Maternal-Fetal Psychiatry: Managing Psychiatric High-Risk Pregnancies

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CME Outfitters

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Disclosure

- ***Research Support:*** Takeda Pharmaceuticals U.S.A., Inc.

Audience Response 1

A patient with ***bipolar I disorder*** being treated effectively with lamotrigine (200 mg/day) monotherapy contacts you to tell you that she is pregnant. How would you advise her?

A. Continue lamotrigine at current dose
B. Reduce lamotrigine dose
C. Discontinue lamotrigine
D. Switch lamotrigine to another medication
E. Contact her obstetrician for advice

Audience Response 2

A patient with ***seizure disorder*** being treated effectively with lamotrigine (200 mg/day) monotherapy contacts you to tell you that she is pregnant. How would you advise her?

A. Continue lamotrigine at current dose
B. Reduce lamotrigine dose
C. Discontinue lamotrigine
D. Switch lamotrigine to another medication
E. Contact her obstetrician for advice

Audience Response 3

Both maternal depression during pregnancy and maternal use of antidepressants during pregnancy have been associated with all of the following EXCEPT:

A. Increased risk for preterm delivery
B. Increased use of tobacco during pregnancy
C. Increased risk for newborn complications
D. Increased risk for low birthweight
E. Possible developmental consequences for the child

Audience Response 4

Which of the following CNS agents has been most consistently shown to carry risks for both birth defects and adverse neurodevelopmental effects?

A. Lithium
B. Lamotrigine
C. Divalproex
D. Fluoxetine
E. Olanzapine

Maternal-Fetal Psychiatry

Conclusion & Clinical Application

Magnitude of the Issue

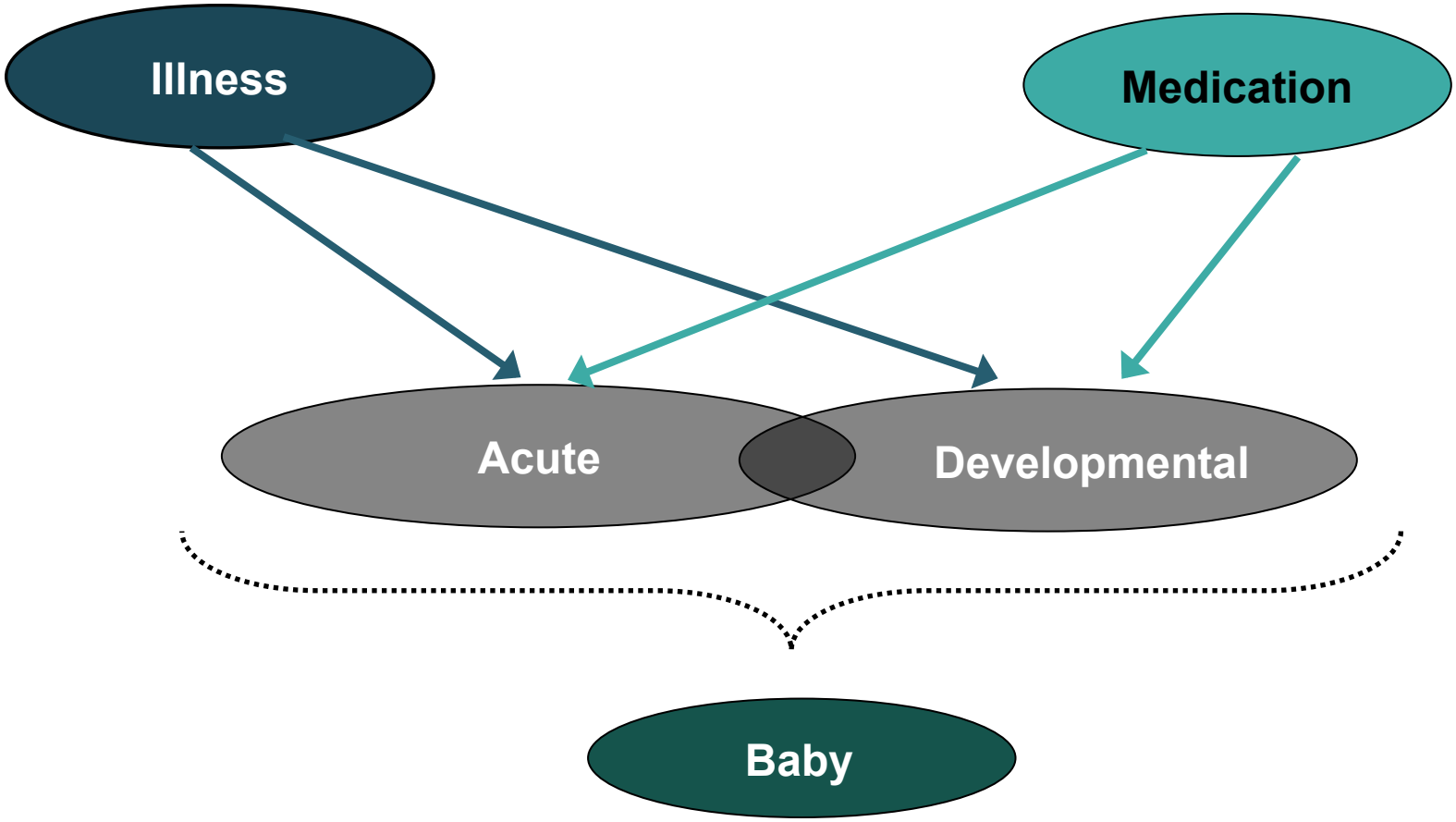
Illness Risks

Treatment Risks

Potential Consequences of Fetal Exposure

MEDICATION	STRESS/ILLNESS
Structural Teratogenesis	Maternal Health Behaviors
Fetal Growth	Fetal Growth
Timing of Delivery	Timing of Delivery
Neonatal Adaptation	Neonatal Adaptation
Neurodevelopment	Neurodevelopment

Maximizing Outcome: Minimizing Fetal Exposure



Working Assumptions

- **IF MOM IS TREATED, INFANT IS EXPOSED**
  - Anything that crosses the maternal blood-brain barrier will also cross:
    - Placenta
    - Blood-milk barrier
    - Fetal blood-brain barrier.
- **NO MEDICATION IS SAFE**
  - Risks include birth defects, adverse obstetrical & neonatal outcomes, neurodevelopmental affects.
  - Reproductive safety data derived from observational studies with varying degrees of scientific rigor.
  - No medication has complete safety data across the entire risk spectrum.
- **MUST WEIGH RISK OF USING vs. NOT USING MEDICATION**

Guidelines to Clinical Decision Marking

- **DECIDE UPON PRIMARY OBJECTIVE**
  - Avoid fetomaternal conflict without making false promises.
- **DECIDE WHETHER TO USE MEDICATION.**
  - Weigh risk of illness versus risk of medication.
  - Consider likelihood of illness recurrence/exacerbation.
  - Estimate likely efficacy of non-medication treatments
- **DECIDE WHAT MEDICATION TO USE.**
  - Efficacy Considerations
    - Indication(s)
    - Prior treatment response
    - Avoid subtherapeutic dosing
  - Safety Considerations
    - Reproductive safety data (early/late gestation, lactation)
    - Prior fetal exposures
    - Avoid exacerbating existing obstetrical/medical complications or risks

Maternal-Fetal Psychiatry

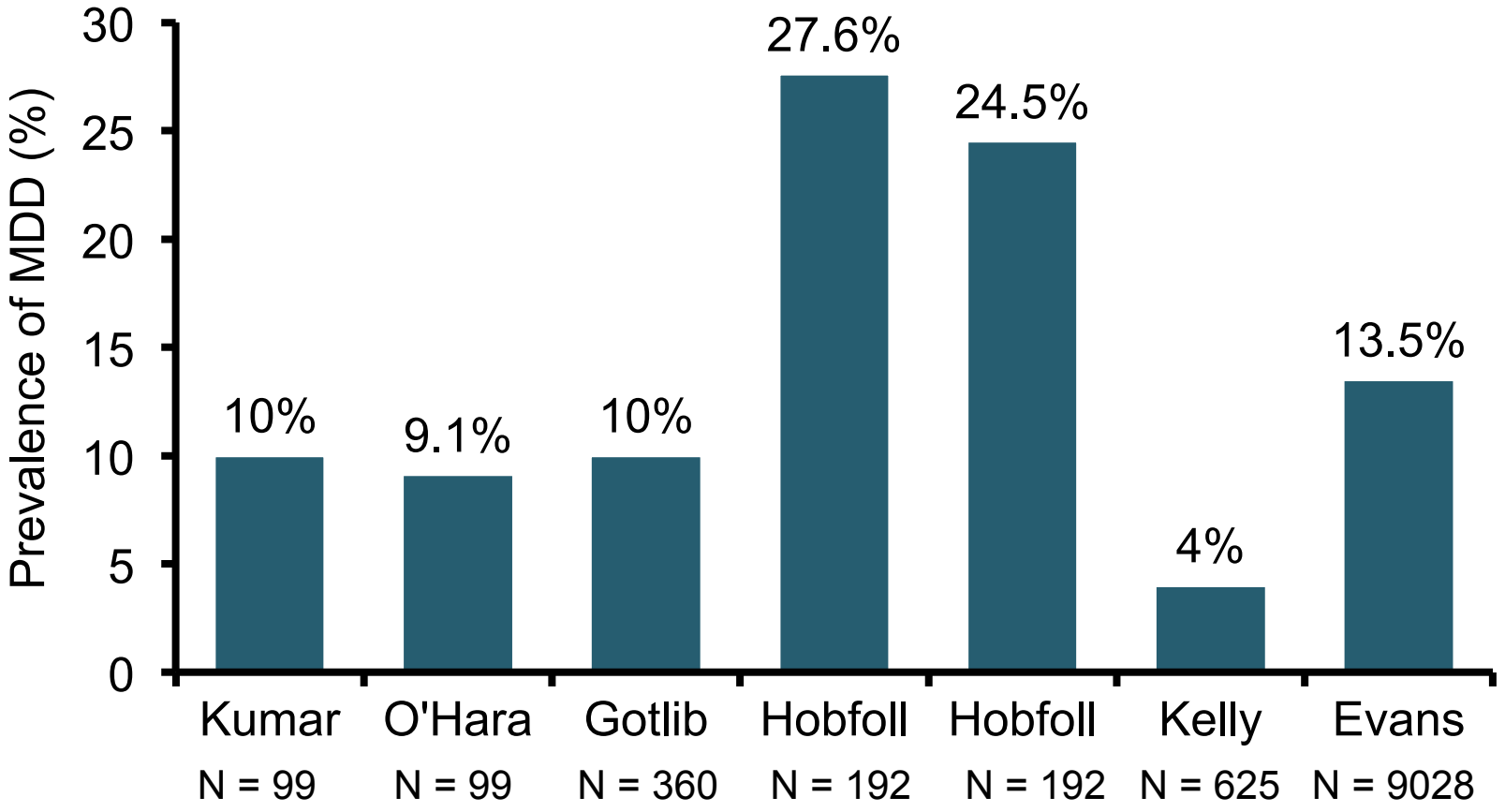
Conclusion & Clinical Application

Magnitude of the Issue

Illness Risks

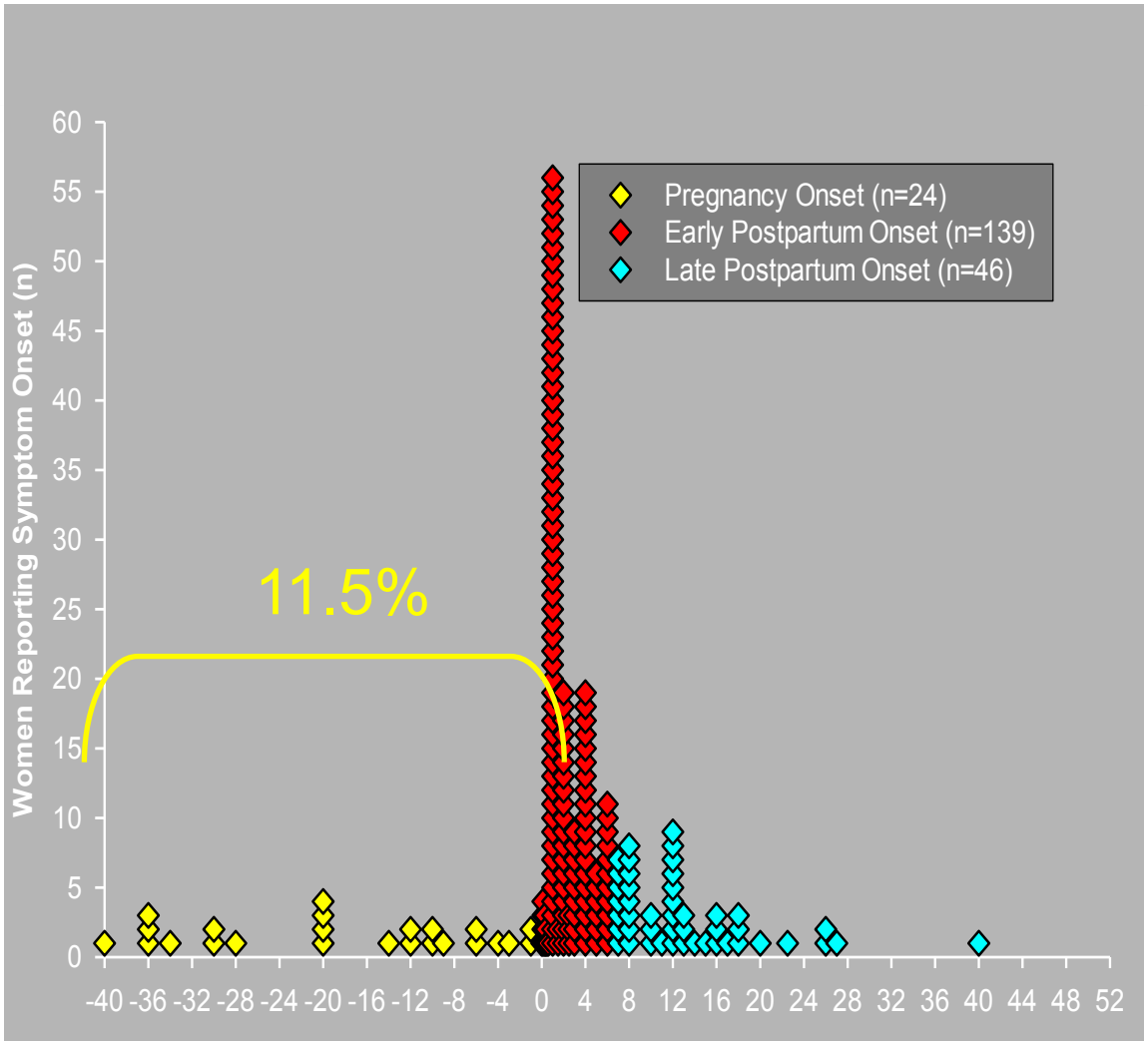
Treatment Risks

Antenatal Depression: Prevalence



Kumar et al. *Br J Psychiatry* 1984;144:35-47.; O'Hara MW. *Arch Gen Psychiatry* 1986;43(6):569-573.; Gotlib et al. *J Consult Clin Psychol* 1989;57(2):269-274.; Hobfoll et al. *J Consult Clin Psychol* 1995;63(3):445-453.; Kelly et al. *Am J Psychiatry* 2001;158(2): 213-219.; Evans et al. *BMJ* 2001;323(7307):257-260.

