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Psychopharmacology Across the Reproductive Lifespan: From Menarche to Menopause

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Disclosures

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Abbreviations:
SSRIs – Selective Serotonin Reuptake Inhibitor
SNRIs – Serotonin Norepinephrine Reuptake Inhibitors
SRIs – Serotonin Reuptake Inhibitors, both SSRIs and SNRIs

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Premenstrual dysphoric disorder (PMDD)

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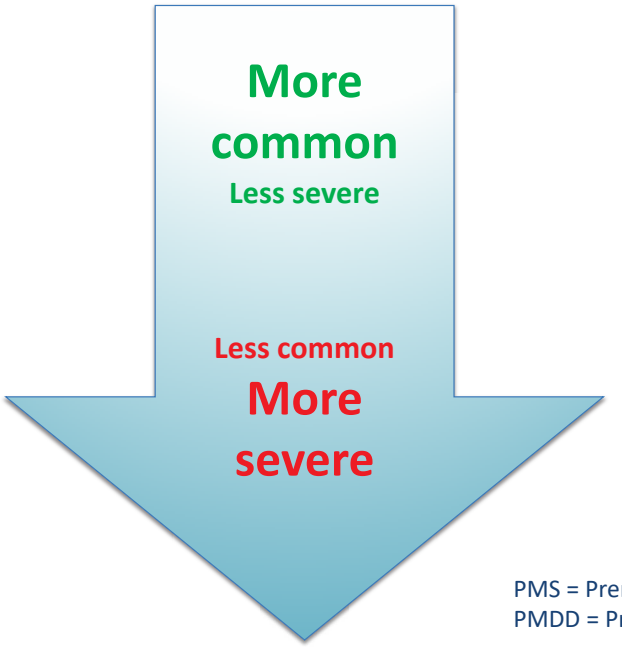
Premenstrual Symptoms ≠ An illness



Premenstrual Molimina
(normal, non-problematic)

PMS
(bothersome)

PMDD
(significant impairment)

PMS = Premenstrual syndrome
PMDD = Premenstrual dysphoric disorder

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Ginsburg KA, Dinsay R. Premenstrual syndrome. In: Ransom SB, ed. Practical Strategies in Obstetrics and Gynecology. Philadelphia: W.B. Saunders Company, 2000: 684–694.

Symptoms of Premenstrual Dysphoric Disorder

≥5 symptoms, including at least 1 core symptom

Core Symptoms

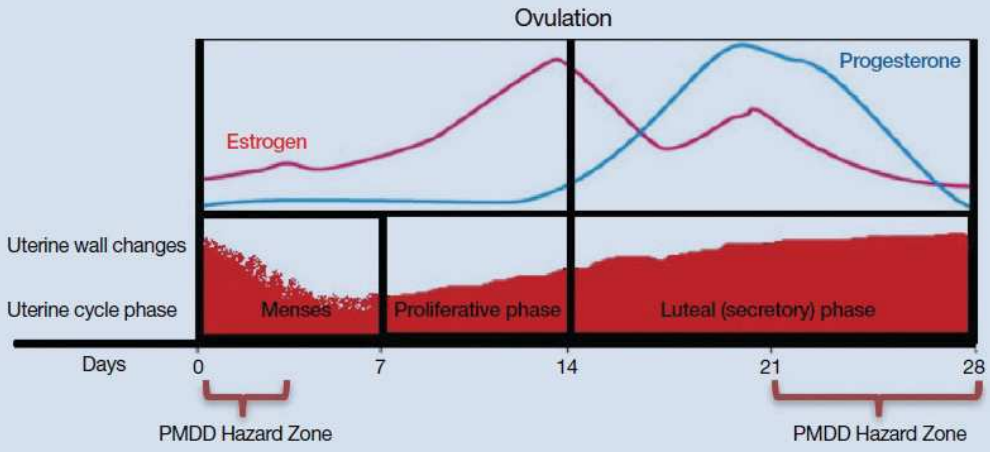
- Depressed mood
- Anxiety, tension, edginess
- Affective lability
- Anger or irritability

Other Symptoms

- Feeling overwhelmed/out of control
- Decreased interest in usual activities
- Difficulty concentrating
- Fatigue, lethargy
- Insomnia/hypersomnia
- Appetite changes/cravings
- Physical symptoms (headache, breast tenderness/swelling, bloating, joint/muscle pain, etc.)

Premenstrual Dysphoric Disorder. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Washington, DC: American Psychiatric Association, 2013

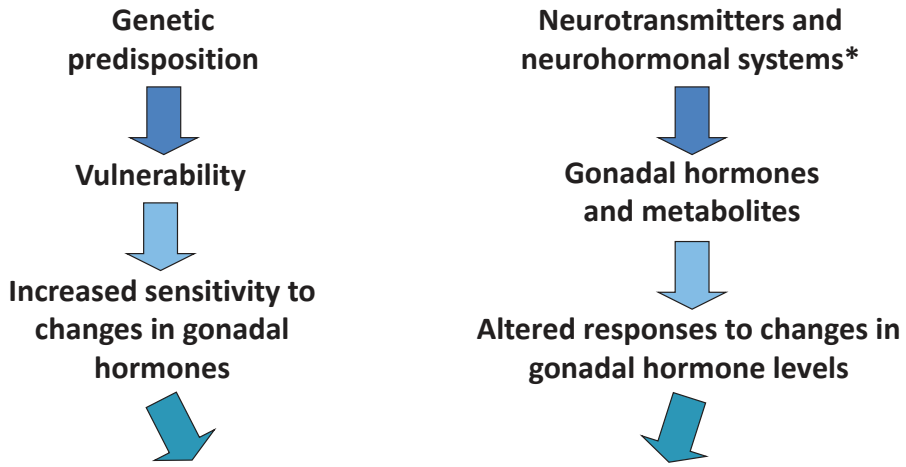
The menstrual cycle and the 'PMDD Hazard Zone'



The diagnosis of PMDD is made when a patient has at least 5 of 11 specific symptoms that occur during the week before onset of menses, improve within a few days after the onset of menses (indicated here as the "PMDD Hazard Zone"), and are minimal or absent post-menses.

PMDD: premenstrual dysphoric disorder

Proposed Etiology of Premenstrual Disorders



*Serotonin, renin-angiotensin-aldosterone system, γ-aminobutyric acid (GABA), cholecystokinin

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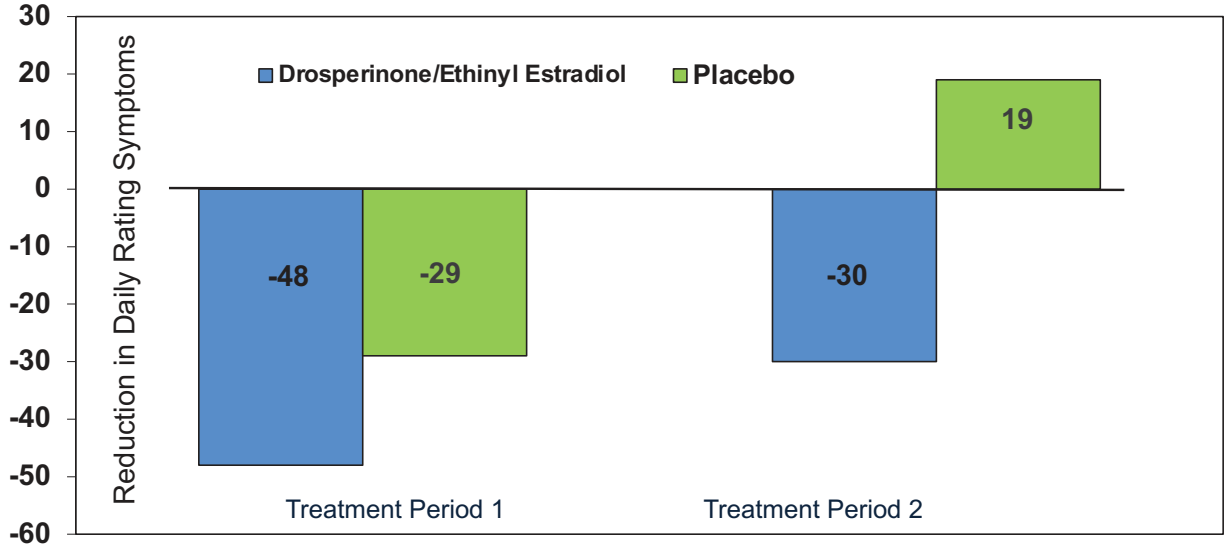
SRIs for Treatment of PMDD

