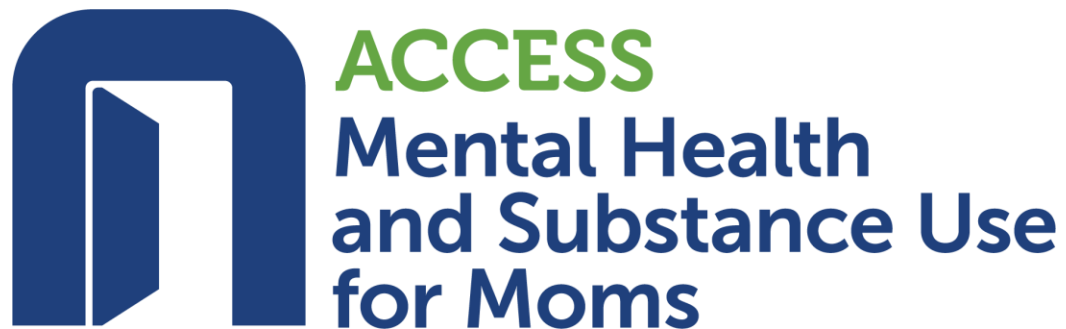
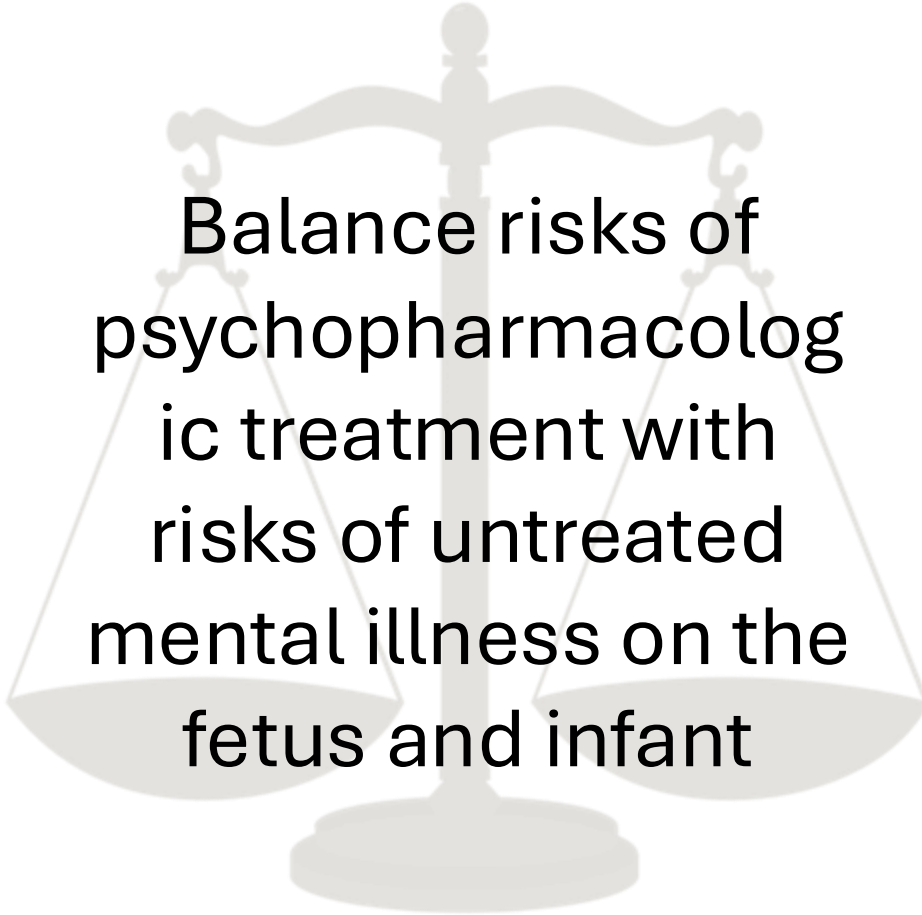


