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ADHD in Pregnancy: Trying To Focus On Safety Of Mom and Baby

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What Is ADHD?

- Attention-deficit/hyperactivity disorder (ADHD)
- Patients show a persistent pattern of inattention and/or hyperactivity–impulsivity that interferes with functioning or development
  - DSM 5 (see later slide) has more defining details
- One of the most common neurobehavioral disorders of childhood
  - 2022 CDC data: 7 million (11.4%) U.S. children age 3-17 have the diagnosis
- Up to 60% of children with ADHD will continue to have symptoms as adults
  - 2023 CDC data: 15.5 million (6.0%) U.S. Adults have the diagnosis
- Common comorbid conditions include:
  - Depression, anxiety, substance misuse, impaired functioning, oppositional defiant disorder (ODD), bipolar, personality disorders

BMC Psychiatry 20, 404 (2020).
CDC. Data and Statistics on ADH
J Clin Child Adolesc Psychol. 2024 May-Jun;53(3):343-360.
Journal of Attention Disorders, *26*(2), 143-148.
Kessler et al. *Biol Psychiatry*. 2005
National Institutes of Mental Health. (ADHD)
NS Drugs. 2024 Apr;38(4):303-314.

Pathophysiology

Neuroimaging

- Structural brain differences
- Most common findings:
  - Smaller pre-frontal, parietal circuits
- Dysfunction also found in:
  - Caudate*
  - Putamen*
  - Globus pallidus*

*Subcortical brain structures for motor control, inhibition of behavior, executive functions, modulation of reward pathways.

Neurotransmitters

- Hypoactivity of dopamine, norepinephrine
- Norepinephrine/Noradrenaline
  - Brain: cognitive function, attention,
  - Periphery: vasoconstriction (↑ blood pressure)
  - Heart: increase rate and contraction force
- Dopamine
  - Brain: pleasure motivation, reward
  - Periphery/heart: ↑ blood pressure
  - Metabolic: changes in food intake/glucose control

StatPearls . Dopamine
StatPearls. Physiology, Noradrenergic Synapse

Genetics

- Heritability has been estimated at 71-90%
- Studies have shown several genes that can contribute to ADHD (effect appears small)
- Polymorphisms (variations on DNA sequences) found in dopamine transporters are often associated with ADHD
- Likely a complex interaction between genetics and environmental factors that contribute to the condition

StatPearls. Physiology, Noradrenergic Synapse
J Child Psychol Psychiatry. 2013 Jan;54(1):3-16.

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DSM 5 CRITERIA

- PRESENT IN AT LEAST 2 SETTINGS; MUST HAVE IMPAIRMENT IN FUNCTIONING

Inattention:

6 + (5 if 17 years +) and > 6 months

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

Hyperactivity:

6 + (5 if 17 years +) and > 6 months

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

CDC. Diagnosis ADHD.
National Institutes of Mental Health. (ADHD)

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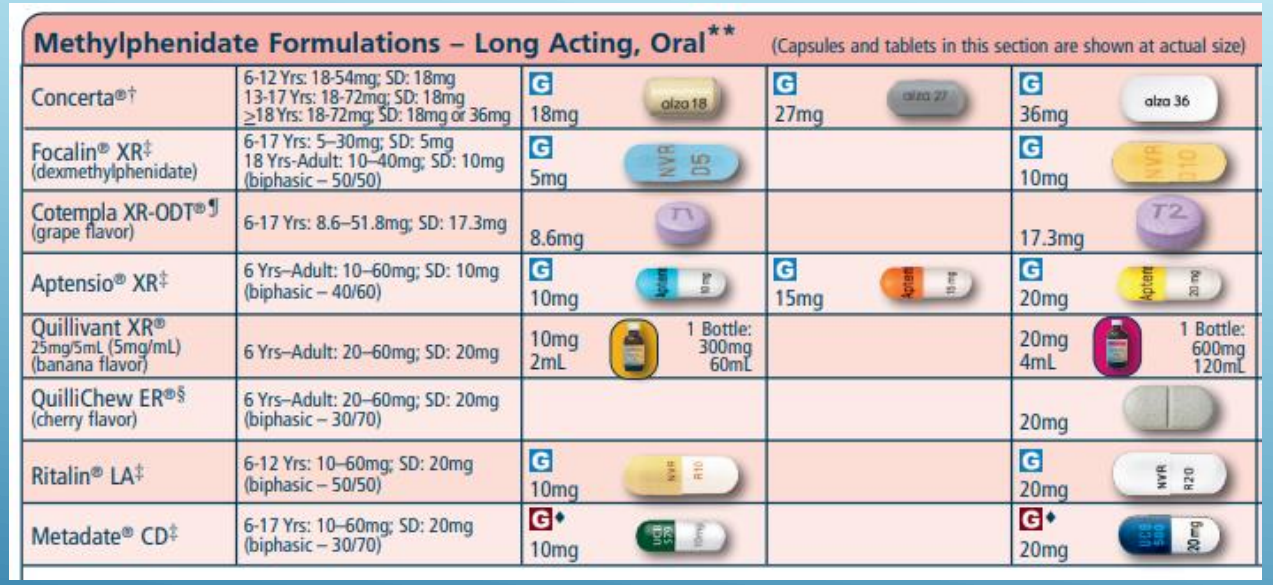
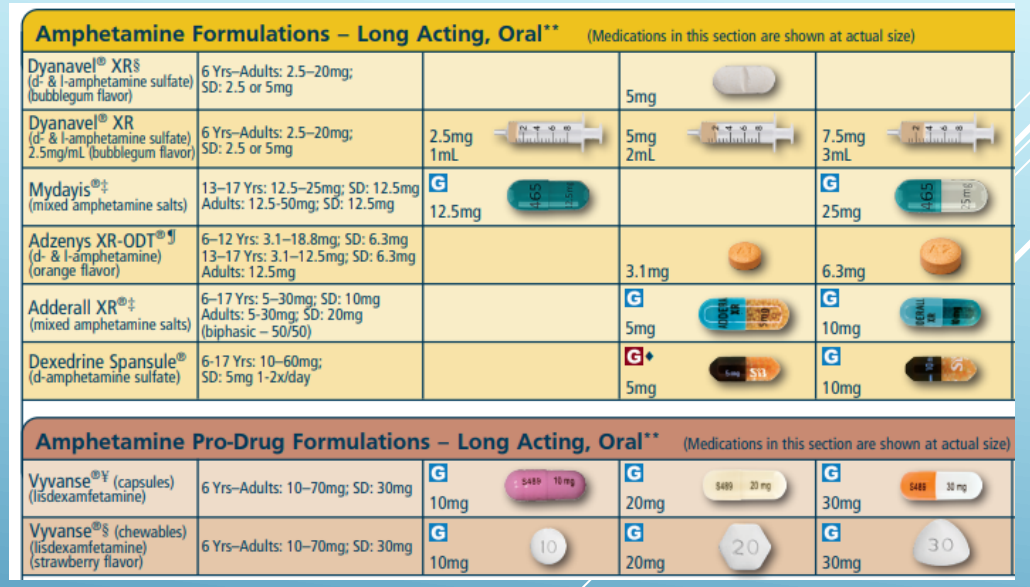
Treatment

- **Combination Cognitive-Behavioral Therapy (CBT) + Medications**
- **First line Medications: Stimulants**
  - **Methylphenidate (e.g. Concerta, Ritalin)**
  - **Amphetamine Salts (e.g. Adderall, Vyvanse)**



Methylphenidate Formulations – Long Acting, Oral** (Capsules and tablets in this section are shown at actual size)

