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PSYCHIATRY ACADEMY

Stimulant Treatment of ADHD

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Disclosures

Timothy Wilens, MD has served as a consultant, or has received grant support from the following:

- NIH (NIDA), Food and Drug Administration, 3D Therapy
- Licensing agreement with Ironshore (Before School Functioning Questionnaire)
- Clinical care: MGH, Bay Cove Human Services, Gavin, Major/Minor League Baseball
- (Co)Edited Straight Talk About Psychiatric Medications for Kids (Guilford); ADHD Across the Lifespan (Cambridge), MGH Comprehensive Clinical Psychiatry (Elsevier), MGH Psychopharmacology and Neurotherapeutics (Elsevier), Update on Pharmacotherapy of ADHD (Elsevier)

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)

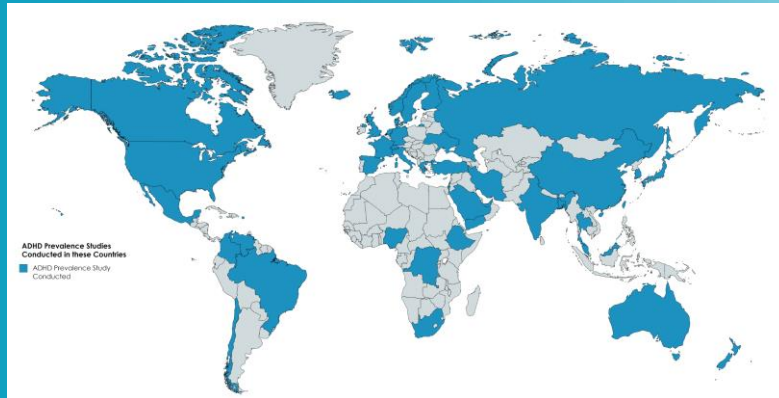
The World Federation of ADHD International Consensus Statement: 208 Evidence-Based Conclusions About the Disorder



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Stephen V Faraone, Tobias Banaschewski, David Coghill, et al.



Abstract

Background: Misconceptions about ADHD stigmatize affected people, reduce credibility of providers, and prevent/delay treatment. To challenge misconceptions, we curated findings with strong evidence base.

Methods: We reviewed studies with more than 2000 participants or meta-analyses from five or more studies or 2000 or more participants. We excluded meta-analyses that did not assess publication bias, except for meta-analyses of prevalence. For network meta-analyses we required comparison adjusted funnel plots. We excluded treatment studies with waiting-list or treatment as usual controls. From this literature, we extracted evidence-based assertions about the disorder.

Results: We generated 208 empirically supported statements about ADHD. The status of the included statements as empirically supported is approved by 80 authors from 27 countries and 6 continents. The contents of the manuscript are endorsed by 366 people who have read this document and agree with its contents.

Conclusions: Many findings in ADHD are supported by meta-analysis. These allow for firm statements about the nature, course, outcome causes, and treatments for disorders that are useful for reducing misconceptions and stigma.

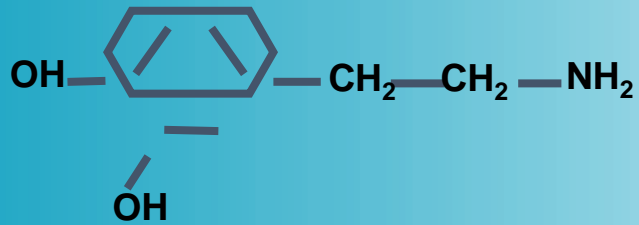
Keywords: ADHD; Brain; Course; Diagnosis; Genetics; Outcome; Treatment.

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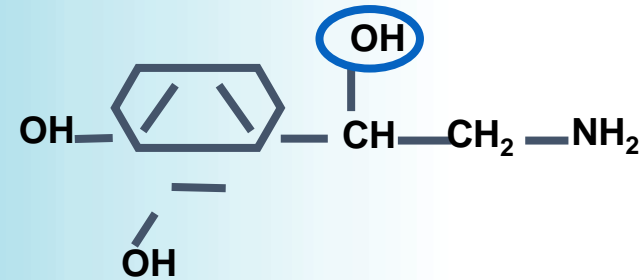
> [Neurosci Biobehav Rev.](https://doi.org/10.1016/j.neubiorev.2021.01.022) 2021 Sep;128:789-818. doi: 10.1016/j.neubiorev.2021.01.022. Epub 2021 Feb 4.

Structural Comparisons

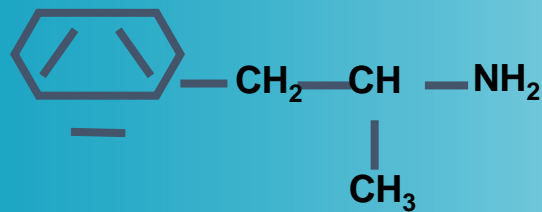
Dopamine



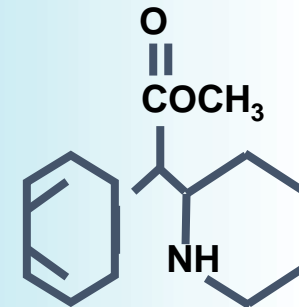
Norepinephrine



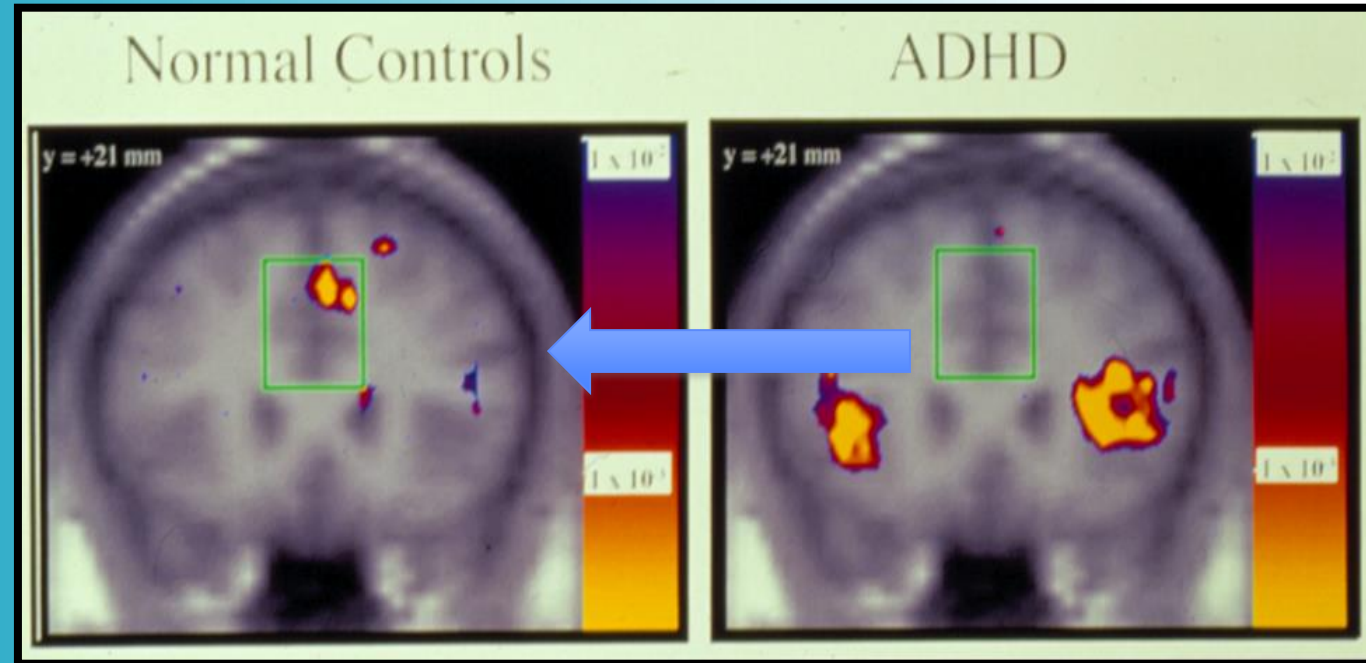
Amphetamine



Methylphenidate



fMRI in Adults with ADHD



MGH NMR Center and Harvard-MIT CITP.
fMRI, functional magnetic resonance imaging.
Bush G et al. *Biol Psychiatry*. 1999;45(12):1542-1552.
Bush G et al. *Arch Gen Psychiatry*. 2008;65(1):102-114.



Methylphenidate (MPH)

- **Low bioavailability (~20 – 25%)**
 - **(+)-MPH isomer much greater bioavailability than the (–)-MPH isomer**
- **Typical IR therapeutic doses provide**
 - **$T_{\max} = 1.5 - 2.5$ h**
 - **$C_{\max} = 6 - 15$ ng/mL**
 - **$T_{1/2} = 2 - 3.5$ h**

Wilens and Spencer. *Child Adolesc Psychiatr Clin N Am.* 2000;9:573-603.

Patrick and Markowitz. *Hum Psychopharmacol Clin Exp.* 1997;12:527-546.

Markowitz and Melchert, *Stimulants in Pharmacotherapy of ADHD.* Elsevier Press 2022.



Methylphenidate (MPH)

- **Primarily de-esterified-may be susceptible to genetic polymorphisms (ultra slow metabolizer)**
- **Prominent metabolism (L-MPH) in intestinal wall**
- **Stereo-isomeric metabolism (L>D)**
- **Linear pharmacokinetics at moderate doses**
- **No pharmacokinetic drug interactions**
- **No food effects noted**