# Antipsychotics in Pregnancy 101

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**Yale School of Medicine**



# There is no such thing as non-exposure



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



# Context: Impact of Untreated Maternal Mental Illness

## Maternal

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

## Pregnancy

- Preterm delivery
- Placental abruption\*
- Antepartum hemorrhage\*
- Fetal distress\*
- Preeclampsia

## Infant

- Low birthweight
- Small for gestational age\*
- Cardiovascular anomalies\*
- Cognitive delays
- Behavioral problems
- Insecure attachment patterns
- Anxiety and depression
- ADHD and learning disabilities

\*Jablensky et al. Am J Psychiatry. 2005;162:79-91

Bodnar et al, J Clin Psych, 2009

Cripe et al, Pedi & Perinatal Epid, 2011

\*Findings specific to schizophrenia and major affective disorders

# What Guides Prescribing?












Patient  
preference

Severity of  
illness  
episodes

Previous  
response to  
treatments

Degree of  
recurrence of  
illness

Duration of  
current  
stability

Conceptus		Embryonic development (weeks)						Fetal period (weeks)				
1	2	3	4	5	6	7	8	9	16	20-36	38	
												
		<b>Neural</b>										
		<b>Heart</b>										
		<b>Upper limbs</b>										
		<b>Lower limbs</b>										
		<b>Ear</b>										
		<b>Eye</b>										
						<b>Palate</b>						
						<b>Teeth</b>						
							<b>External genitalia</b>					
<b>Loss</b>		<b>Major abnormalities</b>					<b>Functional and Minor abnormalities</b>					

# 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

\* Quetiapine and aripiprazole have significant decrease in serum concentration in 3<sup>rd</sup> trimester

# 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

# Management of psychosis in pregnancy and postpartum

# Association of Antipsychotic Exposure During Pregnancy with Preterm Birth

Study	Antipsychotics		Control		Weight	Odds Ratio
	Events	Total	Events	Total		
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)					

# 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	
<b>Maternal outcomes</b>										
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)	<b>6.6</b>	<b>(2.5, 10.8)</b>
Perinatal death	<5		<5		931	(0.3)	-	-	-	-
<b>Child outcomes</b>										
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)	<b>5.7</b>	<b>(1.8, 9.6)</b>	<b>6.1</b>	<b>(2.6, 9.5)</b>
Adverse birth outcome <sup>a</sup>	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.

<sup>a</sup> For this outcome cohort A comprises women prescribed antipsychotics in third trimester (N = 233).

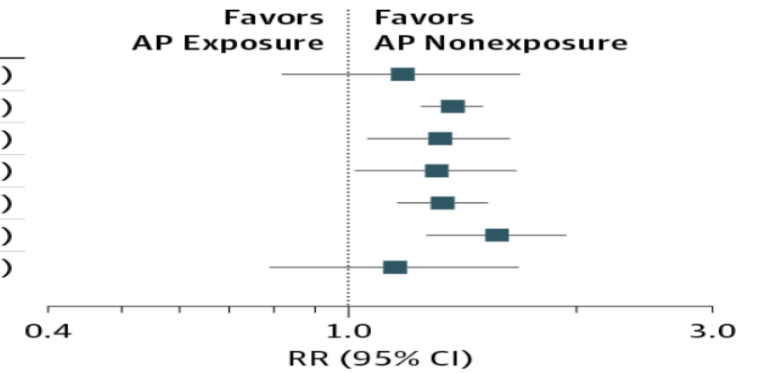
(n=318,434)

