MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Psychiatric Disorders in Women:

Diagnostic and Treatment Considerations Across the Female Lifespan

THURSDAY, OCTOBER 22, 2020

COURSE DIRECTORS:

Lee Cohen, MD

Marlene Freeman, MD

44TH ANNUAL PSYCHOPHARMACOLOGY CONFERENCE

LIVE STREAM CONFERENCE

THURSDAY – SUNDAY, OCTOBER 22-25, 2020

PRESENTED BY

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Psychiatric Disorders in Women: Diagnostic and Treatment Considerations Across the Female Lifespan

Thursday, October 22, 2020 • Virtual

WELCOME

On behalf of the entire Massachusetts General Hospital Department of Psychiatry, we are proud to welcome you to our *Psychiatric Disorders in Women: Diagnostic and Treatment Considerations Across the Female Lifespan*.

Thank you for joining us this year.

TARGET AUDIENCE

The target audience for this event is Psychiatrists, Psychologists, Nurse Practitioners, Primary Care Physicians, OB-GYN's, Midwives, and Social Workers.

EVALUATION FORMS/CME/CEU CERTIFICATES

Every participant needs to complete the activity evaluation online to claim CME/CEU credits for this course. Please refer to the **Evaluation and CME Information** document in this syllabus for more information. We strongly encourage you to complete the evaluation, even if you do not require a certificate. Your comments are important to us as we plan future programs. The link to claim credit is as follows: **www.mghcme.org/womensmentalhealth**

QUESTIONS

Opportunity for questions will be provided at the end of each module during the panel discussion. Please write your questions in the chat box on Zoom. Experience has shown that this method is preferable to that of spontaneous questions.

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CONTACT INFORMATION

For questions or comments, please contact MGH Psychiatry Academy member services at 866-644-7792 or mghcme@mgh.harvard.edu.

LEARNING OBJECTIVES

At the end of this educational activity, participants should be able to:

- Assess reproductive safety of psychiatric medication during pregnancy
- Distinguish normal physical, hormonal and emotional changes at menopause from pathophysiologic conditions occurring during the menopausal transition
- Discuss diagnosis, etiology, and treatment of co-occurring PTSD and SUD in women
- Describe best treatment modalities for co-occurring PTSD and SUD in women
- Describe the pharmacologic and non-pharmacologic treatment options available to their patients with ADHD during pregnancy and lactation
- Describe the pathophysiology and treatment of PMDD.

ACCREDITATION

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of McLean Hospital and Massachusetts General Hospital. McLean Hospital is accredited by the ACCME to provide continuing medical education for physicians.

McLean Hospital designates this live activity for a maximum of ***6.25 AMA PRA Category 1 Credits™***. Physicians should only claim credit commensurate with the extent of their participation in the activity.

PSYCHOLOGISTS

The Massachusetts General Hospital Department of Psychiatry is approved by the American Psychological Association to sponsor continuing education (CE) for psychologists. The Massachusetts General Hospital Department of Psychiatry maintains responsibility for this program and its content. This offering meets the criteria for ***6.25*** Continuing Education (CE) credits for psychologists.

REGISTERED NURSES

This program meets the requirements of the Massachusetts Board of Registration in Nursing (244 CMR 5.00) for ***6.25*** contact hours of nursing continuing education credit. Advance practice nurses, please note: Educational activities which meet the requirements of the ACCME (such as this activity) count towards 50% of the nursing requirement for ANCC accreditation.

SOCIAL WORKERS

The Collaborative of NASW, Boston College, and Simmons College Schools of Social Work authorizes social work continuing education credits for courses, workshops, and educational programs that meet the criteria outlined in 258 CMR of the Massachusetts Board of Registration of Social Workers.

This program has been approved for **6** Social Work Continuing Education hours for relicensure, in accordance with 258 CMR. Collaborative of NASW and the Boston College and Simmons Schools of Social Work Authorization Number D 81572.

Other CE Licenses: Other Providers can claim a Participation Certificate upon successful completion of this course. Participation Certificates will specify the title, location, type of activity, date of activity, and number of *AMA PRA Category 1 Credits*™ associated with the activity. Providers should check with their regulatory agencies to determine ways in which *AMA PRA Category 1 Credits*™ may or may not fulfill continuing education requirements. Providers should also consider saving copies of brochures, agenda, and other supporting documents.

PROGRAM AGENDA

THURSDAY, OCTOBER 22, 2020

8:00-8:15 AM	**Welcome & Introduction** Marlene Freeman, MD, Lee Cohen, MD
8:15-8:45 AM	**Major Depressive Disorder in Pregnancy and the Postpartum** Lee S. Cohen, MD
8:45-9:15 AM	**Bipolar Disorder: Considerations Across the Reproductive Lifespan** Marlene P. Freeman, MD
9:15-10:00 AM	**Question & Answer** Lee S. Cohen, MD, Marlene P. Freeman, MD
10:00-10:15 AM	**Break**
10:15-10:45 AM	**PMDD** Laura Petrillo, MD
10:45-11:15 AM	**The Menopausal Transition and Depression** Ruta Nonacs, MD, PhD
11:15-12:00 PM	**Question & Answer** Laura Petrillo, MD, Ruta Nonacs, MD, PhD
12:00-1:00 PM	**Break**
1:00-1:30 PM	**Substance Use Disorders and Posttraumatic Stress Disorder in Women of Reproductive Age** Edwin Raffi, MD, MPH
1:30-2:00 PM	**ADHD in Women** Allison Baker, MD
2:00-2:30 PM	**Psychotherapies for Perinatal Psychiatry** Rachel Vanderkruik, PhD, MSc
2:30-3:15 PM	**Question & Answer** Edwin Raffi, MD, MPH; Allison Baker, MD, Rachel Vanderkruik, PhD, MSc
3:15-3:30 PM	**Conclusion & Closing Remarks** Lee S. Cohen, MD, Marlene P. Freeman, MD

FACULTY

PLANNERS & COURSE DIRECTORS

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Harvard Medical School

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Medical Director, CTNI
Abra Prentice Foundation Chair in Women's Mental Health

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Department of Psychiatry
Executive Director, Massachusetts General Hospital
Psychiatry Academy
Massachusetts General Hospital

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Assistant Professor of Psychology
Harvard Medical School

SPEAKERS

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Rachel C. Vanderkruik, PhD, MSc
Massachusetts General Hospital

FACULTY DISCLOSURE STATEMENTS

FACULTY DISCLOSURE STATEMENTS

In accord with the disclosure policy of McLean Hospital as well as guidelines set forth by the Accreditation Council on Continuing Medical Education, all people in control of educational content, including speakers, course directors, planners, and reviewers, have been asked to disclose all relevant financial relationships with commercial interests of both themselves and their spouses/partners over the past 12 months, as defined below:

Commercial Interest

The ACCME defines a "commercial interest" as any entity producing, marketing, re-selling, or distributing health care goods or services, used on, or consumed by, patients. The ACCME does not consider providers of clinical service directly to patients to be commercial interests. For more information, visit www.accme.org.

Financial relationships

Financial relationships are those relationships in which the individual benefits by receiving a salary, royalty, intellectual property rights, consulting fee, honoraria, ownership interest (e.g., stocks, stock options or other ownership interest, excluding diversified mutual funds), or other financial benefit. Financial benefits are usually associated with roles such as employment, management position, independent contractor (including contracted research), consulting, speaking and teaching, membership on advisory committees or review panels, board membership, and other activities from which remuneration is received, or expected. ACCME considers relationships of the person involved in the CME activity to include financial relationships of a spouse or partner.

Relevant financial relationships

ACCME focuses on financial relationships with commercial interests in the 12-month period preceding the time that the individual is being asked to assume a role controlling content of the CME activity. ACCME has not set a minimal dollar amount for relationships to be significant. Inherent in any amount is the incentive to maintain or increase the value of the relationship. The ACCME defines "'relevant' financial relationships" as financial relationships in any amount occurring within the past 12 months that create a conflict of interest.

Conflict of Interest

Circumstances create a conflict of interest when an individual has an opportunity to affect CME content about products or services of a commercial interest with which he/she has a financial relationship.

The following planners, speakers, and content reviewers, on behalf of themselves and their spouse or partner, have reported financial relationships with an entity producing, marketing, re-selling, or distributing health care goods or services (relevant to the content of this activity) consumed by, or used on, patients:

NAME	COMPANY	RELATIONSHIP
Lee S. Cohen, PhD	National Pregnancy Registry for Atypical Antipsychotics, Alkermes Biopharmaceuticals; Forest/Actavis Pharmaceuticals; Otsuka Pharmaceuticals; Sunovion Pharmaceuticals, Inc.; Teva Pharmaceuticals	Research Support/ PI
	Brain & Behavior Research Foundation; JayMac Pharmaceuticals; National Institute on Aging; National Institutes of Health; SAGE Therapeutics	Other Research Support, PI/Co-investigator
	Alkermes Biopharmaceuticals; Praxis Precision Medicines, Inc.	Advisory/Consulting (through MGH Clinical Trials Network Initiative)

NAME	COMPANY	RELATIONSHIP
Marlene P. Freeman, MD	JayMac, Sage; Advisory boards: Otsuka, Alkermes, Sunovion;	Investigator Initiated Trials / Research:
	Janssen (Johnson& Johnson); Steering Committee for Educational Activities: Medscape.	Independent Data Safety and Monitoring Committee:
	Dr. Freeman is an employee of Massachusetts General Hospital, and works with the MGH National Pregnancy Registry [Current Registry Sponsors: Teva (2018- present), Alkermes, Inc. (2016-Present); Otsuka America Pharmaceutical, Inc. (2008-Present); Forest/Actavis (2016-Present), Sunovion Pharmaceuticals, Inc. (2011-Present)].	
	As an employee of MGH, Dr. Freeman works with the MGH CTNI, which has had research funding from multiple pharmaceutical companies and NIMH.	

All other individuals including course directors, planners, reviewers, faculty, staff, etc., who are in a position to control the content of this educational activity have, on behalf of themselves and their spouse or partner, reported no financial relationships related to the content of this activity.

PLEASE NOTE THAT THIS IS NOT THE OFFICIAL PROGRAM EVALUATION

Psychopharmacology 2020

Use this page to take notes on the speakers for their presentations.

Evaluations will be available for completion online at www.mghcme.org/psychopharm2020

Rating scale: **1** = Strongly Disagree, **2** = Disagree, **3** = Agree, **4** = Strongly Agree.

Talk Time and Speaker	Rating	Notes

The quality of the following presentations met or exceeded my expectations:

THURSDAY, OCTOBER 22, 2020

4:00 – 8:00 PM—Psychosomatic Medicine 1 2 3 4

4:00 – 8:00 PM—Law & Psychiatry 1 2 3 4

4:00 – 8:00 PM—Neuroscience Revolution 1 2 3 4

FRIDAY, OCTOBER 23, 2020

8:15 – 8:30 AM Introduction and Overview 1 2 3 4

Module Topic – Mood Disorders

8:30 – 9:15 AM—Andrew A. Nierenberg, MD 1 2 3 4

9:15 – 10:00 AM—Roy H. Perlis, MD, MSc 1 2 3 4

10:15 – 11:00 AM—Maurizio Fava, MD 1 2 3 4

11:00 – 12:00 PM—Panel Discussion 1 2 3 4

Module Topic – Anxiety/PTSD

1:00 – 1:45 PM—Eric Bui, MD, PhD, Luana Marques, PhD 1 2 3 4

1:45 – 2:30 PM—Jerrold Rosenbaum, MD 1 2 3 4

2:30 – 3:15 PM—Panel Discussion 1 2 3 4

Module Topic-Women's Health

3:30 – 4:10 PM—Lee S. Cohen, MD 1 2 3 4

4:10 – 4:40 PM—Marlene P. Freeman, MD 1 2 3 4

4:40 – 5:30 PM—Panel Discussion 1 2 3 4

Friday Evening Seminars:

6:30 – 8:30 PM-Pre-recorded

David Mischoulon, MD, PhD 1 2 3 4

Theodore A. Stern, MD 1 2 3 4

Jodi Gilman, PhD 1 2 3 4

John W. Winkelman, MD, PhD 1 2 3 4

Jacqueline Clauss, MD, PhD 1 2 3 4

Michael W. Otto, PhD 1 2 3 4

Franklin King, PhD 1 2 3 4

SATURDAY, OCTOBER 24, 2020

8:00 – 8:15 AM— Welcoming Remarks 1 2 3 4

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Module Topic – Psychosis

8:15 – 9:00 AM—Oliver Freudenreich, MD, FACLP 1 2 3 4

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9:00 – 9:45 AM—Oliver Freudenreich, MD, FACLP 1 2 3 4

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Module Topic-Ketamine & Esketamine

10:00 – 10:45 AM—Cristina Cusin, MD 1 2 3 4

_____

10:45 – 11:45 AM—Panel Discussion 1 2 3 4

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Module Topic – New Therapies: What is on the Horizon?

1:00 – 1:45 PM—Joan Camprodon, MD, PhD 1 2 3 4

_____

1:45 – 2:30 PM—Oliver Freudenreich, MD, FACLP 1 2 3 4

_____

2:45 – 3:30 PM—Michael E. Henry, MD 1 2 3 4

_____

3:30 – 4:15 PM—John F. Kelly, PhD 1 2 3 4

_____

4:15 – 5:15 PM—Panel Discussion 1 2 3 4

_____

Saturday Evening Seminars:

6:30 – 7:30 PM-Pre-recorded: Ronald Schouten, MD, JD, Lieutenant Fred Cabral 1 2 3 4

_____

Feyza E. Marouf, MD 1 2 3 4

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Kaloyan S. Tanev, MD 1 2 3 4

_____

David H. Rubin, MD 1 2 3 4

_____

Laura Petrillo, MD 1 2 3 4

_____

SUNDAY, OCTOBER 25, 2020

7:45 – 8:00 AM—Welcoming Remarks 1 2 3 4

_____

Module Topic – Addiction

8:00 – 8:45 AM— Vinod Rao, MD, PhD 1 2 3 4

_____

8:45 – 9:30 AM—A. Eden Evins, MD, MPH 1 2 3 4

_____

9:30 – 10:00 AM—Panel Discussion 1 2 3 4

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Module Topic – OCD

10:15 – 10:55 AM—Michael A Jenike, MD 1 2 3 4

_____

10:55 – 11:35 AM—Lisa M. Zakhary, MD, PhD 1 2 3 4

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11:35 – 12:15 PM—Sabine Wilhelm, PhD 1 2 3 4

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12:15 – 12:45 PM —Panel Discussion 1 2 3 4

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Module Topic – Across the Lifespan

1:45 – 2:30 PM—Janet Wozniak, MD 1 2 3 4

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2:30 – 3:15 PM—Joseph Biederman, MD 1 2 3 4

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3:30 – 4:15 PM—Jonathan E. Alpert, MD, PhD 1 2 3 4

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4:15 – 4:45 PM—Panel Discussion 1 2 3 4

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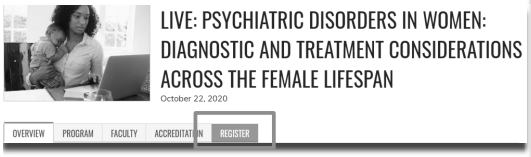
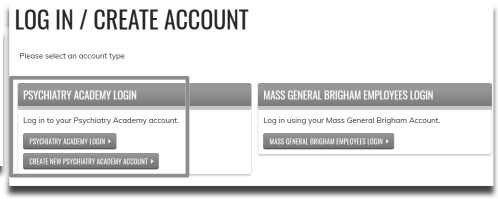
Complete the course evaluation online at www.mghcme.org/psychopharm2020

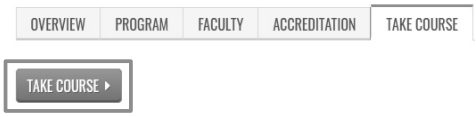
Three Steps to Claiming your CME Credit for attending Psychiatric Disorders in Women ONLY

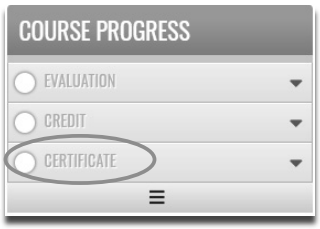


1: Visit **mghcme.org/womensmentalhealth** and click on the blue '**Register**' button.



2: Enter your '**Academy Login**' **username** and **password** then click the '**Login**' button.
If you have forgotten your password, please click the '**Forgot Visitor Password**' button. Once logged in, click Take Course**.**

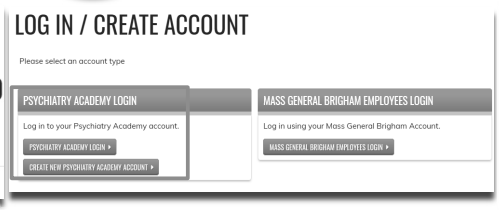




3: Click on the '**Evaluation**' button. Once you have completed your evaluation, and attested to the number of sessions you attended, your certificate will be generated. You should claim only the credit commensurate with the extent of your participation in the activity. Complete the evaluation and claim your credit by: **November 24, 2020**.

Three Steps to Claiming your CME Credit for attending the *BUNDLED* Psychiatric Disorders in Women and Psychopharmacology

1: Visit **mghcme.org/psychopharm2020** and click on the blue '**Register**' button.



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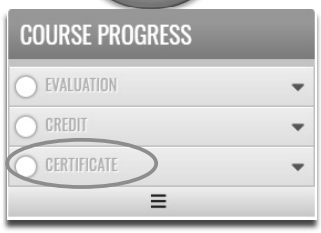

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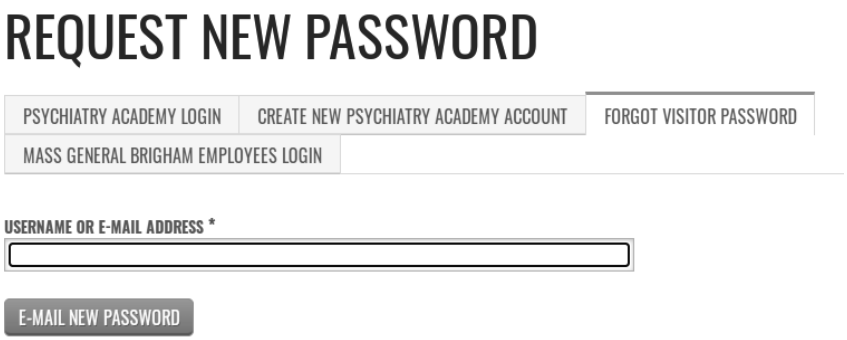
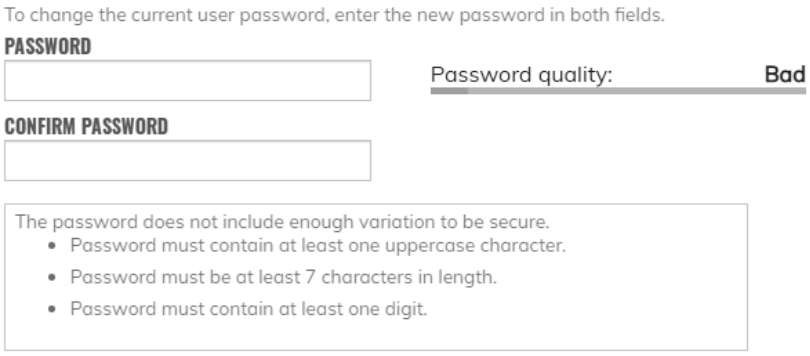
How to Reset Your Password...

Please visit **https://lms.mghcme.org/user/password** and enter the email address that you used to set up your account. Click “Email New Password” for a password reset link to be sent to your registered email address.



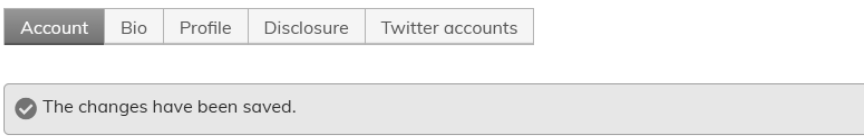
You will receive an email from the Psychiatry Academy (mghcme@mgh.harvard.edu) with instructions to reset your password. If you do not receive an email within a few minutes, please check your **Spam/Junk Mail** folder.

You will receive a one-time sign in link to reset your password. Click the link, and you will be prompted to reset your password by entering your new, desired password twice.



After entering your new password, click “Save” at the bottom of the screen:

If you receive this message, your password has been reset.



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CONTACT: SHAUNA FUTCH
(617) 620-3063
sfutch@mgh.harvard.edu

Welcome & Introduction

NOTES

Major Depressive Disorder in Pregnancy and the Postpartum

Lee S. Cohen, MD

MGHCME.org

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Course and Treatment of Depression during Pregnancy and the Postpartum Period : Lessons Learned Across Two Decades

Lee S. Cohen, MD
Director, Ammon-Pinizzotto Center for Women's Mental Health
Massachusetts General Hospital
Edmund and Carroll Carpenter Professor of Psychiatry
Harvard Medical School

Reproductive Psychiatry and the COVID-19 Pandemic

- Family planning and the pandemic
- Telemedicine and implications for pregnancy and postpartum period
- Infertility treatment and the pandemic
- Perinatal anxiety during the COVID 19 crisis
- Importance of euthymia during pregnancy
- Reframing postpartum experience

JAMA Psychiatry. Published online July 15, 2020. doi:10.1001/jamapsychiatry.2020.1947
https://womensmentalhealth.org/obgyn/reproductive-psychiatry-during-the-covid-19-pandemic/

Virtual Rounds at CWMH during COVID : Wednesdays at 2 PM

‹ Previous Next ›

Resource: Join us for Virtual Rounds at the Center for Women's Mental Health on Wednesdays

By MGH Center for Women's Mental Health | April 3rd, 2020 | Resources | 0 Comments

As our faculty at the Center for Women's Mental Health (CWMH) have gone fully remote with respect to clinical and research activity, we have managed to stay connected these last three weeks with "virtual rounds". For over 25 years, our group has met on Wednesdays at midday to discuss clinical cases we have seen across the week and also to discuss recently published papers in reproductive psychiatry. We look forward to Wednesdays as we get to talk about how we think about treatment options with respect to presented cases and the decisions patients make about treatment before, during, and after pregnancy. Particular attention is given to the safest use of psychiatric medications during pregnancy, the postpartum period and lactation. Three decades after founding the Center, I still love Wednesday rounds and always learn something by listening to cases and hearing how my colleagues think about perinatal psychiatric disorders. We are continuing to round during the COVID19 epidemic and Zoom proves to be the next best thing to being there.

https://womensmentalhealth.org/posts/resource-join-us-for-virtual-rounds-at-the-center-for-womens-mental-health-on-wednesdays/

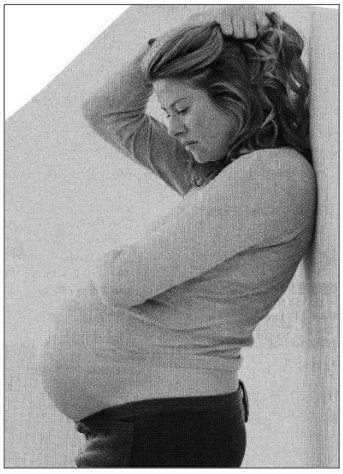
Treatment considerations for women with MDD in pregnancy and the postpartum period

- Depression during pregnancy is strongest predictor of postpartum depression
- **Nothing is more important maternal euthymia**

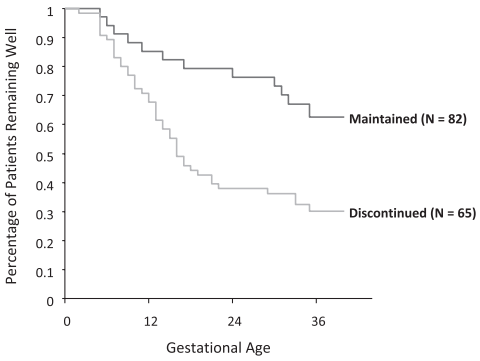
Major Depression During Pregnancy

Are pregnant women protected against relapse or new onset of major depression?

O'Hara et al. *J Abnorm Psychol.* 1990
Evans et al. *BMJ.* 2001
Yonkers et al. *Epidemiology* 2011
Roca et al. *J Affective Disorders* 2013

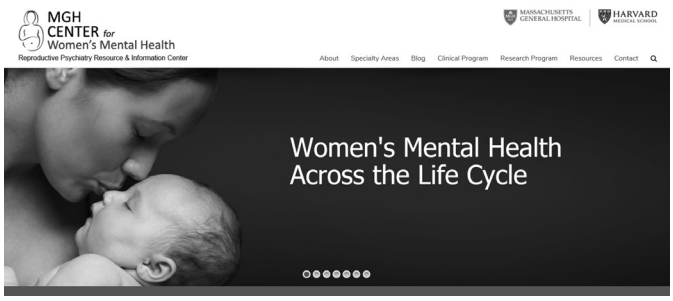


Time to Relapse in Patients Who Maintained or Discontinued Antidepressant



Cohen LS, et al. *JAMA*. 2006

Womensmentalhealth.org



Psychotropic Drug Use in Pregnancy

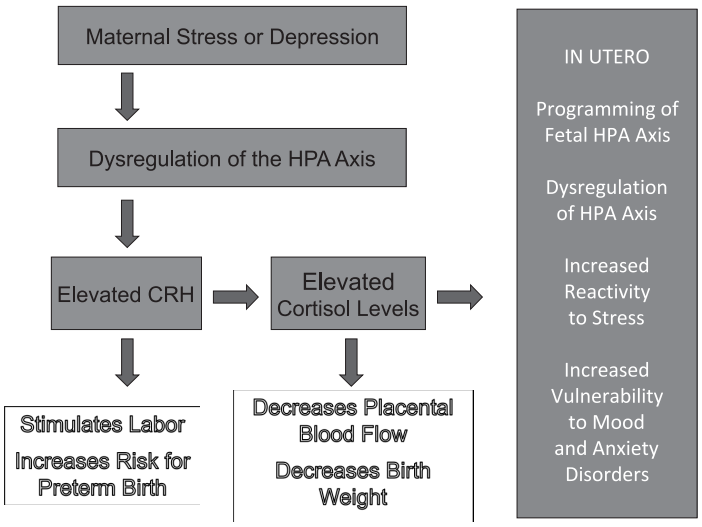
- Medications used when risk to mother and fetus from disorder outweighs risks of pharmacotherapy
- Optimum risk/benefit decision for psychiatrically ill pregnant women
- Patients with similar illness histories make different decisions regarding treatment during pregnancy
- No decision is risk-free
- Collaborative, patient-centered approach required

Henshaw *Fam Plann Perspect*. 1998

Treatment of Depression During Pregnancy:
Lessons Learned and New Directions

- Focus of concern regarding known and unknown risks of fetal exposure to psychiatric medications is increasingly balanced by data supporting risk of exposure to ***disorder, stress and HPA-axis dysregulation on fetoplacental unit***

- **Enhanced appreciation for impact of disorder and chronic stress on long term behavioral outcomes**




Research

Original Investigation | META-ANALYSIS

Neonatal Outcomes in Women With Untreated Antenatal Depression Compared With Women Without Depression
A Systematic Review and Meta-analysis

Alexander Jarde, PhD; Michelle Morais, MD; Dawn Kingston, PhD; Rebecca Giallo, PhD; Glenda M. MacQueen, MD; Lucy Giglia, MD; Joseph Beyene, PhD; Yi Wang, BHSc; Sarah D. McDonald, MD

JAMA Psychiatry. doi:10.1001/jamapsychiatry.2016.0934
Published online June 8, 2016.