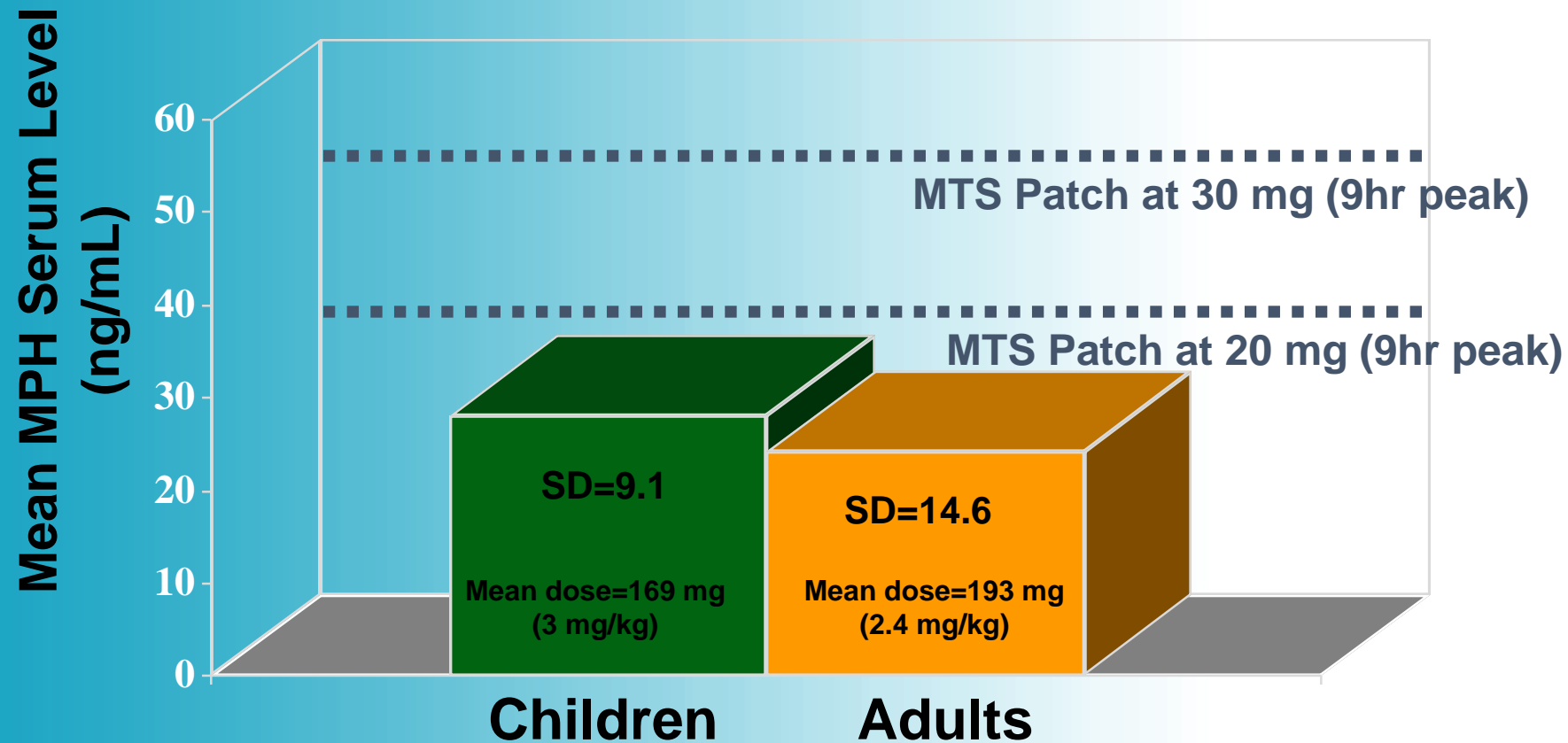
Wilens and Spencer. *Child Adolesc Psychiatr Clin N Am.* 2000;9:573-603.

Stevens and Wilens. *ADHD Across the Lifespan.* 2013.

Zhu et al. *Clin Pharm.* 2009;270:59-65.

Markowitz and Melchert. *Stimulants, in Pharmacotherapy of ADHD.* Elsevier Press 2022.

High-Dose OROS MPH in Youth (N=21) and Adults (N=4)



Stevens et al. *J Child Adoles Psychopharm.* 2010.



Amphetamine (AMPH)

- High bioavailability (~75%)
- Typical therapeutic doses of IR *dextroamphetamine* provide
 - $T_{\max} = 2 - 3 \text{ h}$
 - $C_{\max} = 40 - 70 \text{ ng/mL}$
 - $T_{1/2} = 7 \text{ h}$

Wilens and Spencer. *Child Adolesc Psychiatr Clin N Am.* 2000;9:573-603.

Stevens and Wilens; *ADHD Across the Lifespan*, 2017.

Markowitz et al. *J Child Adolesc Psychopharm.* 2017;8:678-689.

Markowitz and Melchert. *Stimulants, in Pharmacotherapy of ADHD.* Elsevier Press 2022.



Amphetamine (AMPH)

- Redundant hepatic metabolism
- Linear pharmacokinetics
- No pharmacokinetic drug interactions
- Food effects noted (delayed onset of action)

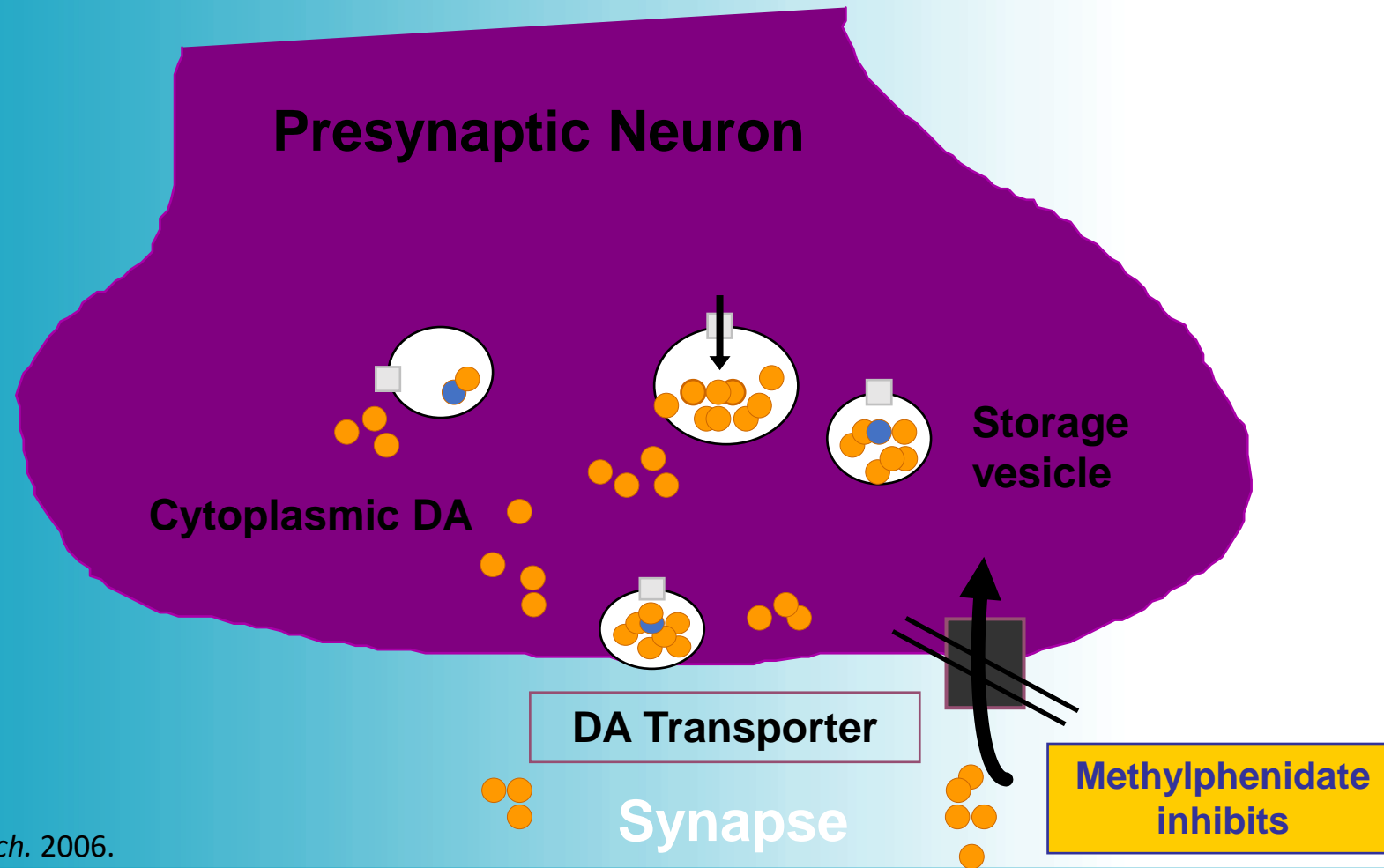
Wilens and Spencer. *Child Adolesc Psychiatr Clin N Am.* 2000;9:573-603.

Patrick and Markowitz. *Hum Psychopharmacol Clin Exp.* 1997;12:527-546.

Markowitz et al. *J Child Adolesc Psychopharm.* 2017;8:678-689.

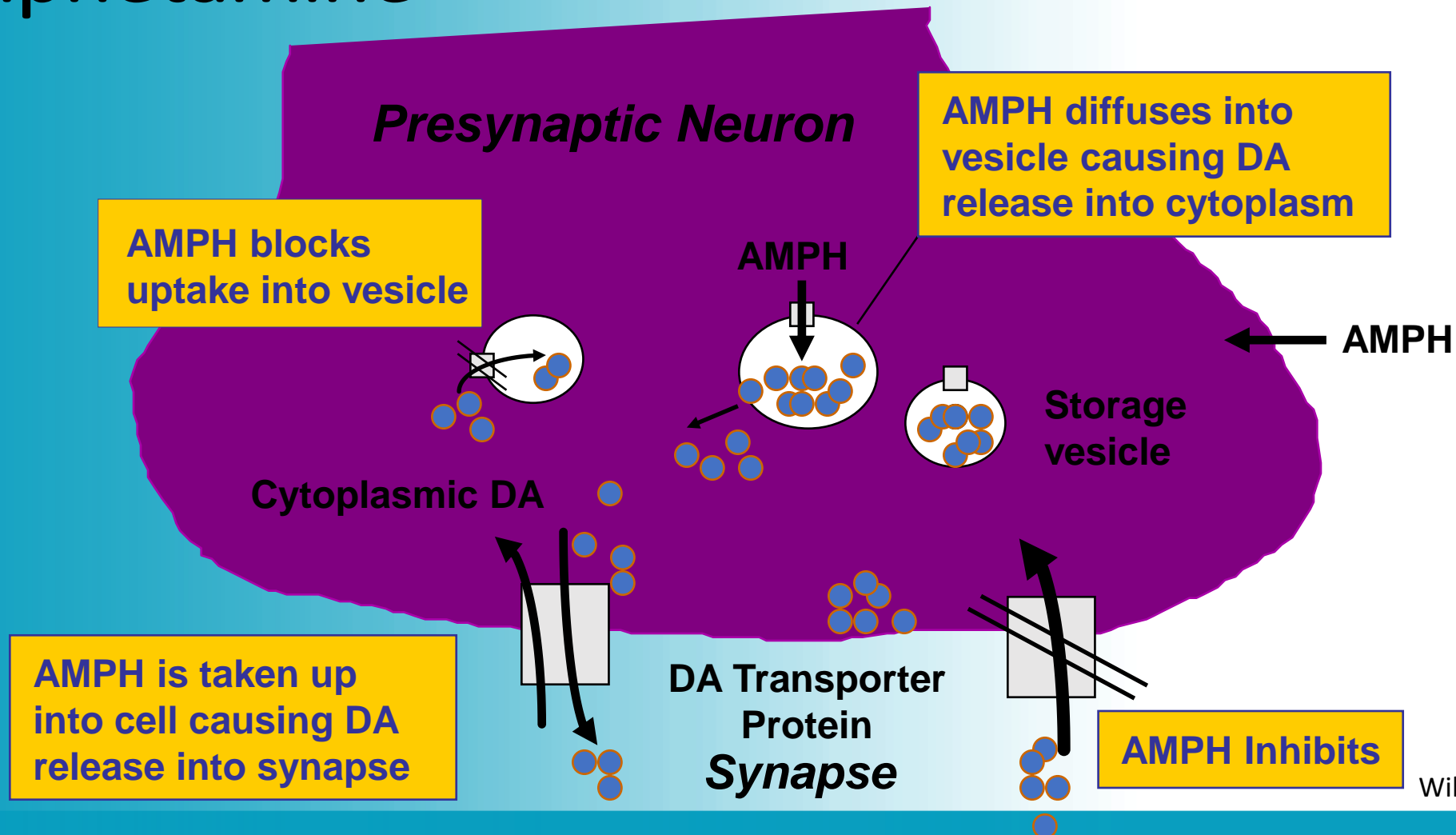
Markowitz and Melchert. *Stimulants, in Pharmacotherapy of ADHD.* Elsevier Press 2022.