# Risk of Malformations for offspring exposed to antipsychotic agents in utero

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

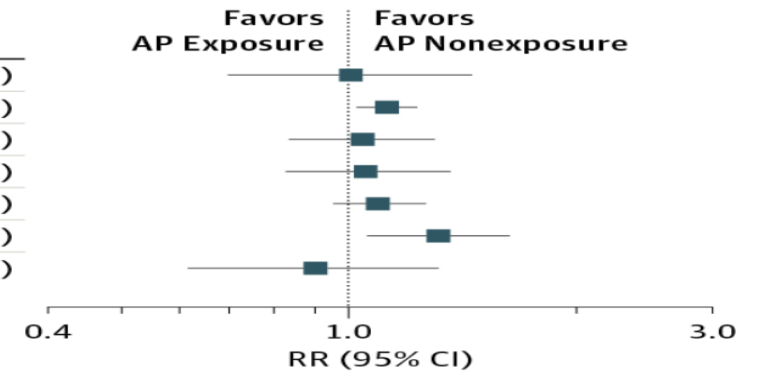
## A Unadjusted analysis

Source	RR (95% CI)
Typical APs	1.17 (0.81-1.68)
Atypical APs	1.36 (1.24-1.50)
Aripiprazole	1.31 (1.05-1.63)
Olanzapine	1.30 (1.01-1.66)
Quetiapine	1.32 (1.15-1.52)
Risperidone	1.56 (1.26-1.94)
Ziprasidone	1.14 (0.78-1.67)



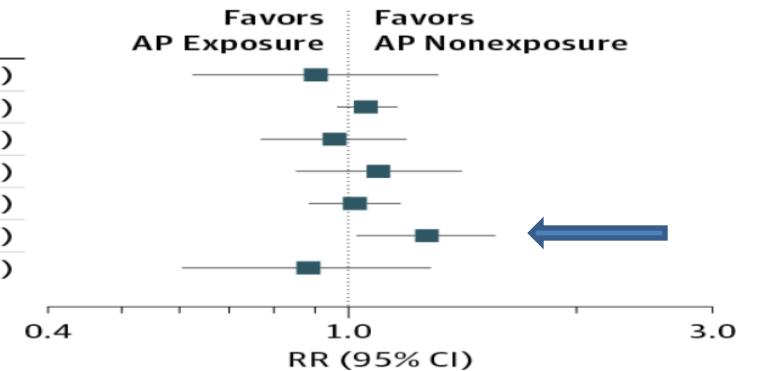
## B Adjusted for psychiatric indications

Source	RR (95% CI)
Typical APs	1.00 (0.69-1.45)
Atypical APs	1.12 (1.02-1.23)
Aripiprazole	1.04 (0.83-1.30)
Olanzapine	1.05 (0.82-1.36)
Quetiapine	1.09 (0.95-1.26)
Risperidone	1.31 (1.05-1.63)
Ziprasidone	0.90 (0.61-1.31)