What is the Safest Antidepressant for Women of Childbearing Age?

Phasing Out: FDA Pregnancy Categories

- **Category A:**
  - Well controlled studies in human pregnancy show no increased risk to the fetus
- **Category B:**
  - Animal studies show no increased risk to the fetus OR
  - Animal studies show an increased risk to the fetus but well controlled human studies do not.
- **Category C:**
  - Animal studies show an increased risk to the fetus and there are no well controlled studies in human pregnancy OR
  - There aren't any animal studies or well controlled human studies.

http://womensmentalhealth.org/posts/fda-finalizes-guidelines-pregnancy-lactation-labeling-information/

Timeline to Changes in Product Labeling

	NDAs, BLA, ESs	Required Submission Date of PLLR Format
New Applications	Submitted on or after 6/30/2015	At time of submission
------------------------------ PLLR Implementation Date (6/30/2015) ------------------------------		
Older Approved Applications	Approved 6/30/2001 to 6/29/2002 Approved 6/30/2005 to 6/29/2007	6/30/2018
	Approved 6/30/2007 to 6/29/2015 Or pending on 6/30/2015	6/30/2019
	Approved 6/30/2002 to 6/29/2005	6/30/2020
	For applications approved prior to 6/30/2001 in old format labeling	Not required to be in PLLR format. However, must remove Pregnancy Category by 6/29/2018

SSRI Use During Pregnancy

- Recent findings and more data inform the pharmacologic treatment of depression during pregnancy
  - Consistent conclusions that the *absolute* risk of SSRI exposure in pregnancy is small[1-3]
  - Consistent pattern of malformations with SSRI exposure is lacking
  - Case-control studies reveal inconsistent data regarding teratogenic risk of individual SSRIs[4-9]

Reproductive safety data on SSRIs exceed what is known about most other medicines used in pregnancy

[1] Louik C et al. *N Engl J Med* 2007; [2] Einarson TR, Einarson A. *Pharmacoepidemiol Drug Saf* 2005; [3] Einarson A, et al. *Am J Psychiatry* 2008; [4] Alwan S, et al. *N Engl J Med* 2007; [5] Greene MF. *N Engl J Med* 2007; [6] Hallberg P, Sjoblom V. *J Clin Psychopharmacol* 2005; [7]Wogelius P, et al. *Epidemiology* 2006; [8] www.gsk.ca/english/docs-pdf/PAXIL_PregnancyDHCPL_E-V4.pdf Dear Healthcare Professional (3/17/08); [9] www.fda.gov/medwatch/safety/2005/Paxil_dearhcp_letter.pdf Dear Healthcare Professional (3/17/08); Grigoriadis et al. *J Clin Psychiatry* 2013.

JAMA Psychiatry

Research

JAMA Psychiatry | Original Investigation

Maternal Use of Specific Antidepressant Medications During Early Pregnancy and the Risk of Selected Birth Defects

Kayla N. Anderson, PhD; Jennifer N. Lind, PharmD, MPH; Regina M. Simeone, MPH; William V. Bobo, MD, MPH; Allen A. Mitchell, MD; Tiffany Riehle-Colarusso, MD, MPH; Kara N. Polen, MPH; Jennita Reefhuis, PhD

IMPORTANCE Antidepressants are commonly used during pregnancy, but limited information is available about individual antidepressants and specific birth defect risks.

OBJECTIVE To examine associations between individual antidepressants and specific birth defects with and without attempts to partially account for potential confounding by underlying conditions.

DESIGN, SETTING, AND PARTICIPANTS The population-based, multicenter case-control National Birth Defects Prevention Study (October 1997–December 2011) included cases with selected birth defects who were identified from surveillance systems; controls were randomly sampled live-born infants without major birth defects. Mothers of cases and controls participated in an interview after the expected delivery date. The data were analyzed after the completion of the National Birth Defects Prevent Study's data collection.

EXPOSURES Self-reported antidepressant exposure was coded to indicate monotherapy exposure to antidepressants.

MAIN OUTCOMES AND MEASURES We used multivariable logistic regression to calculate adjusted odds ratios (aORs) and 95% confidence intervals for associations between maternal antidepressant use and birth defects. We compared early pregnancy antidepressant-exposed women with those without antidepressant exposure and, to partially account for confounding by underlying maternal conditions, those exposed to antidepressants outside of the birth defect development critical period.

Editorial

Supplemental c

EDITORIAL

The Association Between Antidepressant Exposure and Birth Defects—Are We There Yet?

Katherine L. Wisner, MD, MS; Tim F. Oberlander, MD, FRCPC; Krista F. Huybrechts, MS, PhD

Few moments are more concerning to parents than learning that their infant has a birth defect. Compounding this news is the possibility that the medication used to manage the mother's mood disorder may have increased the risk for her infant developing a birth defect. As health care professionals, we have an enormous obligation to get the science right. In 2007, an editorial was published in response to 2 large case-control studies, "Teratogenicity of SSRIs: Serious Concern or Much Ado about Little?"[1] What have we learned over the ensuing 13 years?

Related article

Anderson et al[2] aimed to determine which antidepressants are associated with birth defects. They state, "such analyses can support work to identify medications with the highest and lowest birth defect risks independent of the underlying condition."[2] This statement implies that the broad adverse effects of psychiatric illness can be distinguished from the effect of medications on the risk for birth defects, a formidable challenge in observational research.

Data from the National Birth Defects Prevention Study were used to compare the risks of congenital malformations in women exposed in early pregnancy to 2 reference groups: (1) unexposed women and (2) women treated with antidepressants 2 to 3 months before and/or after embryogenesis (months 4-9). The second group was included to account for confounding by indication, the major challenge plaguing observational studies. However, the National Birth Defects Prevention Study data set does not include psychiatric diag-

able is unlikely to change the effect estimate by at least 10%, several variables together might. Other principled approaches to confounder selection have been recommended over data-driven statistical methods.[4] Selective serotonin reuptake inhibitor exposure may be a proxy for unidentified environmental and/or genetic factors associated with maternal mental illness that are associated with birth defects. The absence of information on characteristics, such as socioeconomic disadvantage, toxin exposures, and substance use that often accompany poor mental health, renders the results challenging to interpret owing to concern about residual confounding.

The second comparison focused on women exposed to antidepressants during the first trimester vs exposed outside of the first trimester. The validity of this comparison depends on equivalence of the groups relative to the severity and functional sequelae of the underlying psychiatric disorder. Using the same 10% change-in-estimate approach, the authors adjusted only for maternal education. The set of characteristics presented in Table 2 are helpful but insufficient to demonstrate their comparability with respect to the psychiatric disorder, comorbid conditions (eg, diabetes and/or hypertension), or concomitant drug exposures (eg, anticonvulsants and/or antimanic agents) that may be associated with increased risk for fetal malformations. The authors highlighted the results for the serotonin-norepinephrine reuptake inhibitor venlafaxine, which is not a first-line drug for pregnant women, as indicated by the relatively low frequency of use

Read our blog post on this topic: https://womensmentalhealth.org/posts/antidepressant-birth-defects/

Anderson KN, Lind JN, Simeone RM, Bobo WV, Mitchell AA, Riehle-Colarusso T, Polen KN, Reefhuis J. Maternal Use of Specific Antidepressant Medications During Early Pregnancy and the Risk of Selected Birth Defects. JAMA Psychiatry. 2020 Aug 5:e202453.
Huybrechts KF, Palmsten K, Avorn J, Cohen LS, Holmes LB, Franklin JM, Mogun H, Levin R, Kowal M, Setoguchi S, Hernández-Díaz S. Antidepressant use in pregnancy and the risk of cardiac defects. N Engl J Med. 2014 Jun 19;370(25):2397-407.
Wisner KL, Oberlander TF, Huybrechts KF. The Association Between Antidepressant Exposure and Birth Defects-Are We There Yet? JAMA Psychiatry. 2020 Aug 5.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

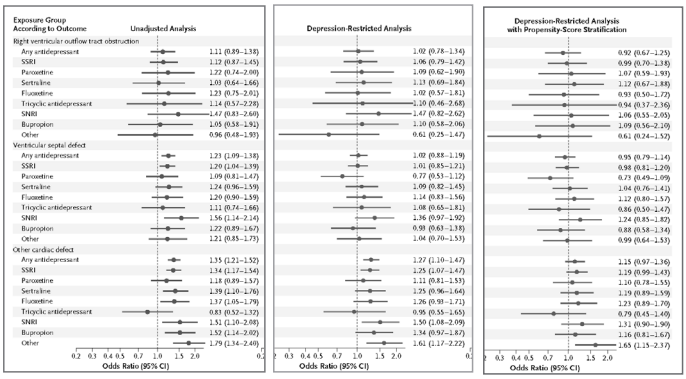
Antidepressant Use in Pregnancy and the Risk of Cardiac Defects

Krista F. Huybrechts, Ph.D., Kristin Palmsten, Sc.D., Jerry Avorn, M.D., Lee S. Cohen, M.D., Lewis B. Holmes, M.D., Jessica M. Franklin, Ph.D., Helen Mogun, M.S., Raisa Levin, M.S., Mary Kowal, B.A., Soko Setoguchi, M.D., Dr.P.H., and Sonia Hernández-Díaz, M.D., Dr.P.H.

N ENGL J MED 370;25 NEJM.ORG JUNE 19, 2014

- No evidence of increased risk for major malformations or cardiovascular malformations in children of pregnant women exposed to SSRIs

Cardiovascular Malformation and Fetal SSRI Exposure



Huybrechts et al. *NEJM* 2014.

"Poor Neonatal Adaptation" and SSRI Use During Pregnancy

- **Consistent data**: Late trimester exposure to SSRIs is associated with *transient* irritability, agitation, jitteriness, and tachypnea (25-30%)
- Overall studies do not adequately control for maternal mental health condition, adequate blinding of exposure in neonatal assessments
- **Clinical implication: Should women be treated with antidepressants late in pregnancy and during labor and delivery (Warburton et al. 2010)**
- Are any subgroups of newborns vulnerable to enduring symptoms beyond the first days of life ?

Levinson-Castiel R, et al. *Arch Pediatr Adolesc Med.* 2006
Chambers CD, et al. *N Engl J Med.* 2006
Chambers, *BMJ*, 2009
CWMH Blog, July 27 2005: http://womensmentalhealth.org/posts/neonatal-symptoms-after-in-utero-exposure-to-ssris/

What are the Long-term Neurobehavioral Effects of Prenatal Exposure to an Antidepressant?

In Utero Antidepressants and Neurodevelopmental Outcomes in Kindergarteners

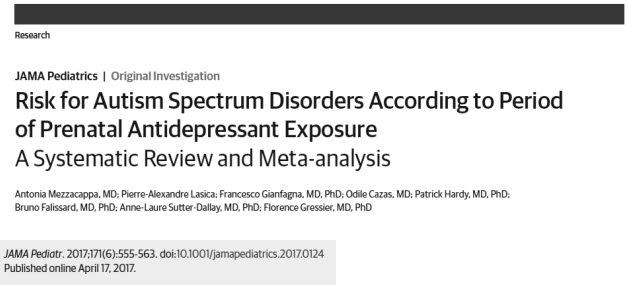
Neurodevelopmental Outcomes in Kindergartners with Prenatal Exposure to Antidepressants

By MGH Center for Women's Mental Health | June 2nd, 2020 | Antidepressants and Pregnancy, Child Development, Psychiatric Disorders During Pregnancy | 0 Comments

While we have data to support the use of antidepressants, including the selective serotonin reuptake inhibitors (SSRIs) and the serotonin norepinephrine reuptake inhibitors (SNRIs), during pregnancy, most studies have focused on risk of congenital malformations, and we have less information on longer term neurodevelopmental outcomes. In a recent study, Singal and colleagues look at neurodevelopmental outcomes in kindergartners with prenatal exposure to

Full blog post: https://womensmentalhealth.org/posts/antidepressants-neurodevelopment/

Singal D, Chateau D, Struck S, Lee JB, Dahl M, Derksen S, Katz LY, Ruth C, Hanlon-Dearman A, Brownell M. In Utero Antidepressants and Neurodevelopmental Outcomes in Kindergarteners. Pediatrics. 2020 May;145(5).
Andrade C. Genes as Unmeasured and Unknown Confounds in Studies of Neurodevelopmental Outcomes After Antidepressant Prescription During Pregnancy. J Clin Psychiatry. 2020 May 26;81(3):20f13463. Free Article
Rommel AS, Bergink V, Liu X, Munk-Olsen T, Mahmassar NM. Long-Term Effects of Intrauterine Exposure to Antidepressants on Physical, Neurodevelopmental, and Psychiatric Outcomes: A Systematic Review. J Clin Psychiatry. 2020 May 12;81(3):19r12965.
Andrade C. Offspring Outcomes in Studies of Antidepressant-Treated Pregnancies Depend on the Choice of Control Group. J Clin Psychiatry. 2017 Mar;78(3):e294–e297. Free Article



Research

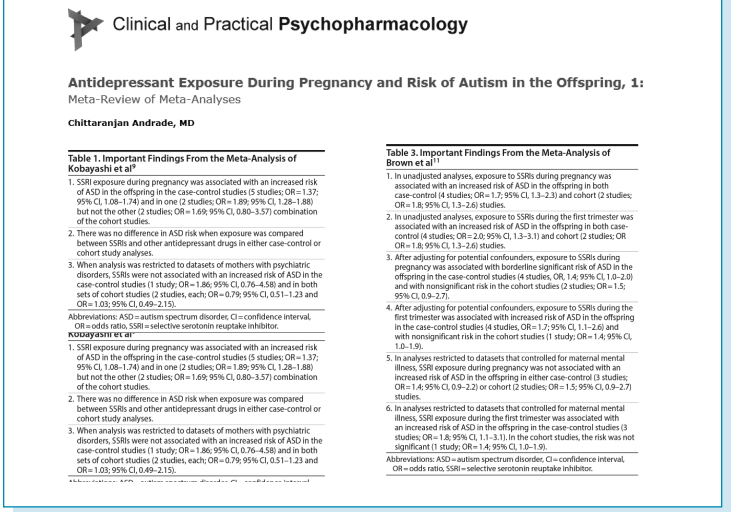
JAMA Pediatrics | Original Investigation

Risk for Autism Spectrum Disorders According to Period of Prenatal Antidepressant Exposure

A Systematic Review and Meta-analysis

Antonia Mezzacappa, MD; Pierre-Alexandre Lasica; Francesco Gianfagna, MD, PhD; Odile Cazas, MD; Patrick Hardy, MD, PhD; Bruno Falissard, MD, PhD; Anne-Laure Sutter-Dallay, MD, PhD; Florence Gressier, MD, PhD

JAMA Pediatr. 2017;171(6):555-563. doi:10.1001/jamapediatrics.2017.0124
Published online April 17, 2017.



Clinical and Practical **Psychopharmacology**

Antidepressant Exposure During Pregnancy and Risk of Autism in the Offspring, 1: Meta-Review of Meta-Analyses

Chittaranjan Andrade, MD

Table 1. Important Findings From the Meta-Analysis of Kobayashi et al[9]

1. SSRI exposure during pregnancy was associated with an increased risk of ASD in the offspring in the case–control studies (5 studies; OR = 1.37; 95% CI, 1.08–1.74) and in one (2 studies; OR = 1.89; 95% CI, 1.28–1.88) but not the other (2 studies; OR = 1.69; 95% CI, 0.80–3.57) combination of the cohort studies.
2. There was no difference in ASD risk when exposure was compared between SSRIs and other antidepressant drugs in either case-control or cohort study analyses.
3. When analysis was restricted to datasets of mothers with psychiatric disorders, SSRIs were not associated with an increased risk of ASD in the case-control studies (1 study; OR = 1.86; 95% CI, 0.76–4.58) and in both sets of cohort studies (2 studies, each; OR = 0.79; 95% CI, 0.51–1.23 and OR = 1.03; 95% CI, 0.49–2.15).

Abbreviations: ASD = autism spectrum disorder, CI = confidence interval, OR = odds ratio, SSRI = selective serotonin reuptake inhibitor.

Kobayashi et al:

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Table 3. Important Findings From the Meta-Analysis of Brown et al[11]

1. In unadjusted analyses, exposure to SSRIs during pregnancy was associated with an increased risk of ASD in the offspring in both case-control (4 studies; OR = 1.7; 95% CI, 1.3–2.3) and cohort (2 studies; OR = 1.8; 95% CI, 1.3–2.6) studies.
2. In unadjusted analyses, exposure to SSRIs during the first trimester was associated with an increased risk of ASD in the offspring in both case-control (4 studies; OR = 2.0; 95% CI, 1.3–3.1) and cohort (2 studies; OR OR = 1.8; 95% CI, 1.3–2.6) studies.
3. After adjusting for potential confounders, exposure to SSRIs during pregnancy was associated with borderline significant risk of ASD in the offspring in the case-control studies (4 studies, OR, 1.4; 95% CI, 1.0–2.0) and with nonsignificant risk in the cohort studies (2 studies; OR = 1.5; 95% CI, 0.9–2.7).
4. After adjusting for potential confounders, exposure to SSRIs during the first trimester was associated with increased risk of ASD in the offspring in the case-control studies (4 studies, OR = 1.7; 95% CI, 1.1–2.6) and with nonsignificant risk in the cohort studies (1 study; OR = 1.4; 95% CI, 1.0–1.9).
5. In analyses restricted to datasets that controlled for maternal mental illness, SSRI exposure during pregnancy was not associated with an increased risk of ASD in the offspring in either case-control (3 studies; OR = 1.4; 95% CI, 0.9–2.2) or cohort (2 studies; OR = 1.5; 95% CI, 0.9–2.7) studies.
6. In analyses restricted to datasets that controlled for maternal mental illness, SSRI exposure during the first trimester was associated with an increased risk of ASD in the offspring in the case-control studies (3 studies; OR = 1.8; 95% CI, 1.1–3.1). In the cohort studies, the risk was not significant (1 study; OR = 1.4; 95% CI, 1.0–1.9).

Abbreviations: ASD = autism spectrum disorder, CI = confidence interval, OR = odds ratio, SSRI = selective serotonin reuptake inhibitor.

Treatment Guidelines Depression : Does Severity Drive Treatment Recommendations (and Patient Choice)

- **Psychotherapy: First-line for mild to moderate MDD**
- Lifestyle components: Nutrition, weight management, prenatal care ; treatment for co-morbid substance abuse
- Evidence base for CBT , Behavioral Activation and MBCT (prevention)
- **Women trying to conceive who have histories of MDD:**
  - –Encourage period of euthymia
  - –Sustained remission: consider tapering and discontinuing ?
  - –More recently depressed or with symptoms: consider remaining on medication, optimizing medication
- **Pregnant women with severe MDD:** Medication is first-line
- **Pregnant women on antidepressants during pregnancy:** take into account patient preferences, previous course of illness
- Medication selection should be based on known safety information

MDD, major depressive disorder.
Yonkers KA et al. *Obstet Gynecol.* 2009;114(3):703-713.

Treatment of Depression During Pregnancy: Lessons Learned

- Treatment decisions are complex (maternal and fetal benefits and risks)
- Absolute quantification of risk associated with fetal exposure to medication or maternal disease is impossible
- No treatment decision is “perfect”

  - Each treatment decision should try to optimize pregnancy outcomes for the mother and her child

  - Consider the risks of untreated disease and the risks of medication treatment

  -wisdom of changing AD dose proximate to delivery is sparse

Kallen *Obstet Gynecol Int.* 2012
Palmsten and Hernandez-Diaz *Epidemiology* 2012

Summary of treatment considerations for women with MDD in pregnancy (cont.)

- Depression during pregnancy is strongest predictor of postpartum depression
- There are known and unknown risks associated with AD use during pregnancy
- Adverse effects of depression in pregnancy on patient, infant and families
- **Nothing trumps maternal euthymia**

Postpartum Depression (PPD)

- 10-15% of women experience PPD after delivery
- Similar to non-puerperal major depression
- Most common complication in modern obstetrics
- Impairment of functioning

Postpartum Depression: Non-Pharmacologic Strategies

- Maximize social supports – Postpartum Support International (https://www.postpartum.net/)
- Psychoeducation of patient and family members
- Group therapy and support groups
- Interpersonal therapy (IPT)
- Cognitive-behavioral therapy (CBT)
- Behavioral Activation – (BA)
- MBCT – relapse prevention ?

Cohen et al. *Psychiatr Clin North Am.* 2010; Perlstein et al. *Am J Obstet Gynecol* 2009; Appleby et al., 1997. https://www.postpartum.net/ ;

Antidepressant Trials for the Treatment of PPD

Study	Design and Size	Medication studied, result
Appleby et al., 1997	Placebo-controlled, N=87 CBT studied in same trial	Fluoxetine - superior to placebo
Yonkers et al, 2008	placebo controlled, N=70	Paroxetine - not superior to placebo)
Wisner et al., 2006	RCT, Setraline vs. Nortriptyline, N=109	Sertraline vs. Nortriptyline - no significant difference
Hantsoo et al., 2013	Placebo-controlled RCT, N=36	Setraline- superior to placebo
Bloch et al., 2012	N=40, all received brief psychodynamic therapy, RCT to sertraline or placebo	Both groups improved – no significant difference for sertraline vs. placebo
Sharp et al., 2010	RCT, AD selected by general practitioner or counseling, N=254	Antidepressants- superior to placebo
Misri et al., 2012	Open trial, N=15	Citalopram – open study
Misri et al., 2004	N=35, all received parox, half randomized to CBT also	Paroxetine – no control group
Stowe et al., 1995	Open-label; N=21	Sertraline – open study
Cohen et al., 1997	Open-label; N=19	Venlafaxine- open study
Suri et al., 2001	Open-label; N=6	Fluvoxamine - open
Nonacs et al., 2005	Open-label; N=8	Bupropion- open

Brexanolone

- FDA approval in 2019
- IV delivered analogue of allopregnanolone
- Allosteric modulator of GABA receptors
- Two positive, controlled trials in postpartum depression (onset during late pregnancy or postpartum, presented within six months postpartum with MDD)
- Rapid onset of benefit, durable efficacy to 30 days
- Implementation challenges: cost, in hospital

Meltzer-Brody et al., Lancet 2018; Wisner 2019, Cohen , 2019

SAGE 217 (Zuranolone)

- Neurosteroid with similar mechanism of action to brexanolone
- Data supporting efficacy in oral formulation for major depression mixed
- Studies underway for postpartum major depression

Deligiannidis et al , presented at annual meeting ASCP, Scottsdale , Arizona, June 2019

Postpartum Psychosis

Postpartum Psychosis

- 1 to 2 per 1000 pregnancies
- Rapid, dramatic onset within first 2 weeks
- **High risk of harm to self and infant**
- **Suspect Bipolar disorder**:
  - Underlying diagnosis: affective psychosis (bipolar disorder or schizoaffective disorder)
  - Family and genetic studies, index episode follow-up

Nonacs and Cohen, 1998; Jones & Craddock, 2001; Spinelli, AJP, April 2009

Postpartum Psychosis

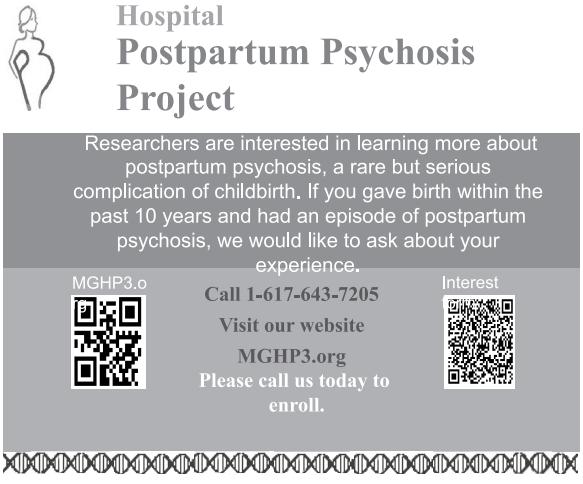
- Psychiatric emergency
- Estimated that 4% of women with postpartum psychosis commit infanticide
  - Actual rates of infanticide are difficult to estimate, as infanticide may be under-reported

- Spinelli, AJP 2004; Spinelli, AJP 2009

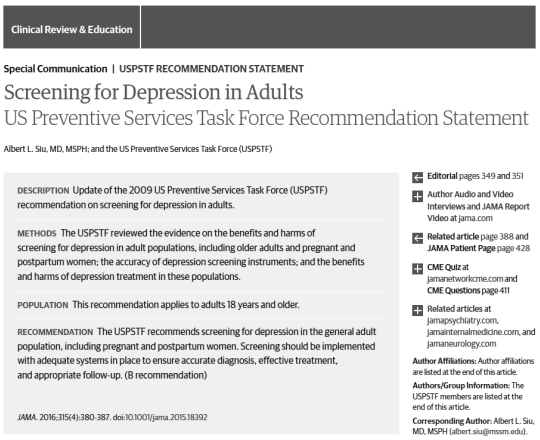
MGHP3 – The MGH Postpartum Psychosis Project

- **Specific aims:**
  - 1) Describe phenomenology of PPP with respect to time of onset, symptomology, and comorbidities
  - 2) Identify clinical and genomic predictors of this disorder

- **Eligibility:**
  - Women ages 18+
  - Experienced psychotic episode within 6 months of live birth, stillbirth, or intrauterine fetal demise
  - PPP episode occurred in the past 10 years
  - No prior diagnosis of schizophrenia, schizoaffective disorder, or psychosis NOS



Screening for Postpartum Depression



Clinical Review & Education

Special Communication | USPSTF RECOMMENDATION STATEMENT

Screening for Depression in Adults
US Preventive Services Task Force Recommendation Statement

Albert L. Siu, MD, MSPH; and the US Preventive Services Task Force (USPSTF)

DESCRIPTION Update of the 2009 US Preventive Services Task Force (USPSTF) recommendation on screening for depression in adults.

METHODS The USPSTF reviewed the evidence on the benefits and harms of screening for depression in adult populations, including older adults and pregnant and postpartum women; the accuracy of depression screening instruments; and the benefits and harms of depression treatment in these populations.

POPULATION This recommendation applies to adults 18 years and older.

RECOMMENDATION The USPSTF recommends screening for depression in the general adult population, including pregnant and postpartum women. Screening should be implemented with adequate systems in place to ensure accurate diagnosis, effective treatment, and appropriate follow-up. (B recommendation)

JAMA. 2016;315(4):380-387. doi:10.1001/jama.2015.18392

Editorial pages 349 and 351

Author Audio and Video Interviews and JAMA Report Video at jama.com

Related article page 388 and JAMA Patient Page page 428

CME Quiz at jamanetworkcme.com and CME Questions page 411

Related articles at jamapsychiatry.com, jamainternalmedicine.com, and jamaneurology.com

Author Affiliations: Author affiliations are listed at the end of this article.