Onset of Postpartum Depression



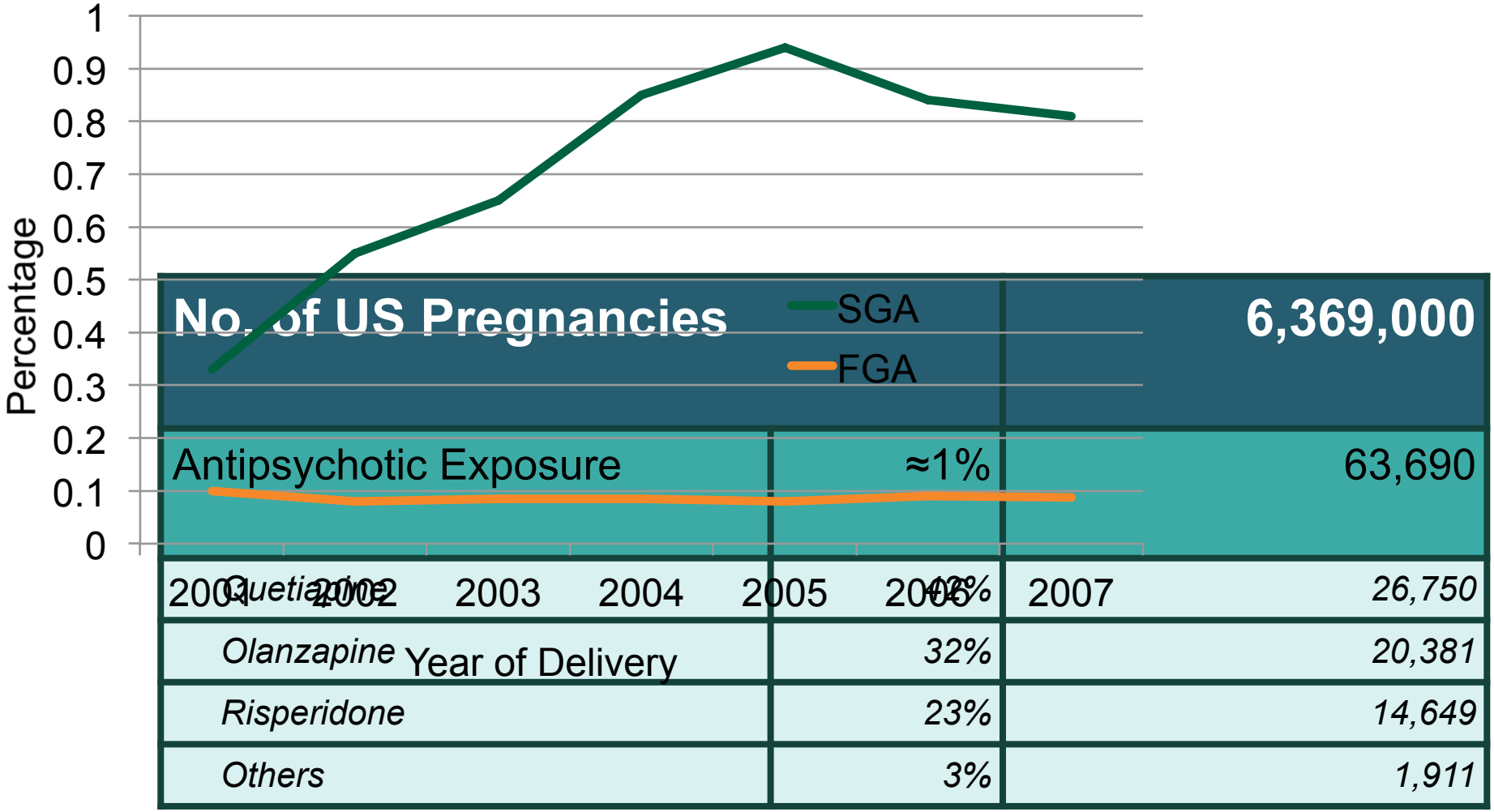
Stowe ZN, et al. *Am J Obstet Gynecol*. 2005;192(2):522-526.

CNS Agents Commonly Used During Pregnancy & Lactation

- **Antidepressants** (fluoxetine, sertraline, citalopram, bupropion, amitriptyline)
  - Depression, anxiety, pain/migraine, smoking cessation, insomnia
- **Antiemetics** (ondansetron, promethazine)
  - Nausea (hyperemesis gravidarum), migraine
- **Antiepileptic Drugs** (valproate, lamotrigine, carbamazepine, gabapentin)
  - Epilepsy, bipolar disorder, pain/ migraine
- **Antipsychotics** (haloperidol, olanzapine, quetiapine, risperidone)
  - Psychosis, bipolar, depression, anxiety, insomnia, nausea
- **Benzodiazepines** (clonazepam, lorazepam, alprazolam)
  - Anxiety, epilepsy, insomnia
- **Lithium**
  - Bipolar
- **Hypnotics** (zolpidem, doxylamine, diphenhydramine)
  - Insomnia
- **Opiate analgesics** (methadone, buprenorphine, oxycodone)
  - Pain, addiction
- **Stimulants** (Methylphenidate, Mixed Amphetamine Salts)
  - ADHD, Narcolepsy

Harding J, Timko J, The Use of Psychotropic Medications During Pregnancy and Lactation. Glob. libr. women's med.,(ISSN: 1756-2228) 2008; DOI 10.3843/GLOWM.10416

Prenatal Antipsychotic Use: US Prevalence



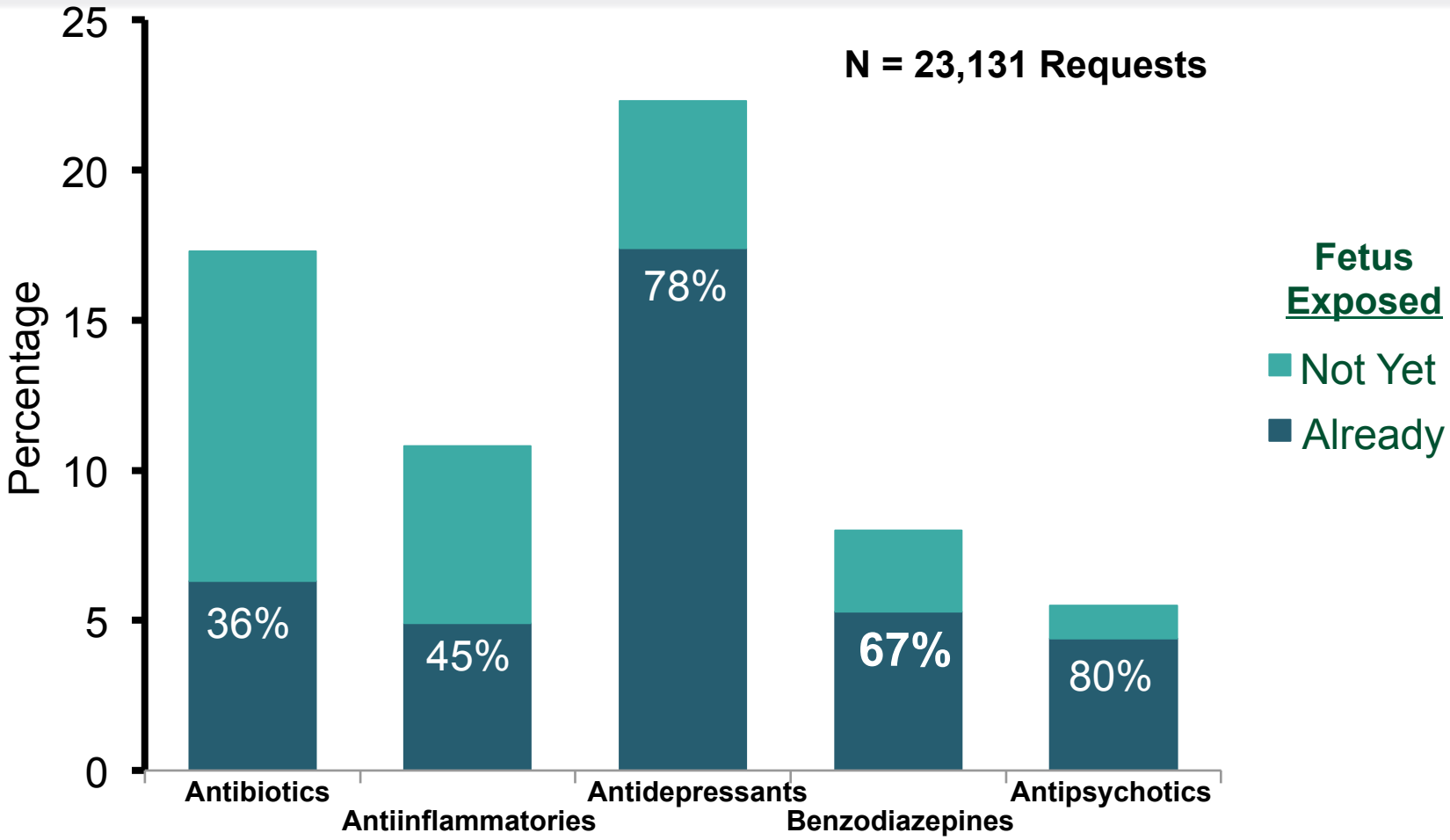
No. of US Pregnancies		6,369,000
Antipsychotic Exposure	≈1%	63,690
Quetiapine	*42%*	*26,750*
Olanzapine	*32%*	*20,381*
Risperidone	*23%*	*14,649*
Others	*3%*	*1,911*

Toh S, et al. *Arch Womens Ment Health* 2013;16(2): 149-157.

Curtin SC, et al. *NCHS Data Brief* 2013;136:1-8.