Concerta®†	6-12 Yrs: 18-54mg; SD: 18mg 13-17 Yrs: 18-72mg; SD: 18mg ≥18 Yrs: 18-72mg; SD: 18mg or 36mg	G 18mg	G 27mg	G 36mg
Focalin® XR‡ (dexmethylphenidate)	6-17 Yrs: 5–30mg; SD: 5mg 18 Yrs-Adult: 10–40mg; SD: 10mg (biphasic – 50/50)	G 5mg		G 10mg
Cotempla XR-ODT®¶ (grape flavor)	6-17 Yrs: 8.6–51.8mg; SD: 17.3mg	8.6mg		17.3mg
Aptensio® XR‡	6 Yrs–Adult: 10–60mg; SD: 10mg (biphasic – 40/60)	G 10mg	G 15mg	G 20mg
Quillivant XR® 25mg/5mL (5mg/mL) (banana flavor)	6 Yrs–Adult: 20–60mg; SD: 20mg	10mg 2mL 1 Bottle: 300mg 60mL		20mg 4mL 1 Bottle: 600mg 120mL
QuilliChew ER®§ (cherry flavor)	6 Yrs–Adult: 20–60mg; SD: 20mg (biphasic – 30/70)			20mg
Ritalin® LA‡	6-12 Yrs: 10–60mg; SD: 20mg (biphasic – 50/50)	G 10mg		G 20mg
Metadate® CD‡	6-17 Yrs: 10–60mg; SD: 20mg (biphasic – 30/70)	G♦ 10mg		G♦ 20mg



Amphetamine Formulations – Long Acting, Oral** (Medications in this section are shown at actual size)

Dyanavel® XR§ (d- & l-amphetamine sulfate) (bubblegum flavor)	6 Yrs–Adults: 2.5–20mg; SD: 2.5 or 5mg		5mg	
Dyanavel® XR (d- & l-amphetamine sulfate) 2.5mg/mL (bubblegum flavor)	6 Yrs–Adults: 2.5–20mg; SD: 2.5 or 5mg	2.5mg 1mL	5mg 2mL	7.5mg 3mL
Mydayis®‡ (mixed amphetamine salts)	13–17 Yrs: 12.5–25mg; SD: 12.5mg Adults: 12.5-50mg; SD: 12.5mg	G 12.5mg		G 25mg
Adzenys XR-ODT®¶ (d- & l-amphetamine) (orange flavor)	6–12 Yrs: 3.1–18.8mg; SD: 6.3mg 13–17 Yrs: 3.1–12.5mg; SD: 6.3mg Adults: 12.5mg		3.1mg	6.3mg
Adderall XR®‡ (mixed amphetamine salts)	6–17 Yrs: 5–30mg; SD: 10mg Adults: 5-30mg; SD: 20mg (biphasic – 50/50)		G 5mg	G 10mg
Dexedrine Spansule® (d-amphetamine sulfate)	6-17 Yrs: 10–60mg; SD: 5mg 1-2x/day		G♦ 5mg	G 10mg

Amphetamine Pro-Drug Formulations – Long Acting, Oral** (Medications in this section are shown at actual size)

Vyvanse®¥ (capsules) (lisdexamfetamine)	6 Yrs–Adults: 10–70mg; SD: 30mg	G 10mg	G 20mg	G 30mg
Vyvanse®§ (chewables) (lisdexamfetamine) (strawberry flavor)	6 Yrs–Adults: 10–70mg; SD: 30mg	G 10mg	G 20mg	G 30mg

Abbreviated chart shown above, full chart available at: adhdmedicationguide.com
Dose Calculator/Converter available at: adhdmedcalc.com

CDC. Diagnosing ADHD.
National Institutes of Mental Health. (ADHD)

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Treatment Continued

- **Second Line:**
  - **Non-stimulants**
    - **Guanfacine**
    - **Clonidine**
    - **Atomoxetine**
    - **Viloxazine**
- **Off-label:**
  - **Bupropion**

Non-Stimulants** (Medications in this section are shown at actual size)

Onyda™ XR (clonidine, extended release) (orange flavor)	6–17 Yrs: 0.1-0.4mg; SD: 0.1mg (dosed at bedtime)	0.1mg/1mL	0.2mg/2mL	0.3mg/3mL	0.4mg/4mL
Kapvay®† (clonidine, extended release)	6–17 Yrs: 0.1-0.2mg BID; SD: 0.1mg qHS	G 0.1mg			
Intuniv®† (guanfacine, extended release)	6–12 Yrs: 1-4mg; SD: 1mg 13–17 Yrs: 1-7mg; SD: 1mg Weight-based dosing: SD: 0.05-0.08 mg/kg/day; may increase to 0.12 mg/kg/day	G 1mg	G 2mg	G 3mg	G 4mg
Strattera®† (atomoxetine)	≤70kg: 0.5mg/kg x ≥3days, then 1.2mg/kg (max:1.4mg/kg, not to exceed 100mg) >70 kg: 40mg x ≥3days, then 80mg (max:100mg)	G 10mg	G 18mg	G 25mg	G 40mg
Qelbree®‡ (viloxazine)	6–11 Yrs: 100-400mg; SD: 100mg 12–17 Yrs: 200-400mg; SD: 200mg Adults: 200-600mg; SD: 200mg	100mg SPN 100	200mg SPN 200	300mg SPN 150 + SPN 150	

Abbreviated chart shown above, full chart available at: adhdmedicationguide.com

ADHD in Women

- ADHD diagnosis is increasing
  - CDC 2016 data 4.4% vs 2024 data 6.0% of adults had diagnosis
- One in 30 women is affected
- Medication use is increasing
  - Study compared Apr 2018 – Mar 2020 to Apr 2020 – Mar 2022 RXs filled

Stimulants	Non-stimulants
14% overall increase	32% overall increase
30% increase in ages 20-39	81% increase in ages 20-39
25% increase women (vs 4% male)	59% increase in women (vs 15% male)

JAMA Psychiatry. 2024;81(4):396–405.
Journal of Attention Disorders, *26*(2), 143-148.
CNS Drugs. 2024 Apr;38(4):303-314.
Pharmacoepidemiology and Drug Safety 2014; 23: 526–533.

ADHD in Women

- Sex difference prevalence found in the literature
  - Approximately 3:1 boys to girls
- Clinical referrals for boys are higher 3:1-16:1 depending on the report
  - Likely leading to undertreatment in females
- Growing evidence females present differently, resulting in undertreatment

BMC Psychiatry 20, 404 (2020).

ADHD in Women

- ADHD Symptom differences in females (only some listed):
  - Inattention in girls and women with ADHD may present as being easily distracted, disorganized, overwhelmed and lacking in effort or motivation.
  - Symptoms may be exacerbated by hormonal changes during menstrual cycle, pregnancy and menopause.
  - Internalizing symptoms secondary to, or comorbid with ADHD may be misinterpreted as primary conditions. Low mood, emotional lability, or anxiety may be especially common in females with ADHD.
- In one study (pregnant patients), compared with the reference group, women with ADHD (both medicated and non-medicated) were more likely:
  - To be younger, single, have less education, low income, take comedication, have comorbidity, smoke, and be nulliparous

BMC Psychiatry 20, 404 (2020).
Clin Epidemiol. 2015 Jan 29;7:139-47

ADHD Medication Use in Women

- Unintended pregnancies in the United States
  - 43.3% in 2010, 41.6% in 2019
- Medication use is increasing
  - Pregnant patients aged 15-44 (US data): 0.9% in 2003, 4% in 2015
  - Danish study: 2003–2010 increased 5 per 100k person years to 533
- Safety of medication in pregnancy/lactation is lacking
- Current data is not well disseminated into health care system, reducing latest recommendations and counseling points

CDC. Vital Health and Statistics.
CNS Drugs. 2024 Apr;38(4):303-314.
Pharmacoepidemiology and Drug Safety 2014; 23: 526–533.