Authors/Group Information: The USPSTF members are listed at the end of this article.

Corresponding Author: Albert L. Siu, MD, MSPH (albert.siu@mssm.edu).

PPD, Screening, and Large Scale Efforts

- Federal legislation includes provisions for postpartum depression
  - Language on screening for PPD and increased funding for its treatment and research
- Multiple states have implemented universal screening or are in the process of implementing screening
- Political impetus to screen for PPD

The Perinatal Depression Treatment Cascade:

Baby Steps Toward Improving Outcomes

Elizabeth Q. Cox, MD[a,*]; Nathaniel A. Sowa, MD, PhD[a]; Samantha E. Meltzer-Brody, MD, MPH[a]; and Bradley N. Gaynes, MD, MPH[a]

J Clin Psychiatry 2016

MGH Perinatal Depression Scale

It Takes A Village

Womensmentalhealth.org

Cohen et al. *Psychosomatics* 1989

Treatment Guidelines for Psychotropic Drug Use in Pregnancy

LEE S. COHEN, M.D.
VICKI L. HELLER, M.D.
JERROLD F. ROSENBAUM, M.D.

Despite the apparent risks of psychotropic drug exposure in pregnancy, many pregnant women receive psychotropics. The major concerns associated with the use of antipsychotics, antidepressants, benzodiazepines, and lithium carbonate in pregnancy are reviewed, with clinical approaches for assessing the relative risks and benefits of treatment of psychiatrically ill pregnant patients and for choosing and instituting therapy with these agents.

NOTES

NOTES

Bipolar Disorder: Considerations Across the Reproductive Lifespan

Marlene P. Freeman, MD

MGHCME.org

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Bipolar Disorders in Women

Marlene P. Freeman, M.D.
Abra Prentice Foundation Chair in Women's Mental Health
Professor of Psychiatry, Harvard Medical School
Associate Director, Perinatal & Reproductive Psychiatry Program,
Medical Director, Clinical Trials Network and Institute (CTNI)
Massachusetts General Hospital

Questions to Keep in Mind:

- Does she have a bipolar spectrum disorder?
- Might this patient become pregnant during her treatment?
- What are the risks of the mood stabilizer(s) to a baby (in utero, breastfeeding)?
- What are the implications of reproductive events – pregnancy, postpartum, menstrual cycle, perimenopause?

Does She Have a Bipolar Disorder?

- Bipolar disorder is often a missed diagnosis
- Women often present with bipolar depression – need to take careful history to assess for bipolar disorder
- Hypomania may be easy to overlook

Bipolar Disorders Across the Female Reproductive Lifespan

- General Considerations
- Menstrual cycle
- Pregnancy
- Postpartum
- Menopause

Bipolar Disorder: Sex Differences

Bipolar Disorders in Women

- Women experience more rapid-cycling
- More mixed episodes
- More depressive symptoms
- Later age of onset
- More bipolar II
- More medical and psychiatric comorbidity
- Higher rates of obesity

Leibenluft, 1996 & 1997; Goodwin & Jamison, 1990; Angst et al., 1978; Roy-Burne et al., 1995; McElroy et al., 1995; Diflorio and Jones, 2010; Baldassano et al., 2005; Baskaran et al., 2014; Erol et al., 2015

Menstrual cycle

- May be exacerbation of symptoms premenstrually or menstrually for some women
- Case reports, retrospective data (Teatero et al, 2014)
- Up to 66% reported regularly occurring exacerbations (Blehar et al., 1998)
- 25% reported premenstrual depressive syndrome, increased anxiety (Roy-Byrne et al., 1985)
- Prospective studies – inconsistent findings (Leibenluft et al., 1999; Rasgon 2003; Shivakumar et al., 2008)
- Meds for PMDD may precipitate mania – mood stabilize first (Smith and Frey, 2016)
- Poorer outcomes in women with prospectively documented PMDD based on DSM5 criteria and bipolar disorder (Slyepchenko et al., 2017)

Mood Stabilizers and Menstrual Cycles

- Disruptions in menstrual cycles:
  - Valproic Acid
    - Associated with polycystic ovarian syndrome (PCOS)
  - Hyperprolactinemia
    - Galactorrhea, irregular menses/amenorrhea, infertility, sexual dysfunction
      - Associated most commonly with first generation antipsychotics and risperidone

Pacchiarotti et al., 2015; Gotlib et al., 2017

Pregnancy and Postpartum

Treating Women of Childbearing Potential

- 49% of pregnancies in U.S. are unintended[1]
- 80% of teen pregnancies unintended[1]
- 82% of U.S. women have had a child by age 40[2]

[1]Centers for Disease Control and Prevention. Unintended Pregnancy Prevention. http://www.cdc.gov/reproductivehealth/UnintendedPregnancy/index.htm. Accessed June 19, 2013;
[2]Martinez G et al. Centers for Disease Control and Prevention. National Health Statistics Reports. Number 51. April 12, 2012.

Context for Assessing Risk

- Rate of major malformations: 3-4%
- Rate of premature delivery: 11-12%
- Rate of gestational diabetes: 2-7%
- Untreated psychiatric disorders carry risks for woman and baby
- Alcohol and tobacco use prevalent in patients with untreated psychiatric disorders
- Obesity increases obstetrical risks

March of Dimes website, CDC website; Nonacs R, Cohen LS. *J Clin Psychiatry*. 2002;63 Suppl 7:24-30; King JC, Fabro S. *Clin Obstet Gynecol*. 1983;26(2):437-448.

Risks of Untreated Bipolar Disorder During Pregnancy

- >330,000 women; included comparisons of women with bipolar disorder, with and without treatment
  - Bipolar disorder increases risk of:
    - C-section
    - Small for gestational age
    - Prematurity
  - Congenital Malformations:
    - Without bipolar disorder: 2.0%; untreated 1.9%
    - 3.4% treated with a mood stabilizer (lithium or anticonvulsant)

Boden et al, BMJ, 2012

Breastfeeding

- …The experience of breastfeeding is special for so many reasons – the joyful bonding with your baby, the cost savings, and the health benefits for both mother and baby…
  - http://www.womenshealth.gov/breastfeeding/why-breastfeeding-is-important/index.html
- …Time to declare an end to the breastfeeding dictatorship that is drowning women in guilt and worry just when they most need support...

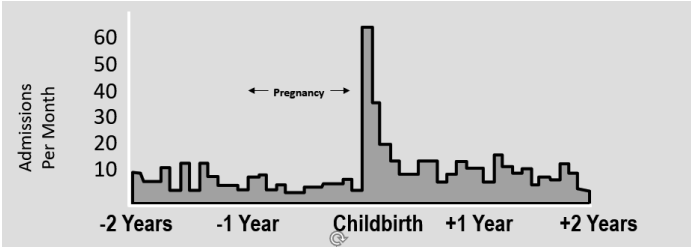
Gayle Tzemach Lemmon, **Breastfeeding is a Choice, Let's Treat it that Way** Posted: 05/11/2012 http://www.huffingtonpost.com/gayle-tzemach/breastfeeding_b_1509658.html

Pregnancy and Postpartum: Risks of Discontinuing Medication

- Retrospective and prospective data show mean rates of relapse during pregnancy between 55% to 70%
- Women who discontinue medication more likely to experience recurrences (85.5% vs. 37%) and spend more time ill
- Particularly high rate of mood episodes postpartum (70%)
- Recurrence risk greater after rapid discontinuation (≤2 wks) than gradual (2 to 4 weeks)
- Unplanned pregnancy associated with greater risk of recurrence

Viguera AC et al. *Am J Psychiatry*. 2000;157(2):179-184; Viguera AC et al. *Am J Psychiatry*. 2007;164(12): 1817-1824.

Risk of Psychiatric Hospitalization During Pregnancy and Postpartum



Highest risk of hospitalization for new mothers is 10 to 19 days postpartum, increased outpatient contacts first three months

Kendell et al. *Br J Psychiatry*. 1987;150:662; Munk-Olsen et al., *JAMA*. 2006;296(21):2582-2589.

Postpartum Psychosis

Postpartum Psychosis

- 1 to 2 per 1,000 pregnancies
- Rapid, dramatic onset within first 2 weeks
- **High risk of harm to self and infant**
- **Suspect bipolar disorder**
  - Underlying diagnosis: affective psychosis (bipolar disorder or schizoaffective disorder)
  - Family and genetic studies, index episode follow-up

Nonacs R, Cohen LS. *J Clin Psychiatry*. 1998;59(Suppl 2):34-40; Jones I, Craddock N. *Ann Med*. 2001;33(4):248-256; Spinelli MG. *Am J Psychiatry*. 2009;166(4):405-408.

Postpartum Psychosis (cont'd)

- Psychiatric emergency
- Estimated that 4% of women with postpartum psychosis commit infanticide
  - Actual rates of infanticide are difficult to estimate, as infanticide may be underreported

Spinelli MG. *Am J Psychiatry*. 2004;161:1548–1557; Spinelli MG. *Am J Psychiatry*. 2009;166(4):405-408.

Risk Factors for Postpartum Psychosis

Risk factor	% that developed postpartum psychosis
Hospitalization for psychotic episode **during** the pregnancy	44%
Hospitalization for a psychotic episode **prior** to the pregnancy	14.5%
Any previous psychiatric hospitalization	9.2%
Previous hospitalization for bipolar mood episode	2.0%
Baseline population risk	0.07%

Harlow BL. *Arch Gen Psychiatry*. 2007;64:42-48.

Acute Treatment

- Inpatient psychiatric hospitalization
- Rule out medical conditions
- Length of stay depends on clinical condition
- Many women will need to stop breastfeeding
- Primary pharmacotherapy: mood stabilizer and an antipsychotic, with medications for anxiety, insomnia, and agitation as needed
  - Sequential use of benzodiazepines, antipsychotics, lithium and ECT proposed

Sit et al., J Women's Health, 2006; Bergink et al., AJP 2015

Acute Treatment

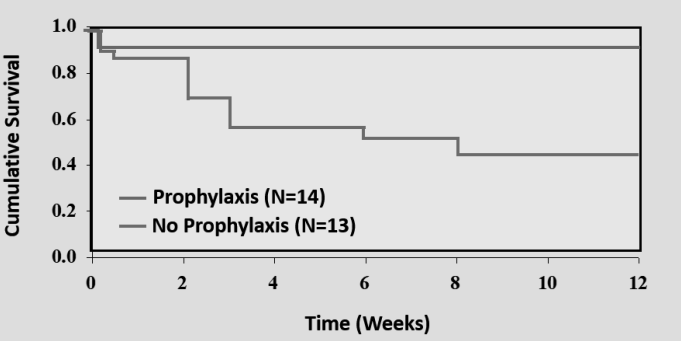
- Inpatient Protocol: Sequential use: N=64
  - Step 1: Benzodiazepine (lorazepam), 3 days - 6% remitted (N=4)
  - Step 2: Antipsychotic: haloperidol or atypical – 19% remitted (N=12)
  - Step 3: lithium – 73% remitted (N=48)
  - Step 4: ECT – none underwent
  - Total of 98% remission; only 1 patient did not fully remit
    - Most women responded to by addition of lithium
  - Sustained remission at 9 months postpartum in 80%
    - Affective diagnosis more associated with remission than non-affective
    - Relapse rates higher with antipsychotics than with lithium

Bergink et al., AJP 2015

Treatment After Discharge

- Little data to inform length of care
  - 6-12 months of pharmacotherapy
  - psychotherapy and close monitoring
- Treatment planning for adequate sleep, support, help in meeting the needs of caring for a baby
- Close monitoring is required for safety
  - Psychoeducation of family and friends

Postpartum Prophylaxis of Bipolar Disorder



Cohen LS, Sichel DA, et al. *Am J Psychiatry*. 1995.

Prevention of Postpartum Bipolar Episodes and Postpartum Psychosis

Group	During Pregnancy	With postpartum prophylaxis	Did not start postpartum prophylaxis	
Women with histories of **psychosis in the postpartum only**	**All (29/29) remained stable** off of medication during pregnancy	Started Postpartum Prophylaxis: No relapses (N=20)	Did not start Postpartum Prophylaxis: 44% relapse (N=9)	
Women with bipolar disorder	**24.4% relapse:** 75.6% on maintenance meds Relapse rates: 19.4% on meds 40% off meds	Of those who stayed well during pregnancy: postpartum relapse rate 7.7% on prophylaxis	Of those who stayed well during pregnancy: 20% relapse rate not on prophylaxis	**60% postpartum relapse among those who experienced mood episodes during pregnancy**

Main points

- **History of isolated postpartum psychosis**
  - High risk for recurrence **postpartum**
  - Prophylaxis may be deferred to immediately postpartum if mother well throughout pregnancy
- Bipolar disorder
  - **High risk for recurrence throughout pregnancy and the postpartum**, particularly with medication discontinuation
  - High risk postpartum relapse, postpartum prophylaxis decreases risk
  - Clinical picture during pregnancy greatly factors into postpartum prognosis – do not delay treatment

Postpartum Treatment

- **Prescribe Sleep!**
  - Sleep deprivation – similar to antidepressants regarding risk of induction of mania/hypomania (10%)
- **Prescribe Support!**
  - Good social support associated with quicker recovery, less symptomatic; better prophylaxis against episodes

Colombo, et al. 1999; Johnson, et al. 1999; Stefos, et al. 1996

Differentiating OCD and Psychosis

Postpartum OCD	Postpartum psychosis
• Thoughts are ego-dystonic	•Thoughts are ego-syntonic
• Disturbed by thoughts	•Rarely distressed by thoughts
• Avoid objects or being with their newborn	•Do not have avoidant behaviors
• Very common disorder	•Not common disorder
• Low risk of harm to baby	•High risk of harm to baby

OCD, obsessive-compulsive disorder
Brandes M et al. *Arch Womens Ment Health*. 2004;7(2):99-110.

Mood Stabilizers in Pregnancy

- **Lithium: First-trimester risk of cardiovascular malformations**[1]
  - Ebstein's anomaly: 0.1% to 0.2% (risk ratio 10 to 20)
  - Risk ratio for cardiac malformations is 1.2 to 7.7 and the risk for Ebstein's anomaly rises from 1/20,000 to 1/1000
- **Lithium**
  - Complicated by maternal glomerular filtration rate (GFR) changes during pregnancy. Excreted more rapidly—may need to increase dose[2]
  - After delivery, GFR decreases rapidly, should follow lithium levels during labor and delivery, adjust dose as needed[2]

[1]Yonkers KA et al. *Am J Psychiatry*. 2004;161:608-620; [2]Newport DJ et al. *Am J Psychiatry*. 2005;162:2162–2170.

Valproic Acid

- **Worst Teratogen Known Among Psychotropics**
- Rate of major malformations: ≥ 10%
  - Neural tube defects, craniofacial, cardiovascular, and others
  - Risk of defects is substantial in very early pregnancy
- Associated with increased risk for adverse cognitive and neurodevelopmental effects
  - Long-term follow-up (up to 3 years) suggests fetal exposure to valproate associated with lower IQ scores (not observed with lamotrigine)

Yonkers KA, et al. *Am J Psychiatry*. 2004;161(4):608-620. Newport DJ, et al. *Am J Psychiatry*. 2005;162(11):2162-2170. Meador KJ, et al. *Epilepsy Behav*. 2009;15(3):339-343.

IQ Scores of Children at 3 Years of Age According to In Utero Exposure to Antiepileptic Drugs

Variable	Carbamazepine (N=73)	Lamotrigine (N=84)	Phenytoin (N=48)	Valproate (N=53)
Mean IQ (95% CI)†	98 (95–102)	101 (98–104)	99 (94–104)	92 (88–97)
Mean difference in IQ from valproate group (95% CI)‡	6 (0.6–12.0)	9 (3.1–14.6)	7 (0.2–14.0)	
P value§	0.04	0.009	0.04	

* The results are based on regression models for the intention-to-treat population (309 children). See Table 1 in the Supplementary Appendix for full results of the regression models. IQ at 3 years of age was imputed for 77 of the original 309 children born alive who were not assessed at that age (1 of these children died from severe heart malformation, 6 were enrolled in the NEAD study from the United Kingdom study after they had reached 3 years of age, 31 withdrew before 3 years of age, and 39 did not present for testing).
† Least-squares means from the primary analysis are given after adjustment for maternal IQ and age, antiepileptic-drug dose, infant's gestational age at birth, and maternal preconception use of folate.
‡ Although the confidence intervals for carbamazepine and phenytoin overlap with the confidence interval for valproate, the confidence intervals for the differences between carbamazepine and valproate and between phenytoin and valproate do not include zero.
§ P values are for the comparison with the valproate group. P values from tests of the null hypothesis of no difference from the valproate-group mean were adjusted for multiple comparisons.[23]

Meador KJ et al. *N Engl J Med*. 2009;360(16):1597–1605.

Lamotrigine in Pregnancy

- No increased risk of major malformations
- Association with oral clefting NOT seen with larger numbers
  - Early data suggested it might be when numbers were smaller
  - Recent large study of registries did not find any association between oral clefts and lamotrigine
- Pregnancy increases lamotrigine clearance by > 50%
  - Returns to baseline after delivery

Myllynen PK, et al. *Eur J Clin Pharmacol*. 2003;58(10):677-682. Tran TA, et al. *Neurology*. 2002;59(2):251-255. Dolk H, et al. *Neurology*. 2008;71(10):714-722.

Atypical Antipsychotics in Pregnancy

- Large administrative Medicaid database
  - Nationwide sample of N= 1 360 101 pregnant women
  - After confounding adjustment, the RR was reduced to 1.05 (95% CI, 0.96-1.16) for atypical APs and 0.90 (95% CI, 0.62-1.31) for typical APs. The findings for cardiac malformations were similar
  - For the individual agents examined, a small increased risk in overall malformations (RR, 1.26; 95% CI, 1.02-1.56) and cardiac malformations (RR, 1.26; 95% CI, 0.88-1.81) was found for risperidone that was independent of measured confounders
- Pooled odds ratios of prospective studies
  - Antipsychotic exposure associated with slightly increased risk of major malformations , heart defects), preterm delivery , small-for-gestational-age births , decreased birth weight
  - There was no significant difference in the risk of major malformations differences between typical (and atypical antipsychotic medications.

Hubrechts et al., 2016; Coughlin et al., 2016.

National Pregnancy Registry for Atypical Antipsychotics

Research Study at the Massachusetts General Hospital Center for Women's Mental Health

To determine the safety of atypical antipsychotics in pregnancy for women and their babies

Participation will involve 3 brief phone interviews over approximately 8 months

Call toll-free: 1-866-961-2388

National Pregnancy Registry for Atypical Antipsychotics

Now > 2000 participants enrolled

Aggregate Risk Analyses: As of Dec 2014, N=487 enrolled, N=303 eligible for analyses; 89 controls:

- Rates of major malformations in the two groups similar:
  - 1.4% (3/214 live births) in exposed group ; 1.1% (1/89) in control group
  - Odds ratio comparing exposed with unexposed infants was 1.25 (95% CI=0.13-12.19) – not statistically significant

Quetiapine: N=152 exposure to quetiapine compared with 205 controls

- 2/155 malformations were confirmed (1.3%), compared with 3/210 (1.4%) in control group
- Odds ratio for major malformations between infants with and without quetiapine exposure was 0.90 (95% CI=0.15, 5.46), which is consistent with the pooled estimate of the available controlled data on fetal exposure to quetiapine

Cohen et al., Am J Psychiatry 2016: Cohen et al., Am J Psychiatry 2018

Benzodiazepines and Pregnancy

- 1st trimester exposure: previously inconsistent findings of association with cleft palate or other congenital abnormalities
  - Recent studies do not suggest teratogenicity
- Recent study suggested association with c-section, low birth weight, use of ventilator support for newborn
- Timing of exposure likely makes difference in obstetrical outcomes
- May contribute to poor neonatal adaptation syndrome when used with antidepressants
- Possible longer-term impact on language development
- Difficult to disentangle confounding variables, disease state, concomitant medications

Kanto JH. Drugs 1982;23:354-380. Hanley and Mintzes. BMC Pregnancy Childbirth 2014. Ornoy A, et al. Reprod Toxicol 1998;12:511-515. Eros E, et al. Eur J Obstet Gynecol Reprod Biol 2002. Whitelaw AG, et al. Br Med J (Clin Res Ed) 1981. Mazzi E. Am J Obstet Gynecol 1977. Iqbal MM. et al. Del Med J 2002. Askaa et al., Obstet Gynecol Int 2014. Wikner and Kallen. J Clin Psychopharmacol 2011. Yonkers et al., JAMA Psychiatry, 2017; Salisbury et al., AJP 2016; Odsbu et al., Eur J Clin Pharmacol 2015

Mood Stabilizers and Breastfeeding

Lithium

- Toxicity reported in cases with infant serum levels at 0.1 to 0.5 times the maternal level
- Contraindicated at one time by the American Academy of Pediatrics[1]
- Revised to classification “Drugs That Have Been Associated With Significant Effects on Some Nursing Infants and Should Be Given to Nursing Mothers With Caution”

American Academy of Pediatrics Committee on Drugs. *Pediatrics*. 2001;108(3):776-789.

Mood Stabilizers and Breastfeeding (cont'd)

Lithium and Breastfeeding
•N=10 mother-baby pairs
•Mothers stable, lithium monotherapy 600 to 1,200 mg/day
•Babies'serum levels 0.09 to 0.3 meq/L (average 0.16)
•Transient increases in elevated infant TSH, BUN, Cr

Recommendations
Consider lithium when:
- Bipolar disorder in mother who is stable
- Lithium monotherapy (or simple regimen)
- Adherence to infant monitoring (lithium level, TSH, BUN, Cr immediately postpartum, 4 to 6 weeks of age, and then every 8 to 12 weeks)
- Healthy infant
- Collaborative pediatrician

BUN, blood urea nitrogen; Cr, creatinine; TSH, thyroid-stimulating hormone.
Viguera AC et al. *Am J Psychiatry*. 2007;164(2):342-345.

Menopause

- Very sparse data
- There may be mood worsening associated with the menopausal transition, particularly depressive episodes and symptoms

Blehar et al., 1998; Marsh et al., 2015; Marsh et al., 2012; Freeman et al., 2002

Thank you!

- Marlene P. Freeman, M.D.
- mfreeman@mgh.harvard.edu

NOTES

Question & Answer

NOTES

PMDD

Laura Petrillo, MD

Premenstrual Dysphoric Disorder (PMDD)

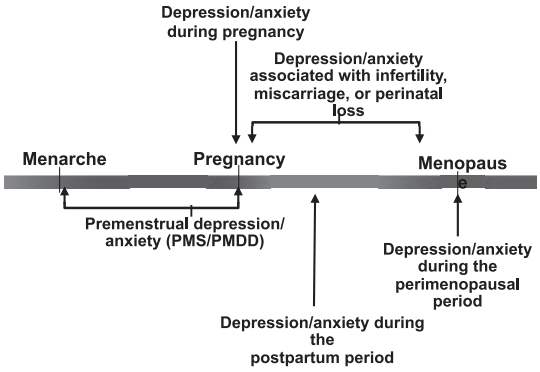
Laura Fagioli Petrillo, M.D.

Director of Training, The Ammon-Pinizzotto Center for Women's Mental Health

Massachusetts General Hospital

Instructor in Psychiatry, Harvard Medical School

Depression and Anxiety Across the Female Reproductive Cycle

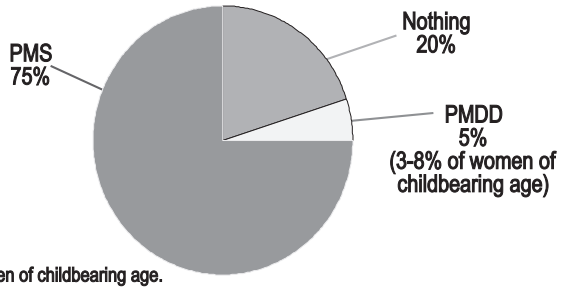


Premenstrual Mood Changes

- Majority of reproductive age women report unpleasant symptoms around the time of menstruation
  - Physical and psychological symptoms
  - "More emotional"
  - Minimal effect on functioning
- 2.5 million women affected annually

Clayton, *Jnl of Psych Prac*. 2008;14:13-21.
Winer & Rapkin, *Jnl Reproductive Med*. 2006;51(4): 339-347.

Prevalence of Premenstrual Conditions



100%=all women of childbearing age.

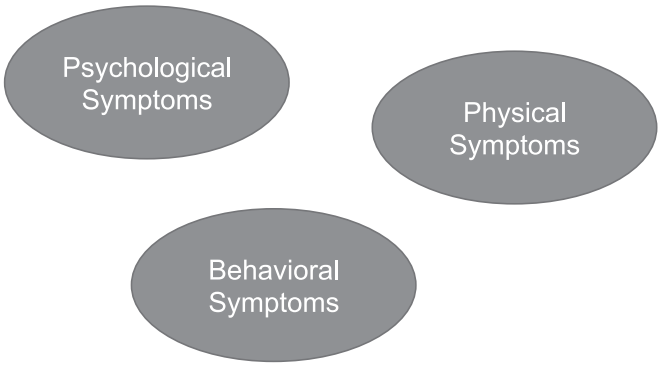
Haskett RF. *Prog Neuropsychopharmacol Biol Psychiatry.* 1987;11(2-3):129-135.
Johnson SR, et al. *J Reprod Med.* 1988;33(4):340-346.
Rivera-Tovar AD, Frank E. *Am J Psychiatry.* 1990;147(12):1634-1636.
Ramcharan S, et al. *J Clin Epidemiol.* 1992;45(4):377-392.

Premenstrual Syndrome (PMS)

- Pattern of physical, emotional and behavioral symptoms occurring 1-2 weeks before menstruation
- Symptoms remit with the onset of menstruation
- 30-80% of women
- Significant in 3-8% of women
- Occurs cross-culturally

Wittchen HU, Becker E, Lieb R, et al. *Psychol Med.* 2002;32:119-132.

PMS Symptoms



PMDD - DSM-V Criteria

- Criterion A: in most menstrual cycles during the past year, at least 5 of 11 symptoms (including at least 1 of the first 4 listed) were present:
  - Markedly depressed mood, hopelessness, or self-deprecating thoughts
  - Marked anxiety, tension, feelings of being "keyed up" or "on edge"
  - Marked affective lability
  - Persistent/marked anger or irritability or interpersonal conflicts
  - Decreased interest in usual activities
  - Subjective sense of difficulty in concentrating
  - Lethargy, easy fatigability, or marked lack of energy
  - Marked change in appetite, overeating, or specific food cravings
  - Hypersomnia or insomnia
  - A subjective sense of being overwhelmed or out of control
  - Other physical symptoms, such as breast tenderness or swelling, headaches, joint or muscle pain, a sensation of bloating, or weight gain
- The symptoms must have been present for most of the time during the last week of the luteal phase, begun to remit within a few days of the onset of menstrual flow, and absent in the week after menses

DSM-V Criteria

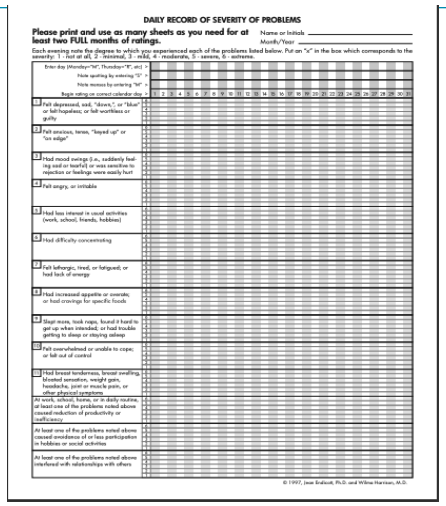
- Criterion B is that the symptoms must be severe enough to interfere significantly with social, occupational, sexual, or scholastic functioning.
- Criterion C is that the symptoms must be discretely related to the menstrual cycle and must not merely represent an exacerbation of the symptoms of another disorder, such as major depressive disorder, panic disorder, dysthymic disorder, or a personality disorder.
- Criterion D is that criteria A, B, and C must be confirmed by prospective daily ratings during at least 2 consecutive symptomatic menstrual cycles. The diagnosis may be made provisionally before this confirmation.

