

Northern California Psychiatric Society  
Fall Conference  
Sunday, October 27, 2019

## Reproductive Psychopharmacology Update

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Women's Wellness Psychiatry, Burlingame

# Disclosures

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None

# Objectives for Today

- Learn about recent literature on the reproductive safety of commonly used psychotropic medications in pregnancy
- Become familiar with most recent pharmaceutical developments in the management of mood disorders in pregnant/postpartum women
- Gain skills and confidence in the management of acutely ill pregnant patients
- Develop openness to the use of non-prescription treatment options in pregnant patients

# The Case of Ms. W

- Ms. W is a 29-year-old married woman who has a history of depression and possibly mixed episodes, who is coming to see you for a second opinion because she plans to start a family and is concerned about the medications she is taking.
- One prior hospitalization in late teens following a suicidal gesture
- Off and on in psychotherapy
- Currently employed as an administrative assistant
- Current medication includes fluoxetine, lamotrigine, as needed alprazolam, and as needed trazodone

As a review...

- Episodes of depression and bipolar disorder have a high risk of recurrence during pregnancy

[Archives of Women's Mental Health](#)

October 2004, Volume 7, [Issue 4](#), pp 217–221 | [Cite as](#)

## Relapse of depression during pregnancy following antidepressant discontinuation: a preliminary prospective study

Authors

[Authors and affiliations](#)

L. S. Cohen, R. M. Nonacs, J. W. Bailey, A. C. Viguera, A. M. Reminick, L. L. Altshuler, Z. N. Stowe, S. V. Faraone



European Neuropsychopharmacology

Volume 29, Issue 7, July 2019, Pages 803-812



## Impact of antidepressant use, discontinuation, and dosage modification on maternal depression during pregnancy

Anick Bérard <sup>a, b</sup>  , Odile Sheehy <sup>b</sup>, Jin-Ping Zhao <sup>b</sup>, Christina Chambers <sup>c</sup>, Mark Roth <sup>d</sup>, Pina Bozzo <sup>e</sup>, Diana Johnson <sup>c</sup>, Kelly Kao <sup>c</sup>, Sharon Lavigne <sup>f</sup>, Lori Wolfe <sup>g</sup>, Dee Quinn <sup>h</sup>, Kristen Dieter <sup>i</sup>, the MotherToBaby Collaborative Research Committee

# Bipolar Disorder - Demographics

- Bipolar disorder affects about 2.6% of the adult US population<sup>1</sup>
- Rates of relapse are generally high (50% at 1 year, 70% at 4 years)<sup>2</sup>
- Rates of relapse are particularly high during
  - Pregnancy (37% with mood stabilizer, 81% when medication free)<sup>4</sup>
  - The postpartum period (23% when taking mood stabilizer, 66% when medication free)<sup>3</sup>
- Depressive or dysphoric-mixed episodes predominate in the perinatal period<sup>4</sup>

1. NIMH, via [dbsalliance.org](http://dbsalliance.org)

2. Lobban et al., *The British Journal of Psychiatry* Dec 2009, 196 (1) 59-63;

3. Wesseloo et al., *Am J Psychiatry*. 2016 Feb 1;173(2):117-27

4. Viguera et al., *Am J Psychiatry* 2007, 164(12):1817

# Risk of Recurrence in Women With Bipolar Disorder During Pregnancy: Prospective Study of Mood Stabilizer Discontinuation

Adele C. VigueraTheodore WhitfieldRoss J. BaldessariniD. Jeffrey NewportZachary StoweAlison ReminickAmanda ZurickLee S. Cohen

