MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Treatment of ADHD: Stimulants

Timothy E. Wilens, MD

Chief, Division of Child & Adolescent Psychiatry, Massachusetts General Hospital

Professor of Psychiatry, Harvard Medical School

Faculty Disclosure

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

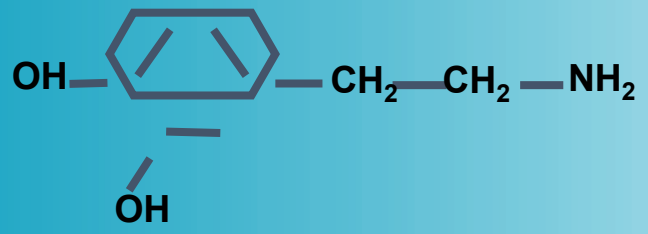
Timothy Wilens, MD has served as a consultant, or has received grant support from the following:

- NIH (NIDA), Food and Drug Administration
- Licensing agreement with 3D Therapy
- Clinical care: MGH, Bay Cove Human Services, Gavin, Major/Minor League Baseball
- (Co)Edited Straight Talk About Psychiatric Medications for Kids (Guilford); Update on Pharmacotherapy of ADHD (Elsevier)

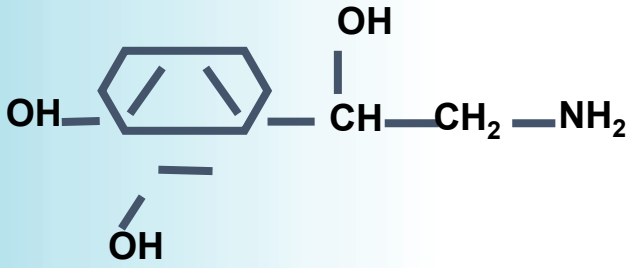
Some of the medications discussed may not be FDA approved in the manner in which they are discussed including diagnosis(es), combinations, age groups, dosing, or in context to other disorders (e.g., substance use disorders)

Structural Comparisons

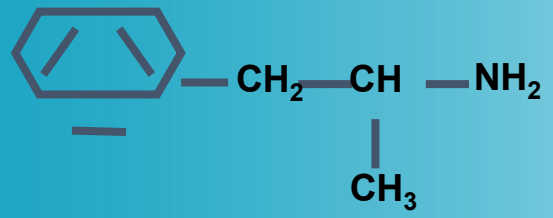
Dopamine



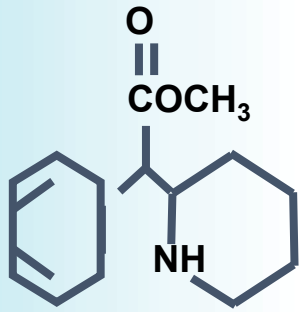
Norepinephrine



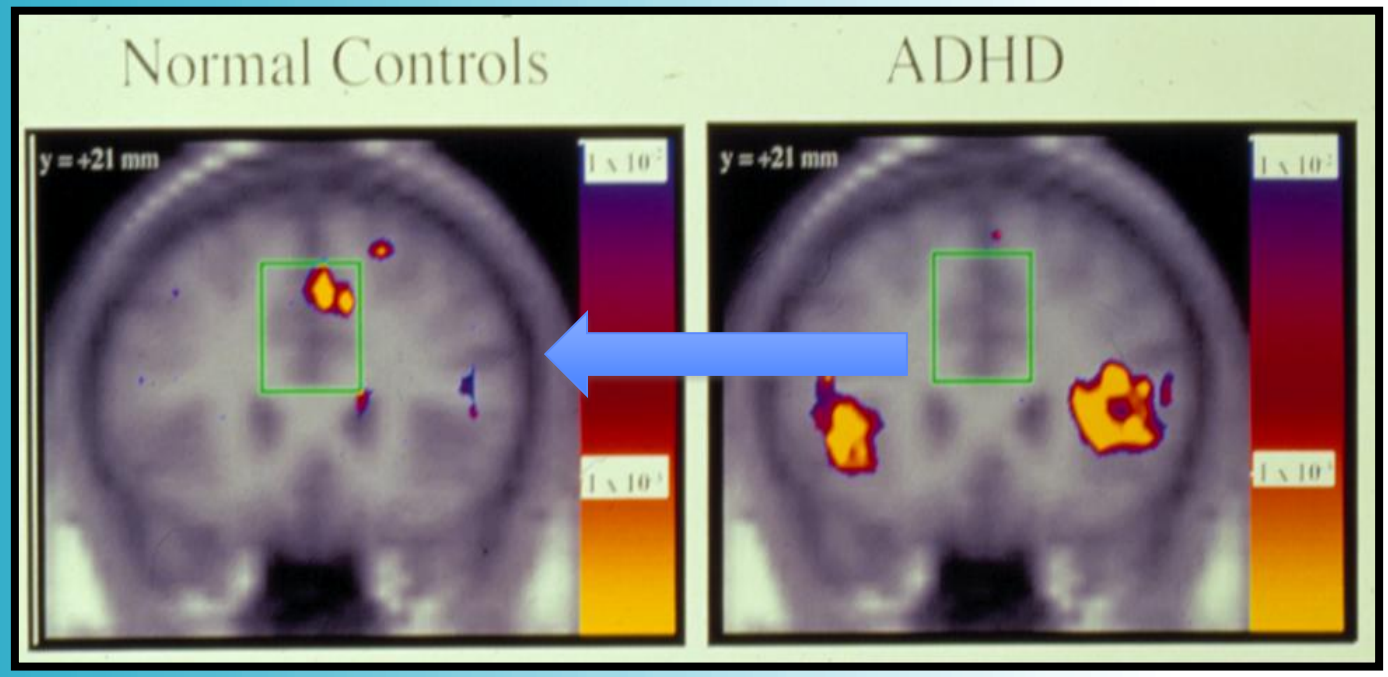
Amphetamine



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)

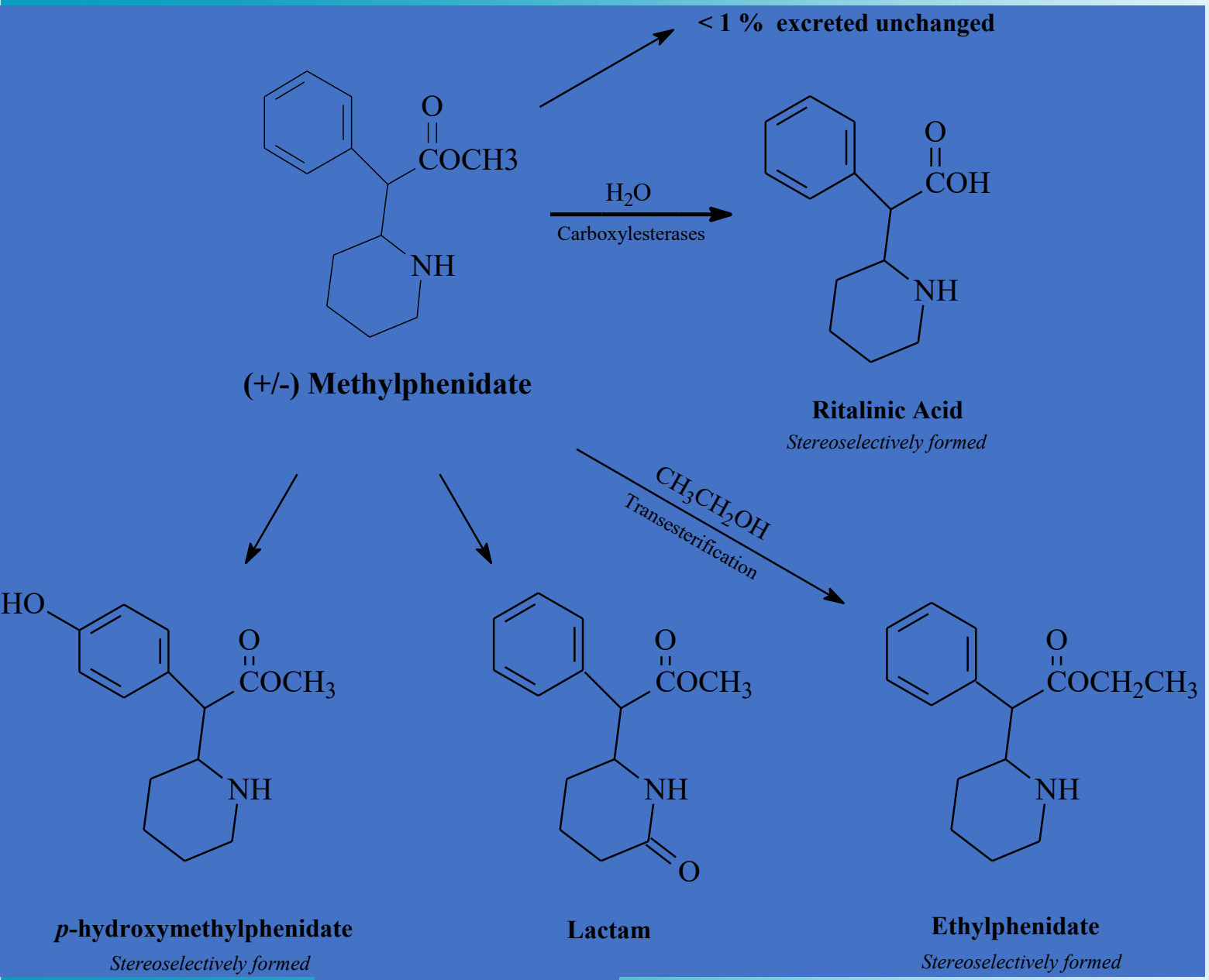
- **Low bioavailability (~20 – 25%)**
  - **(+/d)-MPH isomer much greater bioavailability than the (–/l)-MPH isomer**
- **Typical IR therapeutic doses provide**
  - **T_{max} = 1.5 – 2.5 h**
  - **C_{max} = 6 – 15 ng/mL**
  - **$T_{½}$ = 2 – 3.5 h**