- Sertraline, Paroxetine and Fluoxetine have FDA approval for PMDD
- Can be dosed continuously as you would typically
- Can also be dosed at symptom onset or at onset of luteal phase

Medication	Starting Dose	Target Dose
Sertraline	25-50mg	50-200mg
Paroxetine	10-20mg	20-50mg
Fluoxetine	10-20mg	20-60mg

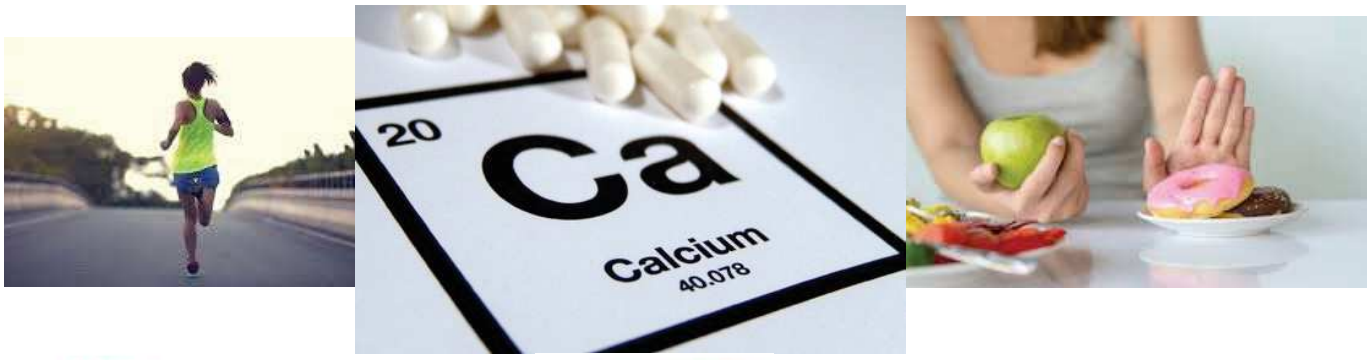
Certain Contraceptive Agents are Effective for Treatment of PMDD: Drosperinone/Estradiol or Placebo



Adjusted mean DRSP difference –12.47(95% CI=-18.28, -6.66; p<0.001)

Pearlstein et al, Contraception, Vol 73: 421-425, 2005

Complementary approaches



Which Should You Recommend?

Serotonin Reuptake Inhibitors

- You suspect an underlying mood disorder
- Patient who does not want to pills daily
- Patient with medical contraindications to hormonal treatment
- Patient has OC induced side effects
- Patient preference

Selected Hormonal Contraceptives

- Patient is seeking contraception in addition to PMDD treatment
- Patient has not responded to an SRI
- Patient has a contraindication for SRIs (e.g., mania)
- Patient has had SRI induced side effects
- Patient has severe physical symptoms
- Patient preference

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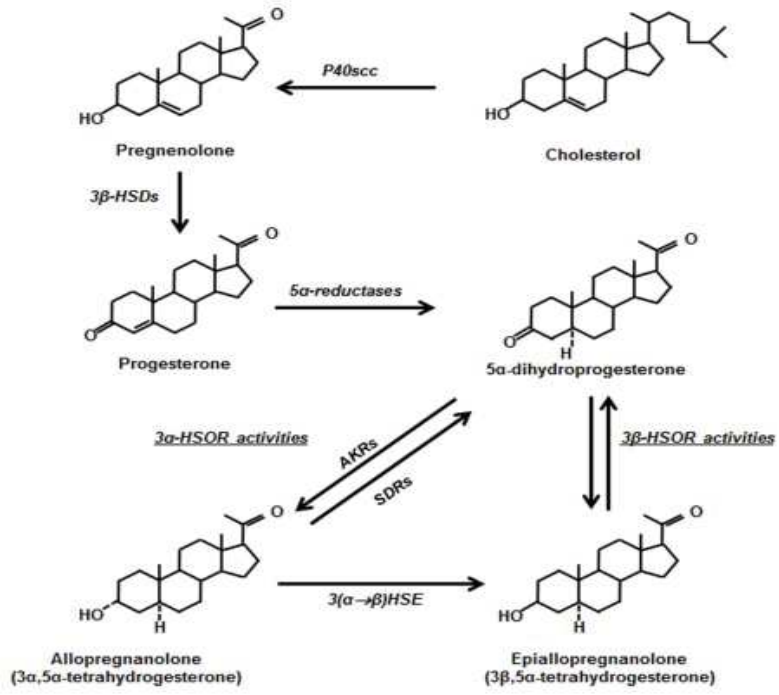
Role of Neurosteroids in Treatment



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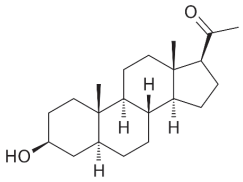
Schumacher et al. Front Neurosci, 2012, Vol 6, pp 10

Isoallopregnanolone as Progesterone Antagonist

- Isoallopregnanolone is an endogenous neurosteroid
- Acts as a negative allosteric modulator of the $GABA_A$ receptor
- Selectively antagonizes allopregnanolone



- The medication is administered subcutaneously and is in development
- Half life is ~48 hours to achieve > 4 nmol/ml concentration

➡ A potential treatment for women with a paradoxical reaction to progesterone and allopregnanolone

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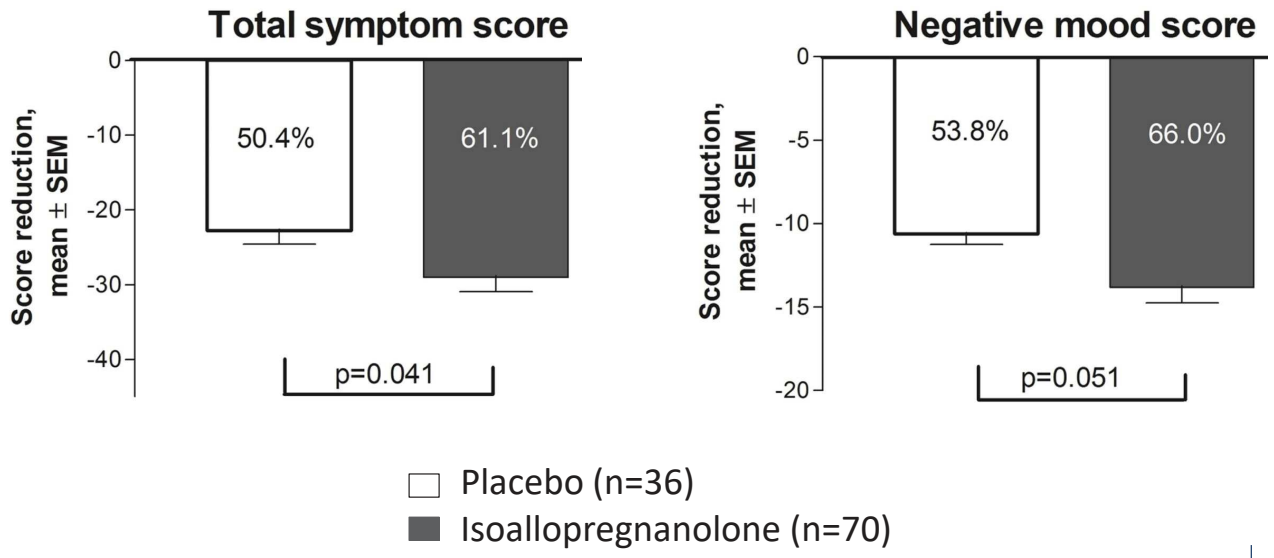
Isoallopregnanolone as Treatment for PMDD