Medication Use in Pregnancy

- Default medical position is often to avoid all medication in pregnancy and lactation assuming the safest option
  - Two patients are being treated and their outcomes are often intertwined
- A careful risk-benefit analysis with a patient and provider should be completed
  - Risks of medication exposure should be weighed against risks of untreated ADHD
- Commonly overlooked issues with untreated ADHD
  - Driving safety
  - Occupational role
  - Domestic role
  - Comorbid mental health conditions

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Categories of Risk to Review

- Congenital Malformations (gets the most press)
- Gestational and Neonatal Outcomes
- Neurobehavioral Outcomes
- Risk of Untreated Condition

Patient Case – "Kate"

- 33 y/o female
- Newly pregnant G1P0
- Current Medications:
  - Mixed amphetamine salt (Adderall) XR 20 mg daily for ADHD
- Pt currently well controlled but was advised by her physician, "You cannot take that in pregnancy and I will not prescribe it."
- Pt recently lost her job and feels like she can do without the medication at this time

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Congenital Malformation Data

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The Old Data – Methylphenidate (N ~ 469)

Briggs, G. G., Freeman, R. K., Towers, C. V., & Forinash, A. B. (2017). Drugs in pregnancy and lactation: A reference guide to fetal and neonatal risk (online ed.) "Methylphenidate." Last updated 6/3/22.

Study/Source	Date	N (size)	Exposure	Results
Publishing Sciences Group, 1977:346–7.	Published 1977	11	Methylphenidate	No increased malformation
Michigan Medicaid	Published 1993	13	Methylphenidate, 1st trimester	1 major birth defect observed (7.7%)(one expected) and 1 cardiovascular defect (none expected)
Lancet 1962;1:1270–3.	Published 1962	1	Methylphenidate 3rd-6th week	Microtia
JAMA 1975;231:62–4.	Published 1975	1	First 7 weeks: haloperidol, methylphenidate, phenytoin	Delivered at 30 weeks, multiple congenital limb malformations, aortic valve defect, infant died at 2 hours (subdural hemorrhage)
Am J Dis Child 1993;147:1062–5.	Published 1993	39 (1 set of twins)	IV pentazocine, methylphenidate abuse, cigarettes, alcohol, other drugs of abuse common	8 were delivered prematurely, 12 were growth restricted, and 11 had withdrawal symptoms. 4 had birth defects (twins) fetal alcohol syndrome, 1 ventricular septal defect,1 case of polydactyly. Of the 21 infants that had formal developmental testing, 17 had normal development and 4 had low-normal developmental quotients
J Clin Psychol 2014;75:e88–93.	Published 2014	222; 2200 controls	Methylphenidate 1st trimester	No difference found
J Clin Psychiatry 2016;77:1176–81.	Published 2016	382	Methylphenidate (90% 1st trimester)	No association with malformations or cardiovascular malformations (higher elective abortion in med group)

The Old Data – Amphetamine (N ~ 5000)

Briggs, G. G., Freeman, R. K., Towers, C. V., & Forinash, A. B. (2017). Drugs in pregnancy and lactation: A reference guide to fetal and neonatal risk (online ed.) "Amphetamine." Last updated 5/23/22.

Study/Source	Date	N (size)	Exposure	Results
Lancet 1965;2:1021–2.	Published 1967	219 153	219 infants w/ heart defects compared to 153 controls	No increased risk
Lancet 1967;1:570–1.	Published 1970	184 108	184 infants w/ heart defects compared to 108 controls	Increased risk heart defects. Exposure to dextroamphetamine (18% vs. 8%, $p < 0.05$), exposure during the vulnerable period (11% vs. 3%, $p = 0.025$), and positive family history of congenital heart disease (27% vs. 6%, $p < 0.001$).
Lancet 1970;1:1290–1.	Published 1962	31 1st trimester 34 later trimesters	Appetite suppressants (often dextroamphetamine)	8 (3.3%) had major congenital heart defect (similar to expected in US)
Int Surg 1968;50:79–85.	Published 1968	1	20-30 mg dextroamphetamine daily throughout pregnancy	Bifid exencephalia (infant died during surgical correction)
J Pediatr 1970;76:638.	Published 1970	1	Dextroamphetamine daily	Full term, infant died 6 days later of congenital heart defect
J Pediatr 1971;79: 130–1.	Published 1971	11; 50 controls	Biliary atresia (amphetamine exposure retrospective)	Exposure in 5 of study and 3 of controls
JAMA 1966;197:62–3.	Published 1966	4	Methamphetamine and phenobarbital (different pregnancies, same mother)	Microcephaly, mental retardation, motor dysfunction in 1st/3rd, 2nd spontaneous abortion, 4th no medication, healthy child

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Amphetamine Continued

Briggs, G. G., Freeman, R. K., Towers, C. V., & Forinash, A. B. (2017). Drugs in pregnancy and lactation: A reference guide to fetal and neonatal risk (online ed.) "Amphetamine." Last updated 5/23/22.

Study/Source	Date	N (size)	Exposure	Results
LSD. *Am J Dis Child* 1972;123:145–8.	Published 1972	1	Amphetamines, LSD, meprobamate, marijuana	Multiple brain, eye anomalies
Br Med J 1971;1:523–7.	Published 1971	175 major 283 minor 911 controls	184 infants w/ heart defects compared to 108 controls	Dextroamphetamine consumption accounted for 13 of the 18 maternal exposures in the anomaly group. During the first 56 days of pregnancy, dextroamphetamine-containing compounds were used by 10 mothers in the anomaly group compared with only 5 of the controls (2.2% vs. 0.5%; $p < 0.05$). The abnormalities (3 major and 7 minor) observed in the 10 infants were urogenital system defects (4 cases), and 1 case each of congenital heart disease, cleft lip, severe limb deformity, accessory auricles, congenital dislocation of hip, and pilonidal sinus.
Am J Obstet Gynecol 1977;129:637–42.	Published 1977	1824 8989 controls	Appetite suppressants compared to control	3.7% (Study) and 3.4% (control) severe congenital anomalies. except for three infants with cleft lip and/or palate, no pattern of malformations was observed.
Acta Paediatr Scand 1980;69:675–80.	Published 1978-81	71	Amphetamine, some alcoholics	1 stillborn w/ myelomeningocele, 1 extensive telangiectasis, 6 pre-term, 3 small for gestational age, 1 seizure. 2 intestinal atresia (both died, 1with hydrocephalus), congenital heart defect (1 case), epidermolysis bullosa (1 case). In one of the four cases, the mother was an alcoholic. Drowsiness was observed in 8 infants and jitteriness in 11 infants; 4 full-term infants required tube feedings.

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Amphetamine Continued

Briggs, G. G., Freeman, R. K., Towers, C. V., & Forinash, A. B. (2017). Drugs in pregnancy and lactation: A reference guide to fetal and neonatal risk (online ed.) "Amphetamine." Last updated 5/23/22.

Study/Source	Date	N (size)	Exposure	Results
Collaborative Perinatal Project: Littleton, MA: Publishing Sciences Group, 1977.	Published 1977	671 1st trimester, 1898 any	Amphetamines	No increased risk of major or minor malformations; 2 cases of high dose for narcolepsy found no effects
Lancet 1992;339:1416–7.	Published 1992	1	Lovastatin Dextroamphetamine	Multiple malformations termed VATER association
Obstet Gynecol 1988;72:541–4.	Published 1988	52 study 52 controls	IV meth, multiple other exposures heroin, opium, LSD, alcohol, etc	No difference obstetric complications Birth weight, length, head circumference lower in study group. 6 (12%) study group had congenital defects vs 7(14%) control group
Am J Obstet Gynecol 1992;166:353.	Published 1992	48 519 controls	Abuse of methamphetamine with multiple other exposures	Lower birth rate only difference in study
BMJ 1992;304:548.	Published 1992	1	500 mg amphetamine injected	Mother had toxic signs; 24 hours later stillborn infect without congenital abnormalities delivered
Am J Dis Child 1963;106:325–30.	Published 1963	4	"addicted to amphetamines"	Shrill cries, irritability, jerking, sneezing in 2 infants

Amphetamine Continued

Study/Source	Date	N (size)	Exposure	Results
J Pediatr 1989;115:770–8.	Published 1989	32	Methamphetamine	One case of absent septum pellucidum, same infant had bilateral optic nerve atrophy and diffused attenuation of the white matter
J Obstet Gynaecol Br Commonw 1970;66:1117–22.	Published 1970	4	Methamphetamine	1 newborn with drowsiness for 4 days
Clin Pediatr 1974;13:596–7.	Published 1974	1	"Known amphetamine addict"	Infant at 6 hours started having diaphoresis, agitation alternating with lassitude and anpea, seizure on day 6; 3 months of slow development, but no evidence of neurologic issues at 2.5 years