## C Fully adjusted

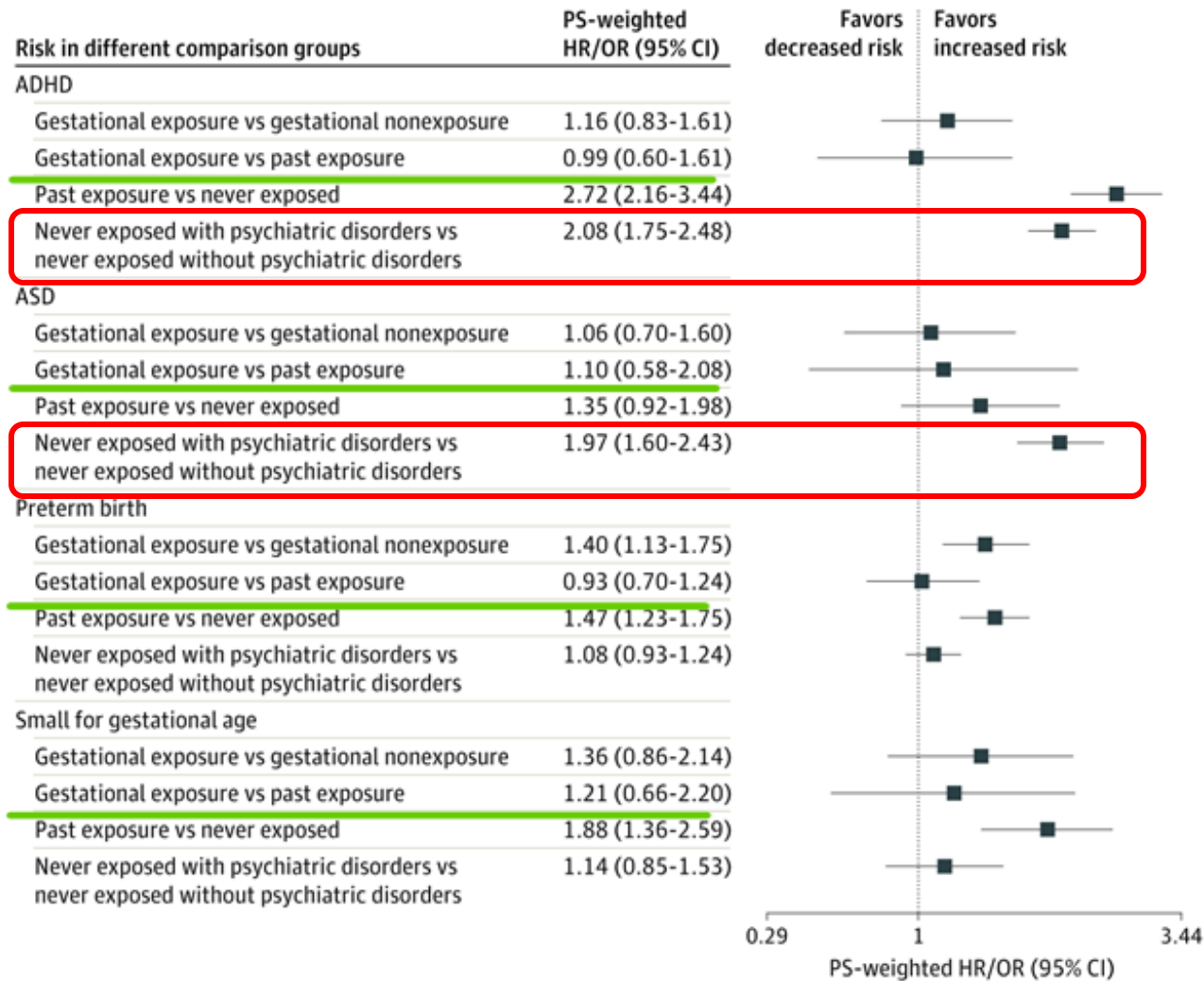
Source	RR (95% CI)
Typical APs	0.90 (0.62-1.31)
Atypical APs	1.05 (0.96-1.16)
Aripiprazole	0.95 (0.76-1.19)
Olanzapine	1.09 (0.85-1.41)
Quetiapine	1.01 (0.88-1.17)
<b>Risperidone</b>	1.26 (1.02-1.56)
Ziprasidone	0.88 (0.60-1.28)



# 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, but additional analysis did not support increased risk
- 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

# Comparison between gestationally exposed, past exposure and never exposed



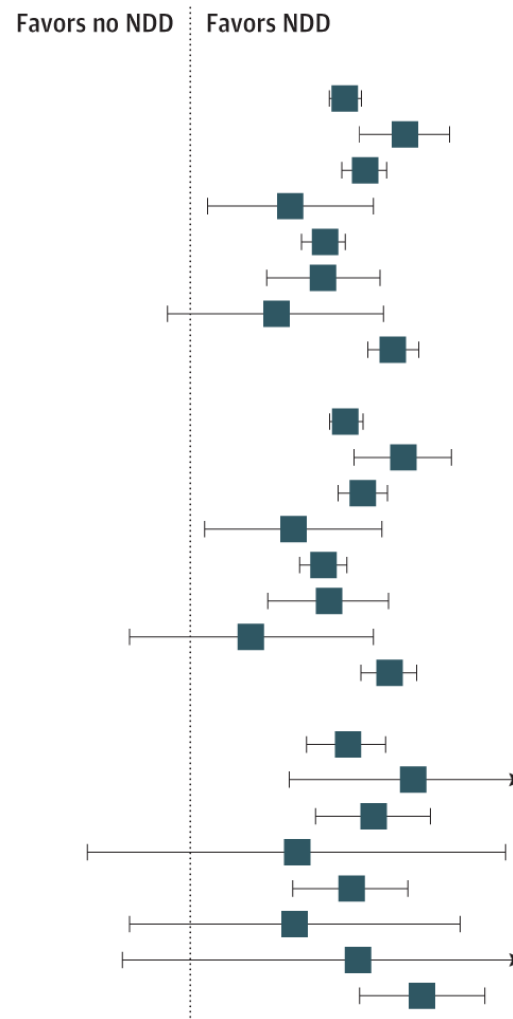
Results suggest:

