Pharmacotherapy of ADHD Across the Lifecycle: Stimulants

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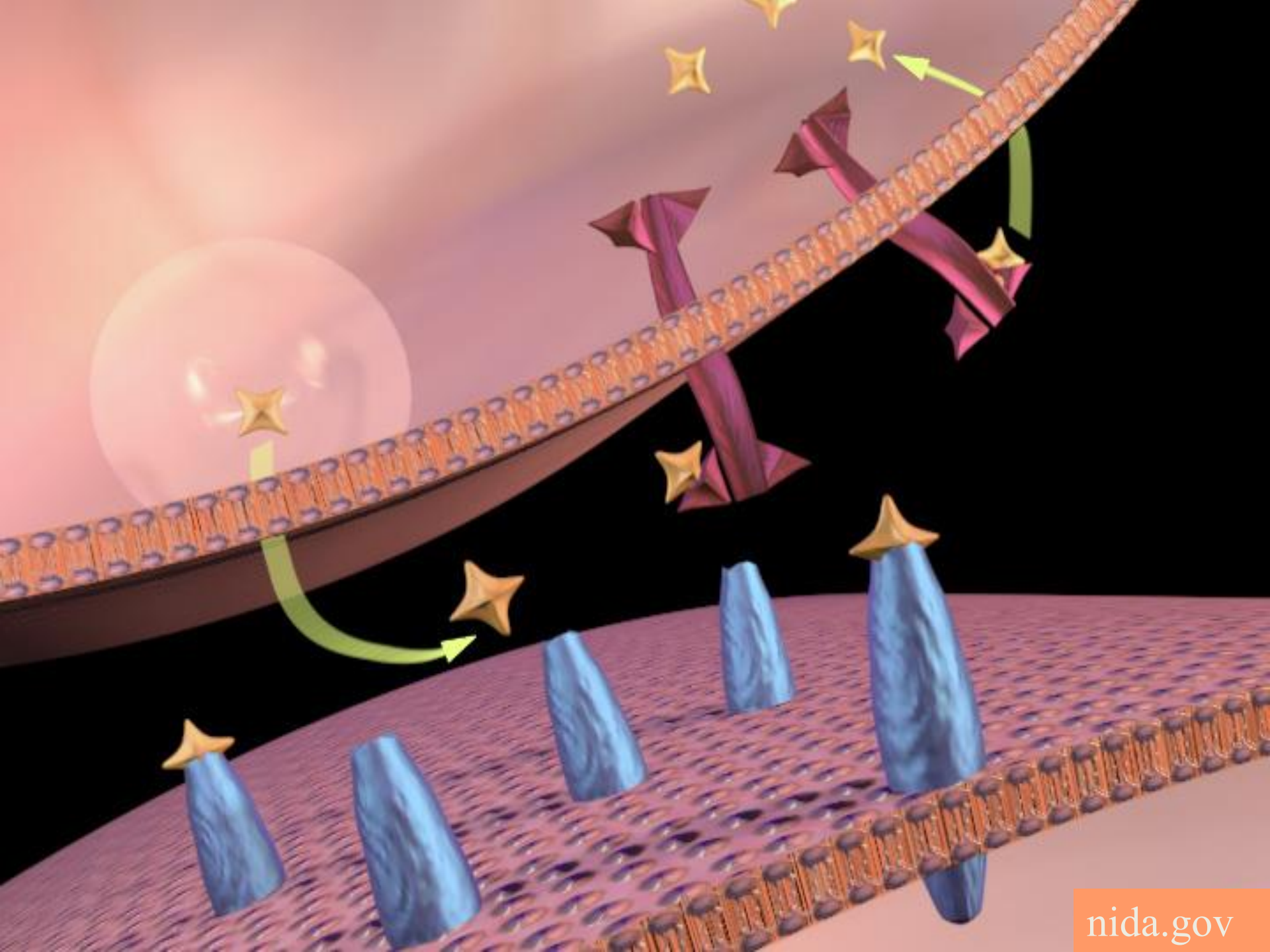
Disclosures

FDA	Research Support
Department of Defense	Research Support
Avekshan	Consultant
Sunovion	Research Support

Research Support and Consultant fees are paid to the MGH Clinical Trials Network and not directly to Dr. Spencer

Dr. Spencer receives support from Royalties and Licensing fees on copyrighted ADHD scales through MGH Corporate Sponsored Research and Licensing.

Dr. Spencer has a US Patent (#14/027,676) for a non-stimulant treatment for ADHD and a US Patent Application pending (Provisional Number 61/233. 686), on a method to prevent stimulant abuse. Both through MGH corporate licensing



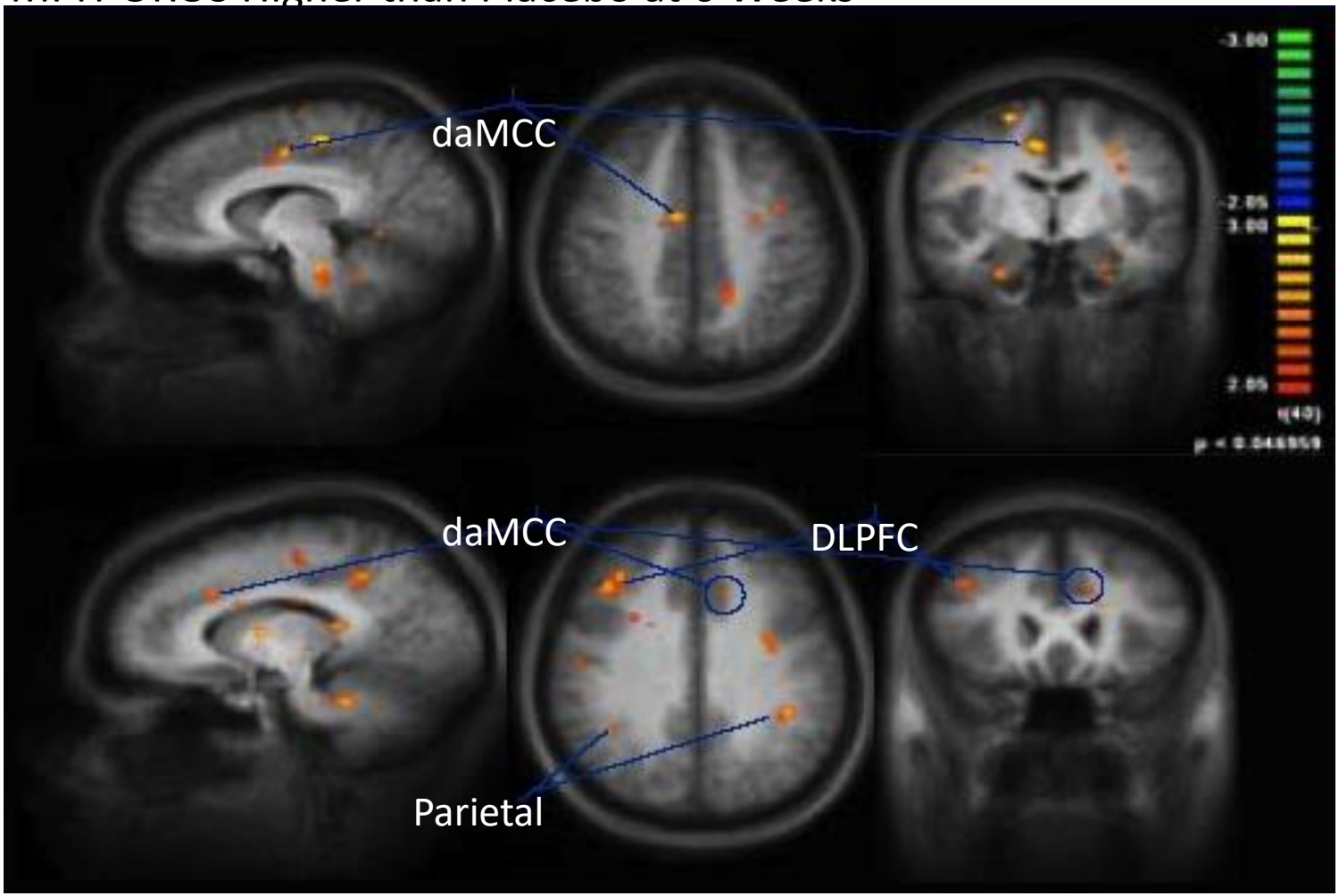
Mechanism of Action MPH: Insights from PET Imaging Studies

