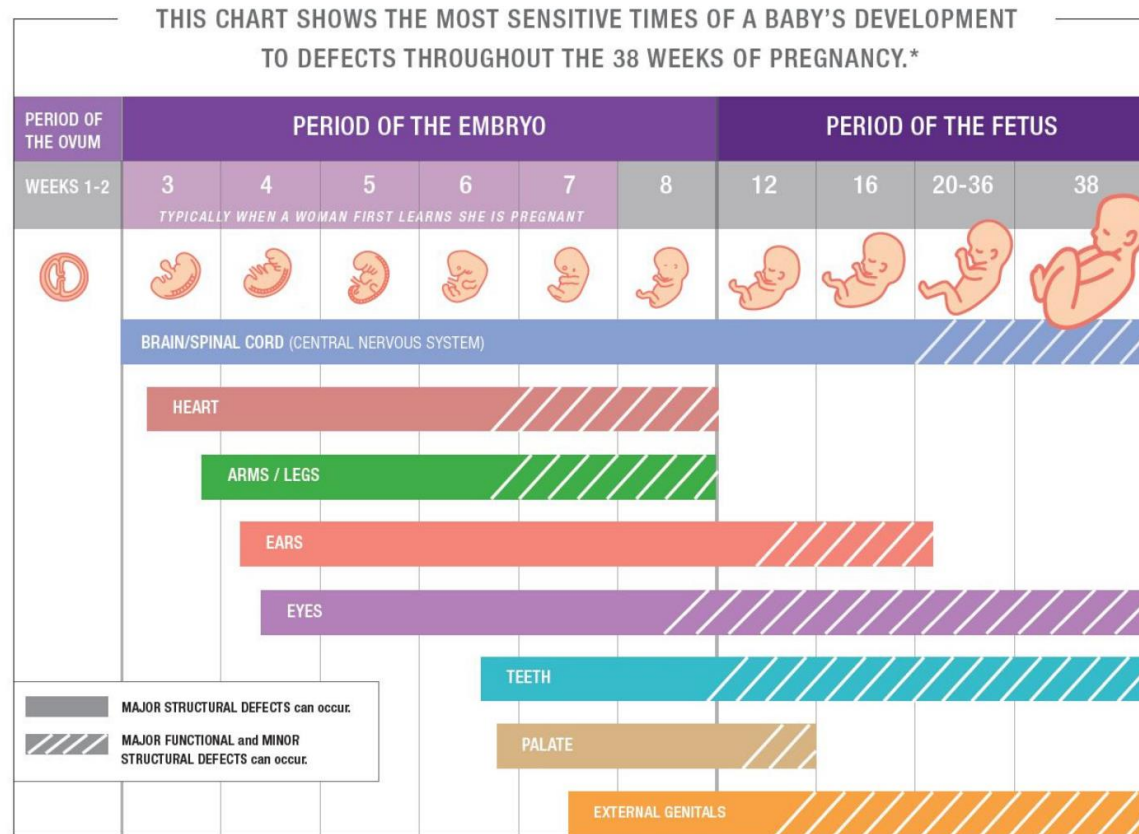


Fig. 2 Flow chart for risk assessment of perinatal episodes in women with bipolar disorder who have already had children.

Hypomania was not included in the analyses, because of the difficulties in assessing the clinical relevance of hypomanic symptoms in the postpartum period and the validity and reliability of a retrospective account.¹²

Use of Mood Stabilizers in Pregnancy



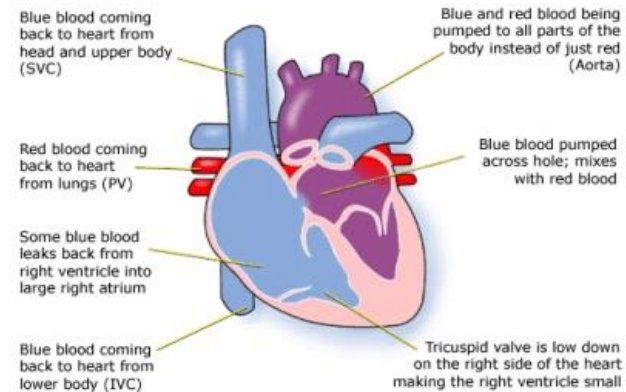
*mothertobaby.org; Adapted from Moore 1993, and the National Organization of Fetal Alcohol Syndrome (NOFAS) 2009.