Newer Data – 2017 JAMA Psychiatry

Association Between Methylphenidate and Amphetamine Use in Pregnancy and Risk of Congenital Malformations: A Cohort Study From the International Pregnancy Safety Study Consortium

- 1.8 million pregnancies in the US and 2.6 million in Nordic Countries
  - 2072 infants exposed to methylphenidate, 5517 to amphetamines
- US Data congenital malformation absolute risks:
  - 35.0 per 1000 or 3.5% (95% CI 34.8-35.3) - not exposed
  - 45.9 per 1000 or 4.59% (95% CI 37.7-55.7) - methylphenidate exposed
  - 45.4 per 1000 or 4.54% (95% CI 40.3-51.2) - amphetamine exposed
- US data cardiac malformation absolute:
  - 12.7 per 1000 or 1.27% (95% CI 12.6-12.9) – not exposed
  - 18.8 per 1000 or 1.88% (95% CI 13.8-25.6) – methylphenidate exposed
  - 15.4 per 1000 or 1.54% (95% CI 12.5-19.0) – amphetamine exposed

JAMA Psychiatry: 2018 Feb 1;75(2):167-175.

JAMA Psychiatry Continued

- US Data:
  - When controlled for confounders (ie maternal psychiatric illness) – IT WAS NOT SIGNIFICANT!
  - Methylphenidate
    - 1.11 (95% CI 0.91-1.35) any malformation
    - 1.28 (95% CI 0.94-1.74) cardiac
  - Amphetamines
    - 1.05 (95% CI 0.93-1.19) any malformation
    - 0.96 (95% CI 0.78-1.19) cardiac
- Nordic Data:
  - Methylphenidate cardiac malformations 1.28 (95% CI 0.83-1.97), not statistically significant!
- US combined with Nordic Data:
  - 1.28 (95% CI 1.00-1.64) trend towards statically significant

JAMA Psychiatry: 2018 Feb 1;75(2):167-175.

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What Do All the Numbers Mean?

- 28% relative increased risk for cardiac malformations with 1st trimester exposure to methylphenidate
- Absolute risk (unadjusted data):
  - 1.27% (baseline risk) – 13 infants per 1000
  - 1.88% with methylphenidate exposure – 19 infants per 1000
  - Number Needed to Harm (NNH): 164
- No statistically significant risk with methylphenidate and congenital malformations overall
- No statistically significant risk with amphetamines and congenital malformations overall or cardiac malformations

MGH. Good News: More Data on the Use of ADHD Medications During Pregnancy

Newer Data Continued

Study	N (size)	Exposure	Results
J Clin Psychiatry 2021;82(1):20m13458	364,012 569 exposed	ADHD Meds: Dexamphetamine, methylphenidate, modafinil, atomoxetine, lisdexamphetamine	Majority of exposures methylphenidate (473/569, 83%) ***Any malformation:*** 5.1% (exposed), 4.6% (unexposed); 1.10 (95% CI 0.77-1.57) ***Any cardiac*** 2.1% (exposed), 1.0% (unexposed); 2.05 (95% CI 1.17-3.59), NNH 92 (cardiac) ***Adjusted***: any malformations 1.04 (95% CI 0.70-1.55), cardiac 1.65 (95% CI 0.89-6.90) ***For methylphenidate (adjusted):*** 1.04 (95% CI 0.70-1.55) for all malformations, 1.65 (95% CI 0.89-3.05) for cardiac malformations, NNH = 92. Septum defects 10 out of 12 cases. Ventricular defects 27.4 (1.03-7.28), Severe cardiac malformation 2.59 (0.98-6.90)
J Clin Psychiatry 2016;77(9):1176-1181	382 exposed 382 controls	Methylphenidate	Major anomalies 3.2% (exposed), 3.6% (unexposed); 0.89 (95% CI 0.40-2.00) Cardiovascular anomalies 0.8% (exposed), 0.8% (unexposed), 0.96 (95% CI 0.16-5.7)

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Gestational and Neonatal Outcomes

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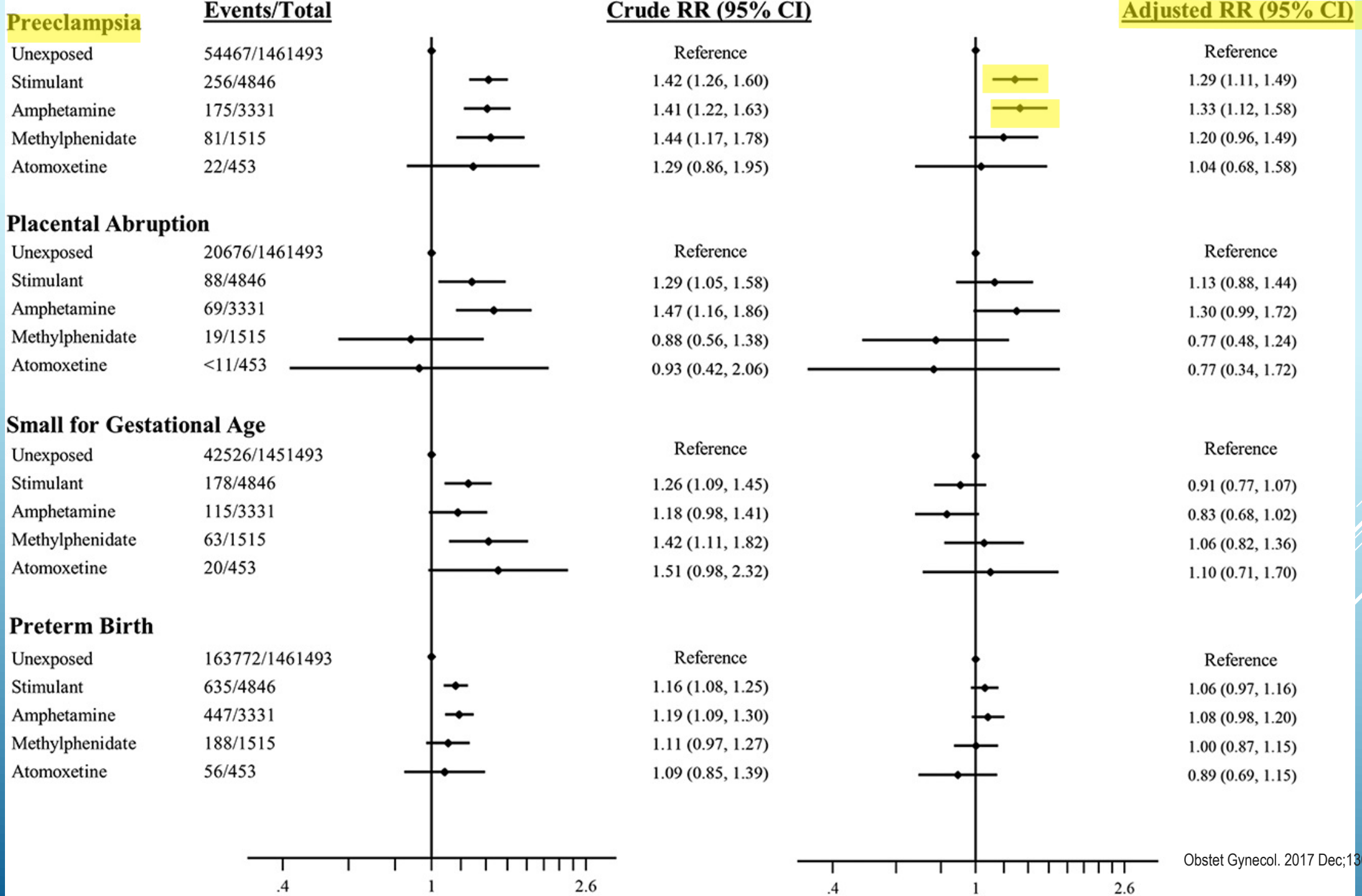
Gestational/Neonatal Outcomes