Premenstrual Exacerbation (PME)

- Mood disorders can worsen premenstrually
- PMDD vs. PME
- 40% of women screened for PMDD have an underlying mood disorder with PME
- Charting to determine cyclicity of symptoms

Bailey & Cohen. *J Women's Health Gender Based Med*. 1999;8(9):1181.

Prospective Rating Chart – Daily Record of Severity of Problems
DRSP


DAILY RECORD OF SEVERITY OF PROBLEMS

Please print and use as many sheets as you need for at least two FULL months of ratings.

Name or Initials _____

Month/Year _____

Each evening rate the degree to which you experienced each of the problems listed below. Put an "x" in the box which corresponds to the severity: 1 - Not at all, 2 - minimal, 3 - mild, 4 - moderate, 5 - severe, 6 - extreme.

Enter day (Monday="M", Thursday="R", etc.) x

Note spotting by entering "S" x

Note menses by entering "M" x

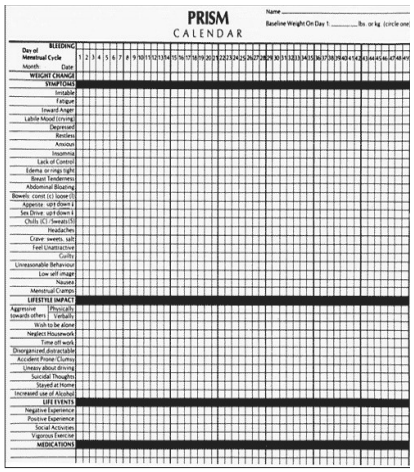
Begin rating on correct calendar day 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30

1. Felt depressed, sad, "down," or "blue" or felt hopeless; or felt worthless or guilty
2. Felt anxious, tense, "keyed up" or "on edge"
3. Had mood swings (i.e., suddenly feeling sad or tearful or was sensitive to rejection or feelings were easily hurt
4. Felt angry, or irritable
5. Had less interest in usual activities (work, school, friends, hobbies)
6. Had difficulty concentrating
7. Felt lethargic, tired, or fatigued; or had lack of energy
8. Had increased appetite or overate; or had cravings for specific foods
9. Slept more, took naps, found it hard to get up when intended; or had trouble getting to sleep or staying asleep
10. Felt overwhelmed or unable to cope; or felt out of control
11. Had breast tenderness, breast swelling, bloated sensation, weight gain, headache, joint or muscle pain, or other physical symptoms
12. At work, school, home, or in daily routine, at least one of the problems noted above caused reduction of productivity or inefficiency
13. At least one of the problems noted above caused avoidance of or less participation in hobbies or social activities
14. At least one of the problems noted above interfered with relationships with others

© 1997, Jean Endicott, Ph.D. and Wilma Harrison, M.D.

Borenstein JE, Dean BB, Yonkers KA, Endicott J. *Obstet Gynecol*. 2007;109(5):1068-1075.
Endicott J, Nee J, Harrison W. *Arch Women's Ment Health*. 2006;9(1):41-49.

Prospective Rating Chart – Prospective Record of the Severity of Menstruation
PRISM


PRISM
CALENDAR

Name _____

Baseline Weight On Day 1: _____ lbs. or kg (circle one)

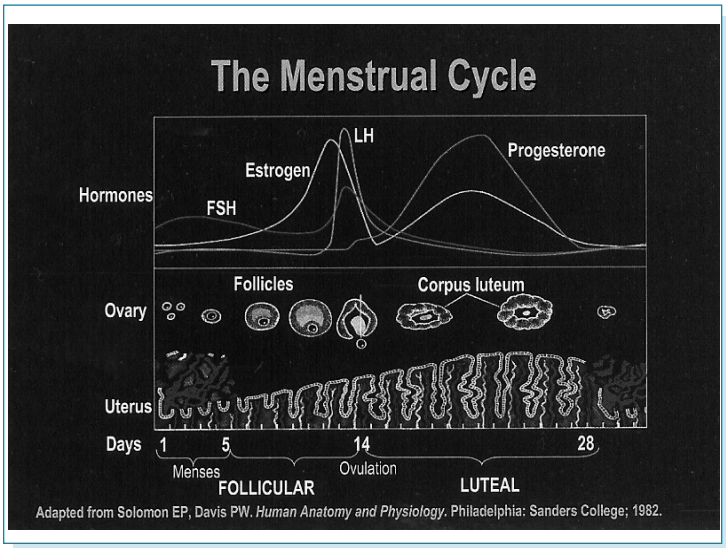
BLEEDING
Day of Menstrual Cycle 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49
Month
Date
WEIGHT CHANGE
SYMPTOMS
Irritable
Fatigue
Inward Anger
Labile Mood (crying)
Depressed
Restless
Anxious
Insomnia
Lack of Control
Edema or rings tight
Breast Tenderness
Abdominal Bloating
Bowels: const (c) loose (l)
Appetite: up(u) down (d)
Sex Drive: up(u) down (d)
Chills (C) Sweats (S)
Headaches
Crave: sweets, salt
Feel Unattractive
Guilty
Unreasonable Behaviour
Low self-image
Nausea
Menstrual Cramps
LIFESTYLE IMPACT
Aggressive towards others: Physically, Verbally
Wish to be alone
Neglect Housework
Time off work
Disorganized, distractable
Accident Prone / Clumsy
Uneasy about driving
Suicidal Thoughts
Stayed at Home
Increased use of Alcohol
LIFE EVENTS
Negative Experience
Positive Experience
Social Activities
Vigorous Exercise
MEDICATIONS

Many additional charts and apps:

Premenstrual Symptoms Screening Tool (PSST)

Calendar of Premenstrual Experiences (COPE)

Renske C. et al. *J Affect Disord.* 2016;189:43–53



Adapted from Solomon EP, Davis PW. *Human Anatomy and Physiology*. Philadelphia: Sanders College; 1982.

Risk Factors for PMDD and PMS

- Family history of PMS and PMDD[1,2]
- History of postpartum depression[3]
- Major depression past[3,4] or future[5]
- Trauma history[6]

1. van den Akker OB, et al. *Acta Genet Med Gemellol (Roma).* 1987;36(4):541-548. 2. Kendler KS, et al. *Psychol Med.* 1992;22(1):85-100. 3. Warner P, et al. *J Affect Disord.* 1991;23(1):9-23. 4 Bancroft J, et al. *Psychosom Med.* 1994;56(3):225-231. 5. Graze KK, et al. *Acta Psychiatr Scand.* 1990;81(2):201-205. 6. Perkonigg A, Yonkers KA, Pfister H, et al. *J Clin Psychiatry.* 2004;65:1314-1322.

PMS/PMDD Longitudinal Course

- Women seek treatment in their late 20s/early 30s
- Peaks around 30-39 years old[1]
- Physical/mood symptoms stable from cycle to cycle[2]
- Diagnosis appears stable over time[3]
- **Chronic course** although symptoms may improve during suppression of the ovarian cycle (lactational amenorrhea, pregnancy, post-menopause)[4]

1Johnson. *Clin Obstet Gynecol.* 1987;30:369.
2Block. *Am J Psychiat.* 1997;154:1741.
3Roca et al. *J Clin Psychiatry.* 1999;60:763.
4Reid RL. Endotext [Internet]. MDText.com, Inc.; 2017-.

Diversity Research and PMDD

- Most studies do not involve diverse populations
- Unclear whether the prevalence varies by race
- Prevalence among Black women may be lower per one study[1]
- Among non-white populations of US women (Asian, Latinx, Black), perceived discrimination may be a risk factor[2]
- Rates of severe PMS and PMDD in East Asian women were lower than Western women[3-4]

1. Pilver CE, et al. *Psychol Med*. 2011;41(8):1741-1750
2. Pilver CE, et al. *J Womens Health (Larchmt)*. 2011;20(6):923-931
3. Takeda T, et al. *Arch Womens Ment Health*. 2006;9(4):209-212
4. Schatz DB, et al. *Int J Psychiatry Med*. 2012;43(4):365-380.

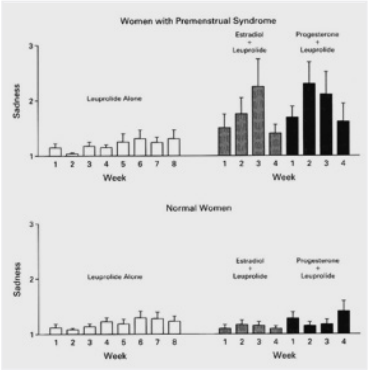
Pathophysiology

- No clear evidence of "hormonal dysregulation"
- Levels of progesterone and estradiol remain within normal range
- PMS/PMDD may represent an abnormal response to normal fluctuations of gonadal steroids

Schmidt et al., *American Journal of Psychiatry*:2017;174(10), 980-989.

Hormonal Basis of PMDD

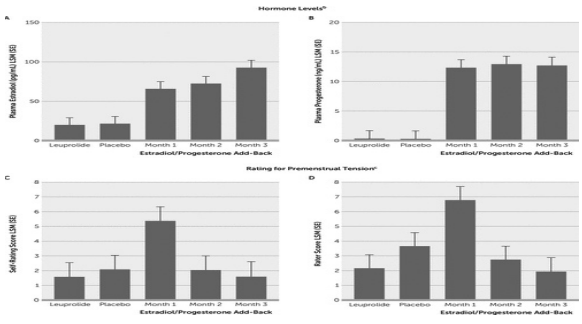
- Differential sensitivity to normal changes in estrogen and progesterone
- GnRH agonists are effective therapy
  - Eliminate hormonal fluctuation
  - PMS re-occurs with add-back therapy



GnRH = gonadotropin-releasing hormone.

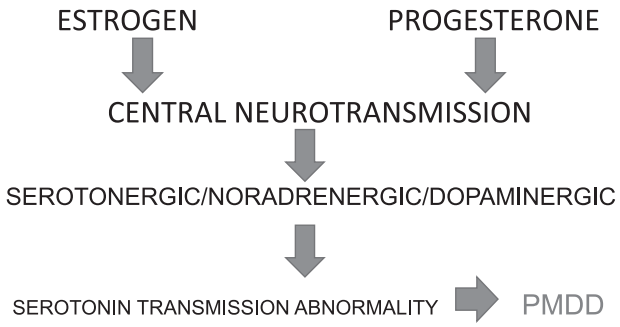
Schmidt et al. *N Engl J Med.* 1998;338:209.

Hormonal Basis of PMDD



Schmidt PJ, Martinez PE, Nieman LK, et al. *Am J Psychiatry*. 2017;174:980-989.

Pathophysiology



Pathophysiology

Role of gamma amino-butyric acid (GABA)

- Allopregnanolone enhances effects of GABA, acts as an anxiolytic

Paradoxical effect of allopregnanolone mediated via the GABA-A receptor => neg mood symptoms[1]

PMDD = greater ALLO/prog ratio vs. controls in luteal phase[2]

Treatment with ALLO antagonist during the luteal phase reduced PMDD scores on the DRSP[3]

1.Bäckström T, et al. *Prog Neurobiol.* 2014;113:88-94.
2.Girdler SS, et al. *Biol Psychiatry*. 2001;49(9):788-797.
3.Bixo M, et al. *Psychoneuroendocrinology.* 2017;80:46-55.

Pharmacologic Treatment

SSRIs are first line treatment in patients without bipolar disorder

- fluoxetine
- sertraline
- controlled release paroxetine

Antidepressants with serotonergic activity

- venlafaxine
- duloxetine
- clomipramine

Sundblad et al. *Acta Psychiatr Scand*. 1992;85:39-47.
Freeman et al. *Obstet Gynecol.* 2001;98:737-44.
Ramos & Hara. *Int J Neuropsychopharmacol.* 2009;12(8):1081-8.

Antidepressant Dosing

- Continuous
  - Steady dose throughout the month
- Intermittent
  - Luteal phase (day 14 to onset of menstruation)
- Symptom onset
  - Women with irregular cycles
- Luteal phase increase
  - Continuous with luteal phase "bump up"

SSRI Treatment Considerations

- Start with low dose
- If no response after first cycle, increase for second cycle and continue for 2-4 cycles
- If unsatisfactory response, consider alternative SSRI and/or change dosing
- If no response to 2 SSRIs, may try a 3rd or SNRI/TCA; if incomplete response, consider adjunctive symptom targeted treatment

Adjunctive Psychopharmacologic Treatment

- Benzodiazepines
  - Alprazolam – mixed results
- Buspirone
  - Mixed results; benefit may be modest
- Gabapentin
  - Anecdotally helpful
- Quetiapine SR
  - Modest benefit
  - Small sample size

Schmidt PJ, Grover GN, Rubinow DR. *Arch Gen Psychiatry*. 1993;50(6):467-473.
Harrison WM, Endicott J, Nee J. *Arch Gen Psychiatry*. 1990;47(3):270-275.
Freeman EW. *CNS Drugs*. 2004;18(7):453-468.
Jackson C, Pearson B, Girdler S, et al. *Hum Psychopharmacol*. 2015;30(6):425-434.

Duration of Treatment in PMDD

- Optimal length of treatment is unclear
- Many women relapse when they stop treatment–as early as 1 to 2 cycles[1-4]
- Some studies suggest 12 months of treatment, then stop and observe or switch to intermittent treatment[1-5]
  - If using intermittent treatment, discontinue after a year
  - If symptoms recur, resume treatment until pregnancy or menopause
- Chronic treatment may be necessary

1.de la Gandara Martin JJ. *Actas Luso Esp Neurol Psiquiatr Cienc Afines.* 1997;25(4):235-242. 2. Pearlstein TB, Stone AB. *J Clin Psychiatry.* 1994;55(8): 332-335.3. Elks ML. *South Med J.* 1993;86(5):503-507. 4. Freeman EW, et al. *Am J Psychiatry.* 1992;149(4):531-533. 5. Freeman EW, et al. *Arch Gen Psychiatry.* 2009;66(5):537-544.

Oral Contraceptives (OC)

- Evidence from double-blind, randomized, placebo-controlled trials supports use of some OCs for treatment of PMDD
- Progesterone only pill unlikely to be helpful[1-3]
- OCs containing drospirenone may be more effective
  - 4 day vs 7 day placebo
- Comparison drospirenone vs other progestins

1.Ford O, et al. *Cochrane Database Syst Rev*. 2006;(4):CD003415.
2.Wyatt K, et al. *BMJ*. 2001;323:776-780
3.Freeman E, et al. *JAMA*. 1990;264(3):349-353.

OC Dosing

- Cyclic
  - 21-24 days active pill, 4-7 days placebo
- Continuous
  - Consecutive pill packs without a placebo
  - Efficacy greater than cyclic dosing
- Begin with cyclic dosing
- Move to continuous dosing if symptoms persist

Always consider medical risks of OCP

Freeman et al. *Contraception.* 2012;85(5): 437-445
Skovlund et al. *Am Jnl Psychiatry*. 2018;175(4): 336-342

Gonadotropin-Releasing Hormone Agonists

- Leuprolide – depot injection every 1-3 months
- Buserelin – intranasal spray daily
- PLUS Add-back of estrogen, progestin or both
- Down-regulate gonadotropin receptors in pituitary to create a hypogonadotropic state
- Treatment usually restricted to six months
- Long term effects are unknown

Mortola JF et al. *J Clin Endocrinol Metab.* 1991; 72: 252A–252F
Ripps BA et al. *J Reprod Med.* 2003;48:761–766.
Wyatt et al. *Br J Obstet Gynaecol.* 2004; 111: 585-593

Gonadotropin-Releasing Hormone Agonists

- Double-Blind, placebo-controlled trials
  - Several show superiority of GnRH agonists over placebo[1–8]
  - Some show GnRH agonists equal to placebo[9,10]
  - Not first line
    - Consider after failure of non-pharmacologic agents, SSRIs and OCs

1. Brown CS, et al. *Obstet Gynecol.* 1994;84(5):779-786. 2. Freeman EW, et al. *Psychopharmacol Bull.* 1997;33(2):303-309. 3. Hammarback S, Backstrom T. *Acta Obstet Gynecol Scand.* 1988;67(2):159-166. 4. Hussain SY, et al. *Gynecol Endocrinol.* 1992;6(1): 57-64. 5. Leather AT, et al. *Gynecol Endocrinol.* 1999;13(1):48-55. 6. Muse KN, et al. *N Engl J Med.* 1984;311(21):1345-1349. 7. Schmidt PJ, et al. *N Engl J Med.* 1998;338(4):209-216. 8. Sundstrom I, et al. *Acta Obstet Gynecol Scand.* 1999;78(10):891-899. 9. Helvacioglu A, et al. *J Reprod Med.* 1993;38(11):864-870. 10. West CP, Hillier H. *Hum Reprod.* 1994;9(6):1058-1063.

Non-Pharmacologic Treatment

- Mood Charting
- Lifestyle Modification
  - Diet, exercise, sleep
- Psychotherapy
- Nutritional Supplements
- CAM

Andrzej, M & Diana, J. *Maturitas*. 2006;55:S47-S54.
Samadi, Z., et al. *Iran J Nurs Midwifery Res.* 2013;18:14–19.

Nutritional Supplements

- Calcium (1200 mg daily)
- Vitamin B6 (50-100 mg daily)
- Magnesium (200-460 mg daily)
- Vitamin E (400 IU daily)

Thys-Jacobs S et al. *Am J Obstet Gynecol.* 1998;179: 444–52. Chocano-Bedoya P et al. *The Am Jnl Clin Nutr.* 2011;93(5):1080-1086. Fathizadeh N et al. *Iran J Nurs Midwifery Res.* 2010;15:401-5. Shobeiri et al. *Obstetrics & Gynecology Science*, 2018;*60*:100–105.

Complementary and Alternative Medicine

- Omega-3
  - Limited data
  - Potential benefit
- Vitex agnus-castus (Chasteberry)
  - Data are inconclusive
  - Potential benefit
- St. John's Wort
  - Physical symptoms > emotional symptoms
  - 13-15% reduction in the level of OCP
- Light therapy
  - Inconclusive

Cerqueira RO, et al. *Arch Womens Ment Health*. 2017;20:713-719.
Verkaik S, et al. *Am J Obstet Gynecol*. 2017;217:150-166.
Jang SH, et al. *BMC Complement Altern Med*. 2014;14:11.
Sohrabi N, et al. *Complement Ther Med*. 2013;21(3):141-146.
Krasnik C, et al. *Am Jnl of Obstetrics and Gyn. 2005;193*:658-661.

Summary

- Premenstrual symptoms are common.
- A smaller percentage of women experience severe physical and emotional symptoms that interfere with their ability to function.
- Screening for these symptoms is important as it may lead to treatments that can be beneficial.
- The etiology is unclear but data are accumulating.
- Treatments can be non-pharmacologic or pharmacologic.
  - Hormonal or psychotropic
- More research is needed.

NOTES

The Menopausal Transition and Depression

Ruta Nonacs, MD, PhD

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

The Menopausal Transition and Depression

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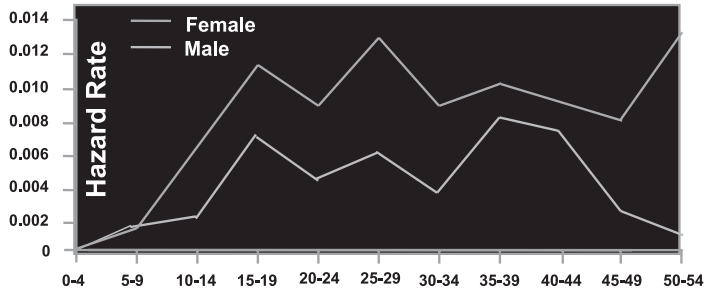
Ammon-Pinizzotto Center for Women's Mental Health
Massachusetts General Hospital, Harvard Medical School

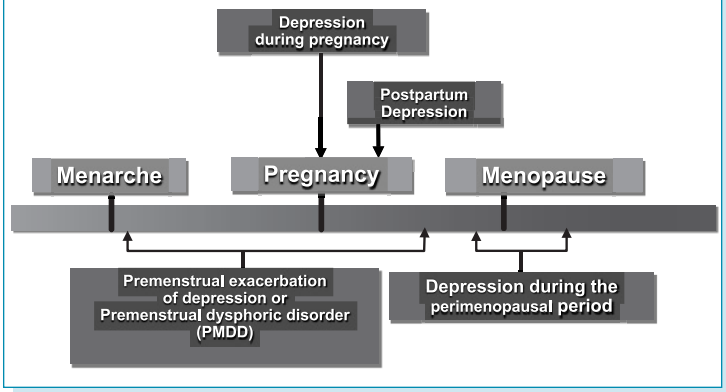
Affective Disorders in Women

Risk for Depression by Age and Sex



Kessler R. *J Affect Disord.* 1993;29:85-96.

Depression Across the Female Reproductive Cycle



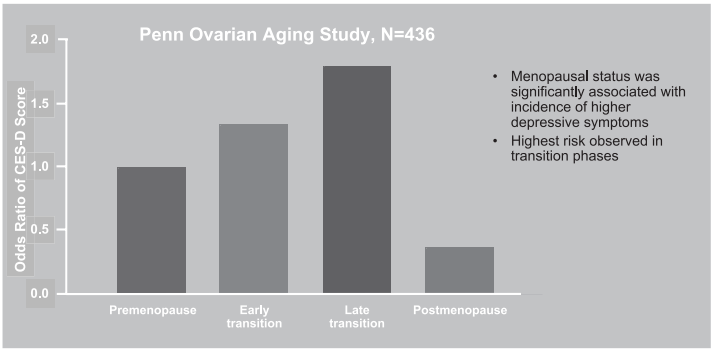
Risk for Mood Disorder During the Menopause Transition

Are Women At increased Risk for New Onset of Depression?

NEW ONSET Of Depression and Menopause Transition: Population Studies

Studies	Population	References
The Study of Women's Health Across the Nation (SWAN)	N=266 midlife women with no history of depression for 7 years	Bromberger et al. Psychol Med. 2009;39:55-64.
The Harvard Study of Moods and Cycles	N=460 women with no history of depression for up to 8 years	Cohen et al. Arch Gen Psychiatry. 2006;63:385-390.
The Penn Ovarian Aging Study	N=231 women with no history of depression for up to 8 years	Freeman E et al. Arch Gen Psychiatry. 2006;63:375-382.

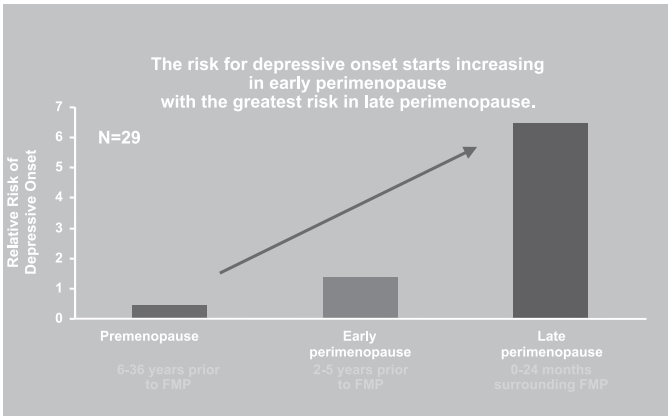
Menopausal Status is Associated With Increased Depressive Symptoms



CES-D=Center for Epidemiologic Studies Depression Scale.
CES-D score ≥16 signify high depressive symptoms.

Freeman EW. *Arch Gen Psychiatry.* 2004;61:62-70

Risk for Depression Among Perimenopausal Women



FMP = final menstrual period
Schmidt PJ, et al. *Am J Psychiatry*. 2004;161:2238-2244.

ORIGINAL ARTICLE

Risk for New Onset of Depression During the Menopausal Transition

The Harvard Study of Moods and Cycles

Lee S. Cohen, MD; Claudio N. Soares, MD, PhD; Allison F. Vitonis, BA; Michael W. Otto, PhD; Bernard L. Harlow, PhD

Context: Transition to menopause has long been considered a period of increased risk for depressive symptoms. However, it is unclear whether this period is one of increased risk for major depressive disorder, particularly for women who have not had a previous episode of depression.

Objective: To examine the association between the menopausal transition and onset of first lifetime episode of depression among women with no history of mood disturbance.

Design: Longitudinal, prospective cohort study.

Setting: A population-based cross-sectional sample.

Participants: Premenopausal women, 36 to 45 years of age, with no lifetime diagnosis of major depression (N=460), residing in 7 Boston, Mass, metropolitan area communities.

Main Outcome Measure: Incidence of new onset of depression based on structured clinical interviews, Center for Epidemiologic Studies Depression Scale scores, and an operational construct for depression.

Results: Premenopausal women with no lifetime history of major depression who entered the perimenopause were twice as likely to develop significant depressive symptoms as women who remained premenopausal, after adjustment for age at study enrollment and history of negative life events. The increased risk for depression was somewhat greater in women with self-reported vasomotor symptoms.

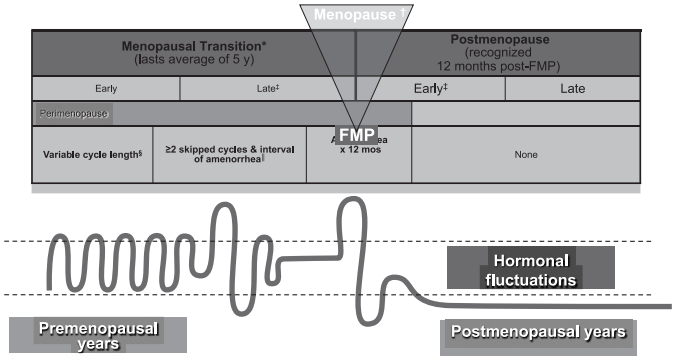
Conclusions: The current study suggests that within a similarly aged population of women with no lifetime history of depression, those who enter the menopausal transition earlier have a significant risk for first onset of depression. Further studies are needed to determine more definitively whether other factors, such as the presence of vasomotor symptoms, use of hormone therapy, and the occurrence of adverse life events, independently modify this risk. Physical symptoms associated with the menopausal transition and mood changes seen during this period may affect many women as they age and may lead to a significant burden of illness.