Mechanism of Action of Methylphenidate



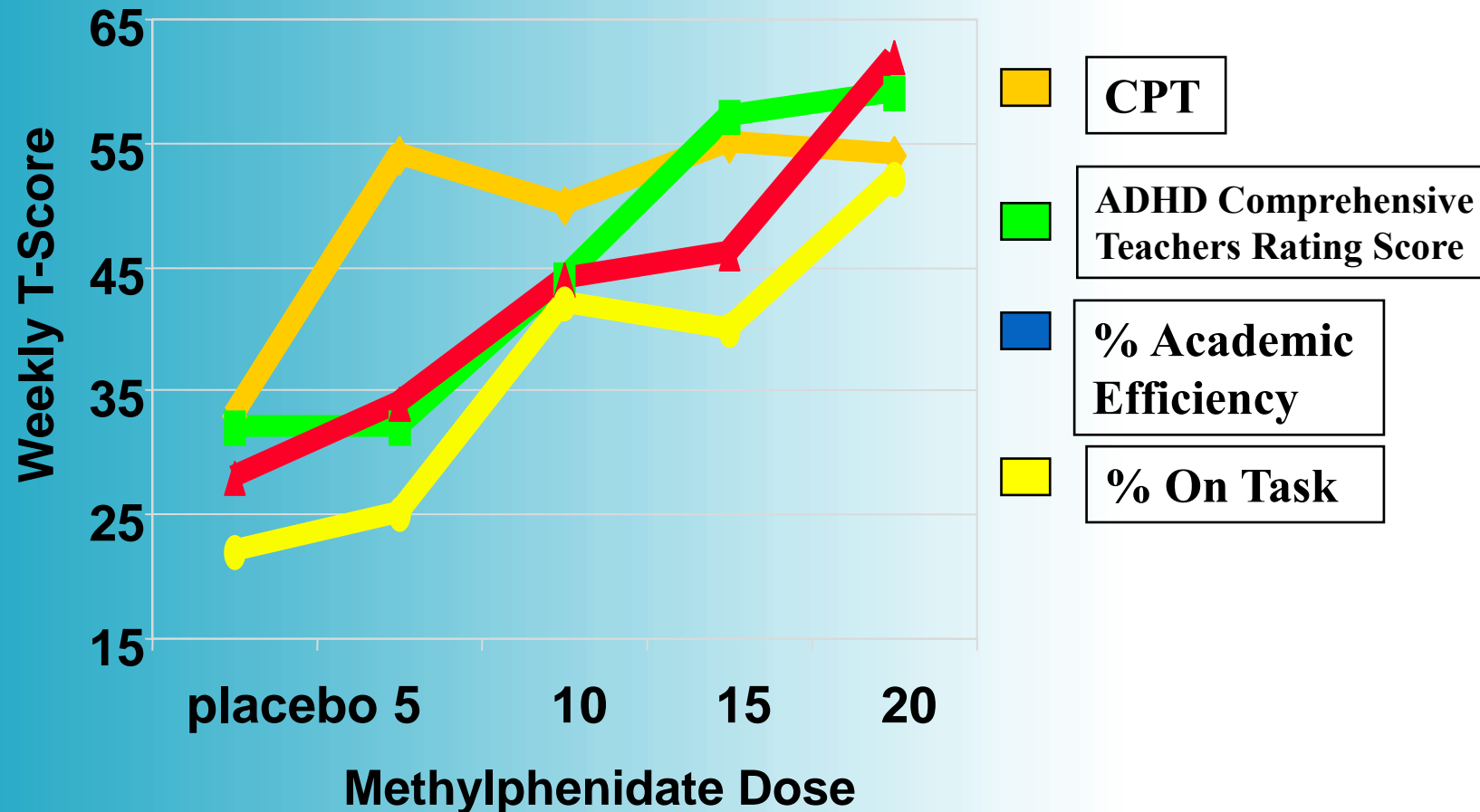
Wilens T. *J Clin Psych.* 2006.

The Mechanisms of Action of Amphetamine



Wilens T. *J Clin Psych.* 2006.

ADHD and Methylphenidate: Dose Effects on Attention in Clinic and Classroom



Rapport et al. 1987.

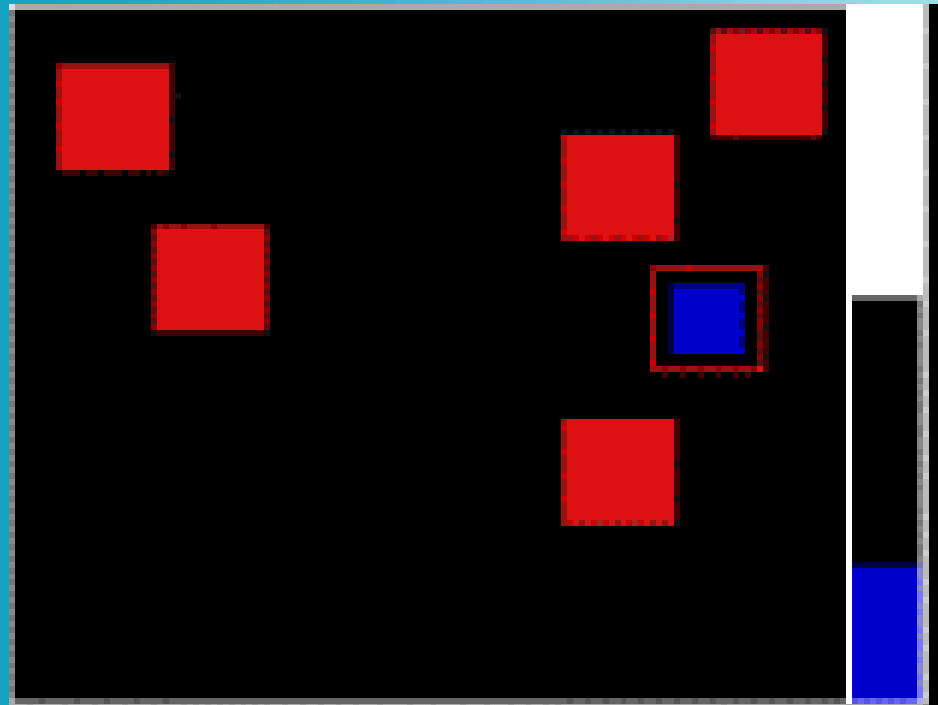
IR MPH Improved Spatial Working Memory



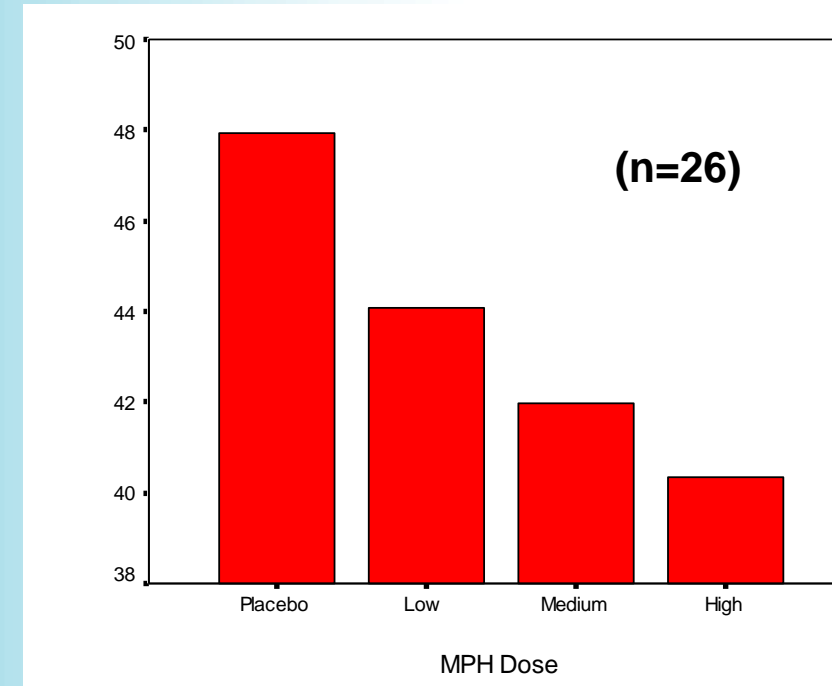
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CANTAB Spatial Working Memory Task



Spatial Working Memory Tasks



No drug effects were demonstrated on strategy, indicating real effect on working memory.

CANTAB = Cambridge Neuropsychological Test Automated Battery.

Bedard AC, et al. *J Am Acad Child Adolesc Psychiatry*. 2004;43:260-268.

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		16 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.

Childress A. *Stimulants*. In Newcorn & Wilens (eds). Update on Pharmacotherapy of ADHD. *Child Adoles Psych Clin N Am*. Elsevier, 2022. www.drugs.com.
Drugs@FDA: FDA Approved Drug Products. www.accessdata.fda.gov/scripts/cder/daf/.



Amphetamine (AMPH) in ADHD

Medication	Starting Dose	Maximum Dose*	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
Xelstrym (patch)	4.5 mg QD	18 mg	12 hr/ QD

*May exceed FDA approved dose (e.g., >20–30 mg/day).

Childress A. *Stimulants*. In Newcorn & Wilens (eds). Update on Pharmacotherapy of ADHD. *Child Adoles Psych Clin N Am*. Elsevier, 2022. www.drugs.com.

