

Update in ADHD: Focus on Pharmacotherapy

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Disclosures*

Source	Consultant	Employee	Grant Support	Royalties
Bay Cove Human Services (Clinical)	X			
Cambridge University Press				X
Food and Drug Administration			X	
Gavin Foundation (Clinical)	X			
Guilford Press				X
Massachusetts General Hospital		X		
National Institute on Drug Abuse			X	
US Minor/Major League Baseball	X			

*past year

Some of the medications discussed may not be FDA approved in the manner in which they are discussed including diagnosis(es), combinations, age groups, dosing, or in context to other disorders (e.g., substance use disorders).

ADHD Overview



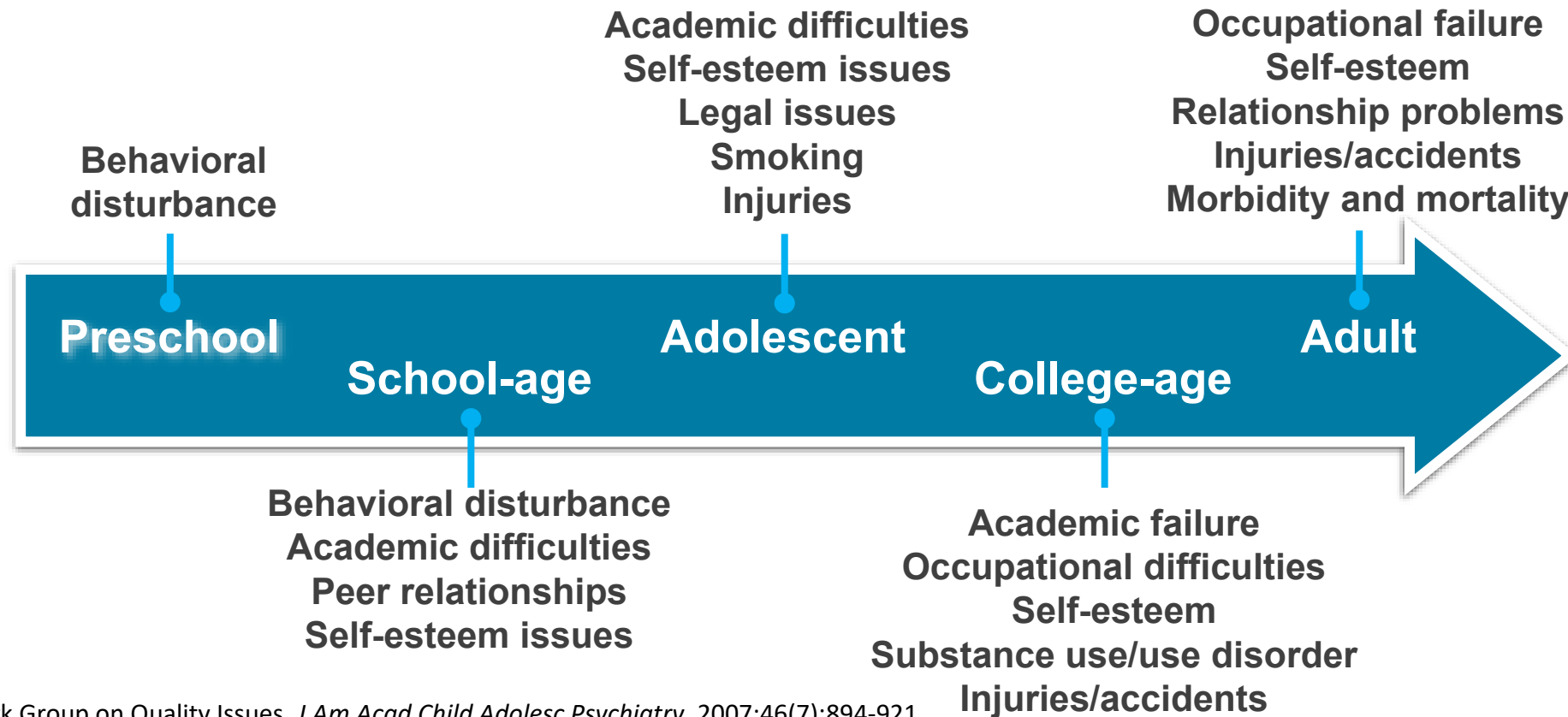
- **ADHD prevalence among 8- to 15-year-olds: 8.7%**
- **ADHD prevalence among 18- to 44-year-olds: 4.4%**
- **Associated with chronic course**
 - **Circa 75% persistence from childhood into adolescence**
 - **Circa 50% persistence from childhood into adulthood**
- **Associated with high degrees of psychiatric comorbidity**
- **Associated with impairment in multiple domains**

Kessler RC, et al. *Am J Psychiatry*. 2006;163(4):716-723.

Newcorn J & Wilens T. Update on Pharmacotherapy of ADHD, Elsevier Press, 2022.

International Statement on ADHD, 2021.

Developmental Impact of Untreated ADHD



Pliszka S. AACAP Work Group on Quality Issues. *J Am Acad Child Adolesc Psychiatry*. 2007;46(7):894-921.

Brown TE, et al. *Postgrad Med*. 2010;122(5):42-51.

Adler, Spencer, Wilens ADHD in Children and Adults, 2015, Cambridge Press.

ADHD: Core Symptom Areas

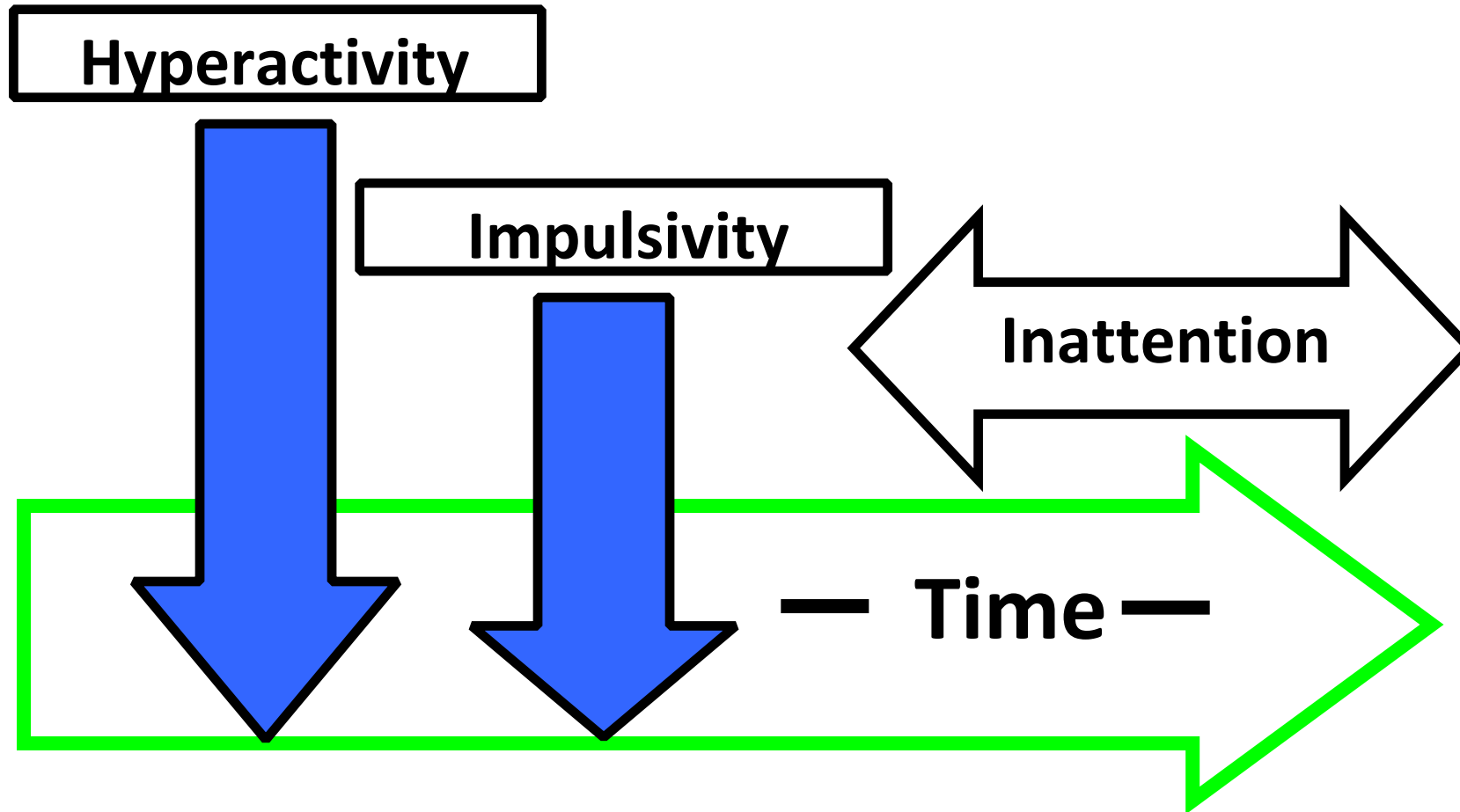


Inattention



Impulsivity/Hyperactivity

ADHD: Course of the Disorder



Diagnosis of ADHD

- **Developmentally inappropriate symptoms**
 - **6/9 Symptoms of Inattention, Hyperactivity or Combination**
 - **5/9 if ≥ 17 years of age (adult)**
 - **95% of cases are either combined or inattentive subtype**
- **Age of onset ≤ 12 years**
- **Not accounted for by other disorder**
 - **Can make diagnosis of Autism Spectrum and ADHD**
- **Diagnosis Clinically Derived**
- **Rating Scales Helpful (Parent, School)**
 - **Narrow: Vanderbilt (AAP), others**
 - **Broadband: Child Behavior Checklist**

Vanderbilt ADHD Diagnostic Parent Rating Scale

Patient Name: _____ Today's Date: _____

Date of Birth: _____ Age: _____

Grade: _____

Each rating should be considered in the context of what is appropriate for the age of your child.

Frequency Code: 0 = Never; 1 = Occasionally; 2 = Often; 3 = Very Often

1. Does not pay attention to details or makes careless mistakes, such as in homework	0	1	2	3
2. Has difficulty sustaining attention to tasks or activities	0	1	2	3
3. Does not seem to listen when spoken to directly	0	1	2	3
4. Does not follow through on instruction and fails to finish schoolwork (not due to oppositional behavior or failure to understand)	0	1	2	3
5. Has difficulty organizing tasks and activities	0	1	2	3
6. Avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort	0	1	2	3
7. Loses things necessary for tasks or activities (school assignments, pencils, or books)	0	1	2	3
8. Is easily distracted by extraneous stimuli	0	1	2	3
9. Is forgetful in daily activities	0	1	2	3
10. Fidgets with hands or feet or squirms in seat	0	1	2	3
11. Leaves seat when remaining seated is expected	0	1	2	3
12. Runs about or climbs excessively in situations when remaining seated is expected	0	1	2	3
13. Has difficulty playing or engaging in leisure activities quietly	0	1	2	3
14. Is "on the go" or often acts as if "driven by a motor"	0	1	2	3
15. Talks too much	0	1	2	3
16. Blurts out answers before questions have been completed	0	1	2	3
17. Has difficulty waiting his or her turn	0	1	2	3
18. Interrupts or intrudes on others (butts into conversations or games)	0	1	2	3
19. Argues with adults	0	1	2	3
20. Loses temper	0	1	2	3
21. Actively defies or refuses to comply with adults' requests or rules	0	1	2	3
22. Deliberately annoys people	0	1	2	3
23. Blames others for his or her mistakes or misbehaviors	0	1	2	3
24. Is touchy or easily annoyed by others	0	1	2	3
25. Is angry or resentful	0	1	2	3

ADHD Scoring:

Predominantly Inattentive subtype ■

Must score a 2 or 3 on 6 out of 9 items on questions 1–9 AND ■ Score a 4 or 5 on any of the Performance questions 48–55 Predominantly

Hyperactive/Impulsive subtype ■

Must score a 2 or 3 on 6 out of 9 items on questions 10–18 AND ■ Score a 4 or 5 on any of the Performance questions 48–55 ADHD Combined ■
Requires the above criteria on both inattention and hyperactivity/impulsivity

Also screens conduct, oppositional, anxiety

Adult ADHD Self-Report Scale (ASRS-v1.1) Symptom Checklist

Patient Name	Today's Date						
Please answer the questions below, rating yourself on each of the criteria shown using the scale on the right side of the page. As you answer each question, place an X in the box that best describes how you have felt and conducted yourself over the past 6 months. Please give this completed checklist to your healthcare professional to discuss during today's appointment.			Never	Rarely	Sometimes	Often	Very Often
1. How often do you have trouble wrapping up the final details of a project, once the challenging parts have been done?							
2. How often do you have difficulty getting things in order when you have to do a task that requires organization?							
3. How often do you have problems remembering appointments or obligations?							
4. When you have a task that requires a lot of thought, how often do you avoid or delay getting started?							
5. How often do you fidget or squirm with your hands or feet when you have to sit down for a long time?							
6. How often do you feel overly active and compelled to do things, like you were driven by a motor?							
Part A							
7. How often do you make careless mistakes when you have to work on a boring or difficult project?							
8. How often do you have difficulty keeping your attention when you are doing boring or repetitive work?							
9. How often do you have difficulty concentrating on what people say to you, even when they are speaking to you directly?							
10. How often do you misplace or have difficulty finding things at home or at work?							
11. How often are you distracted by activity or noise around you?							
12. How often do you leave your seat in meetings or other situations in which you are expected to remain seated?							
13. How often do you feel restless or fidgety?							
14. How often do you have difficulty unwinding and relaxing when you have time to yourself?							
15. How often do you find yourself talking too much when you are in social situations?							
16. When you're in a conversation, how often do you find yourself finishing the sentences of the people you are talking to, before they can finish them themselves?							
17. How often do you have difficulty waiting your turn in situations when turn taking is required?							
18. How often do you interrupt others when they are busy?							
Part B							

WHO ADHD Screener

Adults with ADHD Underreport Past Childhood Symptoms

Article

Accuracy of Adult Recall of Childhood Attention Deficit Hyperactivity Disorder

Salvatore Mannuzza, Ph.D.

