Chicago, IL USA

Northwestern Medicine®

Anxiety Disorders and Anxiety Symptoms in the Perinatal Period

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of Depressive Disorders

Perinatal Mood Disorder is Common

N=10,000 screened obstetrical population 4-6 wks pp

- 14% positive screen (≥10_Edinburgh Postnatal Depression Scale-**EPDS**)

  Cox JL, et al. *Br J Psychiatry* 1987; 150:782-86

- The onset of the episodes for the patients (N=826, who had diagnostic interview) was:
  - during pregnancy, N=276 over 40 weeks (33.4%)
  - postpartum (within 4 weeks of birth), N= 331 (40.1%)
  - prior to pregnancy, N=219 (26.5%)

- *Wisner et al, JAMA Psychiatry 70(5): 490-8, 2013. PMID: 23487258*

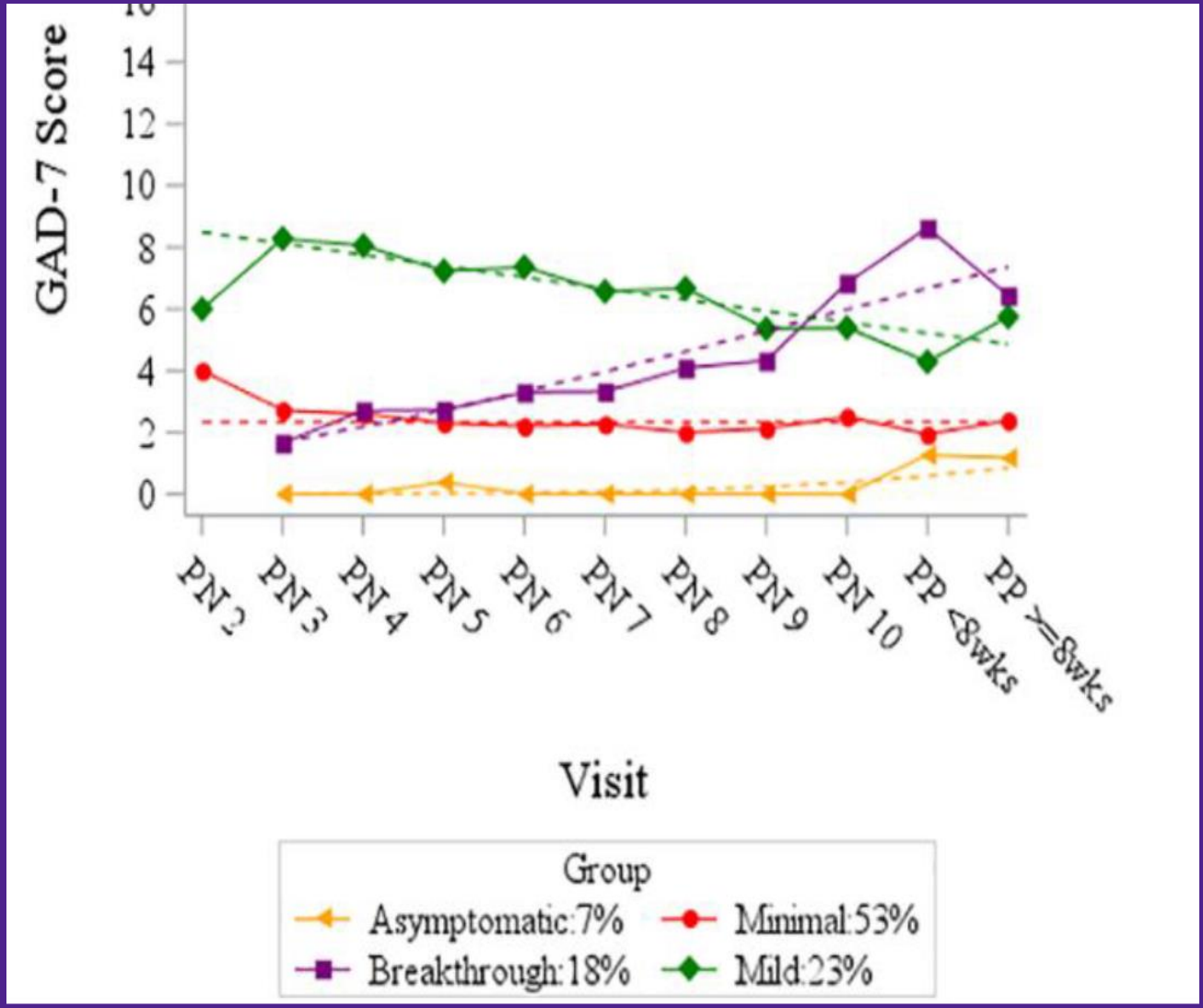
Primary Axis 1 SCID Diagnoses

Primary Diagnoses, N = 826		
	N	%
Depressive Disorders	**566**	**68.5**
Major Depression- Recurrent	368	65.0
Major Depression - Single Episode	146	25.8
Depressive Disorder NOS	38	6.7
Adjustment Disorder With Depressed Mood	11	1.9
Mood Disorder NOS	2	0.4
Dysthymic Disorder	1	0.2
Bipolar Disorders	**187**	**22.6**
Bipolar 2 Disorder	58	31.0
BPD1-Recent Episode Depressed	54	28.9
Bipolar Disorder NOS	35	18.7
BPD1-Recent Episode Mixed	32	17.1
BPD1-Single Manic Episode	7	3.7
Schizoaffective Disorder	1	0.5
Anxiety Disorders	**46**	**5.6**
Generalized Anxiety Disorder	24	52.2
Obsessive-Compulsive Disorder	8	17.4
Anxiety Disorder NOS	8	17.4
Adjustment Disorder With Anxiety	3	6.5
Panic Disorder Without Agoraphobia	1	2.2
Post-traumatic Stress Disorder	1	2.2
Specific Phobia	1	2.2
Substance Use Disorders	**4**	**0.5**
Substance-Induced Mood Disorder	1	25.0
Alcohol Abuse/Dependence	1	25.0
Opioid Abuse/Dependence	1	25.0
Polysubstance Dependence	1	25.0
Other Disorders	**6**	**0.7**
No Diagnosis	**17**	**2.1**

With anxiety disorder comorbidity 83%

Uncommon without depression

Patterns of Anxiety Symptoms Across Pregnancy: 4 Groups



Anxiety Disorders in Pregnancy and Postpartum

- Generalized Anxiety Disorder
- Panic Disorder
- Post-traumatic Stress Disorder
- Obsessive Compulsive Disorder
- Prevalence of anxiety disorders 13-21% in pregnancy and 11-17% postpartum
- Commonly co-occur with Mood Disorders