- 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

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

Source	HR (95% CI)
<b>Any antipsychotic</b>	
Any neurodevelopmental disorder	1.91 (1.79-2.03)
ASD	2.44 (2.02-2.96)
ADHD	2.07 (1.88-2.28)
Learning difficulty	1.51 (1.07-2.14)
Speech/language disorder	1.74 (1.59-1.91)
DCD	1.74 (1.37-2.21)
Intellectual disability <sup>a</sup>	1.43 (0.91-2.24)
Behavioral disorder	2.33 (2.09-2.59)
<b>Atypical antipsychotics</b>	
Any neurodevelopmental disorder	1.91 (1.79-2.05)
ASD	2.42 (1.97-2.97)
ADHD	2.05 (1.85-2.27)
Learning difficulty	1.54 (1.06-2.23)
Speech/language disorder	1.74 (1.58-1.92)
DCD	1.78 (1.38-2.28)
Intellectual disability <sup>a</sup>	1.29 (0.78-2.14)
Behavioral disorder	2.29 (2.04-2.56)
<b>Typical antipsychotics</b>	
Any neurodevelopmental disorder	1.91 (1.62-2.26)
ASD <sup>a</sup>	2.51 (1.51-4.16)
ADHD	2.14 (1.68-2.72)
Learning difficulty <sup>a</sup>	1.55 (0.65-3.73)
Speech/language disorder <sup>a</sup>	1.95 (1.53-2.47)
DCD <sup>a</sup>	1.54 (0.77-3.07)
Intellectual disability <sup>a</sup>	2.00 (0.75-5.33)
Behavioral disorder <sup>a</sup>	2.63 (2.03-3.41)



Birth cohort study that used data from the Medicaid Analytic eXtract (MAX, 2000-2014)

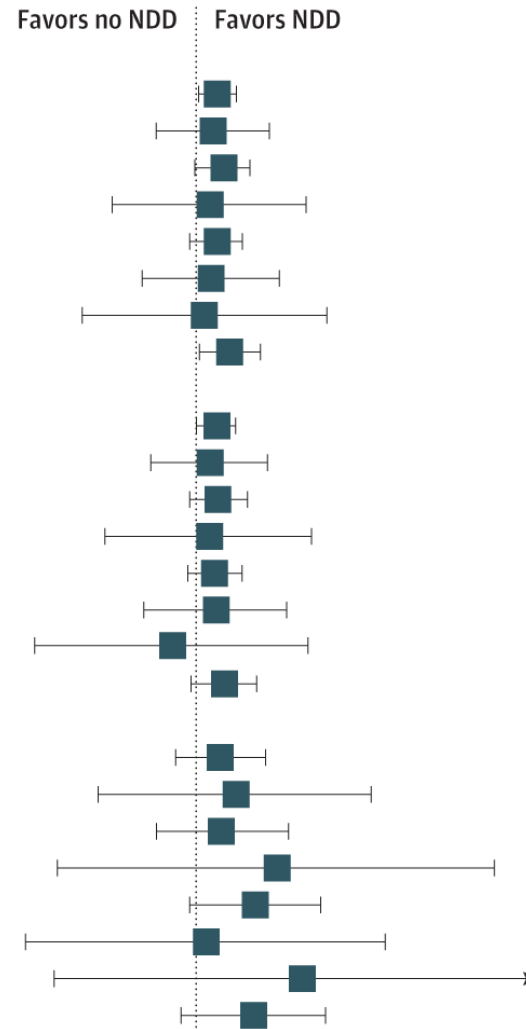
Unadjusted findings

Hazard Ratios before adjusting for treatment indication, substance use, other medication exposures

