Course and Treatment of ADHD and Comorbid Disorders During Pregnancy and the Postpartum Period

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Disclosures

"Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose."

Overview

- Learning objectives
- Background
- ADHD in girls and women
  - diagnostics, treatment
- Special considerations for pregnancy and the postpartum
  - Reproductive and lactation safety of stimulants and non-stimulants
- The risk/risk consultation model and a case
- References

Learning Objectives

By the end of this program, participants will be able to:

1. Discuss general risks of stimulant use during pregnancy with their patients with ADHD;

2. Create a tailored risk/risk analysis of stimulant use vs. risk of stopping treatment for their patient with ADHD;

3. Describe the non-pharmacologic treatment options available to their patients with ADHD.

Background

- 4.4% of US adults have ADHD. Of these adults with ADHD, 38% are women and 62% are men (Kessler et al. 2006).
- Roughly 1 in 30 women has ADHD (Faraone 2018).
- ADHD is linked to elevated risk of poorer general and mental health, increased rates of substance abuse, impaired work performance, and financial distress (Biederman 2012, Biederman 2010).
- Strongly associated with other mental health disorders, such as mood and anxiety disorders (Freeman 2014, Kolar 2008).

ADHD in Girls and Women

- ADHD that persists into adulthood for women has been shown to be associated with depression, anxiety, substance use, occupational, social, and overall impairment domains (Biederman 2010).

- Adult women with ADHD can experience a variety of difficulties at work and in their personal and family lives related to their ADHD symptoms (Owens 2017).

- Given that treatment of adult ADHD improves functioning (Sarkis 2014) and quality of life (Agarwal 2012), women on treatment for ADHD may wish to continue their medications during pregnancy in order to continue to experience the benefits of treatment.

ADHD in Reproductive Age Women

- ADHD that persists into adulthood for women has been shown to be associated with depression, anxiety, substance use, occupational, social, and overall impairment domains.

- Adult women with ADHD can experience a variety of difficulties at work and in their personal and family lives related to their ADHD symptoms.

- Given that treatment of adult ADHD improves functioning and quality of life, women on treatment for ADHD may wish to continue their medications during pregnancy in order to continue to experience the benefits of treatment.

Biederman et al. Am J Psychiatry. 2010
Owens et al. J Consult Clin Psychol. 2017
Sarkis, Postgrad Med. 2014
Agarwal et al. Innov Clin Neurosci. 2012

Functional Impairment*: Implications for Pregnancy and Postpartum Women

- Family
- Work
- Life skills
- Problems with self-concept
- Social functioning
- Risk taking behavior

*Functional Impairment during pregnancy and the postpartum period have long term implications – ? higher risk of later psychopathology

Weissman et al. JAMA. 2006

Diagnostic Issues

- Clinical diagnosis, as there are no laboratory tests.
- DSM 5 proposes specific criteria for the diagnosis in very young children as well as in adults.
- Typical behavior of ADHD should be present in at least 2 settings.
- Must have impairment in functioning in addition to symptoms of ADHD.

ADHD DSM 5

Inattention: 6+, > 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 (such as schoolwork or homework).
- Often loses things necessary for tasks and activities (e.g. school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones).
- Is often easily distracted.
- Is often forgetful in daily activities.

Hyperactive/Impulsive: 6+, >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 his/her turn.
- Often interrupts or intrudes on others (e.g., butts into conversations or games).

Treatment

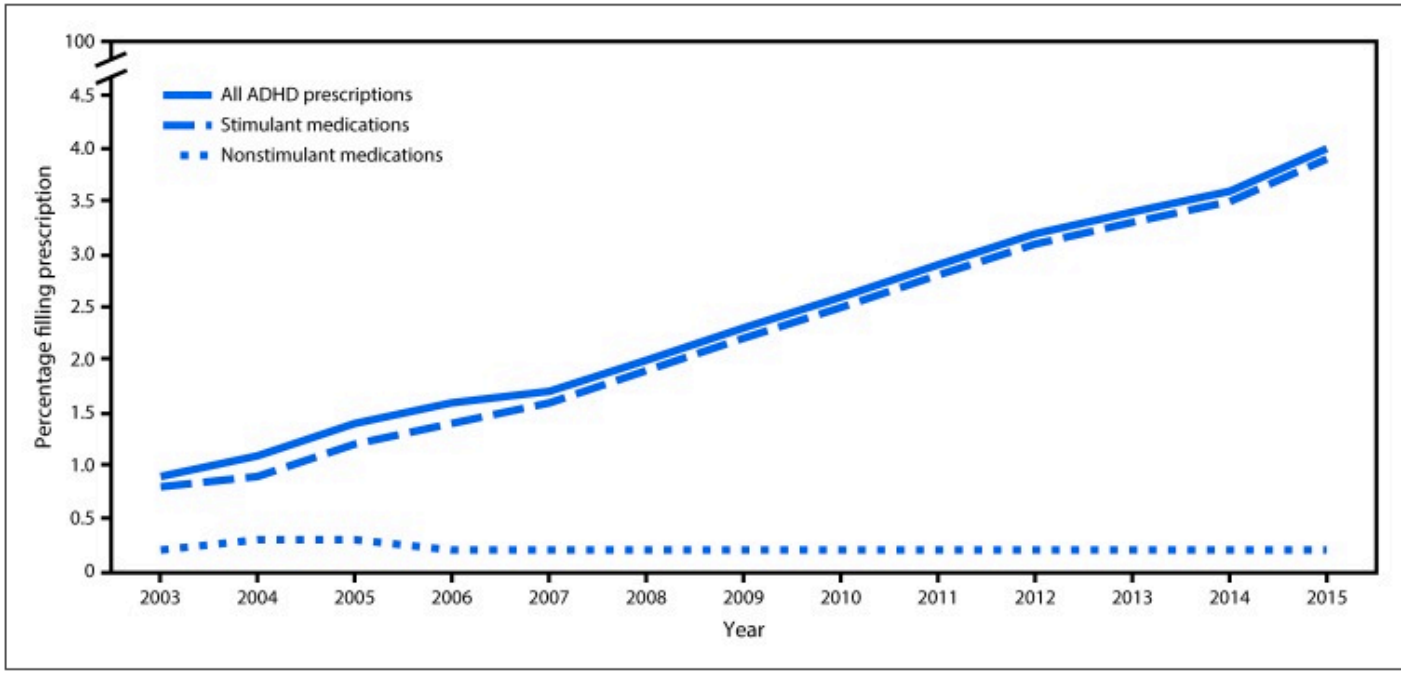
- Treating ADHD requires medical, educational, behavioral and psychological intervention. This approach to treatment is called “multimodal” and, depending on the age of the individual with ADHD, may include:
  - parent training
  - Medication
  - skills training
  - Counseling
  - Cognitive behavioral therapy
  - educational supports
  - education regarding ADHD

- Most guidelines recommend a stepwise approach to treatment, beginning with non-drug interventions and then moving to pharmacological treatment in those more significantly affected.

Pregnancy Considerations

- ADHD medication use among pregnant women is increasing but consensus about the safety of ADHD medication use during pregnancy is lacking.

- Given that nearly half of U.S. pregnancies are unintended and early pregnancy is a critical period for fetal development, these are matters of great clinical importance.