Generalized Anxiety Disorder

- Anxiety symptoms and anxiety disorders are associated with stress and postpartum depression
- 5 to 10% of pregnant women have extreme fear of childbirth
- They request surgical deliveries to avoid labor
- Treatment: birth support and focused, short-term psychotherapy (Cognitive Behavior Therapy) to reduce anxiety
- GAD-7 scale:

  https://adaa.org/sites/default/files/GAD-7_Anxiety-updated_0.pdf

Panic Disorder

- Panic attacks are brief (5-15 minutes)
  - Palpitations, sweating, shortness of breath, choking, nausea, abdominal discomfort, dizziness, unsteadiness, numbness or tingling, chills, hot flashes
  - fear of dying or losing control.
- Panic Disorder- attacks are recurrent or associated with fear of future attacks.
- Severity Scale: https://qxmd.com/calculate/calculator_508/panic-disorder-severity-scale-pdss

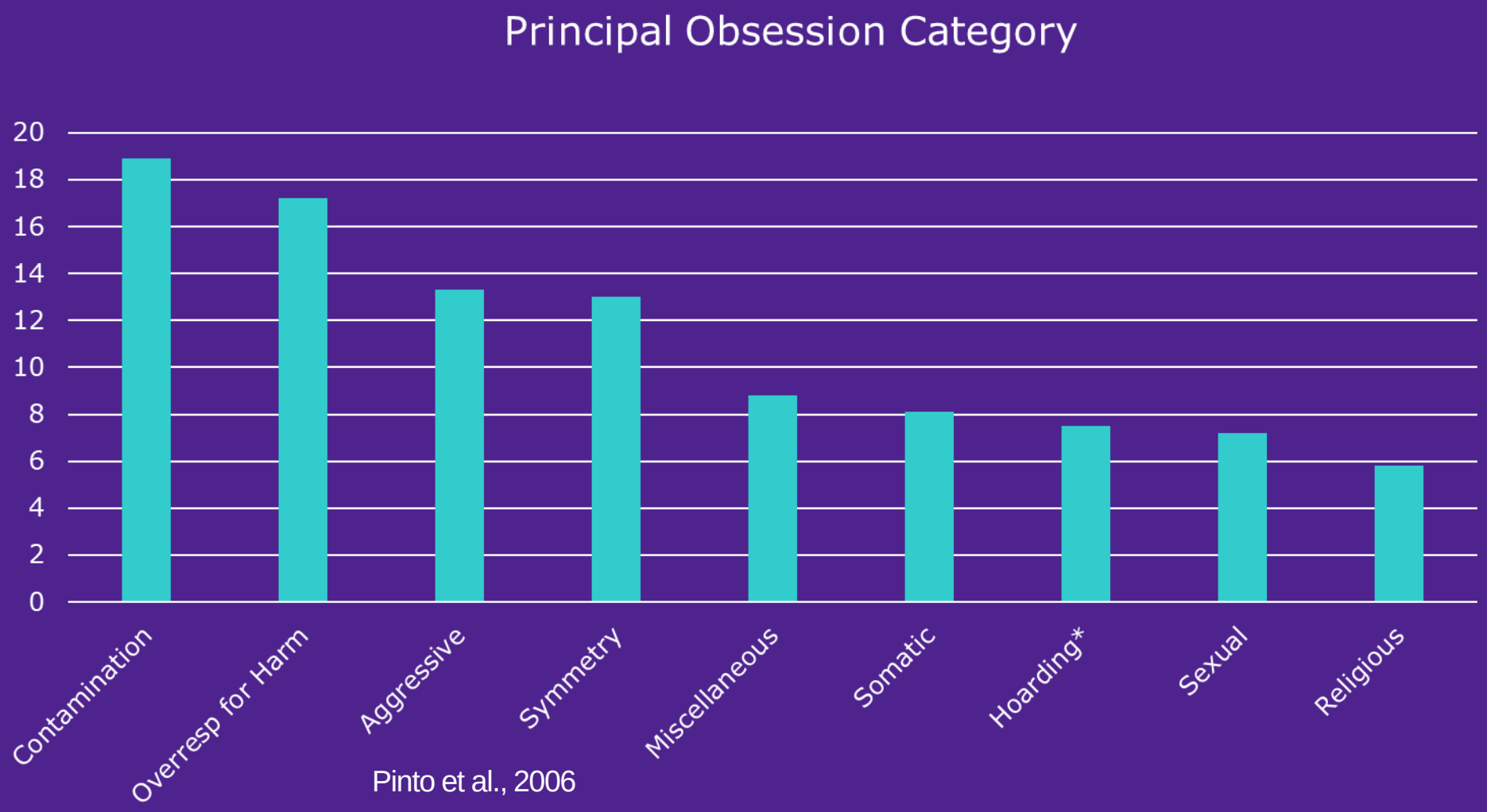
- Agoraphobia- 30 to 40% of patients, disabling
- Course variable across pregnancy
- Postpartum intensification or recurrence is frequent
- *Rule out hyperthyroidism -occurs in 7- 8% new mothers, up to 25% in those with type 1 diabetes

Obsessive Compulsive Disorder

- Prevalence - 1-3%
- Risk for worsening / new onset in the postpartum period
- Differentiating postpartum obsessional thoughts and images from delusions and hallucinations can be challenging (*Hudak R, Wisner KL. Am J Psychiatry. 2012 Apr;169:360-3. PMID: 22476676)*
- Obsessions are recognized as part of one's mind
- Mothers are highly distressed by the thoughts but are not at risk of harming their infant
- *Presentation as an acute crisis in pregnancy associated with severe nausea/vomiting