Serdexmethylphenidate/MPH for ADHD

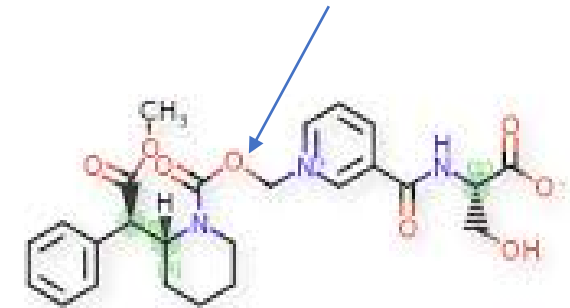
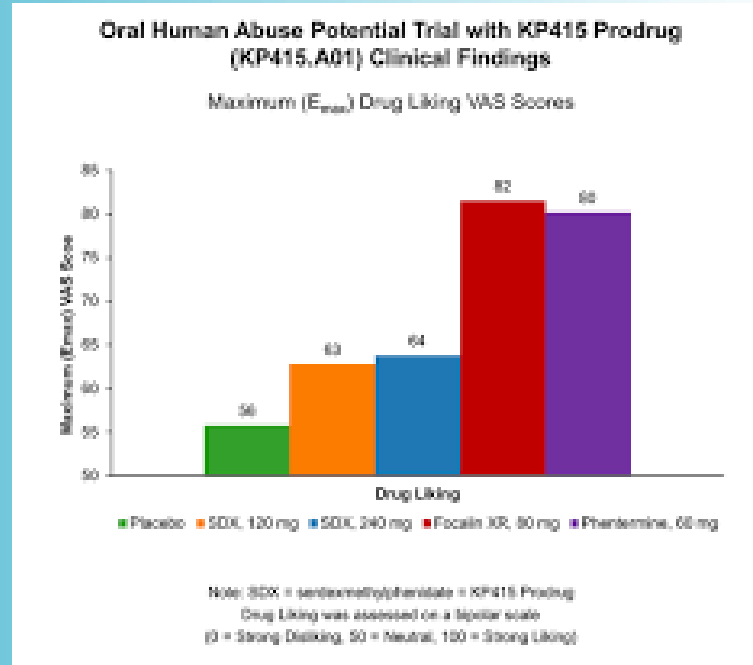
Consider for concerns of stimulant misuse (?)

- Dosing 26/5 – 52/10
- Duration of action: Up to 12 hours
- (e.g., extended release)

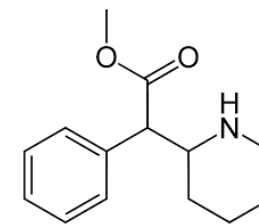


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Serdexmethylphenidate



Methylphenidate

Night-Time Administered Delayed/Extended Release MPH for ADHD: Jornay

Consider for early-morning difficulties, parents who work in early AM

Newly approved extended-release methylphenidate

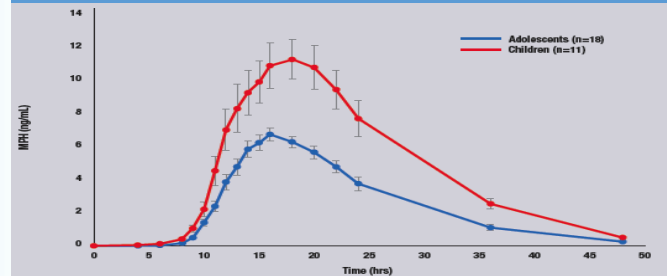
Formulation: PM administration → AM release
 Dosing: 20 – 100 mg QD
 Capsules: 20, 40, 60, 80, 100 mg
 Duration of action: 12+ hours (effect noted into evening)
 Optimal admin time: 8 pm



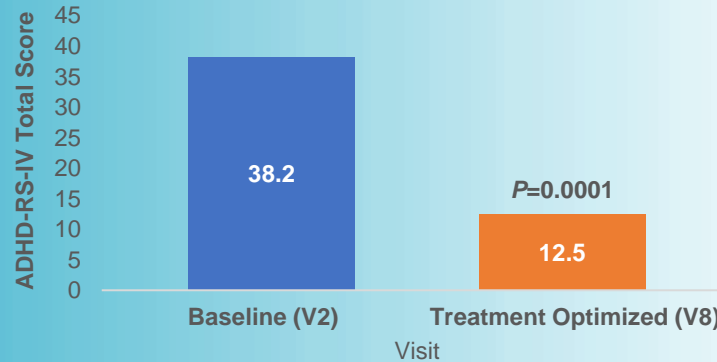
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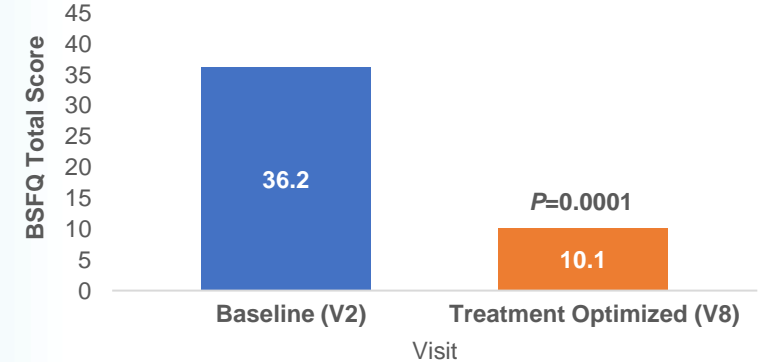
Mean Observed MPH Plasma Concentration (± S.E.M.) Following a Single Evening Administration of HLD200 (54 mg)



ADHD-RS-IV Total Score at Visit 2 and Visit 8



BSFQ Total Score at Visit 2 and Visit 8



Ironshore Pharmaceutical 6-week open study (presented) followed by controlled trial (not shown) n=43 children aged 6-12 years.

Findings: Improvement in ADHD RS, Before School Functioning Scale, DPRMB.

Adverse effects: Stimulant like—no major effects on sleep Drugs.com; Plizka et al, *J Child Adolesc Psychopharm* 2017; Wilens et al., *APSARD* 2018; Wigal et al. *AACAP* 2018; Children et al. *J Child Adolesc Psychopharm*. 2020.

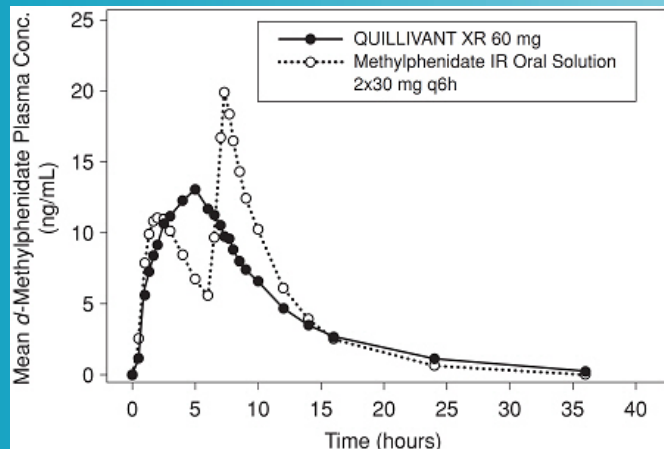


Extended Release MPH Solution and Chewable Preparations

Consider for difficulty swallowing pills

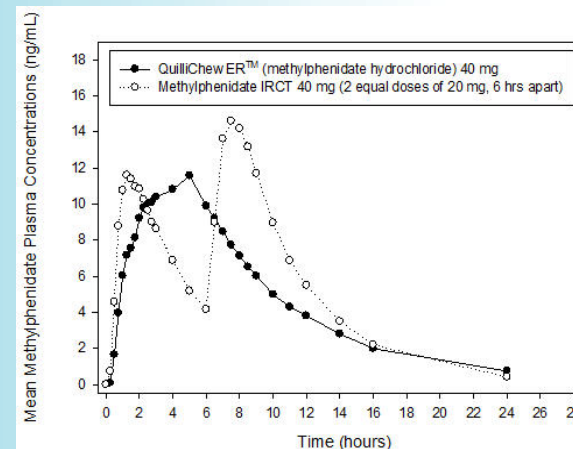
Quillivant XR

- Suspension
- 12 hour duration
- 25 mg/5 cc (tsp)
- Dosing to 60 mg daily
- Approved in pediatrics



QuilliChew ER

- Chewable tablet
- 8 hour duration
- 20 s, 30 s, 40 mg tablets
- Dosing to 60 mg daily
- Approved in pediatrics



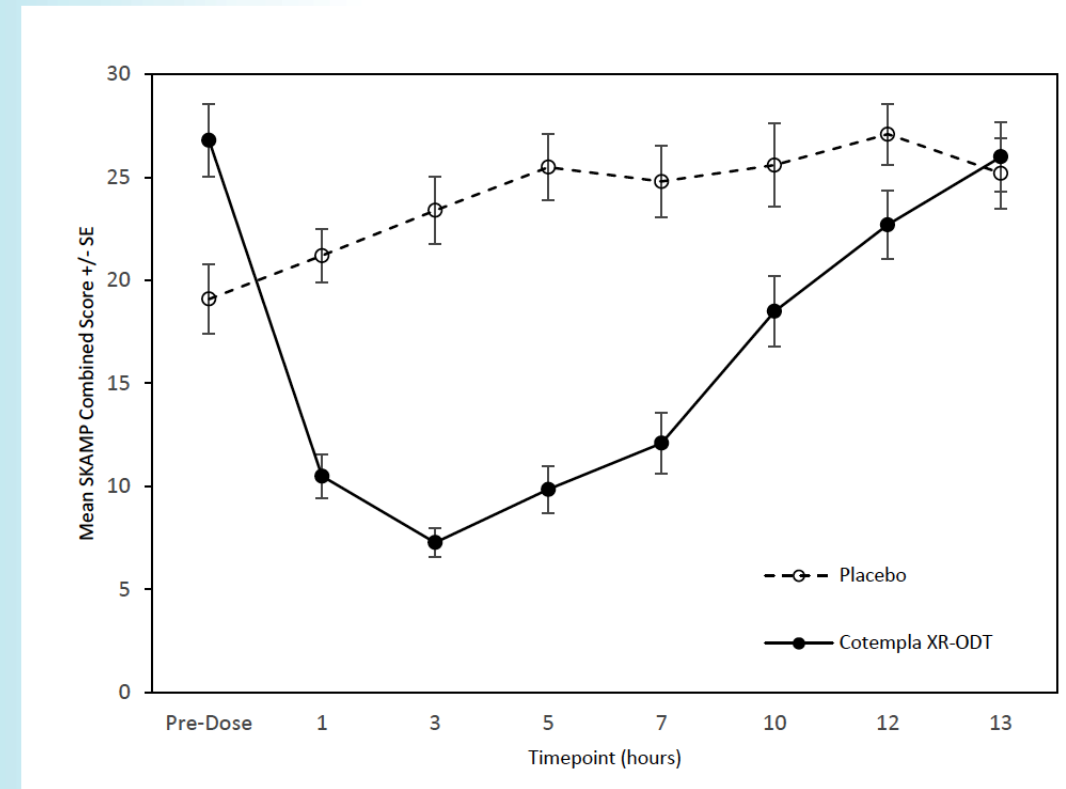
Rx list.com; PI



Extended-Release Oral Disintegrating Methylphenidate: Contempla XR

Consider for difficulty swallowing pills

- **Extended-release methylphenidate**
- **Formulation: oral disintegrating tablets**
- **Dosing: 8.6 – 25.9 mg QD**
- **Tablets: 8.6, 17.3, 25.9 mg**
- **Duration of action: 12 hours**