Rachel G. Klein, Ph.D.

Donald F. Klein, M.D.

Abrah Bessler, Ph.D.

Patrick Shrout, Ph.D.

Objective: Although reports of childhood status are necessary for making a diagnosis of adult attention deficit hyperactivity disorder (ADHD), systematic investigation of the accuracy of retrospective self-reports has been limited. This study examined accuracy of adult recall of childhood ADHD.

Method: Participants were from a controlled, prospective 16-year follow-up of children with ADHD. At a mean age of 25 years, 176 probands (85% of the 207 subjects in the initial cohort) and 168 non-ADHD comparison subjects were interviewed by clinicians who were unaware of the subjects' childhood status. Subjects were asked about specific childhood ADHD behaviors, and the diagnosis of childhood ADHD was retrospectively established.

Results: Seventy-eight percent of the probands and 11% of the comparison subjects were identified as having childhood ADHD. Six symptoms demonstrated high discriminating power in differentiating the subject groups: distractibility, con-

centration difficulties, complaints of inattention, acting before thinking, being on the go, and fidgeting/squirming. When findings were adjusted for the prevalence of ADHD in the general population, the power of prediction was low. Positive predictive value was 0.27, i.e., of all adults retrospectively given a diagnosis of childhood ADHD, only 27% would be correctly identified. As expected, positive predictive value increased with increases in the estimated prevalence of ADHD.

Conclusions: Retrospective diagnoses of childhood ADHD made on the basis of self-reports will in most cases be invalid in settings such as epidemiological surveys and primary care facilities. Greater accuracy can be expected in settings in which childhood ADHD is frequent. The results stress the importance of obtaining contemporaneous information on childhood symptoms in establishing a childhood history of ADHD. Future directions and implications for DSM-V are discussed.

[Am J Psychiatry 2002; 159:1882-1888]

Table 3 Number of ADHD childhood symptoms reported by participants (self-rating) and their parents

From: The Accuracy of Retrospective Recall of Childhood ADHD: Results from a Longitudinal Study

	Parent rating in childhood (FBB-ADHS) ^a	Retrospective parent rating (FEA-FFB) ^b	Retrospective self-rating (FEA-FSB) ^c
	n = 55	n = 49	n = 53
0–2 ADHD symptoms	n = 0 0.0%	n = 5 10.2%	n = 9 17.0%
3–5 ADHD symptoms	n = 3 5.5%	n = 7 14.3%	n = 8 15.1%
≥ 6 ADHD symptoms	n = 52 94.6%	n = 37 75.5%	n = 36 67.9%
Number of ADHD symptoms	M = 15.00 SD = 5.06	M = 12.10 SD = 6.78	M = 8.70 SD = 5.69

[Home](#) > [Journal of Psychopathology and Behavioral Assessment](#) > [Article](#)

The Accuracy of Retrospective Recall of Childhood ADHD: Results from a Longitudinal Study

[Open access](#) | Published: 07 December 2020

Volume 43, pages 413–426, (2021) [Cite this article](#)

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[Elena von Wirth](#) , [Janet Mandler](#), [Dieter Breuer](#) & [Manfred Döpfner](#)

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) is a childhood-onset condition that may continue into adulthood. When assessing adult patients, clinicians usually rely on retrospective reports of childhood symptoms to evaluate the age-of-onset criterion. Since inaccurate symptom recall may impede the diagnosis and treatment of ADHD, knowledge about the factors influencing retrospective reports is needed. This longitudinal study investigated (a) the accuracy of retrospective symptom ratings by adult participants with a childhood diagnosis of ADHD (self-ratings) and parents or significant others (proxy ratings), and (b) the influence of current ADHD symptom severity and ADHD-associated impairments on retrospective symptom ratings. Participants ($N = 55$) were members of the Cologne Adaptive Multimodal Treatment (CAMT) study who had been referred and treated for ADHD in childhood and were reassessed in adulthood (average age 27 years).

Participants' retrospective self-ratings were substantially lower than, and did not correlate with, parents' ADHD symptom ratings provided at study entry, while retrospective symptom ratings provided by proxy respondents correlated moderately with parents' childhood ratings. In addition, participants were more likely to underreport childhood symptoms (79%) and more frequently denied the presence of three or more childhood symptoms (17%) compared to proxy respondents (65% underreporting, 10% false-negative recall). Proxy respondents' symptom recall was best predicted by childhood ADHD, while participants' symptom recall was best predicted by current ADHD symptom severity. ADHD-associated impairments were not correlated with symptom recall after controlling for childhood ADHD. Together, these findings suggest a recall bias in adult patients and question the validity of retrospective reports, even in clinical samples.

Characteristics and Predictors of Fluctuating Attention-Deficit/Hyperactivity Disorder in the Multimodal Treatment of ADHD (MTA) Study

Margaret H Sibley^{1,2}, Traci M Kennedy³, James M Swanson⁴, L Eugene Arnold⁵, Peter S Jensen⁶, Lily T Hechtman⁷, Brooke S G Molina³, Andrea Howard⁸, Laurence Greenhill⁹, Andrea Chronis-Tuscano¹⁰, John T Mitchell¹¹, Jeffrey H Newcorn¹², Luis A Rohde^{13,14,15}, Stephen P Hinshaw^{16,17}

Affiliations + expand

PMID: 39431909 DOI: 10.4088/JCP.24m15395

Abstract

Objectives: Recent studies report a fluctuating course of attention-deficit/hyperactivity disorder (ADHD) across development characterized by intermittent periods of remission and recurrence. In the Multimodal Treatment of ADHD (MTA) study, we investigated fluctuating ADHD including clinical expression over time, childhood predictors, and between- and within-person associations with factors hypothesized as relevant to remission and recurrence.

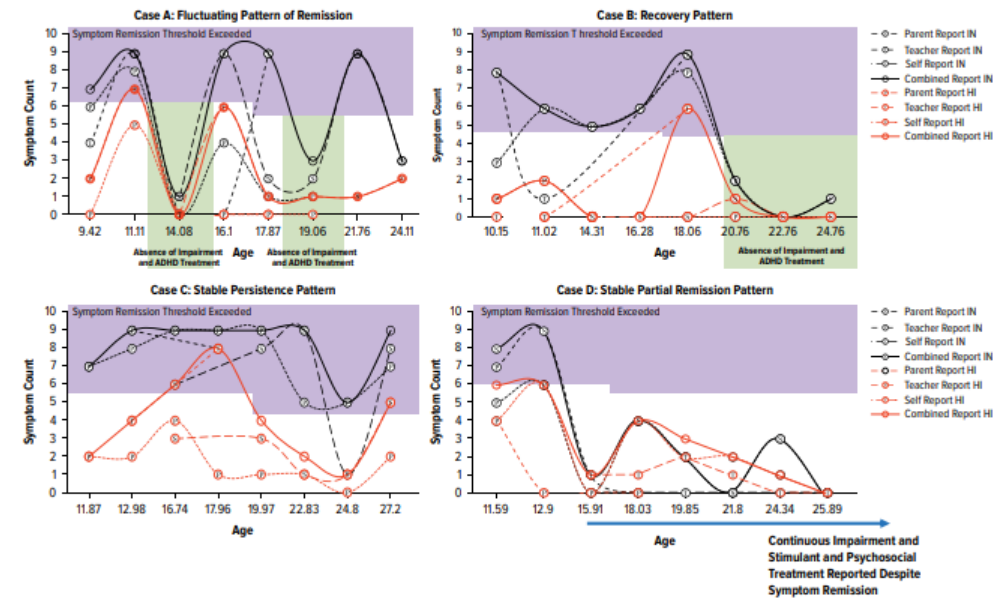
Methods: Children with DSM-5 ADHD, combined type (N = 483), participating in the MTA adult follow-up were assessed 9 times from baseline (mean age = 8.46) to 16-year follow-up (mean age = 25.12). The fluctuating subgroup (63.8% of sample) was compared to other MTA subgroups on variables of interest over time.

Results: The fluctuating subgroup experienced multiple fluctuations over 16 years (mean = 3.58, SD = 1.36) with a 6- to 7-symptom within-person difference between peaks and troughs. Remission periods typically first occurred in adolescence and were associated with higher environmental demands (both between- and within-person), particularly at younger ages. Compared to other groups, the fluctuating subgroup demonstrated moderate clinical severity. In contrast, the stable persistent group (10.8%) was specifically associated with early and lasting risk for mood disorders, substance use problems in adolescence/young adulthood, low medication utilization, and poorer response to childhood treatment. Protective factors were detected in the recovery group (9.1%; very low parental psychopathology) and the partial remission group (15.6%; higher rates of comorbid anxiety).

Conclusions: In the absence of specific risk or protective factors, individuals with ADHD demonstrated meaningful within-individual fluctuations across development. Clinicians should communicate this expectation and monitor fluctuations to trigger as-needed return to care. During remission periods, individuals with ADHD successfully manage increased demands and responsibilities.

Trial Registration: ClinicalTrials.gov identifier: NCT00003388.

Case Examples and Definitions of Longitudinal Remission Subgroups^a

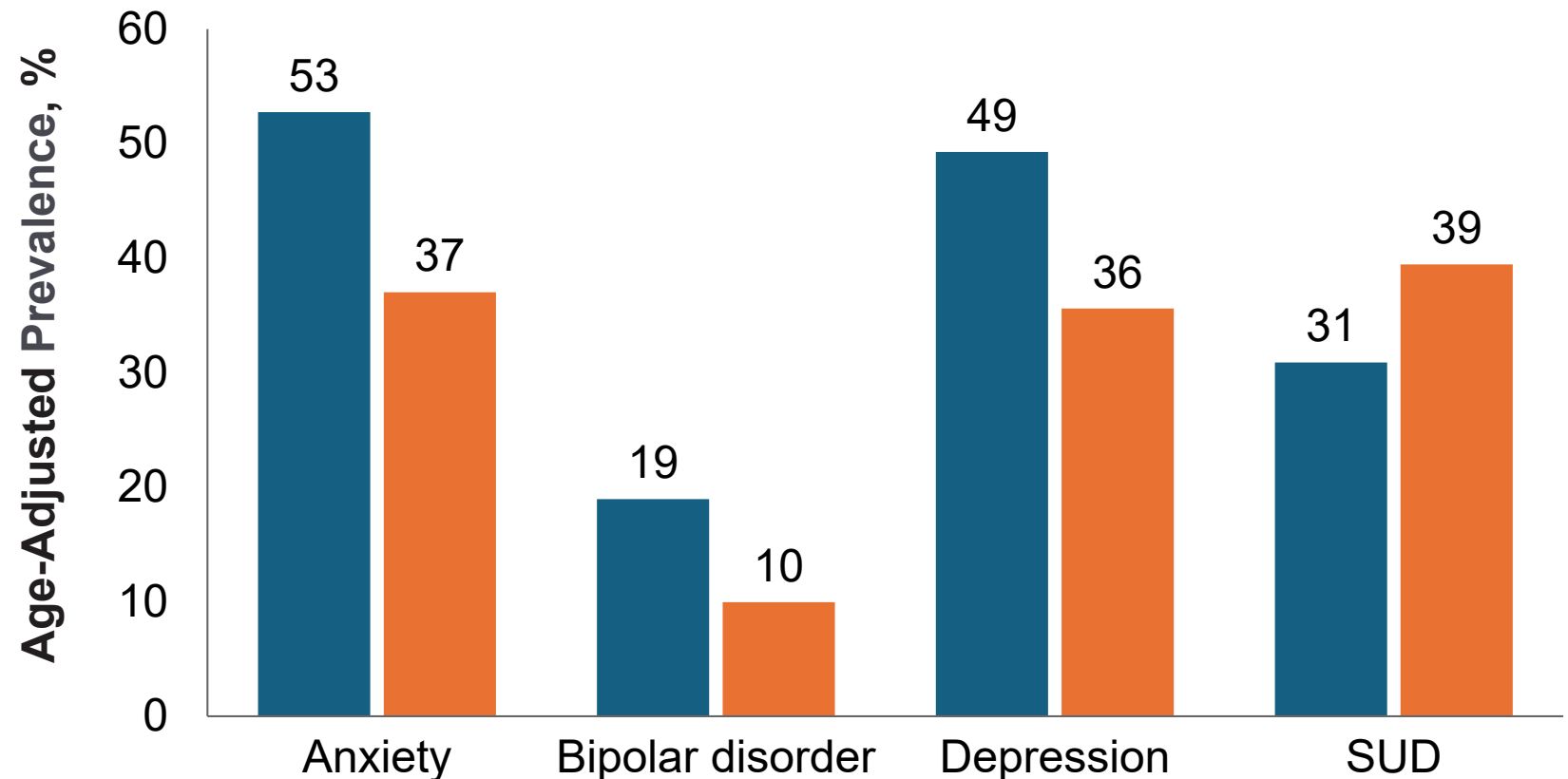


Comorbidity in ADHD Is the Rule, Not the Exception

- **Psychiatric Comorbidities in Adults With ADHD**
- Reported rates vary, but McGough et al found^[1]
 - 87% had ≥ 1
 - 56% had ≥ 2
- Anxiety, depression, and SUD are the most common^[1,2]
- Comorbidities shift from childhood to adulthood^[3]