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Bixo et al., Psychoneuroendocrinology 2017; 80:46-55

Ulipristal Acetate (UPA)

- Selective progesterone receptor modulator that acts as a progesterone antagonist
- Low-dose continuous treatment leads to anovulation

Proof of concept study:

- Double-blind, randomized, parallel-group clinical
  - participants were treated with UPA 5 mg/day (N=48)of UPA or placebo (n=47) for three 28-day treatment cycles
- 18% drop out (8 UPS and 9 placebo)
- Reported side effects in the UPA group: headache (8.3%), nausea (8.3%), and fatigue (6.3%)

Comasco E et al., AJP 2021. 178:3, 256-265

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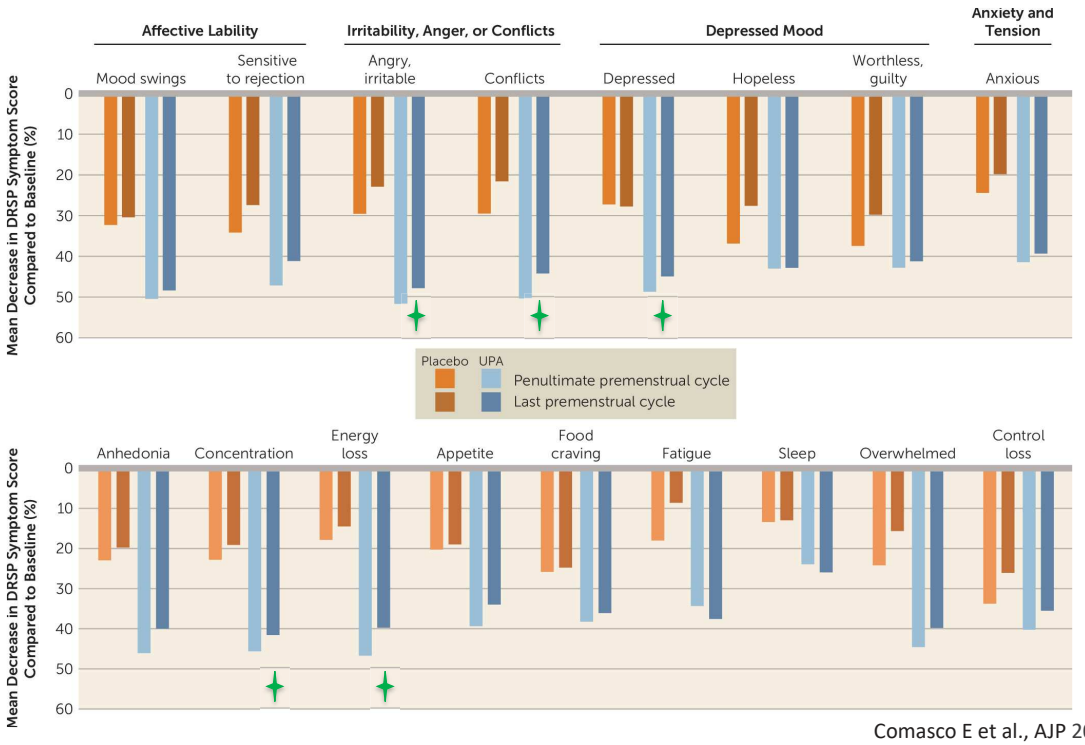
Ulipristal Acetate (UPA)



Comasco E et al., AJP 2021. 178:3, 256-265

Medication use during pregnancy and lactation

There is no such thing as non-exposure

Balance risks of psychopharmacologic treatment with risks of untreated mental illness on the fetus and infant

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Context: Impact of Untreated Maternal Mental Illness

Maternal Impact

- Poor prenatal care
- Substance use
- Preeclampsia
- Maternal suicide
- Relationship discord

Infant Impact

- Low birthweight
- Preterm delivery
- Cognitive delays
- Behavioral problems
- Insecure attachment patterns
- Anxiety and depression
- ADHD and learning disabilities

Bodnar et al, J Clin Psych, 2009
Cripe et al, Pedi & Perinatal Epid, 2011

What Guides Prescribing?

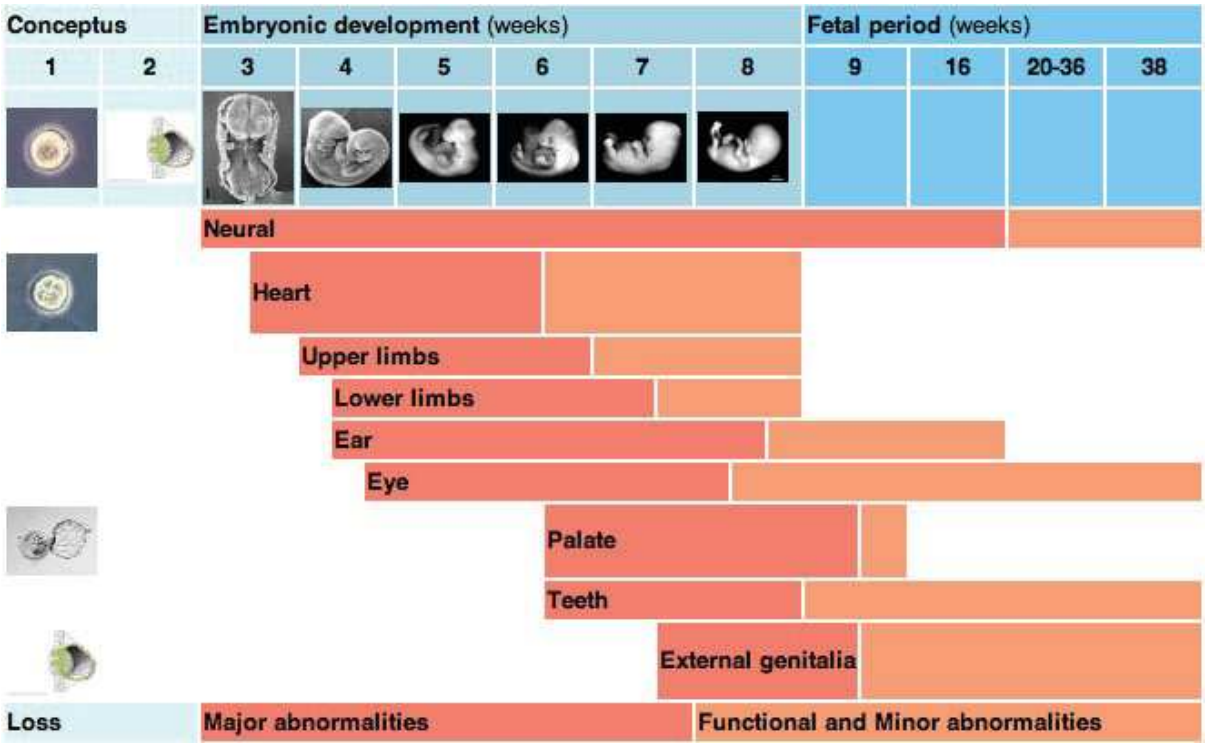
Patient preference

Severity of illness episodes

Previous response to treatments

Degree of recurrence of illness

Duration of current stability



Hill, M.A. (2021, March 25) Embryology Human-critical periods of development.jpg. Retrieved from https://embryology.med.unsw.edu.au/embryology/index.php/File:Human-critical_periods_of_development.jpg

Prescribing Considerations in Pregnancy

- Maximize non-pharmacologic interventions
- Lowest **effective** dose
- Avoid polypharmacy
- Patient-centered care
- Documentation
- Pregnancy physiology

Pregnancy Physiology

- Physiologic Changes
  - Slower gastric emptying and small bowel and colonic transit time
  - Increased plasma volume
  - Reduced plasma albumin concentration
  - Lower ratio of lean muscle to adipose tissue
  - Changes in the hepatic clearance of psychotropic medications
  - Increased renal blood flow with associated increase in GFR
- Monitor closely for symptomatic change throughout pregnancy
- Consider divided doses