Arch Gen Psychiatry. 2006;63:385-390

Increased Risk for First Episode of MDD During Menopausal Transition (cont'd)

- Risk of MDD during menopausal transition is high (OR=1.9), even among women with no history of MDD
- Risk for MDD higher among women with vasomotor symptoms (OR=2.5)
- Adverse life events may exacerbate the risk for depression, BUT are not necessary for its occurrence

Cohen LS, Soares CN, Otto MW, et al. *Arch Gen Psychiatry 2006*; 63:385-390.



Santoro N, et al. *J Clin Endocrinol Metab.* 1996;81:1495-1501.
Kronenberg F. *Ann N Y Acad Sci.* 1990;592:52-86.

Onset of Depressive Symptoms and Hormone Changes

ARCHIVES OF GENERAL PSYCHIATRY

Higher depressive symptoms (CES-D) associated with increased variability (within subject) of levels of:

- Estradiol (P = .03)
- FSH (P<.001)
- LH (P = .005)

Table 6. Odds Ratios (ORs) of Hormones From the Final Multivariable Model for Onset of Depressive Symptoms (CES-D Scale Score ≥ 16) for 116 Participants

Hormone*	OR		95% CI	*P* Value
	Unadjusted	Adjusted		
Estradiol				
Mean	1.10	1.06	(0.63-1.78)	.83
SD†‡	1.30	1.36	(1.02-1.80)	.03
FSH				
Mean	4.38	4.58	(2.03-10.35)	<.001
SD†‡	1.90	2.09	(1.70-3.41)	<.001
Inhibin B				
Mean	0.34	0.37	(0.20-0.66)	<.001
SD†‡	1.32	1.20	(0.89-1.60)	.21
LH				
Mean	2.98	3.00	(1.52-5.93)	.002
SD†‡	1.57	1.57	(1.18-2.22)	.005

Abbreviations: CES-D, Center for Epidemiological Studies of Depression; CI, confidence intervals; FSH, follicle-stimulating hormone; LH, luteinizing hormone.
*Each hormone was examined separately in the final model because of high colinearity of the hormones.
†Standard deviation (SD) is the deviation of the hormone measures around the subjects' mean, calculated for each subject at each assessment period.
‡Refers to odds per 1 unit change in SD.

Freeman, E. W. et al. Arch Gen Psychiatry 2006;63:375-382.

Treatment of Perimenopausal and Menopausal Women with Depression

Diagnostic Challenges

Clinical Presentation

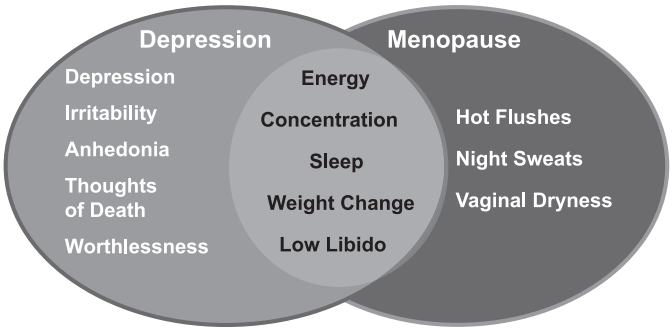
- Most women have a history of MDD, recurrence of depression during transition, similar symptoms
- Typical symptoms: anhedonia, irritability, sleep disruption, fatigue, poor concentration
- "Mood swings" - rule out bipolar disorder
- Psychosocial factors specific to midlife (e.g., caring for aging parents, children leaving home, decline in health)
- Comorbid medical illness

Core Menopause Symptoms

- **Vasomotor Symptoms: Night sweats, hot flashes**
  - Affect 60% to 80%of perimenopausal women
- **Sleep Disturbance**
  - 2-fold increase vs. premenopausal women
- **Depressive Symptoms**
  - 2-fold increase vs. premenopausal women
- **Vaginal Dryness, Changes in Sexual Function**
  - 25% to 60% of women report moderate to severe vaginal dryness or dyspareunia

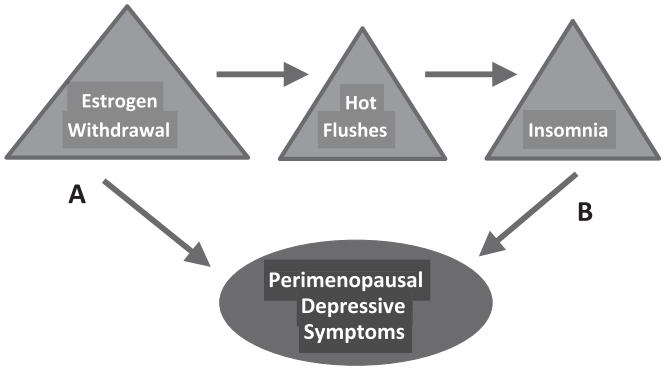
- Gold EB et al. *Am J Public Health*. 2006;96(7):1226-1235.
Ohayon MM. *Arch Intern Med*. 2006;166(12):1262-1268.
Freeman EW et al. *Arch Gen Psychiatry*. 2006;63(4):375-382.
Cohen LS et al. *Arch Gen Psychiatry*. 2006;63(4):385-390.

Menopause vs. Depression-Related Symptoms



Soares CN, et al. *CNS Spectr*. 2005 Jun;10(6):489-497.
Joffe H, et al. *Psychiatr Clin North Am*. 2003;26:563-580.

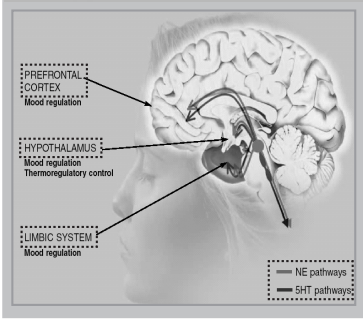
Potential Mechanisms of Perimenopausal Depressive Symptoms



Joffe H and Cohen LS. *Biological Psychiatry.* 1998;44:798-811.

Estrogen Modulation of Key Regions/Systems

Brain regions involved in MDD and Menopausal Symptoms

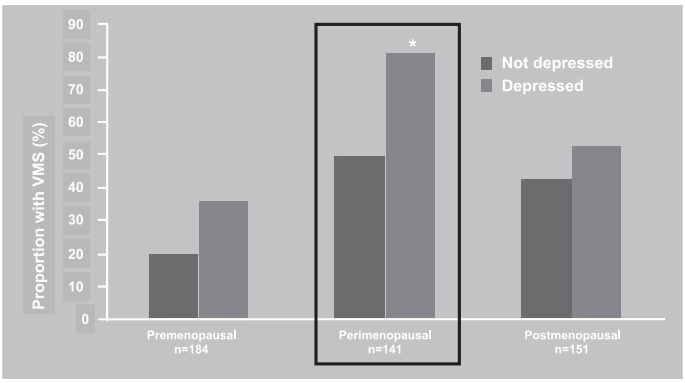


Estrogen has multiple effects on neurotransmitter systems and brain regions involved in MDD and menopausal symptoms (VMS)

During times of estrogen fluctuations/decline, loss of these effects might predispose some women to dysregulation of affected brain regions

Figure adapted from Charney DS. *Am J Psychiatry.* 2004;161:195-216.

Perimenopausal women with depression are more likely to have hot flashes than peri women without depression.

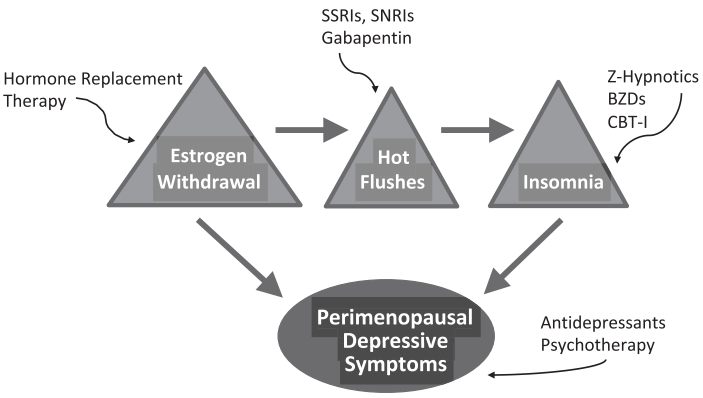


*P=0.008 vs. nondepressed perimenopausal.
Joffe H, et al. *Menopause.* 2002;9:392-398.

Treatment of Perimenopausal and Menopausal Women with Depression

Selecting the Appropriate Intervention

Multiple Targets for Intervention



Estrogen-Based Therapies for the Treatment of MDD in Perimenopausal Women

DEPRESSION AND ANXIETY 32:539–549 (2015)

Research Article

EFFICACY OF ESTRADIOL IN PERIMENOPAUSAL DEPRESSION: SO MUCH PROMISE AND SO FEW ANSWERS

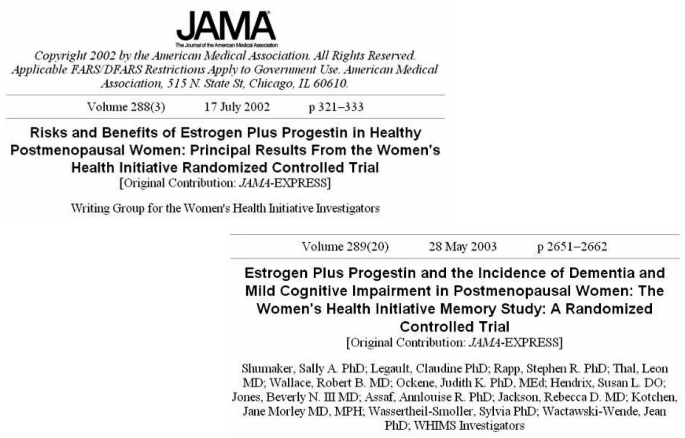
David R. Rubinow, M.D.,[1]* Sarah Lanier Johnson, B.S.,[1] Peter J. Schmidt, M.D.,[2] Susan Girdler, Ph.D.,[1] and Bradley Gaynes, M.D. M.P.H.[1]

- 25 RCT on the effects of estrogen therapy on mood
- Only 5 included symptomatic (depressed) women
- Only 2 E2 RTCs for perimenopausal depression

Treatment of Perimenopausal: Hormonal Interventions

- RCTs with 17β-estradiol
  - Response in 80% of women on estradiol vs. 20% in placebo *(Schmidt 2000)*
  - Remission in 68% of women on estradiol vs. 20% with placebo *(Soares 2001)*
- Primarily in women with vasomotor symptoms
- Secondary to antidepressant effects or to improvements in hot flashes and sleep?
- Perimenopausal women: estrogen superior to placebo
- Little evidence to indicate that estrogen is effective for POST-menopausal depression
- Studies were carried out in women with unopposed estrogen
- No RCTs of combination estrogen plus progestogen for depression

[1] Schmidt, *Am J OBGYN* 2000; [2] Soares, *Arch Gen Psych* 2001;



JAMA

Volume 288(3) 17 July 2002 p 321–333

Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results From the Women's Health Initiative Randomized Controlled Trial

[Original Contribution: *JAMA*-EXPRESS]

Writing Group for the Women's Health Initiative Investigators

Volume 289(20) 28 May 2003 p 2651–2662

Estrogen Plus Progestin and the Incidence of Dementia and Mild Cognitive Impairment in Postmenopausal Women: The Women's Health Initiative Memory Study: A Randomized Controlled Trial

[Original Contribution: *JAMA*-EXPRESS]

Shumaker, Sally A. PhD; Legault, Claudine PhD; Rapp, Stephen R. PhD; Thal, Leon MD; Wallace, Robert B. MD; Ockene, Judith K. PhD, MEd; Hendrix, Susan L. DO; Jones, Beverly N. III MD; Assaf, Annlouise R. PhD; Jackson, Rebecca D. MD; Kotchen, Jane Morley MD, MPH; Wassertheil-Smoller, Sylvia PhD; Wactawski-Wende, Jean PhD; WHIMS Investigators

Hormone Replacement Therapy Study Halted

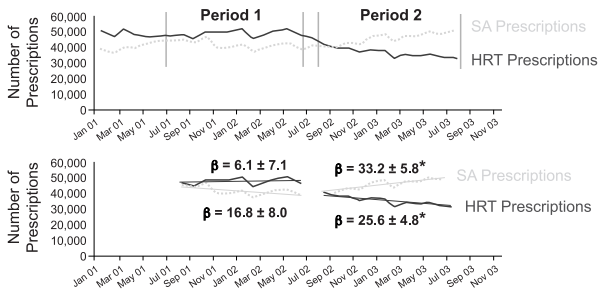
Increased risk of breast cancer a factor, government says

August 14, 2002 Posted: 11:56 AM EDT (1556 GMT)___

WASHINGTON (CNN) -- In a move that may affect millions of women, U.S. government scientists Tuesday stopped a major study of hormone replacement therapy on the risks and benefits of combined estrogen and progestin in healthy menopausal women, citing an increased risk of invasive breast cancer.

Researchers from the National Heart, Lung and Blood Institute of the National Institutes of Health also found increases in coronary heart disease, stroke and pulmonary embolism.

Prescriptions of HRT and Antidepressants* Prior to and After WHI Results



Bottom: Linear regression models of the number of prescriptions against time, for each prescription type (HRT and SA) and for each time period (11 months before and 11 months after July 2002)

*Citalopram, fluoxetine, sertraline, fluvoxamine, paroxetine, venlafaxine, nefazadone, and trazodone.

HRT = hormone replacement therapy; WHI = Women's Health Initiative; SA = serotoninergic antidepressant.

McIntyre RS, et al. *CMAJ*. 2005;172:57-59.

Impact of WHI on Treatment of Women During Menopause Transition

DecreasedHormone therapy use
+
Lowest dose, shortest duration

More symptomatic women

WHI = Women's Health Initiative.

Can estrogen replacement therapy prevent perimenopausal depression?

- 172 euthymic perimenopausal and early postmenopausal women
- Randomly assigned to receive either transdermal estradiol (0.1 mg/d) plus intermittent oral micronized progesterone or placebo
- After 12 months, women receiving active HRT were less likely to develop depressive symptoms compared with women receiving placebo (32.3% vs. 17.3%)
- Greater benefits for women with stressful life events in the preceding 6 months
- Trend toward increased benefit in peri- vs. post-menopausal women

Treatment of Perimenopausal MDD: Antidepressants

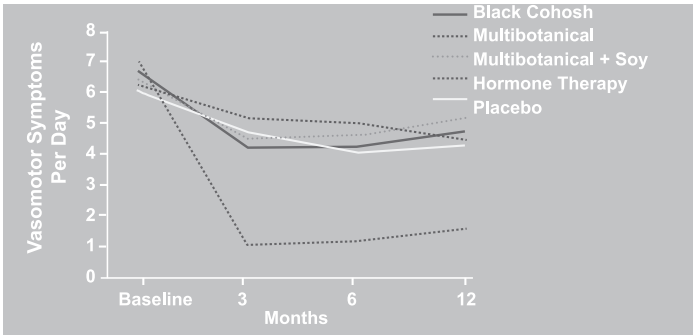
- Two large RCTs support the use of desvenlafaxine, superior to placebo
- Positive results in open trials of SSRIs and SNRIs: citalopram, escitalopram, venlafaxine, vortioxetine, mirtazapine
- Dosage range similar to non-menopausal MDD
- Beneficial effects on sleep, VMS, anxiety, pain
- Effective for peri- and postmenopausal women

Joffe, *J Clin Psych* 2007; Joffe, *J Women's Health Gend Based Med* 2001; Soares, *J Clin Psych* 2003; Dias, *Menopause* 2006; Kornstein, *J Clin Psych* 2010

Treatment of Menopausal Symptoms

- Hormone replacement therapy – gold standard
  - For severe symptoms in healthy younger women
  - Limit treatment to 5 years
- SSRIs, SNRIs improve vasomotor symptoms, depression
- Gabapentin improves VMS and sleep, pain

Treatment of Vasomotor Symptoms With Black Cohosh, Multibotanicals, Soy, Hormone Therapy or Placebo

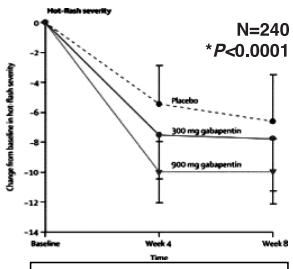


- Black cohosh, a multibotanical herbal product, and soy intake did not appear to significantly reduce the frequency or severity of menopause-related hot flushes or night sweats

Newton KM, et al. *Ann Intern Med.* 2006;145:869-879.

Treatment of hot flashes with gabapentin

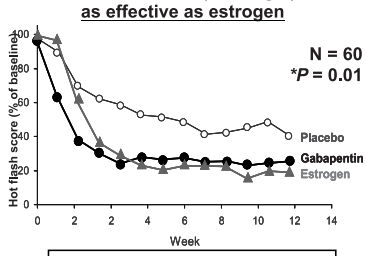
Low-dose (900mg/d) effective



Hot flash score reduction
Gabapentin 900-mg/day: 46%*
Gabapentin 300-mg/day: 31%
Placebo: 15%

Pandya KJ et al, *Lancet* 2005

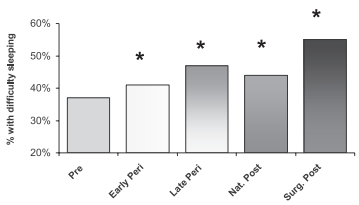
Moderate-dose (2400mg/d) as effective as estrogen



Hot flash score reduction
Gabapentin 2400-mg/day: 71%*
Estrogen (CEE 0.625-mg/day): 72%
Placebo: 54%

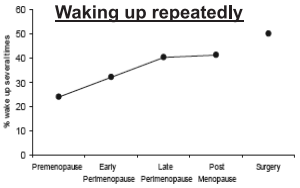
Reddy SY et al. *OBGYN* 2006

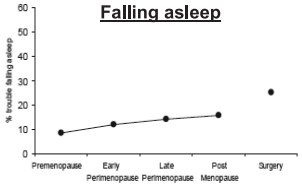
Sleep Disturbance in Peri/Postmenopausal Women



* p<0.005 vs. premenopause

Sleep maintenance is most common symptom[2]





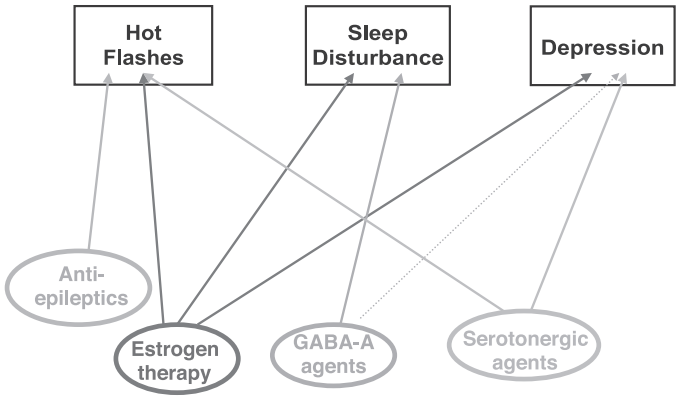
[1] Kravitz, *Menopause* 2003; data for Caucasians

[2] Kravitz, *Sleep* 2008

Treatment of Sleep Disturbance in Perimenopausal Women

- Non-benzodiazepine sedative hypnotics
  - Ezopiclone improved sleep, decreased VMS
- SSRIs – Not sedating but may improve anxiety, VMS
- Gabapentin – Mildly Sedating, improves anxiety, RLS
- CBT-I – Effective and non-menopausal patients, CBT may also be used to treat VMS

Treatment of Menopause-Associated Symptoms



Novel Strategies for the Treatment of Menopausal Symptoms

- Stellate ganglion blockade – VMS
- Acupuncture- VMS
- Neurokinin 3 Receptor Antagonists – VMS
- Amodafenil – fatigue, cognitive function
- New Study: Pregnenolone (neurosteroid) for menopausal depression

Conclusions

1. Etiology of menopause-associated depression is not precisely known
2. Co-occurrence of hot flashes, sleep disturbance, and depression suggests
   - Shared mechanisms
   - Cascade of effects

Current State of Treatment Options

- Antidepressants remain the treatment of choice for depression across the female life cycle.
  - Limited by side effect profile
  - Not effective or fully effective for all patients
- Hormonal strategies can be helpful for the treatment of menopause-related depressive symptoms
  - Either alone or In combination with anti-depressant
  - Risks associated with long-term treatment
- Limited evidence for integrative/ complementary and alternative medicine treatment options despite popularity

Treatment Guidelines

- Antidepressants first line treatment for MDD
  - Past response guides selection
  - Consideration of side effects (sexual side effects with SSRIs, paroxetine, weight gain with mirtazapine)
- Menopausal symptoms may affect response
  - Assess for VMS – gabapentin
  - Assess sleep – gabapentin, Z-hypnotics, BZDs, CBT-I
- Consider adjunctive psychotherapy

Unmet Needs

1. Available treatments are limited to serotonergic antidepressants and traditional hormone replacement therapy
2. No treatments target all aspects of symptom domains- mood, VMS, sleep, anxiety
3. Many patients prefer non-SSRI/SNRI and non-estrogen related treatments
4. Available treatments are not rapidly acting
5. No treatments have received a specific FDA indication for perimenopause-related MDD

NOTES

Question & Answer

NOTES

Substance Use Disorders and Posttraumatic Stress Disorder in Women of Reproductive Age

Edwin Raffi, MD, MPH

Substance Use Disorder and Posttraumatic Stress Disorder in Women of Reproductive Age

Edwin R. Raffi, MD, MPH
2020

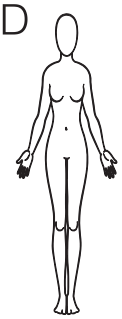
Instructor in Psychiatry | Harvard Medical School
Center for Women's Mental Health | Massachusetts General Hospital

Objectives

- Discuss the etiology of co-occurring PTSD and SUD in women.
- Discuss screening for and diagnosis of co-occurring PTSD and SUD in women.
- Describe best treatment modalities for co-occurring PTSD and SUD in women

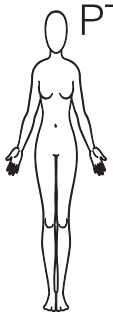
Comorbid SUD & PTSD

SUD



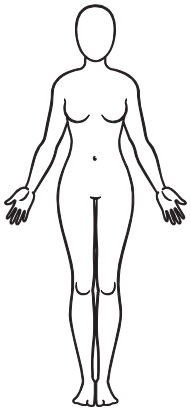
- ~50% seeking SUD treatment meet criteria for current PTSD. (Berenz, Coffey 2013)
- 30-90% of women in SUD Tx experience physical/sexual abuse (Finkelstein et. al. national trauma consortium, Parks and Miller, 1997)
- co-occurring PTSD-SUD = poorer treatment outcomes (Berenz, Coffey 2013)

PTSD



Case

- 23 year old female with history of **Hepatitis C** and **Borderline Personality Disorder**, chief complaint: Fatigue, anxiety and insomnia.
- Angry to "**deal with a *male* nurse**" in waiting room
- Found out she 8 weeks pregnant (G4P111)
- Discontinued all psych medications 4 weeks ago
- Drinks 2-3 glasses of wine / night
- No illicit drugs
- Yes. **Marijuana**. Yes.
- Utox positive for **Fentanyl**? Ok. Yes.

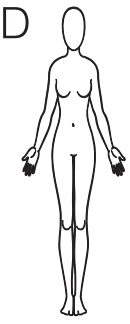


Approach to Diagnosis & Treatment:

- Integrated Care with "parallel treatment" of both disorders
- Biological (family history, genetics, other physical ailments, etc.)
- Psychological (cogn. & behav. routines, coping mech. etc)
- Social- Environmental (spouse, dog, car, finances, etc.)

Comorbid SUD & Trauma

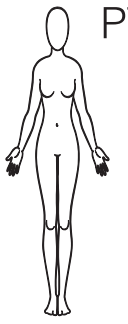
SUD



Sympathetic nervous system.
(Stress) v.

Parasympathetic nervous system (Relaxation)

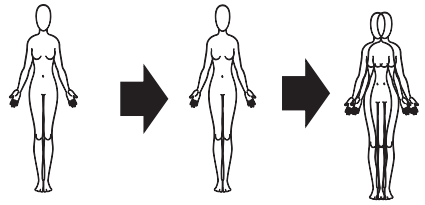
PTSD = Sympathetic Overdrive
SUD = Self Medication



PTSD

(Benson Henry Institute)

Most likely Etiology



(Berenz, Coffey 2013, Kessler et al 1995, Mellman et all 1992, Chilcot et al 1998)

Women…

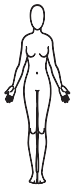
- 2X as likely as men to develop PTSD
- experience a longer duration of posttraumatic symptoms
- display more sensitivity to stimuli that triggers them
- survivors often wait years to receive help, while others never receive treatment at all

Trauma in Women

- ~50 % of women will experience at least one traumatic event in their life.
- most common trauma = sexual assault (~1 in 3 women) or childhood sexual abuse.

(American Psychological Association)

Women are…



more likely to experience sexual assault

↓

sexual assault is more likely to cause PTSD than many other events.

…**more than twice as likely to develop PTSD than men (10% vs 4%):**

(ptsd.va.gov)

Possible genetic susceptibilities

- possible link between Premenstrual Dysphoric Disorder (PMDD) and PTSD
- e.g. the startle response (hypervigilance) shown to be different in women with PMDD.
- theory: suboptimal production of ALLO >>increased arousal and increased stress reactivity to psychosocial or environmental triggers. (Raffi Freeman, 2017. Kask K 2008)

Women Specific Events

- **There are also 'women-specific' experiences and events that can be traumatic…**
  - Miscarriages / TAB
  - Traumatic Births
  - Other obstetrics or gynecological events

Women Specific History Taking

- Obstetrics history : correlation with mental health
- Gynecological history : mood tracking and correlation with mental health
- Contraception: family planning and correlation with mental health

SUD in Women

- **several factors associated with risk of substance use do. (during pregnancy) include:**
  - younger age (less than 25 years)
  - a current or past personal and/or family history of SUD
  - co-morbid psychiatric disorders
  - childhood history of sexual abuse

(Kahan et all 2006 and Chansoff et al 2001)

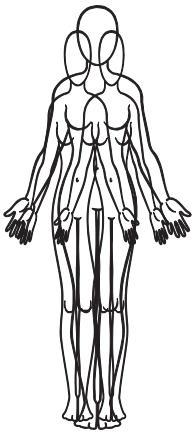
SUD in Women

- Opioid use and withdrawal is known to cause
  - (premature labor, miscarriages, fetal distress, increased risk for relapse, overdose and death)
- alcohol use disorder
  - (fetal alcohol syndrome)
- cocaine/stimulant use disorder, nicotine use disorder, etc.
  - (intra uterine growth retardation, low birth weight, placental previa or abruption, preterm delivery, SIDS, etc.)

(Ebrahim et al 2003, Tran et al, 2017).

Case

- **If you see:** 23 year old female with history of **Hepatitis C** and **Borderline Personality Disorder,** at 8 weeks gestation **(G4P111)** chief complaint : fatigue and insomnia**.**
- **You should think to rule out:** 23 year old female with history of Hep. C, borderline personality disorder, **Substance Use Disorder**, Trauma related do such as **PTSD, Substance induced mood disorder**, Rule out other mood disorder and anxiety disorders, at 8 weeks gestation (G4P111).