Study	N (size)	Exposure	Results
Pediatrics. 2017 Dec;140(6):e20170747.	964,734 infants 1591 exposed	methylphenidate amphetamine dexamphetamine Lisdexamfetamine modafinil atomoxetine	**Increased risk NICU** AOR, 1.5; 95% CI, 1.3–1.7 (exposed to no use) AOR, 1.2; 95% CI, 1.1–1.4 (exposed to use before/after) **Central nervous system-related disorders** AOR, 1.9; 95% CI, 1.1–3.1 (exposed to both groups) **Preterm (moderately):** AOR, 1.3; 95% CI, 1.1–1.6 (exposed to both groups) ***Authors note significant difference in characteristics of exposed women and controls***
J Clin Psychiatry. 2016	382	Methylphenidate (MPH)	**Increased rate miscarriages (and terminations)** in the MPH group. Predictors of miscarriages: MPH exposure (AHR = 1.98; 95% CI, 1.23-3.20; P = .005) Past miscarriage (AHR = 1.35; 95% CI, 1.18-1.55; P < .001)
Clin Epidemiol. 2015 Jan 29;7:139-47.	989,932 pregnancies 186 exposed	Methylphenidate Atomoxetine (Had ADHD dx without exposure cohort)	**SAB:** ARR 1.55, 95% CI 1.03–2.36 (exposed + ADHD) ARR 1.56, 95% CI 1.11–2.20 (not exposed + ADHD) **Apgar scores <10** ARR 2.06, 95% CI 1.11–3.82 (exposed + ADHD) ARR 0.99, 95% CI 0.48–2.05 (not exposed + ADHD)
Pharmacoepidemiology and Drug Safety 2014; 23: 526–533.	1,054,494 pregnancies 480 exposed	ADHD medications: methylphenidate, modafinil, atomoxetine	Among women with an ADHD diagnosis, **induced abortion** on maternal request (OR = 2.17, 95%CI = 1.35–3.48) and **miscarriage** (OR = 1.69, 95%CI =0.79–3.61) occurred more frequent in the pregnancies exposed to ADHD medication compared with unexposed pregnancies.
Obstetrics & Gynecology 130(6):p 1192-1201, December 2017	1,461,493 controls 3,331 amphetamine 1,515 methylphenidate 452 atomoxetine	Amphetamine/Dextroamph Methylphenidate Atomoxetine	***See next slide***



Obstet Gynecol. 2017 Dec;130(6):1192-1201.

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Neurobehavioral Outcomes

Neurobehavioral Outcomes

Study	N (size)	Exposure	Results
Neuroimage. 2009;48(2):391-397.	52 exposed 92 controls	Methamphetamine 70% all 3 trimesters 8% during 2 trimesters 22% during 1st trimester only	Lower performance on visual motor integration (VMI) No other cognitive performance differences at 3-4 years
Mol Psychiatry. 2023 Apr;28(4):1739-1746.	1,068,073 pregnancies 890 exposed during pregnancy 1270 stopped before pregnancy	Methylphenidate (703) Amphetamine, Dexamphetamine, Lisdexamfetamine (20) Modafinil, Clonidine (50) Atomoxetine (125)	Adjusted HR developmental disorders 0.97, 95% CI 0.81 to 1.17, not significant **All medications listed together providing more data on methylphenidate than others
JAMA Psychiatry Published Online: January 24, 2024 2024;81;(5):477-488.	2,496,771 controls 4693 amp/dex 786 methylphenidate	Amphetamine, dexamphetamine Methylphenidate	Unadjusted data: medications associated with 2-3 fold increased risk of neurodevelopment disorders ***Adjusted:*** ***Amp/dex = none significant*** Austism: HR, 0.80; 95% CI, 0.56-1.14 ADHD: HR, 1.07; 95% CI, 0.89-1.28 Any neurodev disorder: HR, 0.91; 95% CI, 0.81-1.28 ***Methylphenidate*** ADHD: HR, 1.43; 95% CI, 1.12-1.82* Autism: HR, 1.06; 95% CI, 0.62-1.81 (significant) Any neurodev disorder: HR, 1.15; 95% CI, 0.97-1.36 *The association between methylphenidate and ADHD did not persist in sensitivity analyses with stricter control for confounding by maternal ADHD.

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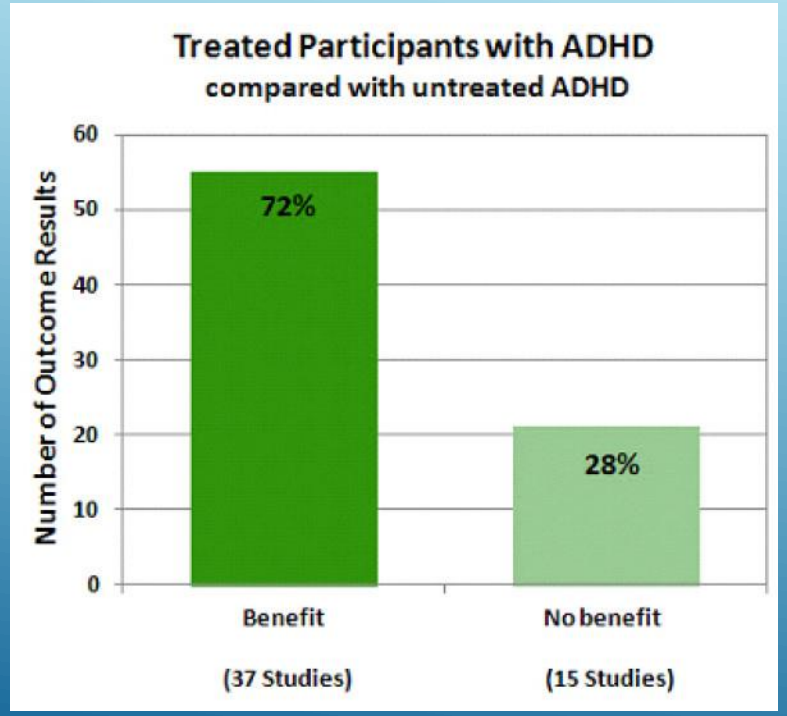
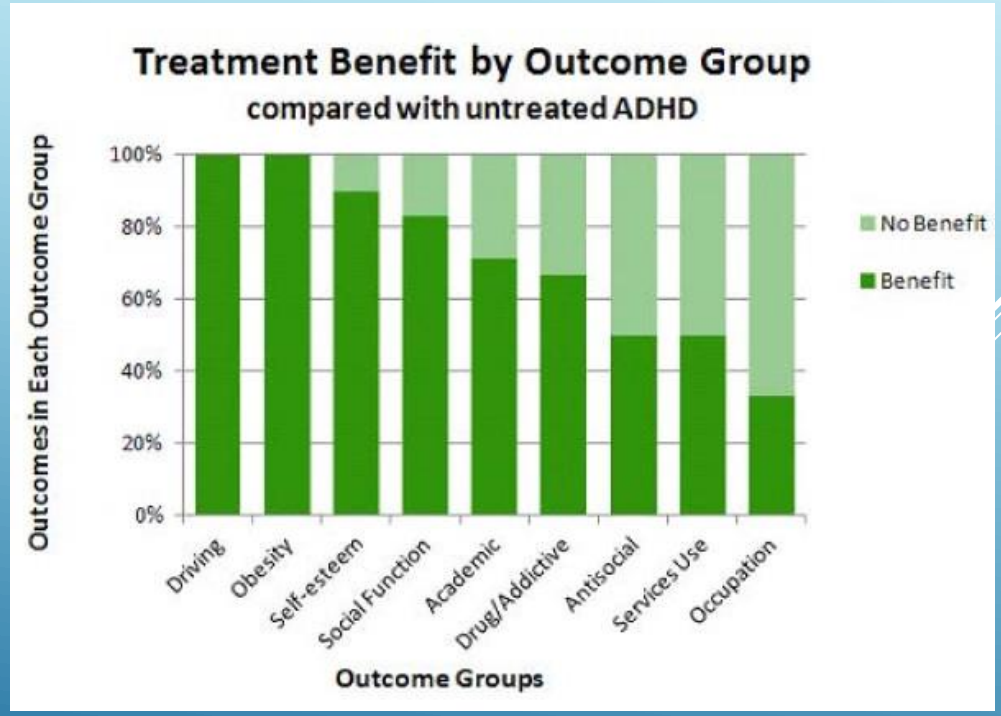
The Condition