Lactation Considerations

- Medications have higher excretion in breast milk if they:
  - High lipid solubility
  - Long half-life
  - High oral availability
  - Small molecular weight
  - Low maternal serum protein binding
- Medication half-life
- Infant medical stability

Antidepressant use during pregnancy

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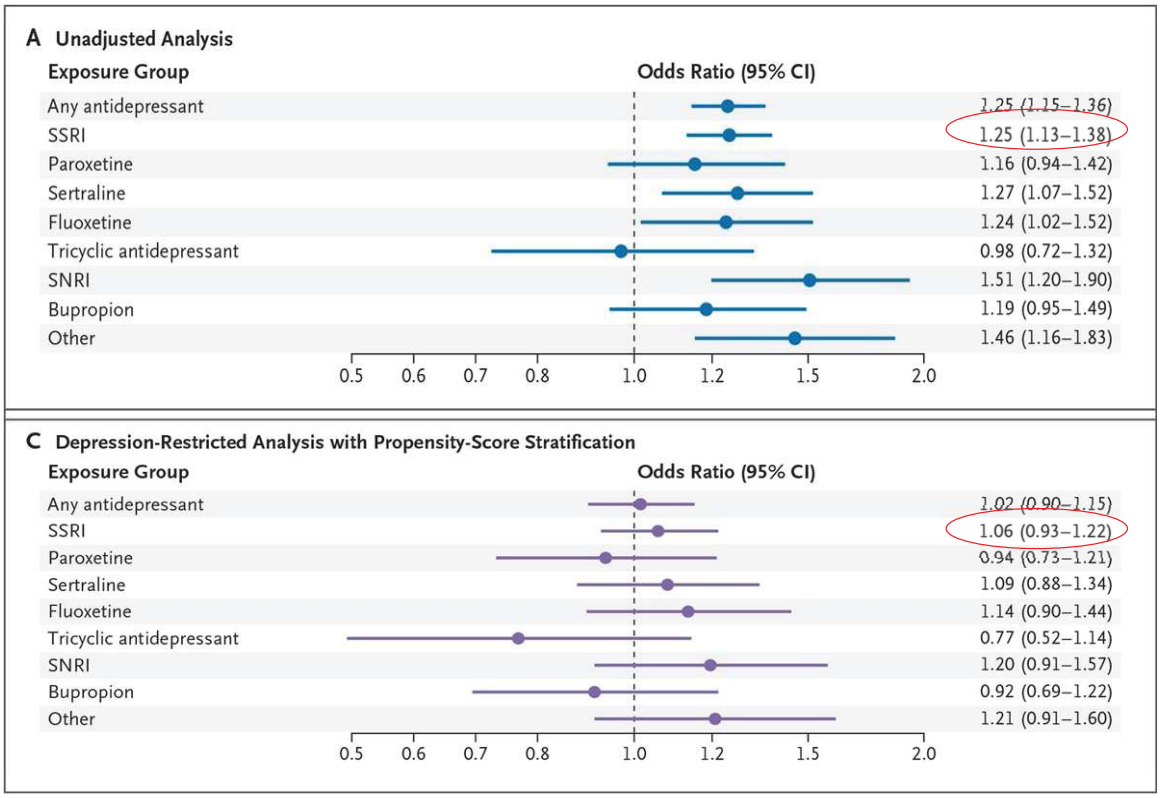
Antidepressant Use in Pregnancy and Associations with Selected Adverse Fetal Outcomes

Outcome	Strength of Finding
Fetal demise	Not associated
Spontaneous miscarriage	Mixed results
Small for Gestational Age/Low Birth Weight	Mixed but weak results; better controlled studies are negative
Major Congenital Anomalies	Mixed but weak results; greater consistency with paroxetine
Persistent Pulmonary Hypertension	Mixed results
Pre-eclampsia, gestational hypertension	Emerging data
Preterm Birth	Highly replicated but small effects
Neonatal adaptation	Moderately well replicated
Autism	Mixed but weak results; better controlled studies are negative
Attention Deficit Hyperactivity Disorder	Mixed but weak results; better controlled studies are negative

SRIs and Risk of Congenital Cardiac Malformations

Medicaid Analytic eXtract:
n=949,504 pregnancies
n=217,342 in depression restricted



Huybrechts et al., NEJM, 2014

Clinical implications: Effects of Antidepressants on Risk of Birth Defects

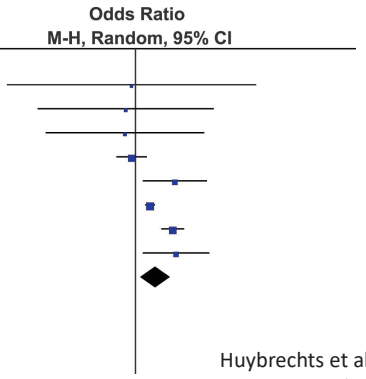
- Most studies do not show an association with between SRI exposure and major malformations
- A small increase the risk of malformations is possible but remains controversial
- Most associations are with ventral septal defects, relatively common malformations
- If risks are real, the absolute risk is low and must be viewed in the context of whether medication is needed
- Other exposures such as alcohol may confound results, particularly in registry studies that typically have limited information about the mother

Persistent Pulmonary Hypertension of the Newborn (PPHN)

- Background risk: 10 to 20 newborns in every 10,000 live births (0.1%-0.2%)
- Absolute risk is small with late pregnancy exposure
- In largest cohort study that adjusted for maternal depression, OR 1.10 (95% CI, 0.94-1.29)
- In a network meta-analysis sertraline has the lowest risk of PPHN

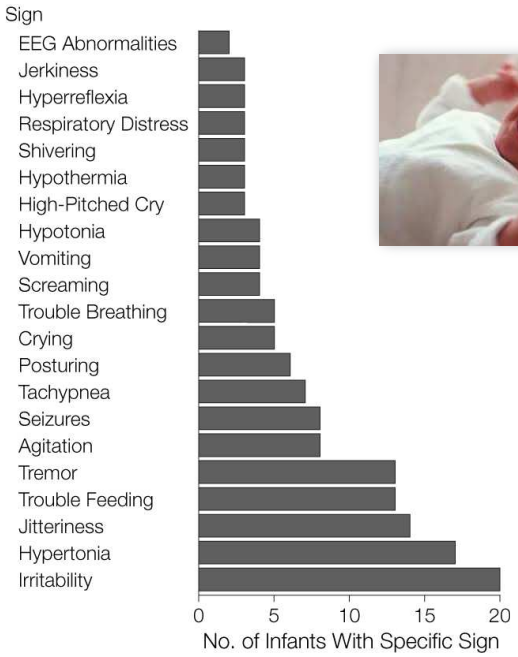
Study or Subgroup	Expsoed Events	Total	Non-Exposed Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
1.1.1 Cohort Studies							
Wichman et al[48]	0	808	16	24406	1.3%	0.91 [0.05, 15.25]	2009
Hammad et al[47]	1	6569	33	173865	2.5%	0.80 [0.11, 5.86]	2009
Andrade et al[46]	2	933	3	1104	2.9%	0.79 [0.13, 4.73]	2009
Kieler et al[49]	33	30115	1899	1588140	17.0%	0.92 [0.65, 1.29]	2012
Colvin et al[23]	8	3297	86	86110	10.4%	2.43 [1.18, 5.03]	2012
Huybrechts et al[10]	322	102179	7630	3360380	20.3%	1.39 [1.24, 1.55]	2015
Nörby et al[50]	60	9100	2051	718533	18.4%	2.32 [1.79, 3.00]	2016
Bérard et al[12]	7	1537	258	141097	10.0%	2.50 [1.18, 5.30]	2017
Subtotal (95% CI)		**154538**		**6093635**	**82.8%**	**1.58 [1.14, 2.19]**	
Total events	433		11976				

Heterogeneity: Tau² = 0.10; Chi² = 25.25, df = 7 (P = 0.0007); I² = 72%
Test for overall effect: Z = 2.72 (P = 0.007)



Huybrechts et al, JAMA, 2015
Masarwa et al, AJOG, 2019

Poor Neonatal Adaptation Syndrome (PNAS)



5-30% of infants exposed to SRI

PNAS Meta-analysis

- 2.2-fold increased risk of respiratory distress (CI=1.81-2.66)
- 7.9-fold increase in tremors (CI=3.33-18.73)

Moses-Kolko, JAMA 2005;293(19):2372-2383
Grigoriadis et al, J Clin Psych 2013;74(4): e309-20

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Breastfeeding and antidepressants

- Breastfeeding is generally recommended with antidepressant use
- The baby should be monitored for problems feeding or sleeping, rather than monitoring levels

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Benzodiazepines and Malformations

- Early case-control studies reported increased risks of facial clefts with benzodiazepine exposure in first trimester
- Recent meta-analyses and cohort studies have failed to find an association between any malformations and benzodiazepine exposure

Dolovich et al, 1998, BMJ, Vol 317:839-43.
Ben et al, 2014, PLoS One, 9(6); e100996.