PTSD Diagnosis: What is Trauma?

"An event where a person experiences actual or threatened death, serious injury, or sexual violence"

Criterion A of DSM 5 (one required)

- directly experiencing the event
- Witnessing, in person, as the event occurred to others
- learning that the event occurred to a close person (usually accidental or violent)
- Experiencing repeated or extreme exposure to aversive details of traumatic events

But, What *is* Trauma? The three Es

event, series of events…

…experienced by an individual as physically or emotionally harmful or life threatening and that has lasting adverse…

- Why me? Feeling powerless, humiliated, guilt, shame, betrayal, silencing.
- Cultural beliefs, social support, developmental stages

…effects on the individual's functioning and mental, physical, social, emotional, or spiritual well-being.

- Immediate or delayed, short or long term
- lack of recognition of connections between symptoms of trauma (SAHMSA, 2014)

PTSD Diagnosis

- Criterion B – re-experiencing symptoms
- Criterion C – avoidance of trauma related stimuli
- Criterion D – negative thoughts or feelings after trauma
- Criterion E – trauma related reactivity and arousal
- Criterion F – symptoms last >1 month
- Criterion G – symptoms create distress & functional impairment
- Criterion H – symptoms not due to medications, substances or other illness.

(DSM 5)

Substance Use Disorders

- Direct activation of the reward system by one of 10 types of substances:

Alcohol	Caffeine	Cannabis
Hallucinogens	Inhalants	Opioids
Sedatives	Stimulants	Tobacco
Other		

(DSM 5)

Substance Used Disorder DSM 5

A. Impaired control over use
B. Social impairment
C. Risky use
D. Pharmacological criteria (tolerance, withdrawal)

"Biological" (Rx) Treatment of Mental Health Disorders In Women

- **50% of all pregnancies in the US are unplanned**
- Pick meds with well-studied reproductive safety profile
- If possible, make changes months prior to pregnancy
- Limit number of Rxs. to decrease exposure of infant (maximize one med prior to adding a second)
- **>80% of pregnancies in SUD (OUD) are unplanned**
- **Discuss contraception & pregnancy planning**

"New" Rule:

The FDA published the "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling, referred to as the:

"Pregnancy and Lactation Labeling Rule" (PLLR)

(i.e. No more letter categories – A, B, C, D and X)

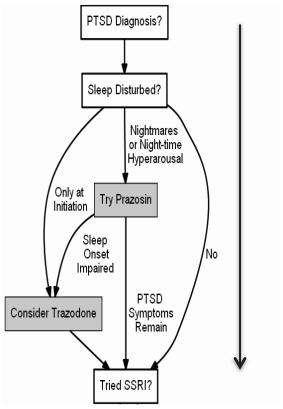
(FDA.gov, Hogan et al 2018)

SUD and Trauma

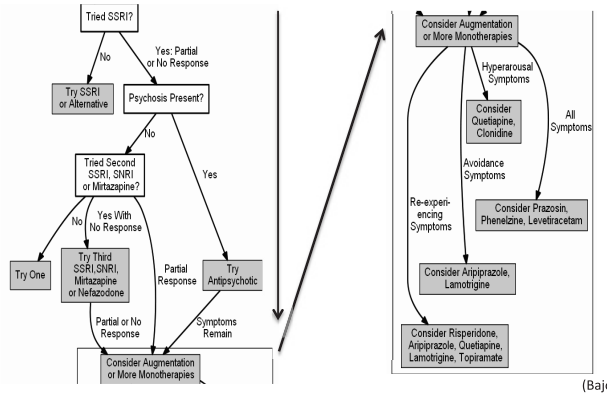
Where can you start?

Sleep

SUD and Trauma



Rx. Treatment of PTSD



(Bajor et al. 2018)

Pharm of PTSD and SUD

- Treat trauma as a likely trigger for worsening SUD
- Weigh risks, benefits, alternatives, including risk of no treatment with medications (e.g. Prazosin, SSRIs) and connection to possible rehab.
  - Consider patient's history
  - Negotiate care and patient preferences

MAT

Medication assisted treatment (MAT) for substance use disorders (SUD)

- patient's history of use and treatment
- patient's preference for treatment
- history of relapse
- need for closer monitoring.

The Maternal Opioid Treatment: Human Experimental Research (MOTHER) project

eight-site, randomized, double-blind, double-dummy, flexible-dosing, parallel-group clinical trial **compared** treatment with **methadone** to that of **buprenorphine**.

(Jones et al 2010)

MOTHER project:

neonates exposed to buprenorphine required…

- shorter hospital stays,
- lower morphine requirements
- average of 4.1 days of tx for NAS vs. 9.9 days for methadone ($p<0.01$).

(Jones et al 2010)

MOTHER project:

33% of women on buprenorphine therapy stopped treatment as vs. 18% of the methadone group (p=0.02).

(Full agonists >>>less cravings)

(Fischer et al 2006)

However, in this study, women in both groups had to present to a clinic daily (vs. buprenorphine prescribed weekly+)

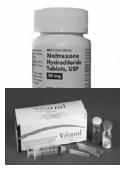
(Jones et al 2010)

MAT

Medication assisted treatment (MAT) for substance use disorders (SUD)

- patient's history of use and treatment
- patient's preference for treatment
- history of relapse
- need for closer monitoring.

Rx. MAT for SUD



- **Naltrexone (PO, IM)**

- **Disulfuram and acamprosate**

- **Nicotine replacement therapy, varenicline & bupropion**

- **Topiramate, Naltrexone, Baclofen**

Psychological Treatment Protocols for Tx of PTSD

- Seeking Safety (non-exposure-based)
- Dialectical Behavioral Therapy (none-exposure based)
- Prolonged Exposure Therapy (exposure-based)
- Cognitive Processing Therapy (exposure-based)
- Eye Movement Desens. & Reprocessing (exposure-based)

Psychological Treatment Protocols for SUD

- Motivational Interviewing
- Cognitive Behavioral Therapy
- Seeking Safety
- Dialectical Behavioral Therapy

Comprehensive Screening

- careful, empathetic, and nonjudgmental interview

>>engage in tx & preserve therapeutic alliance <<

"I ask the same questions about substance use, mental health, family and social history from everyone."

Comprehensive Screening

- **a comprehensive assessment of patient to include:**
  - substance use history (amount, duration, route of use, source, previous treatment outcomes and modalities)
  - mental health history (including history of Trauma)
  - obstetrical and gynecological history
  - other medical health (e.g., sexually transmitted do, hepatitis C),
  - medication trials
  - **psychosocial history**
  - **family history**

(Cruciani et al, 2013, SAMHSA, 2013)

Social/Environmental Factors

- Finances
- Housing
- Food
- Transportation
- Ongoing/ past trauma
- Access to pharmacy
- Access to phone
- Legal Issues
- Education
- Ability to maneuver the healthcare system
- Health Insurance
- Child and Family Services
- Relationship/Partner
- Partner's SUD
- Military Connection

What Works Best?

Integrated, collaborative, and patient centered care

….due to multiple needs for providers and many barriers to care in this patient population

- increase patient participation and retention in prenatal care
- improve pregnancy outcomes

(Cruciani et al 2013)

Summary

- All women of reproductive age: screen for SUD & Hx of Trauma
- Treat symptoms / disorders in parallel
- Biological, Psychological, Social-Environment interventions
- Integrative and collaborative patient centered care approach

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NOTES

NOTES

ADHD in Women

Allison Baker, MD

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Course and Treatment of ADHD and Comorbid Disorders During Pregnancy and the Postpartum Period

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Staff Psychiatrist, Ammon-Pinizzotto Center for Women's Mental Health

Massachusetts General Hospital

Instructor in Psychiatry, Harvard Medical School

Overview

- Learning objectives
- Background
- ADHD in girls and women
  - diagnostics, treatment
- Special considerations for pregnancy and the postpartum
  - Reproductive and lactation safety of stimulants and non-stimulants
- The risk/risk consultation model and a case
- References

Learning Objectives

By the end of this program, participants will be able to:

1. Discuss general risks of stimulant use during pregnancy with their patients with ADHD;
2. Create a tailored risk/risk analysis of stimulant use vs. risk of stopping treatment for their patient with ADHD;
3. Describe the non-pharmacologic treatment options available to their patients with ADHD.

Background

- 4.4% of US adults have ADHD. Of these adults with ADHD, 38% are women and 62% are men (Kessler et al. 2006).
- Roughly 1 in 30 women has ADHD (Faraone 2018).
- ADHD is linked to elevated risk of poorer general and mental health, increased rates of substance abuse, impaired work performance, and financial distress (Biederman 2012, Biederman 2010).
- Strongly associated with other mental health disorders, such as mood and anxiety disorders (Freeman 2014, Kolar 2008).

ADHD in Girls and Women

- ADHD that persists into adulthood for women has been shown to be associated with depression, anxiety, substance use, occupational, social, and overall impairment domains (Biederman 2010).
- Adult women with ADHD can experience a variety of difficulties at work and in their personal and family lives related to their ADHD symptoms (Owens 2017).
- Given that treatment of adult ADHD improves functioning (Sarkis 2014) and quality of life (Agarwal 2012), women on treatment for ADHD may wish to continue their medications during pregnancy in order to continue to experience the benefits of treatment.

ADHD in Reproductive Age Women

- ADHD that persists into adulthood for women has been shown to be associated with depression, anxiety, substance use, occupational, social, and overall impairment domains.
- Adult women with ADHD can experience a variety of difficulties at work and in their personal and family lives related to their ADHD symptoms.
- Given that treatment of adult ADHD improves functioning and quality of life, women on treatment for ADHD may wish to continue their medications during pregnancy in order to continue to experience the benefits of treatment.

Biederman et al. Am J Psychiatry. 2010
Owens et al. J Consult Clin Psychol. 2017
Sarkis, Postgrad Med. 2014
Agarwal et al. Innov Clin Neurosci. 2012

Functional Impairment*: Implications for Pregnancy and Postpartum Women

- Family
- Work
- Life skills
- Problems with self-concept
- Social functioning
- Risk taking behavior

*Functional Impairment during pregnancy and the postpartum period have long term implications – ? higher risk of later psychopathology

Weissman et al. JAMA. 2006

Diagnostic Issues

- Clinical diagnosis, as there are no laboratory tests.
- DSM 5 proposes specific criteria for the diagnosis in very young children as well as in adults.
- Typical behavior of ADHD should be present in at least 2 settings.
- Must have impairment in functioning in addition to symptoms of ADHD.

ADHD DSM 5

Inattention: 6+, > 6 months

- Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or with other activities.
- Often has trouble holding attention on tasks or play activities.
- Often does not seem to listen when spoken to directly.
- Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., loses focus, side-tracked).
- Often has trouble organizing tasks and activities.
- Often avoids, dislikes, or is reluctant to do tasks that require mental effort over a long period of time (such as schoolwork or homework).
- Often loses things necessary for tasks and activities (e.g. school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones).
- Is often easily distracted.
- Is often forgetful in daily activities.

Hyperactive/Impulsive: 6+, >6 months

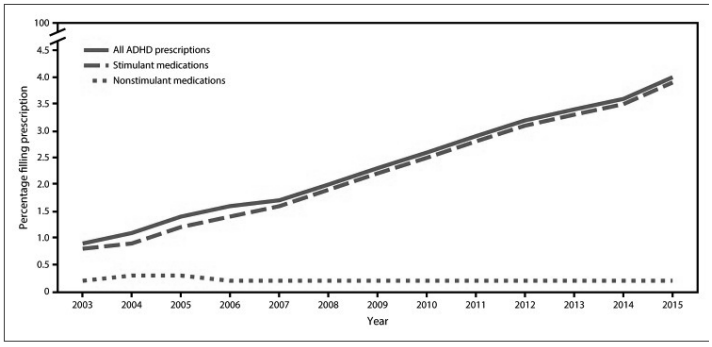
- Often fidgets with or taps hands or feet, or squirms in seat.
- Often leaves seat in situations when remaining seated is expected.
- Often runs about or climbs in situations where it is not appropriate (adolescents or adults may be limited to feeling restless).
- Often unable to play or take part in leisure activities quietly.
- Is often "on the go" acting as if "driven by a motor".
- Often talks excessively.
- Often blurts out an answer before a question has been completed.
- Often has trouble waiting his/her turn.
- Often interrupts or intrudes on others (e.g., butts into conversations or games).

Treatment

- Treating ADHD requires medical, educational, behavioral and psychological intervention. This approach to treatment is called "multimodal" and, depending on the age of the individual with ADHD, may include:
  - parent training
  - Medication
  - skills training
  - Counseling
  - Cognitive behavioral therapy
  - educational supports
  - education regarding ADHD
- Most guidelines recommend a stepwise approach to treatment, beginning with non-drug interventions and then moving to pharmacological treatment in those more significantly affected.

Pregnancy Considerations

- ADHD medication use among pregnant women is increasing but consensus about the safety of ADHD medication use during pregnancy is lacking.
- Given that nearly half of U.S. pregnancies are unintended and early pregnancy is a critical period for fetal development, these are matters of great clinical importance.

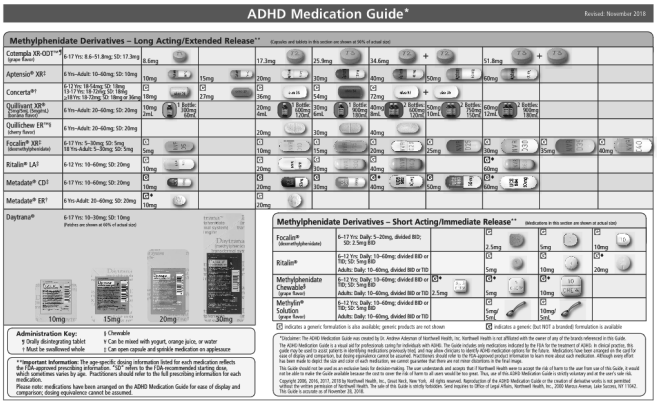


FIGURE

Percentage of women aged 15–44 years with private employer-sponsored insurance who filled one or more prescriptions for an attention-deficit/hyperactivity disorder (ADHD) medication, by medication class — United States, 2003–2015

Attention-Deficit/Hyperactivity Disorder Medication Prescription Claims Among Privately Insured Women Aged 15–44 Years — United States, 2003–2015
MMWR Morb Mortal Wkly Rep. 2018 Jan 19;67(2):66-70.

Treatment


ADHD Medication Guide*

Revised: November 2018

Methylphenidate Derivatives – Long Acting/Extended Release**

Methylphenidate Derivatives – Short Acting/Immediate Release**

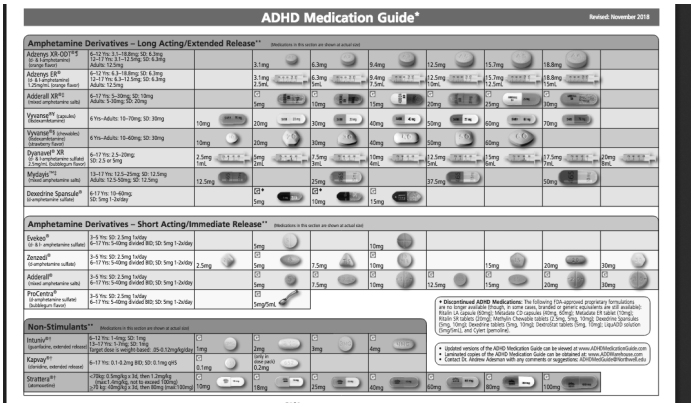
Daytrana®

Administration Key:

Cohen Children's Medical Center
Northwell Health

Guide for free: www.ADHDMedicationGuide.com

Treatment


ADHD Medication Guide*

Revised: November 2018

Amphetamine Derivatives – Long Acting/Extended Release**

Amphetamine Derivatives – Short Acting/Immediate Release**

Non-Stimulants**

ADHD in Reproductive Age Women

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Biederman et al. Am J Psychiatry. 2010
Owens et al. J Consult Clin Psychol. 2017
Sarkis, Postgrad Med. 2014
Agarwal et al. Innov Clin Neurosci. 2012

Considerations for Pregnancy

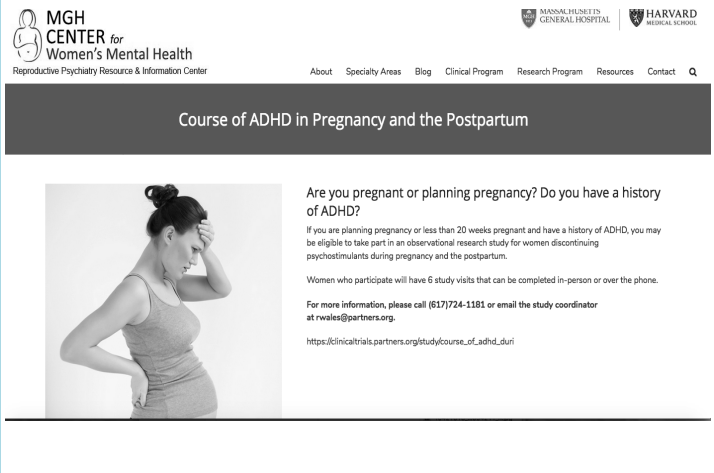
- No studies have evaluated the course of ADHD across pregnancy and the postpartum. We are publishing the first study to date.
- Possible that the perinatal period has an impact upon the course.
  - Hormonal impact on cognition?
  - Distractions?
- Treatment decisions impacted by pregnancy.
  - Many women elect to discontinue stimulants for pregnancy and while breastfeeding.
- The impact of treatment decisions upon occupational functioning, interpersonal relationships, course of comorbid illnesses, and quality of life are not understood.

Course of ADHD During Pregnancy and the Postpartum:

Investigating ADHD Symptoms and Functioning Among Women Who Chose to Discontinue, Alter, or Maintain Pharmacologic Treatment for ADHD in the Perinatal Period

Allison S. Baker, MD, Rebecca Wales, BA, Olivia Noe, BS, Peter Gaccione, PhD, Marlene P. Freeman, MD, and Lee S. Cohen, MD

Funded by Gerstner Family Foundation



Hypothesis

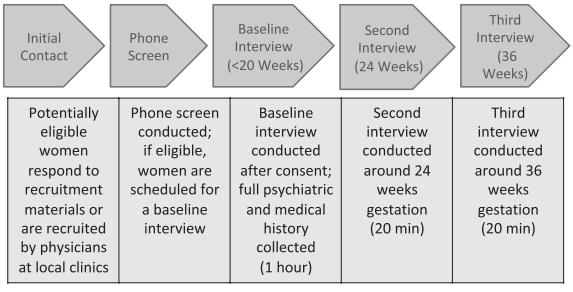
- Risk for attention deficit hyperactivity disorder (ADHD) symptom severity and functional impairment will be greater among women who discontinue/change dose of stimulants compared to those who maintain treatment with these agents.

Inclusion Criteria

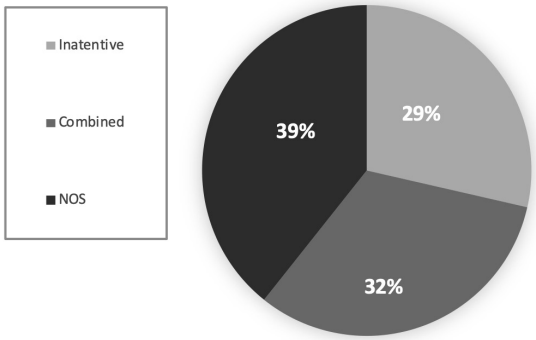
- 18 years or older
- Planning pregnancy or <20 weeks pregnant
- Has treating prescribing physician for ADHD and any other comorbid psychiatric illness
- Past (childhood) and current ADHD diagnosis in ACDS

Study Outline and Procedure

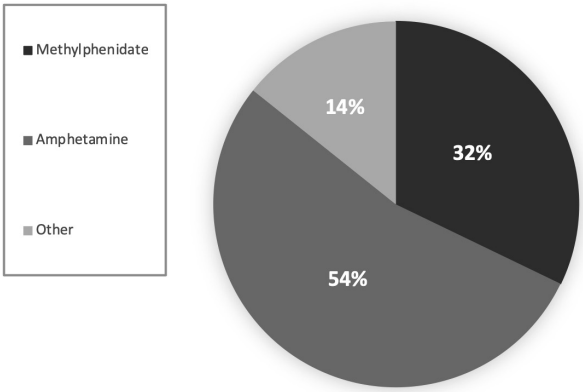
- Pregnant women ages 18-45 were prospectively followed during pregnancy using 3 structured clinical interviews
- ADHD symptoms were recorded at each timepoint using the AISRS
- Additionally, symptoms of anxiety, depression, stress, and functional impairment were monitored



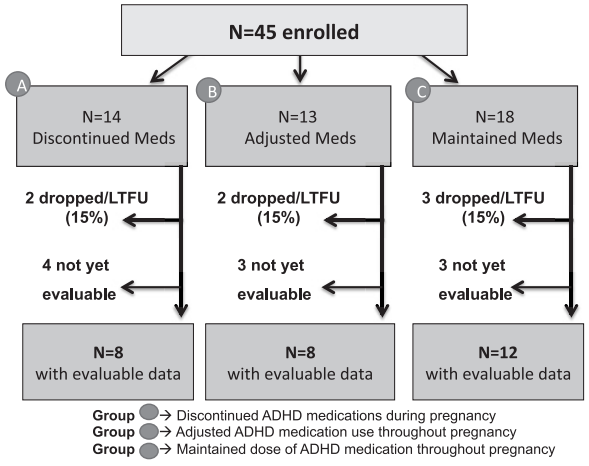
ADHD Type



ADHD Treatment



Use of ADHD Medications Across Pregnancy



Psychiatric Comorbidity in Pregnant Women with ADHD

Diagnosis	Group A (n=8)	Group B (n=8)	Group C (n=12)	Overall (n=28)
	N (%)			
Generalized Anxiety Disorder (GAD)	5 (62.5%)	4 (50%)	5 (41.67%)	14 (50%)
Major Depressive Disorder (MDD)	2 (16.67%)	3 (37.5%)	4 (33.33%)	9 (32.14%)
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Bipolar Disorder II	3 (37.5%)	0	0	3 (10.71%)
Obsessive Compulsive Disorder (OCD)	1 (12.5%)	1 (12.5%)	0	2 (7.14%)
Post-Traumatic Stress Disorder (PTSD)	0	1 (12.5%)	0	1 (3.57%)

Outcome Variables

- Adult ADHD Investigator Symptom Rating Scale (AISRS)
- Weiss Functional Impairment Rating Scale – Self Report (WFIRS-S)
- Edinburgh Postnatal Depression Scale (EPDS)

Results: AISRS

- No difference in AISRS scores across sample regardless of treatment condition

Results: WFIRS-S (Family Functioning)

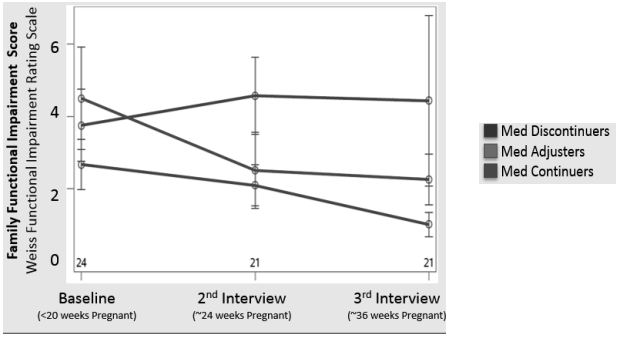


Figure 1. Self-reported impairment in family functioning measured across three pregnancy by medication group. The adjusted mean changes of: discontinuers, 1.55, meds as needed, -1.70, maintainers, -1.54, showing significant differences between those who discontinued meds and those changing meds as needed (3,3, p=0.0309) and discontinuers vs maintainers (3.09, p=0.0197).

Results: EPDS Score

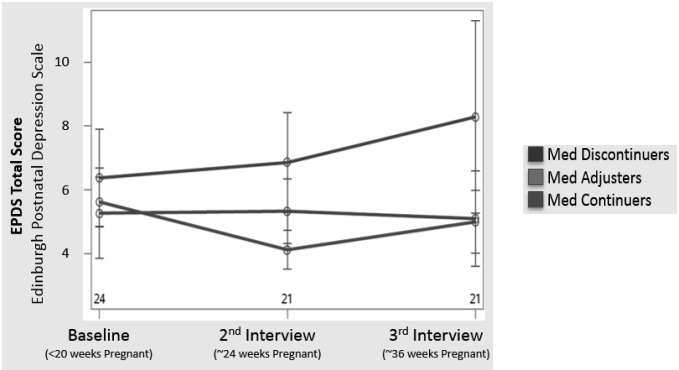


Figure 2. Edinburgh Postnatal Depression Scale (EPDS), self-reported depression and anxiety symptoms across timepoints and treatment groups. Adjusted mean changes of: discontinuers, 4.32, meds as needed, -1.01, and maintainers, -0.65, showing significant differences between those who discontinued meds and those changing meds as needed (5.3, p <0.0001) and discontinuers vs maintainers (4.98, p=0.0009).

Discussion

- Women who discontinued stimulant treatment during pregnancy had a clinically significant increase in depressed mood symptoms as measured by the EPDS during sustained treatment with antidepressant
- Women who discontinued stimulant treatment during pregnancy had significant impairment in family functioning, meaning they are more likely to experience conflict within the family, rate parenting as more difficult, and describe being more isolated from their family
- This preliminary prospective data underscores need for further research in ADHD during pregnancy and the postpartum period and the relationship between ADHD and comorbid psychiatric disorders

Poll Question

- What is a key functional outcome that is most relevant to safety when assessing risk of continuing vs. discontinuing stimulants during pregnancy?

a) Mood
b) Anxiety
c) Academic performance
d) Driving safety

Poll Question

- What is a key functional outcome *that is most relevant to safety* when assessing risk of continuing vs. discontinuing stimulants during pregnancy?

a) Mood
b) Anxiety
c) Academic performance
d) Driving safety

Original Investigation FREE

June 2017

Association Between Medication Use for Attention-Deficit/Hyperactivity Disorder and Risk of Motor Vehicle Crashes

Zheng Chang, PhD, MSc[1,2]; Patrick D. Quinn, PhD[2,3]; Kwan Hur, PhD[2]; et al

» Author Affiliations | Article Information

JAMA Psychiatry. 2017;74(6):597-603. doi:10.1001/jamapsychiatry.2017.0659

Clinical Implications and Treatment Considerations

- Although the default medical position is to interrupt any "non-essential" pharmacological treatment during pregnancy and lactation, in ADHD this may present a significant risk.
- The clinician evaluates each case carefully and performs a risk-risk analysis with the patient prior to developing a treatment plan for pregnancy:
  - the risks of medication exposure throughout the pregnancy weighed against the risks of untreated ADHD, including ***driving safety***, and ***major impairment in fulfilling occupational and domestic roles***
  - Recommendations to reduce workload
  - Recommend CBT for ADHD
  - Increase structure and organization at work or school
  - Employers may be able to offer accommodations

Context

- **The baseline rate of congenital malformations is approximately 3% of all pregnancies in the U.S.**
- Untreated psychiatric disorders are associated with poorer pregnancy outcomes.
- Alcohol, tobacco, illicit drugs are teratogens.
- Psychosocial factors: Socioeconomic status, social support, prenatal care, nutrition, etc.