(Volkow et al. *J Att Dis.* 2002;(suppl)1)

- Because DA enhances task-specific neuronal signaling and decreases noise, MPH-induced increases in DA could improve attention and decrease distractibility
- Since DA modulates motivation, the increases in DA would also enhance the saliency of the task facilitating the "interest it elicits" and thus improving performance

Methylphenidate Increases Dorsal ACC & DLPFC in Patients with ADHD

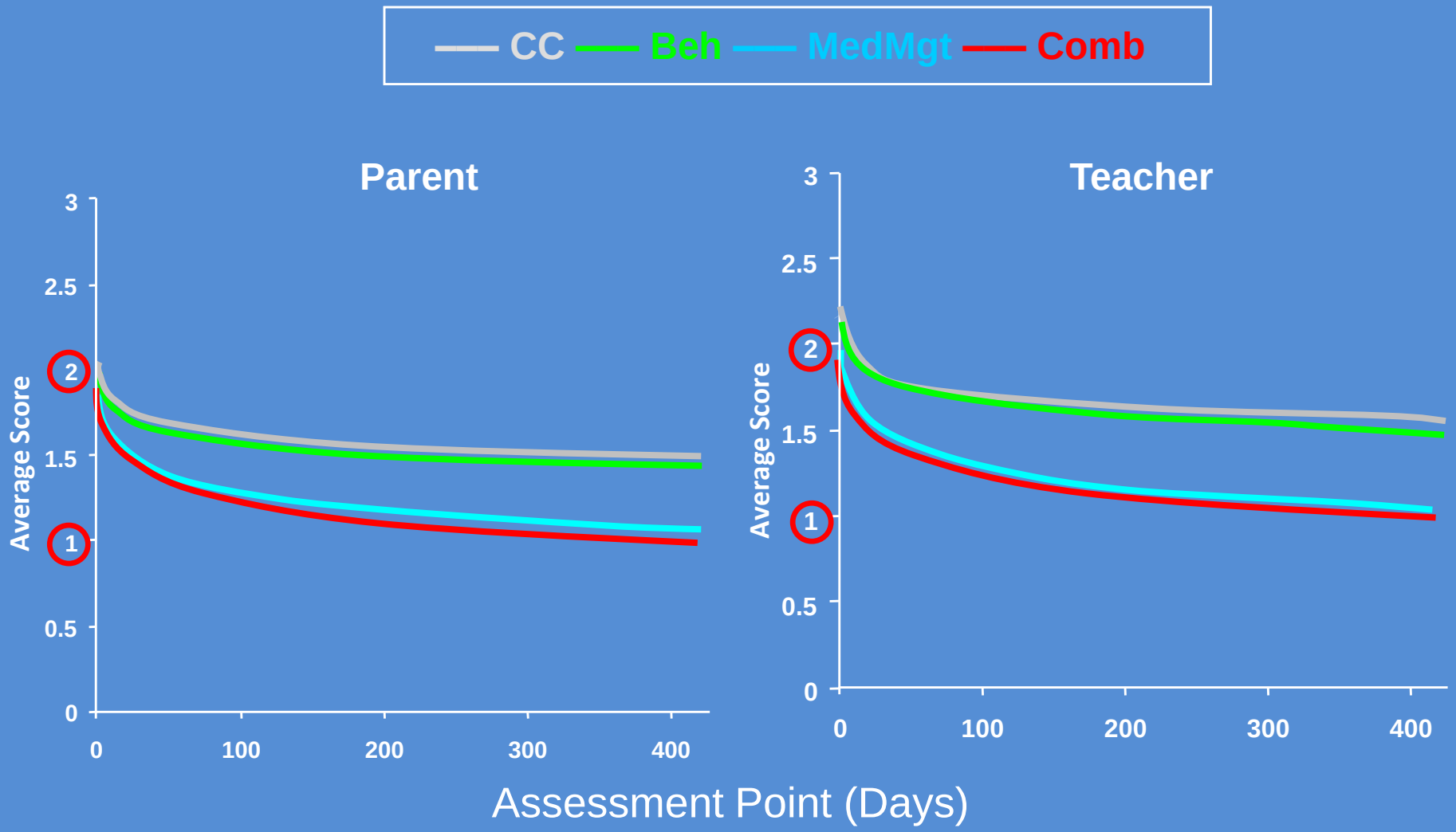
MPH-OROS Higher than Placebo at 6 Weeks



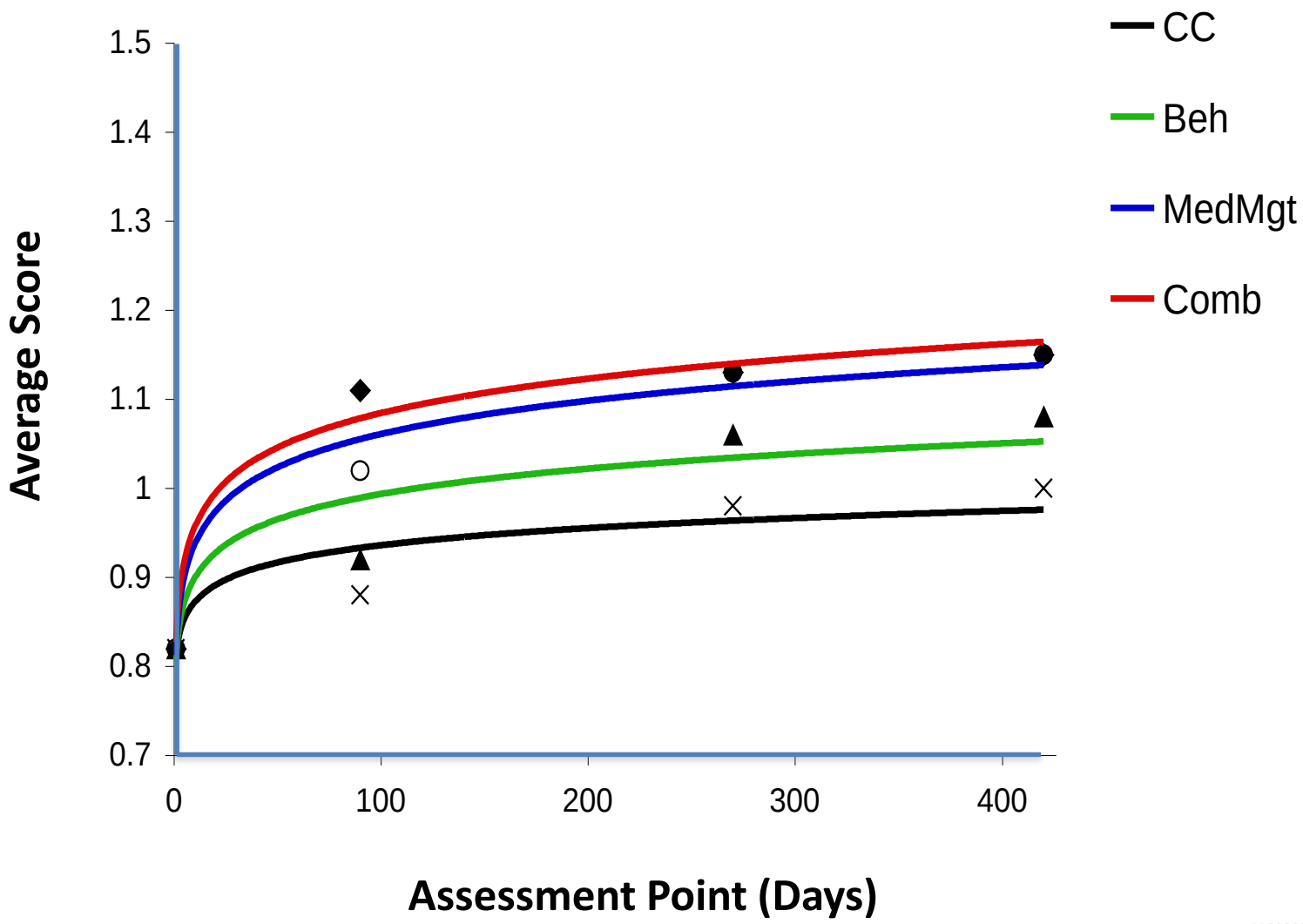
Bush et al. Archives of General Psychiatry. in press

MTA: Treatment Effects on Inattention Scores (SNAP)

[MTA Group, *Arch General Psychiatry,* 1999]



Teacher SSRS Social Skills

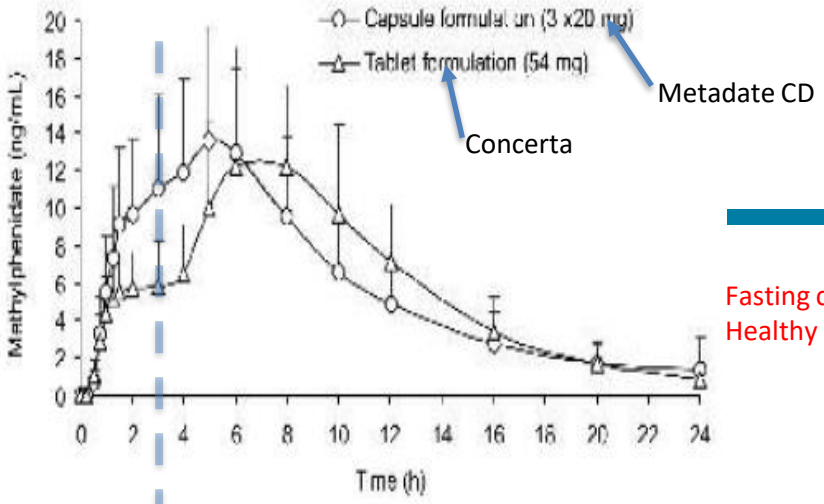


Methylphenidate Formulations

Medication	Formulation	Release % IR/ER	Isomers d,l	Duration
Ritalin® (IR)	Tablet	100/0	1:1	~ 4 hours