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**

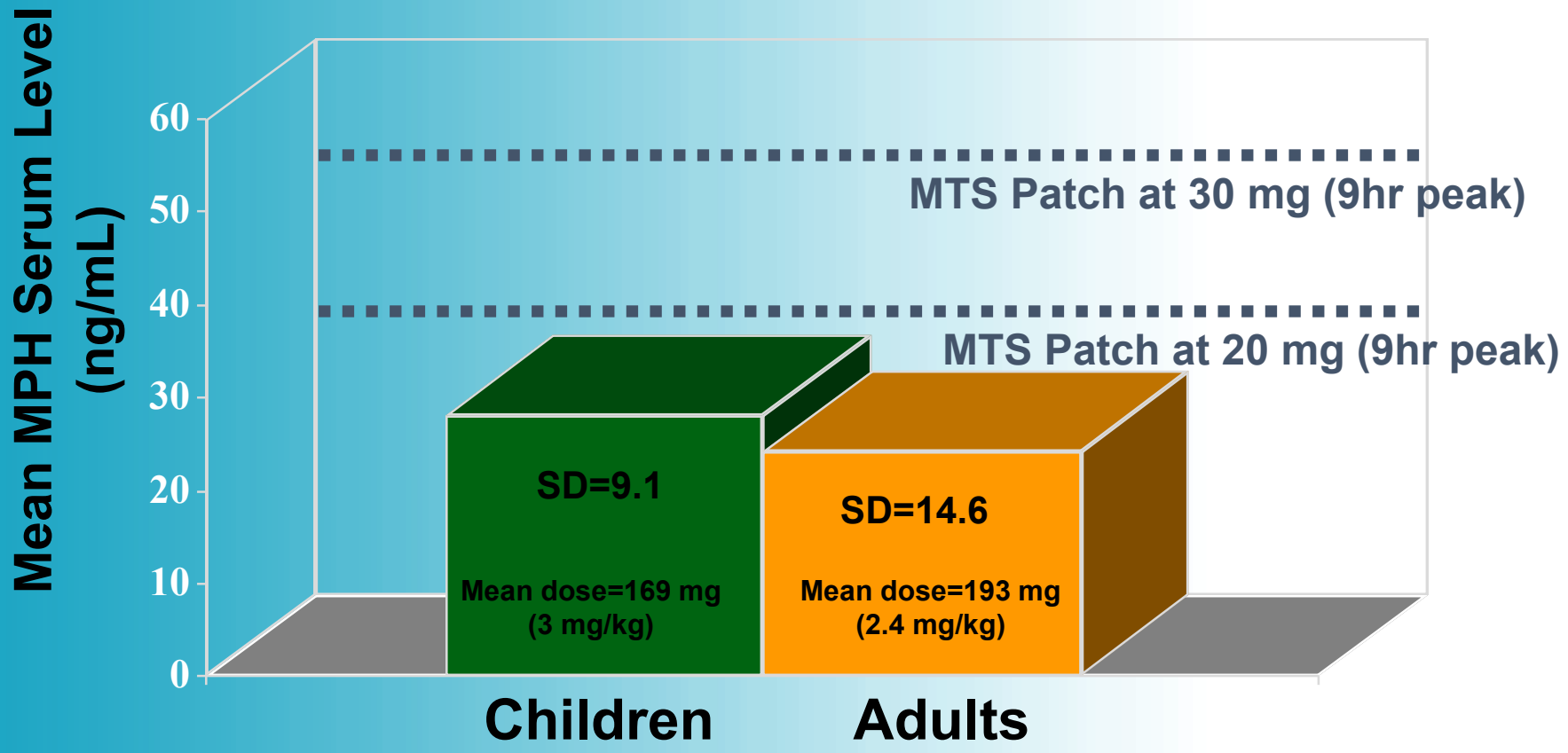
Wilens and Spencer. *Child Adolesc Psychiatr Clin N Am.* 2000;9:573-603.
Stevens and Wilens. ADHD Across the Lifespan. 2013.
Zhu et al. *Clin Pharm.* 2009;270:59-65.
Markowitz and Melchert. *Stimulants, in Pharmacotherapy of ADHD.* Elsevier Press 2022.



MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Markowitz et al. *Pharmacotherapy* 2003; Update in Psychopharmacology of ADHD, 2022.

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



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

Amphetamine (AMPH)

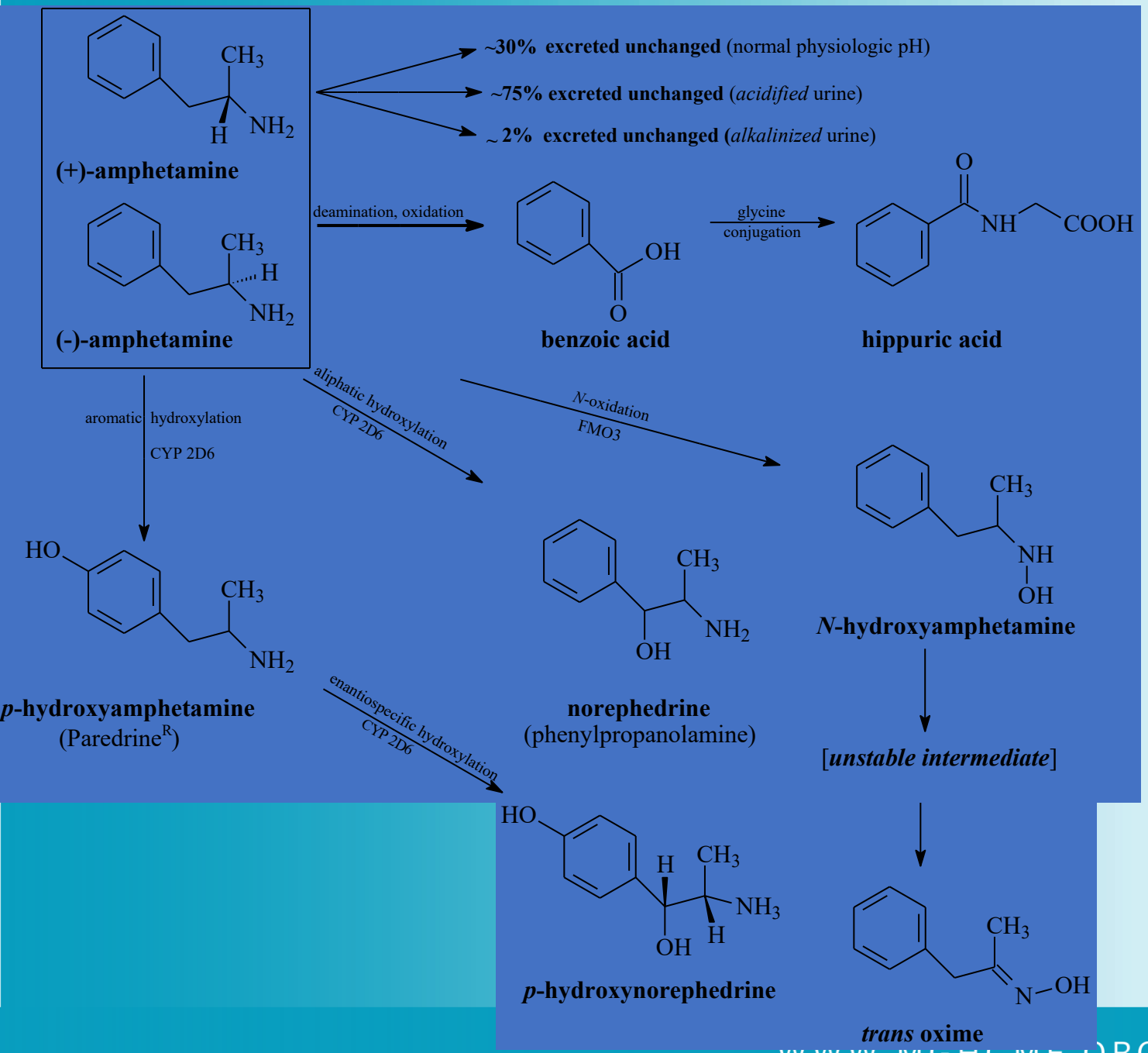
- **High bioavailability (~75%)**
- **Typical therapeutic doses of IR *dextroamphetamine* provide**
  - **T_{max} = 2 – 3 h**
  - **C_{max} = 40 – 70 ng/mL**
  - **$T_{½}$ = 7 h**

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)