TIS Calls from Healthcare Providers

IMAGe Center, Montreal, Quebec



Gendron MP, et al. *Eur J Clin Pharmacol* 2009; 65(5): 523-531. PMID: 19169677

Maternal-Fetal Psychiatry

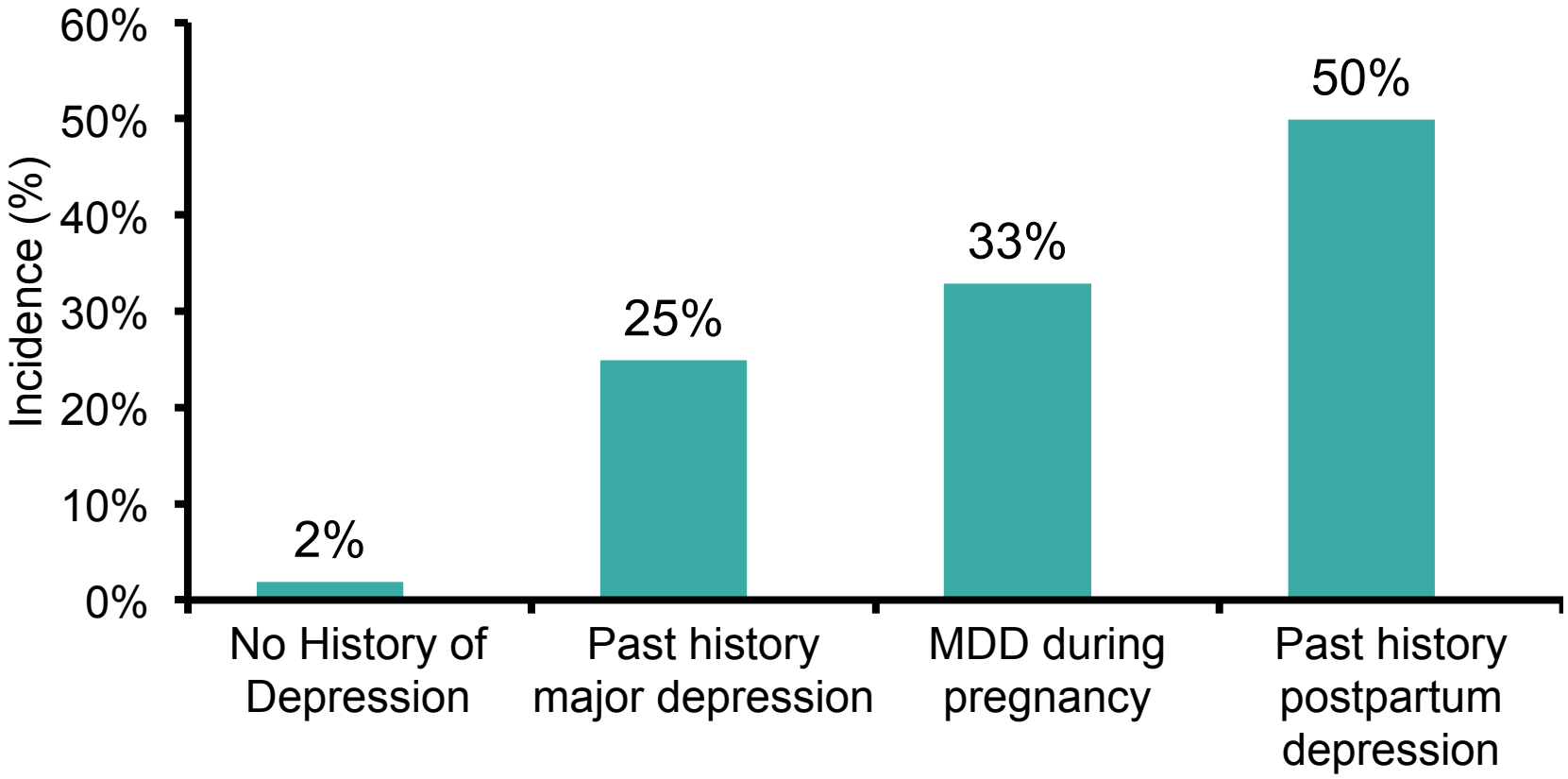
Conclusion & Clinical Application

Magnitude of the Issue

Illness Risks

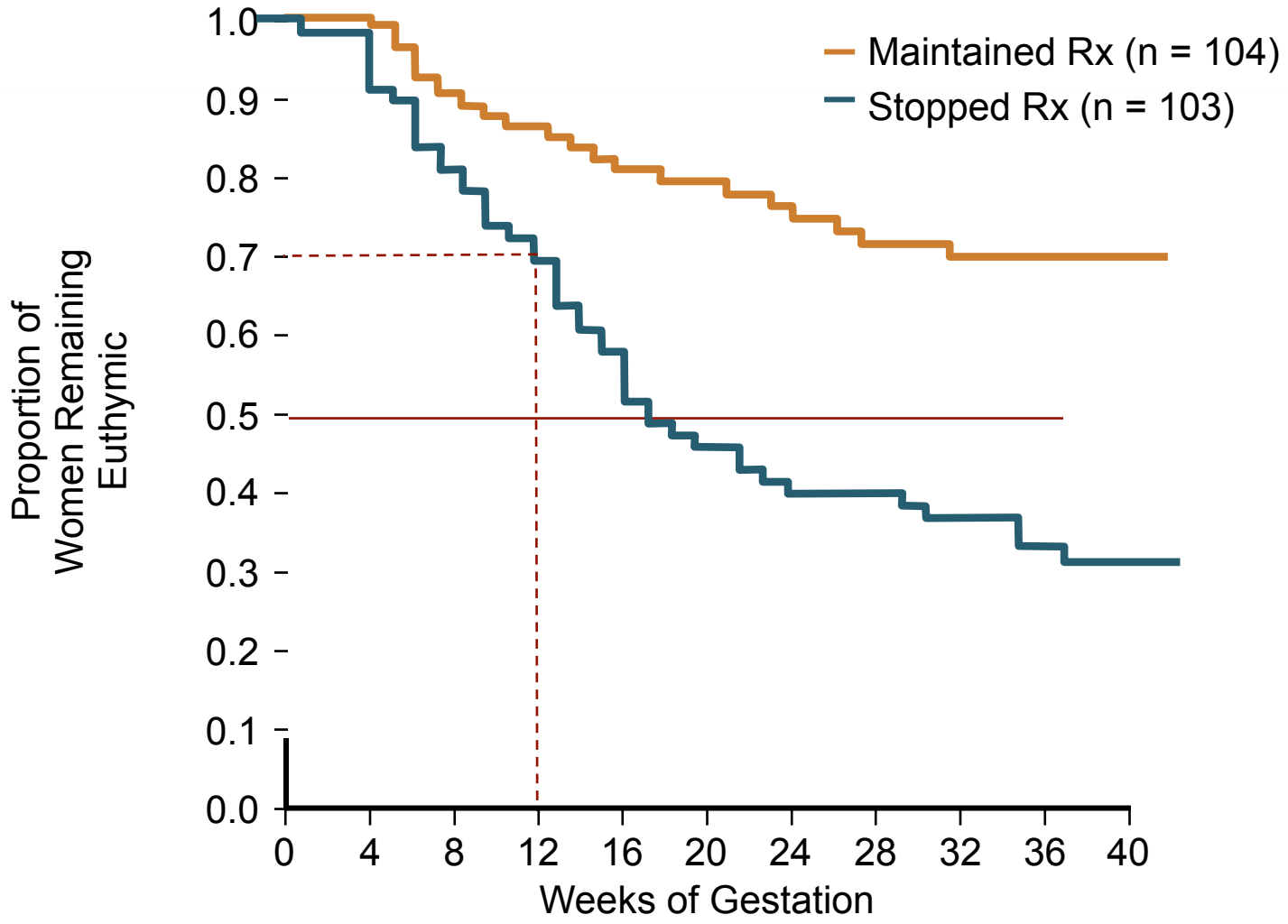
Treatment Risks

Postpartum Depression: Clinical Predictors



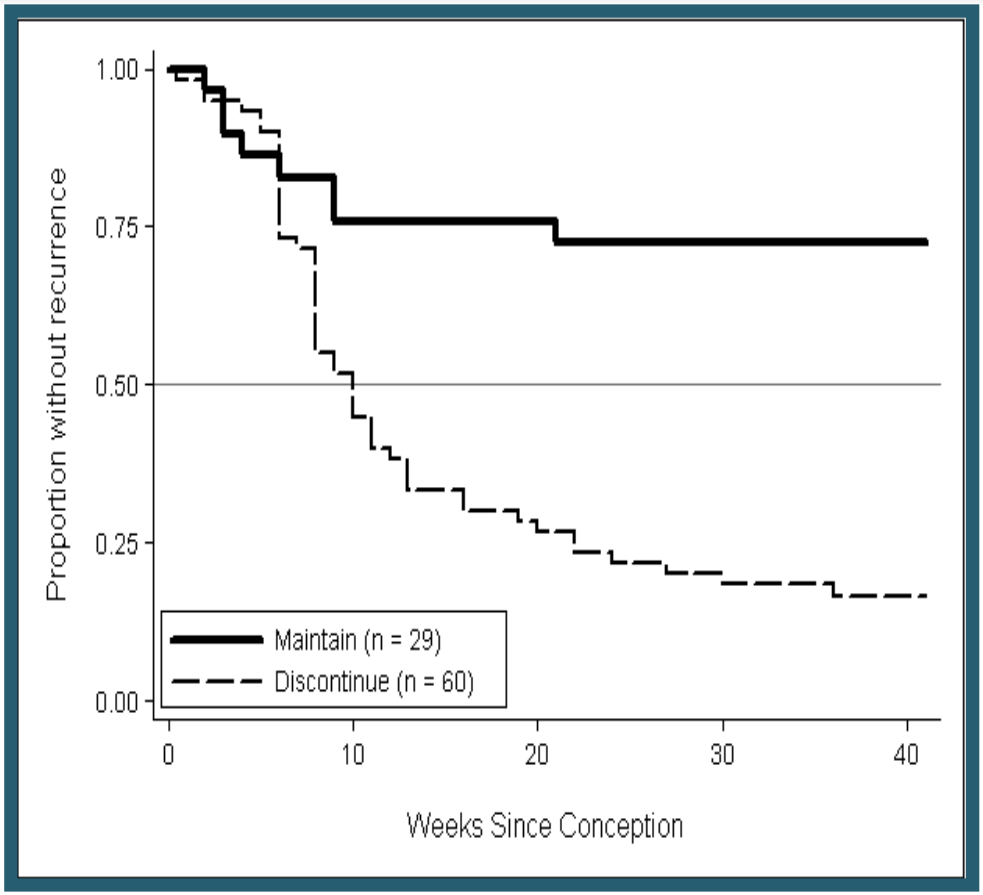
O'Hara MW, et al. *J Abnorm Psychol* 1991;100(1):63-73.

Likelihood of Illness
Medication Discontinuation & Prenatal MDD



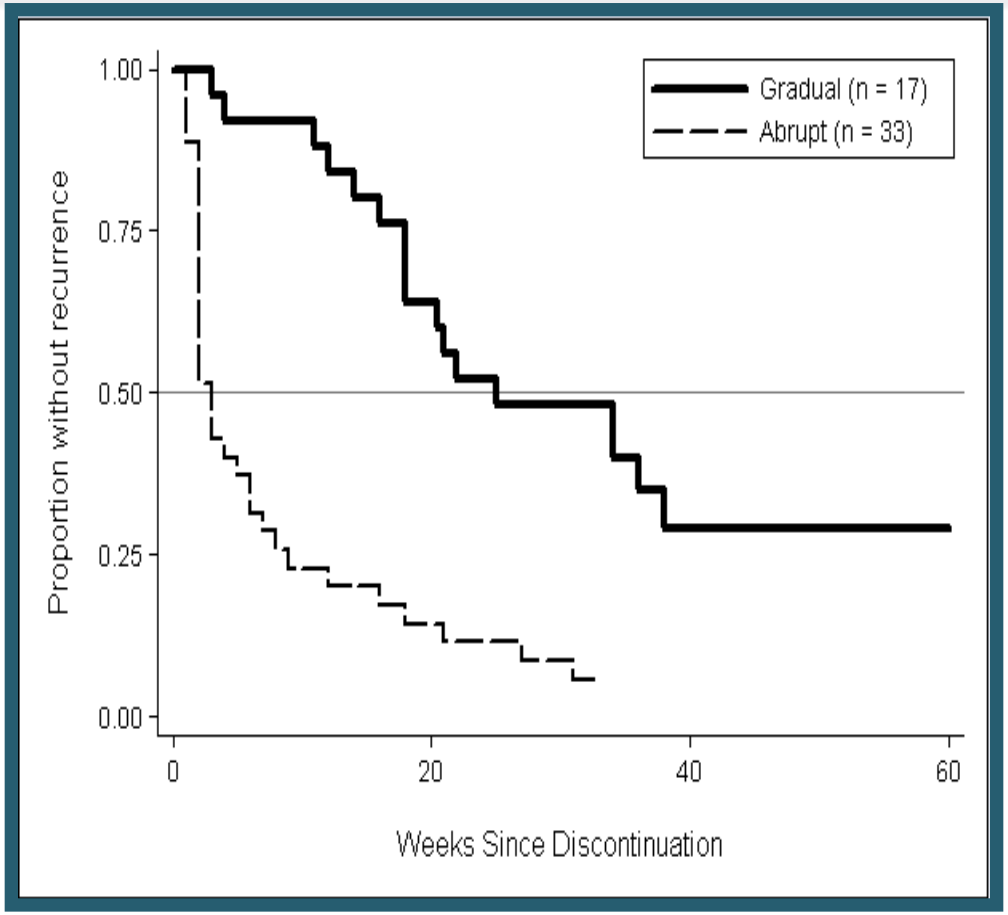
Cohen LS et al. *JAMA* 2006;295(5):499-507.

Likelihood of Illness Mood Stabilizer Discontinuation



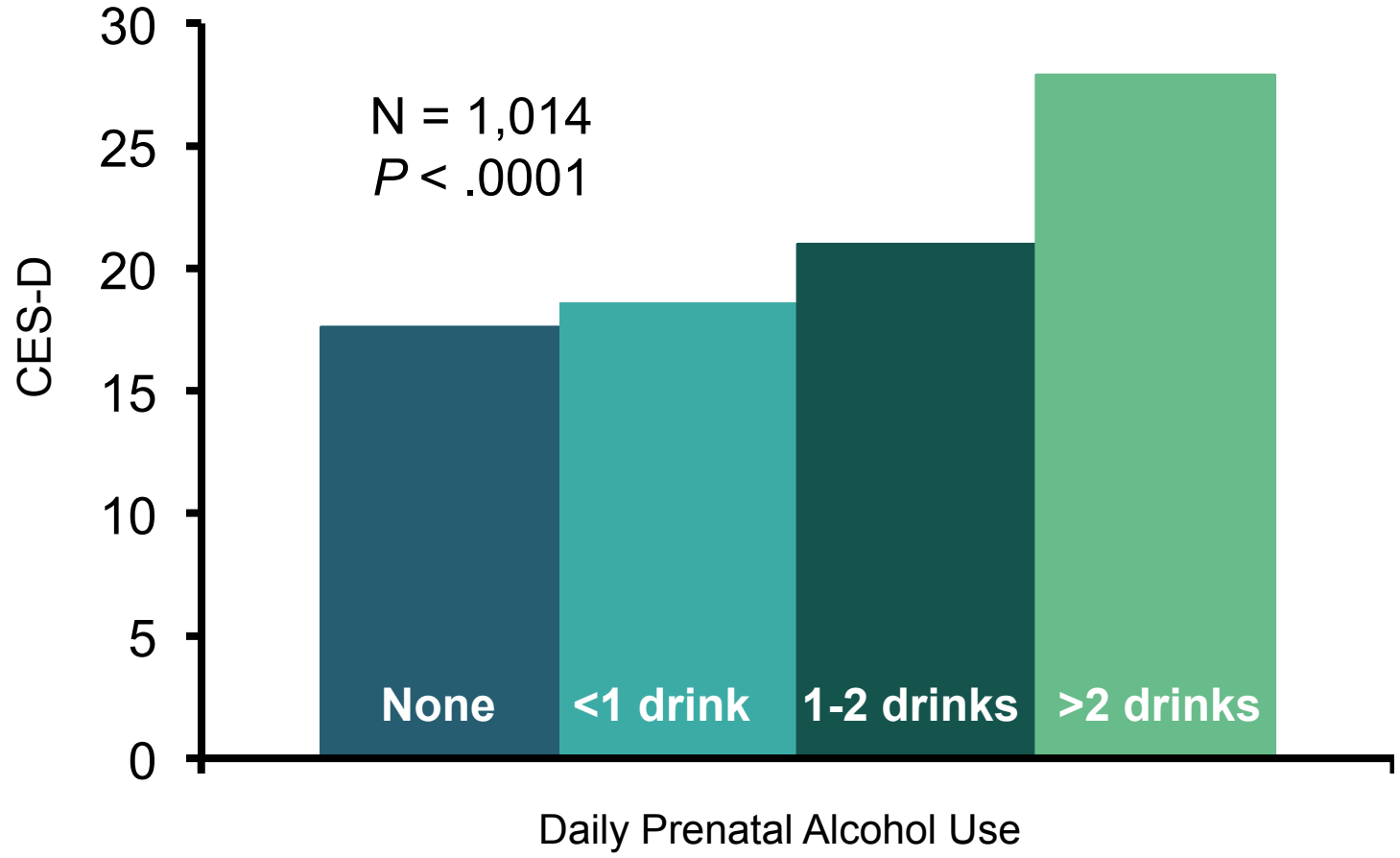
Viguera AC et al, *Am J Psychiatry* 2007;164(112):1817-1824.

Likelihood of Illness Mood Stabilizer Discontinuation: Gradual vs. Abrupt



Viguera AC et al, *Am J Psychiatry* 2007;164(112):1817-1824.

Consequences of Illness Antenatal Depression and Alcohol Use



Zuckerman B, et al. *Am J Obstet Gynecol* 1989;160(5 Pt 1):1107-1111.

Consequences of Illness Depression/Anxiety & Prenatal Drug Exposures

Cumulative Maternal Illness Severity[1]	Cumulative Prenatal Drug Exposure[2] (Drug-Weeks Exposed)											
	Psychotropic				Sleep	GI		Analgesic		Habit Forming		
	AD	BZD	APSY	Other		Nausea	Other	Opio	Other	Tob	ETOH	Caffn
Depression (HRSD AUC)	*r*=-.05 *p*=.53	*r*=.12 *p*=.09	*r*=.13 *p*=.08	*r*=-.01 *p*=.89	*r*=.28 *P*<.0001	*r*=.14 *p*=.05	*r*=.12 *p*=.11	*r*=.14 *p*=.05	*r*=.05 *p*=.45	*r*=.21 *p*=.003	*r*=-.00 *p*=.99	*r*=-.01 *p*=.93
Anxiety (HRSA AUC)	*r*=-.09 *p*=.23	*r*=.17 *p*=.02	*r*=.09 *p*=.21	*r*=.01 *p*=.87	*r*=.19 *p*=.008	*r*=.06 *p*=.40	*r*=.12 *p*=.09	*r*=.10 *p*=.15	*r*=.04 *p*=.61	*r*=.20 *p*=.006	*r*=.00 *p*=.95	*r*=.00 *p*=.99

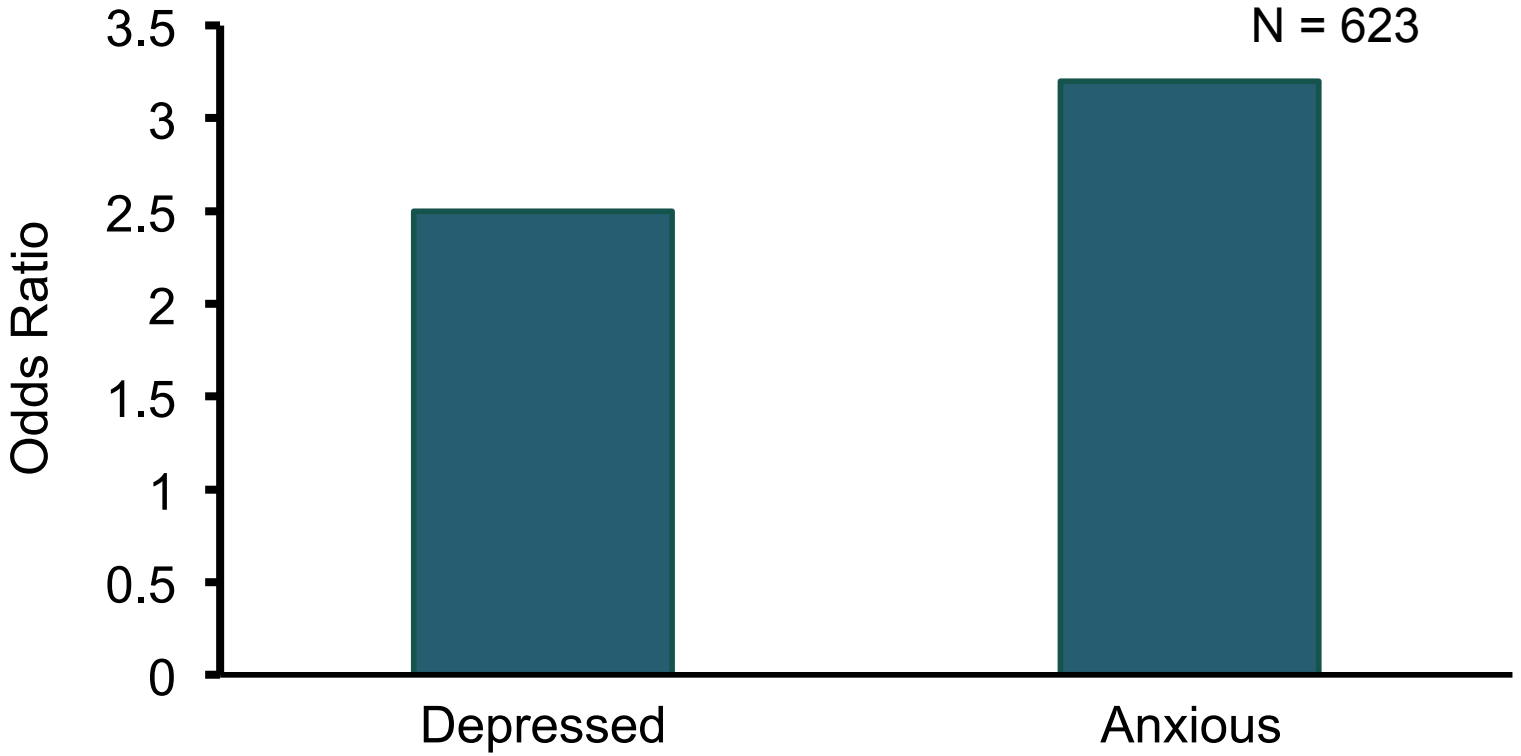
N = 195

1 Illness Severity: HRSD=Hamilton Rating Scale for Depression; HRSA=Hamilton Rating Scale for Anxiety; AUC=Area Under the Curve