- **Prevalence of Psychiatric Comorbidities in Adults Aged 18 to 64 Years With an ADHD Diagnosis^[2]**

■ Women (n = 26,737) ■ Men (n = 34,392)



1. McGough JJ, et al. Am J Psychiatry. 2005;162:1621-1627; 2. Chen Q, et al. PLoS One. 2018;13:e0204516; c. Banaschewski T, et al. Dtsch A

Comorbidity

Developing a Treatment Plan: Education and Support

- Educate about ADHD and the individual's strengths and weaknesses
- Use local and online resources for education and support
- Aid in implementation of home, school, lifestyle accommodations (e.g., quiet work space, extra time for tests)
- Consider vocational assessment/career counseling
- Set reasonable expectations of pharmacologic and psychosocial treatment
- Assist in transitions (e.g., → middle, high school, occupation/college)

Pliszka. AACAP Work Group on Quality Issues. *J Am Acad Child Adolesc Psychiatry*. 2007;46(7):894-921.
Available at:

http://www.aacap.org/cs/root/member_information/practice_information/practice_parameters/practice_parameter_s.

Accessed January 19, 2009. Murphy. *J Clin Psychology*. 2005;61:607-619.

Psychotherapies Are Helpful for ADHD

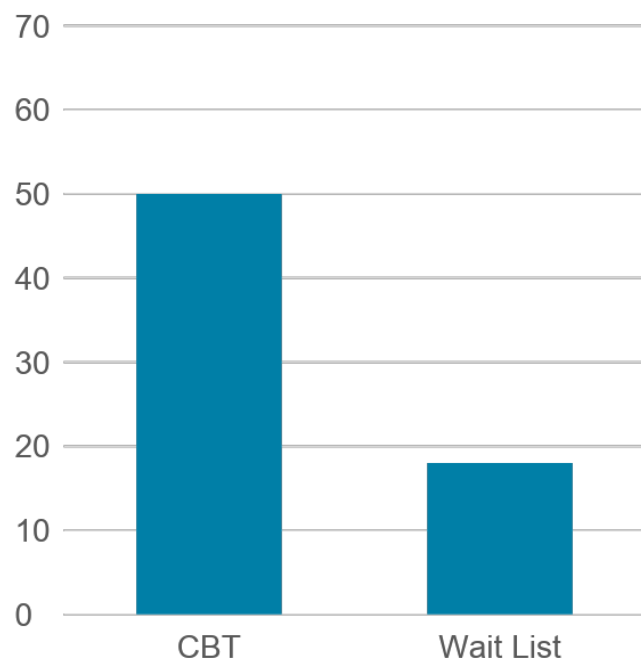


- **Focused psychotherapies:**
 - **Cognitive Behavioral Therapy**
 - **Behavioral Therapy**
- **Parent-based training**
- **Organizational training**
- **Wellness /resilience: *MGH Child Resiliency Program***
 - **Mindfulness/Meditation**
 - **Coping skills**
- **All are telehealth friendly**

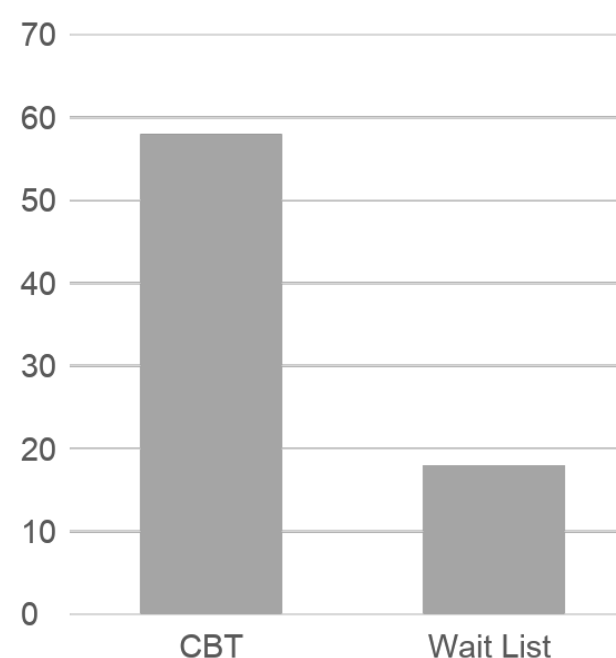
MGH Randomized Controlled Trial of CBT for ADHD in Medication Treated Adolescents

4 Month Responder Status (% responders, n=46)

Parent Report



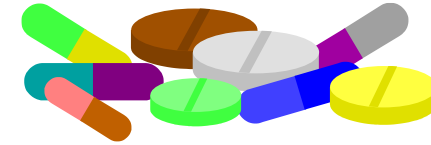
Adolescent Report



30% reduction on the ADHD rating scale=categorical responder, (Chi Sq (1) = 8.98, p=.00 for parent; Chi Sq (1) = 5.87, p=.02 for adolescent)
Sprich, et. al. *J Child Psychology & Psychiatry*. 2016.

Medications: Attention-Deficit/Hyperactivity Disorder

Pharmacological Treatment



FDA Approved

Stimulants
Methylphenidate
Amphetamines

Alpha Agonists
Guanfacine (XR)
Clonidine (XR)
Guan XR or Clon XR +
stimulants

Atomoxetine

Viloxazine XR

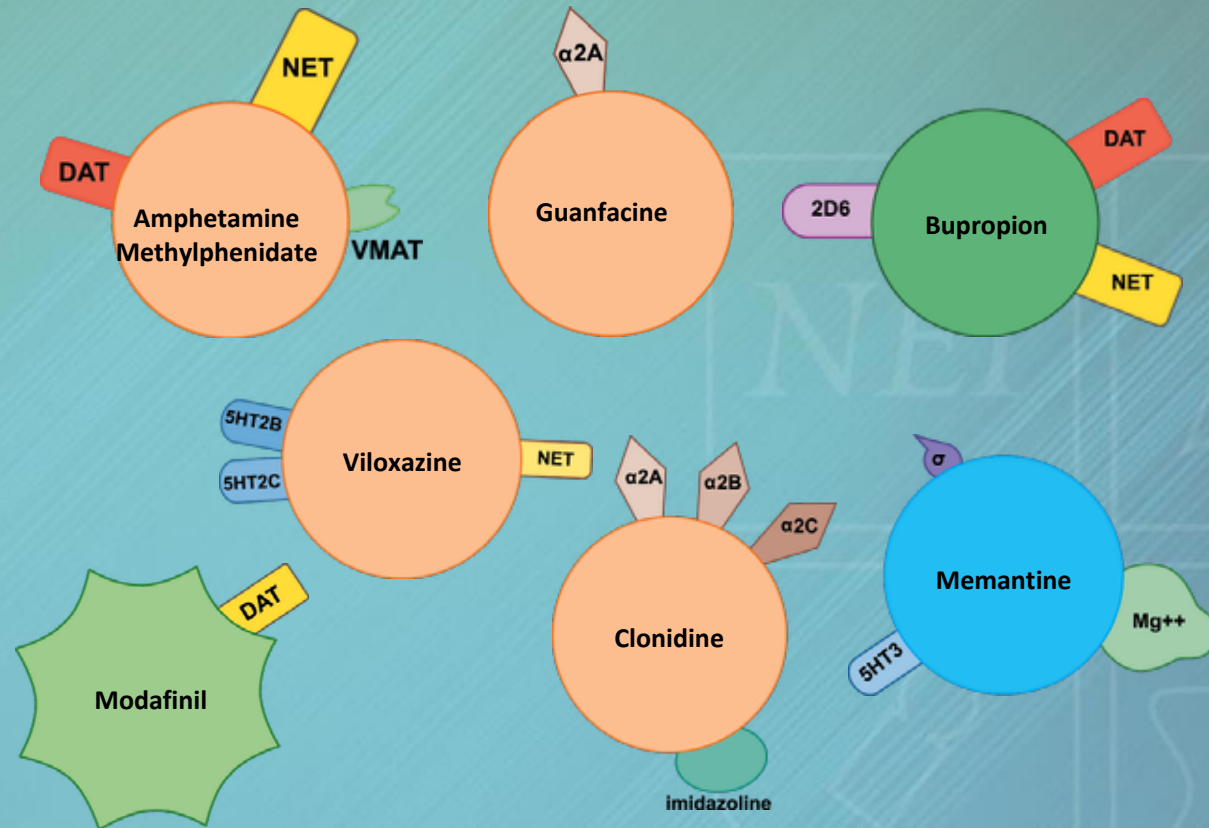
Centanafadine

Not FDA Approved

Antidepressants
Bupropion
Tricyclics

Combination/others
Modafinil
Memantine

Medications for ADHD



Wilens TE et al. Postgrad Med 2010;122(5):97-109; Newcorn JH, Wilens TE. Child Adolesc Psych Clin N Am 2022;31(3):xiii-xiv; www.drugs.com.



Original Investigation | Psychiatry

Treatment of US Children With Attention-Deficit/Hyperactivity Disorder in the Adolescent Brain Cognitive Development Study

Mark Olsson, MD, MPH; Melanie M. Wall, PhD; Shuai Wang, PhD; Gonzalo Laje, MD; Carlos Blanco, MD, PhD

Abstract

IMPORTANCE Characterizing the extent and pattern of unmet needs for treatment of children with attention-deficit/hyperactivity disorder (ADHD) could help target efforts to improve access to ADHD medications and outpatient mental health care.

OBJECTIVE To describe current ADHD medication use and lifetime outpatient mental health care among a large national sample of children with ADHD.

DESIGN, SETTING, AND PARTICIPANTS This study uses cross-sectional survey data from the first wave of the Adolescent Brain and Cognitive Development Study (n = 11 723), conducted from June 1, 2016, to October 15, 2018, among 1206 school children aged 9 and 10 years who met parent-reported *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) criteria for current

Key Points

Question What percentage of children with parent-reported attention-deficit/hyperactivity disorder (ADHD) receive treatment?

Findings In this cross-sectional study of 11 723 children aged 9 and 10 years, 12.9% of children with parent-reported ADHD were currently receiving ADHD medications, including 15.7% of boys, 7.0% of girls, 14.8% of White children, 9.4% of Black children, 32.3% of

This cross-sectional study of children with parent-reported ADHD suggests that most were not receiving ADHD medications and had never received outpatient mental health care

(27.7% [47 of 174]) than \$75 000 or more (20.1% [125 of 599]), and children with the combined subtype of ADHD (33.6% [166 of 505]) than with the predominantly inattentive subtype (20.0% [101 of 523]) or the hyperactive-impulsive subtype (22.4% [34 of 178]) of ADHD.

CONCLUSIONS AND RELEVANCE This cross-sectional study of children with parent-reported ADHD suggests that most were not receiving ADHD medications and had never received outpatient mental health care. Gaps in treatment, which were not directly associated with socioeconomic disadvantage, underscore the challenges of improving communication and access to outpatient mental health care for children with ADHD.