Methylin® Chewable	Chewable Tablets	100/0	1:1	~ 4 hours
Methylin® Oral Solution	Oral Solution	100/0	1:1	~ 4 hours
Focalin® (IR)	Tablet	100/0	1:0	~ 4 hours
Ritalin LA®	Capsule	50/50	1:1	~ 8 hours
Metadate CD®	Capsule	30/70	1:1	~ 8 hours
Focalin XR®	Capsule	50/50	1:0	~ 8-10 hours
Cotempla XR-ODT®	ODT	30/70	1:1	~ 8-12 hours
Quillichew ER®	Chewable Tablet	30/70	1:1	~ 8-10 hours
Concerta®	Capsule	22/78	1:1	~ 12 hours
Quillivant XR®	Oral Solution	20/80	1:1	~ 10-12 hrs
Aptensio XR®	Capsule	37/63	1:1	~ 12 hours
Adhansia XR®	Capsule	20/80	1:1	~ 13-16 hrs
Daytrana®	Patch	N/A	1:1	6-16 hours
Jornay PM®	Delayed Release Capsule	0/100	1:1	Start 8-10 hrs Duration ~ 10-12 hrs

Example of Strong PK/PD Link

Gonzalez, M. A., et al. "Methylphenidate bioavailability from two extended-release formulations." *International journal of clinical pharmacology and therapeutics* 40.4 (2002): 175-184.