2 Drug Exposure: AD=Antidepressants; BZD=Benzodiazepines; APSY=Antipsychotics; Other Psychotropic=Antiepileptic drugs and stimulants; Sleep=Prescription hypnotics; Nausea=Prescription antiemetics; Other GI=All prescription and over-the-counter gastrointestinal agents except antiemetics; Opio=Prescription opioid analgesics; Other Analgesic=All non-opioid prescription and over-the-counter analgesics; Tob=Tobacco; ETOH=Alcohol; Caffn=Caffeine

Newport DJ, et al. *J Clin Psychiatry* 2012;73(2):247-251.

Consequences of Illness Prenatal Depression & Preeclampsia

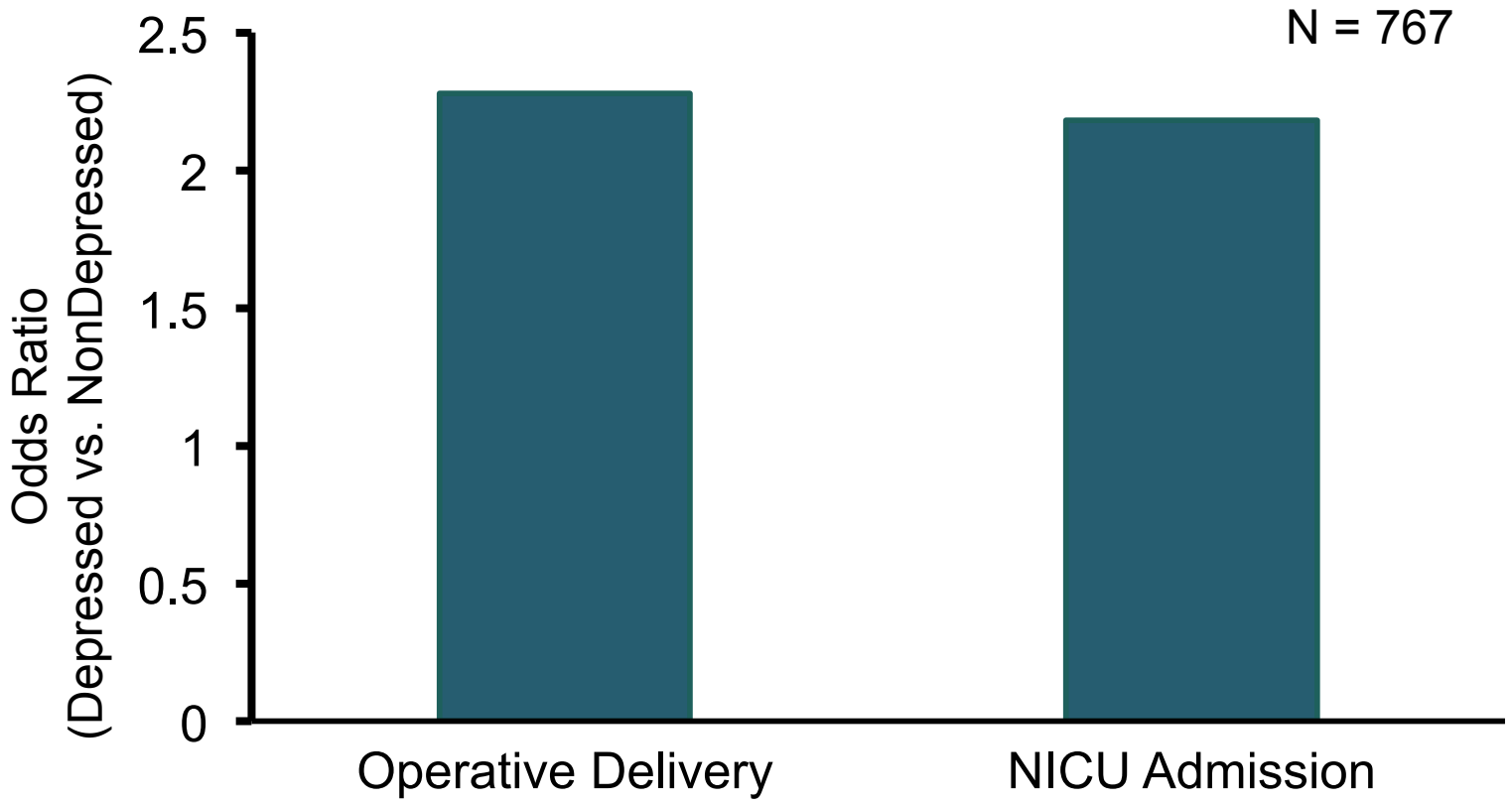


Depression: Short BDI ≥ 3

BDI = Beck Depression Inventory

Kurki T, et al. *Obstet Gynecol.* 2000;95(4):487-490.

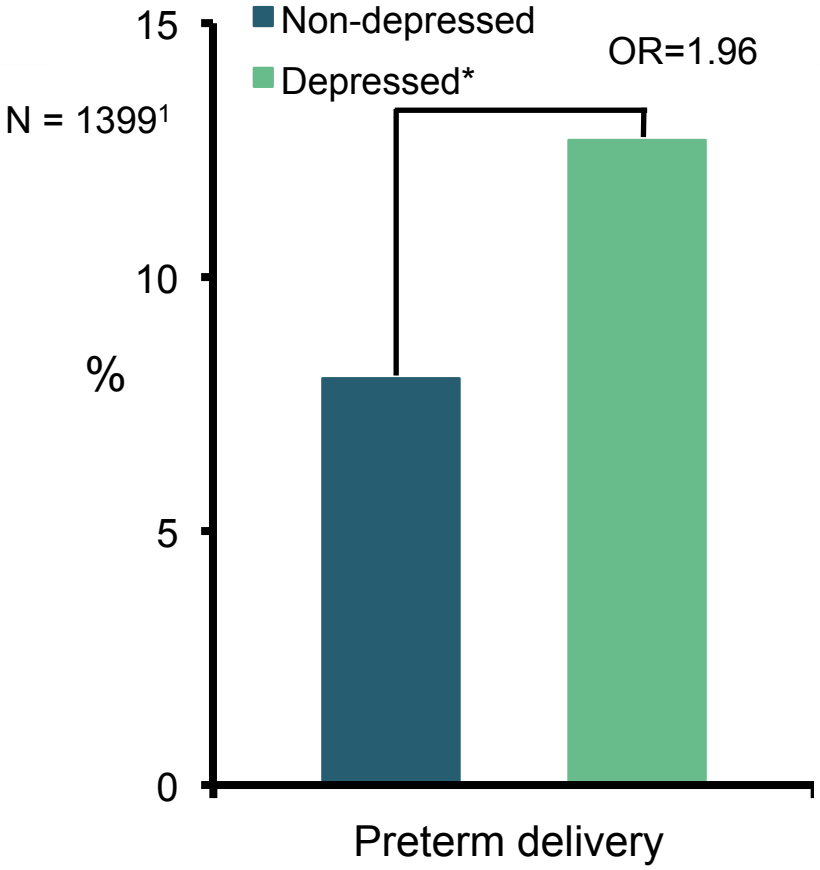
Consequences of Illness
Prenatal Depression & Delivery Outcome

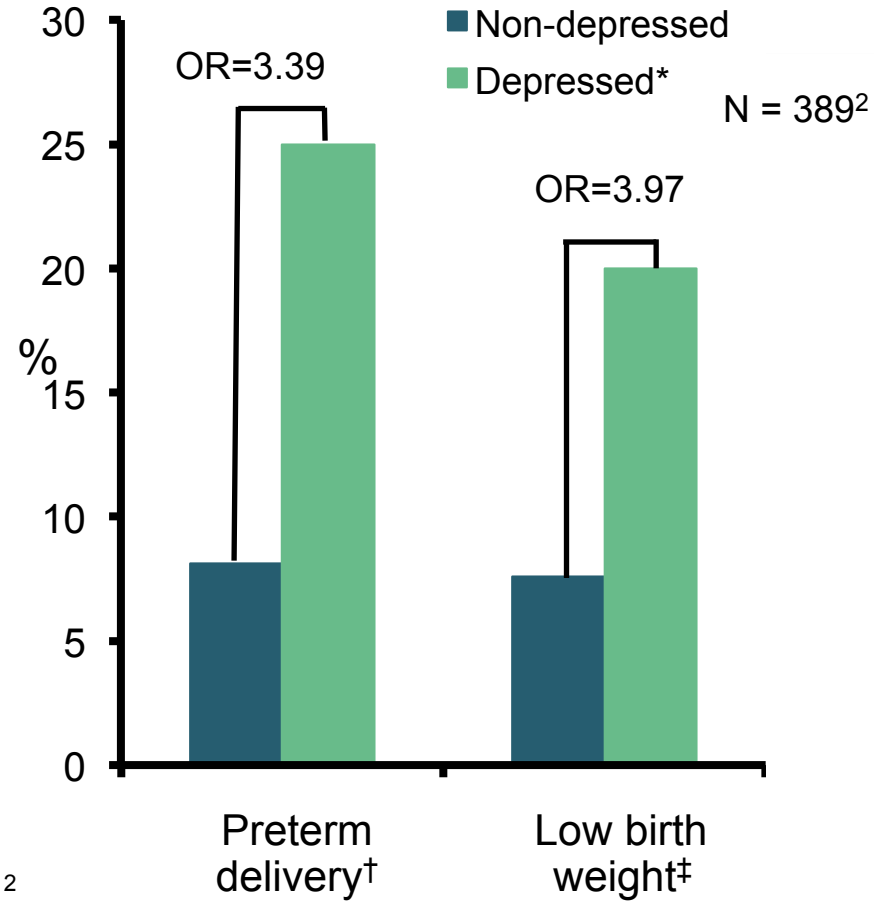


Depression: BDI ≥ 15

Chung TKH, et al. *Psychosom Med* 2001;63(5) 830-834.

Consequences of Illness
Prenatal Depression & Obstetrical Outcomes





*CES-D score in upper 10th percentile[1] or BDI score > 21[2]
†< 37 weeks gestational age; ‡< 2.5 kg

1. Orr ST, et al. *Am J Epidemiol* 2002; 156(9):797-802.
2. Steer RA, et al. *J Clin Epidemiol* 1992;45(10): 1093-1099.

Consequences of Illness Prenatal Stress & Fetal Programming

- Adult Cardiovascular Disease (> 100 studies)
  - Barker DJP, et al. *Lancet* 1989; 2(8663):577-580.
- Type 2 Diabetes
  - Newsome CA, et al. *Diabet Med* 2003;20(5):339-348.
- Osteoporosis
  - Dennison EM, et al. *Pediatr Res* 2005;57(4):582-586.
- Schizophrenia
  - Wahlbeck K, et al. *Arch Gen Psychiatry* 58(1):48-52.
- Depression
  - Thompson C, et al. *Br J Psychiatry* 2001;179:450-455.
  - Gale CR, et al. *Br J Psychiatry* 2004;184:28-33.