JAMA Network Open. 2023;6(4):e2310999. doi:10.1001/jamanetworkopen.2023.10999

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JAMA Network Open. 2023;6(4):e2310999. doi:10.1001/jamanetworkopen.2023.10999

April 28, 2023 1/14

Methylphenidate (MPH) in ADHD

Medication	Starting Dose	Maximum Dose*	Duration
Ritalin IR®	5 mg QD/BID	2 mg/kg/day	4 hr / BID
Focalin®	2.5 mg QD/BID	1 mg/kg/day	4–5 hr / BID–TID
Focalin XR®	5 mg QD	1 mg/kg/day	10–12 hr QD
Daytrana®	10 mg		6–16 hr
Concerta®	18 mg QD	2 mg/kg/day	12 hr / once
Metadate CD®	20 mg QD		8 hr / once
Ritalin LA®	20 mg QD		8 hr / once
Quillivant XR®	<10 mg QD		12 hr / once
Quillichew ER®	<10 mg QD		8 hr / once
Cotempla XR-ODT® (disintegrating tab)	8.6 mg QD	51.8 mg	12 hr / once
Aptensio XR®	10 mg QD	2 mg/kg/day	12 hr / once
Adhansia XR®	25 mg QD		12 hr / once
Jornay PM® (delayed release)	20 mg QD	100 mg	12 hr / once
Azstarys™ (serdexMPH, MPH)	26.1/5.2 mg QD	52.3/10.4 mg	13 hr / once

*May exceed FDA approved dose.

Wilens TE, et al. *CNS News*. 2007.

Wilens TE, et al. *Postgrad Med*. 2010;122(5):97-109.

Childress A. The Stimulants in *Update in the Update in the Pharmacotherapy of ADHD*. *Child Adolesc Psych Clin N Am*. Newcord & Wilens (eds.), Elsevier Press, 2022.

www.drugs.com. US Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products.

www.accessdata.fda.gov/scripts/cder/daf/.

Amphetamine (AMPH) in ADHD

Medication	Starting Dose	Maximum Dose* Usual Dosing	Duration
Adderall®	2.5–5 mg QD	1.5 mg/kg/day	6 hr / BID
Adderall XR®	2.5–5 mg QD		12 hr / QD
Vyvanse®	30 mg QD		12–14 hr / QD
Mydayis®	12.5 mg QD	50/25 mg (adults/adolescents)	To 16 hr / QD
Dexedrine Tablets®	2.5–5 mg BID	1.5 mg/kg/day	3–5 hr / BID–QID
Evekeo®	2.5–5 mg BID		3–5 hr / BID–QID
Dexedrine Spansule®	5 mg QD		6 hr / QD–BID
Dyanavel® XR (suspension)	2.5–5 mg QD	1.5 mg/kg/day	13 hr / QD
Adzenys XR-ODT® (disintegrating tab)	6.3–12.5 mg QD	12.5 mg (adolescents)	12 hr / QD
Xelstryl (Patch)	4.5 mg		12 hr / QD

Wilens TE, et al. *CNS News*. 2007.

Wilens TE, et al. *Postgrad Med*. 2010;122(5):97-109.

Childress A. The Stimulants in *Update in the Pharmacotherapy of ADHD*. *Child Adolesc Psych Clin N Am*. Newcord & Wilens (eds.), Elsevier Press, 2022.

www.drugs.com. US Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. www.accessdata.fda.gov/scripts/cder/daf/.

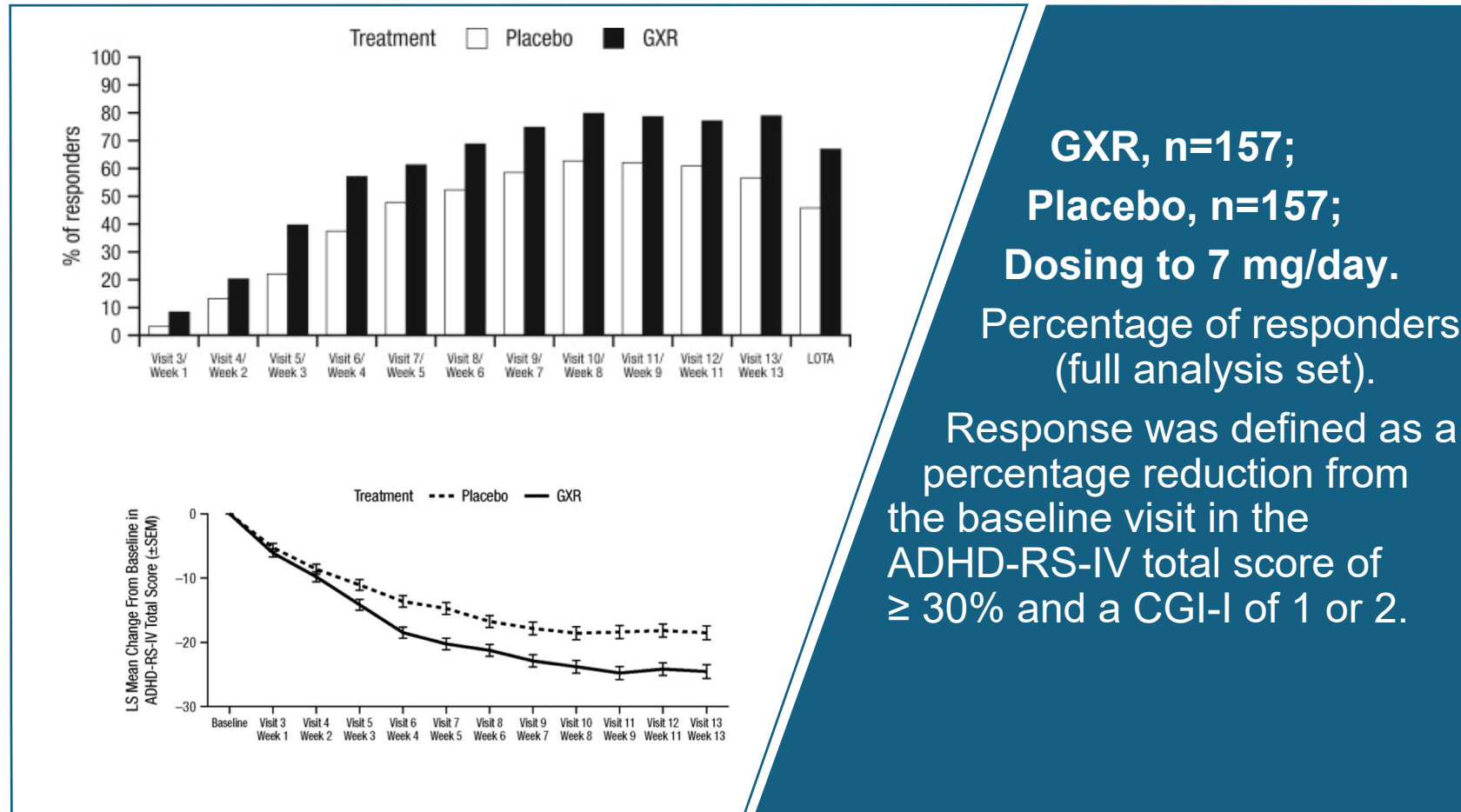
*May exceed FDA approved dose.

Adverse Effects of Stimulants

- Adverse effects (AEs) are similar for all stimulants
 - Decreased appetite
 - Insomnia
 - Headache
 - Stomachache
 - Irritability/rebound phenomena
- Rates of these AEs may be high prior to any medical intervention; thus, baseline levels should always be obtained

Wilens T, Spencer T. In: *Child and Adolescent Psychiatric Clinics of North America*. Philadelphia, Pa: Saunders Press; 2000;573-604.

Guanfacine XR in Adolescent ADHD



CGI-I = Clinical Global Impressions–Improvement

Wilens TE, et al. *J Am Acad Child Adolesc Psychiatry*. 2015;54(11):916-925.e2.

Atomoxetine

Uses

- **Uncomplicated ADHD**
- **Refractory ADHD**
- **Comorbid ADHD**
 - **Anxiety or depressive disorders**
 - **Tic disorders**
 - **Disruptive disorders**
 - **Substance use disorders**

Safety

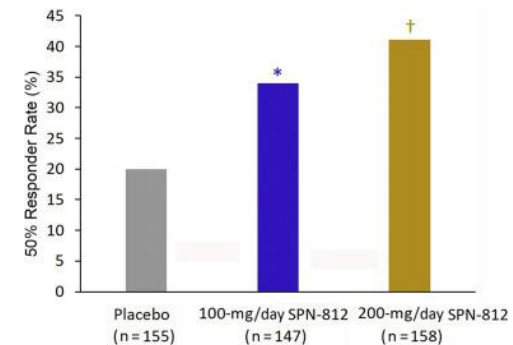
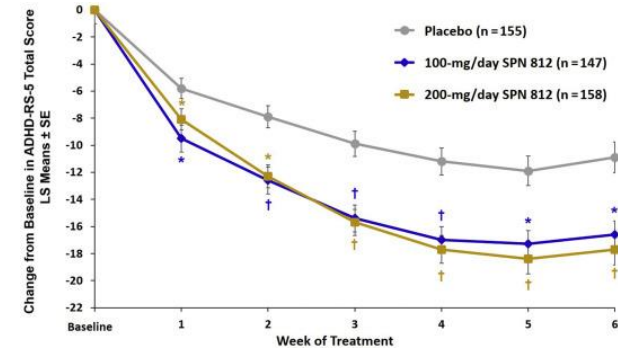
- **Rare hepatitis reported**
 - **Rare possibility – NO LFTs necessary**
- **Slight increase in irritability and suicidal ideation reported in clinical trials**
 - **0.037% atomoxetine vs. 0.0% placebo**
 - **One suicide attempt/1,357 cases; no suicides**

Viloxazine for ADHD

- Noradrenergic & Serotonergic reuptake inhibitor
- Studies in children->adults

Findings

- Improvement in 100/200 mg (children); 200/400 (adolescents), and 600 mg (adults)
- Improvement noted at week 1
- Overall response rate circa 50%



Nasser, et al. *Clin Ther.* 2020;x42(8):1452-1466.

Viloxazine for ADHD

Dosing

- 100 mg x 1 week; then increase by 100 mg daily until target dose (e.g., 200 or 400 mg in child/adolescents; 600 mg in adults)

Side effects

- Somnolence, decreased appetite, headache, insomnia

Drug interactions

- Careful with p448 1A2 inhibition
 - Caffeine, duloxetine

Nasser, et al. *Clin Ther.* 2020;x42(8):1452-1466.

► Paediatr Drugs. 2021 Sep 15;23(6):583–589. doi: [10.1007/s40272-021-00470-2](https://doi.org/10.1007/s40272-021-00470-2) 

Executive Function Outcome of Treatment with Viloxazine Extended-Release Capsules in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder: A Post-Hoc Analysis of Four Randomized Clinical Trials

[Stephen V Faraone](#)¹, [Roberto Gomeni](#)², [Joseph T Hull](#)³, [Gregory D Busse](#)³, [Zare Melyan](#)³, [Jonathan Rubin](#)³,
[Azmi Nasser](#)³, 

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PMCID: PMC8563661 PMID: [34523063](https://pubmed.ncbi.nlm.nih.gov/34523063/)

Design: Meta analysis of 4 Randomized Controlled Trials

Subjects: 1154 Children and Adolescents

Outcome: Conners executive function T score

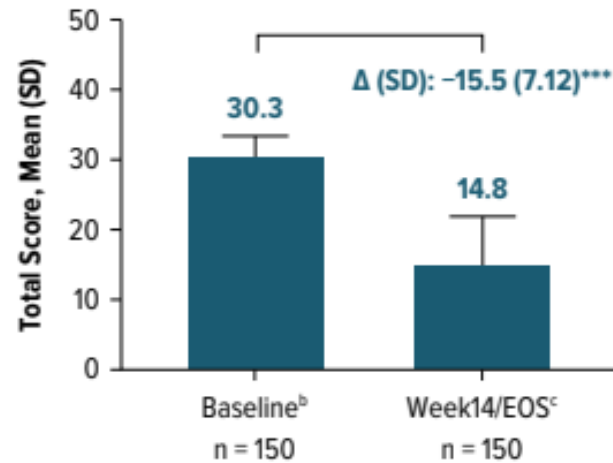
Findings:

Significant improvement vs placebo

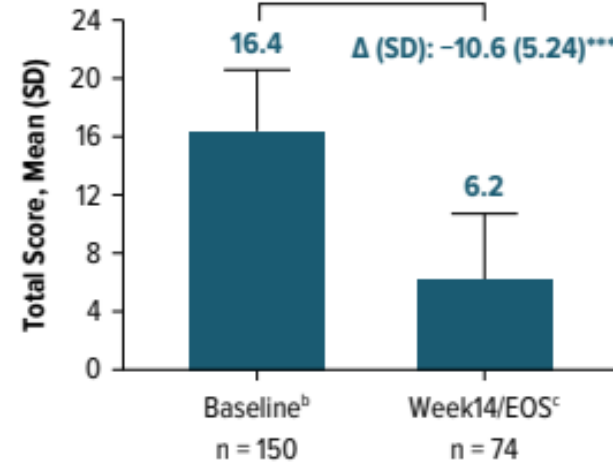
**53% of patients improved in terms of executive functioning
(versus 35% on placebo)**