**Published Online:** 1 Dec 2007 | <https://doi.org/10.1176/appi.ajp.2007.06101639>

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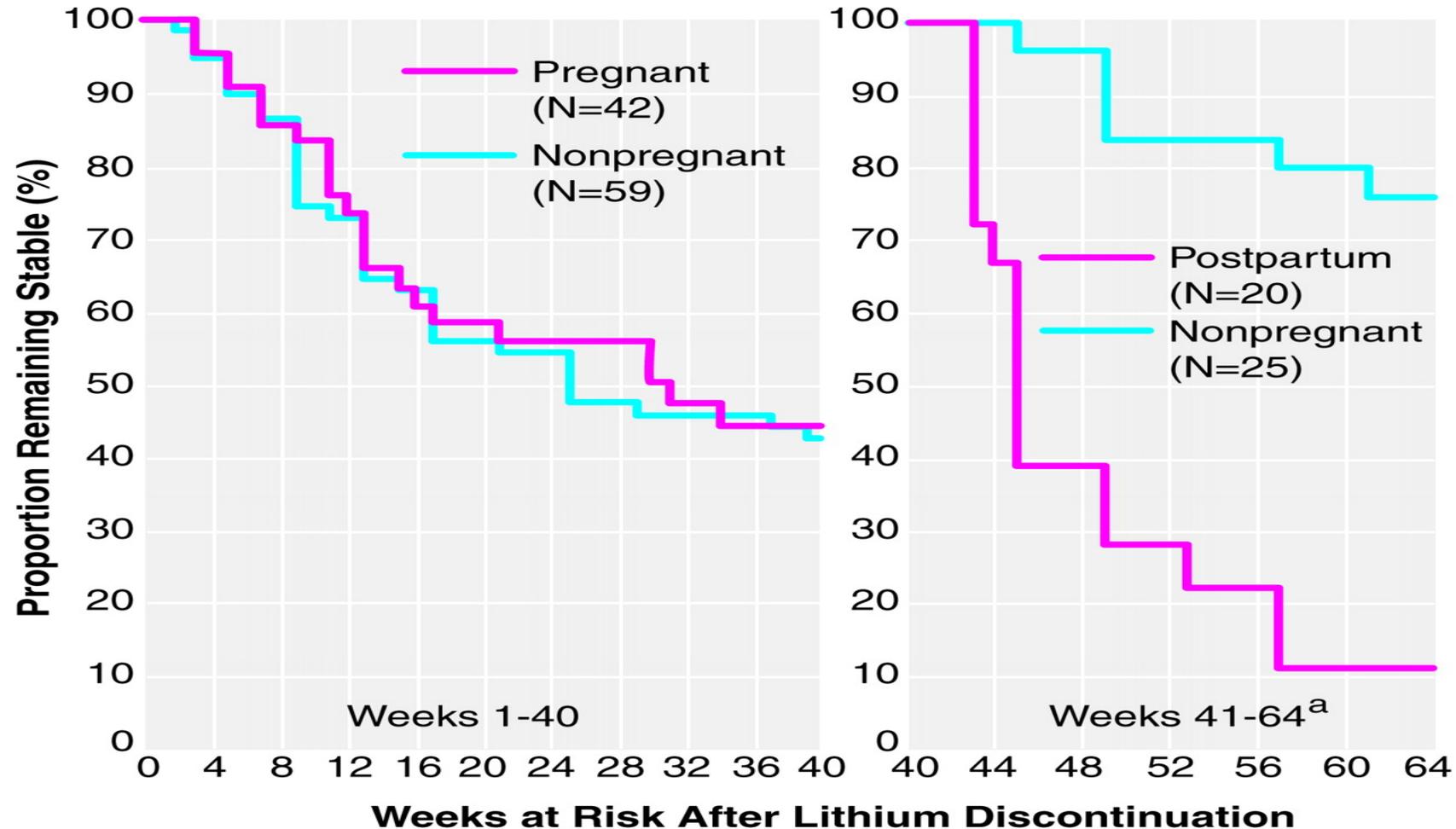
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## Abstract

**Objective:** This study estimated the risk of recurrence of mood episodes among women with a history of bipolar disorder who continued or discontinued treatment with mood stabilizers during pregnancy. **Method:** In a prospective observational clinical cohort study, the authors determined recurrence risk and survival-analysis-based time to recurrence of a new episode in 89 pregnant women with DSM-IV bipolar disorder. Eligible subjects were euthymic at conception and continued mood stabilizer treatment or discontinued treatment proximate to conception. **Results:** The overall risk of at least one recurrence in pregnancy was 71%. Among women who discontinued versus continued mood stabilizer treatment, recurrence risk was twofold greater, median time to first recurrence was more than fourfold shorter, and the proportion of weeks ill during pregnancy was five times greater. Median recurrence latency was 11 times shorter after abrupt/rapid versus gradual discontinuation of mood stabilizer. Most recurrences were depressive or mixed (74%), and 47% occurred during the first trimester. Predictors of recurrence included bipolar II disorder diagnosis, earlier onset, more recurrences/year, recent illness, use of antidepressants, and use of anticonvulsants versus lithium. **Conclusions:** Discontinuation of mood stabilizer, particularly abruptly, during pregnancy carries a high risk for new morbidity in women with bipolar disorder, especially for early depressive and dysphoric states. However, this risk is reduced markedly by continued mood stabilizer treatment. Treatment planning for pregnant women with bipolar disorder should consider not only the relative risks of fetal exposure to mood stabilizers but also the high risk of recurrence and morbidity associated with stopping maintenance mood stabilizer treatment.