Common Obsessions

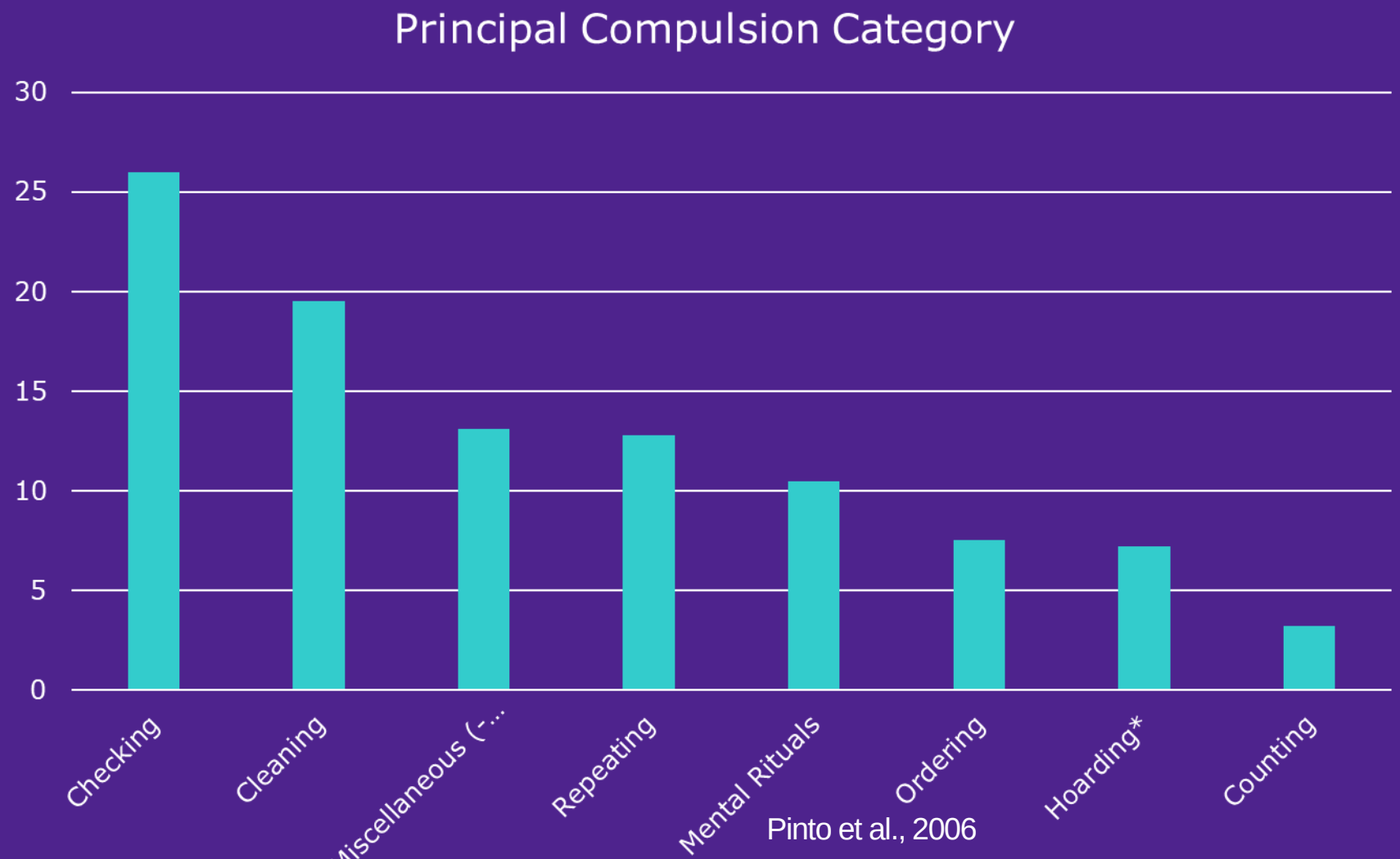
Disturbing recurrent thoughts, images, impulses that are intrusive and cause marked distress



Pinto et al., 2006

Common Compulsions

Performance of actions to relieve the distress generated by obsessional thoughts



Pinto et al., 2006

Assessments

- Yale-Brown Obsessive-Compulsive Scale (YBOCS) Symptom checklist/severity scale
- https://healthcenter1.com/wp-content/uploads/2020/10/HCA_YBOCS_Editable.pdf
- Self-report scale (YBOCS-SR)
- https://static1.squarespace.com/static/58cab82ff5e231f0df8d9cad/t/60945b3af4680c68037f8188/1620335418443/YBOCS-II-SR.pdf
- Brief Obsessive–Compulsive Scale (BOCS):
- https://www.tandfonline.com/doi/full/10.3109/08039488.2014.884631
- Level of insight is variable

Evidence Based Treatment

First line treatments: Cognitive behavioral therapy with exposure and response prevention (ERP)

- ***Goal: change in behavior (compulsions) not thoughts**
  - Exposure to the feared target with prevention of compulsive behavior

    *In vivo, imaginal, interoceptive
- Augment with an SSRI antidepressant
  - Response rates= 40 to 60%
  - All SSRIs are equally effective
  - Dose may need to be higher than for depression
  - Relapse is common following discontinuation of medication unless combined with ERP

Post-Traumatic Stress Disorder

Traumatic persistently re-experienced by:

- recurrent intrusive distressing memories, dreams
- acting or feeling as if the event were occurring (flashbacks)
- intense distress at cues that remind of the trauma
- physiologic hyperarousal, exaggerated startle response
- symptoms for at least 1 month to diagnose PTSD
- *birth trauma may result in new onset or recurrence
  - 3% for delivery-related PTSD in community samples
  - 15% in high-risk samples
  - 14% develop chronic symptoms
  - *often associated with grief

Post-Traumatic Stress Disorder

Trauma is Common in Postpartum Subjects

MDD

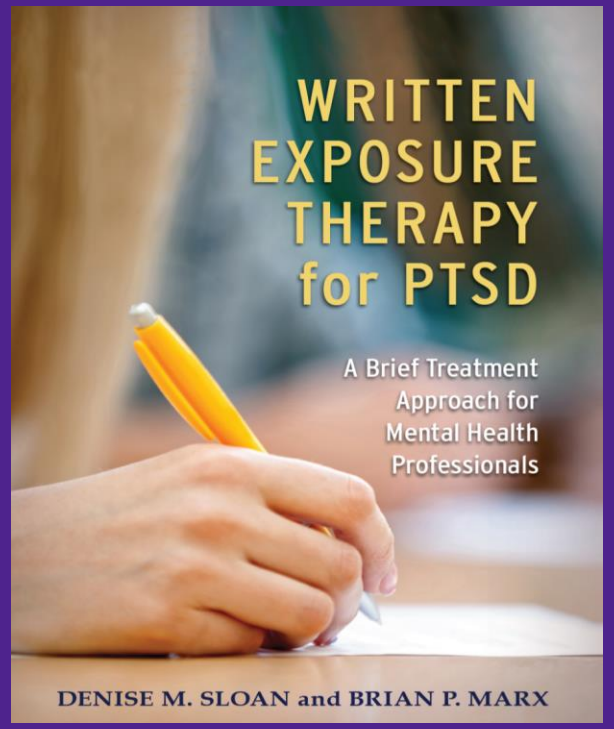
	AA N=177	White N=508	p.overall
PhyAbAdult:			0.003
Yes	74 (43.8%)	154 (31.0%)	
No	95 (56.2%)	343 (69.0%)	
PhyAbChild:			0.030
Yes	42 (24.9%)	84 (16.9%)	
No	127 (75.1%)	413 (83.1%)	
SexAbAdult:			1.000
Yes	24 (14.2%)	72 (14.5%)	
No	145 (85.8%)	425 (85.5%)	
SexAbChild:			0.001
Yes	57 (33.7%)	105 (21.1%)	
No	112 (66.3%)	392 (78.9%)	

BD

	AA N=85	White N=163	p.overall
PhyAbAdult:			0.772
Yes	43 (55.8%)	83 (52.9%)	
No	34 (44.2%)	74 (47.1%)	
PhyAbChild:			0.177
Yes	26 (33.8%)	69 (43.9%)	
No	51 (66.2%)	88 (56.1%)	
SexAbAdult:			0.155
Yes	16 (20.8%)	48 (30.6%)	
No	61 (79.2%)	109 (69.4%)	
SexAbChild:			0.941
Yes	34 (44.2%)	67 (42.7%)	
No	43 (55.8%)	90 (57.3%)	

Written Exposure Therapy: Evidence-based Treatment

- https://www.ptsd.va.gov/understand_tx/talk_therapy.asp
- Brief treatments are efficient for clinicians and patients
- 5 weekly sessions
- Writing occurs while in session
- No homework
- Clear, easy to use therapy manual