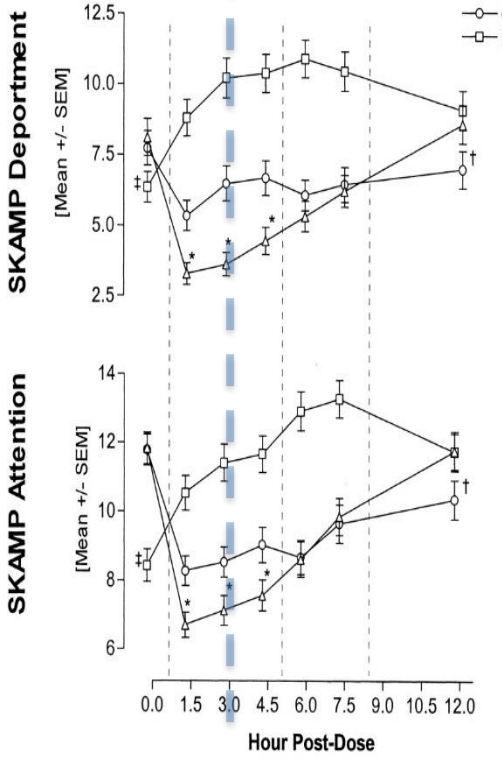
Metadate CD

Concerta

Fasting conditions, Healthy volunteers

MCD = Metadate CD
CON = Concerta
PLA = placebo

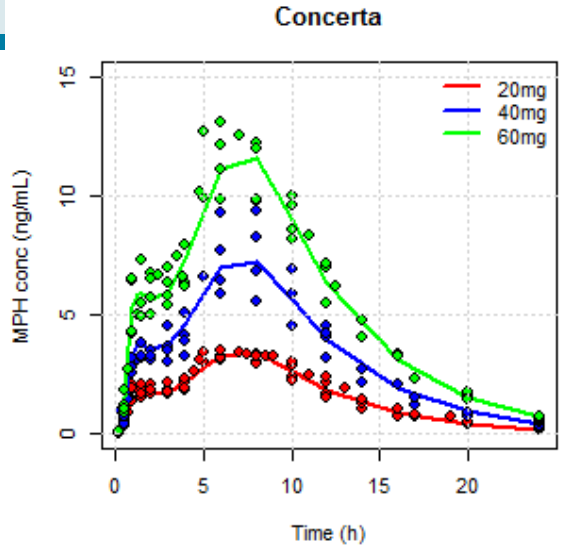
Swanson, James M., et al. "A comparison of once-daily extended-release methylphenidate formulations in children with attention-deficit/hyperactivity disorder in the laboratory school (the Comacs Study)." *Pediatrics* 113.3 (2004): e206-e216.

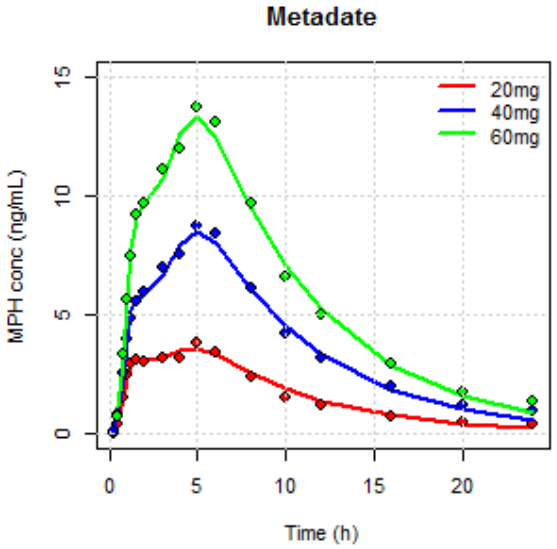


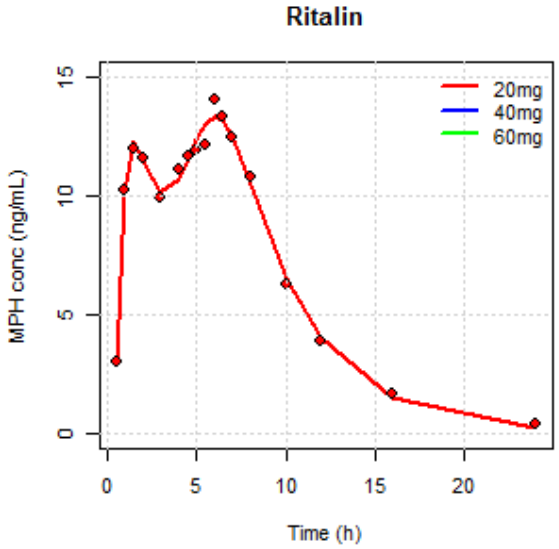
For doses of MPH, differences in PK from 0-3 hours is reflected in the SKAMP ratings

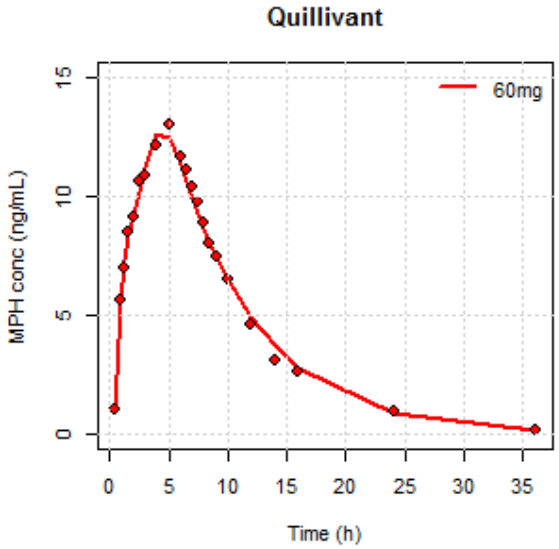
* and †: statistically significance between active treatments