Untreated ADHD

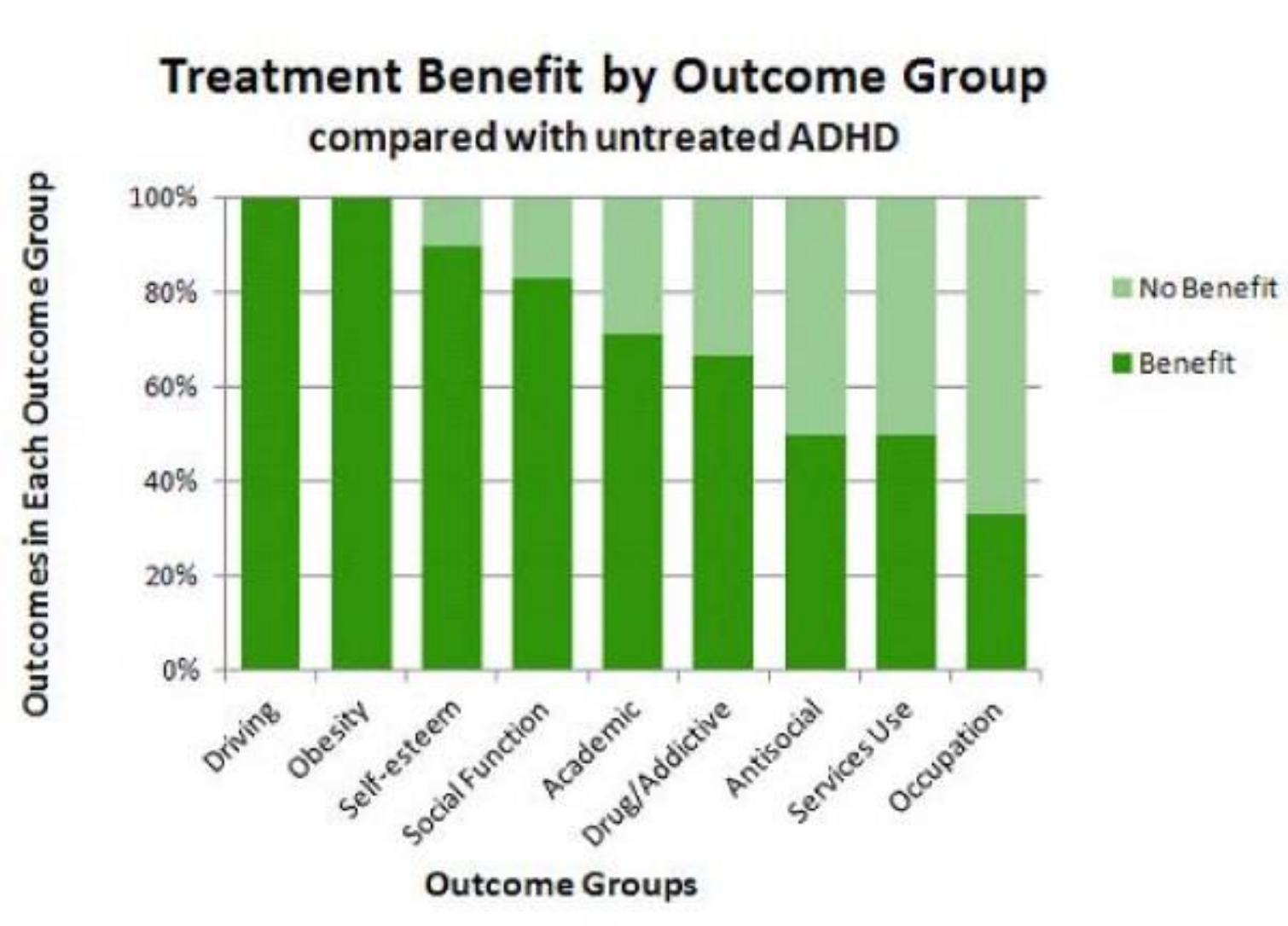
- Systematic review published 2012
- Long-term outcomes and impact of any treatment (pharmacological, non-pharmacological, or multimodal) for ADHD





. BMC Med. 2012 Sep 4;10:99.

Untreated ADHD



. BMC Med. 2012 Sep 4;10:99.

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ADHD and Driving Safety

- 2017 JAMA Psychiatry
- Female patients had a 42% (odds ratio, 0.58; 95% CI, 0.53-0.62) lower risk of motor vehicle accidents when receiving ADHD medication
- Medication may reduce morbidity and mortality associated with motor vehicle accidents

Key Points

Question Is the use of attention-deficit/hyperactivity disorder medication associated with a reduced risk of motor vehicle crashes in patients with the disorder?

Findings In a national cohort study of 2 319 450 patients with attention-deficit/hyperactivity disorder, the use of medication for the disorder was associated with a significant reduction in the risk of motor vehicle crashes in male and female patients.

Meaning Attention-deficit/hyperactivity disorder medication use may lower the risk of motor vehicle crashes, a prevalent and preventable cause of mortality and morbidity among patients with the disorder.

JAMA Psychiatry. 2017;74(6):597–603

What Is ADHD?

- Attention-deficit/hyperactivity disorder (ADHD)
- Patients show a persistent pattern of inattention and/or hyperactivity–impulsivity that interferes with functioning or development
  - DSM 5 (see later slide) has more defining details
- One of the most common neurobehavioral disorders of childhood
  - 2022 CDC data: 7 million (11.4%) U.S. children age 3-17 have the diagnosis
- Up to 60% of children with ADHD will continue to have symptoms as adults
  - 2023 CDC data: 15.5 million (6.0%) U.S. Adults have the diagnosis
- Common comorbid conditions include:
  - Depression, anxiety, substance misuse, impaired functioning, oppositional defiant disorder (ODD), bipolar, personality disorders

ADHD not in Vacuum

- Like with other mental health conditions, ADHD does not often occur alone
- Chronic frustration and disappointment from uncontrolled ADHD symptoms may lead to secondary depression, anxiety
- Patients may be misdiagnosed with symptoms (insomnia, depression)
- Study: 25 women with ADHD: 1) discontinued, 2) maintained or 3) adjusted ADHD medications
  - ADHD symptoms, anxiety, depression, stress and functional impairment were monitored
  - Results:
    - No significant difference in ADHD symptoms
    - Difference with discontinuers versus adjusters for **mood/family functioning (worse)**
    - Difference with discontinuers versus maintainers for **mood/family functioning (worse)**

Journal of Attention Disorders, *26*(2), 143-148.

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Uncontrolled Conditions in Pregnancy

- Uncontrolled depression and anxiety can have poor outcomes in pregnancy including higher risk
  - Miscarriage
  - Cesarean section
  - Lower birth weight
  - Pre-term birth/intrauterine growth restriction
  - Altered immune function
  - Preeclampsia

Health Qual Life Outcomes. 2021;19(1):78.
Sci Rep. 2019 Sep 11;9(1):13101..
Matern Child Health J. 2020;24(6):718-726.
Hum Dev. 2021;152:105243
J Clin Psychiatry. 2018;79(5):17r12011.
Biol Reprod. 2022;106(3):449-462.
Pregnancy Hypertens. 2022;30:36-43..

Patient Case – "Kate"

- 33 y/o female
- 16 weeks pregnant (G1P)
- Current Medications: None
- Previous Medication: Mixed amphetamine salt (Adderall) XR 20 mg daily
- Pt recently got a new job
  - "I am struggling so much with the new job. I'm worried they will fire me. My doctor said he would not prescribe my medicine, what can I do?"