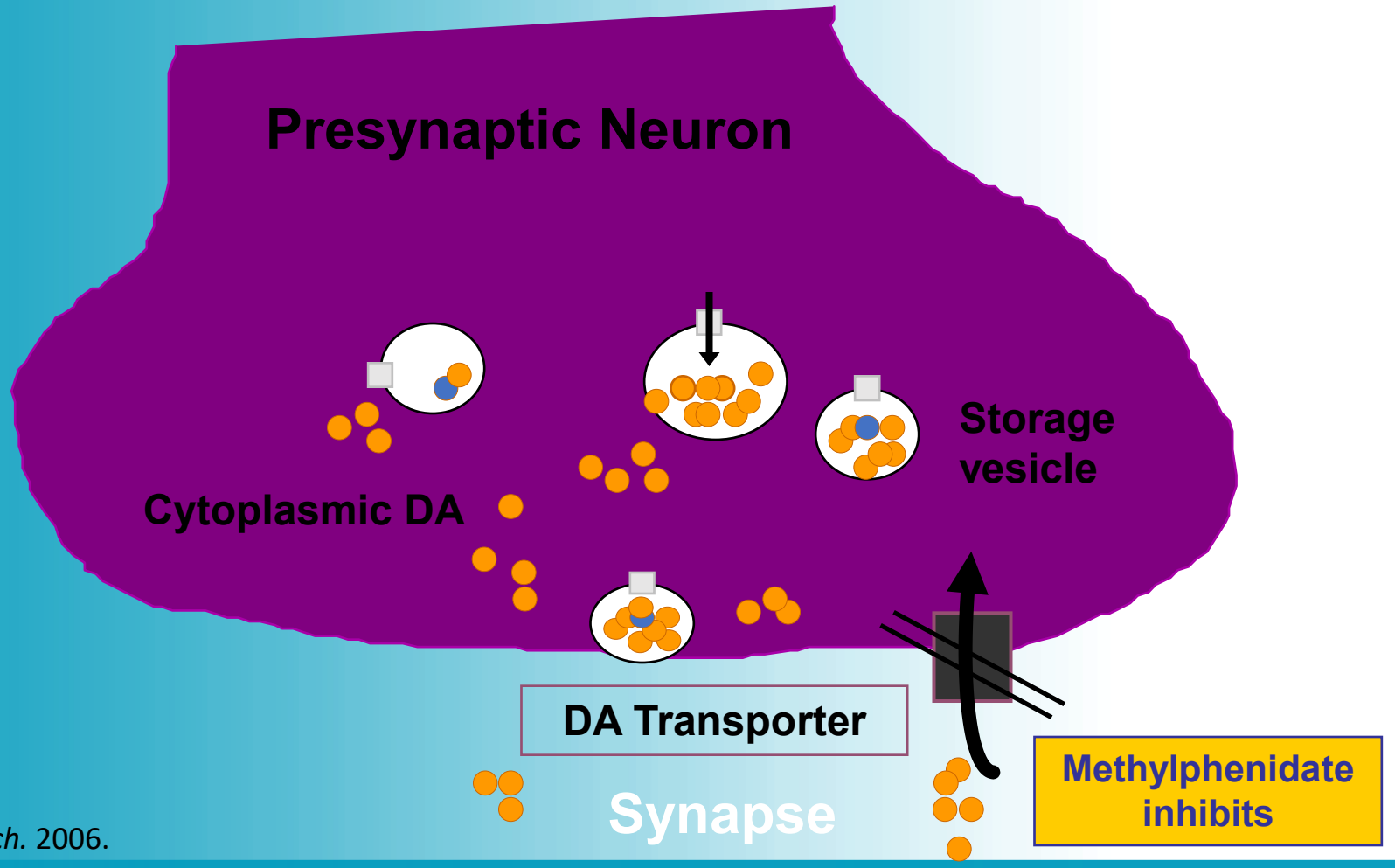
- Redundant hepatic metabolism
- Linear pharmacokinetics
- No pharmacokinetic drug interactions
- Food effects noted
  - Delayed onset of action (fatty meal)
  - Reduced absorption & increased excretion (ascorbic acid)

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.



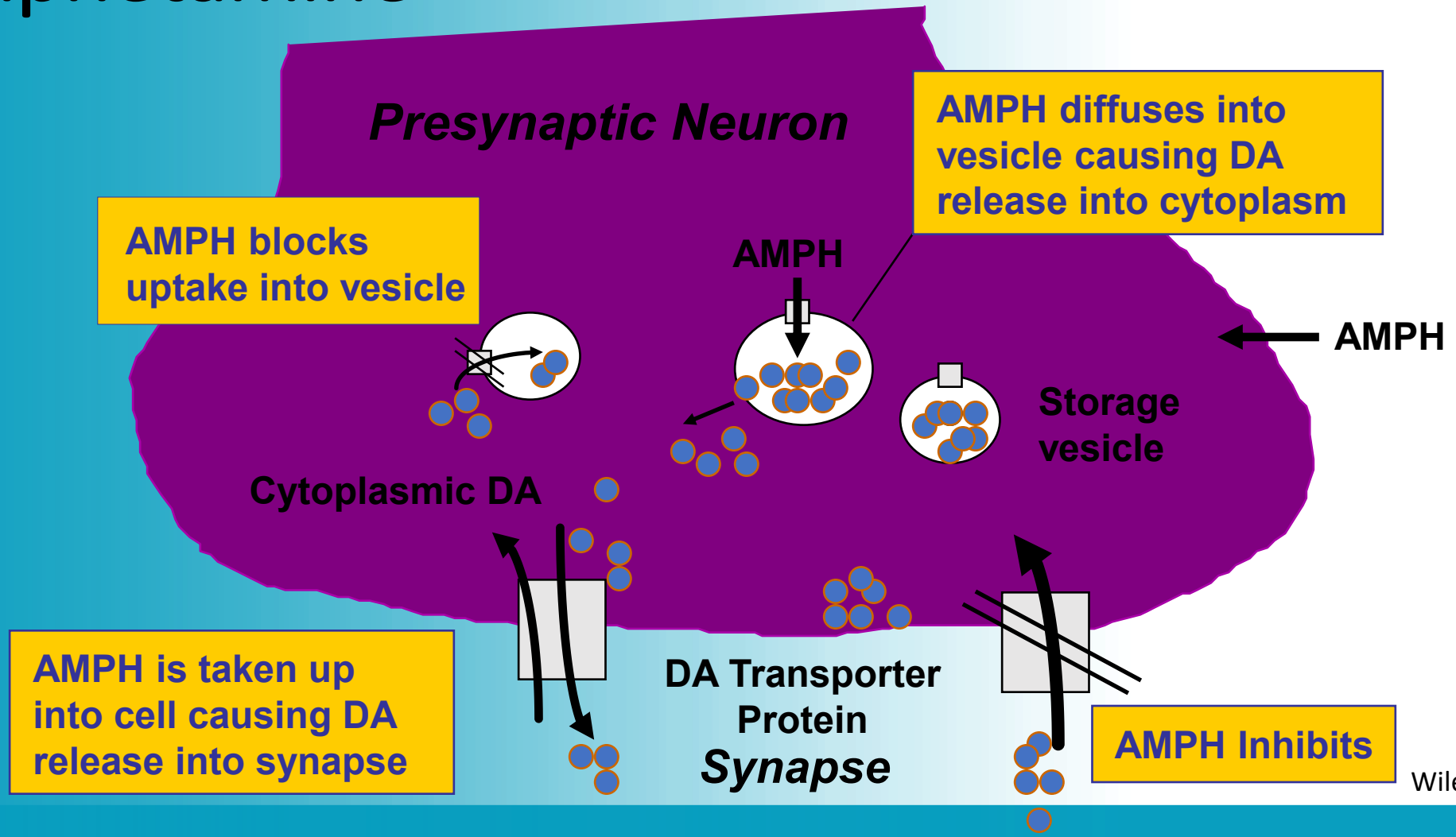
Markowitz et al. *Pharmacotherapy* 2003; Update in Psychopharmacology of ADHD, 2022.

Mechanism of Action of Methylphenidate



Wilens T. *J Clin Psych.* 2006.

The Mechanisms of Action of Amphetamine

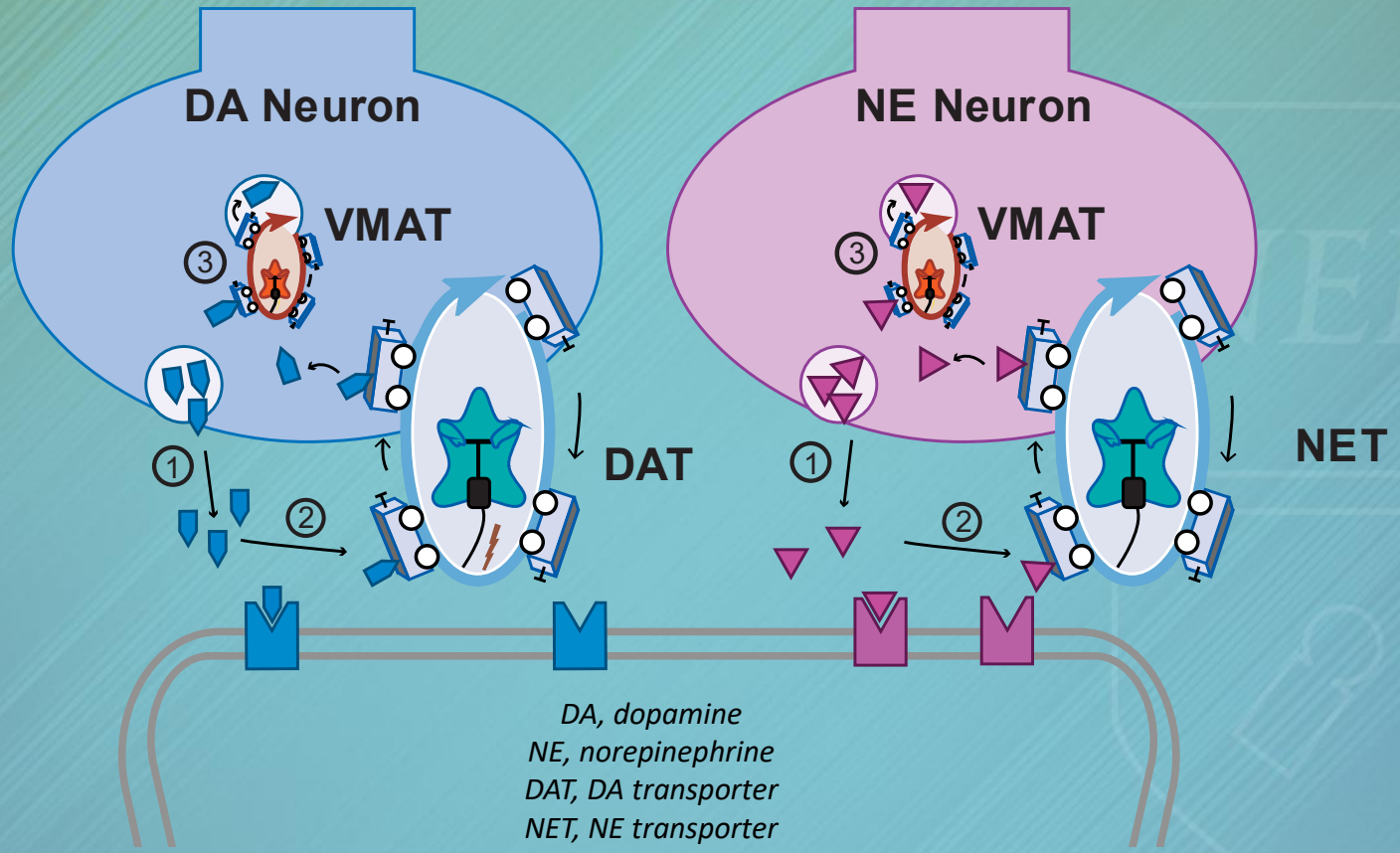


Wilens T. *J Clin Psych*. 2006.