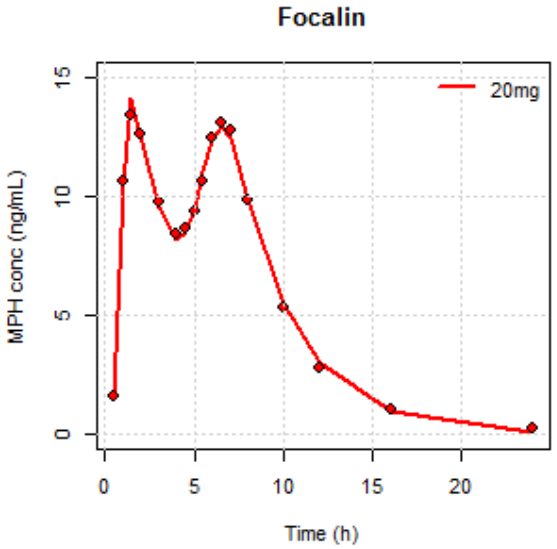
Long Acting MPH formulations

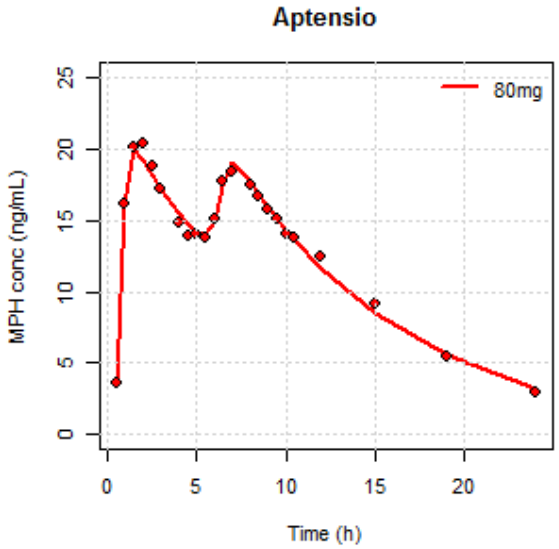




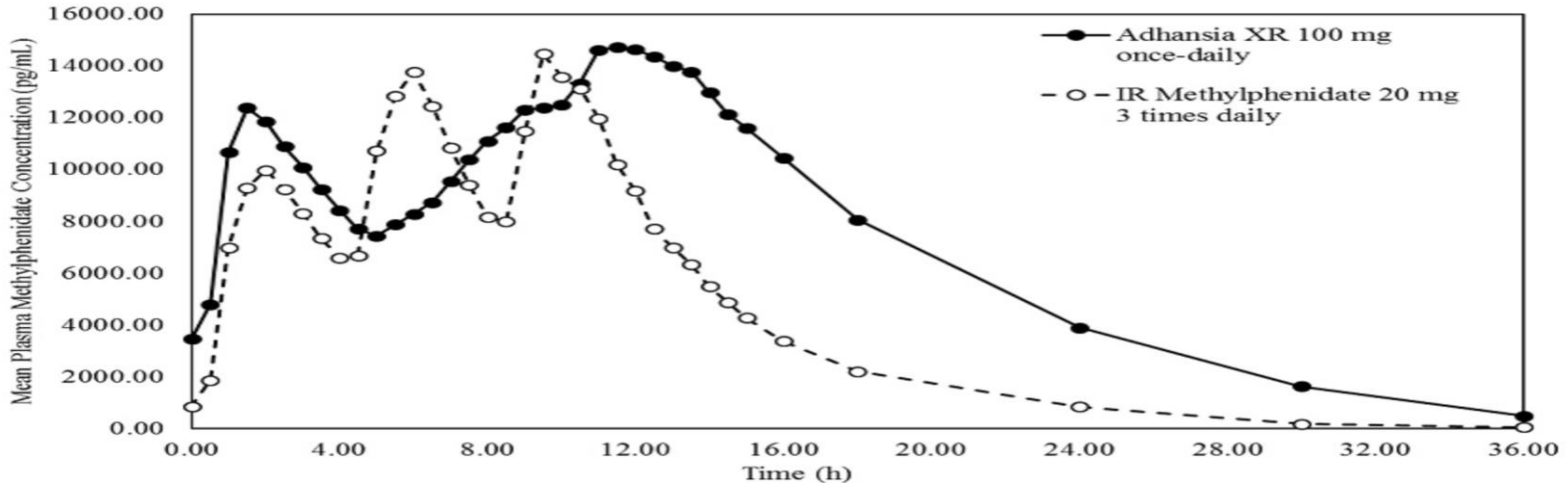


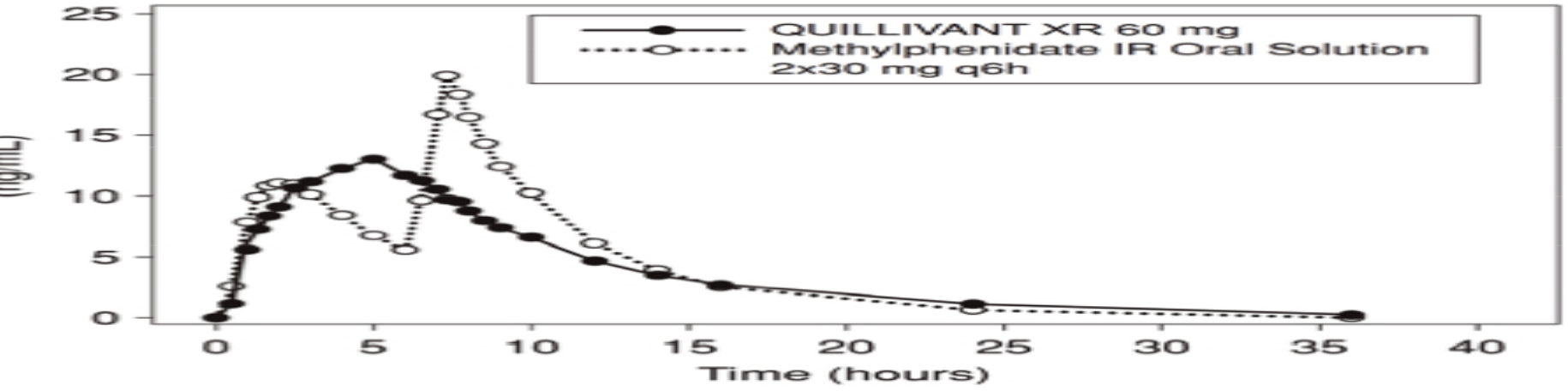




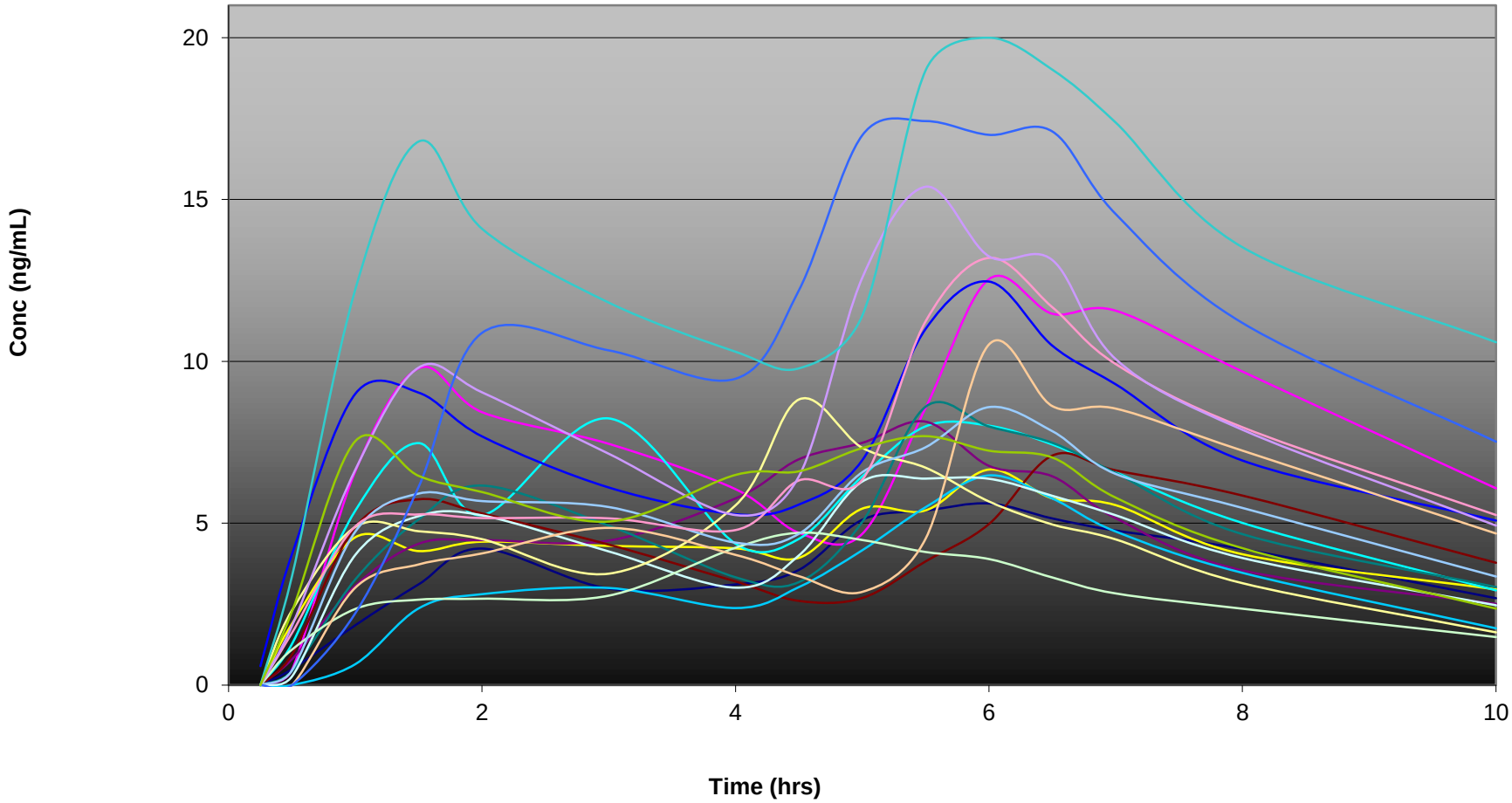


Two MPH 20/80 IR/ER Formulations Markedly Different PK Profiles