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Benzodiazepines and Adverse Birth Outcomes

Increased risk of:

- Cesarean Delivery (OR=2.45; 95% CI=1.36-4.40)
- Low Birth Weight (OR=3.41; 95% CI=1.61-7.26)
- Neonatal Ventilatory Support (OR=2.85; 95% CI=1.17-6.94)
- Preterm delivery (OR=1.41; 95% CI=0.97-4.04)

Yonkers et al, 2017, JAMA Psychiatry; Huitfeldt et al., 2020, JAMA Open

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Treatment of postpartum depression

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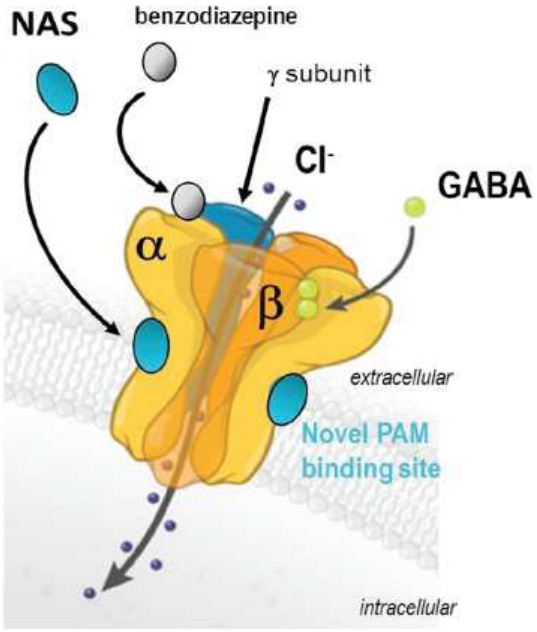
Neurosteroids as Treatment



- Neuroactive steroids (NAS) bind to a unique site and are positive allosteric modulators (PAMs) of the Gamma-Amino-Butyric Acid (GABA) receptor
- Can modulate the receptor in synaptic and extra synaptic sites

Maguire & Mody. Neuron. 2008;59(2):207-13

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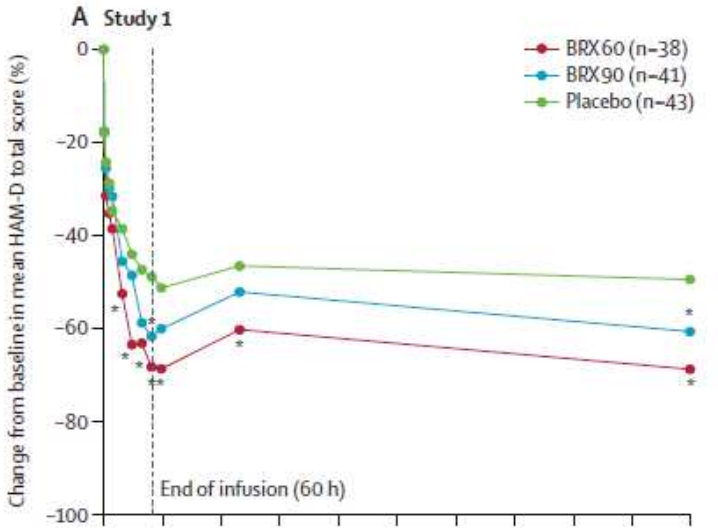
Brexanolone for Postpartum Depression



- Minimal HAM-D total score ≥26
- Onset of depression in 3rd trimester or one month postpartum
- 60-hour infusion
- Follow up to 30 days
- 4% pre-syncope
- * p<.05 in change in HAM-D
- FDA approved 3/2019

Meltzer-Brody et al, 2018, Lancet, 392:10580-1070

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Zuranonlone Study

RCT: Effect of Zuranolone vs Placebo in Postpartum Depression: A Randomized Clinical Trial

POPULATION

150 Women

Women ages 18-45 y with postpartum depression and Hamilton Rating Scale for Depression (HAMD-17) score ≥26

Mean (SD) age, 28.3 (5.4) y

INTERVENTION

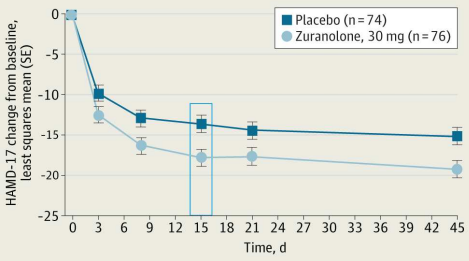
153 Individuals randomized

76 Zuranolone
Oral zuranolone, 30 mg, every evening with food for 14 d

74 Placebo
Oral placebo capsule every evening with food for 14 d

FINDINGS

Individuals with postpartum depression who received zuranolone for 2 wk displayed significantly greater reductions in depressive symptoms compared with placebo at day 15



Difference in change in depressive symptoms at 15 wk, zuranolone vs placebo:
−4.2 (95% CI, −6.9 to −1.5); *P* = .003

SETTINGS / LOCATIONS

27 Clinical sites in the US

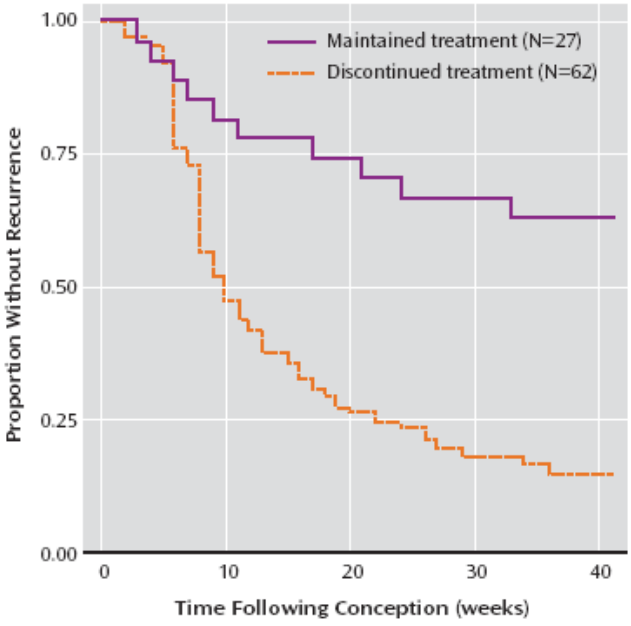
PRIMARY OUTCOME

Change from baseline in depressive symptoms at day 15, as measured by HAMD-17 score (range, 0-52, with higher scores indicating more severe depression)

Deligiannidis KM, Meltzer-Brody S, Gunduz-Bruce H, et al. Effect of zuranolone vs placebo in postpartum depression: a randomized clinical trial. *JAMA Psychiatry.* Published online June 30, 2021. doi:10.1001/jamapsychiatry.2021.1559

Management of bipolar disorder and psychosis in pregnancy and postpartum

Relapse Among Women with Bipolar Disorder Who Maintain or Discontinue Medication



Viguera et al., AJP 2007;164:1817-24

These findings were replicated in more recent meta-analysis were 66% of women who discontinued medications had a relapse vs. 23% of women who remained on medications