Catecholaminergic Neurotransmission Relative to ADHD

Dopamine

- *Striatal – Prefrontal*
- *Enhances signal*
- *Improves attention*
  - *Focus*
  - *Vigilance*
  - *Acquisition*
  - *On-task behavior*
  - *On-task cognitive*
  - *Perception*



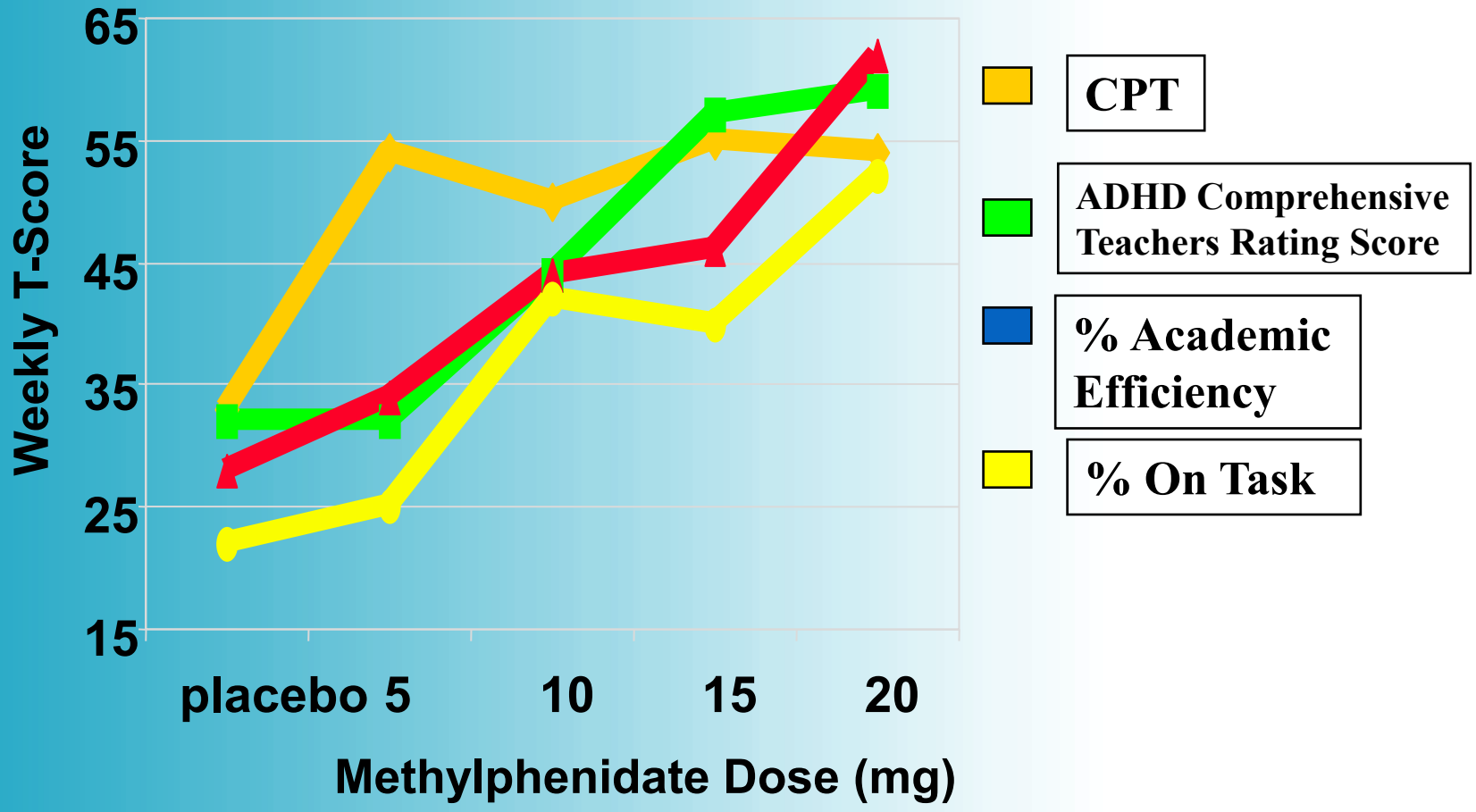
DA, dopamine
NE, norepinephrine
DAT, DA transporter
NET, NE transporter
VMAT, vesicular monoamine transporter

Norepinephrine

- *Prefrontal*
- *Dampens noise*
  - *Distractibility*
  - *Shifting*
- *Executive operations*
- *Increases inhibition*
  - *Behavioral*
  - *Cognitive*
  - *Motoric*

Stahl's Essential Psychopharmacology. 5th ed; 2021. Wilens TE. J Clin Psychopharmacol 2008;28(3 Suppl 2):S46-S53; Solanto et al. Stimulant Drugs and ADHD; Oxford, 2001; Wilens TE et al. Clin Psychiatry 2006;67(suppl 8)32-7; Newcorn JH, Wilens TE. Child Adolesc Psychiatr Clin N Am 2022;31(3):xiii-xiv.

ADHD and Methylphenidate (MPH): Dose Effects on Attention in Clinic and Classroom



Rapport et al. 1987.

Methylphenidate (MPH) in ADHD

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

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

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

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

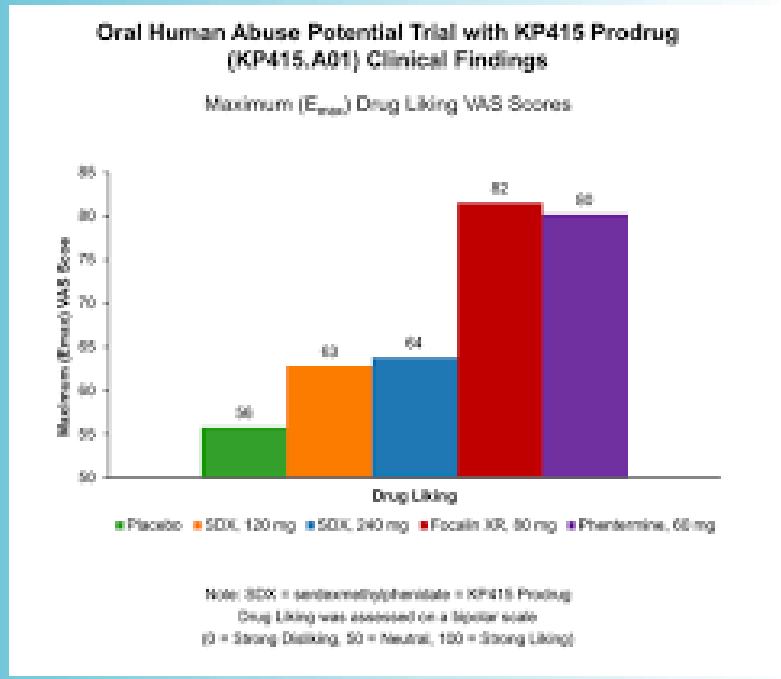
*May exceed FDA approved dose (e.g., >20–30 mg/day).

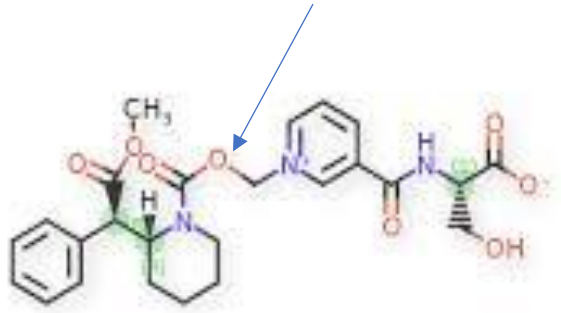
Childress A. *Stimulants.* In Newcorn & Wilens (eds). Update on Pharmacotherapy of ADHD. *Child Adoles Psych Clin N Am.* Elsevier, 2022. www.drugs.com.

Serdexmethylphenidate/MPH for ADHD (Astarys)

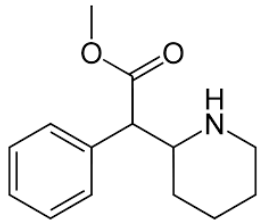
Consider for concerns of stimulant misuse (?)

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





Serdexmethylphenidate

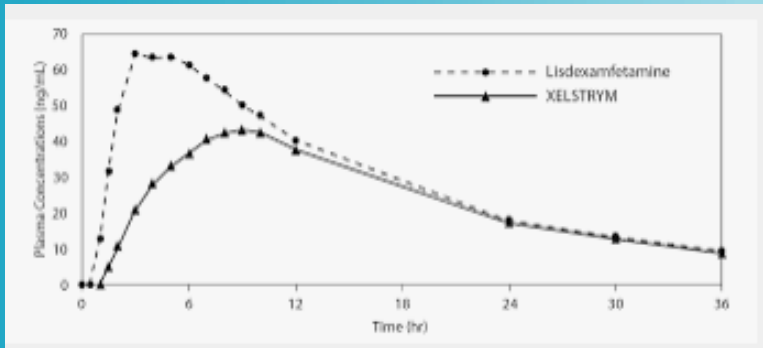


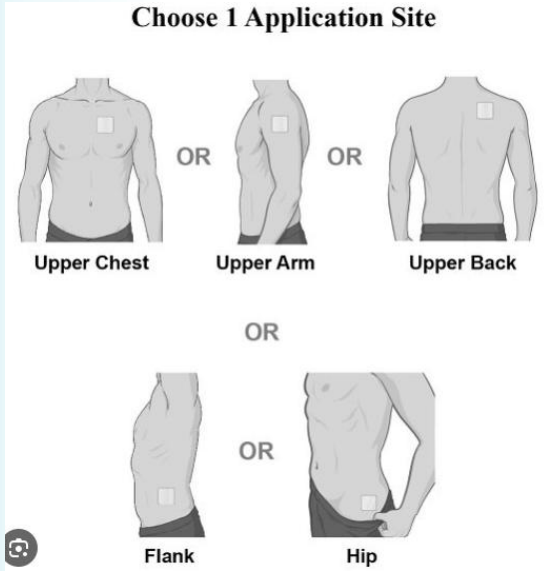
Methylphenidate

AMPH for ADHD (Xelstrym Patch)

Consider for concerns of variable duration needed, PO issues, stimulant misuse (?)