Lithium in pregnancy

- Lithium is the gold standard for bipolar disorder (BD) maintenance and the only mood stabilizer with well-documented efficacy in the perinatal period, significantly reducing postpartum relapse risk from ~66% in unmedicated women to ~23% in those treated with lithium.
- Despite its proven benefits, lithium remains underutilized in women of reproductive age, largely due to worldwide decline in its use driven by promotion of alternative treatments and concerns about teratogenicity.

- First-trimester teratogenic risk exists but is dose-dependent and lower than historically reported, with malformation risk largely restricted to the first trimester and one large study only identifying teratogenicity at doses above 900 mg.

Ebstein's Anomaly



Ebstein's anomaly: abnormalities of tricuspid valve and right ventricle; risk increased from 1:20,000 to 1:2,000
Prevalence cardiac defects increased from ~1% -> 2%

Lithium dosing in pregnancy

- Preconceptional or first-trimester dose reduction may be considered in patients without a clear history of relapse at lower doses.
- Gradual reduction is preferred preconceptionally, while dose reduction at the time of discovery is advised in unplanned pregnancies.
- Dose reduction is generally preferable to discontinuation, given the high relapse risk associated with stopping lithium
- Close monitoring and strong clinical support are essential, as maternal psychiatric stability remains the primary concern throughout this process.
- Long-term neuropsychological outcomes in children with intrauterine lithium exposure are reassuring based on available data, though studies remain small and this area continues to be under-investigated.

Lithium levels in pregnancy

- Serum lithium levels fluctuate predictably throughout pregnancy — gradually declining to a nadir around 18 weeks before rising again — necessitating at least monthly monitoring, with weekly monitoring recommended after 34 weeks.
- Fetal echocardiogram and high-resolution ultrasound at 18-20 weeks

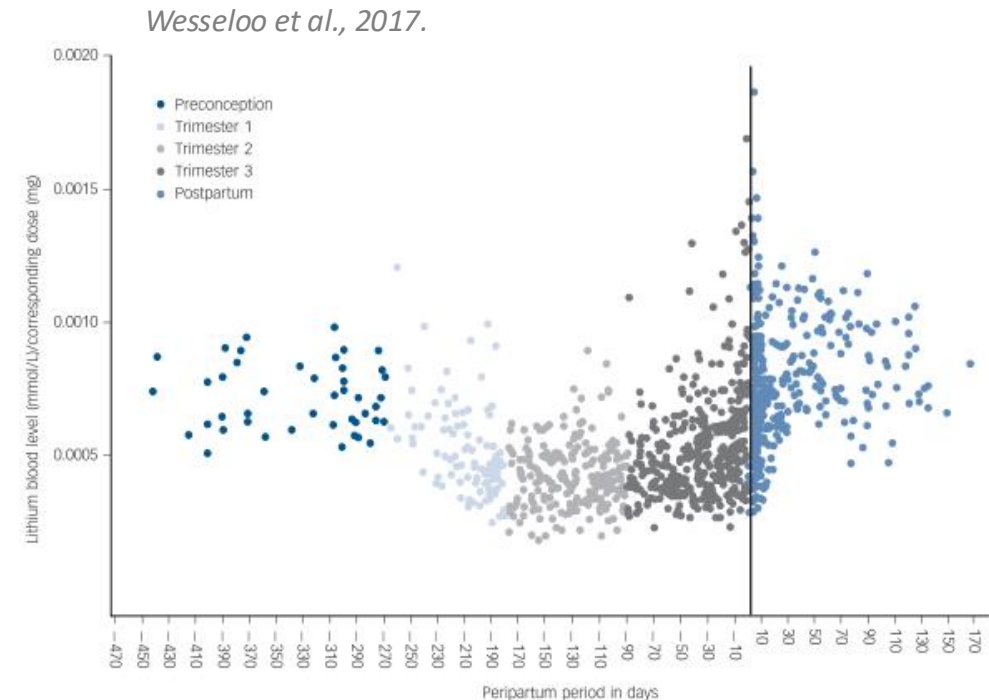


Fig. 1 Course of lithium blood level/dose ratio during the peripartum period.

Delivery is represented by the vertical line (i.e. day zero).