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# Relapse of Bipolar Disorder in Pregnancy and Postpartum



# Missed Bipolarity in Postpartum Depression

- 30 of 56 patients referred for general postpartum depression actually had a bipolar spectrum disorder<sup>1</sup>
- 34 of 60 patients referred for treatment-resistant postpartum depression actually had a bipolar spectrum disorder<sup>2</sup>
- In a multicenter study of first-episode depression (N=885), 15% of those with first-onset postpartum episodes met DSM-IV criteria for bipolar disorder, while only 5% of those with first-onset non-postpartum episodes did<sup>3</sup>

1. Sharma et al., Bipolar Disord 2008: 10: 742–747

2. Sharma V, Khan M. Bipolar Disord 2010: 12: 335–340

3. Azorin et al., J Affective Disord 2012: 136:3:710

# Reproductive Safety of Medications

- Discontinuation of ABCDX categories



## Fear of Medication in Pregnancy

# Pregnant patients use medication!

- Dichotomy between what is beneficial for mom versus baby
- Forgetting to weigh risks of untreated illness versus medication rather than just use versus nonuse of medications
- Pregnant patients are #1 under-represented patient population in medical research
- 2/3 take at least one prescription medication
- 1/3 take psychotropic medication

# Safety Across Stages



Malformations (1<sup>st</sup> trimester) or miscarriage



Obstetric and neonatal outcomes



Long term neurodevelopmental consequences

Most  
commonly  
prescribed  
psychotropic  
in pregnancy:  
SSRI



Indications: mood, anxiety



Well tolerated w/r/t SEs



Most available safety information in pregnancy



Mechanism of action

SSRIs and  
Malformations  
or Miscarriage

No malformations

No increased risk of miscarriage

Hemorrhage 2/2 thrombocytopenia?

SSRIs and  
PPHN

June 2, 2015

## Antidepressant Use Late in Pregnancy and Risk of Persistent Pulmonary Hypertension of the Newborn

Krista F. Huybrechts, MS, PhD<sup>1,2</sup>; Brian T. Bateman, MD, MSc<sup>1,2,3</sup>; Kristin Palmsten, ScD<sup>4</sup>; [et al](#)

» [Author Affiliations](#) | [Article Information](#)

*JAMA*. 2015;313(21):2142-2151. doi:10.1001/jama.2015.5605

- Lower than initially believed
- Risk attenuated when depression accounted for

# SSRIs and Autism

- No causal relationship has been proven

# SSRIs and Neonatal Adaptation

- Poor Neonatal Adaptation: Jittery, tremulous, respiratory difficulty, tremor, difficulty feeding, irritable.
- About 48 hours to 2 weeks
- About a quarter of exposed infants
- No treatment intervention required
- Discontinuing SSRI in 3<sup>rd</sup> trimester does not help



Acta Psychiatrica Scandinavica

A register study of the impact of stopping third trimester selective serotonin reuptake inhibitor exposure on neonatal health

W. Warburton, C. Hertzman, T. F. Oberlander

First published: 04 May 2010 | <https://doi.org/10.1111/j.1600-0447.2009.01490.x> | Cited by: 62

**The Roles of Maternal Depression, Serotonin Reuptake Inhibitor Treatment, and Concomitant Benzodiazepine Use on Infant Neurobehavioral Functioning Over the First Postnatal Month**

Amy L. Salisbury , Ph.D., Kevin E. O'Grady, Ph.D., Cynthia L. Battle, Ph.D., Katherine L. Wisner, M.D., M.S., George M. Anderson, Ph.D., Laura R. Stroud, Ph.D., Cynthia L. Miller-Loncar, Ph.D., Marion E. Young, Ph.D., Barry M. Lester, Ph.D.