PCL 5 digital, fillable form and guide
https://www.ptsd.va.gov/professional/assessment/documents/PCL5_Standard_form.PDF
https://www.ptsd.va.gov/professional/assessment/documents/using-PCL5.pdf

JAMA Psychiatry
2018; 75:233-239
PMID 29344631

JAMA Psychiatry | Original Investigation

A Brief Exposure-Based Treatment vs Cognitive Processing Therapy for Posttraumatic Stress Disorder

A Randomized Noninferiority Clinical Trial

Denise M. Sloan, PhD; Brian P. Marx, PhD; Daniel J. Lee, PhD; Patricia A. Resick, PhD

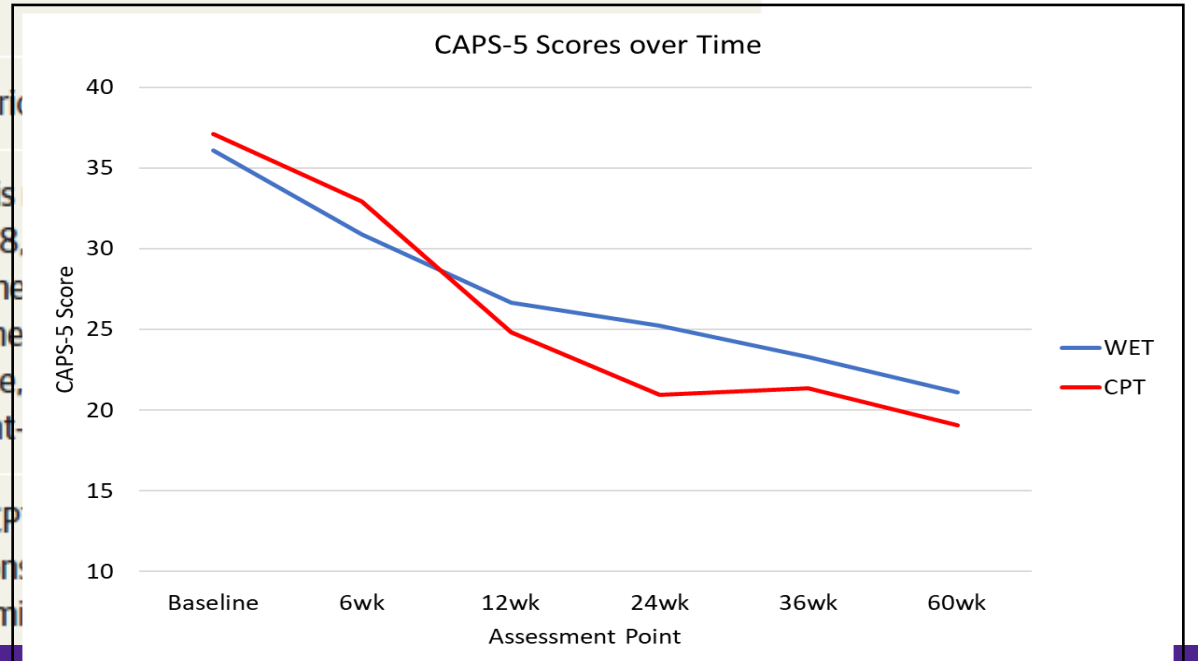
Supplemental content

IMPORTANCE Written exposure therapy (WET), a 5-session intervention, has been shown to efficaciously treat posttraumatic stress disorder (PTSD). However, this treatment has not yet been directly compared with a first-line PTSD treatment such as cognitive processing therapy (CPT).

OBJECTIVE To determine if WET is noninferi

DESIGN, SETTING, AND PARTICIPANTS In this
Affairs medical facility between February 28,
nonveteran adults were randomized to eithe
diagnosis of PTSD and stable medication the
psychotherapy for PTSD, high risk of suicide,
illness. Analysis was performed on an intent-

INTERVENTIONS Participants assigned to CP
assigned to WET (n = 63) received 5 session
accounts was delivered individually in 60-mi



Candidates for Written Exposure Therapy

Good candidates

- Comorbid Axis I disorders
- Personality disorders
- Chronic/Severe PTSD
- Multiple traumas/Chronic trauma

Less responsive candidates

- PTSD is not primary diagnosis
- No memory of the trauma
- Active psychosis
- Substance dependence
- Physical issues that prohibit ability to write

Structure of Treatment

- Select trauma event
- Read the script verbatim for each session
- Write for the full 30 minutes
- 5 sessions weekly
- Assess distress levels before/after writing
- Prepare for an increase in symptoms
- Therapist reads narratives between sessions
- Can be done virtually

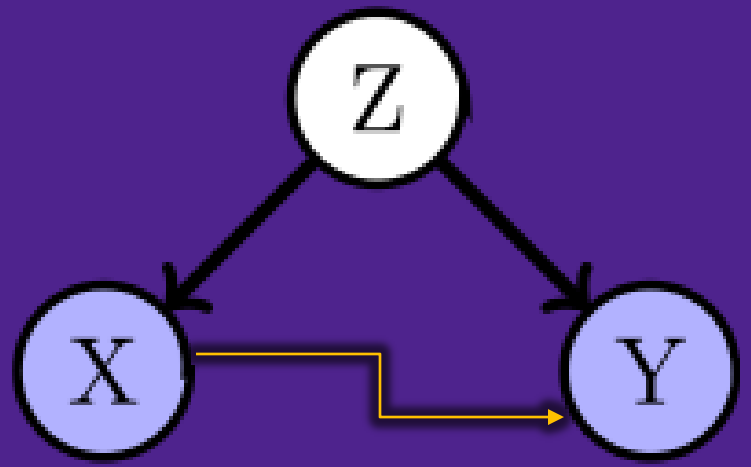
Post-Traumatic Stress Disorder

- *Behavioral therapies are first-line treatments
- Medications include: SSRI, especially with co-existing depression
- Benzodiazepines for short-term, focused treatment
- For severe nightmares, prazosin dosing starts at 1 mg at bedtime and can be increased by 1 mg weekly to establish effectiveness
- Mean doses range from 2-6 mg
- Monitor for low blood pressure

Pharmacotherapy in Pregnancy

Interpreting Observational Studies: Confounding

- A confounding variable (Z) is correlated with both the dependent variable (X) and independent variable (Y) in a way that "explains" the correlation between them.
- Common unmeasured variables assoc'd with PMAD (Z):
  - Stress
  - trauma/abuse
  - medical comorbidities
  - obstetric comorbidities
  - tobacco, drug, alcohol use
  - other medications /exposures
  - environmental exposures
  - nutritional deficiencies
  - paternal factors



SSRI (+Psychiatric disorder)