Wesseloo et al., AJP 2016; 173:117-127

Mood Stabilizers and Antipsychotics in Pregnancy

Lamotrigine	Lithium	Valproic Acid
First generation antipsychotics	Second generation antipsychotics	Carbamazepine

Table 2. Absolute and Relative Risk of Cardiac, Noncardiac, and Overall Malformations among Infants Exposed to Lithium during the First Trimester as Compared with Lamotrigine-Exposed or Unexposed Infants.*

Variable	No Exposure to Lithium or Lamotrigine	Exposure to Lamotrigine	Exposure to Lithium
No. of pregnancies	1,322,955	1945	663
Cardiac malformations			
Events	15,251	27	16
Prevalence per 100 births	1.15	1.39	2.41
Unadjusted risk ratio (95% CI)	Reference	1.20 (0.83–1.75)	2.09 (1.29–3.40)
Propensity-score–adjusted risk ratio (95% CI)	Reference	0.89 (0.61–1.30)	1.65 (1.02–2.68)
Unadjusted risk ratio (95% CI)	—	Reference	1.74 (0.94–3.21)
Propensity-score–adjusted risk ratio (95% CI)	—	Reference	2.25 (1.17–4.34)
Noncardiac malformations			
Events	27,816	49	22
Prevalence per 100 births	2.10	2.52	3.32
Unadjusted risk ratio (95% CI)	Reference	1.20 (0.91–1.58)	1.58 (1.05–2.38)
Propensity-score–adjusted risk ratio (95% CI)	Reference	0.90 (0.68–1.18)	1.22 (0.81–1.84)
Unadjusted risk ratio (95% CI)	—	Reference	1.32 (0.80–2.16)
Propensity-score–adjusted risk ratio (95% CI)	—	Reference	1.63 (0.96–2.78)
Overall malformations			
Events	43,067	76	38
Prevalence per 100 births	3.26	3.91	5.73
Unadjusted risk ratio (95% CI)	Reference	1.20 (0.96–1.50)	1.76 (1.29–2.40)
Propensity-score–adjusted risk ratio (95% CI)	Reference	0.90 (0.72–1.12)	1.37 (1.01–1.87)
Unadjusted risk ratio (95% CI)	—	Reference	1.47 (1.00–2.14)
Propensity-score–adjusted risk ratio (95% CI)	—	Reference	1.85 (1.23–2.78)

* CI denotes confidence interval.

Absolute and Relative Risks of Malformations among Infants Exposed to Lithium as Compared with Lamotrigine-Exposed or Unexposed Infants

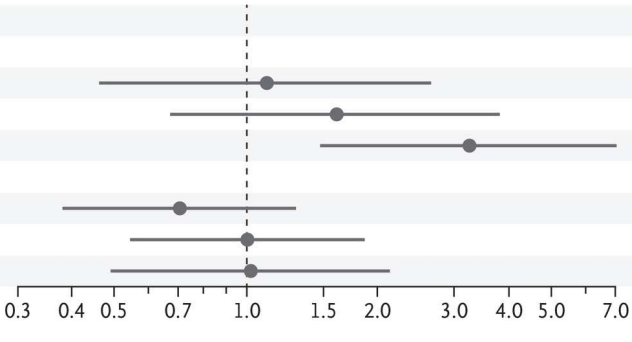
Increased likelihood of 1-2 cases per live birth *if* exposure is causal

The NEW ENGLAND JOURNAL of MEDICINE

Patorno E et al. NEJM 2017;376:2245-2254

Absolute and Relative Risk of Cardiac Malformations among Lithium-Exposed and Lamotrigine-Exposed Infants as Compared with Unexposed Infants, Stratified According to the Mother's Dose of the Drug

Exposure Group	No. of Pregnancies	No. of Events	Prevalence per 100 Births	Propensity-Score-Adjusted Risk Ratio (95% CI)
No exposure	1,322,955	15,251	1.15	Reference
Exposure to lithium				
≤600 mg/day	305	<11	1.64	1.11 (0.46–2.64)
601–900 mg/day	235	<11	2.13	1.60 (0.67–3.80)
>900 mg/day	123	<11	4.88	3.22 (1.47–7.02)
Exposure to lamotrigine				
≤100 mg/day	904	<11	1.11	0.70 (0.38–1.30)
101–200 mg/day	620	<11	1.61	1.00 (0.54–1.86)
>200 mg/day	421	<11	1.66	1.02 (0.49–2.13)



All right ventricular outflow obstruction defects were born to mothers who took more than 600 mg of lithium daily;
No cases of Ebstein's anomaly in lithium exposed infants

Patorno E et al. NEJM 2017;376:2245-2254

The NEW ENGLAND JOURNAL of MEDICINE

Lithium Exposure During Pregnancy and the Postpartum Period: A Systematic Review and Meta-Analysis of Safety and Efficacy Outcomes

The American Journal of Psychiatry

Risk of cardiac anomalies associated with lithium exposure compared with unexposed women

- Any time: **OR 1.86**, 95% CI=1.16-2.96; N=1,348,475

- First trimester: **OR 1.96**, 95% CI=1.28–3.00; N=1,348,403

Comparing lithium exposed women with unexposed women with bipolar disorder

– Difference was not significant, **OR 1.59**, 95% CI 0.91-2.77, p 0.10

Fornaro et al., AJP 2020;177(1):76-92

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What are some special considerations for using Lithium in PREGNANCY?

- Fetal echo at 16-22 weeks
- Monitor lithium levels and symptoms in pregnancy (at least once per trimester)
- 3rd trimester higher doses are usually required
- Stop lithium at onset of labor or 24- 48 hours before scheduled c-section
- Restart pre-pregnancy dose after delivery

Takeaway: Recent Evidence is Reassuring for the Use of Lithium in Pregnancy

- There is potential risk for malformations → the risk is lower than previously thought
- Potential adverse effects appear to be dose dependent
- When maternal illness is controlled for the association for increased risk of cardiac malformations does not hold

Lamotrigine in Pregnancy

- No concerns for major malformations
- Rising estradiol levels in pregnancy lead to increased glucuronidation and subsequent increase in lamotrigine metabolism
- Average dose increase 25% above pre-pregnancy dose
- Need to taper quickly to pre-pregnancy dose postpartum

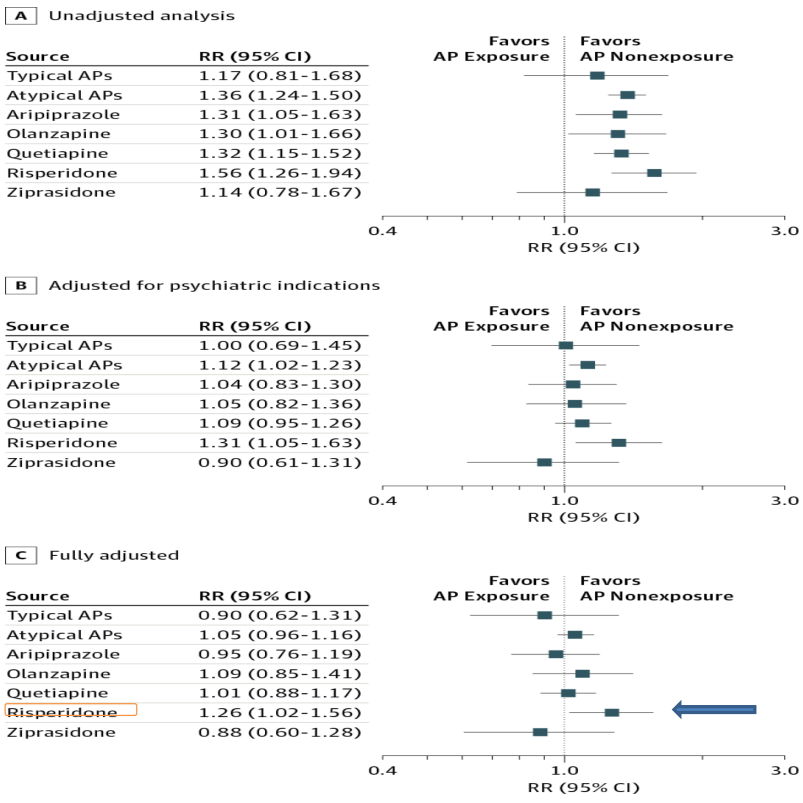
Association of Antipsychotic Exposure During Pregnancy with Preterm Birth