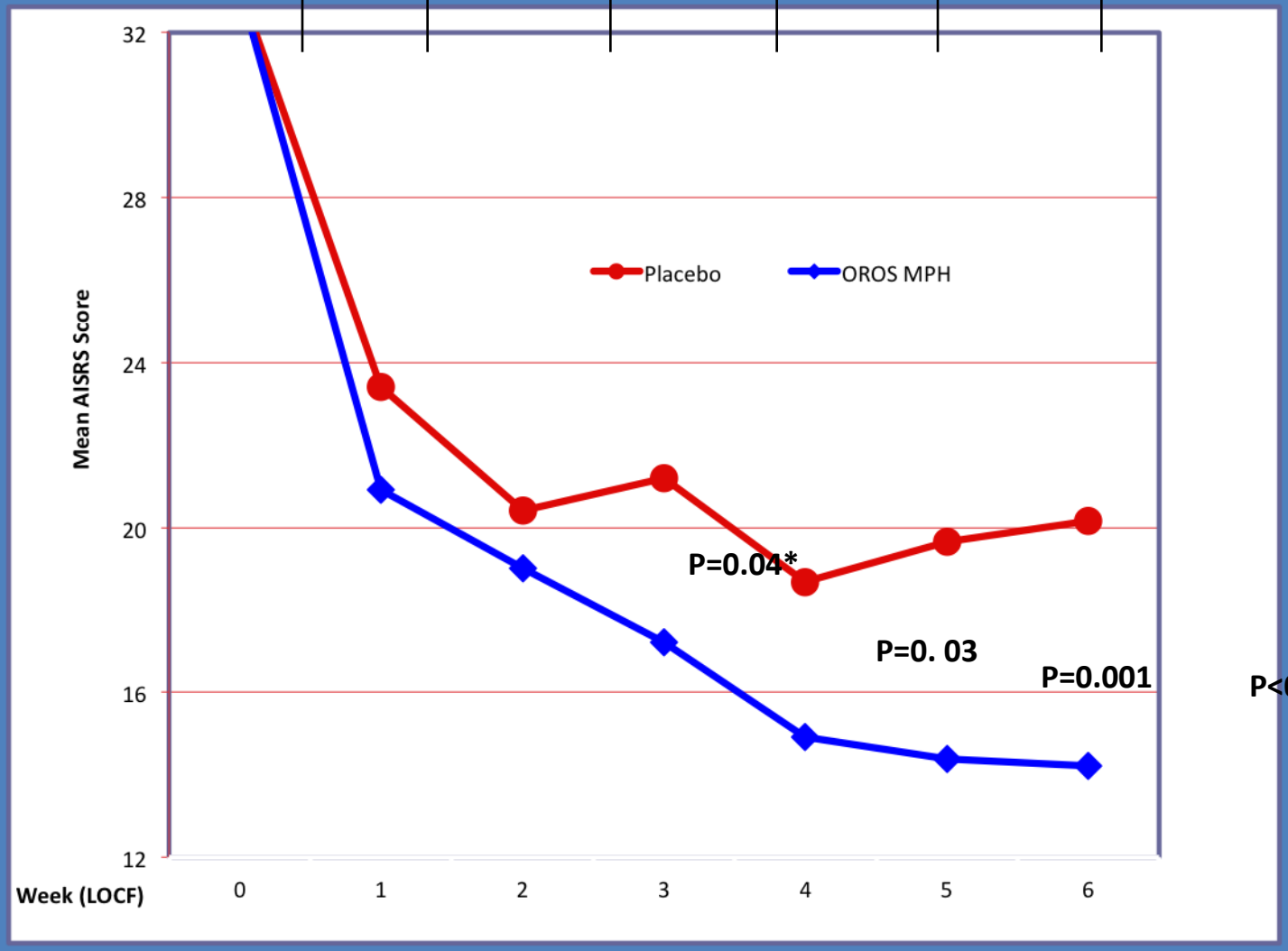


Individual PK Plots in a Single 50/50 IR/ER MPH Delivery Formulation



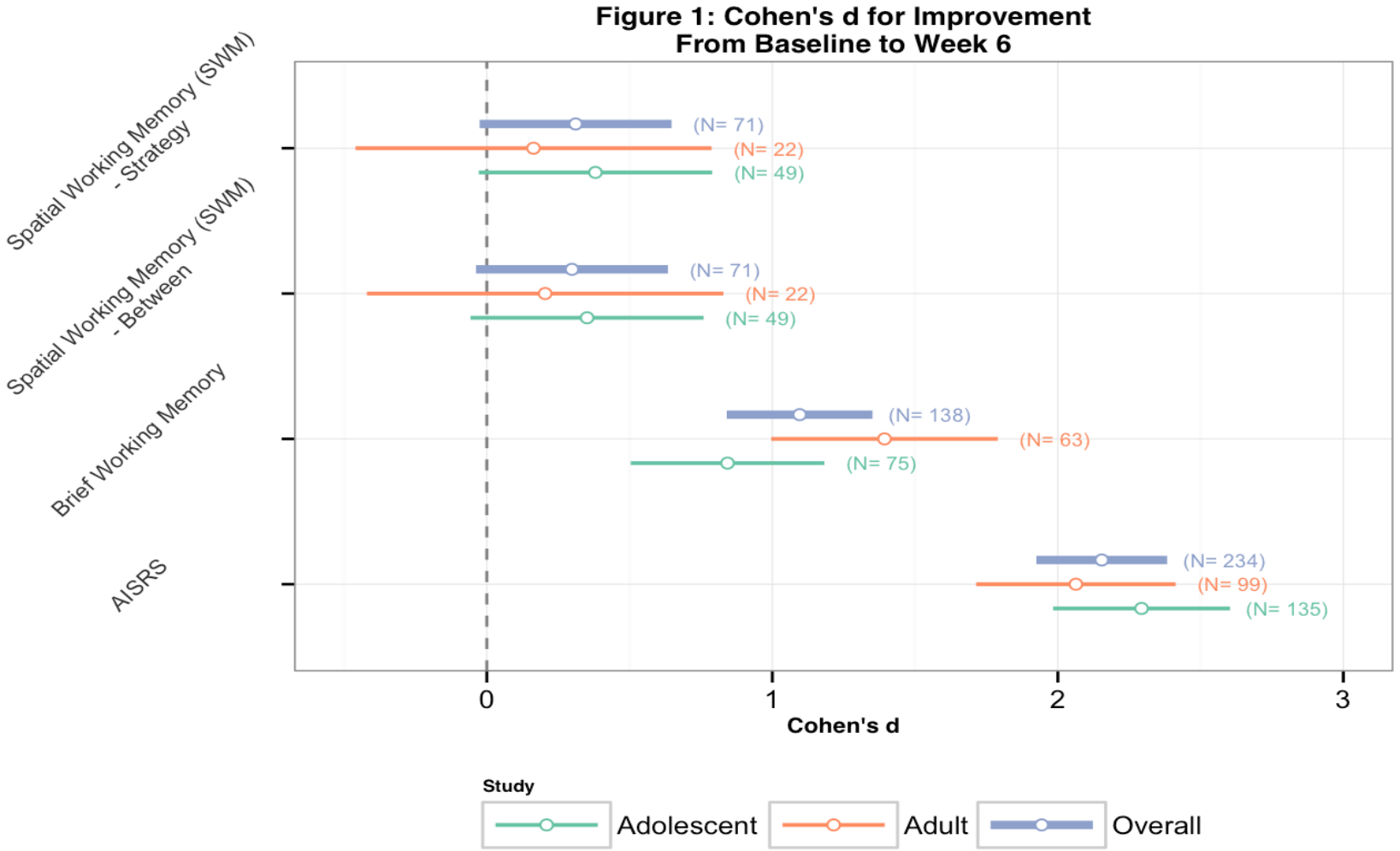
Clinical Ratings of ADHD Symptoms (ADHD-RS)

Week	1	2	3	4	5	6
OROS-MPH mg/day	36.0	58.7±17.8	72.6±26.5	77.9±29.6	81.3±31.0	80.9±31.8