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NON-STIMULANT DATA

Patient Case – "Rose"

- 28 y/o female
- Newly pregnant G2P1
- Current medications:
  - Sertraline (Selective Serotonin-Reuptake Inhibitor – SSRI) for depression
  - Bupropion (Dopamine/Norepinephrine- Reuptake inhibitor) for ADHD
- Pt currently stable and well controlled with 2-year-old daughter
- Outreaching patient to discuss medications in pregnancy
- "I know I have to stop my medication. They did last time."

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Non-Stimulant Treatment: Bupropion

*AD = antidepressants

Study	N (size)	Exposure	Results
Am J Obstet Gynecol 2005;192:932–6.	136 exposed 133 controls	Bupropion for depression or smoking cessation	No major malformations Spontaneous abortions 14.7% (exposed) vs 4.5% (control), p =0.009 Therapeutic abortions 7.4% (exposed) vs 0.75% (control), p = 0.015
Bupropion Pregnancy Registry (2008)	1597	Bupropion - Manufacturer registry for pregnancy exposure	Birth defects from exposure in the 1st trimester was 3.6% (95% CI 2.3–5.3) Birth defects from exposure in the 2nd trimester was 2.1% (95% CI 0.5–6.4) Retrospective reports in 28 infants, 9 with heart defects
Pharmacoepidemiol Drug Saf 2007;16:474–84.	1213 bupropion 1st trimester 4743 other AD* 1049 bupropion after 1st trimester		Congenital anomalies 1st trimester bupropion 23.1/1000 infants, AOR w/ other AD 23.2/1000, 0.95 (95% CI 0.62–1.45), after 1st 21.9/1000, 1.00 (95% CI 0.57–1.73) Cardiovascular anomalies 1st trimester bupropion 10.7/1000, Other AD comparison: 10.8/1000, AOR 0.97 (95% CI 0.52–1.80) After 1st : 9.5/1000, 1.07 (95% CI 0.48–2.40) No likely teratogenic effect of 1st trimester exposure to bupropion
Pharmacoepidemiol Drug Saf 2012;21:1240–2.	Using data from 2007 study above		Left ventricular outflow tract obstruction (LVOTO) 2.47/1000 vs 0.84/1000 with other antidepressants

Non-Stimulant Treatment: Bupropion

*AD = antidepressants

Study	N (size)	Exposure	Results
Can J Psychiatry 2009;54:242–6.	113 exposed 113 controls	Bupropion (part of larger study for many AD)	No major birth defects
Am J Obstet Gynecol 2010;203:52.e1–6.	6853 exposed 5869 controls	Bupropion; Retrospective case control	Exposed higher risk of left outflow ventricular tract defects (OR 2.6, 95% CI 1.2-5.7) Authors noted additional studies needed to confirm
Pharmacoepidemiol Drug Saf 2014;23:1066–75	7913 cardiac defects 8611 no defects	Bupropion (part of larger study with many AD); Retrospective case control	AOR 1st trimester bupropion use in combination with other antidepressants and ventricular septal defect was 1.6, 95% CI 1.0–2.8 Bupropion alone, AOR 2.5, 95% CI 1.3–5.0
J Dev Behav Pediatr 2010;31:641–8	38,074 families (claims data)	Antidepressant (including bupropion) exposure	ADHD in mother or the father increased risk in children (OR = 4.15, p <.001 and OR = 3.54, p <.001). A diagnosis of bipolar disorder (OR = 5.08, p <.001), psychotic disorders (OR = 4.05, p =.02), or depressive disorders (OR = 2.58, p <.001) in the mother, but not in the father, increased the risk of ADHD in their children. Exposure to bupropion during pregnancy (OR = 3.63, p =.02), especially during the second trimester (OR = 14.66, p <.001), was strongly associated with increased risk of ADHD, whereas exposure to selective serotonin reuptake inhibitors was not (OR = 0.91, p =.74).

Non-Stimulant Treatment: Bupropion

*AD = antidepressants

Study	N (size)	Exposure	Results
Prim Care Companion CNS Disord 2017;19. pii. 17r02160.	Meta-analysis, 8 studies		Cardiac defects found in 3 studies in particular, **left ventricular outflow obstructions.** The elevated risk of left ventricular outflow obstructions, if real, **represents a 2 to 3 times higher rate than expected, but absolute risk only 2.1-2.8 per 1,000 births.** An additional finding of concern was the reported tripling in the rate of miscarriage linked with bupropion use in the first trimester. Notably, the rate remained within the general population range. Smoking status could not be controlled for

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Bupropion Summary

- Less data than with traditional selective serotonin-reuptake inhibitors (SSRIs) used in depression/anxiety
- Some studies have shown an increased risk in cardiac defects while others have not
- Per one meta-analysis, while cardiac risk may exist, absolute risk is only 2.1-2.8 per 1000 births
- Another study showed possible increased risk of preterm birth (bupropion was being used for smoking cessation)

Patient Case – "Rose"

- 28 y/o female
- Newly pregnant G2P1
- Current medications:
  - Sertraline (Selective Serotonin-Reuptake Inhibitor – SSRI) for depression
  - Bupropion (Dopamine/Norepinephrine- Reuptake inhibitor) for ADHD
- Patient very concerned about her ability to function during her pregnancy

Non-Stimulant ADHD Treatment

Medication	Briggs	Reprotox	Concerns?
Clonidine 4 studies N ~ 1222	Limited Human Data—Animal Data Suggest Risk	Based on experimental animal studies, clonidine use during pregnancy is not expected to increase the risk of structural malformations. Effects of pregnancy exposure on offspring behavior were suspected based on human experience and experimental animal studies. Alternative anti-hypertensive agents may be preferred during pregnancy.	Low blood pressure
Guanfacine 1 study 3 case reports N~33	Limited Human Data—Animal Data Suggest Low Risk	Based on experimental animal studies, use of guanfacine is not expected to increase the risk of congenital anomalies.	Low blood pressure
Atomoxetine 3 studies N ~ 900	Limited Human Data—Animal Data Suggest Risk	Based on experimental animal data, atomoxetine is not expected to cause birth defects at human therapeutic doses; however, in slow-metabolizers exposure to the fetus can be higher than in fast-metabolizers.	Elevated blood pressure
Viloxazine No studies found	Not listed	Viloxazine decreased fetal viability in rats. We did not locate human data.	Likely similar to atomoxetine, venlafaxine, duloxetine

Briggs, G. G., Freeman, R. K., Towers, C. V., & Forinash, A. B. (2017). Drugs in pregnancy and lactation: A reference guide to fetal and neonatal risk (online ed.) ""Atomoxetine," Clonidine," "Guanfacine." Last updated 5/23/22.
Atomoxetine, Clonidine, Guanfaine (REPROTOX Document). In: REPROTOX Database (electronic version). Truven Health Analytics, Greenwood Village, Colorado, USA, Available at: https://www.micromedexsolutions.com/ cited: 6/20/2025.

How do I approach it?

- One size does NOT fit all
- Each patient is a different person with different history, needs, background, current situation, support, and condition burden
- This is not a lecture to a patient about risks/benefits, this is a conversation
- Questions I like to ask (open ended if possible):
  - Tell me more about your ADHD
  - How long have you been on your medication? Do you think it is working?
  - Have you ever been off the medication – tell me more about that experience.
  - Tell me more about your concerns about being off medication. Continuing medication.
  - What demands do you have on your time daily? Work, childcare, both?

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Common Questions

- Is there a safer time of my pregnancy I can take my medication?
  - Possibly. The first trimester has the most organogenesis (development of organs) for the fetus. Holding off until the second trimester may reduce the risks of malformations (heart development occurs until about 11 weeks), but is not a guarantee.
- If I stop my medication can I restart it?
  - YES! ADHD medications have a fast onset/offset and unlike other treatments (i.e. antidepressants) if we stop them, we can restart them with a quick response
- Should I try to take less medication so the baby gets less?
  - Maybe. We do not know if the risks are dose dependent (possibly). We do know that effectiveness is dose dependent. We want you to be on the lowest EFFECTIVE dose. If we lower the dose just to reduce exposure, but also reduce efficacy, now we have the WORST of both worlds – poor treatment and fetal exposure.