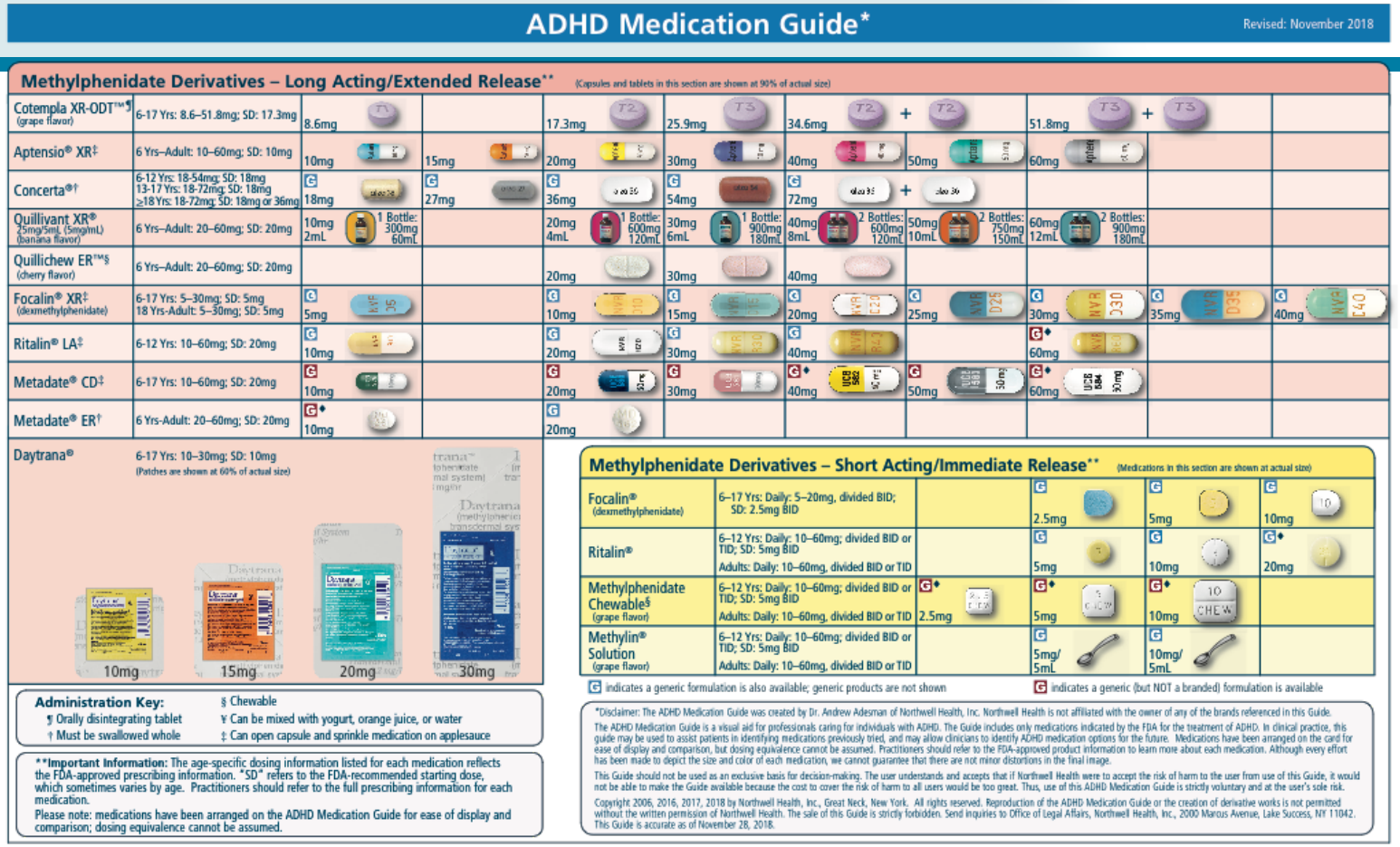
FIGURE

Percentage of women aged 15–44 years with private employer-sponsored insurance who filled one or more prescriptions for an attention-deficit/hyperactivity disorder (ADHD) medication, by medication class — United States, 2003–2015

Attention-Deficit/Hyperactivity Disorder Medication Prescription Claims Among Privately Insured Women Aged 15–44 Years — United States, 2003–2015

MMWR Morb Mortal Wkly Rep. 2018 Jan 19;67(2):66-70.

Treatment



ADHD Medication Guide*

Revised: November 2018

Methylphenidate Derivatives – Long Acting/Extended Release**

(Capsules and tablets in this section are shown at 90% of actual size)

Cotempla XR-ODT™¶ (grape flavor)	6-17 Yrs: 8.6–51.8mg; SD: 17.3mg	8.6mg			17.3mg		25.9mg		34.6mg			51.8mg							
Aptensio® XR‡	6 Yrs–Adult: 10–60mg; SD: 10mg	10mg		15mg		20mg		30mg		40mg		50mg		60mg					
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		G 54mg		G 72mg									
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	30mg 6mL	1 Bottle: 900mg 180mL	40mg 8mL	2 Bottles: 600mg 120mL	50mg 10mL	2 Bottles: 750mg 150mL	60mg 12mL	2 Bottles: 900mg 180mL				
Quillichew ER™§ (cherry flavor)	6 Yrs–Adult: 20–60mg; SD: 20mg					20mg		30mg		40mg									
Focalin® XR‡ (dexmethylphenidate)	6-17 Yrs: 5–30mg; SD: 5mg 18 Yrs-Adult: 5–30mg; SD: 5mg	G 5mg				G 10mg		G 15mg		G 20mg		G 25mg		G 30mg		G 35mg		G 40mg	
Ritalin® LA‡	6-12 Yrs: 10–60mg; SD: 20mg	G 10mg				G 20mg		G 30mg		G 40mg				G◆ 60mg					
Metadate® CD‡	6-17 Yrs: 10–60mg; SD: 20mg	G 10mg				G 20mg		G 30mg		G◆ 40mg		G 50mg		G◆ 60mg					
Metadate® ER†	6 Yrs-Adult: 20–60mg; SD: 20mg	G◆ 10mg				G 20mg													

Daytrana® 6-17 Yrs: 10–30mg; SD: 10mg

(Patches are shown at 60% of actual size)

10mg 15mg 20mg 30mg

Methylphenidate Derivatives – Short Acting/Immediate Release**

(Medications in this section are shown at actual size)

Focalin® (dexmethylphenidate)	6–17 Yrs: Daily: 5–20mg, divided BID; SD: 2.5mg BID		G 2.5mg	G 5mg	G 10mg
Ritalin®	6–12 Yrs: Daily: 10–60mg; divided BID or TID; SD: 5mg BID Adults: Daily: 10–60mg, divided BID or TID		G 5mg	G 10mg	G◆ 20mg
Methylphenidate Chewable§ (grape flavor)	6–12 Yrs: Daily: 10–60mg; divided BID or TID; SD: 5mg BID Adults: Daily: 10–60mg, divided BID or TID	G◆ 2.5mg	G◆ 5mg	G◆ 10mg	
Methylin® Solution (grape flavor)	6–12 Yrs: Daily: 10–60mg; divided BID or TID; SD: 5mg BID Adults: Daily: 10–60mg, divided BID or TID		G 5mg/5mL	G 10mg/5mL	

G indicates a generic formulation is also available; generic products are not shown

G indicates a generic (but NOT a branded) formulation is available

Administration Key:

¶ Orally disintegrating tablet
† Must be swallowed whole
§ Chewable
¥ Can be mixed with yogurt, orange juice, or water
‡ Can open capsule and sprinkle medication on applesauce

**Important Information: The age-specific dosing information listed for each medication reflects the FDA-approved prescribing information. "SD" refers to the FDA-recommended starting dose, which sometimes varies by age. Practitioners should refer to the full prescribing information for each medication.

Please note: medications have been arranged on the ADHD Medication Guide for ease of display and comparison; dosing equivalence cannot be assumed.

*Disclaimer: The ADHD Medication Guide was created by Dr. Andrew Adesman of Northwell Health, Inc. Northwell Health is not affiliated with the owner of any of the brands referenced in this Guide.

The ADHD Medication Guide is a visual aid for professionals caring for individuals with ADHD. The Guide includes only medications indicated by the FDA for the treatment of ADHD. In clinical practice, this guide may be used to assist patients in identifying medications previously tried, and may allow clinicians to identify ADHD medication options for the future. Medications have been arranged on the card for ease of display and comparison, but dosing equivalence cannot be assumed. Practitioners should refer to the FDA-approved product information to learn more about each medication. Although every effort has been made to depict the size and color of each medication, we cannot guarantee that there are not minor distortions in the final image.