Placebo mg/day	36.0	66.3±12.8	82.2±22.4	92.2±23.8	94.9±25.5	96.8±25.9



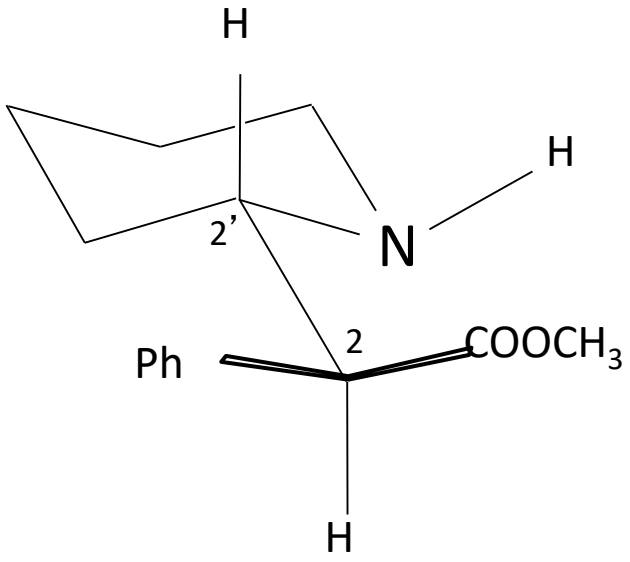
Biederman et al Biol psych 2006

Pharmacological Dissociation Between The Robust Effects Of Methylphenidate On ADHD Symptoms And Weaker Effects On Working Memory