Viloxazine ER Effect on Depression and Anxiety Symptoms in ADHD

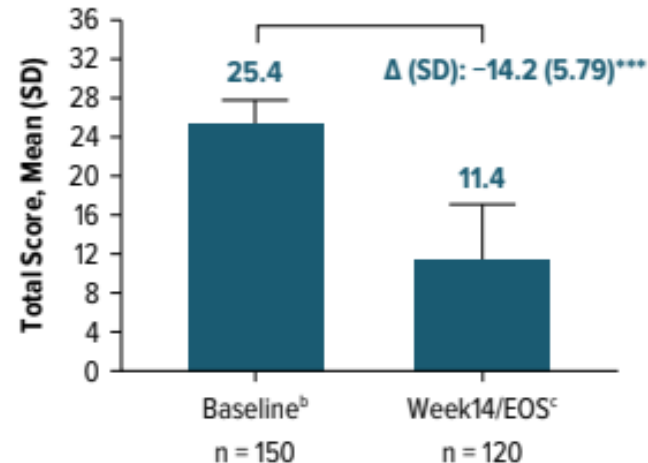
C. MADRS^d (CRO)



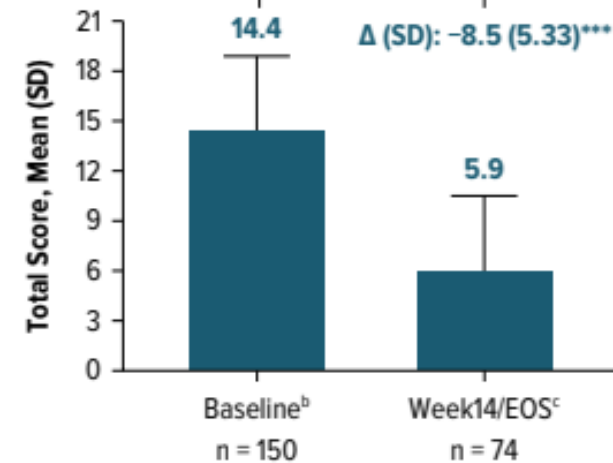
D. PHQ-8 (PRO)



E. HAM-A^e (CRO)



F. GAD-7 (PRO)

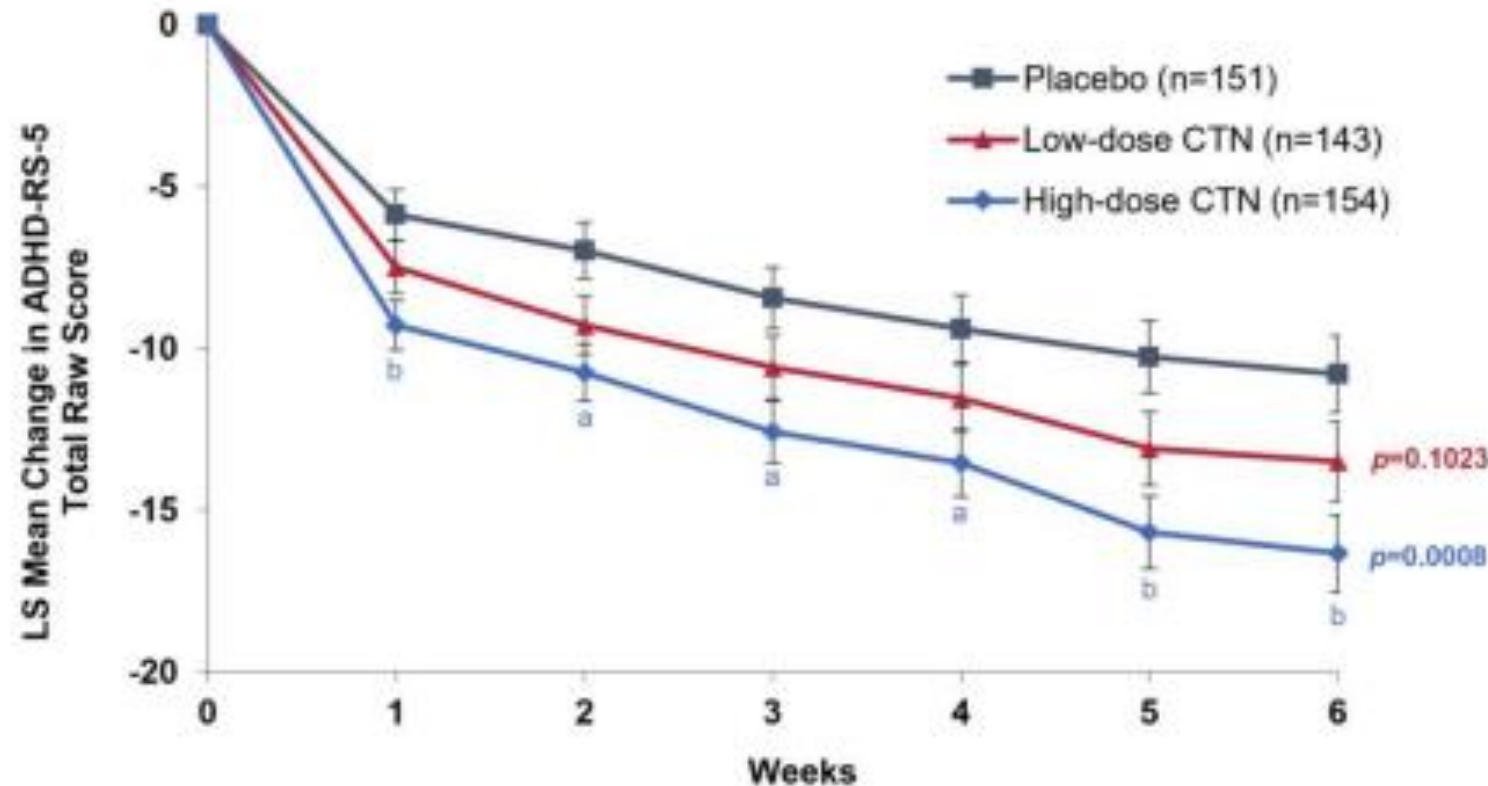


- Most common TEAEs: nausea, insomnia, constipation, headache, fatigue, somnolence, decrease appetite, migraine, dry mouth

Centanafadine

- Brand name: Simtriyo
- Recently FDA approved for ADHD in children, adolescents, and adults
- Mechanism of action dopamine, norepinephrine, and serotonin reuptake inhibition
- Black box (class labeling) : Suicidal ideation and behaviors in pediatric patients aged 6yrs and older; Abuse, misuse, and addiction
- Dosing: 140 mg, 210 mg, and 280 mg (sprinkled caps: can be opened)
 - Children & Adolescents: Start at 140 mg/day (or less); increase to maximum of 140 mg (20-35 kg), 210 mg (35-50 kg) or 280 mg daily (>50 kg)
 - Adults (start at 210; can increase to 280 mg daily)
- Adverse effects: Appetite suppression, rash, headaches, insomnia, dry mouth

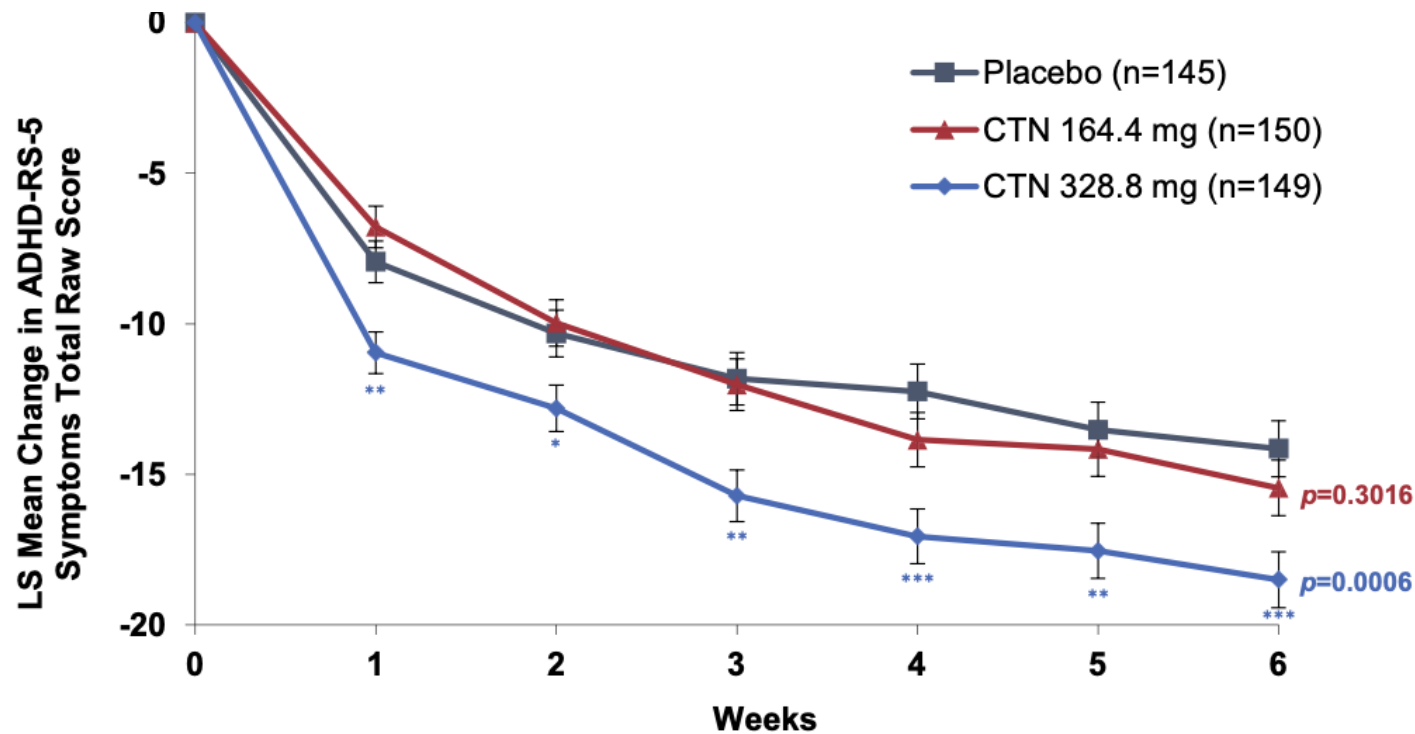
Centanafadine is Efficacious in Children (6-12 yr) with ADHD



Generally, well tolerated in preschool-aged children (aged 4–5 years) over 6 weeks of treatment

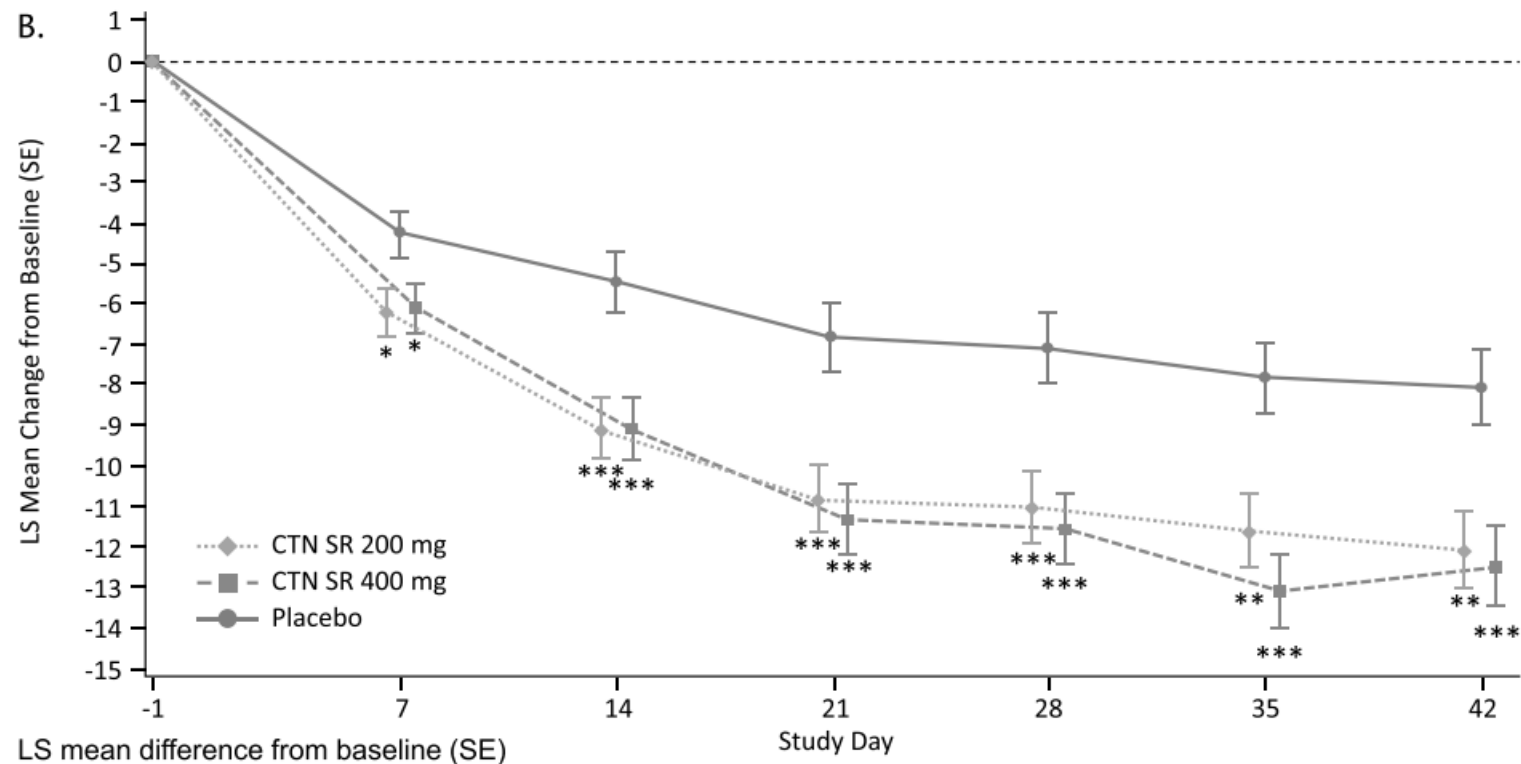
- Adverse effects occurring in $\geq 2\%$ of either CTN group and at a greater rate than placebo:
- Decreased appetite, rash, vomiting, upper respiratory infection, fatigue, nausea, streptococcal pharyngitis, somnolence, pyrexia, and cough