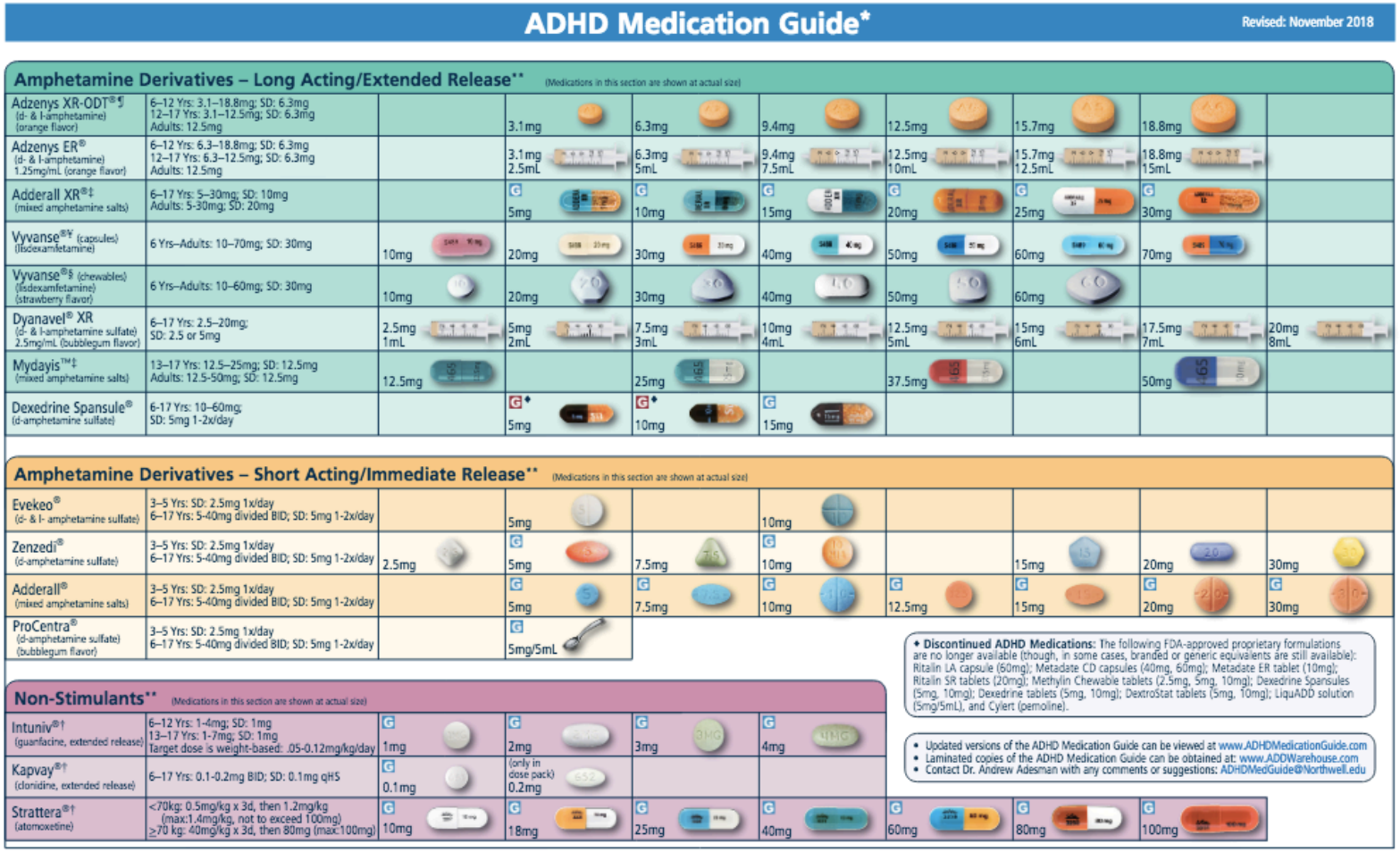
This Guide should not be used as an exclusive basis for decision-making. The user understands and accepts that if Northwell Health were to accept the risk of harm to the user from use of this Guide, it would not be able to make the Guide available because the cost to cover the risk of harm to all users would be too great. Thus, use of this ADHD Medication Guide is strictly voluntary and at the user's sole risk.

This Guide is accurate as of November 28, 2018.

Cohen Children's Medical Center
Northwell Health

Guide for free: www.ADHDMedicationGuide.com

Treatment



ADHD Medication Guide*

Revised: November 2018

Amphetamine Derivatives – Long Acting/Extended Release**

(Medications in this section are shown at actual size)

Adzenys XR-ODT®¶ (d- & l-amphetamine) (orange flavor)	6–12 Yrs: 3.1–18.8mg; SD: 6.3mg 12–17 Yrs: 3.1–12.5mg; SD: 6.3mg Adults: 12.5mg		3.1mg	6.3mg	9.4mg	12.5mg	15.7mg	18.8mg		
Adzenys ER® (d- & l-amphetamine) 1.25mg/mL (orange flavor)	6–12 Yrs: 6.3–18.8mg; SD: 6.3mg 12–17 Yrs: 6.3–12.5mg; SD: 6.3mg Adults: 12.5mg		3.1mg 2.5mL	6.3mg 5mL	9.4mg 7.5mL	12.5mg 10mL	15.7mg 12.5mL	18.8mg 15mL		
Adderall XR®‡ (mixed amphetamine salts)	6–17 Yrs: 5–30mg; SD: 10mg Adults: 5-30mg; SD: 20mg		G 5mg	G 10mg	G 15mg	G 20mg	G 25mg	G 30mg		
Vyvanse®¥ (capsules) (lisdexamfetamine)	6 Yrs–Adults: 10–70mg; SD: 30mg	10mg	20mg	30mg	40mg	50mg	60mg	70mg		
Vyvanse®§ (chewables) (lisdexamfetamine) (strawberry flavor)	6 Yrs–Adults: 10–60mg; SD: 30mg	10mg	20mg	30mg	40mg	50mg	60mg			
Dyanavel® XR (d- & l-amphetamine sulfate) 2.5mg/mL (bubblegum flavor)	6–17 Yrs: 2.5–20mg; SD: 2.5 or 5mg	2.5mg 1mL	5mg 2mL	7.5mg 3mL	10mg 4mL	12.5mg 5mL	15mg 6mL	17.5mg 7mL	20mg 8mL	
Mydayis™‡ (mixed amphetamine salts)	13–17 Yrs: 12.5–25mg; SD: 12.5mg Adults: 12.5-50mg; SD: 12.5mg	12.5mg		25mg		37.5mg		50mg		
Dexedrine Spansule® (d-amphetamine sulfate)	6-17 Yrs: 10–60mg; SD: 5mg 1-2x/day		G◆ 5mg	G◆ 10mg	G 15mg					

Amphetamine Derivatives – Short Acting/Immediate Release**

(Medications in this section are shown at actual size)

Evekeo® (d- & l- amphetamine sulfate)	3–5 Yrs: SD: 2.5mg 1x/day 6–17 Yrs: 5-40mg divided BID; SD: 5mg 1-2x/day		5mg		10mg				
Zenzedi® (d-amphetamine sulfate)	3–5 Yrs: SD: 2.5mg 1x/day 6–17 Yrs: 5-40mg divided BID; SD: 5mg 1-2x/day	2.5mg	G 5mg	7.5mg	G 10mg		15mg	20mg	30mg
Adderall® (mixed amphetamine salts)	3–5 Yrs: SD: 2.5mg 1x/day 6–17 Yrs: 5-40mg divided BID; SD: 5mg 1-2x/day		G 5mg	G 7.5mg	G 10mg	G 12.5mg	G 15mg	G 20mg	G 30mg
ProCentra® (d-amphetamine sulfate) (bubblegum flavor)	3–5 Yrs: SD: 2.5mg 1x/day 6–17 Yrs: 5-40mg divided BID; SD: 5mg 1-2x/day		G 5mg/5mL						

Non-Stimulants**

(Medications in this section are shown at actual size)

Intuniv®† (guanfacine, extended release)	6–12 Yrs: 1-4mg; SD: 1mg 13–17 Yrs: 1-7mg; SD: 1mg Target dose is weight-based: .05-0.12mg/kg/day	G 1mg	G 2mg	G 3mg	G 4mg				
Kapvay®† (clonidine, extended release)	6–17 Yrs: 0.1-0.2mg BID; SD: 0.1mg qHS	G 0.1mg	(only in dose pack) 0.2mg						
Strattera®† (atomoxetine)	<70kg: 0.5mg/kg x 3d, then 1.2mg/kg (max:1.4mg/kg, not to exceed 100mg) ≥70 kg: 40mg/kg x 3d, then 80mg (max:100mg)	G 10mg	G 18mg	G 25mg	G 40mg	G 60mg	G 80mg	G 100mg	

◆ **Discontinued ADHD Medications:** The following FDA-approved proprietary formulations are no longer available (though, in some cases, branded or generic equivalents are still available): Ritalin LA capsule (60mg); Metadate CD capsules (40mg, 60mg); Metadate ER tablet (10mg); Ritalin SR tablets (20mg); Methylin Chewable tablets (2.5mg, 5mg, 10mg); Dexedrine Spansules (5mg, 10mg); Dexedrine tablets (5mg, 10mg); DextroStat tablets (5mg, 10mg); LiquADD solution (5mg/5mL), and Cylert (pemoline).

- Updated versions of the ADHD Medication Guide can be viewed at www.ADHDMedicationGuide.com
- Laminated copies of the ADHD Medication Guide can be obtained at: www.ADDWarehouse.com
- Contact Dr. Andrew Adesman with any comments or suggestions: ADHDMedGuide@Northwell.edu

ADHD in Reproductive Age Women

- ADHD that persists into adulthood for women has been shown to be associated with depression, anxiety, substance use, occupational, social, and overall impairment domains.
- Adult women with ADHD can experience a variety of difficulties at work and in their personal and family lives related to their ADHD symptoms.
- Given that treatment of adult ADHD improves functioning and quality of life, women on treatment for ADHD may wish to continue their medications during pregnancy in order to continue to experience the benefits of treatment.