- **Dosing: 4.5, 9, 13.5, 18 mg/9h**
- **Multiple application sites**





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

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

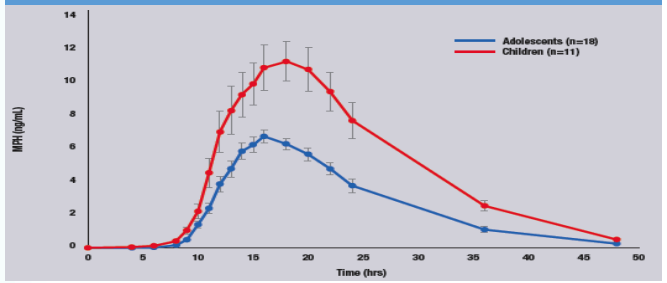
Consider for early-morning difficulties, parents who work in early AM

Delayed, extended-release methylphenidate

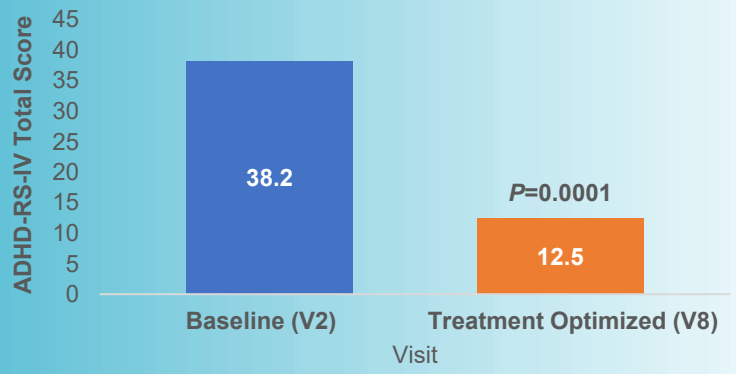
Formulation: PM administration ➔ AM release
Dosing: 20 – 100 mg QD
Capsules: 20, 40, 60, 80, 100 mg
Duration of action: 12+ hours (effect noted into evening)
Optimal admin time: 8 pm

Clinical pearl: Higher doses usually necessary

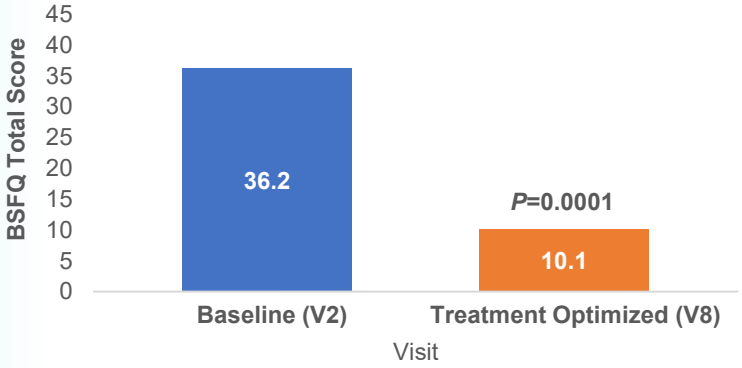
Mean Observed MPH Plasma Concentration (± S.E.M.) Following a Single Evening Administration of HLD200 (54 mg)



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.

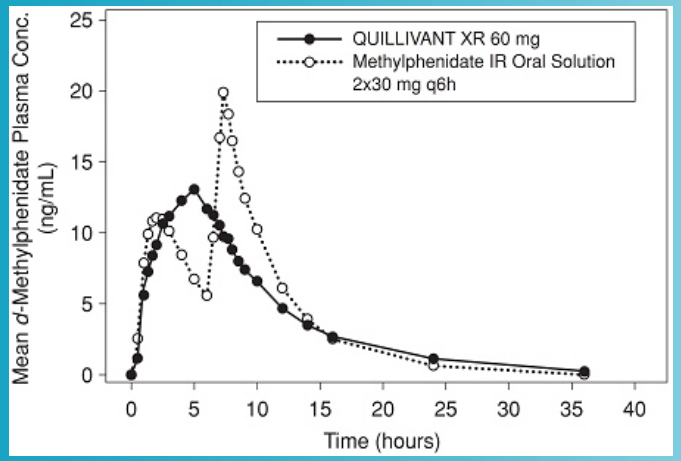
Extended Release MPH Solution and Chewable Preparations

Consider for difficulty swallowing pills

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

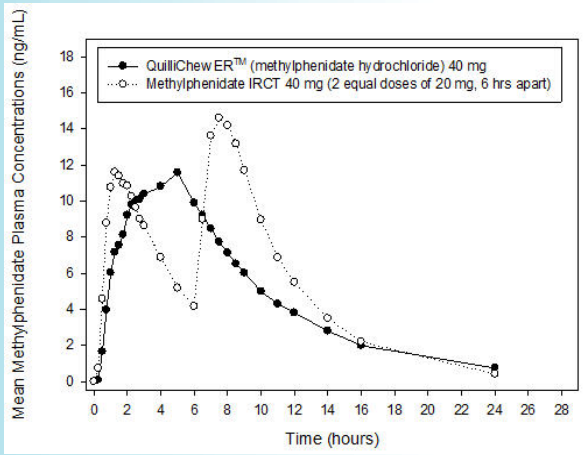
Quillivant XR

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



QuilliChew ER

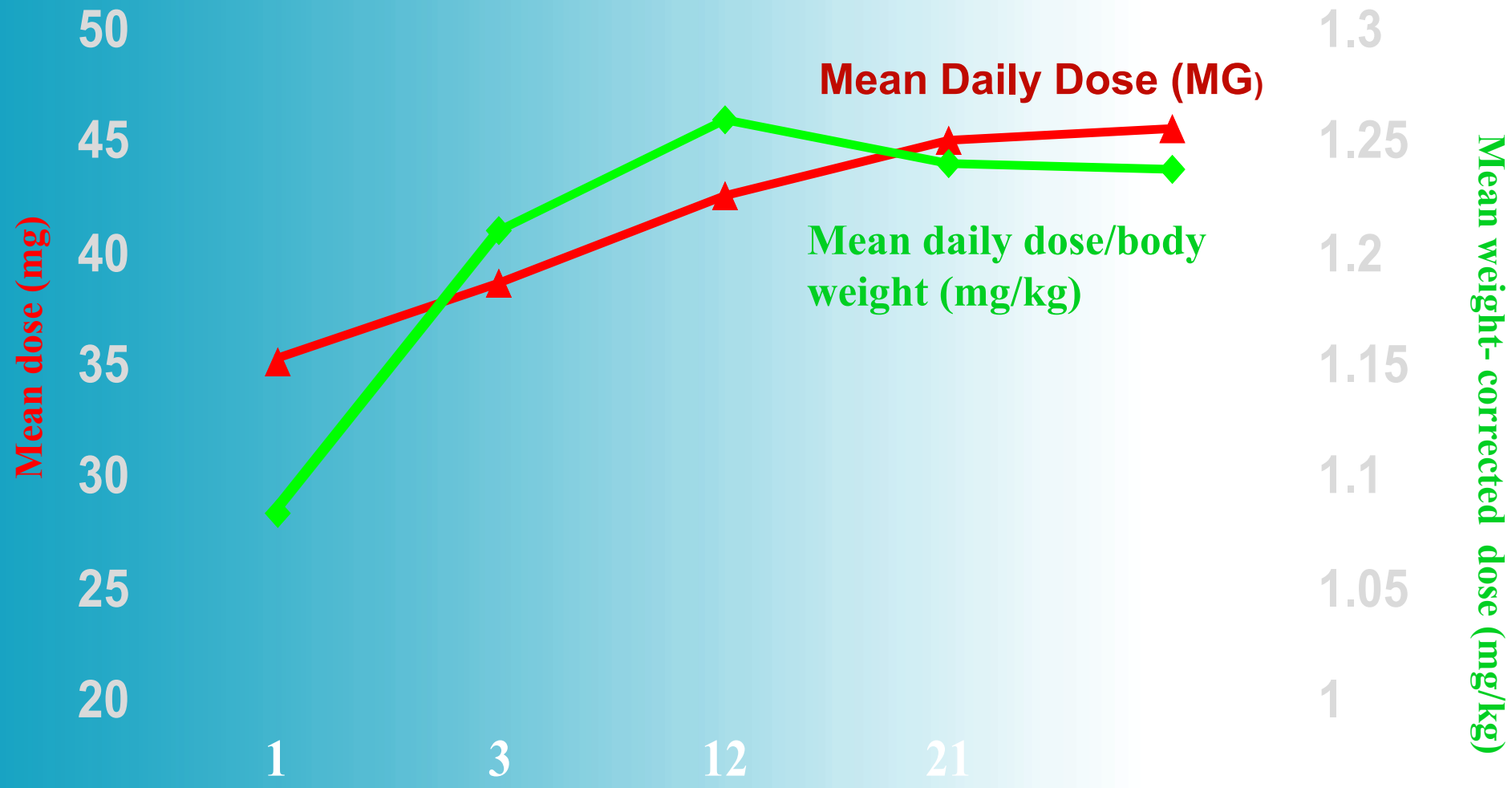
- Chewable tablet
- 8 hour duration
- 20 s, 30 s, 40 mg tablets
- Dosing to 60 mg daily
- Approved in pediatrics



Rx list.com; PI

Tolerance Appears to Develop to Methylphenidate

(Wilens et al. JAACAP:2006)



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 Childress [1], Eric Lloyd [2], Leslie Jacobsen [3], Lhanoo Gunawardhana [2], Steven A Johnson Jr [2], Robert L Findling [4]

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 asigned 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 ± SD pulse/BP changes from baseline at week 6/early termination were numerically greater with LDX vs PBO (pulse beats/min: 2.7 ± 10.79 vs 1.2 ± 9.90; systolic BP, mm Hg: 1.0 ± 7.51 vs 0.3 ± 6.06; diastolic BP, mm Hg: 1.7 ± 5.90 vs 0.0 ± 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.