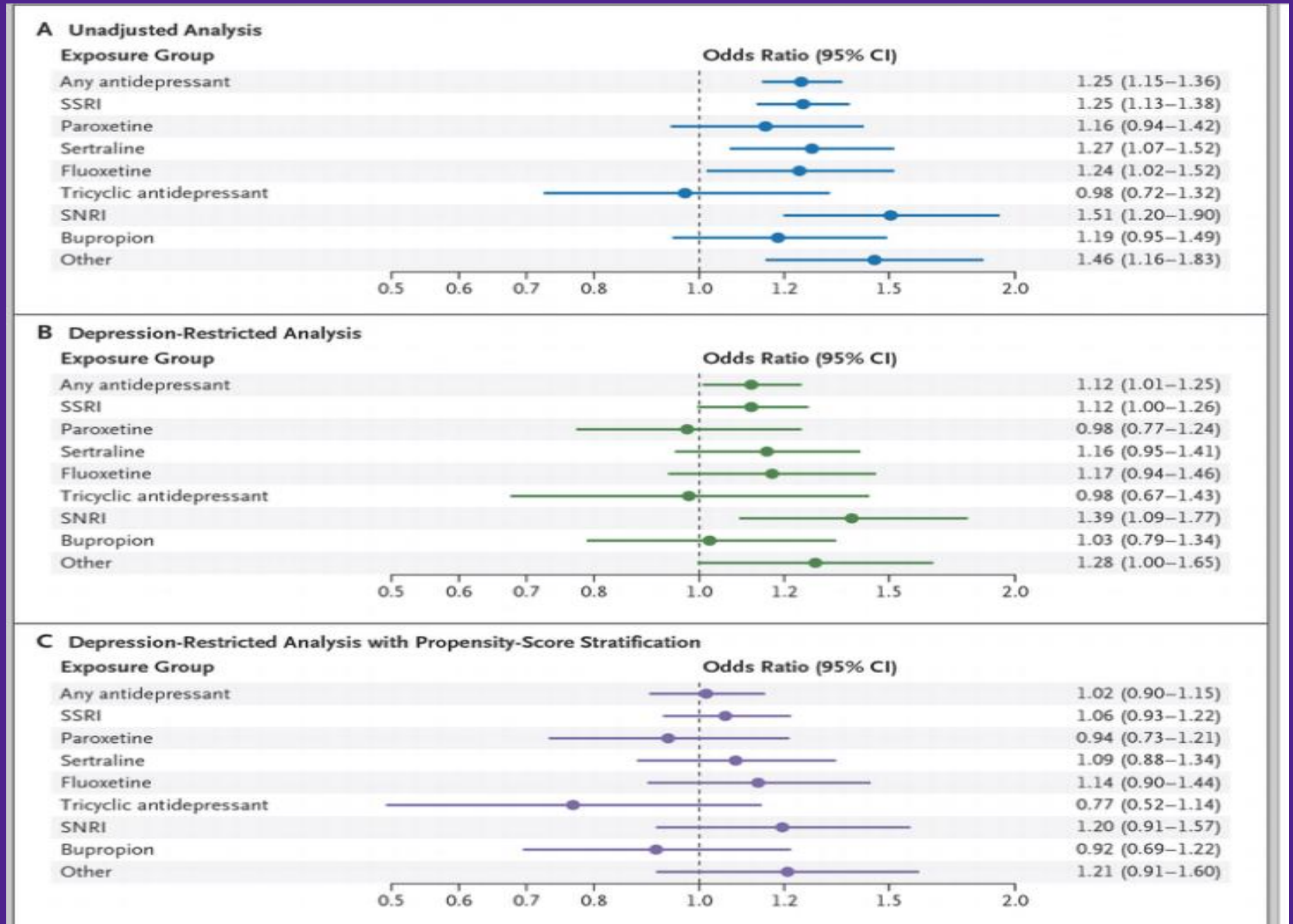
Birth Defects

No Association of SSRI with Cardiac Defects: Key Publication

- *Huybrechts KF et al, Antidepressant Use in Pregnancy and the Risk for Cardiac Defects, NEJM 370:2397-2407, 2014.*

- Medicaid Data: 949,504 pregnant women
- Exposed to antidepressants T1 vs. nonexposed
- Unadjusted, Restricted to MDD, Propensity score matched
- **Cardiac defect SSRI OR=1.25 (1.13-1.38) unadjusted**
- **Cardiac defect MDD only OR=1.12 (1.00–1.26) NS**
- **Cardiac defect MDD/PPS OR=1.06 (.93-1.22) NS**

Huybrechts et al, NEJM 370:2397-2407, 2014



Miscarriage and Stillbirth

- *Miscarriage and Stillbirth are not associated with SSRI/SNRI exposure after controlling for confounding variables
- *Andersen JT et al: Obstetrics and Gynecology. 2014;124(4):655-61.*
- Nationwide cohort study of pregnancies in Denmark from 1997-2010, the adjusted HR for miscarriage after exposure to an SSRI was significant =1.27 (95% CI, 1.22-1.33) compared with no exposure.
- Women discontinuing SSRI treatment 3-12 months before pregnancy (but no exposure in pregnancy) had the same increased HR for miscarriage (1.24, 95% CI, 1.18-1.30), indicating confounding by indication rather than drug risk.