Published Online: 30 Oct 2015 | <https://doi.org/10.1176/appi.ajp.2015.14080989>

# Lamotrigine



[CNS Drugs](#)

June 2017, Volume 31, [Issue 6](#), pp 439–450 | [Cite as](#)

## Pregnancy Outcomes Following In Utero Exposure to Lamotrigine: A Systematic Review and Meta-Analysis

[Authors](#)

[Authors and affiliations](#)

Gali Pariente , Tom Leibson, Talya Shulman, Thomasin Adams-Webber, Eran Barzilay, Irena Nulman

Systematic Review

First Online: 22 April 2017

1

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804

Downloads

12

Citations

- Rates of miscarriages, stillbirths, preterm deliveries, and small for gestational age (SGA) neonates were similar in LTG-exposed pregnancies as compared to the general population
- No increased risk of malformations

# Lamotrigine and breastfeeding

Pediatrics  
July 2008, VOLUME 122 / ISSUE 1  
Article

## Lamotrigine in Breast Milk and Nursing Infants: Determination of Exposure

D. Jeffrey Newport, Page B. Pennell, Martha R. Calamaras, James C. Ritchie, Melanee Newman, Bettina Knight, Adele C. Viguera, Joyce Liporace, Zachary N. Stowe

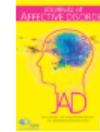
- Mean milk to plasma ratio: 41%
- Relative infant dose 9.2%

# Lamotrigine v. Lithium



Journal of Affective Disorders

Volume 218, 15 August 2017, Pages 394-397



## Risk of postpartum episodes in women with bipolar disorder after lamotrigine or lithium use during pregnancy: A population-based cohort study

Richard Wesseloo <sup>a</sup>, Xiaojin Liu <sup>b</sup>, Crystal T. Clark <sup>c</sup>, Steven A. Kushner <sup>a</sup>, Trine Munk-Olsen <sup>b,1</sup>, Veerle Bergink <sup>a,1</sup>

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<https://doi.org/10.1016/j.jad.2017.04.070>

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- Lamotrigine was not inferior to lithium in the prevention of severe postpartum episodes. Lamotrigine could be a reasonable alternative treatment option for bipolar disorder during pregnancy in patients with vulnerability for depression and may prevent severe episodes postpartum

# Ms. W's Case Continued

- Ms. W continued on the lamotrigine and fluoxetine during pregnancy.
- No significant medical complications during the pregnancy outside of severe N/V in her first trimester and fatigue thereafter
- In her third trimester, she became more depressed, despondent, and wondered if her family would be better off without her. Began having suspicious thoughts about her husband.
- Hospitalized

What treatment would you consider for Ms. W?

- Other mood stabilizers like lithium?
  - Typical antipsychotic such as Haldol?
  - Atypical antipsychotic medication?
  - ECT?
- 
- What if Ms. W becomes agitated while hospitalized?

# No unique treatment guidelines for agitation management in the pregnant patient



ELSEVIER

General Hospital Psychiatry

Volume 29, Issue 1, January–February 2007, Pages 39-41



Emergency Psychiatry in the General Hospital

## Emergency management of agitation in pregnancy

April S. Ladavac M.D., M.P.H. <sup>a, b</sup>, William R. Dubin M.D. <sup>a, b</sup>  , Autumn Ning M.D. <sup>a, b</sup>, Philip A. Stuckeman B.S. <sup>b</sup>

## How should I treat acute agitation in pregnancy?

*Cleveland Clinic Journal of Medicine*. 2019 April;86(4):243-247

**Author(s):** Joshua D. Niforatos, MTS; Jonathon W. Wanta, MD; Anna P. Shapiro, MD; Justin A. Yax, DO, DTMH; Adele C. Viguera, MD, MPH

# Lithium

## THE LANCET Psychiatry

ARTICLES | [VOLUME 5, ISSUE 8, P644-652, AUGUST 01, 2018](#)

### Maternal and infant outcomes associated with lithium use in pregnancy: an international collaborative meta-analysis of six cohort studies

[Trine Munk-Olsen, PhD](#)   • [Xiaoqin Liu, PhD](#) • [Alexander Viktorin, PhD](#) • [Hilary K Brown, PhD](#) •  
[Arianna Di Florio, PhD](#) • [Prof Brian M D'Onofrio, PhD](#) • et al. [Show all authors](#)

Published: June 18, 2018 • DOI: [https://doi.org/10.1016/S2215-0366\(18\)30180-9](https://doi.org/10.1016/S2215-0366(18)30180-9)