Biederman et al. Am J Psychiatry. 2010
Owens et al. J Consult Clin Psychol. 2017
Sarkis, Postgrad Med. 2014
Agarwal et al. Innov Clin Neurosci. 2012

Considerations for Pregnancy

- No studies have evaluated the course of ADHD across pregnancy and the postpartum. We are publishing the first study to date.
- Possible that the perinatal period has an impact upon the course.
    - Hormonal impact on cognition?
    - Distractions?
- Treatment decisions impacted by pregnancy.
  - Many women elect to discontinue stimulants for pregnancy and while breastfeeding.
- The impact of treatment decisions upon occupational functioning, interpersonal relationships, course of comorbid illnesses, and quality of life are not understood.

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Course of ADHD During Pregnancy and the Postpartum:

Investigating ADHD Symptoms and Functioning Among Women Who Chose to Discontinue, Alter, or Maintain Pharmacologic Treatment for ADHD in the Perinatal Period

Allison S. Baker, MD, Rebecca Wales, BA, Olivia Noe, BS, Peter Gaccione, PhD, Marlene P. Freeman, MD, and Lee S. Cohen, MD

Funded by Gerstner Family Foundation

MGH CENTER for Women's Mental Health

Reproductive Psychiatry Resource & Information Center

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Course of ADHD in Pregnancy and the Postpartum

Are you pregnant or planning pregnancy? Do you have a history of ADHD?

If you are planning pregnancy or less than 20 weeks pregnant and have a history of ADHD, you may be eligible to take part in an observational research study for women discontinuing psychostimulants during pregnancy and the postpartum.

Women who participate will have 6 study visits that can be completed in-person or over the phone.

For more information, please call (617)724-1181 or email the study coordinator at rwales@partners.org.

https://clinicaltrials.partners.org/study/course_of_adhd_duri

Hypothesis

- Risk for attention deficit hyperactivity disorder (ADHD) symptom severity and functional impairment will be greater among women who discontinue/change dose of stimulants compared to those who maintain treatment with these agents.

Inclusion Criteria

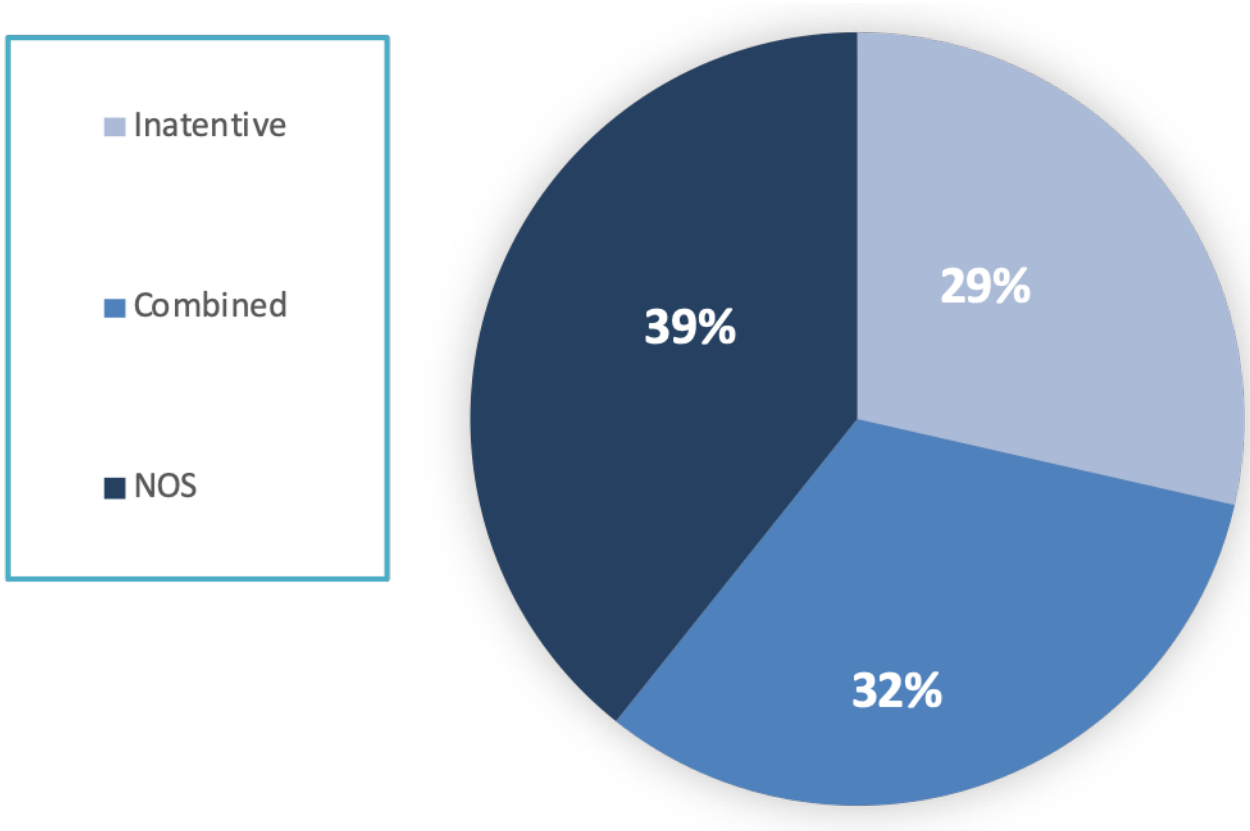
- 18 years or older
- Planning pregnancy or <20 weeks pregnant
- Has treating prescribing physician for ADHD and any other comorbid psychiatric illness
- Past (childhood) and current ADHD diagnosis in ACDS

Study Outline and Procedure

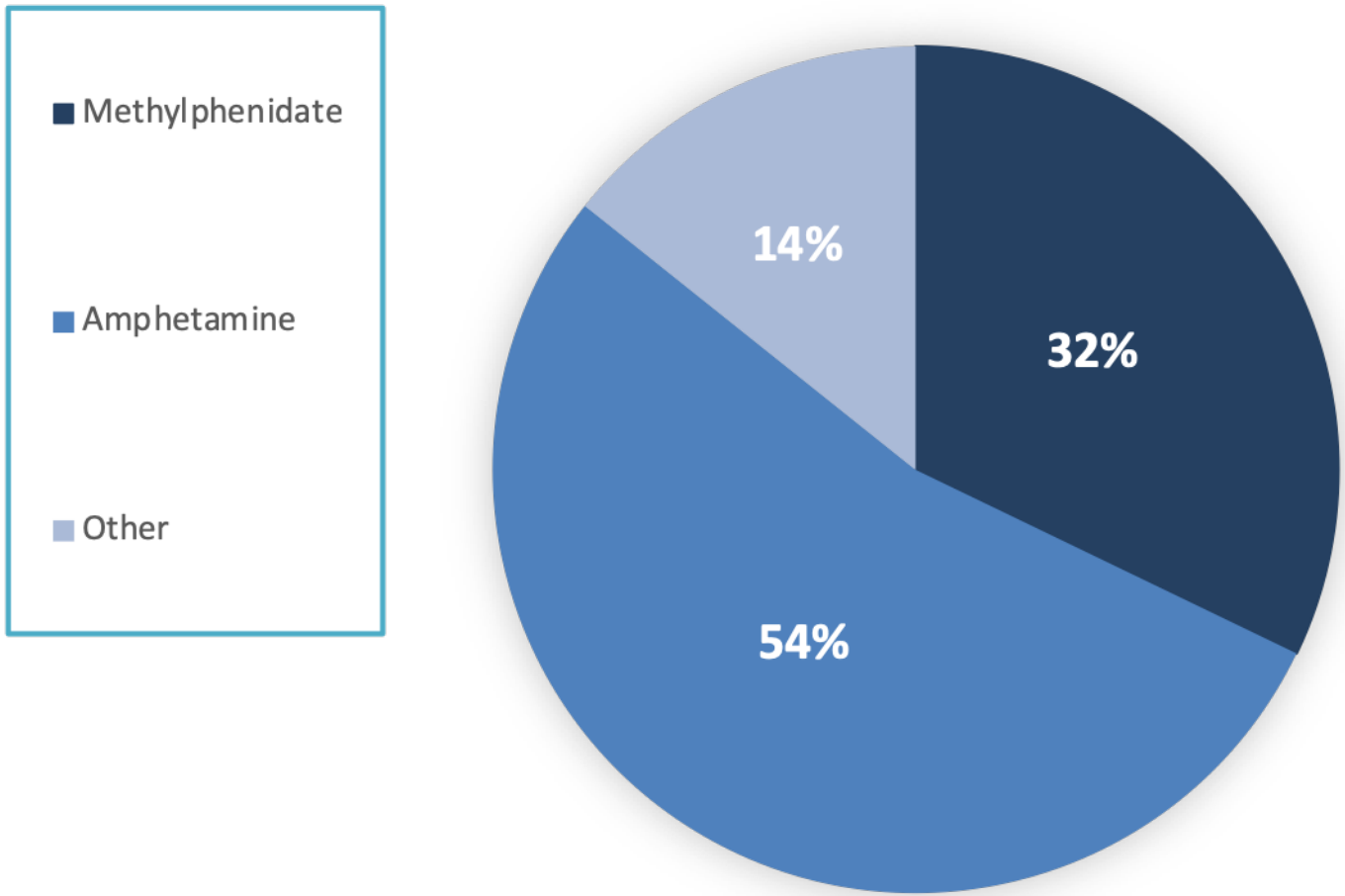
- Pregnant women ages 18-45 were prospectively followed during pregnancy using 3 structured clinical interviews
- ADHD symptoms were recorded at each timepoint using the AISRS
- Additionally, symptoms of anxiety, depression, stress, and functional impairment were monitored