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

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

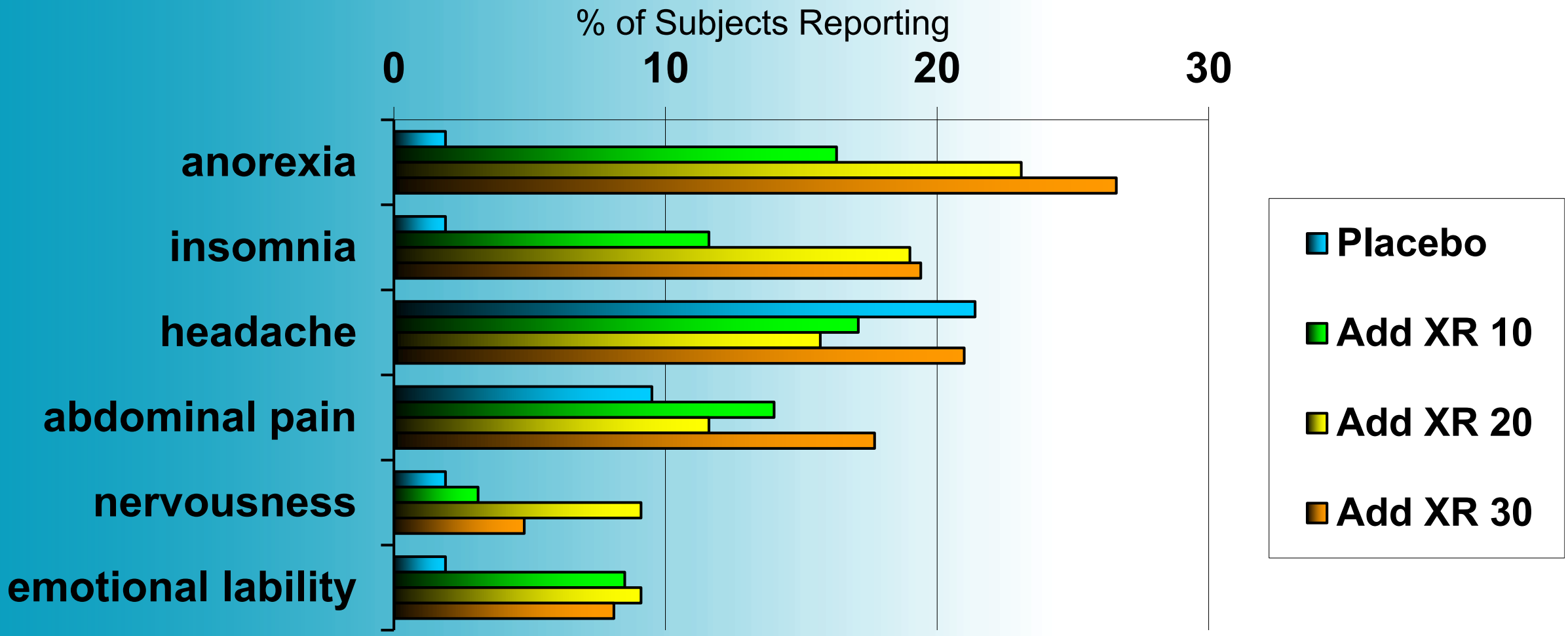
47% LDX v 42% PBO
Decreased appetite and irritability most common
Discontinued: 5.5% LDX v 4.4% PBO

STIMULANT CONTROVERSIES

- Adverse cardiovascular (CV) outcomes
- Growth suppression
- Development of tics

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

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY



Managing Stimulant Side Effects

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

- 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

Wilens and Spencer. *Postgraduate Med*. 2010.
Stevens and Wilens. *CNS Companion*. 2013.
Wilens and Hammerness. *Guilford Press.* 2019.

Managing Stimulant Side Effects

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

- **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)**
- **Cardiovascular**
  - **AAH/APA guidelines-CP, SOB, palpitations, syncope, VS changes**
  - **If positive->PCP/ cardiology consult**

Wilens and Spencer. *Postgraduate Med*. 2010.
Stevens and Wilens. *CNS Companion*. 2013.
Wilens and Hammerness. *Guilford Press.* 2019.

Stimulant Shortages

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

- Stimulant shortages most notable from October 2022 - >
- Multiple pathways
- Increase demand and # of stimulant prescriptions since Covid pandemic
- Production reductions
  - Workforce
  - Raw material shortages
- Quotas (absolute amount, unintended consequences from opioid story)
  - DEA
  - Distributors
  - Pharmacies
- Rapid generic conversion
  - Lisdexamfetamine
- FDA: Monitor, and report shortages (practitioner, patient)! FDA.GOV

JAMA Psychiatry | Original Investigation

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

Le Zhang, PhD; Lin Li, PhD; Pontus Andell, MD, PhD; Miguel Garcia-Argibay, 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

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

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:
Retrospective matching
Main finding hypertension
Recent study from same group-lower mortality

ADHD Meds Are Not Associated with Adverse CV Outcomes: U.S. Data in Children

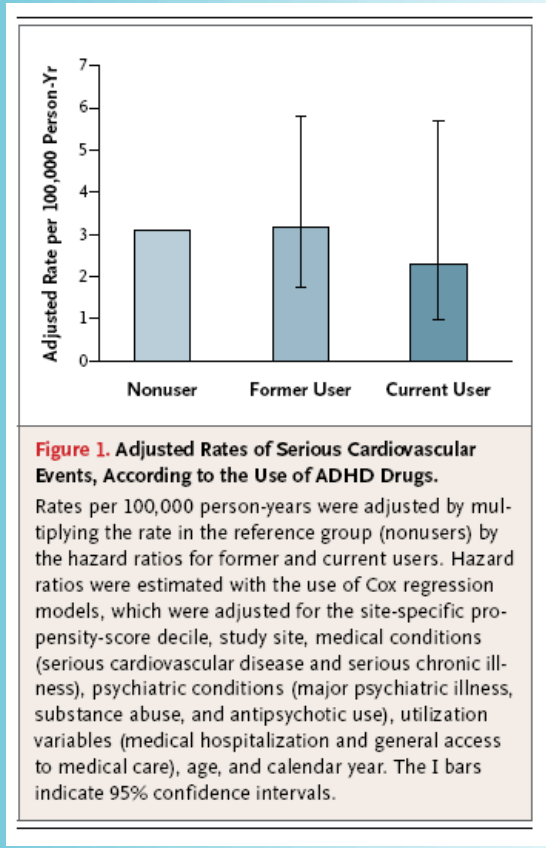


Figure 1. Adjusted Rates of Serious Cardiovascular Events, According to the Use of ADHD Drugs.

Rates per 100,000 person-years were adjusted by multiplying the rate in the reference group (nonusers) by the hazard ratios for former and current users. Hazard ratios were estimated with the use of Cox regression models, which were adjusted for the site-specific propensity-score decile, study site, medical conditions (serious cardiovascular disease and serious chronic illness), psychiatric conditions (major psychiatric illness, substance abuse, and antipsychotic use), utilization variables (medical hospitalization and general access to medical care), age, and calendar year. The I bars indicate 95% confidence intervals.

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

Cardiopulmonary Exercise Testing: MGH Study of Amphetamines in Adults with ADHD

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

MGH Protocol - Electronically braked ergometer, 12-lead ECG Metabolic cart (MedGraphics)

Hammerness, Wilens et al. World J Biol Psych, 2012; Early Online: 1–8

What to Do at Evaluation (Am Heart Assoc Guidelines)

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

- **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**
- ***Suspicion* of CV defect (e.g. ARVD, MI, SVT) --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)

Controversies in the Use of Stimulants: Height and Weight Suppression

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

- **Concern: Potential suppression of height and weight gain associated with stimulant medications**
  - **From 14 mo to 15 yr MTA data indicating up to 1 CM/Year deficits (Caveat-only 6% on meds in adulthood)**
  - **Small group of youth may have significant weight/height issues**
  - **May be attenuation in height weight effect**
  - **Drug holidays may offset more severe weight/height issues**
  - **Lag in growth may be ADHD related**
  - **Adult data suggests lack of evidence of subtle effects on height/weight**

Safer D, et al. *N Engl J Med.* 1972;287:217-220.
Spencer TJ, et al. *J Am Acad Child Adolesc Psychiatry.* 1996;35:1460-1469.
Kramer, et al. *J Am Acad Child Adolesc Psychiatry.* 2000;39:517-524.
MTA Study, Pediatrics 2004; Swanson et al. JAACAP 2007; Faraonet et al JAACAP 2007.

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

Chloe Hutt Vater [1], Joseph Biederman [1 2], Maura DiSalvo [1], Hannah O'Connor [1], Haley Parker [1], K Yvonne Woodworth [1], Janet Wozniak [1 2], Stephen V Faraone [3 4]

Affiliations + expand

PMID: 37966364 DOI: 10.1089/cap.2023.0054

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.