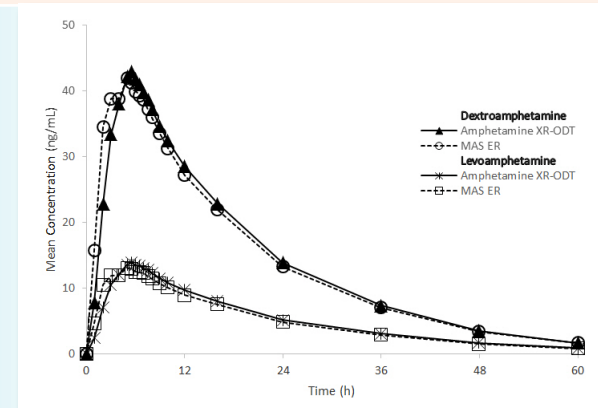
Amphetamine Oral Disintegrating Tabs: Adzenys XR for Pediatric ADHD

Consider for difficulty swallowing pills

Mixed amphetamine formulation (3:1 ratio of d- to l-amphetamine)

Duration of action to 13 hours

Equivalent Dosing						
Amph ER disintegrating (Adzenys XR)						
	3.1 mg	6.3 mg	9.4 mg	12.5 mg	15.7 mg	18.8 mg
Mixed Amph salts ER (Adderall XR)	5 mg	10 mg	15 mg	20 mg	25 mg	30 mg

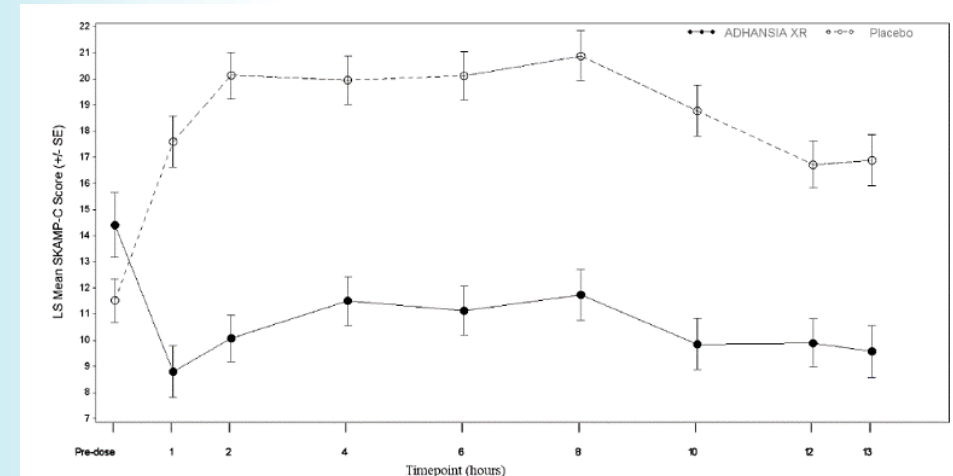




Extended-Extended Release AMPH [Mydayis[®]] or MPH [Adhansia XR] for Adult/Adolescent ADHD

Consider for Very Extended Coverage

- Mydais: Extended mixed AMPH (e.g., XR2)
- Composition: Mixed AMPH salts
- Dosing: 12.5 to 25 mg QD (>13 years old) or 50 mg (adults)
- Capsules: 12.5, 25, 37.5, 50 mg
- Duration of action: 16 hours (onset at 2 to 4 hours)
- Adhansia XR: MPH product
- Capsules: 25, 35, 45, 55, 70, or 85 mg
(up to 100 mg tested in adults)
- Duration of action: 16 hours (onset within 1 hr)



LS = Least squares.
SE = Standard Error.
The raw mean and SE bars are presented at the pre-dose timepoint, rather than the LS mean and SE bars.

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

The Presence of Cognitive Executive Functioning Deficits (EFD) May Negatively Influence Response to Stimulants

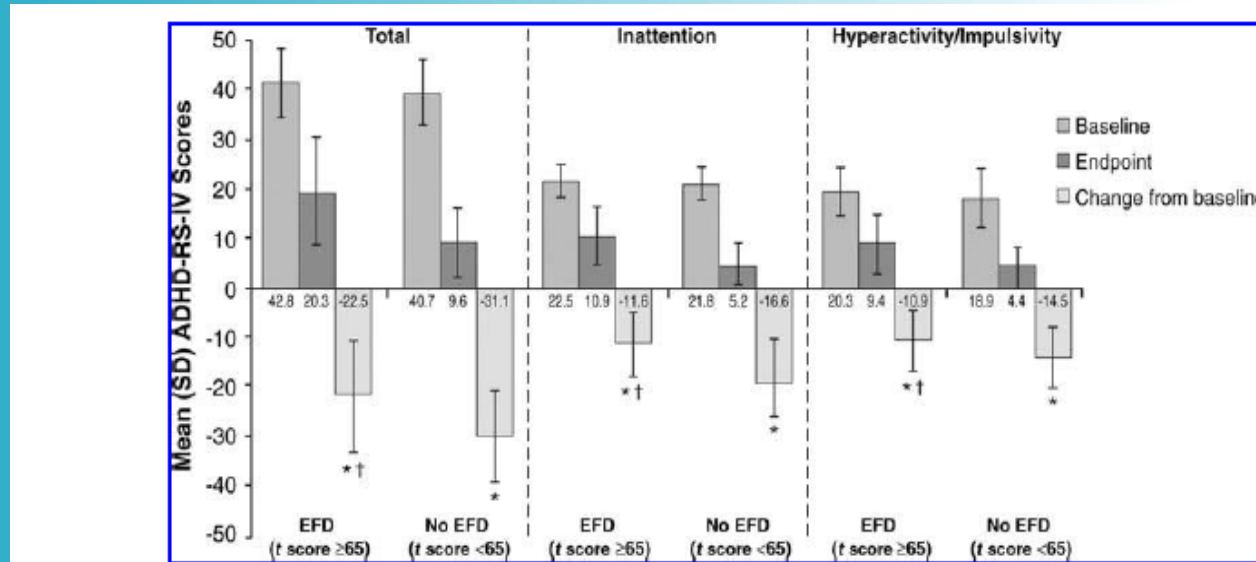


FIG. 2. Attention-Deficit/Hyperactivity Disorder Rating Scale, IV (ADHD-RS-IV) total and subscale scores by endpoint Behavior Rating Inventory of Executive Function (BRIEF) Global Executive Composite (GEC) *t* score category. Clinically significant executive function deficit (EFD), baseline GEC *t*-score ≥ 65 ; no EFD, baseline GEC *t* score < 65 ; error bars indicate standard deviation. $n=78$ for the EFD subgroup; $n=230$ for the no EFD subgroup. $*p<0.0001$, baseline versus endpoint, within endpoint EFD and no EFD categories, based on paired *t* test; $^\dagger p<0.0001$, change from baseline to endpoint, endpoint EFD versus no EFD category, based on two-sample *t* test.



NIMH Preschool ADHD Treatment Study (PATS): Study Results

- **N=303**
- **MPH given tid decreased ADHD symptoms in a dose-dependent fashion**
- **Effect size was lower than observed in school-age children**
 - **dose was limited for safety reasons**
- **Rates of adverse events were higher and were different**
 - **e.g., crying, irritability, outbursts were very common**

Kollins S, et al. *JAACAP*. 2007

Greenhill LL, et al. *JAACAP*. 2007.

Clinical Trial > J Am Acad Child Adolesc Psychiatry. 2022 Dec;61(12):1423-1434.
doi: 10.1016/j.jaac.2022.03.034. Epub 2022 May 13.

Efficacy and Safety of Lisdexamfetamine in Preschool Children With Attention-Deficit/Hyperactivity Disorder

Ann C Childress¹, Eric Lloyd², Leslie Jacobsen³, Lhanoo Gunawardhana², Steven A Johnson Jr², Robert L Findling⁴

Affiliations + expand

PMID: 35577034 DOI: 10.1016/j.jaac.2022.03.034

[Free article](#)

Abstract

Objective: To evaluate the acute efficacy, safety, and tolerability of lisdexamfetamine dimesylate (LDX) vs placebo (PBO) in preschool-aged children with attention-deficit/hyperactivity disorder (ADHD).

Method: This phase 3, double-blind, fixed-dose study randomly assigned children (aged 4-5 years) with ADHD to 6 weeks of LDX (5, 10, 20, 30 mg) or PBO. The prespecified primary (change from baseline at week 6 in ADHD Rating Scale IV, Preschool version, total score [ADHD-RS-IV-PS-TS]) and key secondary (Clinical Global Impression-Improvement [CGI-I] score at week 6) efficacy endpoints were assessed using linear mixed-effects models for repeated measures. Safety and tolerability assessments included treatment-emergent adverse events (TEAEs) and changes in pulse and blood pressure (BP).

Results: The study comprised 199 participants randomly assigned 5:5:5:5:6 to receive 5, 10, 20, 30 mg LDX or PBO, respectively. Least squares (LS) mean (95% CI) treatment difference at week 6 between pooled LDX (10, 20, 30 mg) and PBO was statistically significant for ADHD-RS-IV-PS-TS change (-5.9 [-11.01, -0.78], $p = .0242$; effect size [ES], -0.43). CGI-I scores improved (ie, 1-2 on CGI-I) in 41.7% for pooled LDX and 24.3% for PBO ($p = .0857$). The LS mean (95% CI) treatment difference between pooled LDX and PBO for CGI-I score at week 6 was -0.6 (-1.03, -0.16; $p = .0074$; ES, -0.52). Frequency of TEAEs was 46.6% across all 4 LDX doses vs 42.2% with PBO; the most frequent TEAEs were decreased appetite (13.7% vs 8.9%, respectively) and irritability (9.6% vs 0%). Discontinuations because of TEAEs were 5.5% for all LDX doses and 4.4% for PBO. Mean \pm SD pulse/BP changes from baseline at week 6/early termination were numerically greater with LDX vs PBO (pulse beats/min: 2.7 \pm 10.79 vs 1.2 \pm 9.90; systolic BP, mm Hg: 1.0 \pm 7.51 vs 0.3 \pm 6.06; diastolic BP, mm Hg: 1.7 \pm 5.90 vs 0.0 \pm 6.88).