Maternal-Fetal Psychiatry

Conclusion & Clinical Application

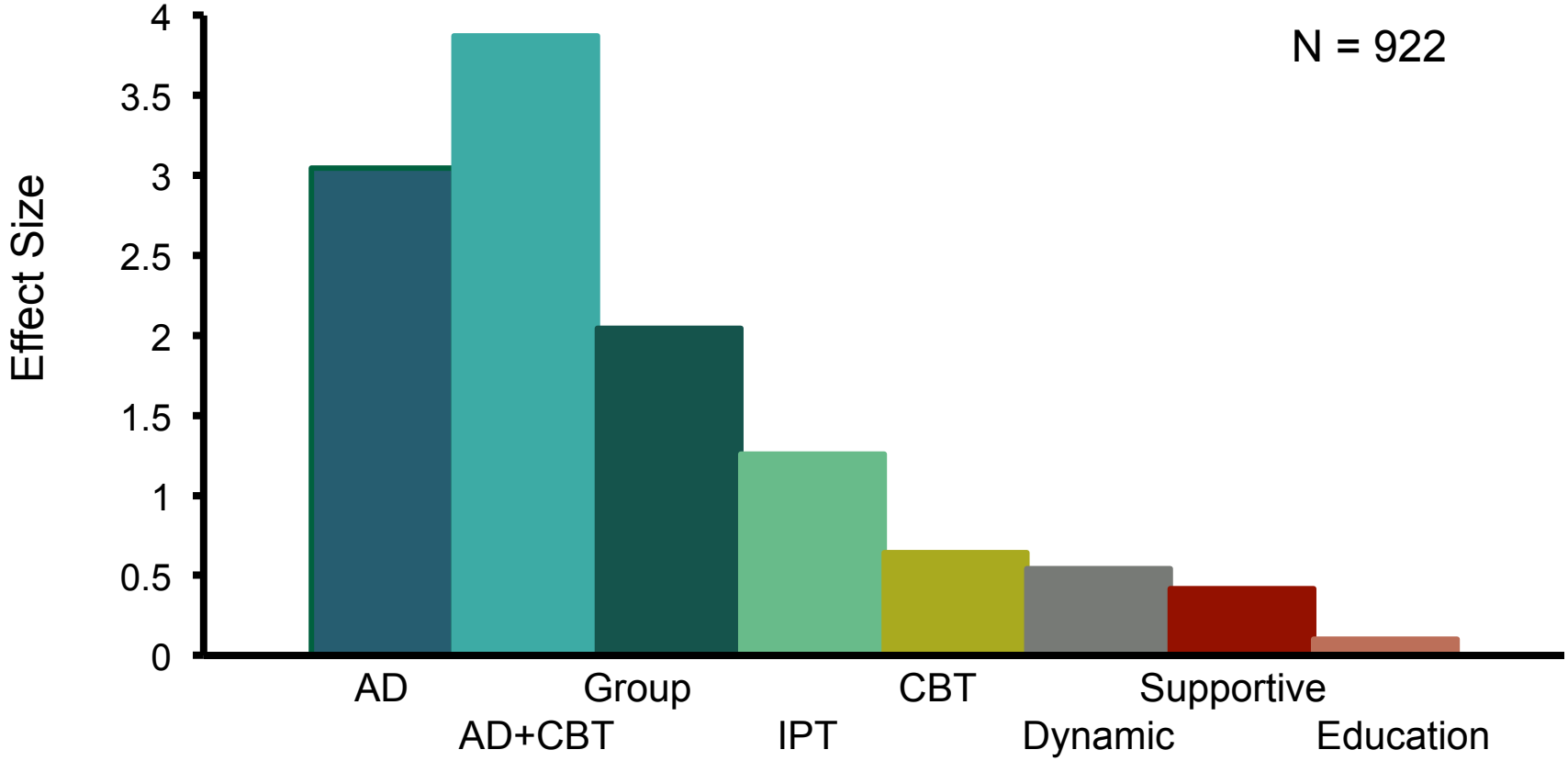
Magnitude of the Issue

Illness Risks

Treatment Risks

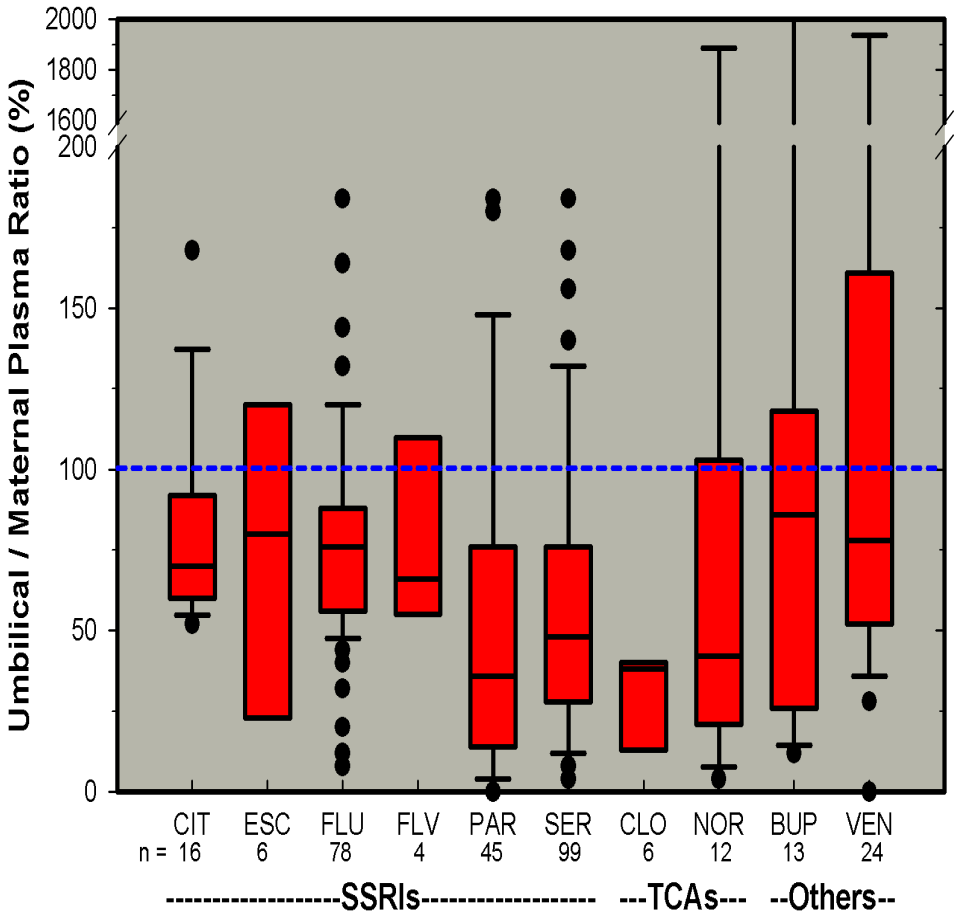
Perinatal Depression: Treatment Efficacy

Meta-Analysis of 16 Intervention Trials



Bledsoe SE, et al. *Res Soc Work Pract* 2006;16:109-120.

PK Studies: Placental Passage
Antidepressants

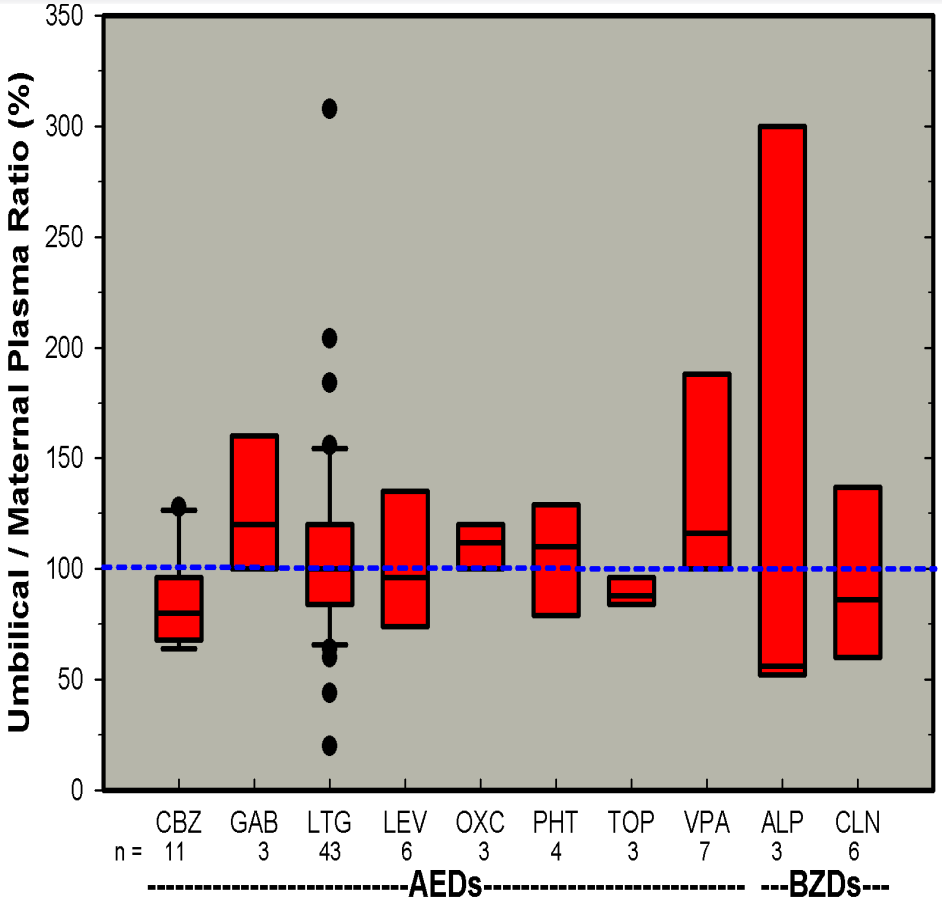


N = 303

Loughhead AM, et al. *Am J Psychiatry*. 2006 Jan;163(1):145-147.

PK Studies: Placental Passage

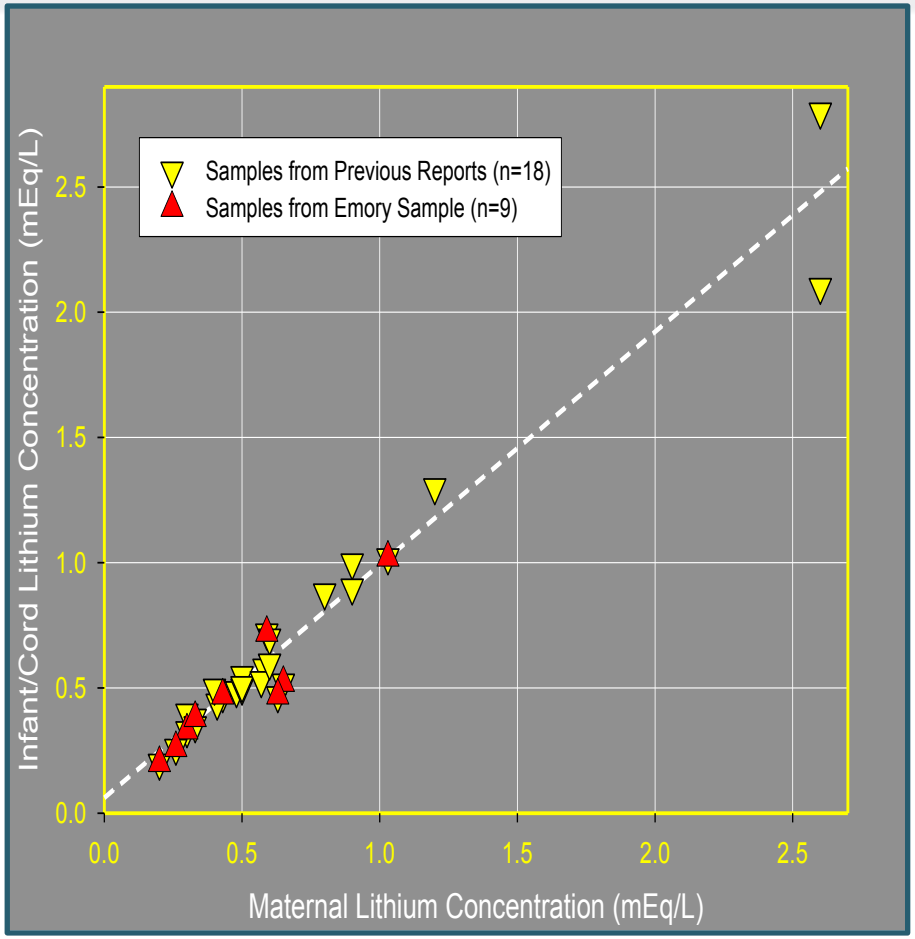
Antiepileptic Drugs & Benzodiazepines



N = 89

Myllynen P, et al. *Toxicol Appl Pharmacol*. 2005;207(2 Suppl):489-494.
Myllynen P, et al. *J Pharmacol Toxicol Methods*. 2002;48(3):131-138.

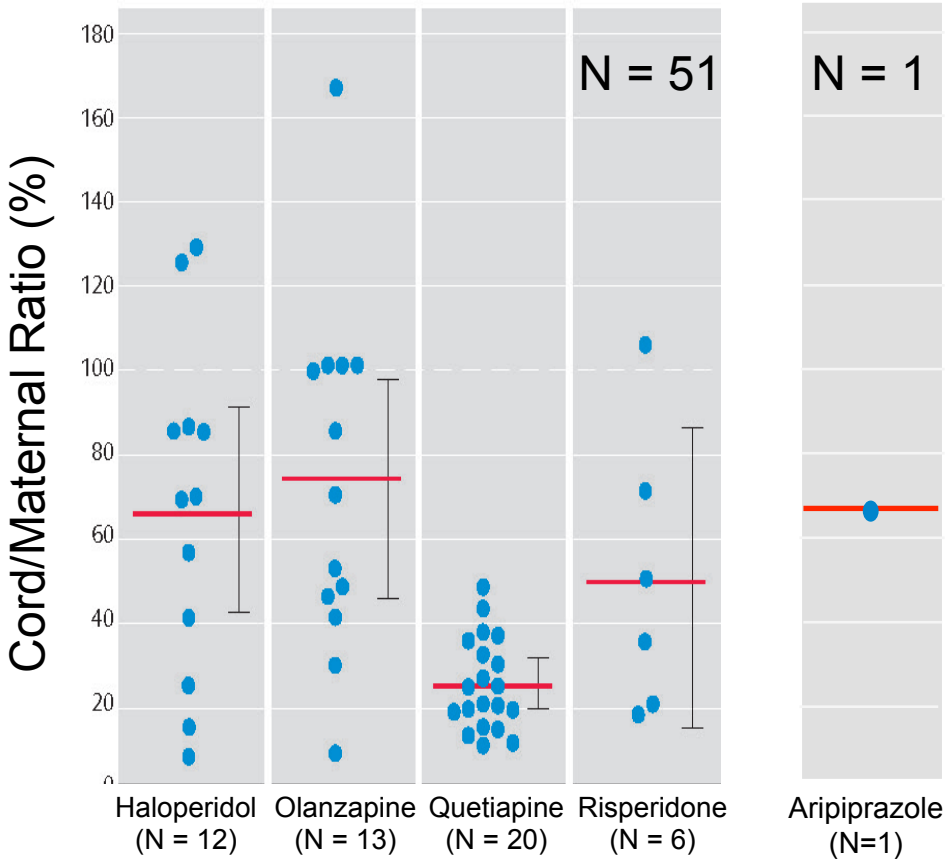
PK Studies: Placental Passage
Lithium



Newport DJ, et al. *Am J Psychiatry* 2005;62(11):2162-2170.

Quantitative Studies: Placental Passage

Antipsychotics



Newport DJ, et al. *Am J Psychiatry* 2007;164(6):1214-1220.
Nguyen T, et al. *Aust NZ J Psychiatry* 2011;45(6):500-501.

Reproductive Safety Data
Antidepressants & Birth Defects

Registry / Antidepressant	(n)	% Major Malformations
NY Dept of Health (95-01)[1]	1,816,343	4.09%
Swedish Registry (95-01)[2]	637,651	3.50%
Fluoxetine	4,679	2.69%
Sertraline	3,393	1.95%
Citalopram	2,688	2.72%
Paroxetine	2,687	3.50%
Bupropion	2,550	2.20%
Venlafaxine	771	1.82%
Escitalopram	235	3.40%

[1]http://www.health.state.ny.us/nysdoh/cmr/docs

[2]http://www.sos.sos.se/epc/epceng.htm

Stowe ZN. et al. Psychiatric Times Website http://www.psychiatrictimes.com/articles/using-antidepressants-during-pregnancy-update. Published August 1, 2006. Accessed May 25, 2016.