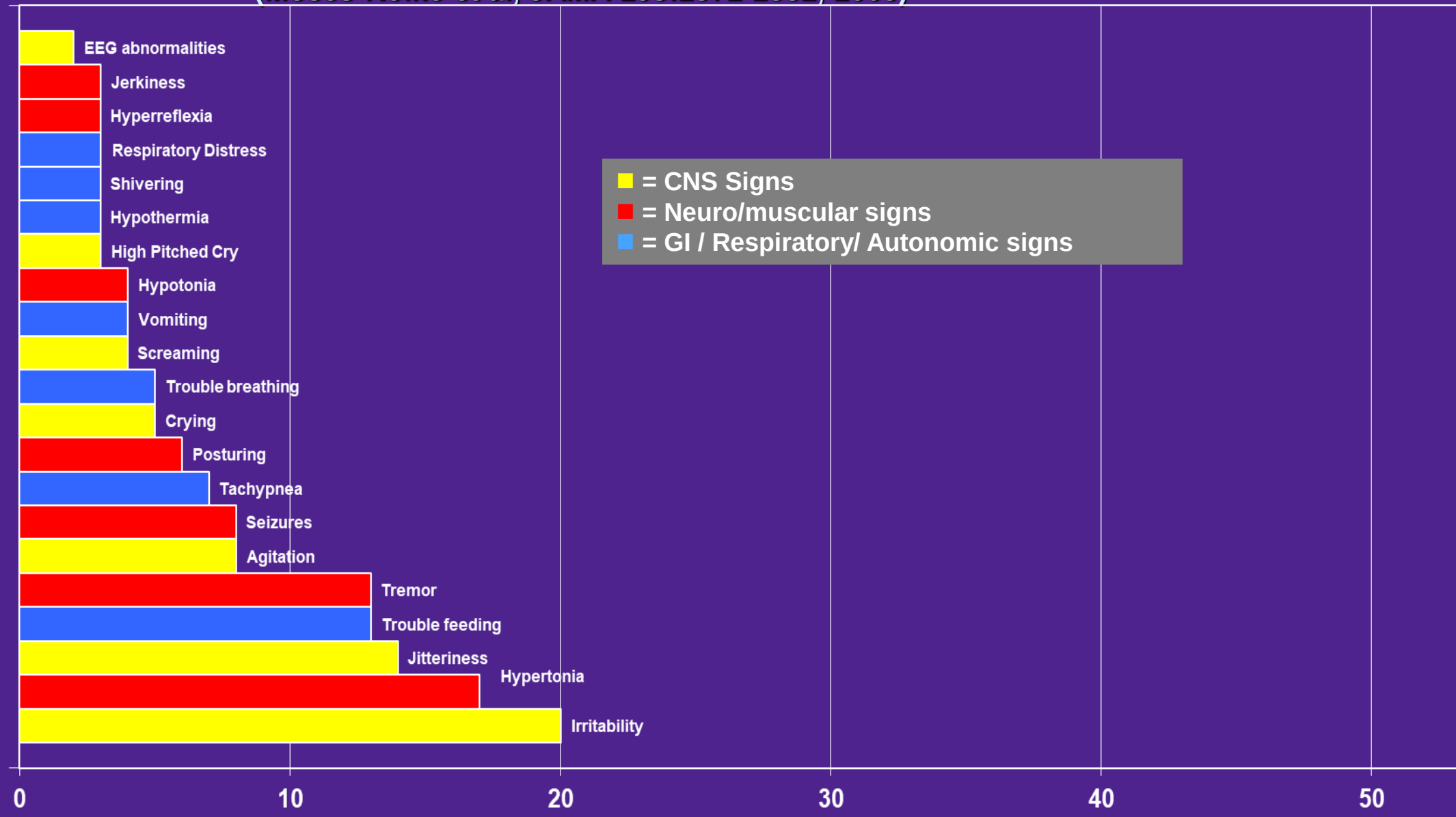
Preterm Birth

- *Preterm birth is not associated with SSRI/SNRI after controlling for confounding variables.
- One large-scale study showed a decrease in risk for antidepressant treated women (*Malm H et al, Am J Psych 172:1224-32, 2015)*
- SSRI Rx during pregnancy compared to no meds for psychiatric disorder
  - lower risk for late PTB (OR=0.84, 95% CI=0.74-0.96)
  - lower risk for early PTB (OR=0.52, 95% CI=0.37-0.74)
  - lower risk for cesarean (OR=0.70, 95% CI=0.66-0.75)

- *SSRI-treated mothers, higher neonatal risk for
  - low Apgar score (OR=1.68, 95% CI=1.34-2.12)
  - Admission to Neonatal Intensive Care Unit (OR=1.24, 95% CI=1.14-1.35).

Neonatal Adaptation: Signs Frequency

(Moses-Kolko et al, JAMA 293:2372-2382, 2005)



Neonatal Adaptation Signs

- Poor neonatal adaptation in 31.5% of infants in late-exposed group, 8.9% in early-exposure group for fluoxetine (*Chambers et al, NEJM 335:1010-1015, 1996)*
- Variable rates 0-30%-No consensus definition or measure
- Acute effects or discontinuation signs possible from any antidepressant (*Moses-Kolko et al, JAMA 293:2372-2382, 2005)*
- Paroxetine, venlafaxine- most common drugs
- Mechanism(s) not elucidated
  - ⬆ Serotonergic tone (side effects)
  - SSRI Withdrawal (rapid drug decline after birth)
  - Neurobehavioral teratologic effects in fetal brain
- Duration is variable from days to weeks

Persistent Pulmonary Hypertension in Newborn

*Associations between antidepressant use and PPHN decreased with increasing levels of confounding adjustment to become non-significant.

Huybrechts KF et al, JAMA 2015;313(21):2142-51

- 7630 unexposed to antidepressants (20.8/10 000 births)
  322 infants exposed to SSRIs (31.5/10 000 births)
  78 infants exposed to non-SSRIs (29.1/10 000 births).
- For SSRIs, OR=1.51 (95% CI, 1.35-1.69) unadjusted
  OR=1.10 (95% CI, 0.94-1.29) for MDD only/ PP score
- For non-SSRIs, OR=1.40 (95% CI, 1.12-1.75) unadjusted
  and 1.02 (95% CI, 0.77-1.35) for MDD only/PP score

How about my mental and motor development?

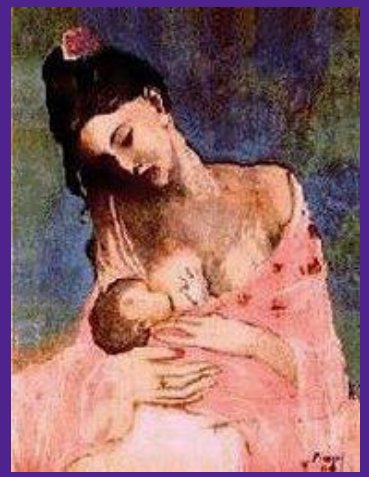
Development

Hutchison SM et al: A 6-year longitudinal study: Are maternal depressive symptoms and Selective Serotonin Reuptake Inhibitor (SSRI) antidepressant treatment during pregnancy associated with everyday measures of executive function in young children?
Early Human Devel 128:21-26, 2019.

- Longitudinal study
- Maternal depressive symptoms were associated with maternal reports of poorer executive function at 6 years.
- Prenatal SSRI exposure was not associated with poorer ratings on the Behavior Rating Inventory following adjustment for maternal depressive symptoms.
- Together these findings highlight that developmental risk associated with perinatal maternal mood disturbances, regardless of prenatal antidepressant treatment, continues long after birth.

Antidepressants do not contribute to the risk of neurodevelopmental disorders in children

- Association of Antidepressant Use During Pregnancy With Risk of Neurodevelopmental Disorders in Children.
- Suarez EA, Bateman BT, Hernández-Díaz S, **Straub L**, Wisner KL, Gray KJ, Pennell PB, Lester B, McDougle CJ, Zhu Y, Mogun H, Huybrechts KF.JAMA Intern Med. 2022 Oct 3. doi: 10.1001/jamainternmed.2022.4268. Online ahead of print.PMID: 36190722