Centanafadine is Effective in Adolescents with ADHD



- Adverse Effects: Decreased appetite, headache, nausea, rash, somnolence, fatigue, abd pain
- Time to rash (largely higher dose: mean 9 d)

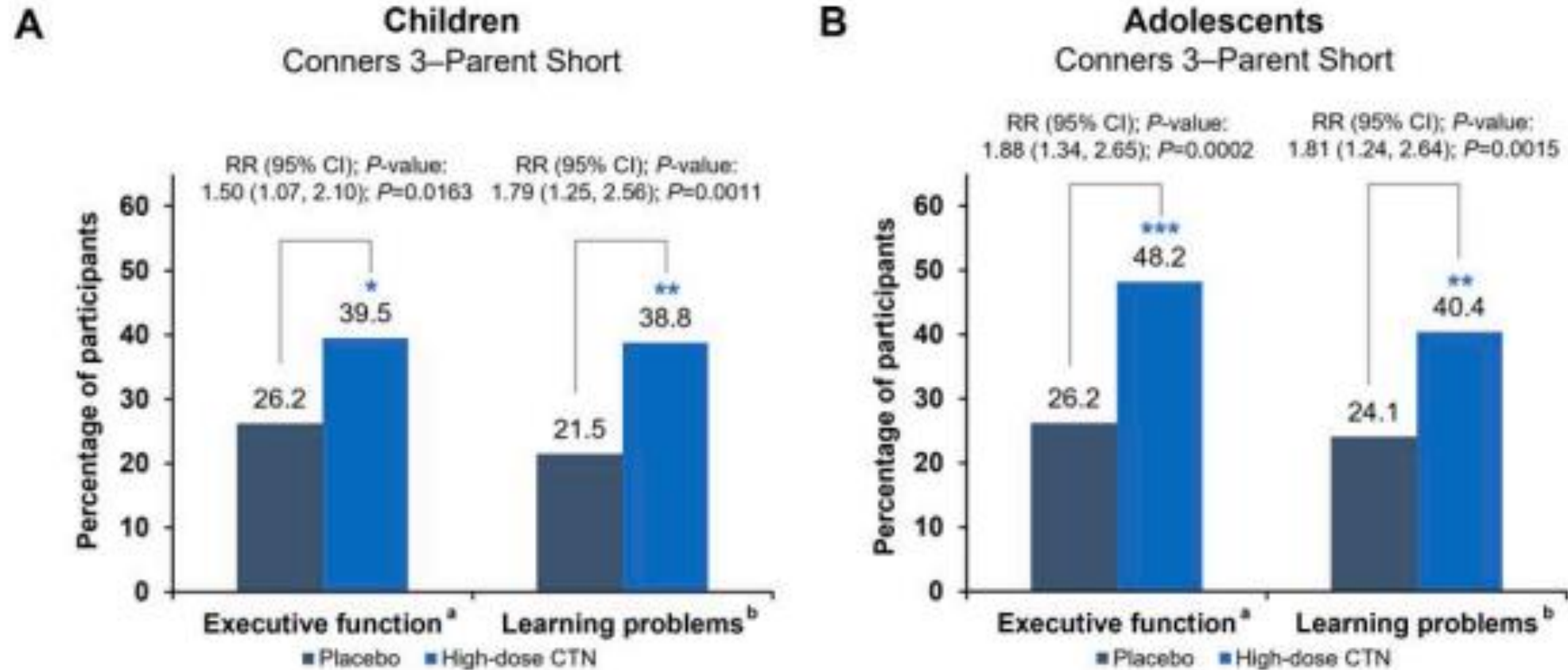
Centanafadine (CTN) is Efficacious in Adults with ADHD



Mechanism:
Tri-amine reuptake inhibitor (norepinephrine, dopamine, serotonin)

Side effects:
headache, decreased appetite, insomnia, dry mouth

Efficacy of Centanafadine for Executive Functioning and Learning Problems in Children and Adolescents with ADHD



Non-FDA Approved, Non-Stimulants in ADHD

- **Bupropion**
 - RCTs in Children (and adults)
 - Generally smaller effect size (ES) vs. stimulants
- **Modafinil**
 - Multiple RCTs positive in children (careful with Stevens-Johnson Syndrome)
 - Failed RCTs in adults
- **Tricyclics (imipramine, nortriptyline, desipramine)**
 - Multiple RCTs in children/adolescents and adults
 - Longer term persistent effect without tolerance
 - Serum levels, ECG monitoring recommended
- **Memantine**
 - (+) RCT in adults (Mohammadzadeh et al. *Human Psychopharm.* 2019)
 - Less effective than MPH in parallel study (Iran, *J Psych.* 2015)
 - Improvements in ADHD, executive functioning, social cognition

Newcorn, et al. Nonstimulants in Update in Pharmacotherapy of ADHD, Newcorn and Wilens (eds.), Elsevier Press, 2022. I Joshi et al, JAMA Network 2025

Managing Comorbidity Pharmacologically in ADHD

- Identify if comorbid symptoms are an autonomous disorder (MDD) or related to ADHD or its treatment (e.g., dysphoria on stimulants)
- Treat more severe disorder initially (e.g., mood disorder)
- If mild/moderate anxiety or disruptive/impulsive/aggressive behaviors, consider treating ADHD and monitor carefully
- In general, co-administration of SSRI/SNRI, SGAs, mood stabilizers are safe with stimulants; caveat-some interactions with nonstimulants (e.g., FLX and atomoxetine; duloxetine and viloxazine XR)
- ADHD can be treated in parallel with substance use disorders (in treatment)
- ADHD response is often influenced by comorbid disorder response

Newcorn & Wilens, Update in ADHD Pharmacotherapy. *Child Adoles Psych Clin N Am*. Elsevier, 2022.

*What Do We Know
About Long-term
Outcomes in
Medication Treated
ADHD Youth
Growing Up?*

ARTICLE

Stimulant medications in children with ADHD normalize the structure of brain regions associated with attention and reward

Feifei Wu^{1,2,✉}, Wenchao Zhang^{1,2,✉}, Weibin Ji^{1,2}, Yaqi Zhang^{1,2}, Fukun Jiang^{1,2}, Guanya Li^{1,2}, Yang Hu^{1,2}, Xiaorong Wei³, Haoyi Wang⁴, Sai-Yung (Ariel) Wang⁵, Peter Manza^{6,7}, Dardo Tomas⁸, Nora D. Volkow^{9,10}, Xinbo Gao^{6,7}, Gene-Jack Wang^{6,7,✉} and Yi Zhang^{1,2,✉}

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Children with ADHD show abnormal brain function and structure. Neuroimaging studies found that stimulant medications may improve brain structural abnormalities in children with ADHD. However, prior studies on this topic were conducted with relatively small sample sizes and wide age ranges and showed inconsistent results. In this cross-sectional study, we employed latent class analysis and linear mixed-effects models to estimate the impact of stimulant medications using demographic, clinical measures, and brain structure in a large and diverse sample of children aged 9–11 from the Adolescent Brain and Cognitive Development Study. We studied 273 children with low ADHD symptoms and received stimulant medication (Stim Low-ADHD), 1002 children with high ADHD symptoms and received no medications (No-Med ADHD), and 5378 typically developing controls (TDC). After controlling for the covariates, compared to Stim Low-ADHD and TDC, No-Med ADHD showed lower cortical thickness in the right insula (INS, $d = 0.340$, $P_{FDR} = 0.003$) and subcortical volume in the left nucleus accumbens (NAc, $d = 0.371$, $P_{FDR} = 0.003$), indicating that high ADHD symptoms were associated with structural abnormalities in these brain regions. In addition, there was no difference in brain structural measures between Stim Low-ADHD and TDC children, suggesting that the stimulant effects improved both ADHD symptoms and ADHD-associated brain structural abnormalities. These findings together suggested that children with ADHD appear to have structural abnormalities in brain regions associated with saliency and reward processing, and treatment with stimulant medications not only improve the ADHD symptoms but also normalized these brain structural abnormalities.