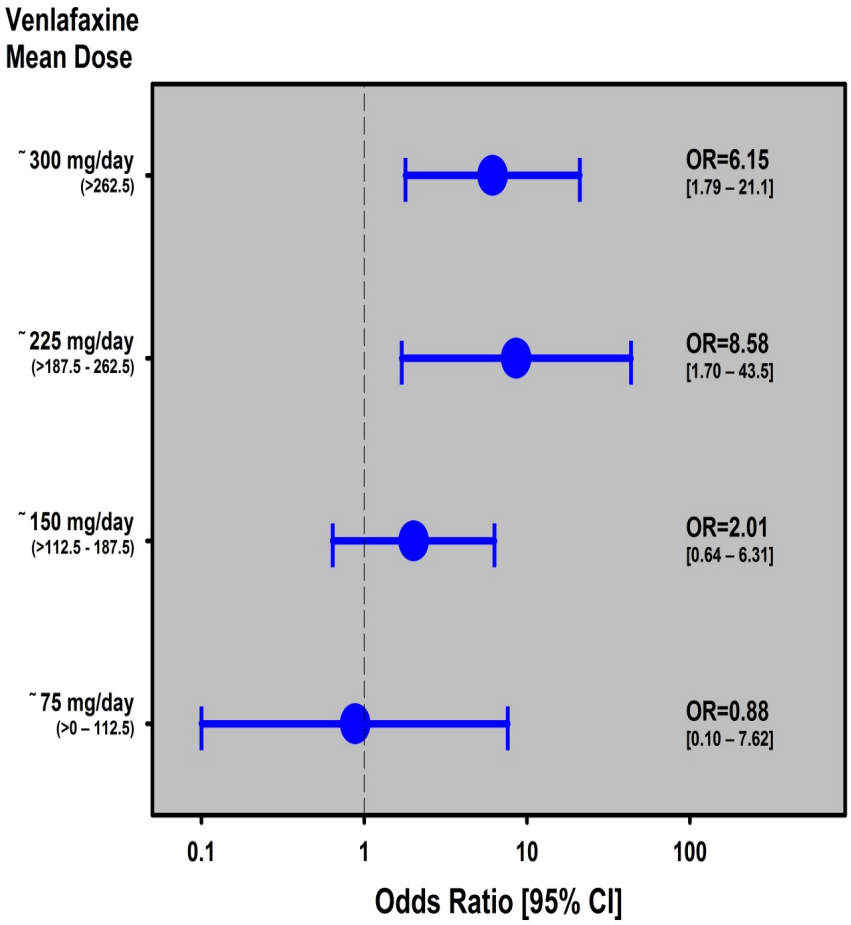
Reproductive Safety Data
Hypertensive Disorders of Pregnancy

Risk Factor		Odds Ratio [95% CI]		X^2	*P* Value
Psychostimulant Exposure	After Pregnancy Week 20	6.11	[1.79 – 20.9]	$X^2 = 8.32$	$P = .004$
Cocaine Dependence	Lifetime History	2.99	[1.12 – 7.98]	$X^2 = 4.76$	$P = .03$
SNRI Exposure	After Pregnancy Week 20	2.57	[1.34 – 4.93]	$X^2 = 8.12$	$P = .004$
Advanced Maternal Age	≥ 40 Years Old at Conception	2.51	[1.21 – 5.20]	$X^2 = 6.11$	$P = .01$
African-American Race		2.33	[1.04 – 5.23]	$X^2 = 4.23$	$P = .04$
Nulliparity		2.18	[1.32 – 3.60]	$X^2 = 9.18$	$P = .002$
Obesity	Preconception Body Mass Index ≥ 30	2.14	[1.18 – 3.89]	$X^2 = 6.24$	$P = .01$
Panic Disorder	Lifetime History	1.78	[1.06 – 2.98]	$X^2 = 4.76$	$P = .03$

Exposure to depression and other psychotropics during gestation was not predictive of prenatal hypertension.

Newport DJ, et al. *J Clin Psychiatry* (in press).

Reproductive Safety Data Venlafaxine and Hypertensive Disorders of Pregnancy: Examination of Dose Effects



Newport DJ et al. *J Clin Psychiatry* (in press).

Cumulative Longitudinal Exposure: Medication & Illness

Preterm Delivery

Predictor	Odds Ratio [95% CI]		X^2	P Value
Severe Depression (Avg. HamD for 3rd Trimester* [21+ vs. 0-15])	8.82	[2.62 –29.8]	X^2=12.3	p=.0004
Placental Abruption	8.73	[1.08 – 70.3]	X^2=4.14	p=.04
Maternal Infection at Delivery (Other than Chorioamnionitis)	7.19	[1.75 – 29.5]	X^2=7.49	p=.006
History of Previous Preterm Delivery	4.64	[2.04 – 10.6]	X^2=13.4	p=.0003
Employed Full Time Outside Home	3.39	[1.76 – 6.53]	X^2=13.3	p=.0003
Zolpidem Exposure (during 3rd Trimester)	3.31	[1.39 – 7.90]	X^2=7.35	p=.007
Gestational Diabetes	2.90	[1.07 – 7.87]	X^2=4.35	p=.04
Moderate Depression (Avg. HamD for 3rd Trimester* [16-20 vs. 0-15])	2.76	[1.15 – 6.64]	X^2=5.17	p=.02
SRI Antidepressant Exposure (during 3rd Trimester)	2.31	[1.14 – 4.67]	X^2=5.40	p=.02

N = 841

HamD = Hamilton Rating Scale for Depression SRI = Serotonin Reuptake Inhibitor

Newport DJ, et al. Unpublished Data

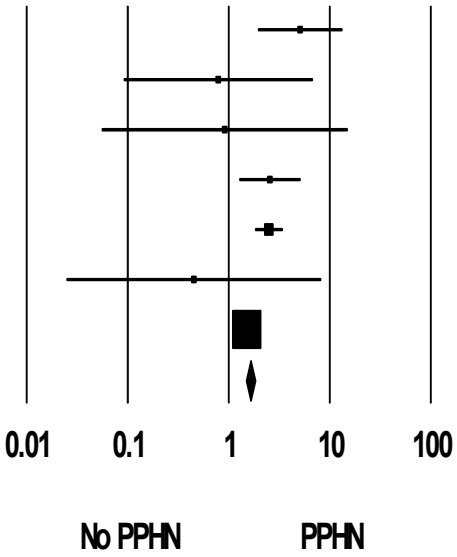
Reproductive Safety Data: Antidepressants Controlled Studies of Neonatal Adaptation

Reference	Study Group	Control Group	Outcome	O.R. Pct. Diff.
Chambers '96	Fluox (n=63)	Early Fluox (n=101)	Poor Adaptation	8.7 [2.9-26.6]
Costei '02	Parox (n=55)	Healthy/Early Parox (n=54)	Respiratory Distress	9.6 [1.1-79.3]
Laine '03	SSRI (n=20)	Healthy (n=20)	Serotonergic Sxs	6.9 [1.6-29.2]
Kallen '04	SSRI (n=563)	Historical (n>560K)	Respiratory Distress Jaundice Hypoglycemia Convulsions	2.0 [1.4-2.8] 1.0 [0.6-1.5] 1.4 [0.9-2.0] 3.6 [1.0-9.3]
Oberlander '04	SSRI (n=28)	Healthy (n=23)	Poor Adaptation	5.6 [1.1 – 25.3]
Zeskind '04	SSRI (n=17)	Healthy (n=17)	Tremulousness Behavioral state chg REM sleep epochs REM sleep bouts REM sleep startles Motor activity Heart rate variability	↑ 29% p<.04 ↓ 57% p<.005 ↑ 13% p<.13 ↓ 49% p<.001 ↑ 48% p<.13 ↑ 46% p<.08 ↓ 17% p<.07
Sivojelezova '05	Citalo (n=63)	Healthy/Early SSRI (n=158)	Any Complication	1.5 [1.0-2.4]
Oberlander '06	SSRI (n=37)	Healthy (n=47)	Respiratory Distress Jitteriness	46% vs. 13% p<.05 35% vs. 6% p<.05

Reproductive Safety Data: Antidepressants SSRIs & PPHN: Timeline of Findings

Reproductive Safety Data: Antidepressants Controlled Studies of SSRI Exposure & PPHN

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Chambers et al 2006	5.100	1.928	13.493	3.282	0.001
Andrade et al 2009	0.790	0.091	6.890	-0.213	0.831
Wichman et al 2009	0.914	0.055	15.251	-0.062	0.950
Reis and Kallen 2010	2.560	1.259	5.206	2.596	0.009
Kieler et al 2011	2.500	1.800	3.472	5.467	0.000
Wilson et al 2011	0.452	0.025	8.336	-0.534	0.593
Huybrechts et al 2016	1.510	1.350	1.689	7.192	0.000
	1.623	1.463	1.802	9.110	0.000



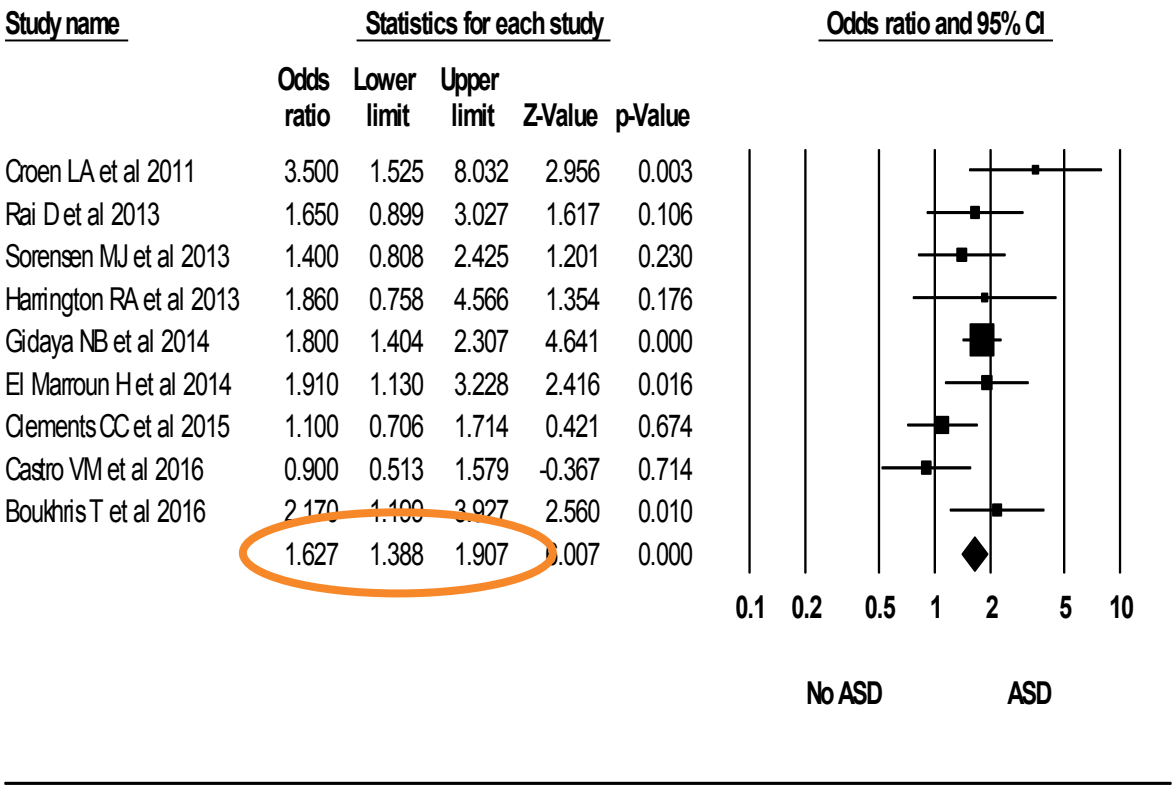
Newport DJ. Unpublished meta-analysis

Reproductive Safety Data: Antidepressants Controlled Studies of Neurodevelopment

Referemce	Study Groups	Bayley Mental Development Index (MDI)	MDI Differences (vs. Control)	Bayley Psychomotor Development Index (PDI)	PDI Differences (vs. Control)
Nulman '97	Fluox (n=63) TCA (n=80) Healthy (n=84)	117 ± 17 118 ± 17 115 ± 14	n.s. n.s.		
Nulman '02	Fluox (n=46) TCA (n=40) Healthy (n=36)	104.4 ± 15.5 110.9 ± 18.0 104.1 ± 13.7	n.s. n.s.	97.7 ± 11.0 100.1 ± 12.5 98.3 ± 9.7	n.s. n.s.
Casper '03	SSRI (n=31) MDD/No Med (n=13)	91.0 ± 13.3 94.3 ± 7.5	n.s.	90.0 ± 11.4 98.2 ± 9.1	t=2.30, p=.03
Oberlander '04 (@ 2 mos)	SSRI (n=28) SSRI+clonazepam (n=18) Healthy (n=23)	97.0 ± 8.3 94.0 ± 5.2 96.7 ± 7.8	n.s. n.s.	104.8 ± 6.1 102.9 ± 6.2 102.6 ± 7.3	n.s. n.s.
Oberlander '04 (@ 8 mos)	SSRI (n=28) SSRI+clonazepam (n=18) Healthy (n=23)	100.7 ± 6.4 97.2 ± 4.5 99.4 ± 5.6	n.s. n.s.	91.5 ± 9.6 93.1 ± 8.6 97.0 ± 9.1	n.s. n.s.

Age Indexes – predictive validity not established
Casper study – 29% enrolled AFTER delivery

Reproductive Safety Data: Antidepressants Controlled Studies of SSRI Exposure & Autism



Newport DJ. Unpublished meta-analysis.

Reproductive Safety Data: Antidepressants SSRI Exposure & Autism

SSRI Exposure Window	Adjusted OR
Preconception	2.1 [1.1 – 4.2]
First Trimester	3.8 [1.8 – 7.8]
Second Trimester	1.9 [0.7 – 5.6]
Third Trimester	2.9 [1.0 – 8.0]
Overall	2.2 [1.2 – 4.2]

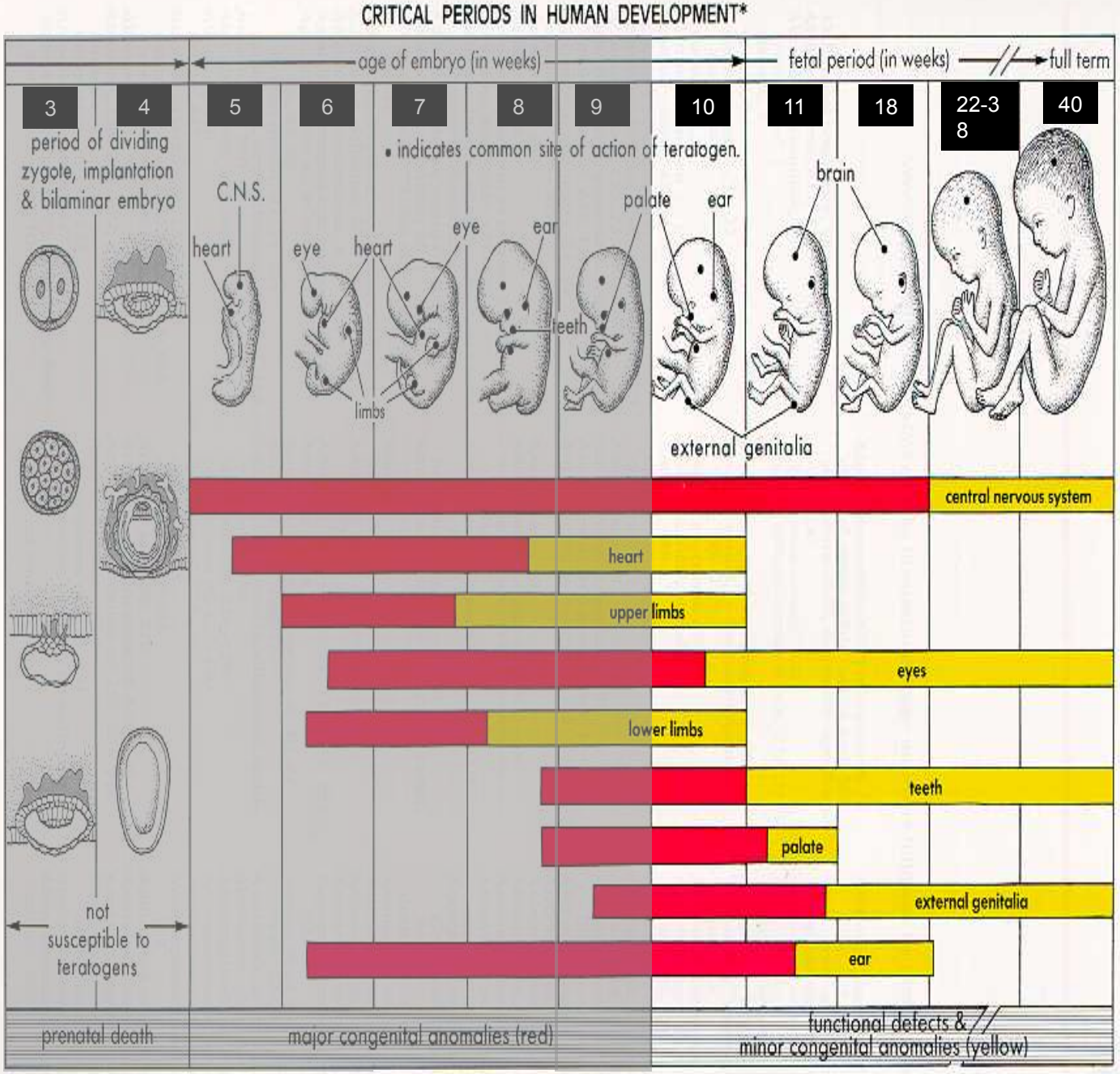
Trait	Cases (N = 298)	Controls (N = 1507)	Test
Age (mean, sd)	31.6 (5.2)	30.2 (5.7)	$p < .001$
Race (white n, %)	163 (54.7)	700 (46.4)	$p < .04$
Education (≤HS n, %)	61 (20.5)	522 (34.6)	$p < .001$
Low Birth Weight (n, %)	25 (8.4)	79 (5.2)	$p < .03$

Croen LA, et al. *Arch Gen Psychiatry* 2011;68(11):1104-1112.