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Common Questions

- When I started medications, I was on fast acting one and was changed to a long-acting one. Should I go back to the fast acting one?
  - Maybe. Why did they change you? Were you having a wearing off and needed a second dose you could not remember? What were your responsibilities in the evenings/afternoons when they made the change?
- I am a teacher. In the summer, the world is my oyster. In the Fall, the world crushes me. Can I stay off the medication until the school year starts?
  - YES. Again, the important issue is ensuring you are able to function (driving, domestic responsibilities, etc) off the medication. If you are not in a situation that needs the medication at this time, we can reassess.
- Can I adjust my doses or experiment with what works best for me?
  - YES! Just make sure we are taking care of your condition while you are adjusting.

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Common Questions

- I have a family history of congenital heart defects. Do I have to take my medication?
  - NO! This is your decision. My job is to help you navigate the data and understand risks and benefits of your decision.
- I work parttime – I really only need my medication to help me at work, can I used in on the days I'm working?
  - Possibly. It does have a fast onset/offset, so you do not have to take it daily, but there are other non-work related concerns we need to assess – do you drive daily? Are you able to manage your domestic responsibilities?
- I've read that methylphenidate (Ritalin) has the highest risk of heart defects, can I change my medication to a mixed amphetamine salt (Adderall) instead?
  - Not typically recommended. While the risk may be higher with methylphenidate, changing medications increases exposure to the fetus and may reduce efficacy for the mother.

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Breastfeeding

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Amphetamine Data (Limited)

Drugs and Lactation Database (LactMed®) [Internet]. Bethesda (MD): National Institute of Child Health and Human Development; 2006-. Amphetamine. [Updated 2024 Jul 15]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK501307

- **Found in milk (low amounts)**
- **No adverse events reported**
- **Unclear affect on milk supply (two small studies showed reduced prolactin by up to 40% and was dose dependent)**

Study/Source	Date	N (size)	Exposure	Results
Eur J Clin Pharmacol 1984;27:123-4	Case report 1984	1	Amphetamine 5 mg four times daily (20 mg/day)	Found in milk Infant urinary excretion tested (0.1-0.3% of mother's urinary excretion No signed of abnormal development at 2 years
J Hum Lact 2015;31:374-6	Case report 2015	1	Amphetamine 35 mg/day	Found in milk Infant serum concentrations ranged 5-15% of maternal dose Breastfed for 6 months, no adverse reactions and normal growth
Neurotoxicol Teratol 2023;98:15.doi:10.1016/ j.ntt.2023.10721	Prospective study 2023	13	7 mixed amphetamine salts 6 lisdexamfetamine	Median age at follow-up 18 months Adverse effects reported among 5 children: somnolence in 1, crying or restlessness in 3, colic or constipation in 4. All children were reported to have normal gross motor development and Neurodevelopment

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Methylphenidate Data (Limited)

Drugs and Lactation Database (LactMed®) [Internet]. Bethesda (MD): National Institute of Child Health and Human Development; 2006-. Methylphenidate. [Updated 2024 Oct 15]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK501310/

- **Found in milk (very low, some cases undetectable)**
- **No adverse events reported**
- **Unclear affect on milk supply, does lower prolactin levels**

Study/Source	Date	N (size)	Exposure	Results
Ther Drug Monit 2005;27:220-1.	Case report 2005	3	Methylphenidate doses 35-80 mg	Found in milk Average infant dose was 0.7% of maternal weigh-adjusted dose Undetectable in infant plasma
Ann Pharmacother 2006;40:1890-1.	Case report 2006	1	Methylphenidate 40 mg twice daily	Found in milk Infant dose 0.2% of maternal weigh-adjusted dose Undetectable in infant plasma (may have been in study above)
Am J Psychiatry 2007;164:348.	Case report 2007	1	Methylphenidate 5 mg AM and at noon	Found in milk Authors estimated 0.16% of the maternal weight-adjusted dosage
Br J Clin Pharmacol 2014;77:96-101.	Case report 2014	1	Methylphenidate ER 72 mg/day	Drug was undetectable in milk at 6-12 months post-partum
Breastfeed Med 2018;13:221-5.	Case report 2018	1	Methylphenidate ER 36 mg/day	Infant dose 0.2% of mother's dose (mother was partially breastfeeding)

Patient Case – "Kate"

- 33 y/o female
- 36 weeks pregnant (G1P)
- Current Medications: Mixed amphetamine salt (Adderall) XR 10 mg daily
- Pt is doing well and calling to discuss breastfeeding options
- Pt has a 6 week maternity leave and wants to breastfeed for one year

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Bupropion Data (Limited)

- **Found in milk**
- **One seizure reported**
- **Unclear affect on milk supply, does increase prolactin levels**

Drugs and Lactation Database (LactMed®) [Internet]. Bethesda (MD): National Institute of Child Health and Human Development; 2006-. Bupropion. [Updated 2024 Jan 15]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK501184/

Study/Source	Date	N (size)	Exposure	Results
Ann Pharmacother 1993;27:431-3.	Case report 1993	1	Bupropion 100 mg three times daily	Found in milk Undetectable (including metabolites) in infant
Tob Control 2004;13:52-6.	Study 2006	10	Bupropion SR 150 mg for 3 days then 300 mg daily for 4 days	Authors estimated that an exclusively breastfed infant would receive an average of 0.2% of the maternal weight-adjusted dosage of bupropion and an average of 2% of the maternal weight-adjusted dosage of bupropion plus metabolites with this maternal dosage regimen
Ann Pharmacother 2014;48:928-31.	Case report 2014	1	Bupropion ER 150 mg daily	Mother on escitalopram 10 mg daily since birth, began bupropion 3 weeks earlier, baby was partially breastfed. At 6.5 months, BF 8 hours after last bupropion dose, infant had seizure. Bupropion was detectable in the infant in serum
J Clin Psychiatry 2009;70:297-8	Case report 2009	4	Bupropion SR 150 mg or 300 mg for smoking cessation	Average infant dose (normalized to a 150 mg maternal dose) was estimated to be 21.5 mcg daily (range 5.1 to 31.1 mcg daily) which averaged 5.1% (range 1.4 to 10.6%) of the

Patient Case – "Rose"

- 28 y/o female
- 29 weeks pregnant G2P1
- Current medications:
  - Sertraline (Selective Serotonin-Reuptake Inhibitor – SSRI) for depression
  - Bupropion (Dopamine/Norepinephrine- Reuptake inhibitor) for ADHD
- Patient doing very well in pregnancy, but concerned about post-partum
- "I know I'm supposed to breastfed, but I'm worried about the medications and my ability to manage it all."
- Fedisbest.org: Unintended Harms of "Breast is Best"

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Breastfeeding Pitfalls

- Does not work for everyone and is not possible for everyone
- Should not change how health care providers (OR ANYONE) treats the mother, baby, or family
- Do what is best for mom and baby and sometimes that is NOT breastfeeding!
- Fedisbest.org:
  - The Unintended Harms of "Breast is Best" Message and How to Find the Right Approach for You and Your Baby

Dear Colleague and Parent:

My name is Christie del Castillo-Hegyi and I am an emergency physician, former NIH scientist, with a background in newborn brain injury research at Brown University, and mother to a 6-year-old child who is neurologically disabled. I am writing to you because my child fell victim to newborn jaundice, hypoglycemia and severe dehydration due to insufficient milk intake from exclusive breastfeeding in the first days of life. As an expectant mom, I read all the guidelines on breastfeeding my first-born child. Unfortunately, following the guidelines and our pediatrician's advice resulted in my child going 4 days with absolutely no milk intake requiring ICU care.

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Summary

- ADHD is a mental health that causes impaired functioning and has common comorbid conditions like depression and anxiety
- Medication use for ADHD, especially among childbearing age is increasing
- Stimulant medications data is reassuring (small absolute risks, but risk cannot be ruled out)
- There are risks to uncontrolled (even treated) ADHD including worsening mental health
- Putting risks in perspective for patient's situation combined with other personal and family history is necessary for appropriate patient counseling
  - There is no one right answer
  - This should be a discussion about next steps, not a lecture on use

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Questions?

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