Potentially eligible women respond to recruitment materials or are recruited by physicians at local clinics	Phone screen conducted; if eligible, women are scheduled for a baseline interview	Baseline interview conducted after consent; full psychiatric and medical history collected (1 hour)	Second interview conducted around 24 weeks gestation (20 min)	Third interview conducted around 36 weeks gestation (20 min)

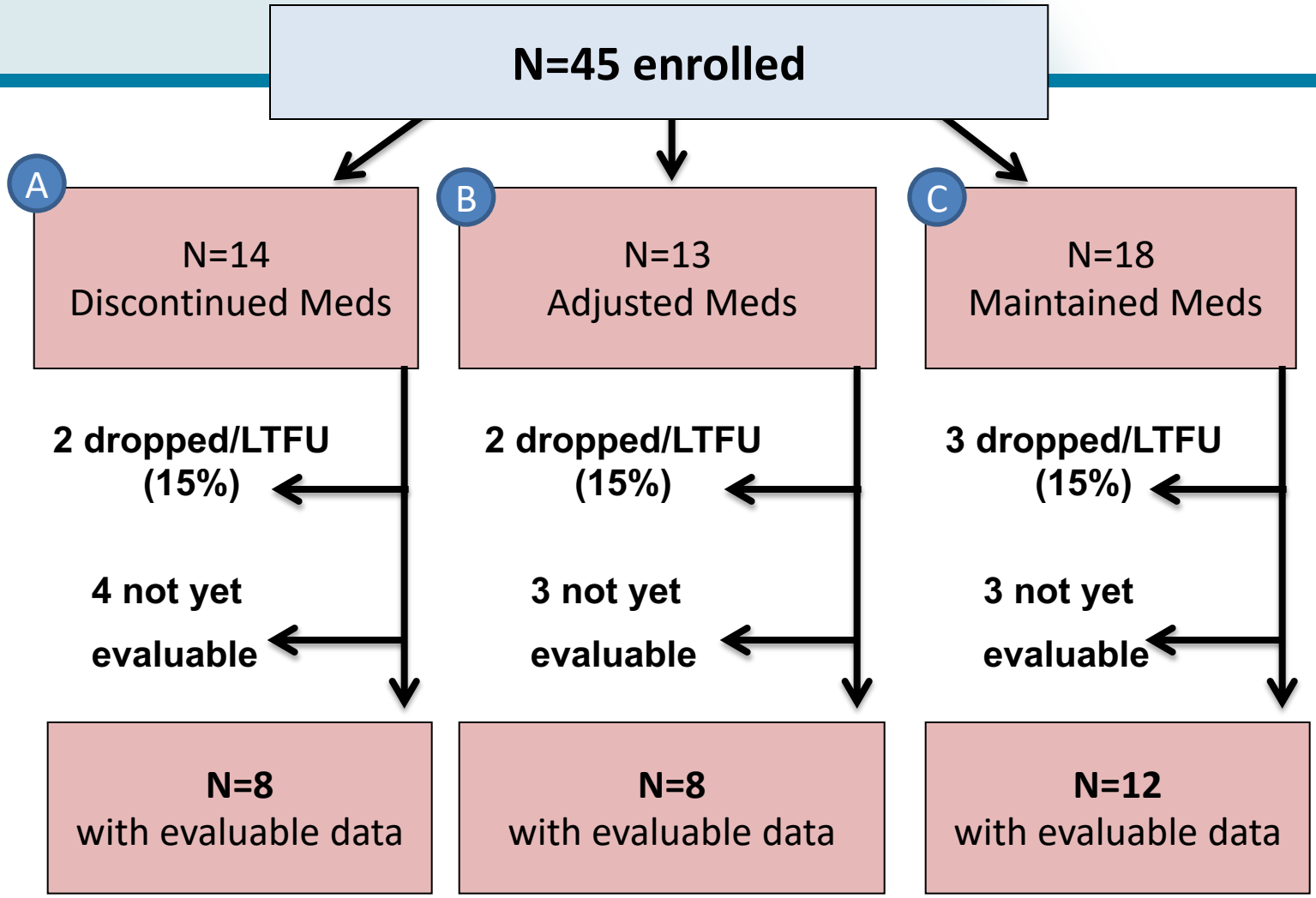
ADHD Type



ADHD Treatment



Use of ADHD Medications Across Pregnancy



Group A → Discontinued ADHD medications during pregnancy
Group B → Adjusted ADHD medication use throughout pregnancy
Group C → Maintained dose of ADHD medication throughout pregnancy

Psychiatric Comorbidity in Pregnant Women with ADHD

Diagnosis	Group A (n=8)	Group B (n=8)	Group C (n=12)	Overall (n=28)
	N (%)			
Generalized Anxiety Disorder (GAD)	5 (62.5%)	4 (50%)	5 (41.67%)	14 (50%)
Major Depressive Disorder (MDD)	2 (16.67%)	3 (37.5%)	4 (33.33%)	9 (32.14%)
Panic Disorder	1 (12.5%)	1 (12.5%)	1 (8.33%)	3 (10.71%)
Bipolar Disorder II	3 (37.5%)	0	0	3 (10.71%)
Obsessive Compulsive Disorder (OCD)	1 (12.5%)	1 (12.5%)	0	2 (7.14%)
Post-Traumatic Stress Disorder (PTSD)	0	1 (12.5%)	0	1 (3.57%)

Outcome Variables

- Adult ADHD Investigator Symptom Rating Scale (AISRS)
- Weiss Functional Impairment Rating Scale – Self Report (WFIRS-S)
- Edinburgh Postnatal Depression Scale (EPDS)

Results: AISRS

- No difference in AISRS scores across sample regardless of treatment condition

Results: WFIRS-S (Family Functioning)