Lithium dosing - delivery

- Dose reduction during the first trimester is advisable given teratogenic risk at higher doses, however, reduction around the time of delivery is not recommended, as levels do not rise peripartum and lowering the dose may increase postpartum relapse risk during a high-vulnerability period.
- Target lithium levels of 0.8–1.0 mEq/L are recommended during the first postpartum month, with weekly level checks initially, transitioning to monthly monitoring once levels are stable; lithium should be promptly restarted postpartum if it was discontinued earlier in pregnancy.
- Prophylactic lithium initiation on the day of delivery should be considered for untreated patients with bipolar spectrum disorders, and all lithium-treated pregnant women should be managed by a collaborative team — including a reproductive psychiatrist and maternal-fetal medicine specialist — with appropriate fetal screening such as level II ultrasound and fetal echocardiogram.

Lamotrigine in pregnancy

- Lamotrigine is recommended as a first-line agent for bipolar disorder (BD) in the perinatal setting, supported by international clinical guidelines (CANMAT/IBSD,2018) for its efficacy in managing acute depressive episodes and long-term maintenance, despite the absence of FDA approval for acute BD treatment.
- Current evidence does not support an association between lamotrigine use in pregnancy and increased risk of major congenital malformations or neurodevelopmental disorders, contradicting earlier data that suggested elevated risk of oral clefts; more recent literature has largely refuted these concerns.

Lamotrigine in pregnancy

- Lamotrigine clearance increases significantly during pregnancy — by as much as 300% or more — due to estradiol-driven upregulation of hepatic glucuronidation beginning as early as 8 weeks' gestation, necessitating dose adjustments to maintain therapeutic levels.
- Dose titration during pregnancy is expected and should be individualized; some experts estimate an average increase of approximately 250% above preconception dosing may be required, with monthly trough level monitoring and a recommended dose increase of 20–25% upon subtherapeutic levels.
- Postpartum dose reduction should be initiated promptly upon delivery, as lamotrigine pharmacometabolism returns to preconception rates within 1–2 weeks; a stepwise reduction of approximately 25% is advised to prevent toxicity as clearance rapidly normalizes.

Agents to be avoided – VPA

- Valproic Acid (VPA):
 - Most powerful teratogen in psychopharmacology
 - Results in “fetal valproate syndrome” that includes a wide range of congenital malformations (5-11%), including spina bifida, cleft lip and palate, limb malformations and rarely anencephaly.
- 30–40% of children exposed to VPA in utero show neurodevelopmental difficulties, including cognitive, language and motor delays, lower IQ levels compared with exposure to other antiepileptics, behavioral challenges, and autism spectrum disorder
- Many international regulatory bodies, including the US Food and Drug Administration (FDA) and World Health Organization (WHO) released statements warning the public and prescribers that VPA should be avoided in patients of childbearing potential, and only prescribed with reliable, effective contraception in severe, refractory cases.

Agents to be avoided – carbamazepine

- Associated with teratogenic effects (3–6%), including neural tube, craniofacial, urogenital, and cardiac malformations, in addition to transient hepatotoxicity, vitamin K deficiency, and coagulopathies, among others.
- 12–14% prevalence of behavioral dysregulation in the offspring exposed to carbamazepine compared with unexposed offspring

Agents to be avoided – topiramate and gabapentin

- Neither gabapentin nor topiramate are FDA approved for treatment of bipolar disorder, hence their use not justified for this indication.
- Topiramate associated with risk for neurodevelopmental delay.
- In the perinatal patient population, mood stabilization should be achieved with therapeutic agents of demonstrated efficacy. The use of these agents is discouraged, as their inclusion contributes to polypharmacy without meaningful clinical benefit and results in avoidable medication exposure.

Antipsychotics in pregnancy

- Antipsychotic use during pregnancy has increased significantly, driven by expanding indications, rapid onset of effect, and lower acute toxicity compared to alternative agents.
- Available data do not suggest significant risks of congenital malformations with AP use in pregnancy, with several large epidemiological studies reporting malformation rates comparable to unexposed comparison groups.
- Large register-based studies similarly show no significant increase in neurodevelopmental disorder diagnoses in children with antenatal AP exposure, supporting a generally reassuring developmental safety profile for the class.
- Safety data for newer AP agents remain limited or entirely absent, warranting caution with their use in pregnancy.