- No increased risk of pregnancy adverse outcomes
- Increased risk of major malformations, but not cardiac
- Confounders related to severity and age



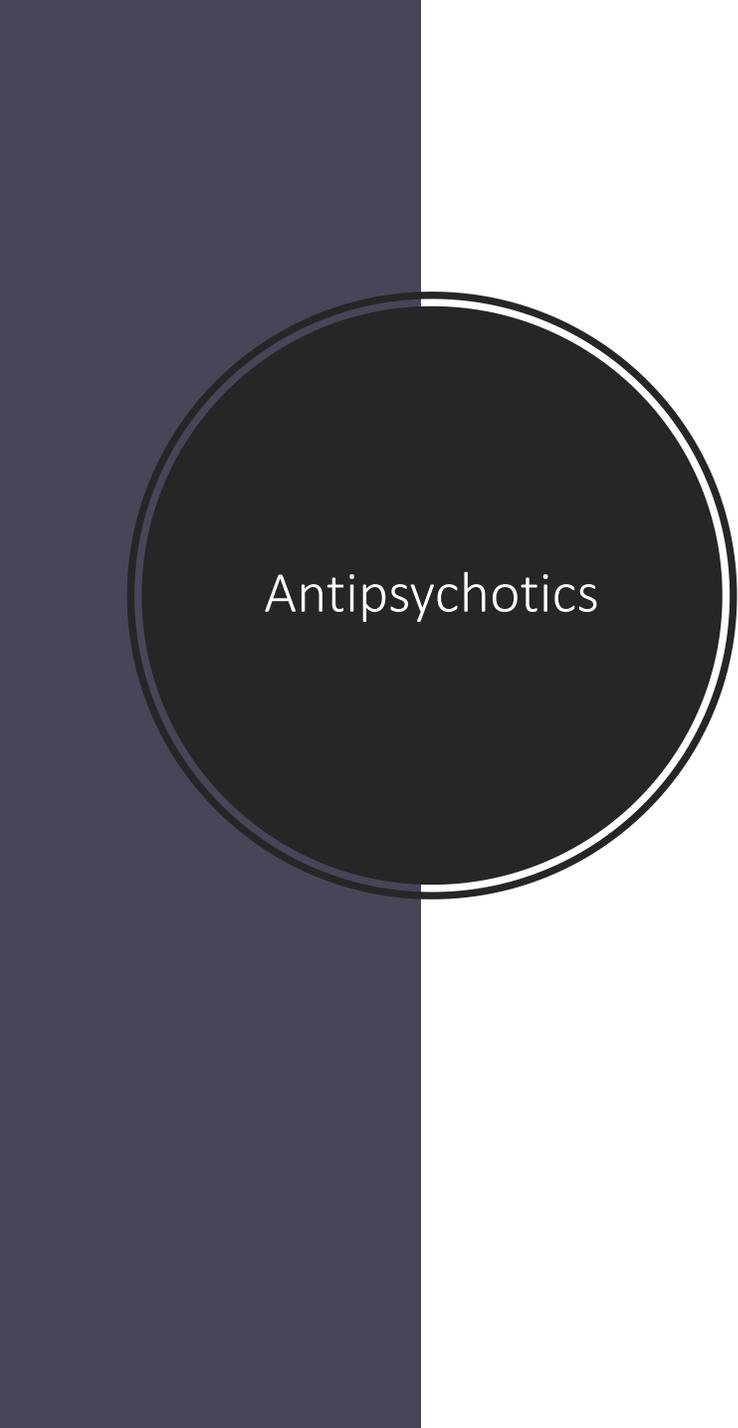
## Lithium

- Cohort study, 1.3+ million pregnancies
- Noted cardiac malformations, but at rates lower than previously postulated
- Dose dependent

ORIGINAL ARTICLE

# Lithium Use in Pregnancy and the Risk of Cardiac Malformations

Elisabetta Patorno, M.D., Dr.P.H., Krista F. Huybrechts, Ph.D., Brian T. Bateman, M.D., Jacqueline M. Cohen, Ph.D., Rishi J. Desai, Ph.D., Helen Mogun, M.S., Lee S. Cohen, M.D., and Sonia Hernandez-Diaz, M.D., Dr.P.H.