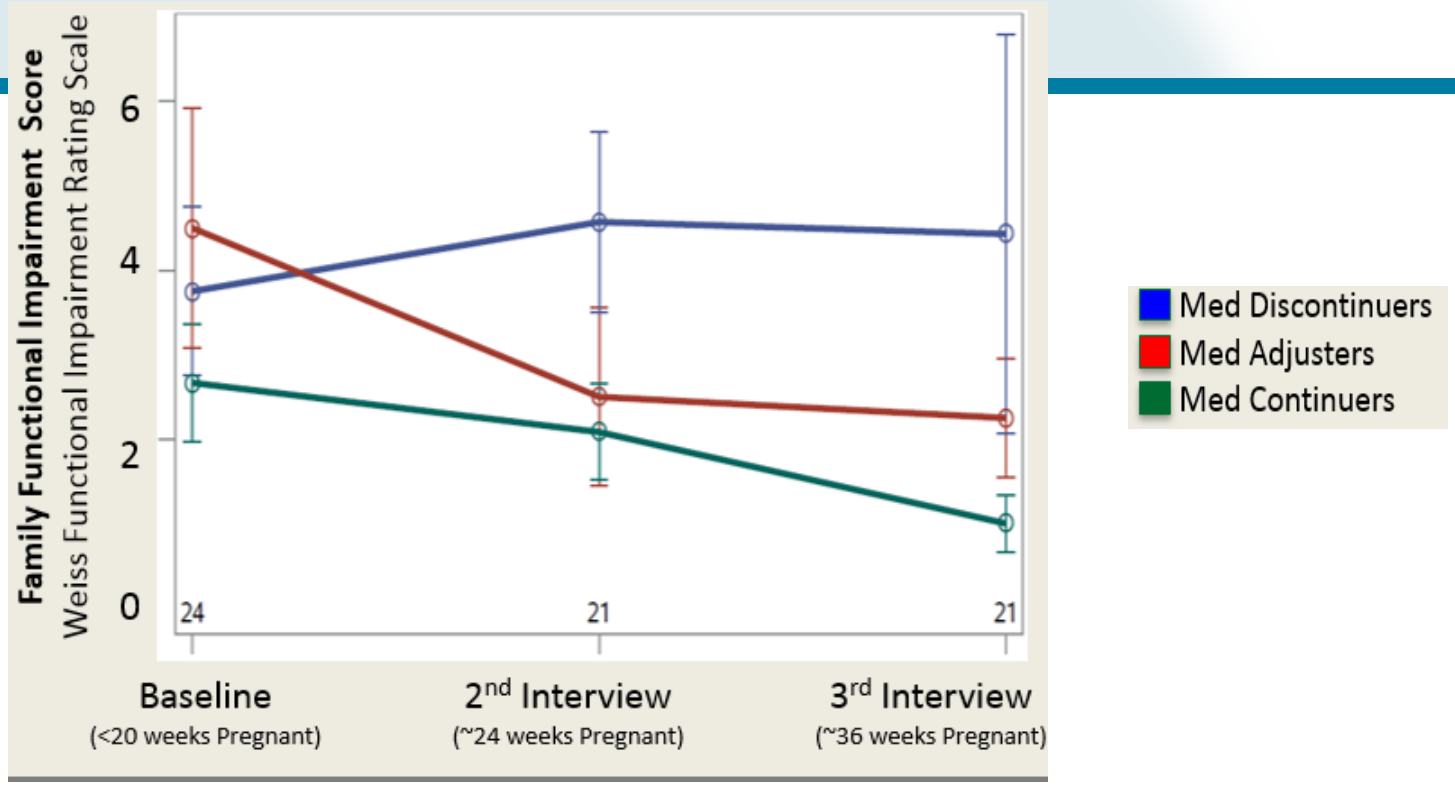


Figure 1. Self-reported impairment in family functioning measured across three pregnancy by medication group. The adjusted mean changes of: discontinuers, 1.55, meds as needed, -1.70, maintainers, -1.54, showing significant differences between those who discontinued meds and those changing meds as needed (3,3, p=0.0309) and discontinuers vs maintainers (3.09, p=0.0197).

Results: EPDS Score

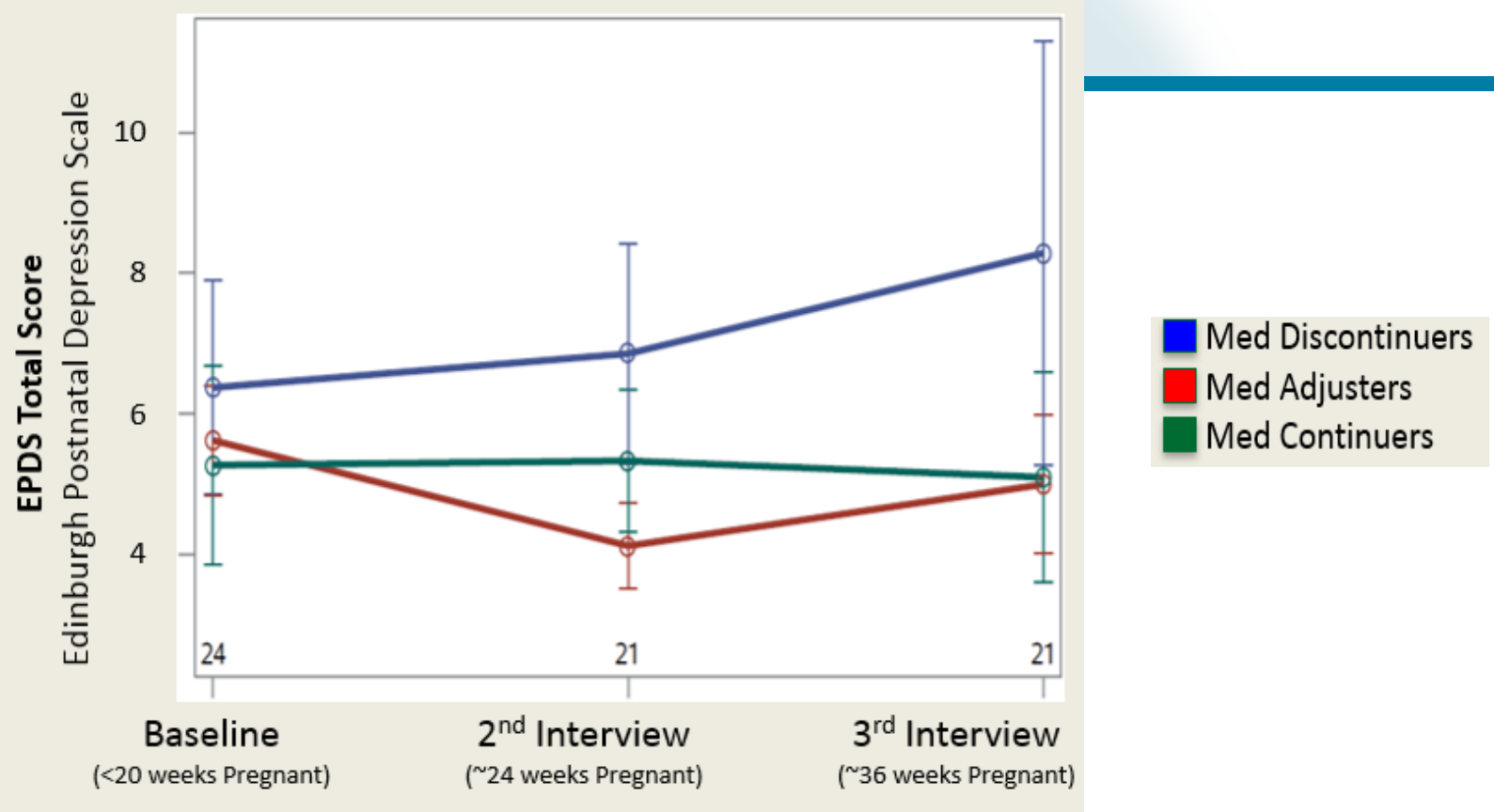


Figure 2. Edinburgh Postnatal Depression Scale (EPDS), self-reported depression and anxiety symptoms across timepoints and treatment groups. Adjusted mean changes of: discontinuers, 4.32, meds as needed, -1.01, and maintainers, -0.65, showing significant differences between those who discontinued meds and those changing meds as needed (5.3, p <0.0001) and discontinuers vs maintainers (4.98, p=0.0009).

Discussion

- Women who discontinued stimulant treatment during pregnancy had a clinically significant increase in depressed mood symptoms as measured by the EPDS during sustained treatment with antidepressant

- Women who discontinued stimulant treatment during pregnancy had significant impairment in family functioning, meaning they are more likely to experience conflict within the family, rate parenting as more difficult, and describe being more isolated from their family

- This preliminary prospective data underscores need for further research in ADHD during pregnancy and the postpartum period and the relationship between ADHD and comorbid psychiatric disorders

Poll Question

- What is a key functional outcome that is most relevant to safety when assessing risk of continuing vs. discontinuing stimulants during pregnancy?

a) Mood

b) Anxiety

c) Academic performance

d) Driving safety

Poll Question

- What is a key functional outcome *that is most relevant to safety* when assessing risk of continuing vs. discontinuing stimulants during pregnancy?

a) Mood

b) Anxiety

c) Academic performance

d) Driving safety

Original Investigation

FREE

June 2017

Association Between Medication Use for Attention-Deficit/Hyperactivity Disorder and Risk of Motor Vehicle Crashes

Zheng Chang, PhD, MSc[1,2]; Patrick D. Quinn, PhD[2,3]; Kwan Hur, PhD[2]; et al

» Author Affiliations | Article Information

JAMA Psychiatry. 2017;74(6):597-603. doi:10.1001/jamapsychiatry.2017.0659

Clinical Implications and Treatment Considerations

- Although the default medical position is to interrupt any "non-essential" pharmacological treatment during pregnancy and lactation, in ADHD this may present a significant risk.

- The clinician evaluates each case carefully and performs a risk-risk analysis with the patient prior to developing a treatment plan for pregnancy:
    - the risks of medication exposure throughout the pregnancy weighed against the risks of untreated ADHD, including ***driving safety***, and ***major impairment in fulfilling occupational and domestic roles***
    - Recommendations to reduce workload
    - Recommend CBT for ADHD
    - Increase structure and organization at work or school
    - Employers may be able to offer accommodations

Context

- **The baseline rate of congenital malformations is approximately 3% of all pregnancies in the U.S.**
- Untreated psychiatric disorders are associated with poorer pregnancy outcomes.
- Alcohol, tobacco, illicit drugs are teratogens.
- Psychosocial factors: Socioeconomic status, social support, prenatal care, nutrition, etc.

HOW SAFE IS THE USE OF ADHD MEDICATION DURING PREGNANCY?