Conclusion: In children aged 4 to 5 years with ADHD, LDX was more efficacious than PBO in reducing symptoms. The observed ES for change in ADHD-RS-IV-PS-TS appears to be smaller in magnitude than has been reported for studies of LDX conducted in older children and adolescents. LDX was generally well tolerated, and no new safety signals were identified.

Clinical trial registration information: Safety and Efficacy Study in Preschool Children Aged 4-5 Years With Attention-Deficit/Hyperactivity Disorder; <http://www.clinicaltrials.gov>; NCT03260205.

Clinicaltrials: gov; [NCT03260205](https://www.clinicaltrials.gov/ct2/show/study/NCT03260205).



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Design RCT of Preschoolers with ADHD Age 4-5 years

Duration 6 weeks

Assigned dosing 5, 10, 20 , 30 mg

Outcome: ADHD RS Preschool v

Results

N = 199 patients

Week 6: $p = 0.0242$

Effect Size 0.43

CGI response: 42% LDX v 24% PBO

Adverse effects

47% LDX v 42% PBO

Decreased appetite and irritability
most common

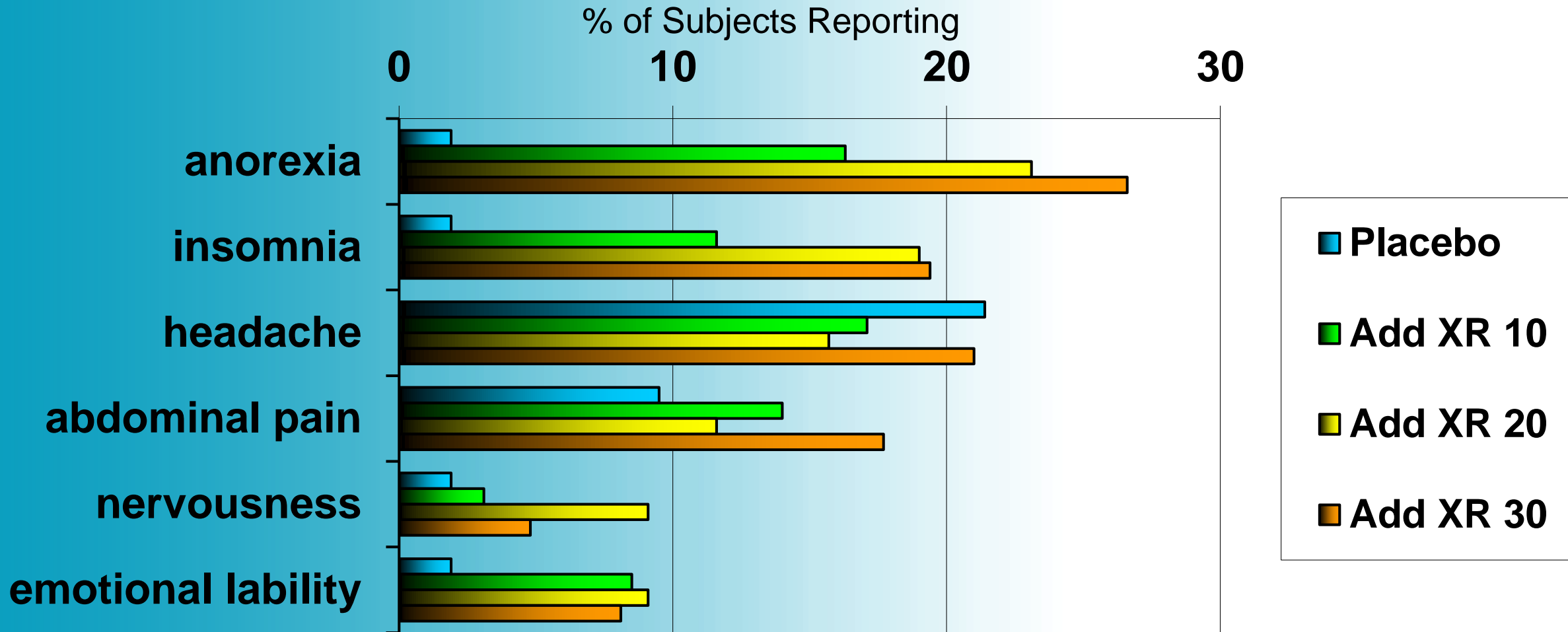
Discontinued: 5.5% LDX v 4.4% PBO

MAS XR Study in Youth with ADHD: Frequently Reported Adverse Effects



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Managing Stimulant Side Effects

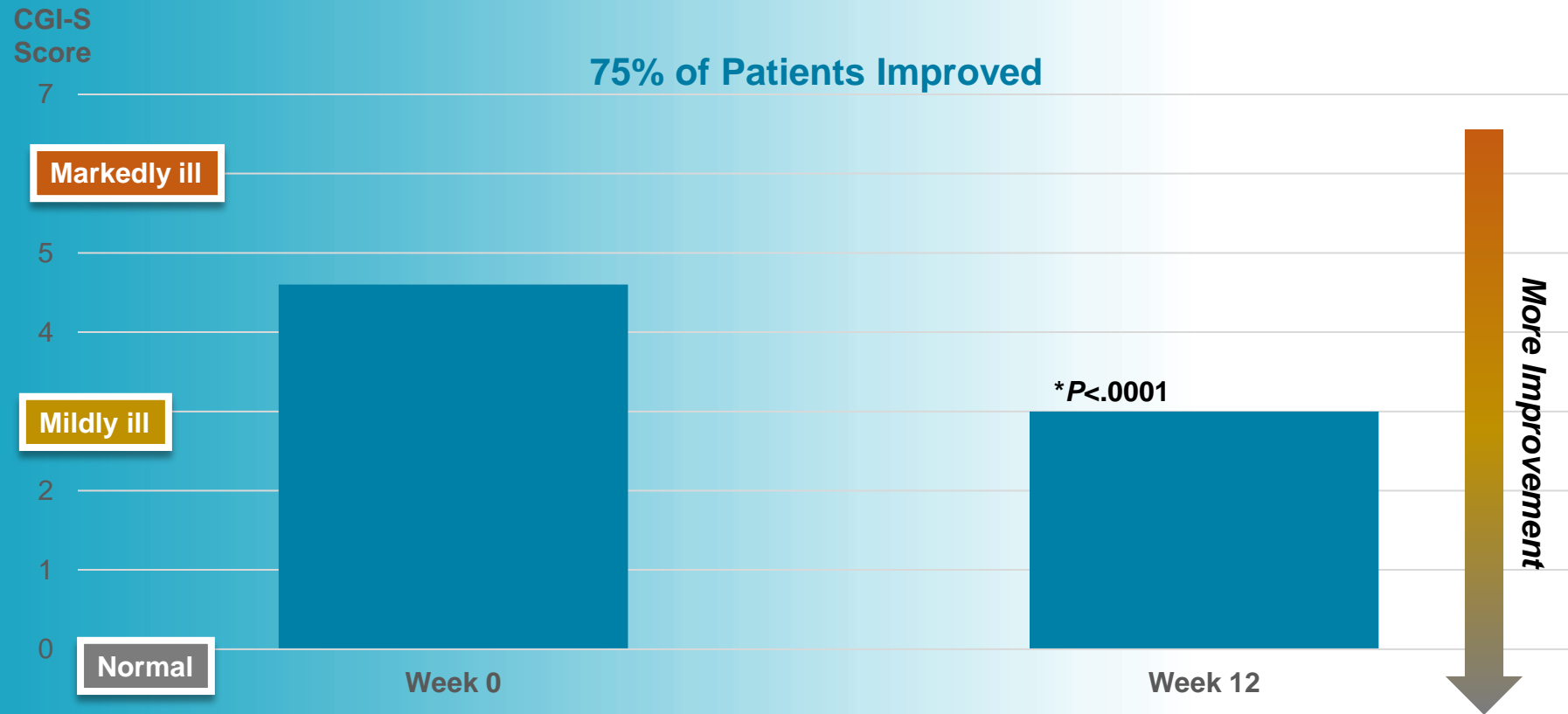
- **Cardiovascular**
 - AAH/APA guidelines-CP, SOB, palpitations, syncope, VS changes
 - If positive->PCP/ cardiology consult
- **Insomnia**
 - Baseline vs stimulant
 - Sleep hygiene, melatonin, clonidine, tricyclic, mirtazapine
- **Appetite decrease**
 - Change timing of meals, caloric supplements, qPM snacking
 - Consider cyproheptadine, nortriptyline
- **Dental issues**
 - Grinding: wear night guard, consider beta-blocker
 - Dry mouth: frequent cleanings, water, pilocarpine solution
- **Mood/irritability**
 - Evaluate when occurring, medication-induced vs comorbid mood
 - Consider change preparation, change medication, address mood
 - Adjunct fish oils, alpha agonist, SGA, mood stabilizer
 - For crash: change preparation, add IR in afternoon, use orange juice (amph)

MGH Open Study: Fish Oils Reduce Emotional Dysregulation in Medication-Treated Children with ADHD



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N=10. CGI-S = CGI-Severity.

Wilens TE, et al. *J Child Adolesc Psychopharmacol.* 2017;27(8):755-756.

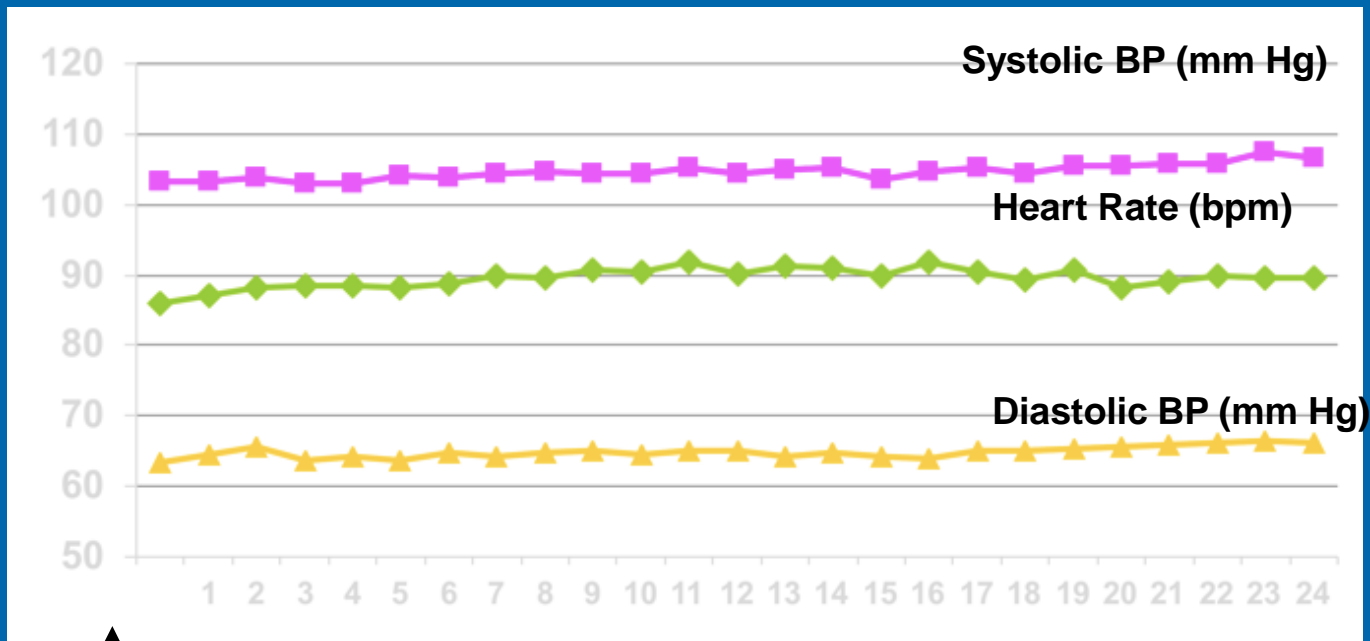


Stimulant Controversies

- **Adverse cardiovascular (CV) outcomes**
- **Growth suppression**
- **Exacerbation of anxiety**
- **Use in concussion/TBI**
- **Use in Substance Use Disorders**