Antipsychotics

**Original Investigation**

September 2016

# Antipsychotic Use in Pregnancy and the Risk for Congenital Malformations

Krista F. Huybrechts, MS, PhD<sup>1</sup>; Sonia Hernández-Díaz, MD, DrPH<sup>2</sup>; Elisabetta Patorno, MD, DrPH<sup>1</sup>; [et al](#)

[» Author Affiliations](#) | [Article Information](#)

*JAMA Psychiatry.* 2016;73(9):938-946. doi:10.1001/jamapsychiatry.2016.1520

- Typicals
- Older atypicals
- Newer atypicals

# Antipsychotics Continued

- Neonatal adaptation
- Gestational diabetes

[Am J Psychiatry](#). Author manuscript; available in PMC 2019 Jun 1.

Published in final edited form as:

[Am J Psychiatry](#). 2018 Jun 1; 175(6): 564–574.

Published online 2018 May 7. doi: [10.1176/appi.ajp.2018.17040393](https://doi.org/10.1176/appi.ajp.2018.17040393)

PMCID: PMC5988929

NIHMSID: NIHMS941330

PMID: [29730938](https://pubmed.ncbi.nlm.nih.gov/29730938/)

## Continuation of Atypical Antipsychotic Medication during Early Pregnancy and the Risk of Gestational Diabetes

[Yoonyoung Park](#), ScD,<sup>1,2</sup> [Sonia Hernandez-Diaz](#), MD DrPH,<sup>2</sup> [Brian T. Bateman](#), MD MSc,<sup>1,3</sup> [Jacqueline M. Cohen](#), PhD,<sup>2</sup> [Rishi J. Desai](#), PhD,<sup>1</sup> [Elisabetta Paterno](#), MD DrPH,<sup>1</sup> [Robert J. Glynn](#), PhD,<sup>1</sup> [Lee S. Cohen](#), MD,<sup>4</sup> [Helen Mogun](#), MS,<sup>1</sup> and [Krista F. Huybrechts](#), MS PhD<sup>1</sup>



Psychosomatics

Volume 59, Issue 2, March–April 2018, Pages 125-134



Original Research Report

## Gestational Weight Gain and Pre-pregnancy Body Mass Index Associated With Second-Generation Antipsychotic Drug Use During Pregnancy ☆

[Marlene P. Freeman](#) M.D. <sup>a</sup>  , [Alexandra Z. Sosinsky](#) B.S. <sup>a</sup>, [Lina Goez-Mogollon](#) M.D. <sup>a</sup>, [Gina M. Savella](#) B.S. <sup>a</sup>, [Danna Moustafa](#) B.S. <sup>a</sup>, [Adele C. Viguera](#) M.D., M.P.H. <sup>a, b</sup>, [Lee S. Cohen](#) M.D. <sup>a</sup>

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<https://doi.org/10.1016/j.psych.2017.09.002>

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SAGE-547,  
Brexanolone

July 2, 2019

# Brexanolone (Zulresso) for Postpartum Depression

## Article Information

*JAMA*. 2019;322(1):73-74. doi:10.1001/jama.2019.6622

- Allosteric modulator of GABA-A receptors
- Pros: rapid results
- Cons: IV infusion

# Ms. W's Case Continued

- Ms. W was stabilized and went on to have an unremarkable delivery.
- Postpartum, some difficulty with breastfeeding led to anxiety and depression
- She weaned at 6 months and returned to work. She is having some difficulty with focus/concentration and as a child the diagnosis of ADHD was considered
- At a year postpartum, she wondered about tapering off of some of her medications and what non-pharmacologic options could be used to help support her mood. She is considering a second pregnancy in the future.

# Stimulant medication in pregnancy

- Extrapolated data: lower birth weights, preterm deliveries (vasoconstriction)
- No increased risk of malformations
- Possible increased risk of gestational hypertension

## Original Investigation

February 2018

### Association Between Methylphenidate and Amphetamine Use in Pregnancy and Risk of Congenital Malformations

A Cohort Study From the International Pregnancy Safety Study Consortium

Krista F. Huybrechts, MS, PhD<sup>1</sup>; Gabriella Bröms, MD, PhD<sup>2</sup>; Lotte Brix Christensen, MSc<sup>3</sup>; [et al](#)

[Author Affiliations](#) | [Article Information](#)

*JAMA Psychiatry.* 2018;75(2):167-175. doi:10.1001/jamapsychiatry.2017.3644

*J Clin Psychiatry.* 2016 Nov;77(11):1538-1545. doi: 10.4088/JCP.15m10506.