First generation antipsychotics in pregnancy

- **Haloperidol** is the only first-generation AP with specific BD efficacy data, carrying higher extrapyramidal symptom risk but no significant malformation signal in human studies of over 750 pregnancies.
- **Phenothiazines (chlorpromazine, prochlorperazine, levomepromazine)** have more extensive human pregnancy data given their use for hyperemesis gravidarum, though neonatal motor abnormalities and adaptation syndrome have been reported at higher doses.
- **Clozapine carries the most concerning perinatal safety signals**, including case reports of floppy infant syndrome, agranulocytosis, meconium plug, fetal drug accumulation, and a possible signal for anorectal atresia, warranting particular caution despite its necessity in treatment-refractory patients.

Second generation antipsychotics in pregnancy

- **Women treated with antipsychotics (APs) during pregnancy should be classified as high risk**, requiring coordinated care between psychiatry and obstetrics or maternal-fetal medicine, with close attention to metabolic health and pregnancy outcomes.
- **Second-generation APs carry well-recognized risks for gestational diabetes and weight gain**; early glucose tolerance testing and dietary/lifestyle counseling are recommended, with agent selection favoring lower metabolic risk options such as aripiprazole over quetiapine or olanzapine in patients with pre-existing metabolic dysfunction.
- **Quetiapine has the lowest placental and breast milk transfer rates among APs**, making it a useful option for sleep, though it carries the highest metabolic and gestational diabetes risk; malformation data are available from over 11,000 pregnancies.
- **Risperidone** carry risks for hyperprolactinemia, which may impair fertility and conception; malformation data for risperidone are available from nearly 3,000 pregnancies without significant concern.
- **Aripiprazole** carries the lowest gestational diabetes risk among second-generation APs but may impair lactation variably due to its partial dopamine agonist mechanism, and can be either activating or sedating depending on the individual.
- **Ziprasidone and lurasidone have more limited but generally non-alarming data**; ziprasidone carries a theoretical cardiac conduction risk relevant to women with additional cardiac risk factors, while lurasidone may be acceptable when other agents have failed.

Relative infant dose of most commonly used antipsychotics and mood stabilizers

Medication	RID %
Haldol	0.12%-12%
Clozapine	1.33%-1.4%
Olanzapine	0.28%-2.24%
Quetiapine	0.02% - 0.1%
Risperidone	2.8%- 9.1%
Aripiprazole	0.7%-6.44%
Ziprasidone	0.07%-1.2%
Lurasidone	0.44%
Lithium	0.87%- 7.29%
Lamotrigine	6.62%- 18.27%

- RID = A valuable tool and practical guide to indicate the extent of drug exposure to the infant while breastfeeding.
- The RID calculates the weight adjusted dose in the infant relative to the weight adjusted dose in the mother.
- RID level <2% = minimal exposure
- RID level 2-5% = small exposure
- RID level <10% = likely safe for the infant
- RID level >25% =potentially unsafe levels

Perinatal relapse prevention plan

1. A collaborative perinatal relapse prevention plan should be developed with the patient, family, and obstetric team, documented in writing and made available to the patient and medical record with appropriate consent.
2. A individualized risk-benefit assessment should guide medication decisions during pregnancy, with strong consideration for continuing prophylactic treatment throughout the perinatal period to sustain maternal euthymia.
3. A postpartum medication plan targeting optimal therapeutic levels should be established prior to delivery, with lithium representing the most evidence-based agent for relapse prevention, particularly for patients who were medication-free during pregnancy.
4. Preferred mode of delivery and intrapartum pain management should be clearly outlined in advance in coordination with the obstetric team.
5. A proactive feeding plan and structured sleep strategy — including family or partner support for night feedings — should be established to protect circadian rhythm stability in the early postpartum period.
6. Early relapse warning signs should be identified and documented based on the patient's individual history, with a clear intervention plan and designated contacts for the patient and family to reach out to if symptoms emerge.



Resources

- **Project TEACH:** <https://projectteachny.org/>
- [Mothertobaby.org](http://mothertobaby.org) (free resources including fact sheets for patients)
- [Reprotox.org](http://reprotox.org) (subscription site)
- Lactmed: <https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm>
- Postpartum Support International: www.postpartum.net
- MGH Center for Women's Mental Health
www.womensmentalhealth.org