Lithium

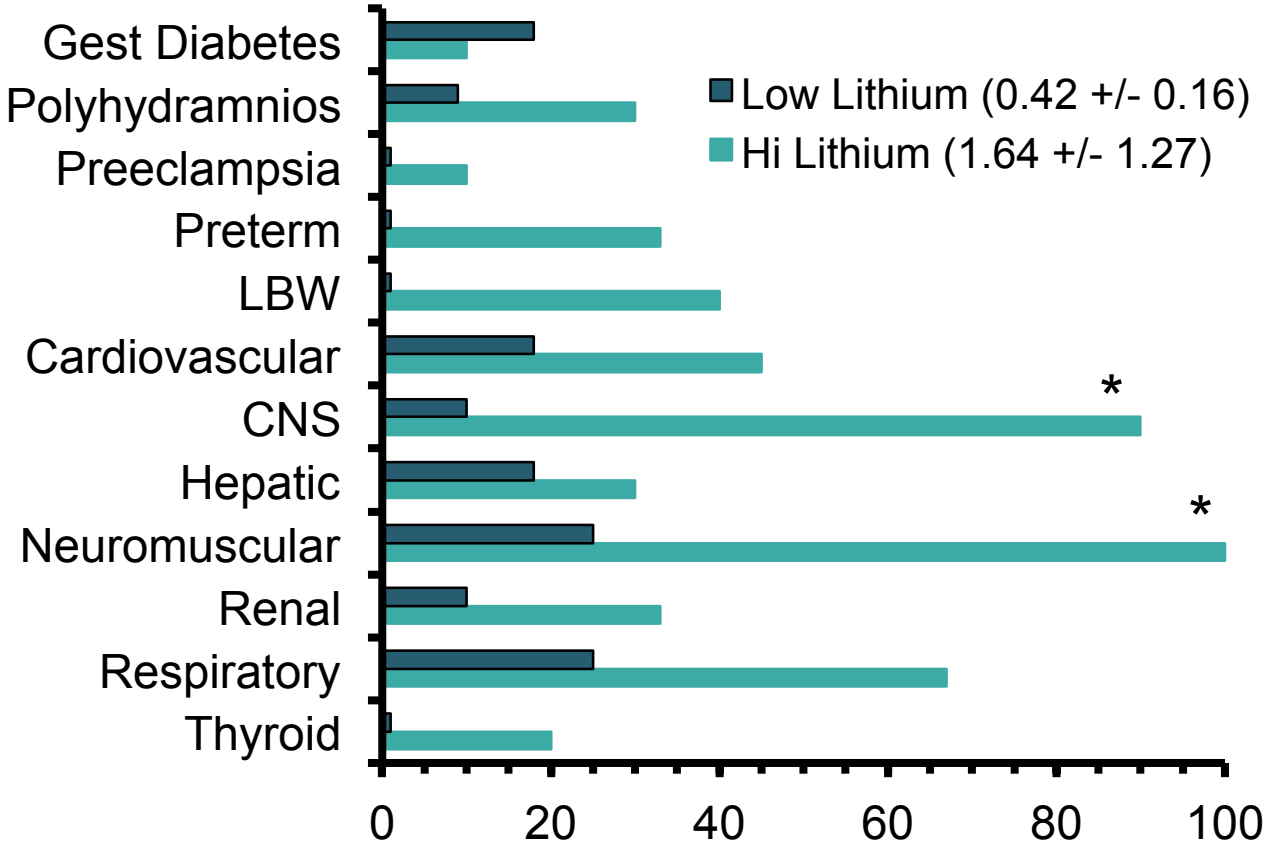
- Lithium registry data 1970s
  - Identified risk for Ebstein's anomaly (<0.1%)[1]
- Neurobehavioral outcome
  - No adverse sequelae in school age kids (n = 60)[2]
- Delivery complications
  - Cyanosis, hypotonia, atrial flutter, bradycardia, fetal diabetes insipidus, hydronephrosis, fluid retention, neonatal hypoglycemia, neonatal goiter

1. Cohen LS, et al. *JAMA* 1994;271(19):146-150.
2. Schou M. *Acta Psychiatr Scand* 1976;54(3):193-197.



* Red indicates highly sensitive periods when teratogens may induce major anomalies.

Neonatal Data: Lithium Delivery Concentration & Neonatal Complications



N = 24

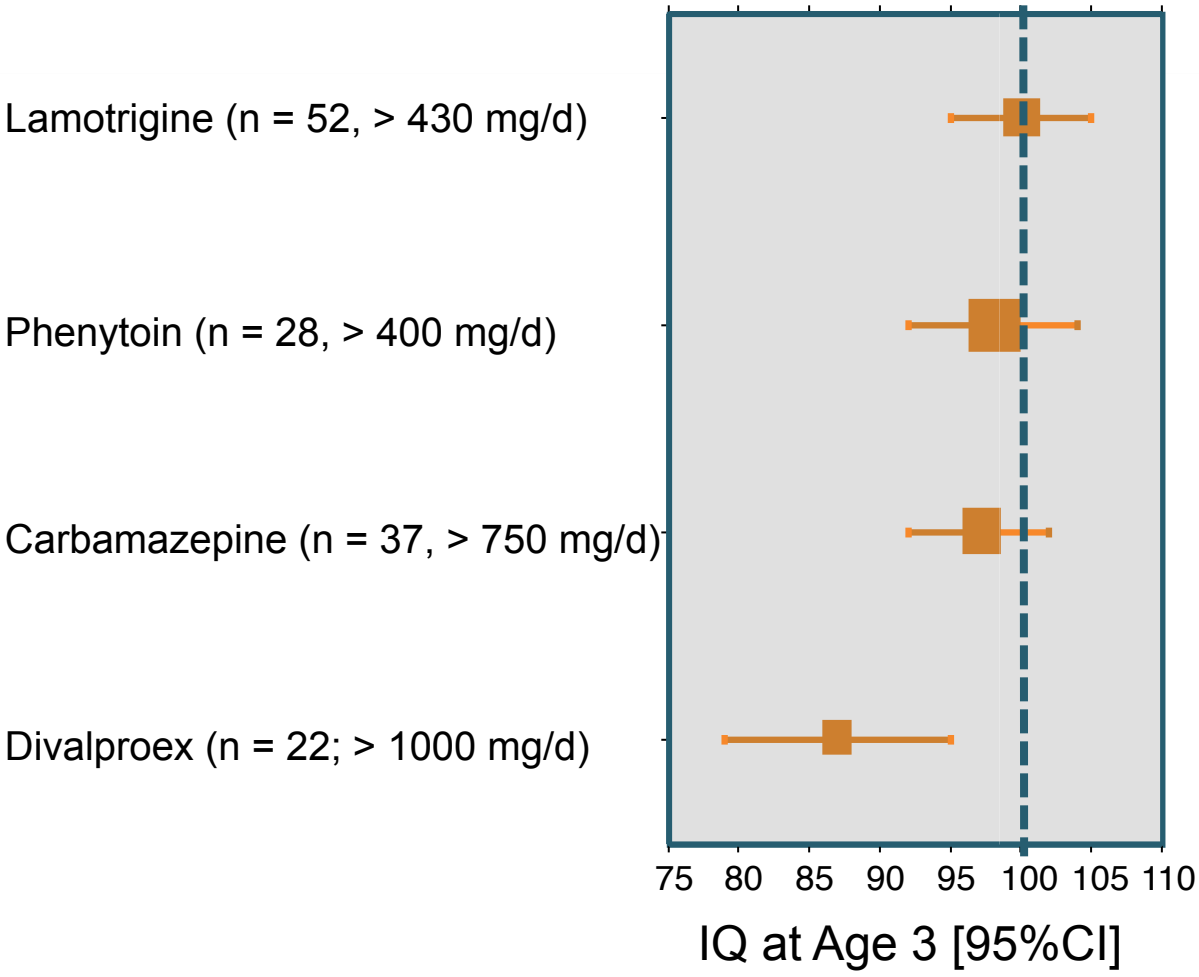
*p < .01

Newport DJ, et al. *Am J Psychiatry* 2005;162(11):2162-2170.

Valproate

- Neural Tube Defects: 3.8% Risk
  - Rosa FW. *New Engl J Med* 1991; 324(10): 674-677.
  - Samren E, et al. *Epilepsia* 1997;38(9):981-990.
- Reduced Risk: [VPA] ≤ 70, VPA daily dose ≤ 1000 mg
  - Kaneko S et al. *Epilepsy Res* 1999;33(2-3):145-158.
  - Samren E et al. *Epilepsia* 1997; 38(9): 981-990.
- Fetal Valproate Syndrome
  - McMahon CL, Braddock SR. *Teratology* 2001;64(2):83-86.
  - Facial, Cardiovascular, & Limb abnormalities
  - Higher rate of homozygosity for MTHFR (folate reductase)
    - Dean JC et al. *Clin Genet* 1999; 56(3): 216-220.
- Delivery Complications:
  - Hepatotoxicity, coagulopathy, hypogylcemia
- Neurobehavioral Outcome
  - Kozma C. *Am J Med Genet* 2001;98(2):168-175.
  - Developmental Delay (20%)
  - Mental Retardation (10%)

High-Dose Maternal AED Exposure & Child IQ



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

Lamotrigine
Prospective Assessment of Teratogenicity

Source	Major Malformations		
	Mono-therapy	Polytherapy	VPA Polytherapy
Intl. Lamotrigine Pregnancy Registry [1]	28 / 1085 2.6%	9 / 350 2.6%	15 / 144 10.4%
UK Independent Pregnancy Registry [2]	21 / 647 3.2%	8 / 289 2.8%	13 / 141 9.2%
North Am. AED Pregnancy Registry [3]	15 / 564 2.7%		
European Registry AEDs Pregnancy Australian Registry AEDs Pregnancy [4] Danish Registry AEDs Pregnancy [5]	0 / 61 0.0%	1 / 51 2.0%	4 / 68 5.9%
Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) Study [6]	1 / 98 1.0%		
Dominguez-Salgado et al [7]	0 / 31 0.0%		
	65 / 2486 2.6%	**18 / 690 2.6%**	**32 / 353 9.1%**
	83 / 3176 2.6%		

1. Lamotrigine Pregnancy Registry. Interim Report. 9/92 – 3/07.; 2. Morrow J, et al. *J Neurol Neurosurg Psychiatr* 2006;77:193-8.; 3. Holmes LB, et al. *Birth Defects Res* 2006;76:318.; 4. Vajda FJ, et al. *J Clin Neurosci* 2003; 10: 543-9.; 5. Sabers A, et al. *Acta Neurol Scand* 2004;109: 9-13.; 6. Meador KJ, et al. *Neurology* 2006;67:407-12.; 7. Dominguez-Salgado M, et al. *J Neurol* 2001; 248(suppl 2):146.

Lamotrigine: Orofacial Clefts

Cohort Studies

Source	Orofacial Clefts	
Intl. Lamotrigine Pregnancy Registry [1]	2 / 1085	1.8 / 1000
UK Independent Pregnancy Registry [2]	1 / 647	1.5 / 1000
North Am. AED Pregnancy Registry [3]	5 / 564	8.9 / 1000
European Registry AEDs Pregnancy		
Australian Registry AEDs Pregnancy[4]	0 / 61	0.0 / 1000
Danish Registry AEDs Pregnancy [5]	0 / 51	0.0 / 1000
Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) Study [6]	0 / 98	0.0 / 1000
Dominguez-Salgado et al [7]	0 / 31	0.0 / 1000
	8 / 2537	3.2 / 1000

EUROCAT Case-Control

Group	Cases	Controls	Total
LTG	2	43	45
No LTG	5,509	80,009	85,518
Total	5,511	80,052	85,563

AOR (Cleft | LTG Exposure)

0.67 [95%CI: 0.10 – 2.34]

2006;77:193-8.; 3. Holmes LB, et al. *Birth Defects Res* 2006;76:318.; 4. Vajda FJ, et al. *J Clin Neurosci* 2003; 10: 543-9.; 5. Sabers A, et al. *Acta Neurol Scand* 2004;109: 9-13.; 6. Meador KJ, et al. *Neurology* 2006;67:407-12.; 7. Dominguez-Salgado M, et al. *J Neurol* 2001; 248(suppl 2):146.