HOW SAFE IS THE USE OF ADHD MEDICATION DURING PREGNANCY?

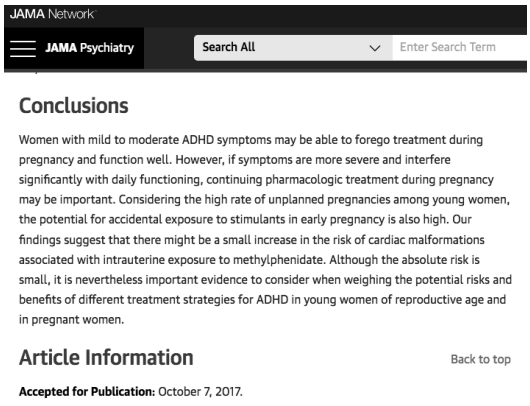
Outcomes to consider

- Congenital Malformations
- Gestational Outcomes
- Neonatal Outcomes
- Neurobehavioral Outcomes

Huybrechts et al. JAMA Psychiatry 2017

- The largest compared 5,571 infants exposed to amphetamines and 2,072 exposed to methylphenidate with unexposed infants. It found no increased risks for adverse outcomes due to amphetamine or methylphenidate exposures.

Huybrechts et al. JAMA Psychiatry 2017


JAMA Network

JAMA Psychiatry | Search All | Enter Search Term

Conclusions

Women with mild to moderate ADHD symptoms may be able to forego treatment during pregnancy and function well. However, if symptoms are more severe and interfere significantly with daily functioning, continuing pharmacologic treatment during pregnancy may be important. Considering the high rate of unplanned pregnancies among young women, the potential for accidental exposure to stimulants in early pregnancy is also high. Our findings suggest that there might be a small increase in the risk of cardiac malformations associated with intrauterine exposure to methylphenidate. Although the absolute risk is small, it is nevertheless important evidence to consider when weighing the potential risks and benefits of different treatment strategies for ADHD in young women of reproductive age and in pregnant women.

Article Information Back to top

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Cohen et al. Obstet Gynecol 2017


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CONTENTS: ORIGINAL RESEARCH

Placental Complications Associated With Psychostimulant Use in Pregnancy

Cohen, Jacqueline M. PhD; Hernández-Díaz, Sonia MD, DrPH; Bateman, Brian T. MD, MSc; Park, Yeonyoung MS, ScD; Desai, Rishi J. MS, PhD; Gray, Kathryn J. MD, PhD; Paterno, Elisabetta MD, DrPH; Mogun, Helen MS; Huybrechts, Krista F. MS, PhD **Author Information**

Obstetrics & Gynecology: December 2017 - Volume 130 - Issue 6 - p 1192-1201

doi: 10.1097/AOG.0000000000002362

CONCLUSION:

Psychostimulant use during pregnancy was associated with a small increased relative risk of preeclampsia and preterm birth. The absolute increases in risks are small and, thus, women with significant ADHD should not be counseled to suspend their ADHD treatment based on these findings.

Cohen et al. Obstet Gynecol 2017

- 3,331 infants exposed to amphetamines
- 1,515 exposed to methylphenidate
- 453 to atomoxetine.
- slightly increased risk of preeclampsia, with an adjusted risk ratio of 1.29 (95% CI 1.11-1.49)
- no statistically significant effect for placental abruption, small gestational age, and preterm birth.
- small increased risk of preterm birth, with an adjusted risk ratio of 1.3 (95% CI 1.10-1.55).
- There was no statistically significant effect for preeclampsia, placental abruption, or small gestational age. Atomoxetine use was free of any indication of increased risk.

Norby et al. Pediatrics 2017

- 1,591 infants exposed to ADHD medication (mostly methylphenidate) during pregnancy, reported increased risks associated with exposure.
- The adjusted odds ratio for admission to a neonatal intensive care unit was 1.5 (95% CI 1.3-1.7), and for central nervous system disorders was 1.9 (95% CI 1.1-3.1).
- There was no increased risk for congenital malformations or perinatal death.

Methlyphenidate Exposure

- Dideriksen et al. 2013
- Kallen et al 2013
- Haervig et al 2014
- Pottegard et al 2014
- Bro et al 2015
- Diav-Citrin et al 2016
- Koren et al 2020

Methylphenidate Data

Author	Exposed	Study Type
Dideriksen et al. 2013	180	Review
Pottegard et al. 2014	222	Population-based, cohort
Kallen et al. 2013	208	Prospective, observational
Bro et al. 2015	186	Population-based, cohort
Haervig et al. 2014	480	Population-based, cohort
Diav-Citrin et al. 2016	382	Prospective, comparative, multicenter observational
Koren et al. 2020	2831 (combined exposures from Pottegard, Diav-Citrin, Huybrechts & Kallen)	Scoping review and meta-analysis

Summary - Safety in Pregnancy

- While some studies have shown increased adverse effects among infants exposed to maternal ADHD medications, most have not.
- There are indications that higher rates of miscarriage are associated with maternal ADHD rather than fetal exposure to psychostimulant medications.
- One study did find a small increased risk of central nervous system disorders and admission to a neonatal intensive care unit. But, again, we do not know whether that was due to exposure to psychostimulant medication, or associated with maternal ADHD.

Take Home Message

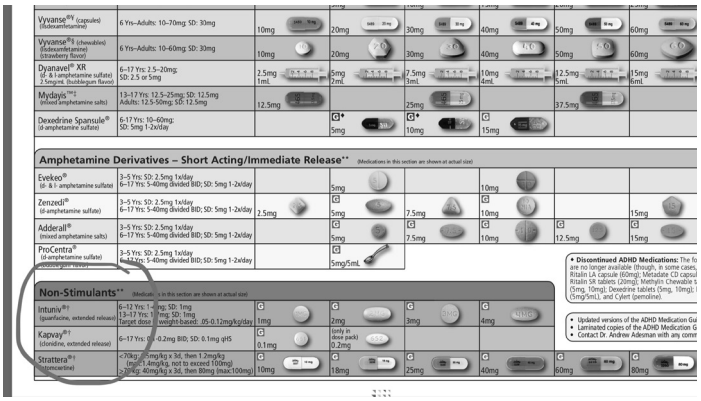
- If there is a risk, it appears to be a small one.
- The question then becomes how to balance that as yet uncertain risk against the disadvantage of discontinuing effective psychostimulant medication.

NEUROBEHAVIORAL OUTCOMES

Neurobehavioral Outcomes

- Behavioral teratogenicity: few human studies, and they are limited to stimulants in context of substance abuse (such as studies of prenatal cocaine exposure).
- Many of the neurodevelopmental studies showed no abnormalities. For example: 40 children exposed during pregnancy to methamphetamine (in some of them the mothers misused methamphetamine) showed no difference in cognitive function at 3–4 years of age compared to sex-matched controls, with the exception of slightly worse testing on the visual motor integration domain (Chang 2009).
- In general, stimulant use is generally not found to have impairment on standard cognitive tests or language/motor development. But the heaviest maternal cocaine use is linked to subtle effects in executive functioning (Freeman 2014).

Non-Stimulants



Non-Stimulants

- Bupropion:
  - May be a reasonable option if has been exposed to it before with good effect, with concurrent depression, and/or need for smoking cessation (Freeman 2014).
  - Amount of data available for bupropion exceeds that for other medications used in the treatment of ADHD.
  - Published reports regarding its safety during pregnancy and lactation are relatively reassuring - not as efficacious as stimulants in the treatment of ADHD.

Non-Stimulants

- Atomoxetine, Guanfacine and Clonidine: No systematic studies in human pregnancy for these agents.
  - Atomoxetine: Swedish registry had 34 women on atomoxetine, 22 in 1st trimester and 12 in 2nd or 3rd trimester; no congenital anomalies (Kallen 2013)
  - Clonidine: One prospective study 1985 on 100 hypertensive pregnant women; no increased malformation rate.
    - 82 hypertensive women: No malformations, one perinatal death (Tuimala 1985)
  - Guanfacine: One study on 30 women with preeclampsia treated with guanfacine for 16-68 days
    - No malformations but 20% had low birth weight (possible 2/2 preeclampsia) (Phillip 1980)

Absence of evidence of risk is not evidence of absence of risk.

Patient and provider engage in shared decision-making via risk/risk analysis.

Assessing Relative Risk:

Case: A 32 year old attorney with ADHD planning pregnancy.

- ADHD combined type since age 6.
- Tried several stimulants and non stimulants.
- Currently on Methylphenidate ER 40 mg daily.
- Decided to stay on until conception and then use PRN.

Case: ADHD during Pregnancy

- Ms. C conceived within 2 months of trying.
- ADHD "under control."
- Plans to stop work at 36 weeks gestation.
- Asks about postpartum and lactation.
- In dosages prescribed for medical indications, limited evidence indicates that methylphenidate levels in milk are very low and not detectable in infant serum.

Case Continued

- Methylphenidate is secreted in small amounts in milk but is generally undetected in infant's blood.
- No contraindication to breast feeding.

Hackett et al. 2006
Spigset et al. 2007
Scharfer et al. 2015

Amphetamines in Breastfeeding

- Amphetamines are excreted in human milk, and a dose of 20 mg/day amphetamine sulfate is enough to transfer measurable amounts of amphetamine to the urine of an exposed infant (Steiner 1984).
- In a study involving 103 nursing infants whose mothers were taking various amounts of amphetamine, no neonatal insomnia or stimulation was observed over a 24- month observation period. The presence of methamphetamine and amphetamine in milk was also demonstrated in two lactating women using intravenous methamphetamine (Illett 2007).
- There seems to be no data on the long-term consequences of exposure through breastfeeding. Due to the relatively high milk levels and possible effects on the nursing infant breast feeding is contraindicated per some authors (Schaefer 2015).
- Clinically, my experience has been that many women elect to nurse on both IR and XR formulations of Adderall. They do this by weighing the 'possible effects on the nursing infant' against case report data of no neonatal insomnia, stimulation, abnormal development or growth problems.

Summary

- From the current available data from prospective, retrospective and case control studies it can be concluded that none of the medications (except guanfacine, where data is unavailable) used for the treatment of ADHD is a major human teratogen.
- Available data do suggest the possibility that psychostimulants, especially amphetamines, may increase the risk of preeclampsia and possibly certain other adverse gestational outcomes; the absolute risk, however, is low.
- Long-term neurodevelopmental studies on the offspring are sparse
- If treatment is pursued, methylphenidate, amphetamine and bupropion appear to be better choices than other medication where reproductive safety data are sparse

Clinical Implications and Treatment Considerations

- Although the default medical position is to interrupt any "non-essential" pharmacological treatment during pregnancy and lactation, in ADHD this may present a significant risk.
- Many patients decide to minimize exposure to ADHD medications during pregnancy with optimization of treatment postpartum
- The clinician evaluates each case carefully and performs a risk-risk analysis with the patient prior to developing a treatment plan for pregnancy:
  - the risks of medication exposure throughout the pregnancy weighed against the risks of untreated ADHD, including ***driving safety***, and ***major impairment in fulfilling occupational and domestic roles***
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NOTES

NOTES

Psychotherapies for Perinatal Psychiatry

Rachel Vanderkruik, PhD, MSc

MGHCME.org

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Psychotherapies for Perinatal Mental Health

Rachel Vanderkruik, PhD, MSc
October 2020

Road Map

1. Types of psychotherapy
2. Value of psychotherapy
3. Evidence for psychotherapy in the perinatal population
4. Spotlight on CBT & application in the perinatal population
5. Addressing treatment gaps

Road Map

1. **Types of psychotherapy**
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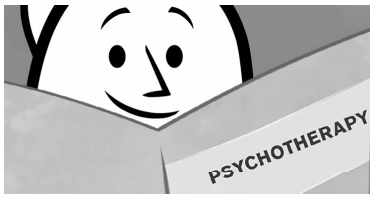
What is Psychotherapy?

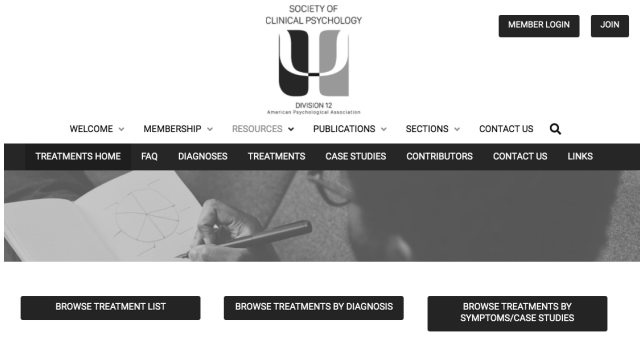
"Psychotherapy is the informed and intentional application of clinical methods and interpersonal stances derived from established psychological principles for the purpose of assisting people to modify their behaviors, cognitions, emotions, and/or other personal characteristics in directions that the participants deem desirable."

(Norcross, 1990, p. 218-220)



Therapy Approaches – Which to Choose?

Evidence-Based Psychotherapy



https://www.div12.org/psychological-treatments/

Evidence-Based Psychotherapy

PSYCHOLOGICAL DIAGNOSES AND OTHER TARGETS OF TREATMENT

Below is an alphabetized list of psychological diagnoses and other targets of treatment. Please note that the absence of a treatment for a particular diagnosis or treatment target does not necessarily suggest the treatment does not have sufficient evidence. Rather, it may indicate that the treatment has not been thoroughly evaluated by our team according to empirically-supported treatment criteria. Click on a diagnosis or target treatment to view a description and information about psychological treatment options. Or, if you prefer, you may search an alphabetized list of all treatments. You may also review diagnoses that may be appropriate for certain case presentations in the case studies section.

- Anorexia Nervosa
- Attention Deficit Hyperactivity Disorder (Adults)
- Binge Eating Disorder
- Bipolar Disorder
- Borderline Personality Disorder
- Bulimia Nervosa
- Chronic Headache
- Chronic Low Back Pain
- Chronic or Persistent Pain
- Chronic or Persistent Pain in General (including numerous conditions)

https://www.div12.org/psychological-treatments/

Evidence-Based Psychotherapy

TREATMENT TARGET: DEPRESSION

For more information on depression and its treatment, please visit the National Institute of Mental Health website.

PSYCHOLOGICAL TREATMENTS

- Acceptance and Commitment Therapy for Depression NEW CONTENT
  2015 EST Status: Treatment pending re-evaluation research support
  1998 EST Status: Modest research support
- Behavioral Activation for Depression NEW CONTENT
  2015 EST Status: Treatment pending re-evaluation research support
  1998 EST Status: Strong research support
- Cognitive Behavioral Analysis System of Psychotherapy for Depression
- Cognitive Therapy for Depression NEW CONTENT
  2015 EST Status: Treatment pending re-evaluation research support
  1998 EST Status: Strong research support
- Emotion Focused Therapy for Depression NEW CONTENT
  2015 EST Status: Treatment pending re-evaluation research support
  1998 EST Status: Modest research support
- Interpersonal Psychotherapy for Depression NEW CONTENT

https://www.div12.org/psychological-treatments/

Evidence-Based Psychotherapy

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Evidence-Based Psychotherapy

PSYCHOLOGICAL TREATMENTS

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Please note, the following treatments have been evaluated to determine the strength of their evidence base; results are listed within each page. The treatments listed below have evidence ratings ranging from "strong" to "insufficient evidence"; click within each treatment to determine its rating.

- Accelerated Resolution Therapy NEW CONTENT
- Acceptance and Commitment Therapy for Obsessive-Compulsive Disorder
- Acceptance and Commitment Therapy for Chronic Pain NEW CONTENT
- Acceptance and Commitment Therapy for Depression NEW CONTENT
- Acceptance and Commitment Therapy for Mixed Anxiety Disorders NEW CONTENT

https://www.div12.org/psychological-treatments/

Evidence-Based Psychotherapy

DIAGNOSIS: DEPRESSION

TREATMENT: BEHAVIORAL ACTIVATION FOR DEPRESSION

2015 EST STATUS: TREATMENT PENDING RE-EVALUATION ⑦

1998 EST STATUS: STRONG RESEARCH SUPPORT ⑦

STRENGTH OF RESEARCH SUPPORT

Empirical Review Status			
2015 Criteria (Tolin et al. Recommendation)	Treatment pending re-evaluation		
1998 Criteria (Chambless et al. EST)	Strong ✓	Modest	Controversial

https://www.div12.org/psychological-treatments/

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Effectiveness

- Avg effects of psychotherapy are widely accepted to be significant and large (e.g., Chorpita et al., 2011; Smith, Glass, & Miller, 1980).
- Variations in outcomes are heavily influenced by patient characteristics, clinician and context factors rather than by particular diagnoses (e.g., Beutler, 2009; Beutler & Malik, 2002; Wampold, 2001)
- Prevention (e.g., depressive relapse Dimidjian et al., 2016)

APA – 2012 Resolution on the Recognition of Psychotherapy Effectiveness

Enduring Effects

Open Access Research

BMJ open

Does cognitive behaviour therapy have an enduring effect that is superior to keeping patients on continuation pharmacotherapy? A meta-analysis

Pim Cuijpers,[1,2] Steven D Hollon,[3] Annemieke van Straten,[1,2] Claudi Bockting,[4] Matthias Berking,[5] Gerhard Andersson[6,7]

To cite: Cuijpers P, Hollon SD, van Straten A, *et al*. Does cognitive behaviour therapy have an enduring effect that is superior to keeping patients on continuation pharmacotherapy? A meta-analysis. *BMJ Open* 2013;3: e002542. doi:10.1136/bmjopen-2012-002542

► Prepublication history for this paper are available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2012-002542).

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ABSTRACT

Objectives: Although cognitive behaviour therapy (CBT) and pharmacotherapy are equally effective in the acute treatment of adult depression, it is not known how they compare across the longer term. In this meta-analysis, we compared the effects of acute phase CBT without any subsequent treatment with the effects of pharmacotherapy that either were continued or discontinued across 6–18 months of follow-up.

Design: We conducted systematic searches in bibliographical databases to identify relevant studies, and conducted a meta-analysis of studies meeting inclusion criteria.

Setting: Mental healthcare.

Participants: Patients with depressive disorders.

Interventions: CBT and pharmacotherapy for depression.

Outcome measures: Relapse rates at long-term follow-up.

Results: 9 studies with 320 patients were included. The quality was relatively high. Short-term outcomes of CBT and pharmacotherapy were comparable, although drop out from treatment was significantly lower in CBT. Acute phase CBT was compared with

ARTICLE SUMMARY

Article focus

- Cognitive behaviour therapy (CBT) and pharmacotherapy are equally effective in the acute treatment of depression.
- Long-term differential effects are not well known.

Key messages

- When acute phase CBT (without continuation treatment) was compared with acute phase pharmacotherapy that was discontinued during 6–18 months' follow-up, we found that acute phase CBT was clearly more effective.
- We found no significant difference between acute phase CBT (without continuation treatment) and acute phase pharmacotherapy with continued pharmacotherapy during follow-up, although there was a trend indicating that there may be such a difference favouring acute phase CBT.

Strengths and limitations of this study

- Too few studies have examined the long-term effects of treatments for depressive disorders.

Therapy, medications, or both?

The symptom-specific efficacy of antidepressant medication vs. cognitive behavioral therapy in the treatment of depression: results from an individual patient data meta-analysis

Lynn Boschloo[1,2], Ella Bekhuis[2], Erica S. Weitz[1], Mirjam Reijnders[1], Robert J. DeRubeis[3], Sona Dimidjian[4], David L. Dunner[5], Boadie W. Dunlop[6], Ulrich Hegerl[7], Steven D. Hollon[8], Robin B. Jarrett[9], Sidney H. Kennedy[10], Jeanne Miranda[11], David C. Mohr[12], Anne D. Simons[13], Gordon Parker[14], Jeffrey R. Vittengl[21], Robert A. Scho…

Cognitive therapy vs. medications for depression: Treatment outcomes and neural mechanisms

Robert J. DeRubeis, University of Pennsylvania
Greg J. Siegle, and University of Pittsburgh
Steven D. Hollon Vanderbilt University

RESEARCH REPORT

Adding psychotherapy to antidepressant medication in depression and anxiety disorders: a meta-analysis

Pim Cuijpers[1-3], Marit Sijbrandij[1,2], Sander L. Koole[1,2], Gerhard Andersson[4,5], Aartjan T. Beekman[2,6], Charles F. Reynolds III[7]

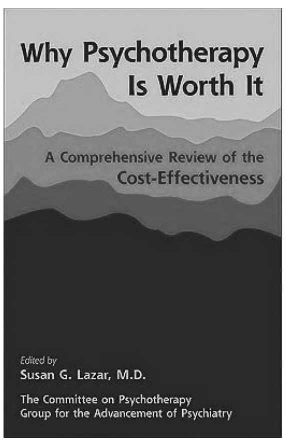
[1]Department of Clinical Psychology, VU University Amsterdam, The Netherlands; [2]EMGO Institute for Health and Care Research, VU University and VU University Medical Center Amsterdam, The Netherlands; [3]Leuphana University, Lünebrug, Germany; [4]Department of Behavioural Sciences and Learning, Swedish Institute for Disability Research, University of Linköping, Sweden; [5]Department of Clinical Neuroscience, Psychiatry Section, Karolinska Institutet, Stockholm, Sweden; [6]Department of Psychiatry, VU University Medical Center Amsterdam, The Netherlands; [7]Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

We conducted a meta-analysis of randomized trials in which the effects of treatment with antidepressant medication were compared to the effects of combined pharmacotherapy and psychotherapy in adults with a diagnosed depressive or anxiety disorder. A total of 52 studies (with 3,623 patients) met inclusion criteria, 32 on depressive disorders and 21 on anxiety disorders (one on both depressive and anxiety disorders). The overall difference between pharmacotherapy and combined treatment was Hedges' g = 0.43 (95% CI: 0.31-0.56), indicating a moderately large effect and clinically meaningful difference in favor of combined treatment, which corresponds to a number needed to treat (NNT) of 4.20. There was sufficient evidence that combined treatment is superior for major depression, panic disorder, and obsessive-compulsive disorder (OCD). The effects of combined treatment compared with placebo only were about twice as large as those of pharmacotherapy compared with placebo only, underscoring the clinical advantage of combined treatment. The results also suggest that the effects of pharmacotherapy and those of psychotherapy are largely independent from each other, with both contributing about equally to the effects of combined treatment. We conclude that combined treatment appears to be more effective than treatment with antidepressant medication alone in major depression, panic disorder, and OCD. These effects remain strong and significant up to two years after treatment. Monotherapy with psychotropic medication may not constitute optimal care for common mental disorders.

Key words: Combined treatment, psychotherapy, antidepressant medication, depressive disorders, anxiety disorders, dysthymia, obsessive-compulsive disorder, meta-analysis

(World Psychiatry 2014;13:56–67)

Cost - Effectiveness



Preferences of Perinatal Women

Women's Attitudes, Preferences, and Perceived Barriers to Treatment for Perinatal Depression

Janice H. Goodman, PhD

ABSTRACT: Background: *Perinatal depression is associated with potential negative consequences for the mother and infant, and therefore efforts to improve treatment access and efficacy are warranted. The purpose of this study was to examine pregnant women's preferences and attitudes about treatment for depression, and perceived potential barriers to accessing treatment.* **Methods:** *Data were collected by means of a questionnaire from a convenience sample of 509 predominantly well-educated, high-income, married women in the northeastern United States during the last trimester of pregnancy. Participants were queried as to treatment modalities in which they would most likely participate if they wanted help for depression, their attitudes toward psychotherapeutic and pharmacological treatments, and perceived barriers to receiving help.* **Results:** *Most women (92%) indicated that would likely participate in individual therapy if help was needed. Only 35 percent stated that they would likely take medication if recommended, and 14 percent indicated that they would participate in group therapy. The greatest perceived potential barriers to treatment were lack of time (65%), stigma (43%), and childcare issues (33%). Most women indicated a preference to receive mental health care at the obstetrics clinic, either from their obstetrics practitioner or from a mental health practitioner located at the clinic. Factors associated with acceptability of various depression treatments are presented.* **Conclusions:** *Understanding what prevents women from seeking or obtaining help for depression and determining what they prefer in the way of treatment may lead to improved depression treatment rates and hold promise for improving the overall health of childbearing women. (BIRTH 36:1 March 2009)*

Key words: *perinatal depression, perinatal depression treatment, women's preferences, treatment barriers*

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Perinatal Antidepressant Use: Understanding Women's Preferences and Concerns

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Warren Alpert Medical School of Brown University, Butler Hospital, and Women & Infants' Hospital of Rhode Island, Providence, RI

AMY L. SALISBURY, PhD,
Warren Alpert Medical School of Brown University and Women & Infants' Hospital of Rhode Island

CASEY A. SCHOFIELD, PhD, and
Warren Alpert Medical School of Brown University and Skidmore College, Saratoga Springs, NY

SAMIA ORTIZ-HERNANDEZ
George Washington University, Washington, DC

Abstract

Perinatal depression is prevalent and linked with a host of adverse consequences for women and newborns. Rates of engagement in depression treatment are, however, strikingly low among pregnant and postpartum women, with the majority of affected women receiving no mental health treatment. Research indicates that perinatal women are extremely reluctant to take antidepressant medications, yet the nature of women's concerns and treatment decisionmaking patterns have not been well documented. Developing a clearer understanding of women's treatment preferences and behaviors may help identify solutions to the under-treatment of perinatal depression. In this mixed methods study, we conducted in-depth interviews with 61 pregnant women, approximately half of whom were experiencing clinical levels of depression. In addition to assessing psychiatric diagnoses, symptoms, and functional impairment, we conducted qualitative interviews addressing women's preferences for depression treatment, concerns, and decision-making patterns. Consistent with prior reports, women were significantly more likely to voice a preference for non-pharmacologic depression treatments, as opposed to antidepressant medications. Many depressed women reported a great degree of uncertainty regarding how to treat their depression, and those with more severe depression symptoms were more likely to endorse decisional conflict. Analysis of qualitative comments yielded detailed information about the nature of women's concerns and preferences related to use of antidepressant medications and other aspects of treatment engagement. We discuss findings in the context of improving patient-centered care for perinatal depression.

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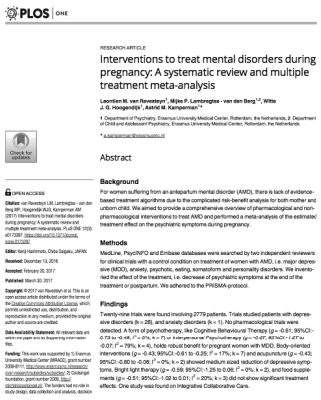
Evidence for Perinatal Mental Health

"This meta-analysis found a robust moderate treatment effect of CBT for MDD during pregnancy, and to a lesser extent for IPT."

van Ravesteyn et al. (2017)



PLOS ONE

RESEARCH ARTICLE

Interventions to treat mental disorders during pregnancy: A systematic review and multiple treatment meta-analysis

Laontien M. van Ravesteyn[1], Mijke P. Lambregtse - van den Berg[1,2], Witte J. G. Hoogendijk[1], Astrid M. Kamperman[1]*

1 Department of Psychiatry, Erasmus University Medical Center, Rotterdam, the Netherlands, 2 Department of Child and Adolescent Psychiatry, Erasmus University Medical Center, Rotterdam, the Netherlands

* a.kamperman@erasmusmc.nl

Abstract

Background

For women suffering from an antepartum mental disorder (AMD), there is lack of evidence-based treatment algorithms due to the complicated risk-benefit analysis for both mother and unborn child. We aimed to provide a comprehensive overview of pharmacological and non-pharmacological interventions to treat AMD and performed a meta-analysis of the estimated treatment effect on the psychiatric symptoms during pregnancy.