	Antipsychotics		Control			
Study	Events	Total	Events	Total	Weight	Odds Ratio
Diav-Citrin 2005	22	158	37	534	13.1%	2.17 (1.24,3.81)
Habermann 2013	77	691	88	1014	23.3%	1.32 (0.96,1.82)
Kallen 2013	111	1409	76727	1526221	30.9%	1.62 (1.33,1.96)
Lin 2010	41	242	255	3480	21.3%	2.58 (1.80,3.69)
McKenna 2005	10	110	7	135	5.4%	1.83 (0.67,4.97)
Newham	14	86	1	41	1.4%	7.78 (0.99,61.35)
Sadwoski 2013	12	113	5	116	4.7%	2.64 (0.90,2.39)
Total (95% CI)		2809		1531541		
Total Events	287		77120			1.86 (1.45,2.39)
Test of overall effect	Z=4.88 (P<0.00001)					

Coughlin et al., Obstetrics & Gynecology, 2015, Vol 125: 1224-35

Risk of Malformations for offspring exposed to antipsychotic agents in utero

Relative risk among 1,341,715 mothers from a Medicaid database



Huybrects et al, 2016, JAMA Psychiatry, 73(9): 938-946

Adverse Birth Events in Women Treated with Antipsychotics During (A) or Before (B) Pregnancy

Absolute risks and risk differences of adverse maternal and child outcomes associated with antipsychotic treatment in pregnancy.

	Absolute risk (%)						Risk difference (95% CI)			
	A		B		C		A vs B		A vs C	
Maternal outcomes										
Total # in cohort	416	(100)	670	(100)	318,434	(100)	–	–	–	–
Pre-eclampsia	18	(4.3)	28	(4.2)	9355	(2.9)	0.1	(−2.3, 2.6)	1.4	(−0.6, 3.3)
Gestational diabetes	11	(2.6)	18	(2.7)	5227	(1.6)	<0.1	(−2, 1.9)	1.0	(−0.5, 2.5)
Caesarean section	104	(25)	145	(21.6)	58,532	(18.4)	3.4	(−1.8, 8.6)	**6.6**	**(2.5, 10.8)**
Perinatal death	<5		<5		931	(0.3)	–	–	–	–
Child outcomes										
Total # in cohort	290	(100)	492	(100)	210,966	(100)	–	–	–	–
Major congenital malformations	10	(3.4)	11	(2.2)	4162	(2)	1.2	(−1.3, 3.7)	1.5	(−0.6, 3.6)
Premature/low birth weight outcome	29	(10)	21	(4.3)	8319	(3.9)	**5.7**	**(1.8, 9.6)**	**6.1**	**(2.6, 9.5)**
Adverse birth outcome[a]	14	(6)	23	(4.7)	5290	(2.5)	1.3	(−2.2, 4.9)	3.5	(0.4, 6.6)

Cohort A: women prescribed antipsychotics in pregnancy, B: women who discontinued antipsychotics before pregnancy, C: women who were not on antipsychotic treatment.
[a] For this outcome cohort A comprises women prescribed antipsychotics in third trimester (N = 233).

(n=318,434)

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Peterson et al, Schizophrenia Research, 2016, Vol 176:349-356

ADHD and Autism Spectrum Disorder and Exposure to Antipsychotics

- Cohort study of 411,251 mother-child pairs, divided in 4 exposure groups
- No increased risk of
  - ADHD, 1.16 (95% CI, 0.83-1.61)
  - ASD, 1.06 (95% CI, 0.70-1.60)
  - Small for gestational age 1.36 (95% CI, 0.86-2.14)
- Prenatal use of antipsychotics associated with 1.40 (95% CI, 1.13-1.75) increased risk for preterm birth
- Maternal psychiatric disorders were associated with a significantly increased risk of ADHD and ASD, but not with preterm birth or small for gestational age in neonates

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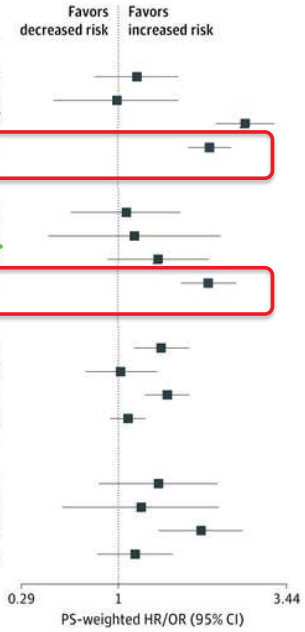
Wang et al., JAMA Intern Med. 2021;181(10):1332-1340

Comparison between gestationally exposed, past exposure and never exposed

Risk in different comparison groups	PS-weighted HR/OR (95% CI)
ADHD	
Gestational exposure vs gestational nonexposure	1.16 (0.83-1.61)
Gestational exposure vs past exposure	0.99 (0.60-1.61)
Past exposure vs never exposed	2.72 (2.16-3.44)
Never exposed with psychiatric disorders vs never exposed without psychiatric disorders	2.08 (1.75-2.48)
ASD	
Gestational exposure vs gestational nonexposure	1.06 (0.70-1.60)
Gestational exposure vs past exposure	1.10 (0.58-2.08)
Past exposure vs never exposed	1.35 (0.92-1.98)
Never exposed with psychiatric disorders vs never exposed without psychiatric disorders	1.97 (1.60-2.43)
Preterm birth	
Gestational exposure vs gestational nonexposure	1.40 (1.13-1.75)
Gestational exposure vs past exposure	0.93 (0.70-1.24)
Past exposure vs never exposed	1.47 (1.23-1.75)
Never exposed with psychiatric disorders vs never exposed without psychiatric disorders	1.08 (0.93-1.24)
Small for gestational age	
Gestational exposure vs gestational nonexposure	1.36 (0.86-2.14)
Gestational exposure vs past exposure	1.21 (0.66-2.20)
Past exposure vs never exposed	1.88 (1.36-2.59)
Never exposed with psychiatric disorders vs never exposed without psychiatric disorders	1.14 (0.85-1.53)



Results suggest:

- no difference in the risk of all outcomes when comparing gestationally exposed vs past exposure
- maternal psychiatric disorders associated with risk of neurodevelopmental disorders, not exposure to antipsychotic drugs

Wang et al., JAMA Intern Med. 2021;181(10):1332-1340

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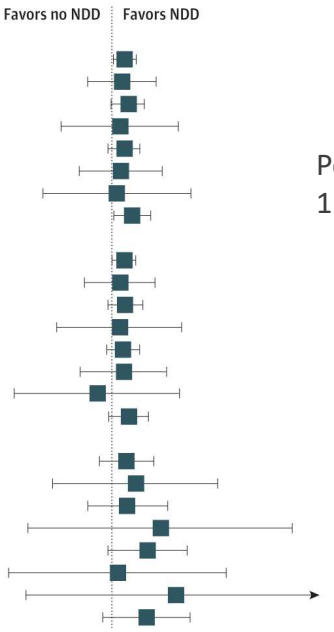
Further support for role of maternal characteristics and not prenatal antipsychotic exposure in neurodevelopmental disorders