Mixed Amph Salts: Mean Blood Pressure and Heart Rate

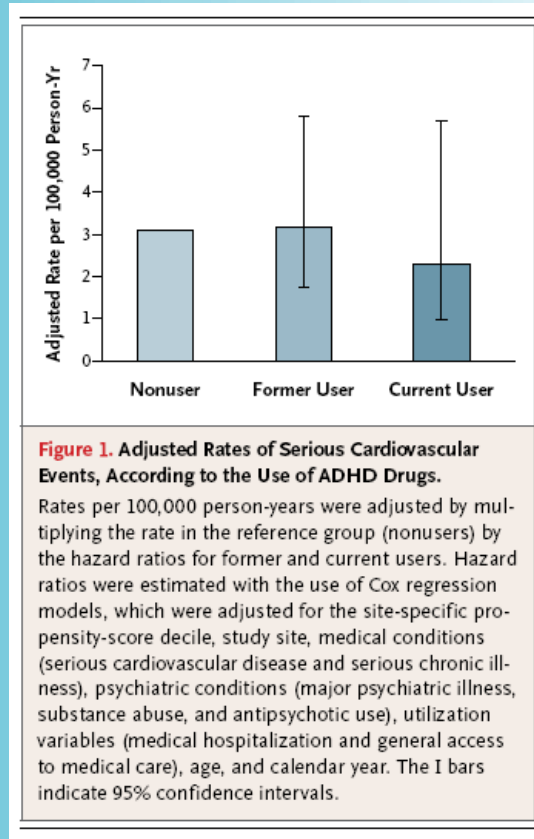


Baseline

Time in Study (months)

Findling, Biederman, Wilens et al. *J Ped.* 2006.

ADHD Meds Are Not Associated with Adverse CV Outcomes: Children



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

ADHD Meds are Not Associated with Adverse CV Outcomes: Adults



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ADHD Medications and Risk of Serious Cardiovascular Events in Young and Middle-aged Adults

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BETWEEN 2001 AND 2010, USE of medications labeled for treatment of attention-deficit/hyperactivity disorder (ADHD) increased even more rapidly in adults

Context More than 1.5 million US adults use stimulants and other medications labeled for treatment of attention-deficit/hyperactivity disorder (ADHD). These agents can increase heart rate and blood pressure, raising concerns about their cardiovascular safety.

Objective To examine whether current use of medications prescribed primarily to treat ADHD is associated with increased risk of serious cardiovascular events in young and middle-aged adults.

Design, Setting, and Participants Retrospective, population-based cohort study using electronic health care records from 4 study sites (OptumInsight Epidemiology, Tennessee Medicaid, Kaiser Permanente California, and the HMO Research Network), starting in 1986 at 1 site and ending in 2005 at all sites, with additional covariate assessment using 2007 survey data. Participants were adults aged 25 through 64 years with dispensed prescriptions for methylphenidate, amphetamine, or atomoxetine at baseline. Each medication user (n = 150 359) was matched to 2 nonusers on study site, birth year, sex, and calendar year (443 198 total users and nonusers).

Main Outcome Measures Serious cardiovascular events, including myocardial infarction (MI), sudden cardiac death (SCD), or stroke, with comparison between current or new users and remote users to account for potential healthy-user bias.

Results During 806 182 person-years of follow-up (median, 1.3 years per person), 1357 cases of MI, 296 cases of SCD, and 575 cases of stroke occurred. There were 107 322 person-years of current use (median, 0.33 years), with a crude incidence per 1000 person-years of 1.34 (95% CI, 1.14-1.57) for MI, 0.30 (95% CI, 0.20-0.42) for SCD, and 0.56 (95% CI, 0.43-0.72) for stroke. The multivariable-adjusted rate ratio (RR) of serious cardiovascular events for current use vs nonuse of ADHD medications was 0.83 (95% CI, 0.72-0.96). Among new users of ADHD medications, the adjusted RR was 0.77 (95% CI, 0.63-0.94). The adjusted RR for current use vs remote use was 1.03 (95% CI, 0.86-1.24); for new use vs remote use, the adjusted RR was 1.02 (95% CI, 0.82-1.28); the upper limit of 1.28 corresponds to an additional 0.19 events per 1000 person-years at ages 25-44 years and 0.77 events per 1000 person-years at ages 45-64 years.

Conclusions Among young and middle-aged adults, current or new use of ADHD medications, compared with nonuse or remote use, was not associated with an increased risk of serious cardiovascular events. Apparent protective associations likely represent healthy-user bias.

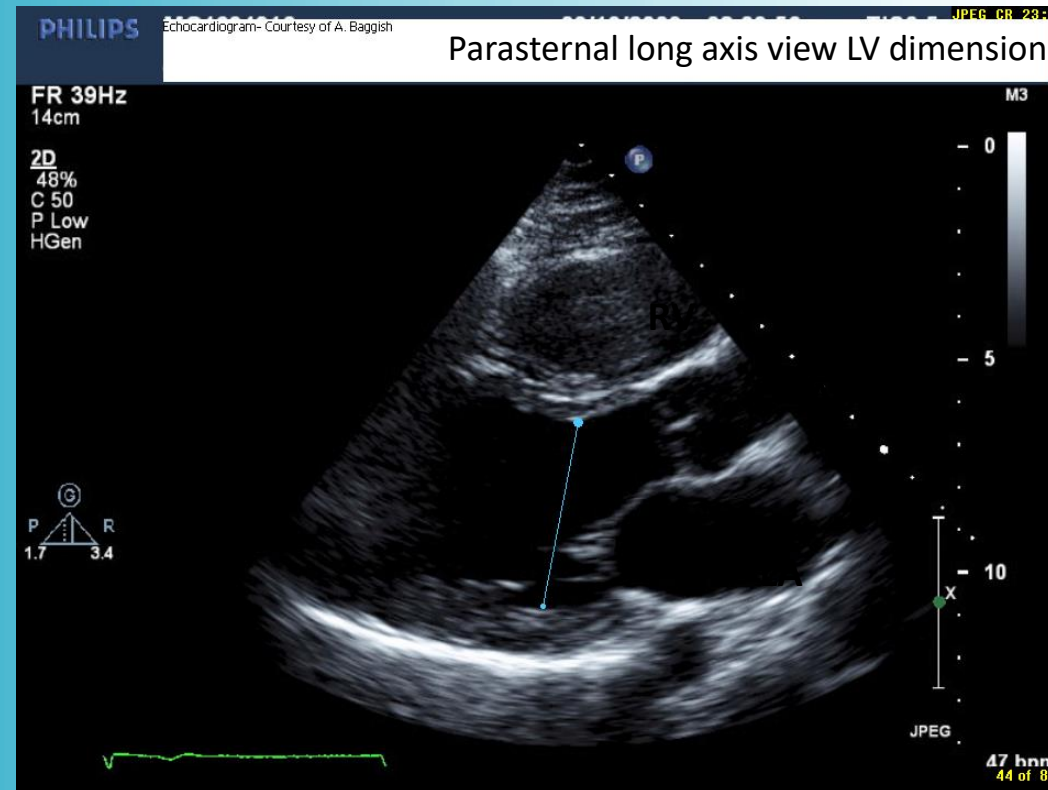
JAMA. 2011;306(24):doi:10.1001/jama.2011.1830

www.jama.com

Habel et al. *JAMA*. 2011; 306(24) 2673-2683.

MGH Study of Cardiovascular Effects of Lisdexamfetamine

Transthoracic Echocardiography (TTE): Structure



Hammerness et al. *World J Biol Psych.* 2012. Early Online: 1–8.



Table I. Resting echocardiogram parameters (TTE; N = 14).

	Baseline	Endpoint	z	P value
Ejection fraction (%)	67.79 ± 6.91	68.21 ± 4.02	0.33	0.74
LV end diastolic dimension (mm) ^ψ				
Healthy subjects (N = 7)	48.29 ± 5.88	44.42 ± 7.07	-3.79	<0.01
Hypertensive subjects (N = 7)	44.00 ± 4.90	43.57 ± 6.13	-0.28	0.70
LV end diastolic volume (ml)	101.46 ± 23.78	98.89 ± 26.00	-0.68	0.50
LV end systolic dimension (mm)	32.50 ± 3.92	29.07 ± 5.30	-3.00	0.01
LV end systolic volume (ml)	36.16 ± 11.91	34.14 ± 12.35	-0.93	0.36
RV end diastolic dimension (mm)	35.93 ± 5.40	34.43 ± 4.94	-1.75	0.08
Left atrium (mm)	33.93 ± 3.27	33.86 ± 4.47	-0.11	0.91
Intraventricular septum thickness (mm)	10.14 ± 1.88	9.64 ± 1.50	-1.67	0.09
LV posterior wall thickness (mm)	9.43 ± 1.50	9.43 ± 1.50	-0.00	1.00
E wave (cm/s)*	80 ± 17.03	71.86 ± 18.88	-2.25	0.02
A wave (cm/s)*	53.43 ± 17.12	62.93 ± 23.26	2.22	0.03
E/A ratio*, ^ψ				
Healthy subjects (N = 7)	2.05 ± 0.39	1.38 ± 0.48	-4.57	<0.01
Hypertension subjects (N = 7)	1.30 ± 0.27	1.36 ± 0.84	-0.35	0.72

LV, left ventricle; RV, right ventricle.

*E, A waves, LV diastolic function indices (Doppler).

^ψChange differed significantly (Healthy vs. HTN).



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.