### Prenatal Psychostimulant and Antidepressant Exposure and Risk of Hypertensive Disorders of Pregnancy.

Newport DJ<sup>1,2</sup>, Hostetter AL<sup>3</sup>, Juul SH<sup>3</sup>, Porterfield SM<sup>4</sup>, Knight BT<sup>5</sup>, Stowe ZN<sup>6</sup>.

# Non-prescription biological options

- SAM-e (studied in pregnancy for cholestasis)
- NAC (studied in pregnancy for acetaminophen OD)
- Inositol (studied in GDM)
- Omega-3s
- EnBrace HR
- Vitamin D supplementation
- Magnesium supplementation

[Archives of Women's Mental Health](#)

June 2014, Volume 17, Issue 3, pp 213–219 | [Cite as](#)

## Low maternal serum vitamin D during pregnancy and the risk for postpartum depression symptoms

Authors Authors and affiliations

Monique Robinson , Andrew J. O. Whitehouse, John P. Newnham, Shelley Gorman, Peter Jacoby, Barbara J. Holt, Michael Serralha, Jessica E. Tearne, Pat G. Holt, Prue H. Hart, Merci M. H. Kusel

[Diabetes Metab Res Rev](#). 2019 Jul; 35(5): e3154.

Published online 2019 Apr 10. doi: [10.1002/dmrr.3154](#)

PMCID: PMC6617769

PMID: [30889626](#)

## Inositol and antioxidant supplementation: Safety and efficacy in pregnancy

[Gloria Formoso](#)<sup>1</sup>, [Maria P.A. Baldassarre](#)<sup>1</sup>, [Federica Ginestra](#)<sup>1</sup>, [Maria Assunta Carlucci](#)<sup>1</sup>, [Ines Bucci](#)<sup>1</sup> and [Agostino Consoli](#)<sup>1</sup>

ANNALS OF CLINICAL PSYCHIATRY 2013;11(4):16

RESEARCH ARTICLE

## A prenatal supplement with methylfolate for the treatment and prevention of depression in women trying to conceive and during pregnancy

Marlene P. Freeman, MD  
Gina M. Sorella, BS  
Taylor R. Church, BS  
Lina Góez-Mogollón, MD, MSc  
Alexandra Z. Spornsky, BS  
Olivia B. Noe, BS  
Anjali Kaimal, MD, MAS  
Lee S. Cohen, MD

**BACKGROUND:** Women often seek antidepressant alternatives for major depressive disorder (MDD) in anticipation of or during pregnancy. In this preliminary study, EnBrace HR, a prenatal supplement containing methylfolate, was investigated for depressive relapse prevention and for acute treatment of MDD in women planning pregnancy or during pregnancy.



Cochrane Database of Systematic Reviews

## Omega-3 fatty acid addition during pregnancy (Review)

Middleton P, Gomersall JC, Gould JF, Shepherd E, Olsen SF, Makrides M

# Non-biological options for managing mood/anxiety in pregnancy

- CBT-I
- Physical activity

[Obstet Gynecol.](#) 2019 May; 133(5): 911–919.

PMCID: PMC6485299

Published online 2019 Apr 9. doi: [10.1097/AOG.00000000000003216](https://doi.org/10.1097/AOG.00000000000003216)

PMID: [30969203](https://pubmed.ncbi.nlm.nih.gov/30969203/)

## Cognitive Behavioral Therapy for Prenatal Insomnia A Randomized Controlled Trial

[Rachel Manber](#), PhD,<sup>✉</sup> [Bei Bei](#), DPsych, PhD, [Norah Simpson](#), PhD, [Lauren Asarnow](#), PhD, [Elizabeth Rangel](#), BA, [Anita Sit](#), MD, and [Deirdre Lyell](#), MD

## Exercise During Pregnancy Attenuates Prenatal Depression: A Randomized Controlled Trial

[M. Perales](#), [I. Refoyo](#), [J. Coteron](#), [M. Bacchi](#), [R. Barakat](#)

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First Published May 28, 2014 | Research Article |  Check for updates

<https://doi.org/10.1177/0163278714533566>



Questions?  
Case  
comments?