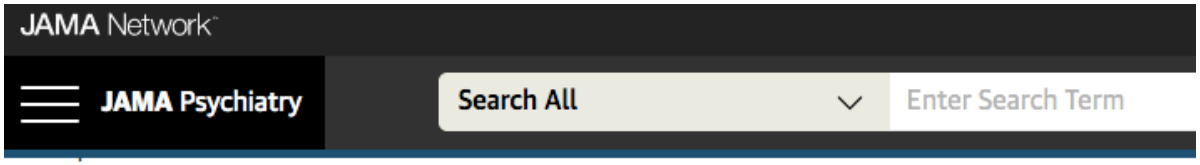
Outcomes to consider

- Congenital Malformations
- Gestational Outcomes
- Neonatal Outcomes
- Neurobehavioral Outcomes

Huybrechts et al. JAMA Psychiatry 2017

- The largest compared 5,571 infants exposed to amphetamines and 2,072 exposed to methylphenidate with unexposed infants. It found no increased risks for adverse outcomes due to amphetamine or methylphenidate exposures.

Huybrechts et al. JAMA Psychiatry 2017



Conclusions

Women with mild to moderate ADHD symptoms may be able to forego treatment during pregnancy and function well. However, if symptoms are more severe and interfere significantly with daily functioning, continuing pharmacologic treatment during pregnancy may be important. Considering the high rate of unplanned pregnancies among young women, the potential for accidental exposure to stimulants in early pregnancy is also high. Our findings suggest that there might be a small increase in the risk of cardiac malformations associated with intrauterine exposure to methylphenidate. Although the absolute risk is small, it is nevertheless important evidence to consider when weighing the potential risks and benefits of different treatment strategies for ADHD in young women of reproductive age and in pregnant women.

Article Information

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Accepted for Publication: October 7, 2017.

Cohen et al. Obstet Gynecol 2017

CONCLUSION:

Psychostimulant use during pregnancy was associated with a small increased relative risk of preeclampsia and preterm birth. The absolute increases in risks are small and, thus, women with significant ADHD should not be counseled to suspend their ADHD treatment based on these findings.

Cohen et al. Obstet Gynecol 2017

- 3,331 infants exposed to amphetamines
- 1,515 exposed to methylphenidate
- 453 to atomoxetine.
- slightly increased risk of preeclampsia, with an adjusted risk ratio of 1.29 (95% CI 1.11-1.49)
- no statistically significant effect for placental abruption, small gestational age, and preterm birth.
- small increased risk of preterm birth, with an adjusted risk ratio of 1.3 (95% CI 1.10-1.55).
- There was no statistically significant effect for preeclampsia, placental abruption, or small gestational age. Atomoxetine use was free of any indication of increased risk.

Norby et al. Pediatrics 2017

- 1,591 infants exposed to ADHD medication (mostly methylphenidate) during pregnancy, reported increased risks associated with exposure.
- The adjusted odds ratio for admission to a neonatal intensive care unit was 1.5 (95% CI 1.3-1.7), and for central nervous system disorders was 1.9 (95% CI 1.1-3.1).
- There was no increased risk for congenital malformations or perinatal death.

Methlyphenidate Exposure

- Dideriksen et al. 2013
- Kallen et al 2013
- Haervig et al 2014
- Pottegard et al 2014
- Bro et al 2015
- Diav-Citrin et al 2016
- Koren et al 2020

Methylphenidate Data

Author	Exposed	Study Type
Dideriksen et al. 2013	180	Review
Pottegard et al. 2014	222	Population-based, cohort
Kallen et al. 2013	208	Prospective, observational
Bro et al. 2015	186	Population-based, cohort
Haervig et al. 2014	480	Population-based, cohort
Diav-Citrin et al. 2016	382	Prospective, comparative, multicenter observational
Koren et al. 2020	2831 (combined exposures from Pottegard, Diav-Citrin, Huybrechts & Kallen)	Scoping review and meta-analysis

Summary - Safety in Pregnancy

- While some studies have shown increased adverse effects among infants exposed to maternal ADHD medications, most have not.
- There are indications that higher rates of miscarriage are associated with maternal ADHD rather than fetal exposure to psychostimulant medications.
- One study did find a small increased risk of central nervous system disorders and admission to a neonatal intensive care unit. But, again, we do not know whether that was due to exposure to psychostimulant medication, or associated with maternal ADHD.

Take Home Message

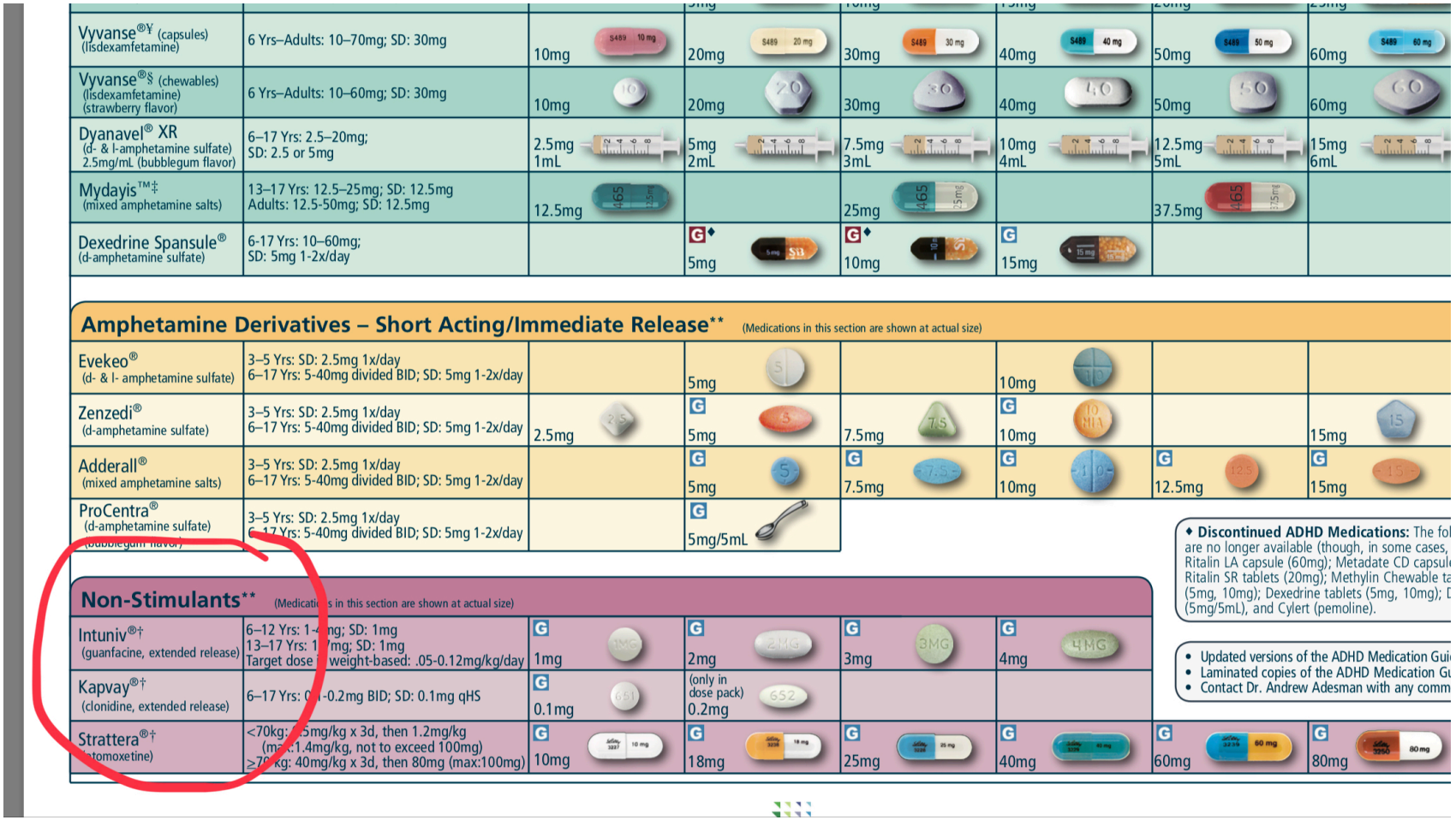
- If there is a risk, it appears to be a small one.
- The question then becomes how to balance that as yet uncertain risk against the disadvantage of discontinuing effective psychostimulant medication.

NEUROBEHAVIORAL OUTCOMES

Neurobehavioral Outcomes

- Behavioral teratogenicity: few human studies, and they are limited to stimulants in context of substance abuse (such as studies of prenatal cocaine exposure).
- Many of the neurodevelopmental studies showed no abnormalities. For example: 40 children exposed during pregnancy to methamphetamine (in some of them the mothers misused methamphetamine) showed no difference in cognitive function at 3–4 years of age compared to sex-matched controls, with the exception of slightly worse testing on the visual motor integration domain (Chang 2009).
- In general, stimulant use is generally not found to have impairment on standard cognitive tests or language/motor development. But the heaviest maternal cocaine use is linked to subtle effects in executive functioning (Freeman 2014).