Straub., JAMA Intern Med. 2022

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

Source	HR (95% CI)
<b>Any antipsychotic</b>	
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 <sup>a</sup>	1.03 (0.62-1.70)
Behavioral disorder	1.14 (1.00-1.29)
<b>Atypical antipsychotics</b>	
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 <sup>a</sup>	0.90 (0.51-1.57)
Behavioral disorder	1.11 (0.97-1.28)
<b>Typical antipsychotics</b>	
Any neurodevelopmental disorder	1.10 (0.91-1.32)
ASD <sup>a</sup>	1.17 (0.67-2.04)
ADHD	1.11 (0.84-1.45)
Learning difficulty <sup>a</sup>	1.39 (0.56-3.40)
Speech/language disorder <sup>a</sup>	1.27 (0.97-1.65)
DCD <sup>a</sup>	1.04 (0.49-2.17)
Intellectual disability <sup>a</sup>	1.53 (0.56-4.23)
Behavioral disorder <sup>a</sup>	1.26 (0.93-1.70)



Pool Adjusted Estimates

Findings do not hold

Straub., JAMA Intern Med. 2022  
<https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2790391>

# Second Generation Antipsychotics and Gestational Diabetes (GDM)

Some earlier studies suggested an increased risk of GDM with exposure to second generation antipsychotics

Recent meta-analyses have not sustained these findings and indicate that underlying maternal diagnoses might be related to the increased risk

- The RR of GDM was similar (RR = 0.78, 95% CI = 0.281-2.164) when comparing women who maintained antipsychotic medication vs. those who discontinued
- The adjusted OR of GDM in women who continued antipsychotics was 0.73 (95% CI: 0.43-1.25) compared with those the discontinued use in pregnancy

# Long-acting Injectable (LAI) Antipsychotics

- Antipsychotics available in LAI formulation in the US: aripiprazole, fluphenazine, haloperidol, olanzapine, paliperidone, and risperidone.
- Available data is limited and only consists of care reports
- Generally available data does not point to major negative outcomes, although some result in prematurity or small for gestational age
- Most women on LAI antipsychotics (64%) had adequate symptom control

# Clinical Guidelines for LAIs

**Table 1. Clinical Scenarios and Recommendations**

Clinical Scenario	Recommendations
Should an LAI be continued for a woman with a history of significant psychiatric illness who wishes to become pregnant?	<ul style="list-style-type: none"> <li>• The LAI should be continued unless there is a compelling reason for discontinuation.</li> <li>• A clinician should engage in an informed consent discussion with the patient and ideally with the father of the baby prior to conception.</li> </ul>
Should an LAI be continued for a woman with a significant psychiatric history once she discovers she is pregnant?	<ul style="list-style-type: none"> <li>• Unless there is a clear contraindication, the LAI should be continued.</li> <li>• The clinician should engage in an informed consent discussion.</li> <li>• This discussion should be tailored to the week of pregnancy, as teratogenic concerns can recede further along in pregnancy.</li> <li>• The importance of psychiatric stability during pregnancy as well as the overall lower plasma medication concentrations offered by an LAI should be reviewed.</li> </ul>
Which historical factors would suggest a pregnant woman would benefit from an LAI?	<p>History of...</p> <ul style="list-style-type: none"> <li>• Medication nonadherence</li> <li>• Long or frequent hospitalizations</li> <li>• Requiring multiple emergent psychiatric medication to achieve psychiatric stability</li> <li>• Illicit substance use</li> <li>• Psychiatric symptom recurrence during the postpartum period</li> </ul>
What should be considered when choosing between LAIs for the pregnant woman?	<ul style="list-style-type: none"> <li>• Metabolic profiles of individual medications</li> <li>• The need for increase in dosage during pregnancy</li> <li>• Longer dosing intervals</li> <li>• FDA indications for schizophrenia vs bipolar disorder</li> <li>• Plans for breastfeeding</li> </ul>

Abbreviation: LAI = long-acting injectable antipsychotic.

## First Generation Antipsychotics

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

McAllister-Williams et al., J Psychopharm 2017;31(5):519-552  
Huybrechts 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

## 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

# Breastfeeding: Mood Stabilizers and Antipsychotics



Antipsychotics

Lamotrigine  
Valproic Acid  
Carbamazepine

Lithium

# Thank You