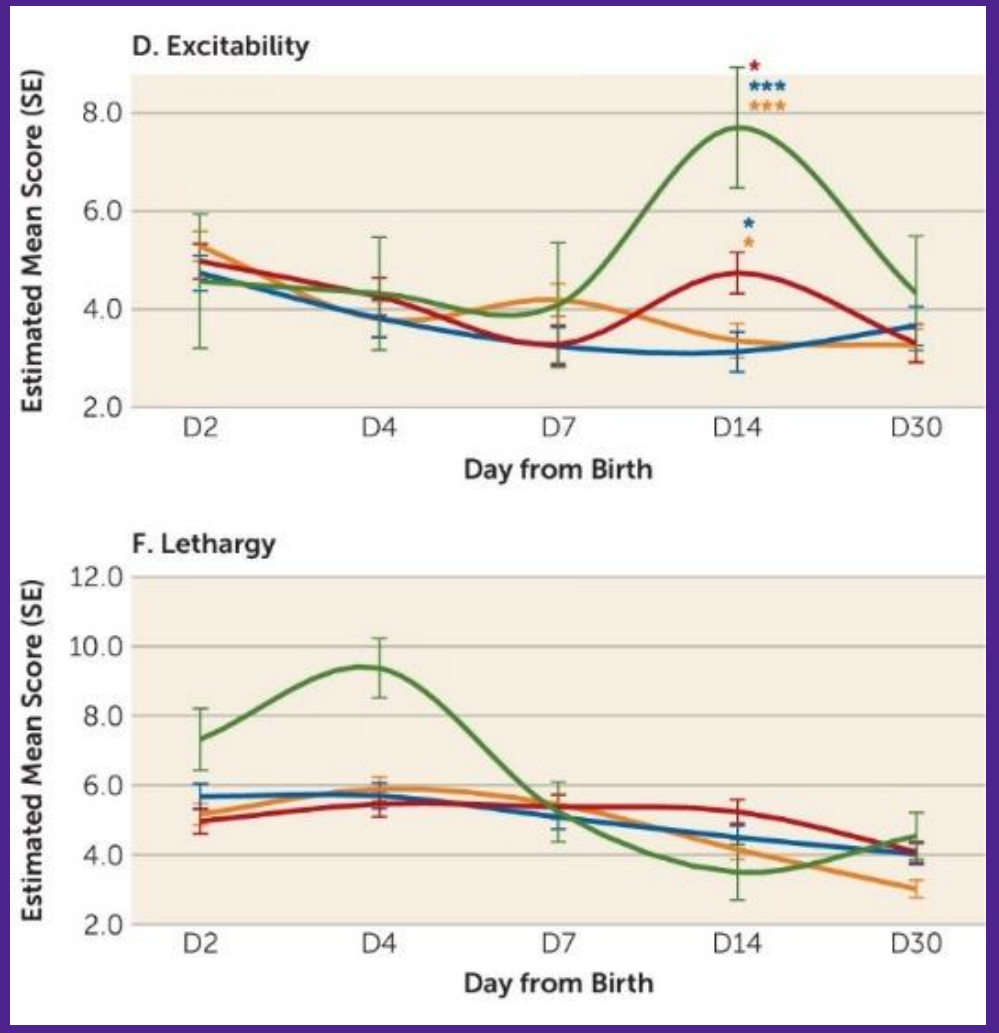


Breastfeeding and Antidepressants

- The benefits of breastfeeding are major and long-term for infant and mother
- Breastfeeding (Surgeon General's report: excess risks if not breastfeeding) www.ncbi.nlm.nih.gov/books/NBK52680/
- Data consist of mother and infant serum levels; some breastmilk
- Infant plasma -below quantifiability: sertraline, paroxetine, tricyclic nortriptyline
- Benzodiazepines associated with low risk of side effects (1.4%-sedation)
- No data for prazocin and breastfeeding
- Routine pediatric monitoring for full-term infants
- LactMed Database: https://www.ncbi.nlm.nih.gov/books/NBK501922/

Benzodiazepines in Pregnancy

- Indications:
  Treat anxiety, agitation, insomnia, seizures, muscle spasms and alcohol withdrawal
- Neonatal Withdrawal:
  Chronic exposure at end of pregnancy: withdrawal symptoms include difficulty breathing and feeding, muscle weakness, irritability, sleep disturbances, tremors, and jitteriness
- Neonatal Signs:
- Newborns exposed to both SSRI and Benzodiazepines have more neonatal signs and they persist longer than SSRI exposed (*Salisbury AL et al, Am J Psychiatry 2016; 1;173(2):147-57).*



Benzodiazepines

- *Grigoriadis S. Canadian J Psych 2020, 65(12) 821-834*
- Metaanalysis: BZD exposure significantly associated with :

  Miscarriage OR= 1.86 (95% CI=1.43 to 2.42)

  PTB OR= 1.96 (95% CI=1.25 to 3.08), mean diff 0.49 wks

  LBW OR = 2.24 (95% CI=1.41 to 3.88), mean diff 151.35 g

  Low Apgar score OR = 2.19 (95% CI = 1.94 to 2.47)

  NICU admission OR =2.61 (95% CI =1.64 to 4.14)
- Conclusions: BZD exposure variably associated with adverse pregnancy outcomes; however, residual confounding (factors associated with the psychiatric disorder) is likely

Other Hypnotics

- *Cognitive Behavioral Therapy-Insomnia (CBT-I)
- https://sleepfoundation.org/sleep-news/cognitive-behavioral-therapy-insomnia
- Doxylamine–contained in Diclegis (FDA approved for nausea)
- Trazodone

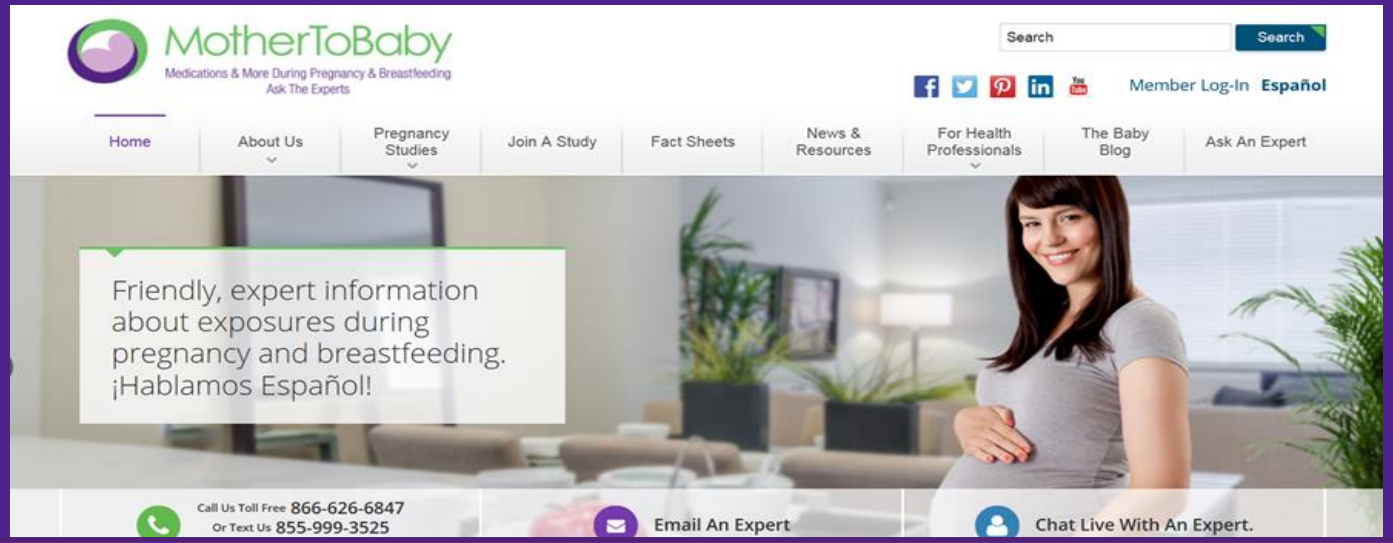
Ban et al, PLoS One. 2014 Jun 25;9(6):e100996. First trimester exposure to anxiolytic and hypnotic drugs and the risks of major congenital anomalies: a United Kingdom population-based cohort study.