Non-Stimulants



Vyvanse®¥ (capsules) (lisdexamfetamine)	6 Yrs–Adults: 10–70mg; SD: 30mg	10mg	20mg	30mg	40mg	50mg	60mg
Vyvanse®§ (chewables) (lisdexamfetamine) (strawberry flavor)	6 Yrs–Adults: 10–60mg; SD: 30mg	10mg	20mg	30mg	40mg	50mg	60mg
Dyanavel® XR (d- & l-amphetamine sulfate) 2.5mg/mL (bubblegum flavor)	6–17 Yrs: 2.5–20mg; SD: 2.5 or 5mg	2.5mg 1mL	5mg 2mL	7.5mg 3mL	10mg 4mL	12.5mg 5mL	15mg 6mL
Mydayis™‡ (mixed amphetamine salts)	13–17 Yrs: 12.5–25mg; SD: 12.5mg Adults: 12.5-50mg; SD: 12.5mg	12.5mg		25mg		37.5mg	
Dexedrine Spansule® (d-amphetamine sulfate)	6-17 Yrs: 10–60mg; SD: 5mg 1-2x/day		G♦ 5mg	G♦ 10mg	G 15mg		

Amphetamine Derivatives – Short Acting/Immediate Release** (Medications in this section are shown at actual size)

Evekeo® (d- & l- amphetamine sulfate)	3–5 Yrs: SD: 2.5mg 1x/day 6–17 Yrs: 5-40mg divided BID; SD: 5mg 1-2x/day		5mg		10mg		
Zenzedi® (d-amphetamine sulfate)	3–5 Yrs: SD: 2.5mg 1x/day 6–17 Yrs: 5-40mg divided BID; SD: 5mg 1-2x/day	2.5mg	G 5mg	7.5mg	G 10mg		15mg
Adderall® (mixed amphetamine salts)	3–5 Yrs: SD: 2.5mg 1x/day 6–17 Yrs: 5-40mg divided BID; SD: 5mg 1-2x/day		G 5mg	G 7.5mg	G 10mg	G 12.5mg	G 15mg
ProCentra® (d-amphetamine sulfate) (bubblegum flavor)	3–5 Yrs: SD: 2.5mg 1x/day 6–17 Yrs: 5-40mg divided BID; SD: 5mg 1-2x/day		G 5mg/5mL				

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

Intuniv®† (guanfacine, extended release)	6–12 Yrs: 1-4mg; SD: 1mg 13–17 Yrs: 1-7mg; SD: 1mg Target dose weight-based: .05-0.12mg/kg/day	G 1mg	G 2mg	G 3mg	G 4mg		
Kapvay®† (clonidine, extended release)	6–17 Yrs: 0.1-0.2mg BID; SD: 0.1mg qHS	G 0.1mg	(only in dose pack) 0.2mg				
Strattera®† (atomoxetine)	<70kg: 0.5mg/kg x 3d, then 1.2mg/kg (max:1.4mg/kg, not to exceed 100mg) ≥70kg: 40mg/kg x 3d, then 80mg (max:100mg)	G 10mg	G 18mg	G 25mg	G 40mg	G 60mg	G 80mg

♦ **Discontinued ADHD Medications:** The fol
are no longer available (though, in some cases,
Ritalin LA capsule (60mg); Metadate CD capsul
Ritalin SR tablets (20mg); Methylin Chewable ta
(5mg, 10mg); Dexedrine tablets (5mg, 10mg);
(5mg/5mL), and Cylert (pemoline).

- Updated versions of the ADHD Medication Gui
- Laminated copies of the ADHD Medication Gu
- Contact Dr. Andrew Adesman with any comm

Non-Stimulants

- Bupropion:
  - May be a reasonable option if has been exposed to it before with good effect, with concurrent depression, and/or need for smoking cessation (Freeman 2014).
  - Amount of data available for bupropion exceeds that for other medications used in the treatment of ADHD.
  - Published reports regarding its safety during pregnancy and lactation are relatively reassuring - not as efficacious as stimulants in the treatment of ADHD.

Non-Stimulants

- Atomoxetine, Guanfacine and Clonidine: No systematic studies in human pregnancy for these agents.
  - Atomoxetine: Swedish registry had 34 women on atomoxetine, 22 in 1st trimester and 12 in 2nd or 3rd trimester; no congenital anomalies (Kallen 2013)
  - Clonidine: One prospective study 1985 on 100 hypertensive pregnant women; no increased malformation rate.
    - 82 hypertensive women: No malformations, one perinatal death (Tuimala 1985)
  - Guanfacine: One study on 30 women with preeclampsia treated with guanfacine for 16-68 days
    - No malformations but 20% had low birth weight (possible 2/2 preeclampsia) (Phillip 1980)

Absence of evidence of risk is not evidence of absence of risk.

Patient and provider engage in shared decision-making via risk/risk analysis.

Assessing Relative Risk:

Case: A 32 year old attorney with ADHD planning pregnancy.

- ADHD combined type since age 6.
- Tried several stimulants and non stimulants.
- Currently on Methylphenidate ER 40 mg daily.
- Decided to stay on until conception and then use PRN.

Case: ADHD during Pregnancy

- Ms. C conceived within 2 months of trying.
- ADHD “under control.”
- Plans to stop work at 36 weeks gestation.
- Asks about postpartum and lactation.
- In dosages prescribed for medical indications, limited evidence indicates that methylphenidate levels in milk are very low and not detectable in infant serum.

Case Continued

- Methylphenidate is secreted in small amounts in milk but is generally undetected in infant's blood.
- No contraindication to breast feeding.

Hackett et al. 2006
Spigset et al. 2007
Scharfer et al. 2015

Amphetamines in Breastfeeding

- Amphetamines are excreted in human milk, and a dose of 20 mg/day amphetamine sulfate is enough to transfer measurable amounts of amphetamine to the urine of an exposed infant (Steiner 1984).

- In a study involving 103 nursing infants whose mothers were taking various amounts of amphetamine, no neonatal insomnia or stimulation was observed over a 24- month observation period. The presence of methamphetamine and amphetamine in milk was also demonstrated in two lactating women using intravenous methamphetamine (Illett 2007).

- There seems to be no data on the long-term consequences of exposure through breastfeeding. Due to the relatively high milk levels and possible effects on the nursing infant breast feeding is contraindicated per some authors (Schaefer 2015).

- Clinically, my experience has been that many women elect to nurse on both IR and XR formulations of Adderall. They do this by weighing the 'possible effects on the nursing infant' against case report data of no neonatal insomnia, stimulation, abnormal development or growth problems.

Summary

- From the current available data from prospective, retrospective and case control studies it can be concluded that none of the medications (except guanfacine, where data is unavailable) used for the treatment of ADHD is a major human teratogen.

- Available data do suggest the possibility that psychostimulants, especially amphetamines, may increase the risk of preeclampsia and possibly certain other adverse gestational outcomes; the absolute risk, however, is low.

- Long-term neurodevelopmental studies on the offspring are sparse

- If treatment is pursued, methylphenidate, amphetamine and bupropion appear to be better choices than other medication where reproductive safety data are sparse

Clinical Implications and Treatment Considerations

- Although the default medical position is to interrupt any “non-essential” pharmacological treatment during pregnancy and lactation, in ADHD this may present a significant risk.

- Many patients decide to minimize exposure to ADHD medications during pregnancy with optimization of treatment postpartum

- The clinician evaluates each case carefully and performs a risk-risk analysis with the patient prior to developing a treatment plan for pregnancy:
  - the risks of medication exposure throughout the pregnancy weighed against the risks of untreated ADHD, including ***driving safety***, and ***major impairment in fulfilling occupational and domestic roles***
  - Recommendations to reduce workload
  - Recommend CBT for ADHD
  - Increase structure and organization at work or school
  - Employers may be able to offer accommodations

Psychiatric Comorbidity in Pregnant Women with ADHD

Diagnosis	Group A (n=8)	Group B (n=8)	Group C (n=12)	Overall (n=28)
	N (%)			
Generalized Anxiety Disorder (GAD)	5 (62.5%)	4 (50%)	5 (41.67%)	14 (50%)
Major Depressive Disorder (MDD)	2 (16.67%)	3 (37.5%)	4 (33.33%)	9 (32.14%)
Panic Disorder	1 (12.5%)	1 (12.5%)	1 (8.33%)	3 (10.71%)
Bipolar Disorder II	3 (37.5%)	0	0	3 (10.71%)
Obsessive Compulsive Disorder (OCD)	1 (12.5%)	1 (12.5%)	0	2 (7.14%)
Post-Traumatic Stress Disorder (PTSD)	0	1 (12.5%)	0	1 (3.57%)

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