First Generation Antipsychotics Reproductive Safety Profile Summary

- Teratogenicity: Major Malformations
  - No association with chlorpromazine, perphenazine, haloperidol
    - Goldberg HL & DiMascio A 1978; Hill RM & Stern L 1979; Nurnberg HG & Prudic J 1984
  - Positive association with aliphatic phenothiazines
    - Rumeau-Rouquette C et al. 1977
- Preterm Birth & Birth Weight
  - No association with haloperidol at antiemetic doses (1.2 mg/day)
    - Van Waes A & Van de Velde EJ 1969
  - No association with trifluoperazine at antiemetic doses
    - Moriarty AJ & Nance NR 1963; Rawlings WJ et al 1963
- Neonate
  - Case reports of EPS, NMS
    - James ME 1988; Cleary MF 1977; Hill RM et al 1966; O'Connor MO et al 1981
  - Intestinal Obstruction
    - Falterman CG & Richardson CJ 1980
- Neurodevelopment (Clinical)
  - No differences in IQ scores at 4yo (generally low antipsychotic doses)
    - Kris EB 1965; Sloan D et al 1977
- Neurodevelopment (Preclinical)
  - Learning Deficits
    - Hoffeld DR et al 1968; Ordy JM et al 1966; Robertson RT et al 1980
  - No Impact upon Learning
    - Dallemagne G & Weiss B 1982

Prenatal Antipsychotic Exposure Teratogenicity

4.5
4
3.5
3
2.5
2
1.5
1
0.5
0

"a detection bias cannot be ruled out . . .

exposed women might be more likely to be offered fetal echocardiography and postnatal diagnosis . . .

all septal defects detected in both the [SGA] cohort and [FGA] cohort were isolated in contrast to most infants of the control cohort where multiple malformations included septal defects"

s Ctl

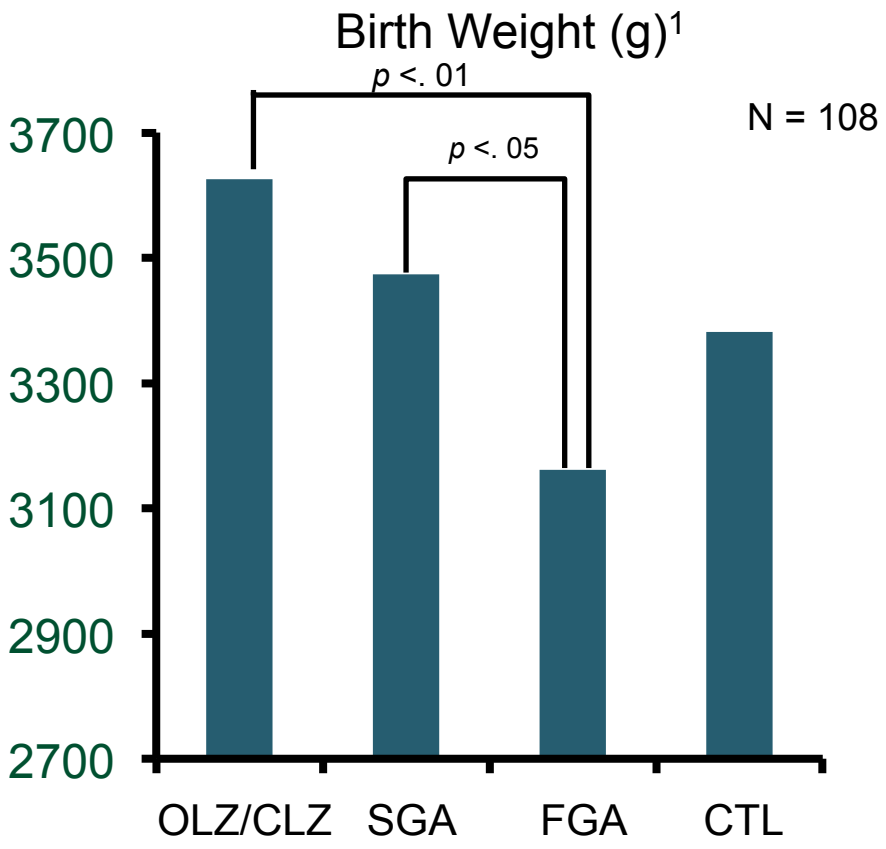
Systems Affected

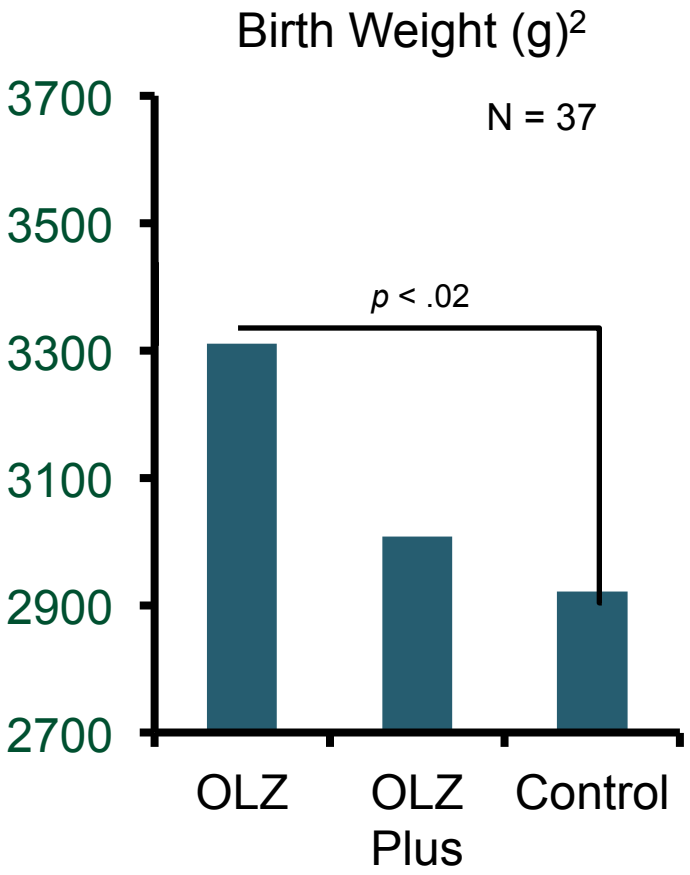
System	SGA	FGA	Ctl
N	430	213	1014
Nervous	2 (0.5)	0 (0.0)	1 (0.1)
CV*	**12 (2.8)**	**3 (1.4)**	**6 (0.6)**
GI	2 (0.5)	0 (0.0)	5 (0.5)
MusSk	2 (0.5)	2 (0.9)	4 (0.4)
Face	2 (0.5)	0 (0.0)	1 (0.1)
ENT	0 (0.0)	0 (0.0)	0 (0.0)
Genital	0 (0.0)	0 (0.0)	1 (0.1)
Urinary	1 (0.2)	1 (0.5)	3 (0.3)
Skin	0 (0.0)	1 (0.5)	0 (0.0)
Multiple	1 (0.2)	2 (0.9)	4 (0.4)

Haberman F, et al. *J Clin Psychopharmacol* 2013;33(4):453-462.

Prenatal Antipsychotic Exposure

Metabolic Effects: Birth Weight

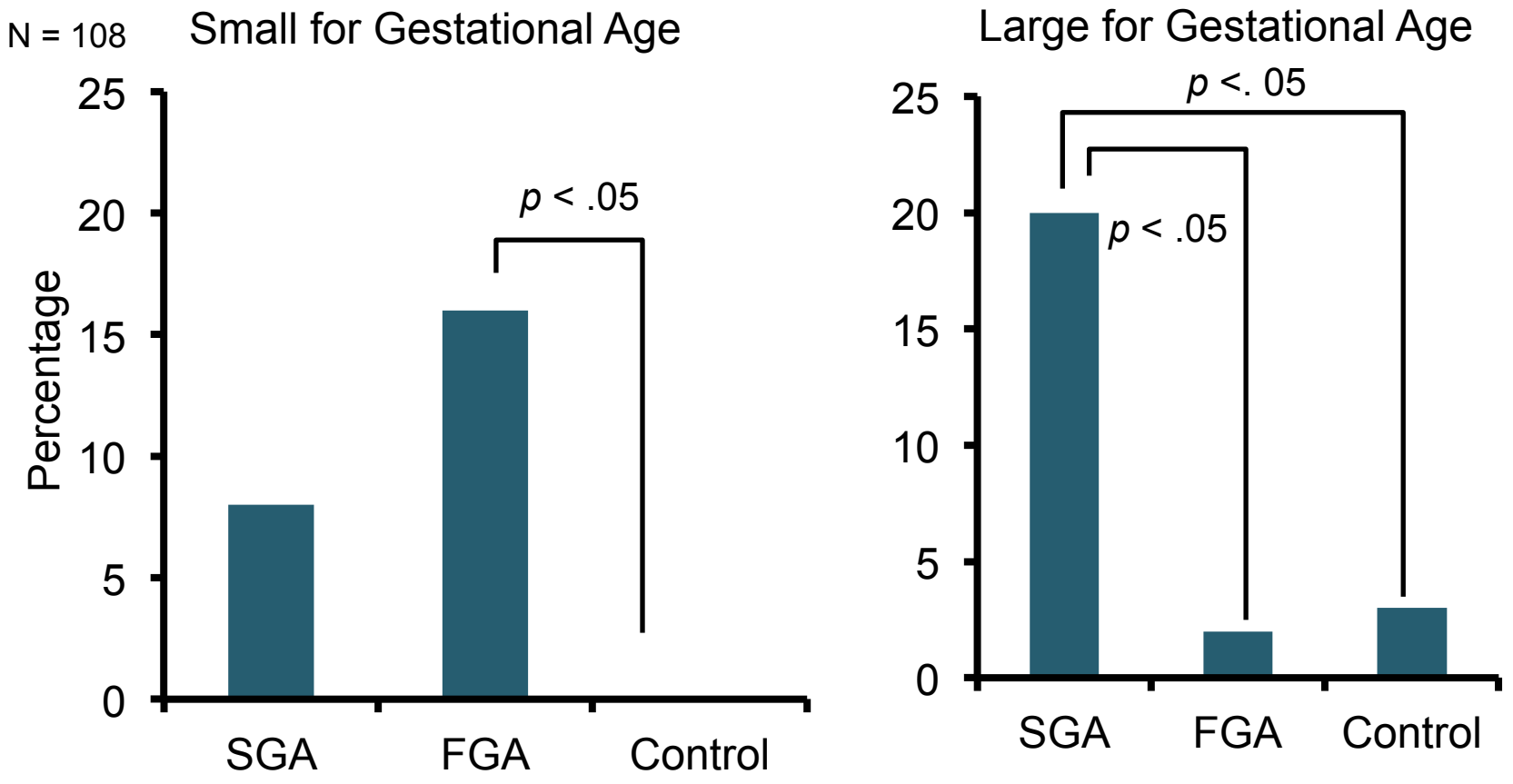




[1]Newham JJ et al. *Br J Psychiatry* 2008; 192(5): 333-337.
[2]Babu GN et al. *J Psychopharmacol* 2010;30(3):331-332.

Prenatal Antipsychotic Exposure

Metabolic Effects: Birth Weight



Newham JJ, et al. *Br J Psychiatry* 2008;192:333-337.

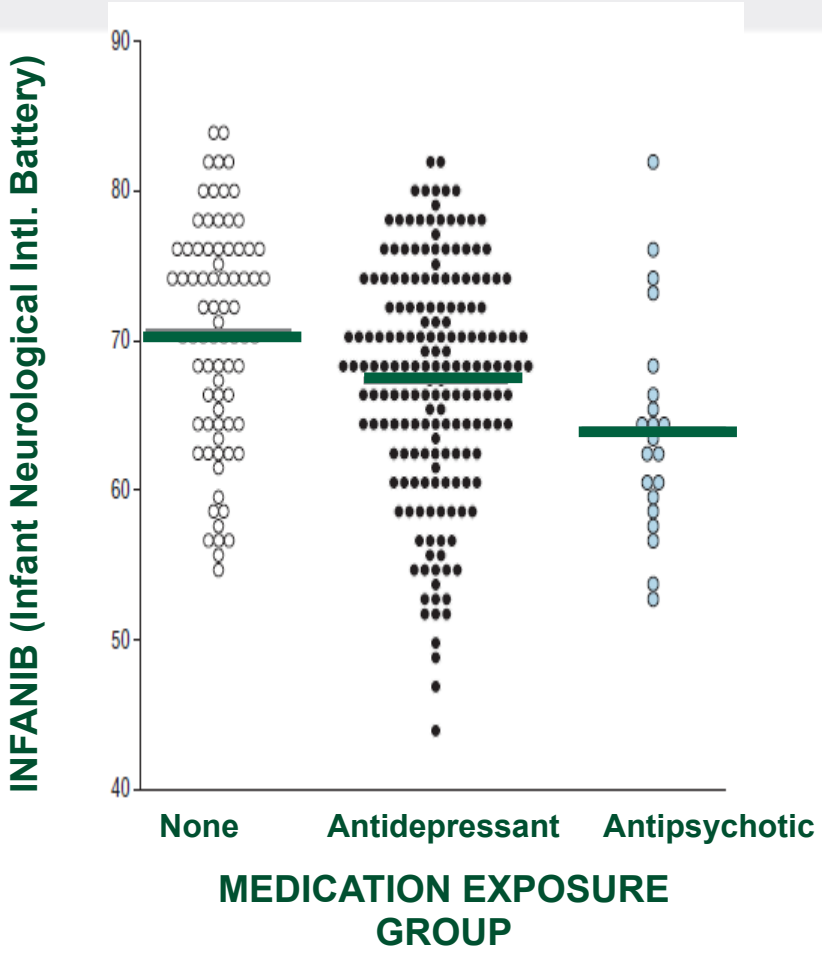
Prenatal Antipsychotic Exposure

Preterm Birth

Source	OR / Pct.	95% CI
McKenna K, et al. *J Clin Psychiatry* 2005;66(4):444-449.	(SGA vs CTL) 1.19	0.79 – 1.80
Reis M, Kallen B. *J Clin Psychopharmacol* 2008;28(3):279-288.	(APSY vs CTL) 1.73	1.31 – 2.29
Haberman F, et al. *J Clin Psychopharmacol* 2013;33(4):453-462.	(SGA vs CTL) 1.96 (SGA vs FGA) 0.54	1.29 – 2.98 0.33 – 0.87
Brunner E, et al. *BMC Pharmacol Toxicol* 2013;14:1-8.	(OLZ) 9.8%	

Prenatal Antipsychotic Exposure

Neuromotor Performance at 6 Months



Exposure Group	INFANIB CLINICAL OUTCOME (n, %)		
	Normal	Transiently Abnormal	Abnormal
None	39 (50.0)	39 (50.0)	0 (0.0)
Antidepressant	59 (32.4)	113 (62.1)	11 (6.0)
Antipsychotic	4 (19.0)	15 (71.5)	2 (9.5)

Measure	FGA	SGA
N	9	12
INFANIB Mean (SE)	67.1 (1.84)	62.9 (1.60)

N = 309

Johnson KC, et al. *Arch Gen Psychiatry* 2012;69(8):787-794.

Prenatal Antipsychotic Exposure
Neurobehavioral Profiles at 2, 6, 12 Months

Bayley III Scales		SGA Exposed N = 76	Control N = 76	t	p
Cognitive	**2 Months**	**90.33 (6.92)**	**97.84 (7.74)**	**39.74**	**<.001**
	6 Months	99.03 (8.26)	101.42 (6.96)	3.74	.055
	12 Months	100.99 (8.17)	103.11 (7.84)	2.66	.105
Language	2 Months	94.43 (7.51)	96.18 (7.67)	2.02	.157
	6 Months	95.72 (7.28)	97.00 (7.16)	1.19	.278
	12 Months	97.26 (6.79)	98.18 (7.18)	0.66	.418
Motor	**2 Months**	**92.28 (7.89)**	**97.53 (7.67)**	**17.37**	**<.001**
	6 Months	100.46 (9.29)	102.79 (6.64)	3.16	.078
	12 Months	101.59 (8.53)	103.68 (7.19)	2.68	.104
Social Emotional	**2 Months**	**95.68 (9.38)**	**101.89 (8.67)**	**17.95**	**<.001**
	6 Months	**99.41 (9.97)**	**103.59 (8.71)**	**7.59**	**.007**
	12 Months	102.54 (9.72)	104.50 (8.63)	1.73	.191
Adaptive Behavior	**2 Months**	**93.14 (8.63)**	**99.32 (6.29)**	**25.38**	**<.001**
	6 Months	**97.57 (8.44)**	**100.66 (6.04)**	**6.74**	**.010**
	12 Months	99.80 (8.56)	101.24 (5.83)	1.46	.229

N = 152

Peng M, et al. *Psychopharmacology* 2013;228(4):577-584.

Audience Response

Both maternal depression during pregnancy and maternal use of antidepressants during pregnancy have been associated with all of the following EXCEPT:

A. Increased risk for preterm delivery
B. Increased use of tobacco during pregnancy
C. Increased risk for newborn complications
D. Increased risk for low birthweight
E. Possible developmental consequences for the child

Audience Response

Which of the following CNS agents has been most consistently shown to carry risks for both birth defects and adverse neurodevelopmental effects?

A. Lithium
B. Lamotrigine
C. Divalproex
D. Fluoxetine
E. Olanzapine

Thank You