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

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.*

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-naive ADHD patients who intended to start methylphenidate treatment (methylphenidate group), medication-naive 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/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

Research Department of Practice and Policy, School of Pharmacy, University College London, London, UK (K K C Man PhD); Centre for Medicines Optimisation Research and Education, University College London Hospitals NHS Foundation Trust, London, UK (K K C Man); Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, Hong Kong Special Administrative Region, China (K K C Man, Prof I C K Wong PhD); Department of Child and Adolescent Psychiatry and Psychotherapy, Medical Faculty Mannheim, Central Institute of Mental Health, University of Heidelberg, Mannheim, Germany (A Häge MD)

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Study of MPH Safety

N=1410 participants f/u 2 years

- **756 in MPH group**
- **398 in no-MPH group**
- **263 controls**

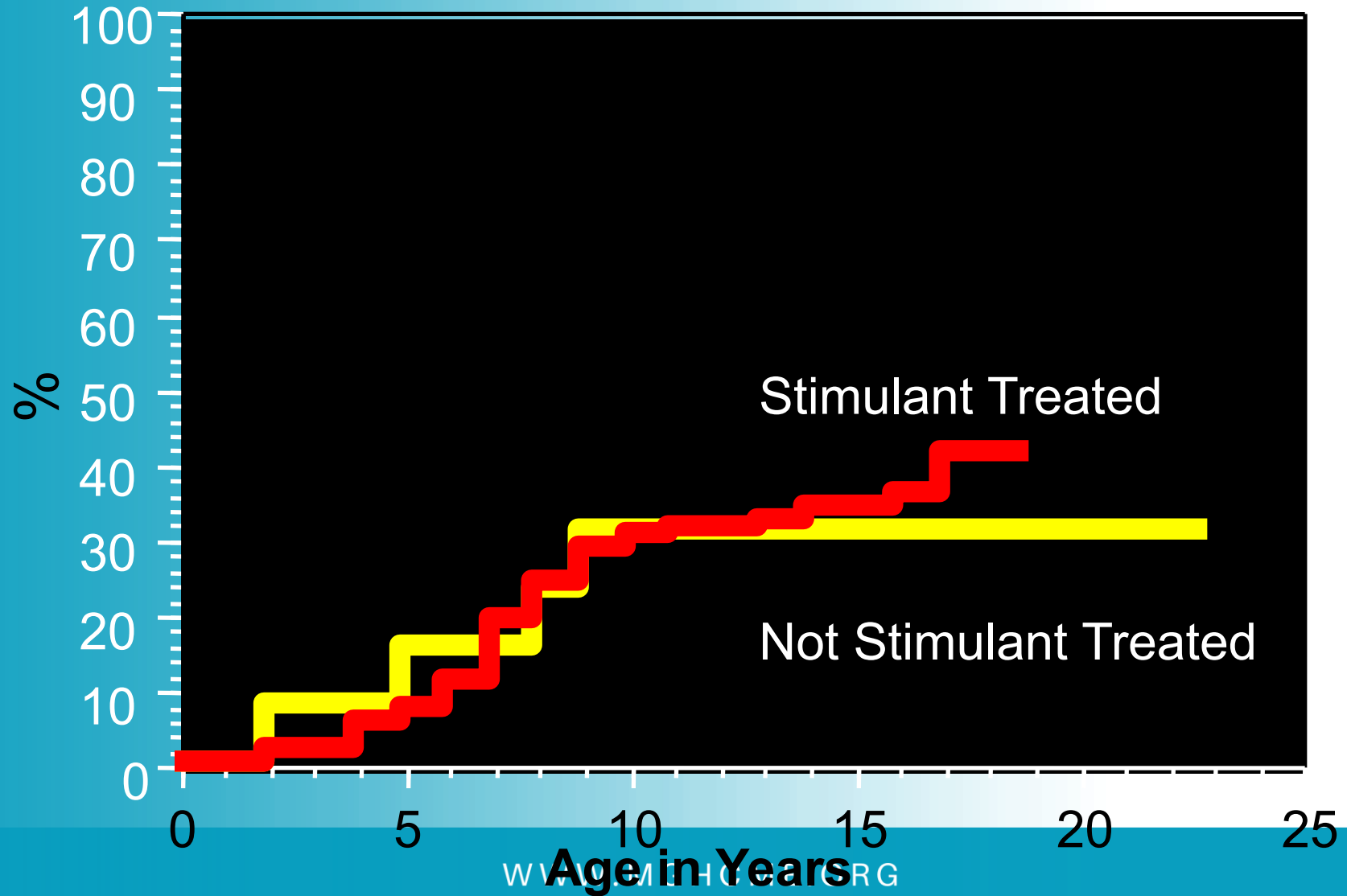
Findings

MPH vs no MPH no difference on height, psych onset, or neuro adverse effects

Increase in BP/HR with MPH

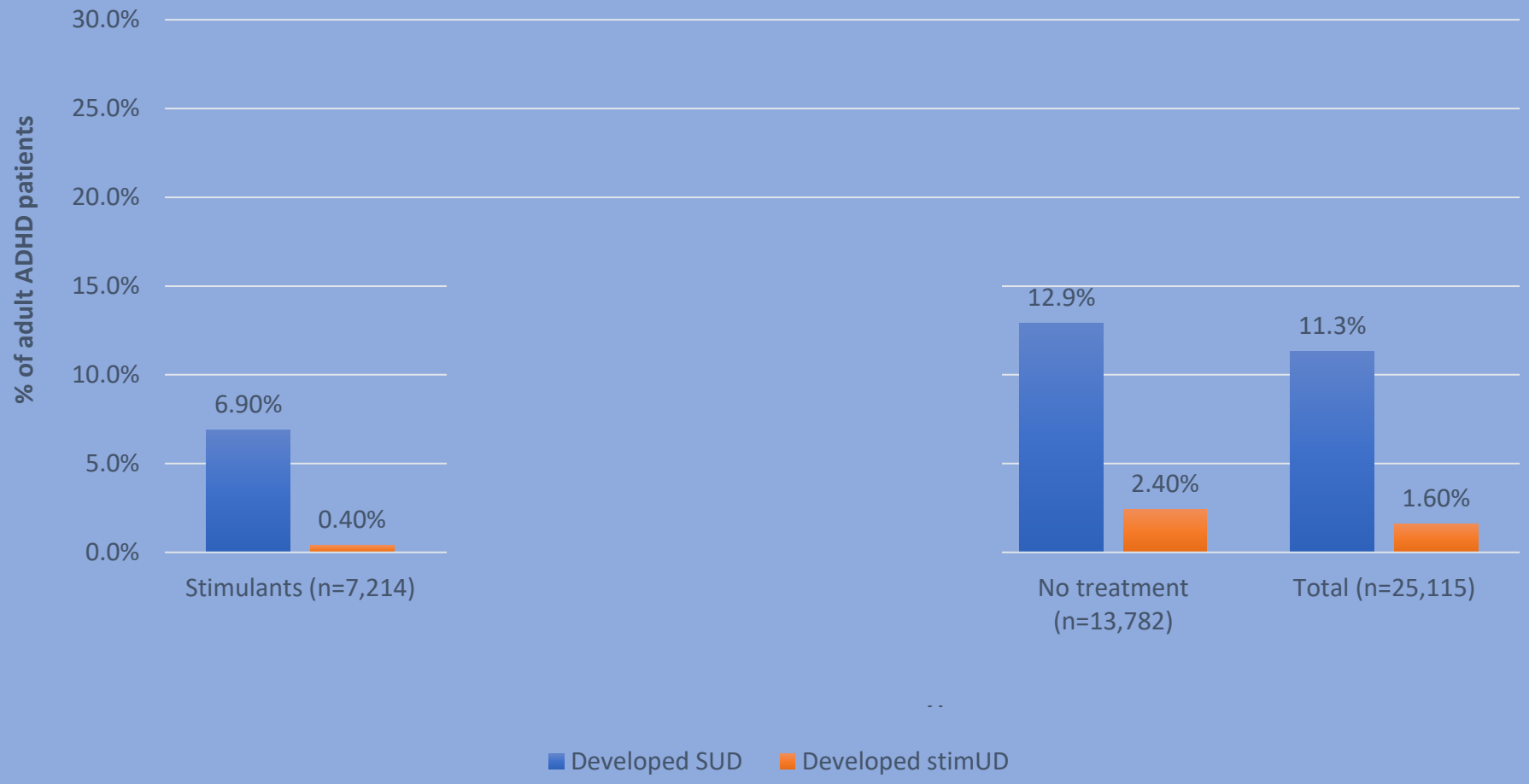
Onset of Tic Disorders in ADHD Probands by Stimulant Treatment

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY



Starting Stimulant Treatment of ADHD in Adults Does Not Increase Stimulant (stimUD) or Substance Use Disorders (SUD)

[N=25,115 Adults with ADHD, MGB Electronic Health Records, Mean age 31.4 years, f/u mean 683 days]