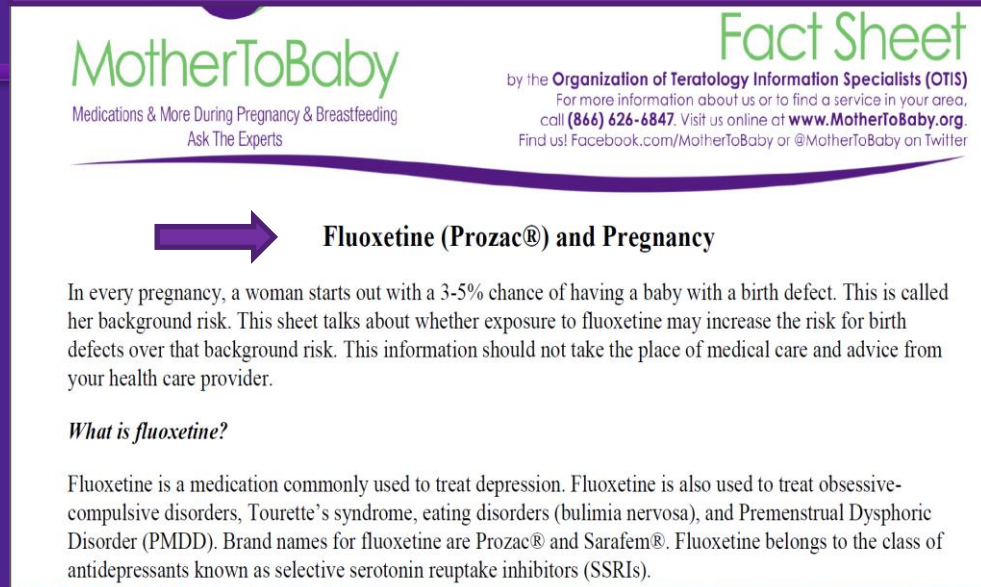
Compared to 2.7% MCA in children with no exposure to depression/anxiety or medication

- aOR=1.02 (99% CI=0.63–1.64) for diazepam
- aOR=1.07 (0.49–2.37) for temazepam
- aOR=0.96 (0.42–2.20) for zopiclone

ENTIS/ OTIS Teratogen Information

https://www.entis-org.eu/teratogen-information





MotherToBaby

Medications & More During Pregnancy & Breastfeeding
Ask The Experts

Fact Sheet

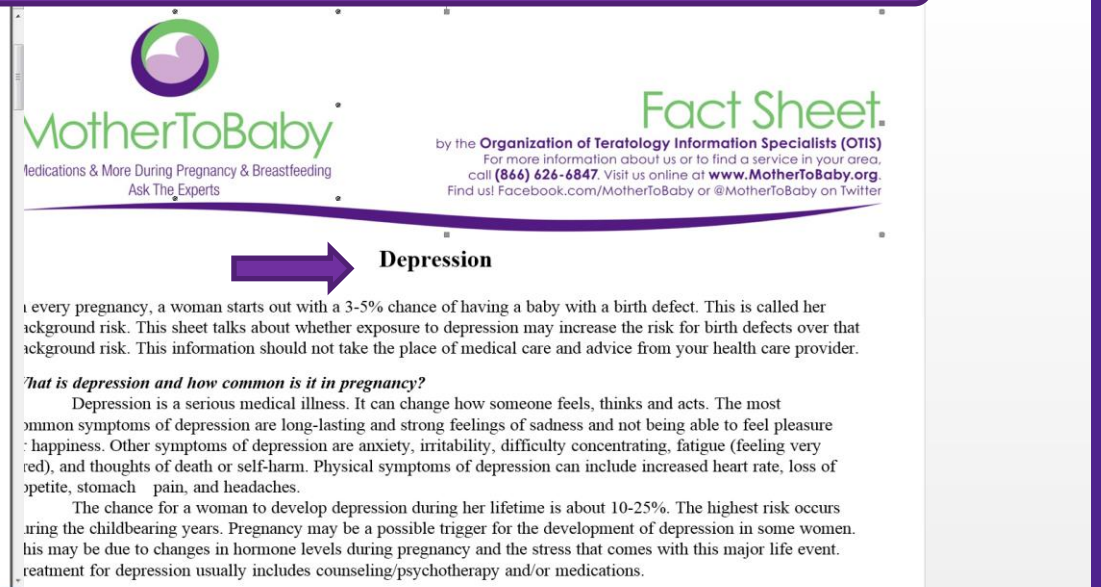
by the **Organization of Teratology Information Specialists (OTIS)**
For more information about us or to find a service in your area, call **(866) 626-6847**. Visit us online at **www.MotherToBaby.org**.
Find us! Facebook.com/MotherToBaby or @MotherToBaby on Twitter

Fluoxetine (Prozac®) and Pregnancy

In every pregnancy, a woman starts out with a 3-5% chance of having a baby with a birth defect. This is called her background risk. This sheet talks about whether exposure to fluoxetine may increase the risk for birth defects over that background risk. This information should not take the place of medical care and advice from your health care provider.

What is fluoxetine?

Fluoxetine is a medication commonly used to treat depression. Fluoxetine is also used to treat obsessive-compulsive disorders, Tourette's syndrome, eating disorders (bulimia nervosa), and Premenstrual Dysphoric Disorder (PMDD). Brand names for fluoxetine are Prozac® and Sarafem®. Fluoxetine belongs to the class of antidepressants known as selective serotonin reuptake inhibitors (SSRIs).



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Depression

every pregnancy, a woman starts out with a 3-5% chance of having a baby with a birth defect. This is called her ackground risk. This sheet talks about whether exposure to depression may increase the risk for birth defects over that ackground risk. This information should not take the place of medical care and advice from your health care provider.

hat is depression and how common is it in pregnancy?

Depression is a serious medical illness. It can change how someone feels, thinks and acts. The most ommon symptoms of depression are long-lasting and strong feelings of sadness and not being able to feel pleasure happiness. Other symptoms of depression are anxiety, irritability, difficulty concentrating, fatigue (feeling very red), and thoughts of death or self-harm. Physical symptoms of depression can include increased heart rate, loss of petite, stomach pain, and headaches.

The chance for a woman to develop depression during her lifetime is about 10-25%. The highest risk occurs uring the childbearing years. Pregnancy may be a possible trigger for the development of depression in some women. his may be due to changes in hormone levels during pregnancy and the stress that comes with this major life event. reatment for depression usually includes counseling/psychotherapy and/or medications.

Discussion

Signs Evolve and Vary by Exposure

Salisbury AL et al, Am J Psychiatry 2016 Feb 1;173(2):147-57.

Maternal Depression, SRI Treatment and Concomitant BDZ Use On Infant Neurobehavioral Functioning Over the First Postnatal Month