Neuropsychopharmacology; <https://doi.org/10.1038/s41386-024-01831-4>

ABCD Study
Cross sectional study
Aged 9–11 years

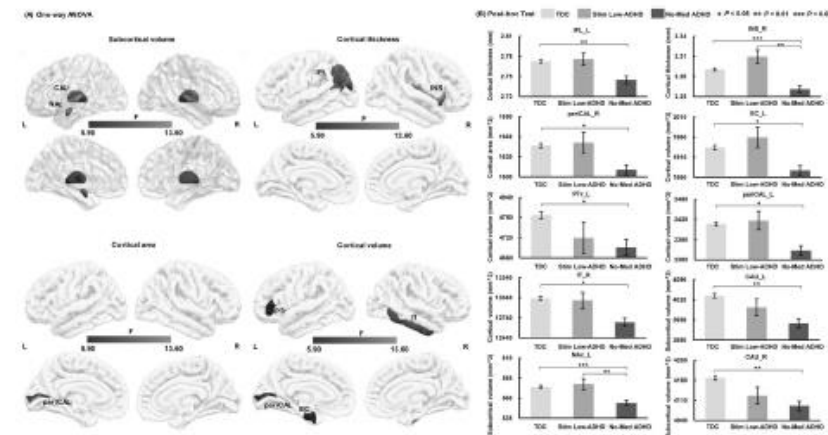
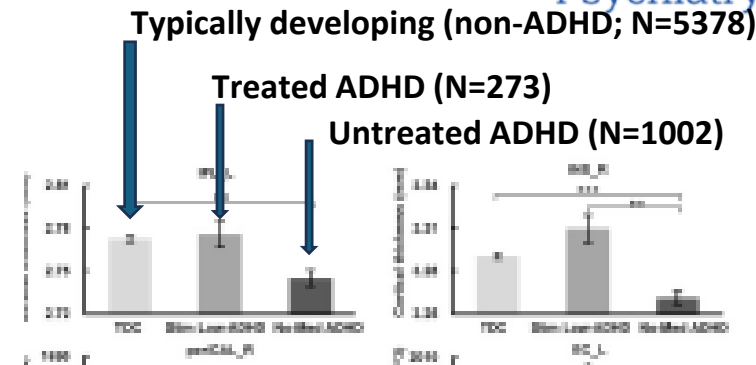
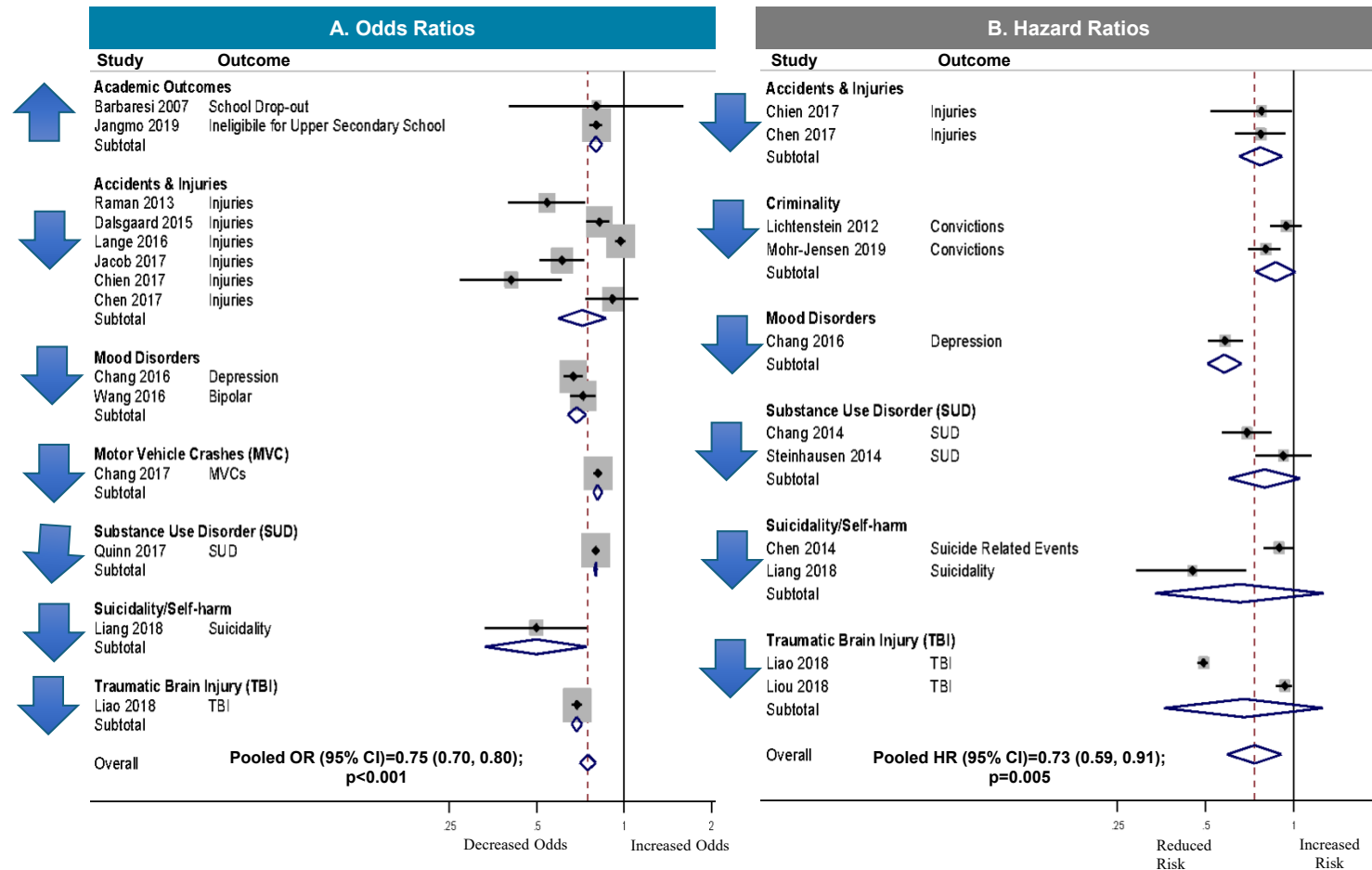


Fig. 2 One-way ANOVA analysis and post-hoc test. A One-way ANOVA analysis for brain structures. **B** Post-hoc test for brain structures. ADHD Attention-deficit/hyperactivity disorder, No-Med ADHD children with high ADHD symptoms and received no medications, Stim Low-ADHD children with low ADHD symptoms and received stimulant medication, TDC typically developing controls, L left hemisphere, R right hemisphere, IPL inferior parietal, INS insula, CUN cuneus, EC entorhinal cortex, PTr pars triangularis, perCAL pericalcarine, PCUN precuneus, IT inferior temporal, AMY Amygdala, CAU caudate, NAc nucleus accumbens.

Wu et al., 2024; Neuropsychopharmacology; <https://doi.org/10.1038/s41386-024-01831-4>

Long Term Studies of ADHD: Stimulant Treated vs. Untreated

Odds ratios and hazard ratios <1 indicate decreased risk in medicated vs. unmedicated ADHD patients



(from Boland, et al , Psychiatric Research 2020))

What about short- and longer-term side effects of medication treatment?

Height and Weight

Cardiovascular

Pregnancy?

Dementia?

Review > J Child Adolesc Psychopharmacol. 2023 Nov;33(9):344-355.
doi: 10.1089/cap.2023.0054.

Growth Trajectories in Stimulant Treated Children and Adolescents: A Qualitative Review of the Literature from Comprehensive Datasets and Registries

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Affiliations + expand

PMID: 37966364 DOI: 10.1089/cap.2023.0054

Conclusions: This review of ecologically informative samples revealed that the effects of stimulant treatment on growth trajectories are mainly small and transient. These effects seem to be clinically insignificant for most youth with ADHD who receive stimulant treatment from childhood onto adolescence and adulthood.

significant decreases in height associated with chronic stimulant treatment that normalized over time in 2 studies. Three articles found no significant association between stimulant treatment and height. No clear associations were identified between cumulative duration and dose of stimulant treatment and adult height. All articles examining weight and six of eight articles examining body mass index (BMI) found significant initial decreases that tended to normalize then increase over time. Longer duration of stimulant medication use was predominantly associated with significant weight and BMI reductions. The effects of stimulant dose on weight and BMI were mostly weak and clinically insignificant. Most studies found no significant association between age at start of stimulant treatment and change in height, weight, or BMI. Most studies did not find significant sex effects in relation to growth parameters. **Conclusions:** This review of ecologically informative samples revealed that the effects of stimulant treatment on growth trajectories are mainly small and transient. These effects seem to be clinically insignificant for most youth with ADHD who receive stimulant treatment from childhood onto adolescence and adulthood.

Keywords: ADHD; children and adolescents; growth trajectories; stimulants.

Long-term safety of methylphenidate in children and adolescents with ADHD: 2-year outcomes of the Attention Deficit Hyperactivity Disorder Drugs Use Chronic Effects (ADDUCE) study



Kenneth K C Man*, Alexander Häge*, Tobias Banaschewski*, Sarah K Inglis, Jan Buitelaar, Sara Carucci, Marina Danckaerts, Ralf W Dittmann, Bruno Falissard, Peter Garas, Chris Hollis, Kerstin Konrad, Hanna Kovshoff, Elizabeth Liddle, Suzanne McCarthy, Antje Neubert, Peter Nagy, Eric Rosenthal, Edmund J S Sonuga-Barke, Alessandro Zuddas†, Ian C K Wong‡, David Coghill‡, on behalf of the ADDUCE Consortium

Summary

Background Methylphenidate is the most frequently prescribed medication for the treatment of ADHD in children and adolescents in many countries. Although many randomised controlled trials support short-term efficacy, tolerability, and safety, data on long-term safety and tolerability are scarce. The aim of this study was to investigate the safety of methylphenidate over a 2-year period in relation to growth and development, psychiatric health, neurological health, and cardiovascular function in children and adolescents.

Methods We conducted a naturalistic, longitudinal, controlled study as part of the ADDUCE research programme in 27 European child and adolescent mental health centres in the UK, Germany, Switzerland, Italy, and Hungary. Participants aged 6–17 years were recruited into three cohorts: medication-naïve ADHD patients who intended to start methylphenidate treatment (methylphenidate group), medication-naïve ADHD patients who did not intend to start any ADHD medication (no-methylphenidate group), and a control group without ADHD. Children with ADHD diagnosed by a qualified clinician according to the DSM-IV criteria and, in the control group, children who scored less than 1.5 on average on the Swanson, Nolan, and Pelham IV rating scale for ADHD items, and whose hyperactivity score on the parent-rated Strengths and Difficulties Questionnaire was within the normal range (<6) were eligible for inclusion. Participants were excluded if they had previously taken any ADHD medications but remained eligible if they had previously taken or were currently taking other psychotropic drugs. The primary outcome was height velocity (height velocity SD score; estimated from at least two consecutive height measurements, and normalised with reference to the mean and SD of a population of the same age and sex).

Findings Between Feb 01, 2012, and Jan 31, 2016, 1410 participants were enrolled (756 in methylphenidate group, 391 in no-methylphenidate group, and 263 in control group). 1070 (76.3%) participants were male, 332 (23.7%) were female, and for eight gender was unknown. The average age for the cohort was 9.28 years (SD 2.78; IQR 7–11). 1312 (93.0%) of 1410 participants were White. The methylphenidate and no-methylphenidate groups differed in ADHD symptom severity and other characteristics. After controlling for the effects of these variables using propensity scores, there was little evidence of an effect on growth (24 months height velocity SD score difference -0.07 (95% CI -0.18 to 0.04 ; $p=0.20$) or increased risk of psychiatric or neurological adverse events in the methylphenidate group compared with the no-methylphenidate group. Pulse rate and systolic and diastolic blood pressure were higher in the methylphenidate group compared with the no-methylphenidate group after 24 months of treatment. No serious adverse events were reported during the study.

Interpretation Our results suggest that long-term treatment with methylphenidate for 2 years is safe. There was no evidence to support the hypothesis that methylphenidate treatment leads to reductions in growth. Methylphenidate-related pulse and blood pressure changes, although relatively small, require regular monitoring.

Lancet Psychiatry 2023;

10: 323–33

Published Online

March 20, 2023

[https://doi.org/10.1016/](https://doi.org/10.1016/S2215-0366(23)00042-1)

[S2215-0366\(23\)00042-1](https://doi.org/10.1016/S2215-0366(23)00042-1)

See [Comment](#) page 306

*Joint first authors

†We would like to dedicate this manuscript to our friend and colleague Alessandro Zuddas who contributed greatly to the ADDUCE Consortium and who sadly passed away in July, 2022

‡Joint senior authors

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Study of MPH Safety
N=1410 participants
756 in MPH group
398 in no-MPH group
263 controls

Findings
MPH vs no MPH no difference on
height, psych onset, or neuro adverse
effects
Increase in BP/HR

Attention-Deficit/Hyperactivity Disorder Medications and Long-Term Risk of Cardiovascular Diseases

Le Zhang, PhD; Lin Li, PhD; Pontus Andell, MD, PhD; Miguel Garcia-Arribas, PhD; Patrick D. Quinn, PhD; Brian M. D'Onofrio, PhD; Isabell Brikell, PhD; Ralf Kuja-Halkola, PhD; Paul Lichtenstein, PhD; Kristina Johnell, PhD; Henrik Larsson, PhD; Zheng Chang, PhD

IMPORTANCE Use of attention-deficit/hyperactivity disorder (ADHD) medications has increased substantially over the past decades. However, the potential risk of cardiovascular disease (CVD) associated with long-term ADHD medication use remains unclear.

OBJECTIVE To assess the association between long-term use of ADHD medication and the risk of CVD.

DESIGN, SETTING, AND PARTICIPANTS This case-control study included individuals in Sweden aged 6 to 64 years who received an incident diagnosis of ADHD or ADHD medication dispensation between January 1, 2007, and December 31, 2020. Data on ADHD and CVD diagnoses and ADHD medication dispensation were obtained from the Swedish National Inpatient Register and the Swedish Prescribed Drug Register, respectively. Cases included individuals with ADHD and an incident CVD diagnosis (ischemic heart diseases, cerebrovascular diseases, hypertension, heart failure, arrhythmias, thromboembolic disease, arterial disease, and other forms of heart disease). Incidence density sampling was used to match cases with up to 5 controls without CVD based on age, sex, and calendar time. Cases and controls had the same duration of follow-up.

EXPOSURE Cumulative duration of ADHD medication use up to 14 years.

MAIN OUTCOMES AND MEASURES The primary outcome was incident CVD. The association between CVD and cumulative duration of ADHD medication use was measured using adjusted odds ratios (AORs) with 95% CIs.

RESULTS Of 278 027 individuals with ADHD aged 6 to 64 years, 10 388 with CVD were identified (median [IQR] age, 34.6 [20.0-45.7] years; 6154 males [59.2%]) and matched with 51 672 control participants without CVD (median [IQR] age, 34.6 [19.8-45.6] years; 30 601 males [59.2%]). Median (IQR) follow-up time in both groups was 4.1 (1.9-6.8) years. Longer cumulative duration of ADHD medication use was associated with an increased risk of CVD compared with nonuse (0 to <1 year: AOR, 0.99 [95% CI, 0.93-1.06]; 1 to <2 years: AOR, 1.09 [95% CI, 1.01-1.18]; 2 to <3 years: AOR, 1.15 [95% CI, 1.05-1.25]; 3 to <5 years: AOR, 1.27 [95% CI, 1.17-1.39]; and >5 years: AOR, 1.23 [95% CI, 1.12-1.36]). Longer cumulative ADHD medication use was associated with an increased risk of hypertension (eg, 3 to <5 years: AOR, 1.72 [95% CI, 1.51-1.97] and >5 years: AOR, 1.80 [95% CI, 1.55-2.08]) and arterial disease (eg, 3 to <5 years: AOR, 1.65 [95% CI, 1.11-2.45] and >5 years: AOR, 1.49 [95% CI, 0.96-2.32]). Across the 14-year follow-up, each 1-year increase of ADHD medication use was associated with a 4% increased risk of CVD (AOR, 1.04 [95% CI, 1.03-1.05]), with a larger increase in risk in the first 3 years of cumulative use (AOR, 1.08 [95% CI, 1.04-1.11]) and stable risk over the remaining follow-up. Similar patterns were observed in children and youth (aged <25 years) and adults (aged ≥25 years).