Source	HR (95% CI)
Any antipsychotic	
Any neurodevelopmental disorder	1.08 (1.01-1.17)
ASD	1.06 (0.85-1.34)
ADHD	1.11 (0.99-1.24)
Learning difficulty	1.05 (0.70-1.57)
Speech/language disorder	1.08 (0.97-1.21)
DCD	1.06 (0.80-1.40)
Intellectual disability[a]	1.03 (0.62-1.70)
Behavioral disorder	1.14 (1.00-1.29)
Atypical antipsychotics	
Any neurodevelopmental disorder	1.08 (1.00-1.17)
ASD	1.05 (0.82-1.33)
ADHD	1.09 (0.97-1.23)
Learning difficulty	1.05 (0.68-1.60)
Speech/language disorder	1.08 (0.96-1.21)
DCD	1.08 (0.80-1.44)
Intellectual disability[a]	0.90 (0.51-1.57)
Behavioral disorder	1.11 (0.97-1.28)
Typical antipsychotics	
Any neurodevelopmental disorder	1.10 (0.91-1.32)
ASD[a]	1.17 (0.67-2.04)
ADHD	1.11 (0.84-1.45)
Learning difficulty[a]	1.39 (0.56-3.40)
Speech/language disorder[a]	1.27 (0.97-1.65)
DCD[a]	1.04 (0.49-2.17)
Intellectual disability[a]	1.53 (0.56-4.23)
Behavioral disorder[a]	1.26 (0.93-1.70)



Possible exception of aripiprazole: 1.36 (1.14-1.63)
- Interpret with caution as requires replication

Straub., JAMA Intern Med. 2022

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First Generation Antipsychotics

- Most safety data for haloperidol
- Not associated with major malformations
- Potential association with preterm birth, replicated

Second Generation Antipsychotics

- Some early concern for gestational diabetes recent studies do not suggest increased risk
- Potential association with preterm birth, replicated
- Not associated with major malformations, with the possible exception of risperidone

McAllister-Williams et al., J Psychopharm 2017;31(5):519-552
Huybrects et al, 2016, JAMA Psychiatry, 73(9): 938-946
Coughlin et al., Obstetrics & Gynecology, 2015, Vol 125: 1224-35
Peterson et al, Schizophrenia Research, 2016, Vol 176:349-356

Breastfeeding: Mood Stabilizers and Antipsychotics

Antipsychotics

Lamotrigine
Valproic Acid
Carbamazepine

Lithium

Wald et al., Psychiat Clin Amer 2016;39:57-74

Mood and cognition in the menopause transition

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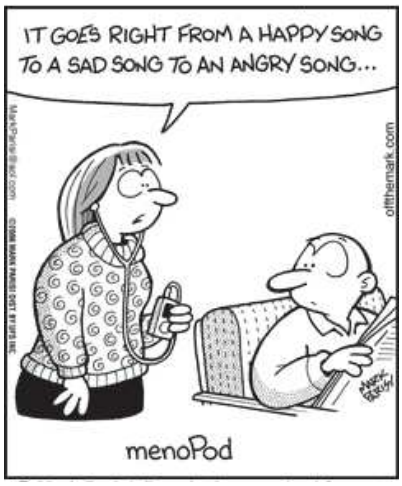
Mood in the Menopause Transition



- Mood lability
- Depression
- Irritability

23-28%

Depression

- 2-3 times more likely in women with no history of depression
- 5 times more likely in women with a history of depression

Freeman et al., Arch Gen Psychiatry 2006;63:375-382.
Freeman et al., Arch Gen Psychiatry 2004;61:62-70
Bromberger el al., Psychol Med 2011;41(9):1879-88.
Bromberger et al., Psychol Med 2015;45(8):1653-64.

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Factors that Influence Depression in the Menopause Transition

- Changing hormonal milieu
- Poor sleep
- Hot flashes
- Premenstrual syndrome
- Stressful or negative life events
- Employment status
- Age
- Race

- History of premenstrual syndrome or PMDD -> 2 fold increased risk of developing major depressive disorder in perimenopause

Freeman EW et al., Obst & Gynecol, 2004;103:960
Freeman EW, Menopause, 2010;17:823-27
Freeman EW, Wom Mid Health, 2015;1(2)

Estrogen Effects on Neurotransmission

Estrogen enhances serotonin neurotransmission

- Biosynthesis- increases tryptophan hydroxylase mRNA
- Release- reduces 5-HT1B mRNA increasing availability of serotonin via disinhibition of serotonin release
- Reuptake - reduces rate of clearance of 5-HT by serotonin transporter (SERT)

Sanchez RL et al., Mol Brain Res, 2005;35:94-203.
Benmansour S et al., Neuropsychopharm, 2009;34:555-64
Hiroi R & Neumaier JF, Neuroscience, 2009;158:456-464

Estrogen effects on noradrenergic neurotransmission

- Increases available norepinephrine
- Increases norepinephrine synthesis
- Alters adrenergic receptor gene expression
- Reduces norepinephrine turnover rate

Paul DL et al., J. Neuroendocrinol., 2000;12:899–909
Etgen MA et al., Horm. Behav., 2001;40:169–177
Deecher D et al., Psychoneuroendocrinol, 2008;33:3–17

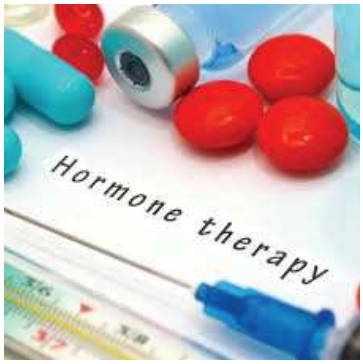
Antidepressant Treatment

SRI	Starting dose	Target dose
*Escitalopram	10 mg/day	10-20 mg/day
Citalopram	20 mg/day	20-40 mg/day
Sertraline	50 mg/day	50-200 mg/day
Fluoxetine	20 mg/day	20-60 mg/day
*Venlafaxine	37.5 mg/day	75-225 mg/day
Duloxetine	20 mg BID	40-60 mg/day
Desvenlafaxine	50 mg/day	50-100 mg/day

*studied in peri- and postmenopausal populations and shown to decrease nighttime awakenings and improve sleep quality.

Hormonal Treatment

- 17β-estradiol (50–100 µg) given transdermally for 6–12 weeks is efficacious in the treatment of depression in perimenopausal women
- Estrogen not beneficial in postmenopausal women
- Estrogen therapy (100 µg transdermally) accelerates SSRI antidepressant response



Schmidt et al., Am J Obstet Gynecol, 2000;183:414–20
Soares et al., Arch Gen Psychiatry, 2001;58:529–34
Rasgon et al., J Psych Res, 2007;41:338–343
Maki et al, Menopause, 2018;25(10):1069-1085

Sleep and Hot flashes

- Vasomotor symptoms and insomnia are strongly correlated with depression
- Treatment of *both* insomnia and hot flashes leads to improvement of mood symptoms

Cohen et al., Arch Gen Psychiatry 2006;63:385-390.

Cognition in the Menopause Transition

- 60% of women report memory problems during the menopause transition
- Common complaints include:
  - Memory lapse for things
  - Lack of focus and attention
  - Inability to multi-task effectively
  - "Brain fog"

Greendale et al., Neurology 2009;72:1850–1857

Hormones and Cognition

- Estrogen has pronounced effects upon multiple neurotransmitters systems involved in learning and memory
  - Hippocampus and prefrontal cortex are rich in estrogen receptors
  - Estrogens elevate levels of neurotransmitters, promote neuronal growth and formation of synapses
- Estrogen has been shown to modulate cholinergic neurotransmission in the brain
- Estrogen attenuates the anticholinergic drug-induced impairments on tests of attention and episodic memory in postmenopausal women

Dumas J et al., Horm Behav, 2008;53:159-169

ET Effects on Cognitive in Perimenopause

- Estrogen therapy (ET) selectively improves executive functioning in perimenopausal and early postmenopausal women
- ET use before the final menstrual period is associated with better processing speed and verbal memory
- Studies with ET in postmenopausal women have found it does not protect against cognitive function decline

Joffe H et al., Menopause 2006;13:411-422
Greendale et al., Neurology 2009;72:1850–1857
Gava et al., Medicina 2019; 55(10):668

Summary

The treatment of women and individuals with intact ovarian function generates some unique issues

- Novel methods (intermittent treatment for PMDD) and roles (vasomotor symptoms) have been found for the use of antidepressant agents
- Antidepressant and antipsychotic use in pregnancy may be associated with particular reproductive risks although in general these appear to be small
- Neurosteroids have a role in the treatment of psychiatric symptoms

Thank You

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