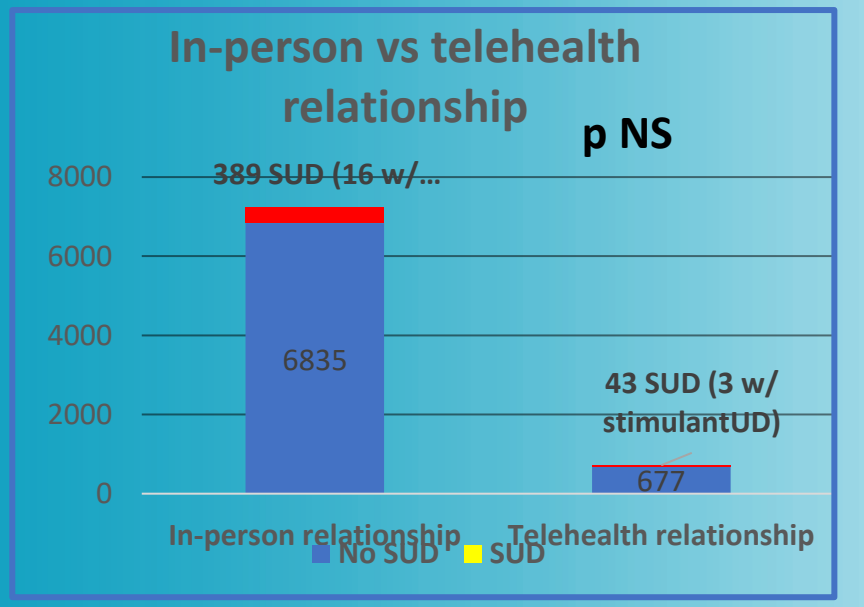


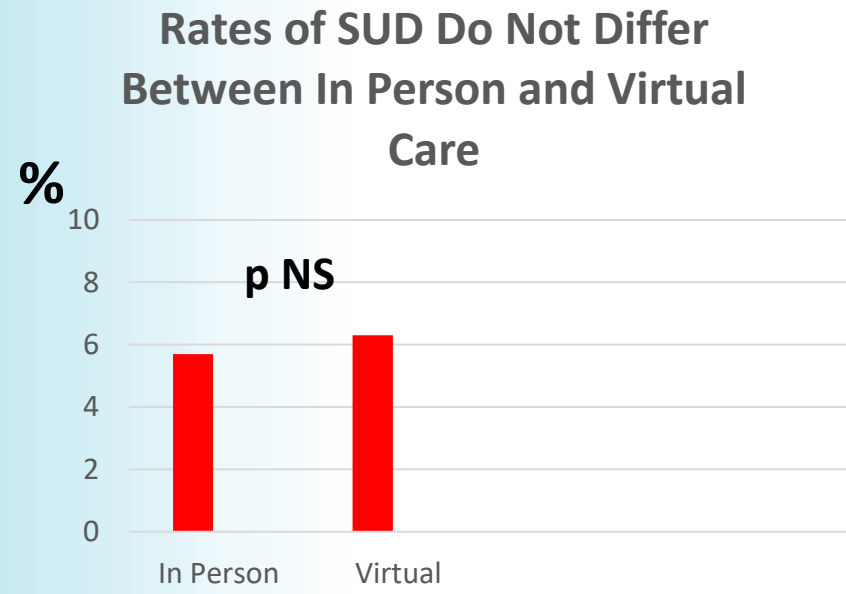
(Rao V et al, Presentation to FDA 3/19/25; AACAP presentation 10/25; in preparation 2026)

Telehealth Compared to In Person Experience Does Not Increase Subsequent Stimulant or other SUDs

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

(N=7944 patients)



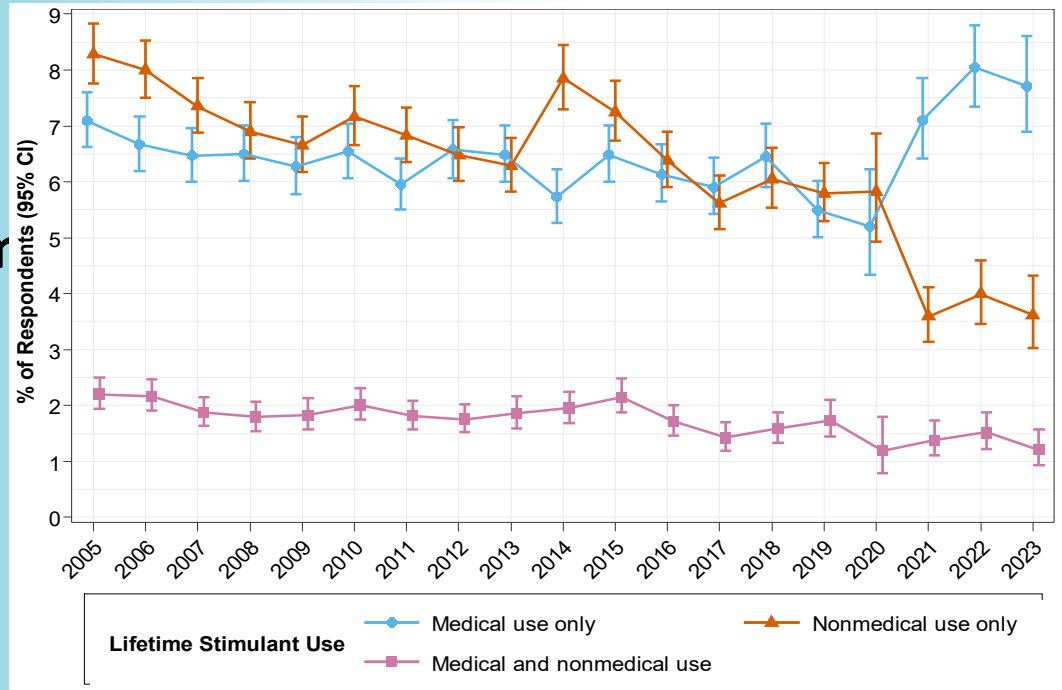


Rao et al, Am J Psychiatry, 2025

Stimulant Misuse and Diversion

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

- N > 120 studies; mostly survey studies in college students (80%)
- 10% to 20% with nonmedical use of stimulants
- 65% to 85% of stimulants diverted from "friends"
  - Majority not "scamming" local practitioners
  - Not seen as dangerous
  - Excess supply --> Diversion
- Extended-release lower abuse liability than immediate-release stims



Medical Use

Nonmedical Use

Med+Nonmed

Arria AM, et al. *Subst Abus*. 2008;29(4):19-38. Wilens TE, et al. *J Am Acad Child Adolesc Psychiatry*. *J Am Acad Child Adolesc Psychiatry*. 2008;47(1):21-31. Wilens TE, et al. *J Clin Psychiatry*. 2016;77(7):940-947. : Faraone et al. J Am Acad Child Adoles Psych, 2020; McCabe et al JAMA Network Open 2023). McCabe et al., JAMA 2025.

NBA / Getty Images

Chris Kaman

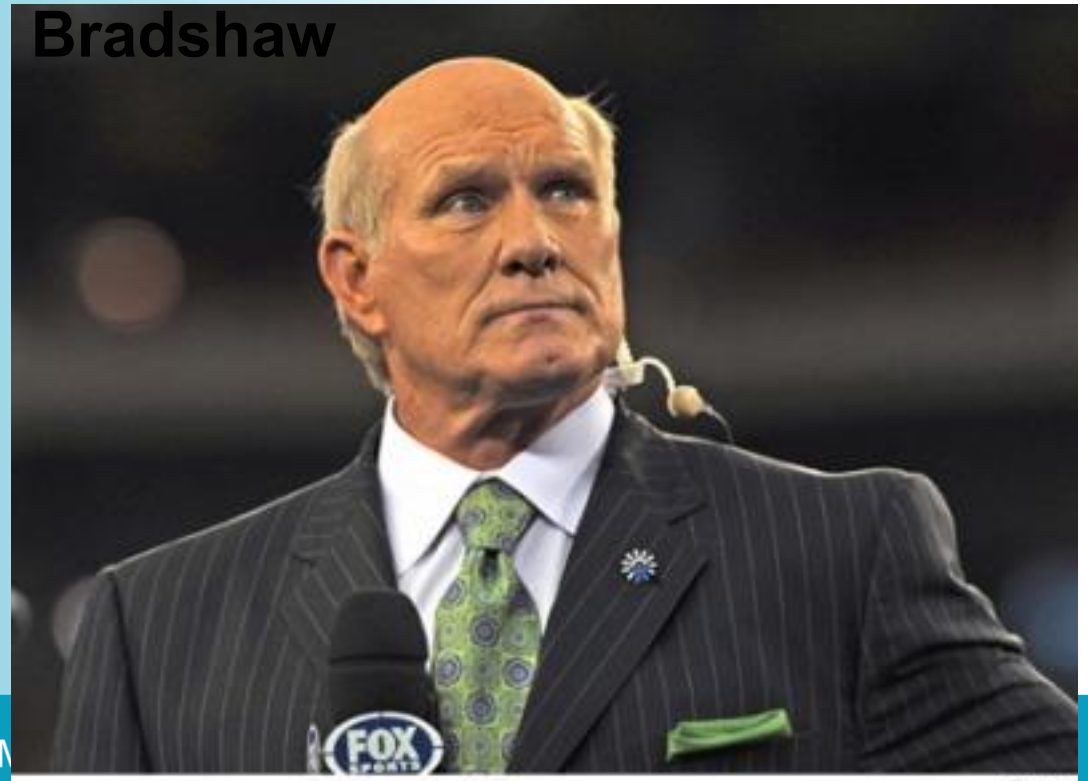
Scott Eyre

ETTS
OSPITAL

ACADEMY

Jason Kidd

Terry Bradshaw



Getty

WW.M

League Rules & Stimulant Use

- **High School Sports**
  - **Generally not urine tested**
  - **Generally no specific rules for stimulant use**

- **College Sports/ NCAA**
  - **Urine tested for drugs of misuse**
  - **Requires documented clinical diagnosis and ongoing monitoring by physician**

League Rules & Stimulant Use

- **Professional Sports**
  - **Urine tested for steroids & drugs of misuse**
  - **Generally requires physician monitoring and waiver**

- **International Olympic Committee**
  - **Urine tested for steroids & drugs of misuse**
  - **Generally not allowed**

Knowing when to stop

- Evaluate ongoing need for treatment (at least yearly)
- Consider effects of missed doses of stimulants on symptoms/functional outcomes
  - Stimulant shortages/prescription difficulties
  - Purposeful discontinuation trials by parents/individuals
- Consider trials off stimulants (e.g. second semester trial)
- Medication free times (e.g. "*Drug Holidays*")
  - Adverse effects
  - Less severe ADHD

Summary: Stimulants in ADHD

- **Highly effective in treating ADHD**
- **Largely predictable adverse effects**
- **Longer term effects encouraging at both neurobiological and outcome levels**
- **Regular monitoring required including misuse/diversion in older adolescents/young adults**