CONCLUSIONS AND RELEVANCE This case-control study found that long-term exposure to ADHD medications was associated with an increased risk of CVDs, especially hypertension and arterial disease. These findings highlight the importance of carefully weighing potential benefits and risks when making treatment decisions about long-term ADHD medication use. Clinicians should regularly and consistently monitor cardiovascular signs and symptoms throughout the course of treatment.

JAMA Psychiatry. 2024;81(2):178-187. doi:10.1001/jamapsychiatry.2023.4294
Published online November 22, 2023.

Design

Swedish registry study

N=278,027 (6-64 yrs)

Mean 4 yr follow-up

2007-2020

Findings:

10,388 (3.7%) with CVD (cardiovascular disease)

Longer duration meds-more CVD

Hypertension main finding>arterial disease

Each 1 yr (only for 3 yrs) increased risk

Caveat:

Non-US data (US studies not supportive)

Retrospective matching

Main finding hypertension

Recent study from same group-lower mortality

ADHD Pharmacotherapy and Mortality in Individuals With ADHD

Lin Li, PhD; Nanbo Zhu, MSc; Le Zhang, PhD; Ralf Kuja-Halkola, PhD; Brian M. D'Onofrio, PhD; Isabella Brikell, PhD; Paul Lichtenstein, PhD; Samuele Cortese, MD, PhD; Henrik Larsson, PhD; Zheng Chang, PhD

IMPORTANCE Attention-deficit/hyperactivity disorder (ADHD) is associated with increased risks of adverse health outcomes including premature death, but it is unclear whether ADHD pharmacotherapy influences the mortality risk.

OBJECTIVE To investigate whether initiation of ADHD pharmacotherapy was associated with reduced mortality risk in individuals with ADHD.

DESIGN, SETTING, AND PARTICIPANTS In an observational nationwide cohort study in Sweden applying the target trial emulation framework, we identified individuals aged 6 through 64 years with an incident diagnosis of ADHD from 2007 through 2018 and no ADHD medication dispensation prior to diagnosis. Follow-up started from ADHD diagnosis until death, emigration, 2 years after ADHD diagnosis, or December 31, 2020, whichever came first.

EXPOSURES ADHD medication initiation was defined as dispensing of medication within 3 months of diagnosis.

MAIN OUTCOMES AND MEASURES We assessed all-cause mortality within 2 years of ADHD diagnosis, as well as natural-cause (eg, physical conditions) and unnatural-cause mortality (eg, unintentional injuries, suicide, and accidental poisonings).

RESULTS Of 148 578 individuals with ADHD (61 356 females [41.3%]), 84 204 (56.7%) initiated ADHD medication. The median age at diagnosis was 17.4 years (IQR, 11.6–29.1 years). The 2-year mortality risk was lower in the initiation treatment strategy group (39.1 per 10 000 individuals) than in the noninitiation treatment strategy group (48.1 per 10 000 individuals), with a risk difference of –8.9 per 10 000 individuals (95% CI, –17.3 to –0.6). ADHD medication initiation was associated with significantly lower rate of all-cause mortality (hazard ratio [HR], 0.79; 95% CI, 0.70 to 0.88) and unnatural-cause mortality (2-year mortality risk, 25.9 per 10 000 individuals vs 33.3 per 10 000 individuals; risk difference, –7.4 per 10 000 individuals; 95% CI, –14.2 to –0.5; HR, 0.75; 95% CI, 0.66 to 0.86), but not natural-cause mortality (2-year mortality risk, 13.1 per 10 000 individuals vs 14.7 per 10 000 individuals; risk difference, –1.6 per 10 000 individuals; 95% CI, –6.4 to 3.2; HR, 0.86; 95% CI, 0.71 to 1.05).

CONCLUSIONS AND RELEVANCE Among individuals diagnosed with ADHD, medication initiation was associated with significantly lower all-cause mortality, particularly for death due to unnatural causes.

JAMA. 2024;331(10):850–860. doi:10.1001/jama.2024.0851

 Editorial page 831
 Supplemental content
 CME Quiz at
jamacmelookup.com

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Design:

Swedish study 2007-2018

Ages 6-64 years with ADHD

148 578 individuals with ADHD

84 204 (57%) initiated ADHD

medication

F/u ADHD to death, 2 yrs post

ADHD Dx, lost to f/u

Findings:

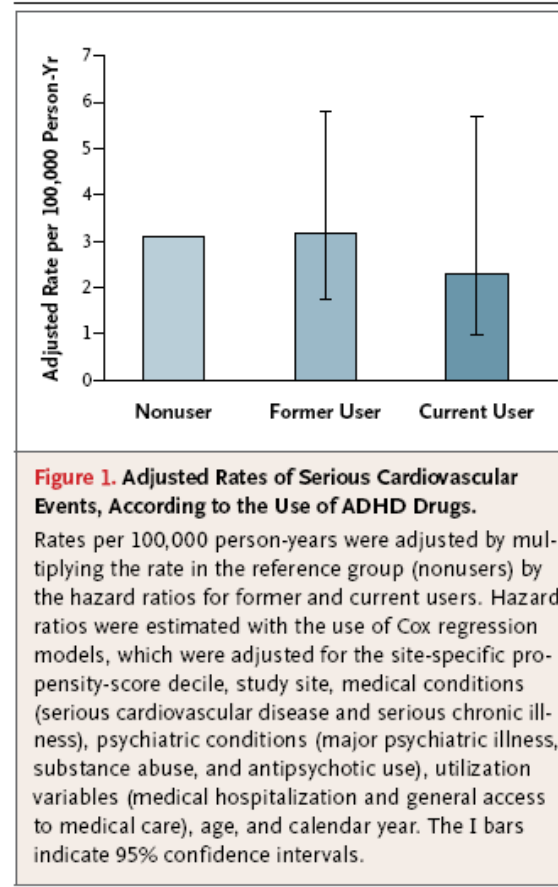
Lower mortality in treated vs untreated groups

ADHD medication associated with HR 0.79 for all cause mortality (especially unnatural causes)

Conclusion:

Lower mortality associated with ADHD treatment

ADHD Meds are Not Associated with Adverse CV Outcomes: Children



Cooper, et al. *The New England Journal of Medicine*. 2011; 365(20) 18960-1904.

What to Do at Evaluation

(AHA Guidelines)

- **Medical History (*essentially screening of sudden death risk*)**
 - Personal congenital or acquired cardiac disease
 - Palpitations, chest pain, syncope, seizures, post-exercise symptoms
 - Family history or premature cardiac disease (<30 yrs of age)
 - Other meds (including OTC)
 - Routine med history (neurological, etc.)
- **BP/heart rate – particularly in adults**
- **Peds: no ECG, Holter, or GXT**
- **Adults: work-up as indicated**
- ***Suspicion* of CV defect (e.g., IHSS, ARVD) --w/u as indicated**
- **Monitor above during treatment**
- **Issues of informed consent**

Gutgesell H, et al. *Circulation* 1999;99:979-982.

AAP Guidelines 2008.

Perrin, et al. *Pediatrics*. 2008.

Wilens, et al. *Pediatrics*. 2006.

Cooper, et al. *NEJM*. 2012.

Cooper, et al. *JAMA*. 2012.

Hammerness, et al. in *Updates on Pharmacotherapy of ADHD*.

Newcorn & Wilens (eds.), Elsevier Press 2022.

ARTICLE

OPEN



In utero exposure to methylphenidate, amphetamines and atomoxetine and offspring neurodevelopmental disorders – a population-based cohort study and meta-analysis

Kathrine Bang Madsen^{1,2,3,10}, Henrik Larsson^{4,5}, Charlotte Skoglund^{6,7}, Xiaoqin Liu^{2,3}, Trine Munk-Olsen¹, Veerle Bergink^{8,9}, Jeffrey H. Newcom¹⁰, Samuele Cortese^{10,11,12,13,14}, Paul Lichtenstein⁵, Ralf Kuja-Halkola⁵, Zheng Chang⁵, Brian D'Onofrio^{5,15}, Per Hove Thomsen^{16,17}, Kari Klungsoyr^{18,19}, Isabell Brikell^{5,14,20,21} and Miguel Garcia-Argibay^{5,16,21}

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The use of Attention-Deficit/Hyperactivity Disorder (ADHD) medications during pregnancy is increasing, raising concerns about potential long-term effects on offspring. This study investigates in utero exposure to methylphenidate, amphetamines and atomoxetine and risk of offspring neurodevelopmental disorders (NDDs). The population-based cohort study identified from Swedish registers included 861,650 children born by 572,731 mothers from 2008–2017. We categorized exposure based on redeemed medication during pregnancy and compared exposed children to those whose mothers discontinued medication before conception. Main outcomes were any NDD, including ADHD and autism spectrum disorder (ASD). Cox proportional hazards regression estimated hazard ratios (HRs), adjusting for maternal psychiatric and sociodemographic factors. Sensitivity analyses included stratifications by medication type, timing, and duration of exposure, and sibling comparisons. We also performed a meta-analysis combining data from the present study with those from a previous Danish study. Results showed no increased risk for any NDD (HR_{adjusted} 0.95, 95% CI 0.82–1.11), ADHD (HR_{adjusted} 0.92, 95% CI 0.78–1.08), or ASD (HR_{adjusted} 0.86, 95% CI 0.63–1.18). Sensitivity analyses showed consistent patterns of no increased risks across different exposure durations, medication types and between siblings. Meta-analyses further supported the findings (pooled HR for any NDD 1.00, 95% CI 0.83–1.20). Our study provides evidence that in utero exposure to ADHD medications does not increase the risk of long-term NDDs in offspring. This study replicates safety data for methylphenidate and extends it with new safety data on amphetamines and atomoxetine. These findings are crucial for informing clinical guidelines and helping healthcare providers and expectant mothers make informed decisions.

Molecular Psychiatry; <https://doi.org/10.1038/s41380-025-02968-4>

INTRODUCTION

Attention-Deficit/Hyperactivity Disorder (ADHD) is the most prevalent neurodevelopmental disorder (NDD), affecting individuals across their lifespan [1]. With the increasing prescription rate of ADHD medications among women of reproductive age [2], there has been a concurrent rise in the use of these medications during pregnancy. Estimates suggest that up to 0.8% of pregnant women in the Nordic countries and over 1% of pregnant women in the United States are currently prescribed ADHD medications, making these among the most commonly used medications during pregnancy [3, 4]. Despite their widespread use, there is still

insufficient replicated empirical evidence concerning the long-term safety of in utero exposure to ADHD medications, leading many expectant mothers to discontinue use due to concerns about potential harm to the unborn child [5, 6].

Several studies have focused on short-term outcomes of in utero exposure to ADHD medications in offspring, including congenital malformations [7–15] and adverse outcomes related to labour and delivery [6, 11–13, 16–18]. However, long-term outcomes in the offspring have received less attention. A recent study from our group, conducted using Danish national registers, provided initial insights by investigating long-term

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Received: 12 July 2024 Revised: 3 March 2025 Accepted: 20 March 2025
Published online: 27 March 2025

SPRINGER NATURE

Design:

Population based cohort study

Swedish registry study

N=861,650 children born

2008-2107

Examined amphetamine, methylphenidate,

atomoxetine

Examination of exposed pregnant mothers vs

those off meds at conception

Findings:

No increased risk for any ASD, ADHD, or other neurodevelopmental disorder in offspring

Additional metanalyses with Danish cohort study

resulted in similar outcome

[N=4 large recent datasets with similar outcomes]

Other Treatments for ADHD?

Other treatments for ADHD

- Transcranial magnetic stimulation (FDA approved)
- Digital therapeutics (e.g. Akili Endeavor)(FDA approved)
- Cognitive training (not FDA approved)
- Naturalceuticals (not FDA approved)
 - Fish oils
 - S-adenosyl methionine (SAME)
 - Ginko and others
 - Combination OTC

Summary

- ADHD is common, worldwide, chronic and functionally impairing
- Treatment of ADHD includes educational planning, nonpharmacological and pharmacological options
- Multiple stimulant preparations and nonstimulants available for ADHD
- Long term outcomes more favorable with pharmacological treatment

QUESTIONS?