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

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Abstract

Objective: Attention-deficit/hyperactivity disorder (ADHD) treatment with stimulant products has been shown to be safe and effective; however, there are remaining concerns about their possible adverse effects on growth trajectories. We conducted a systematic review of the extant literature derived from ecologically valid databases and registries to assess the body of knowledge about the effects of stimulants on growth trajectories in naturalistic samples. **Methods:** Using PubMed and PsycINFO, we searched for articles published before February 8, 2023 that focused on growth findings associated with stimulant treatment in pediatric ADHD from comprehensive datasets derived from naturalistic population studies. **Results:** Of the 1070 articles initially identified, 12 met all inclusion criteria. Sample sizes ranged from 157 to 163,820 youths. Seven of 10 articles examining height found 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.



Review of Literature

N = 12 Studies (157-163,820 pts)

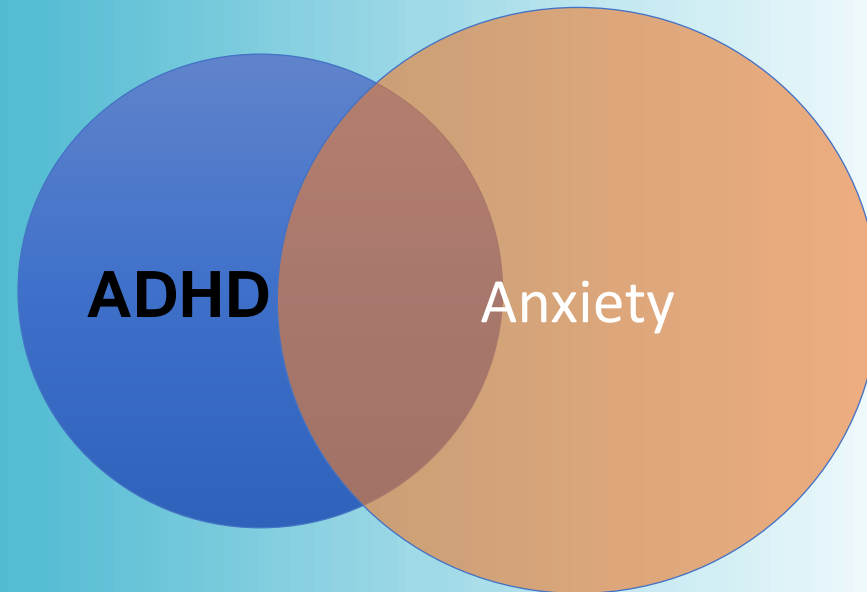
Findings:

- 3/10 studies showed no decrease in height
- 7/10 studies showed sig decrease in height that normalized over two years
- 10/10 studies showed initial decreases in weight that normalized over time
- 8/10 showed reduced BMI reductions that normalized over time

Conclusion: ...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.



During the Pandemic, There Has Been Increases in the Prevalence of Anxiety and Depressive Disorders in Children





Meta-Analysis > J Child Adolesc Psychopharmacol. 2015 Oct;25(8):611-7.

doi: 10.1089/cap.2015.0075. Epub 2015 Sep 24.

Meta-Analysis: Reduced Risk of Anxiety with Psychostimulant Treatment in Children with Attention-Deficit/Hyperactivity Disorder

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[Free PMC article](#)

Abstract

Objective: Anxiety is a commonly reported side-effect of psychostimulant treatment. Our goal was to quantify the risk of anxiety as a side effect of psychostimulant treatment for attention-deficit/hyperactivity disorder (ADHD).

Meta-analysis suggests that treatment with psychostimulants significantly reduced the risk of anxiety when compared with placebo. This finding does not r/o the possibility that some children experience increased anxiety when treated with psychostimulants...

psychostimulants when compared with placebo ($p = 0.0033$ [95% CI: -0.007 to -0.00004], $Z = -2.54$, $p = 0.019$).

Conclusions: Meta-analysis suggests that treatment with psychostimulants significantly reduced the risk of anxiety when compared with placebo. This finding does not rule out the possibility that some children experience increased anxiety when treated with psychostimulants, but suggests that those risks are outweighed by the number of children who experience improvement in anxiety symptoms (possibly as a secondary effect of improved control of ADHD symptoms). Clinicians should consider

Stimulants Improved Anxiety in ADHD Over Time



N= 57
12 week open
study
Age: 6 -15 yrs
Mostly MPH

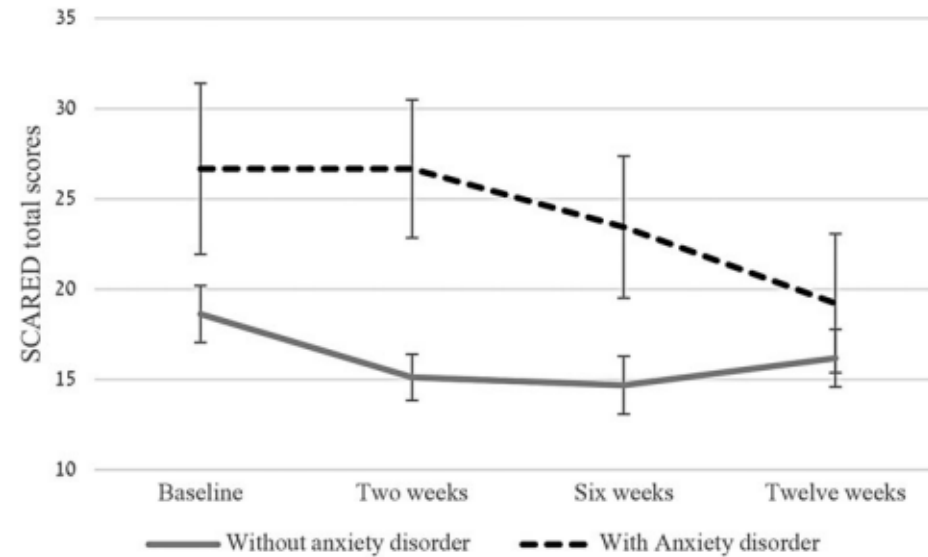


FIG. 2. Change in SCARED scores in children with ADHD with and without comorbid anxiety disorders showing a significant time by group interaction [$F(2, 87) = 3.34, p = 0.032$]. ADHD, attention-deficit/hyperactivity disorder; SCARED, screen for child anxiety related disorders.

SCARED: screen for child anxiety related disorders



ADHD, Post-Concussion, & Treatment

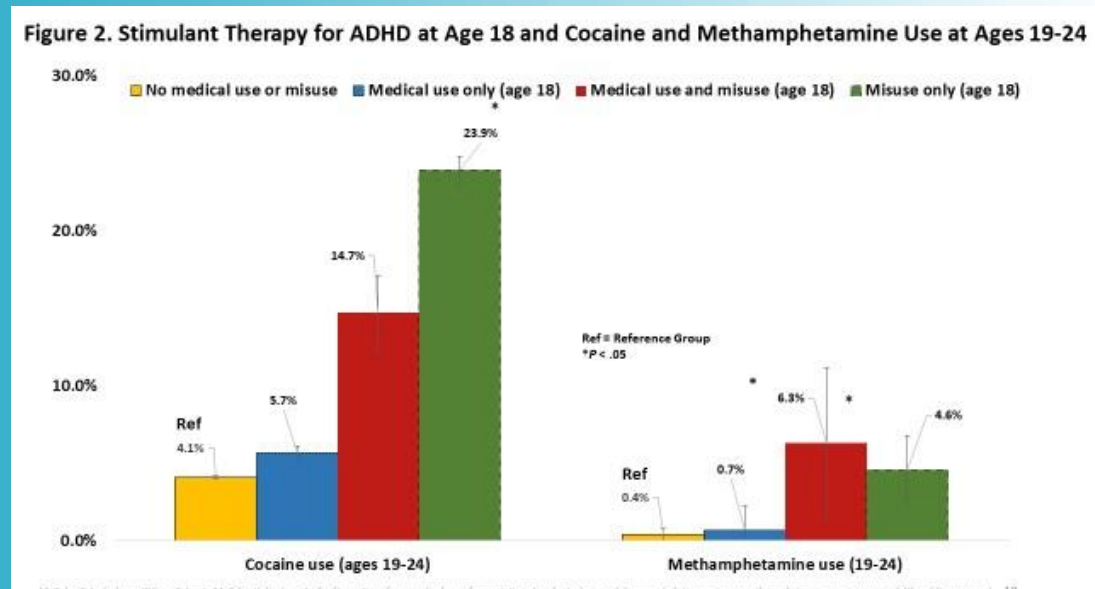
- Treatment of ADHD may also improve post-concussive syndrome
- Use of stimulants & modafinil for concussion and/or (traumatic) brain injury
 - Targeted symptoms: arousal, disinhibition
 - General focus and concentration
 - Enhanced processing speeds
 - Unclear effects on complex processing
- Non-specific response to stimulants
 - Nonspecific response (Wilens and Kaminski, 2020)
- Caveats
 - Careful with side effects: some indication of increased adverse effects with more “brain injury” (vs ADHD)
 - To “return to play” faster, some players are using stimulants to improve post-concussive testing

Wilens & Spencer. Stimulants Revisited. *Psych Clin N Am*. 2000.

Willmott C and Ponsford J. *J Neurol Neurosurg Psychiatry*. May 2009;80:552.



Prescription Stimulant Misuse Not Medical Use of Stimulants is Linked to Later Cocaine & Methamphetamine Use



National longitudinal multi-cohort panels of U.S. high school 12th graders (N=5,034) who were followed from ages 17–18 (baseline cohort years 2005–2017) to ages 23/24. At ages 17–18, an estimated 6.4% reported medical use only of prescription stimulants to treat ADHD, 3.8% indicated both medical use and misuse, 14.6% reported misuse only, and 75.2% of adolescents did not report medical use or misuse of prescription stimulants (population controls).

McCabe SE, Schulenberg JE, Wilens TE, et al. 2023 JAMA Open Network

Strategies for ADHD and Substance Use Disorders (SUD)



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In context to SUD, ADHD should be treated:

If misuse or less severe SUD, treat ADHD concomitantly (e.g., MJ use) --> brief SUD intervention

More severe SUD --> address SUD (e.g., daily use)

For ADHD --> use CBT, nonstimulants, extended-release or prodrug stimulants (may need higher dose)

Levin et al. *JAMA Psychiatry*. 2015.

Berger and Wilens. Overlap of ADHD and SUD, in Update of ADHD Pharmacotherapy. *Child Adoles Psych Clin of N Amer*. Elsevier, 2022.



Summary: Stimulants in ADHD

- **Highly effective in treating ADHD**
- **Improvements in the release mechanisms of the stimulants**
- **Largely predictable adverse effects**
- **Longer term effects encouraging at both neurobiological and outcome levels**
- **Data on combination with other medications emerging**
- **Future research**