Methods

MedLine, PsycINFO and Embase databases were searched by two independent reviewers for clinical trials with a control condition on treatment of women with AMD, i.e. major depressive (MDD), anxiety, psychotic, eating, somatoform and personality disorders. We inventoried the effect of the treatment, i.e. decrease of psychiatric symptoms at the end of the treatment or postpartum. We adhered to the PRISMA-protocol.

Findings

Twenty-nine trials were found involving 2779 patients. Trials studied patients with depressive disorders (k = 28), and anxiety disorders (k = 1). No pharmacological trials were detected. A form of psychotherapy, like Cognitive Behavioural Therapy (g= -0.61; 95%CI:-0.73 to -0.48; I^2 = 0%, k = 7) or Interpersonal Psychotherapy (g= -0.47; 95%CI:-0.47 to -0.07; I^2 = 79%, k = 4), holds robust benefit for pregnant women with MDD. Body-oriented interventions (g= -0.43; 95%CI:-0.81 to -0.05; I^2 = 17%, k = 7) and acupuncture (g= -0.43; 95%CI:-0.80 to -0.06; I^2 = 0%, k = 2) showed medium sized reduction of depressive symptoms. Bright light therapy (g= -0.59; 95%CI:-1.25 to 0.08; I^2 = 0%, k = 2), and food supplements (g= -0.51; 95%CI:-1.02 to 0.01; I^2 = 20%, k = 3) did not show significant treatment effects. One study was found on Integrative Collaborative Care.

Evidence for Perinatal Mental Health

HHS Public Access

Author manuscript

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Published in final edited form as:

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Treatment of depression, anxiety, and trauma-related disorders during the perinatal period: A systematic review

Yael I. Nillni[a,b,*], Aydan Mehralizade[a], Laura Mayer[b], and Snezana Milanovic[b]

[a]National Center for PTSD, Women's Health Sciences Division at VA Boston Healthcare System, United States

[b]Department of Psychiatry, Boston University School of Medicine, United States

[c]Boston Medical Center, United States

Abstract

Women with psychiatric disorders during pregnancy and the postpartum period (i.e., perinatal period) are at increased risk for adverse maternal and child outcomes. Effective treatment of psychiatric disorders during the perinatal period is imperative. This review summarizes the outcomes of 78 studies focused on the treatment of depression, anxiety, and trauma-related disorders during the perinatal period. The majority of studies focused on perinatal depression (n = 73). Of the five studies focused on anxiety or trauma-related disorders, only one was a randomized controlled trial (RCT). The most studied treatment was cognitive behavioral therapy (CBT; n = 22), followed by interpersonal psychotherapy (IPT; n = 13). Other interventions reviewed include other talk therapies (n = 5), collaborative care models (n = 2), complementary and alternative medicine approaches (n = 18), light therapy (n = 3), brain stimulation (n = 2), and psychopharmacological interventions (n = 13). Eleven studies focused specifically on treatment for low-income and/or minority women. Both CBT and IPT demonstrated a significant benefit over control conditions. However, findings were mixed when these interventions were examined in low-income and/or minority samples. There is some support for complementary and alternative medicine approaches (e.g., exercise). Although scarce, SSRIs demonstrated good efficacy when compared to a placebo. However, SSRIs did not outperform another active treatment condition (e.g., CBT). There is a tremendous need for more studies focused on treatment of perinatal anxiety and trauma-related disorders, as well as psychopharmacological effectiveness studies. Limitations and future directions of perinatal treatment research, particularly among low-income and/or minority populations, are discussed.

78 studies focused on the treatment of depression, anxiety, and trauma-related disorders during the perinatal period.

The majority of studies focused on perinatal depression (n = 73)

The most studied treatment was CBT (n = 22) followed by IPT (n= 13)

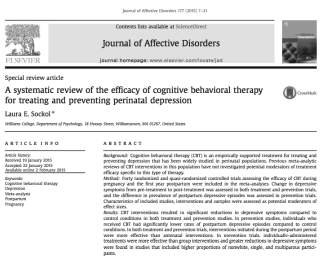
"There is a tremendous need for more studies focused on treatment of perinatal anxiety and trauma-related disorders…. "

Nillnia et al. (2018)

Evidence for Perinatal Mental Health

Research supporting use of CBT in perinatal populations

- Reduction of depressive symptoms
- Reduction of anxiety symptoms
- Prevention of perinatal depression symptoms



Journal of Affective Disorders

Special review article

A systematic review of the efficacy of cognitive behavioral therapy for treating and preventing perinatal depression

Laura E. Sockol *

ANZJP

Research

Cognitive behavioral therapy for perinatal anxiety: A randomized controlled trial

Sheryl M Green[1,2], Eleanor Donegan[1,2], Randi E McCabe[1,2], David L Streiner[1], Arcia Agako[1] and Benicio N Frey[1,2,3]

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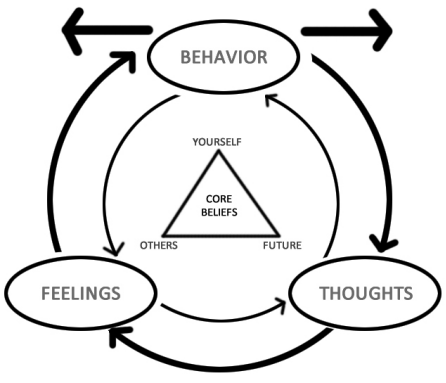
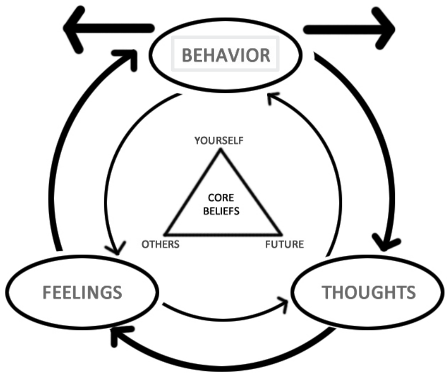
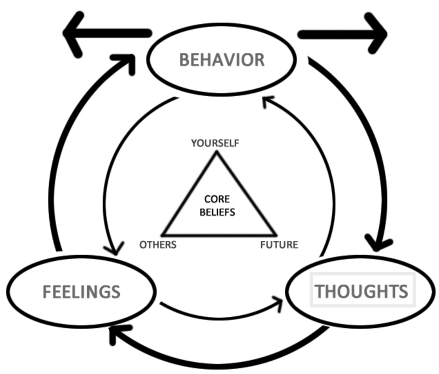
Spotlight on CBT



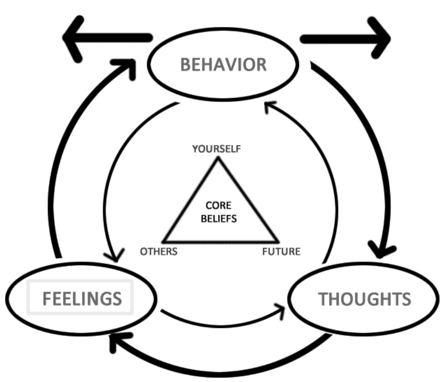
Spotlight on CBT



Spotlight on CBT



Spotlight on CBT



Spotlight on CBT

- Common CBT Techniques
  1. Socratic Questioning
  2. Homework
  3. Self-monitoring
  4. Behavioral Experiments
  5. Exposure/Systematic Desensitization

- Structured sessions

Example: Thought Log

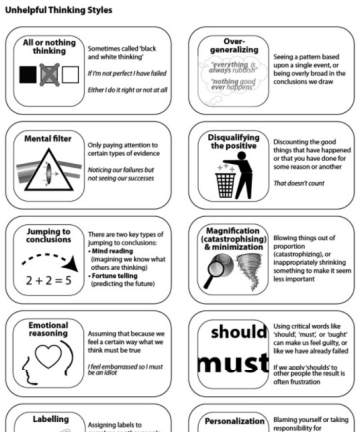
Thought Record

Directions: When you notice a change in your confidence, ask yourself "What is going through my mind right now?" and jot down the thought or mental image in the automatic thought column.

Date/ Time	Situation	Automatic thought(s)	Emotion(s)	Adaptive response	Outcome
	1. What actual event, stream of thoughts, daydreams, or recollection led to the unpleasant emotion? 2. What (if any) distressing physical sensations did you have?	1. What thought(s) and/or image(s) went through your mind? 2. How much did you believe each one at the time?	1. What emotion(s) did you feel at the time? 2. How intense (0-100%) was the emotion?	1. Use the questions at bottom to compose a response to the automatic thought(s) 2. How much do you believe each response?	1. How much do you now believe each automatic thought? 2. What emotion(s) do you feel now? How intense (0-100%) is the emotion? 3. What will you do (or did you do)?

Questions to help compose an alternative response: (1) What is the evidence that the automatic thought is true? Not true? (2) Is there an alternative explanation? (3) What's the worst that could happen? Could I live through it? What's the best thing that could happen? What's the most realistic outcome? (4) What's the effect of my believing the automatic thought? What could be the effect of my changing my thinking? (5) What should I do about it? (6) If _____ (friend or family member's name) was in the situation and had this thought, what would I tell him/her?

Unhelpful Thinking Styles



Worksheet from:
Psychologytools.org

Challenging Thoughts

THOUGHTS ≠ **FACTS**

Challenging Thoughts

challenging unhelpful thinking styles

Evidence Testing is all about trying to be objective about our thoughts. It is about asking yourself questions that will help you look for other information and make an informed decision about your thoughts, instead of just accepting them as fact.

1. **CHECK THE EVIDENCE**

If this thought was put on trial, what evidence would the defence present (what facts support the thought being true)?

What evidence would the prosecution present against (what information works against the thought or shows that it isn't true all the time)?

2. **CHALLENGE UNHELPFUL THINKING STYLES**

Unhelpful Thinking Style		Disputation Questions
Mental Filter	➡	Consider the whole picture - *Am I taking all the information into account?* - *What else is going on that I'm ignoring?*
Jumping to Conclusions	➡	You know what they say about assuming… - *How do I know this?* - *What are some alternative explanations for this?* - *If I was feeling differently, would I still think this?*
Personalisation	➡	Find all the causes - *Was this entirely my responsibility?* - *What other factors might have affected the outcome?*
Catastrophising	➡	Put it in perspective - *What are the possible outcomes – best, worst, most likely?* - *Am I jumping ahead of myself?* - *How important is this in the scheme of things?*
Black and White Thinking	➡	Find the shades of grey - *Am I being extreme or rigid?* - *Is there an in-between where things are not perfect but not a disaster?*
Shoulding and Musting	➡	Be flexible - *Is this a strict rule, or is it a desire or possibility that didn't work in this instance?* - *Can I replace this with a "could" or "would have liked to"?*

Worksheet from: Centre for Clinical Interventions

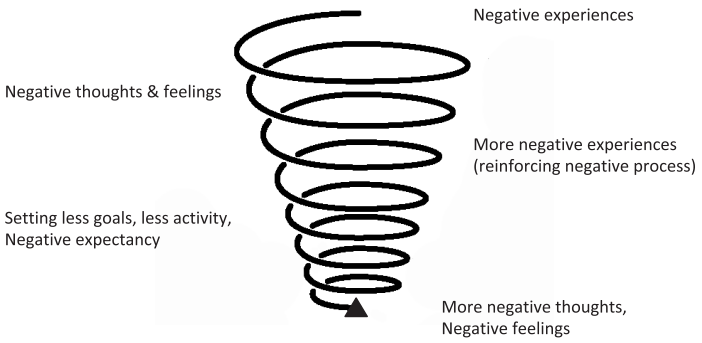
Example: Mood and Activity Tracking

Activity Monitoring Chart – Monitoring Activity/Mood

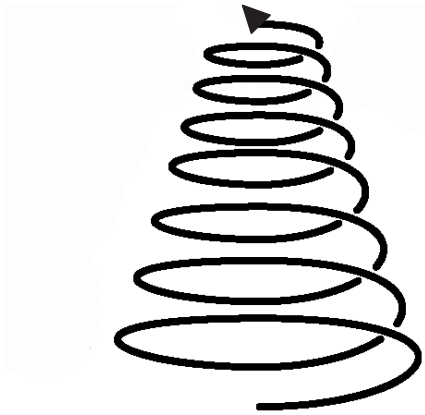
Instructions: Record your activity for each hour of the day (what were you doing, with whom, where, etc.). Record a mood rating associated with each activity. Mood is rated between 0-10, with "0" indicating "most negative" and "10" indicating "most positive."

	Sun.	Mon.	Tues.	Weds.	Thurs.	Fri.	Sat.
5am-7am							
7:00am							
8:00am							
9:00am							
10:00am							
11:00am							
12:00pm							
1:00 pm							
2:00pm							
3:00pm							
4:00pm							
5:00pm							
6:00pm							
7:00pm							
8:00pm							
9:00pm							
10:00pm							
11pm-5am							

Downward Spiral of Depression



Creating an Upward Spiral



Finding Your

Behavioral

Antidepressants

CBT with Perinatal Women

Key Considerations...

1) Checking Expectations

Motherhood: expectation vs reality

2) Normalization

FEATURES

An Exploration of Negative Thoughts as a Normal Phenomenon After Childbirth

Pauline L. Hall, DClinPsy, and Anja Wittkowski, ClinPsyD

The period following the birth of a child brings many transitions into a woman's life, which can effect major psychological and social changes, including feelings of loss. If new mothers experience negative thoughts at this time, when societal expectations are of happiness, this may lead to feelings of unacceptability and guilt. This study aimed to investigate the prevalence of negative thoughts after childbirth in nondepressed mothers. Following the identification of negative thoughts experienced by women who had suffered postnatal depression, a quantitative survey was conducted, which asked nondepressed mothers to indicate how often they experienced the negative thoughts or images identified by depressed mothers. One hundred and fifty-eight returned questionnaire packs were included in the analyses. The 158 nondepressed mothers acknowledged experiencing all but one of the 54 negative cognitions. Negative cognitions usually associated with postnatal depression are also experienced by mothers who are not considered depressed. This information provides evidence for reassuring new mothers that negative thoughts after childbirth are common. This, in turn, may help to reduce feelings of guilt associated with experiencing negative thoughts in the postpartum period. J Midwifery Womens Health 2006;51:321–330 © 2006 by the American College of Nurse-Midwives.

keywords: cognitions, normalization, postpartum, women

2) Normalization

DEPRESSION AND ANXIETY 22:121–129 (2005)

Research Article

NEGATIVE THOUGHTS AFTER CHILDBIRTH: DEVELOPMENT AND PRELIMINARY VALIDATION OF A SELF-REPORT SCALE

Pauline L. Hall, M.A., R.M.N., M.Sc., D.Clin.Psy* and Costas Papageorgiou, B.Sc., M.A., D.Clin.Psy, Ph.D.

This study describes the development and initial validation of a questionnaire that is suitable for detecting and measuring postpartum negative thoughts. Semistructured interviews with mothers who had suffered from postnatal depression were conducted to inform the content of the questionnaire. The initial questionnaire, alongside other measures, was then administered to a nonclinical sample of mothers with babies aged 0–7 months. Using principal components analysis, a two-factor structure was obtained for the Postnatal Negative Thoughts Questionnaire (PNTQ). The factors included appraisal of cognition, emotion, and situation (ACES) and baby-related and motherhood negative thoughts (BRM-NT). The psychometric properties demonstrated acceptable validity, satisfactory test–retest reliability, and internal consistency. These findings suggest that the PNTQ is a reliable and valid measure for assessing postpartum negative thoughts. Consistent with previous research, findings also suggest that appraisal of negative thoughts is more strongly related to postpartum depression than to the experience of negative thoughts per se. Clinicians may use the PNTQ to offer new mothers the opportunity to assess whether negative thoughts or metacognitive appraisals are being experienced as problematic. Additionally, a direct focus upon the metacognitive appraisals of postpartum negative thoughts may provide a useful adjunct to traditional cognitive therapy approaches. Recommendations for future research are discussed. Depression and Anxiety 22:121–129, 2005. © 2005 Wiley-Liss, Inc.

Key words: *postpartum depression; psychological assessment; test construction; appraisal; negative cognitions*

TABLE 1. PNTQ scale items with factor loadings

Item content	Loading value
Factor 1	
Appraisal of Cognition, Emotion and Situation (ACES)	
If I told people about my thoughts and feelings, there would be terrible consequences.	.841
My negative thoughts are uncontrollable.	.752
Having bad thoughts about my baby means I'm evil.	.732
If I share my thoughts with others, they will think I'm mad.	.649
It's impossible to explain how I feel.	.627
It's not normal to think the way I do.	.598
My situation is completely out of control.	.521
There must be something wrong with me.	.466
Things will never get better.	.452
Factor 2	
Baby-Related and Motherhood Negative Thoughts (BRM-NT)	
Being with my baby is boring.	.761
I am rejected by my baby.	.650
I don't want to be alone with my baby.	.647
I'm trapped in this situation by my baby.	.613
I can't look after my baby.	.602
I shouldn't have considered having a baby.	.545
I could cause emotional damage to my child.	.473
I am a bad mother.	.450

3) Validation

4) Baby Steps

Road Map

1. Types of psychotherapy
2. Value of psychotherapy
3. Evidence for psychotherapy in the perinatal population
4. Spotlight CBT & application in the perinatal population
5. **Addressing treatment gaps**

Treatment Gaps

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Date created: 2012

Research Shows Psychotherapy Is Effective But Underutilized

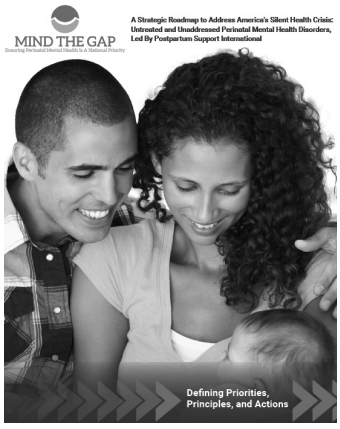
Consumers need better understanding of and access to psychological and behavioral health care, says American Psychological Association

WASHINGTON—Psychotherapy is effective, helps reduce the overall need for health services and produces long-term health improvements, according to a review of research studies conducted by the American Psychological Association.

Common Barriers

- Time
- Costs
- Childcare demands
- Limited access
- Perceptions of need, stigma

Mind the Gap Report



Addressing Disparities

WHAT IS THE GAP?

Perinatal depression alone ranks as the most underdiagnosed complication of pregnancy in the United States and may not manifest itself until many months after delivery.[8]

Women at Higher Risk

African American and Hispanic women have the highest prevalence of perinatal depression, primarily attributed to a lack of social support, access to care, and a history of trauma and prior depression.[9] African American women frequently receive poorer quality care, and when care is received, it is more often fragmentary and inconsistent.

"We need to recognize that we cannot raise healthy children and have healthy families without addressing maternal mental health. We can start by making the detection, assessment and treatment of mood and anxiety disorder a routine part of obstetric care, just like any other medical illness. Let's use diabetes as an example. All women are screened for diabetes. If they screen positive, women are started on treatment and then there is close follow-up to make sure the blood sugar is under control and mom and baby are healthy. Depression is twice a common as diabetes in pregnancy. Just like diabetes, depression affects mom and baby's health. Despite this, depression often goes unaddressed and untreated. Mood and anxiety disorders need to be addressed just as proactively as diabetes."
Nancy Byatt, DO, Medical Director, MCPAP for Moms

Racial disparities are further compounded by a lack of proximity to services, lack of insurance coverage, a stigma associated with mental health, and a mistrust of mental health professionals.[10] For example, four-in-ten low income African American mothers do not access postpartum visits and do not receive care and support for postpartum depression and other challenges.[11]

Economic Impact

RESEARCH AND PRACTICE

Financial Toll of Untreated Perinatal Mood and Anxiety Disorders Among 2017 Births in the United States

Dara Lee Luca, PhD, Caroline Margiotta, MA, Colleen Staatz, MPH, Eleanor Garlow, BA, Anna Christensen, PhD, and Kara Zivin, PhD, MS, MA

Objectives. To estimate the economic burden of untreated perinatal mood and anxiety disorders (PMADs) among 2017 births in the United States.

Methods. We developed a mathematical model based on a cost-of-illness approach to estimate the impacts of exposure to untreated PMADs on mothers and children. Our model estimated the costs incurred by mothers and their babies born in 2017, projected from conception through the first 5 years of the birth cohort's lives. We determined model inputs from secondary data sources and a literature review.

Results. We estimated PMADs to cost $14 billion for the 2017 birth cohort from conception to 5 years postpartum. The average cost per affected mother–child dyad was about $31 800. Mothers incurred 65% of the costs; children incurred 35%. The largest costs were attributable to reduced economic productivity among affected mothers, more preterm births, and increases in other maternal health expenditures.

Conclusions. The US economic burden of PMADs is high. Efforts to lower the prevalence of untreated PMADs could lead to substantial economic savings for employers, insurers, the government, and society. (*Am J Public Health.* Published online ahead of print April 16, 2020: e1–e9. doi:10.2105/AJPH.2020.305619)

Perinatal mood and anxiety disorders (PMADs)—defined as mood and anxiety disorders during pregnancy and the year following birth—are common in the United States, affecting at least 1 in 7 pregnant and postpartum women,[1–12] yet they often go undiagnosed and untreated. Although screening tools and effective treatments exist, 60% of perinatal women with depressive symptoms do not receive a clinical diagnosis, and 50% with a diagnosis do not receive treatment.[13] If left untreated, PMADs can have serious health and social consequences for both mother and child, including lower productivity—defined as lost earnings be-

Health insurers, employers, and policymakers need credible and transparent estimates of the economic burden of PMADs. Several studies have examined the costs of untreated PMADs in other countries, such as the United Kingdom and Australia,[15,16] but, to our knowledge, this study is the first to provide a comprehensive picture of the economic burden of PMADs in the United States.

We developed a mathematical model to quantify the societal costs of untreated PMADs and used recent data and estimates from peer-reviewed literature. We concentrated on the mother–child dyad's costs during the first several years of life (conception through age 5 years) to highlight the most pressing concerns relevant to the public and decision makers. Although other studies have documented long-term impacts of exposure to untreated PMADs on children, these effects do not manifest themselves for many years. Limiting the model timeframe to 6 years enabled us to generate more concrete estimates than would be possible over a longer period.

METHODS

Our model considered impacts of exposure to untreated PMADs on mother and child. It estimated societal costs, including health care payer and employer costs, incurred by mothers and their babies born in 2017, projected forward for 6 years. The model focused on outcomes shown in the literature and recognized by subject matter experts as linked to PMADs (e.g., preterm birth). We looked at direct and indirect costs of untreated PMADs in 3 key domains: (1) income loss because of reduced maternal productivity and labor force participation; (2) greater use of public sector services, including safety net programs and Medicaid; and (3) higher health care costs attributable to worse maternal and child health.

The model used a cost-of-illness approach to synthesize existing evidence from multiple

Addressing the Treatment Gap

- Efforts include:
  - Integrated care
  - Task sharing; utilizing peers, lay health workers
  - Delivery via print; bibliotherapy
  - Leveraging technology; apps, online platforms

Leveraging Technology

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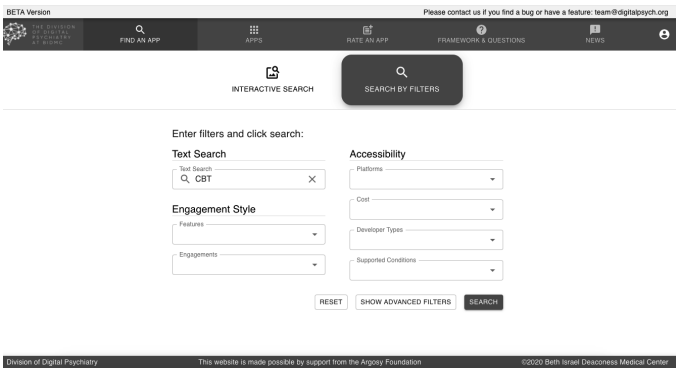
ScienceDirect
Behavior Therapy 51 (2020) 1–14

Behavior Therapy
www.elsevier.com/locate/bt

Cognitive-Behavioral Therapy in the Digital Age: Presidential Address

Sabine Wilhelm*
Hilary Weingarden
Ilana Ladis
Valerie Braddick
Jin Shin
Nicholas C. Jacobson
Massachusetts General Hospital/Harvard Medical School

Leveraging Technology



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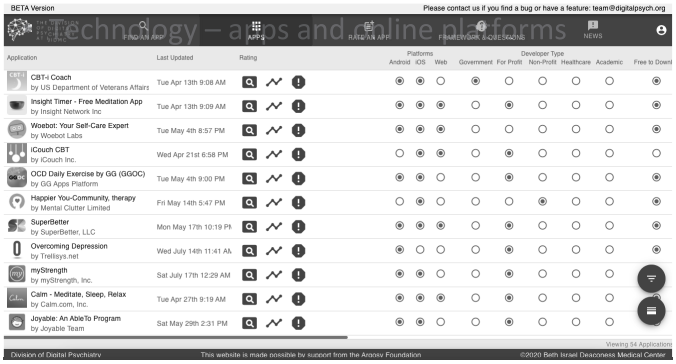
Leveraging Technology



Technology – apps and online platforms

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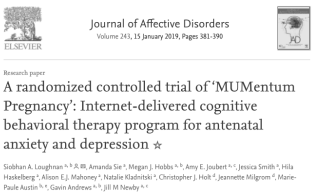
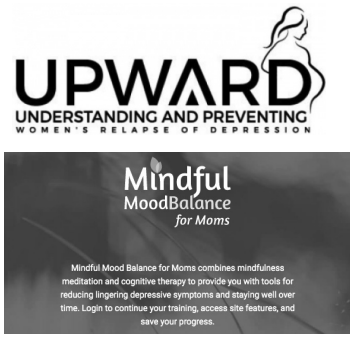
Leveraging Technology


Journal of Affective Disorders
Volume 243, 15 January 2019, Pages 381-390

Research paper

A randomized controlled trial of 'MUMentum Pregnancy': Internet-delivered cognitive behavioral therapy program for antenatal anxiety and depression ☆

Siobhan A. Loughnan [a, b], R.III. Amanda Sie [a], Megan J. Hobbs [a, b], Amy E. Joubert [a, c], Jessica Smith [a], Hila Haskelberg [a], Alison E.J. Mahoney [a], Natalie Kladnitski [a], Christopher J. Holt [d], Jeannette Milgrom [d], Marie-Paule Austin [b, e], Gavin Andrews [a, b], Jill M Newby [a, c]



Thank you!

Questions/comments: rvanderkruik@mgh.harvard.edu

NOTES

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Question & Answer

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Conclusion & Closing Remarks

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