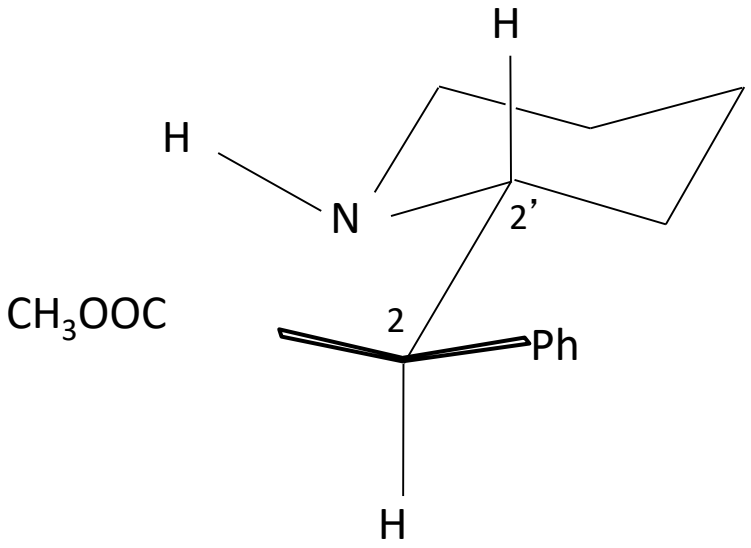


Focalin™ (D-MPH)*

An Isomeric Form of MPH



l (-) Methylphenidate

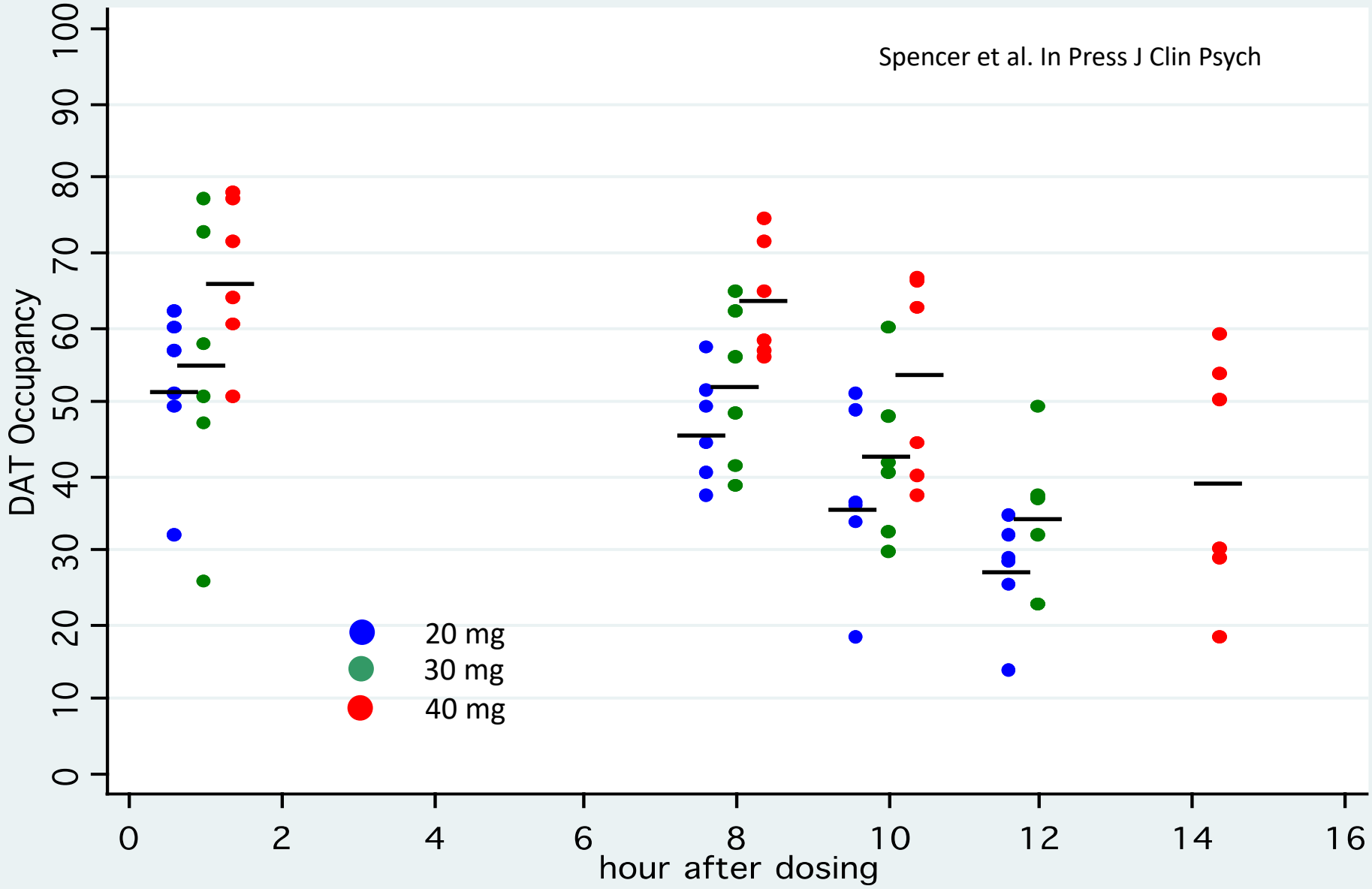


D (+) Methylphenidate

*FDA approved for ADHD.

Courtesy of T. Wilens, MD.

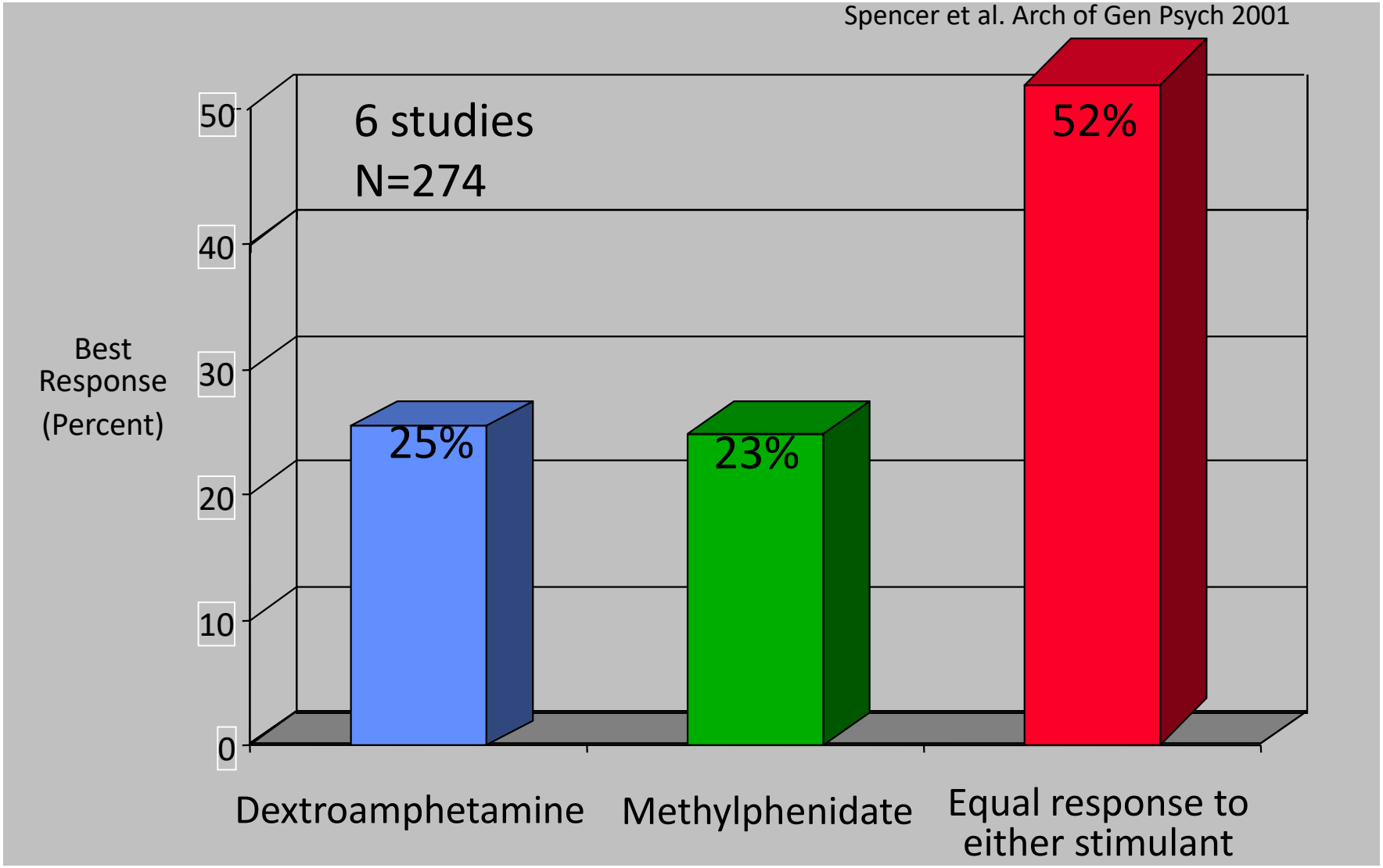
SODAS d-MPH: DAT Occupancy (PET) by Hour and Dose



Amphetamine Formulations

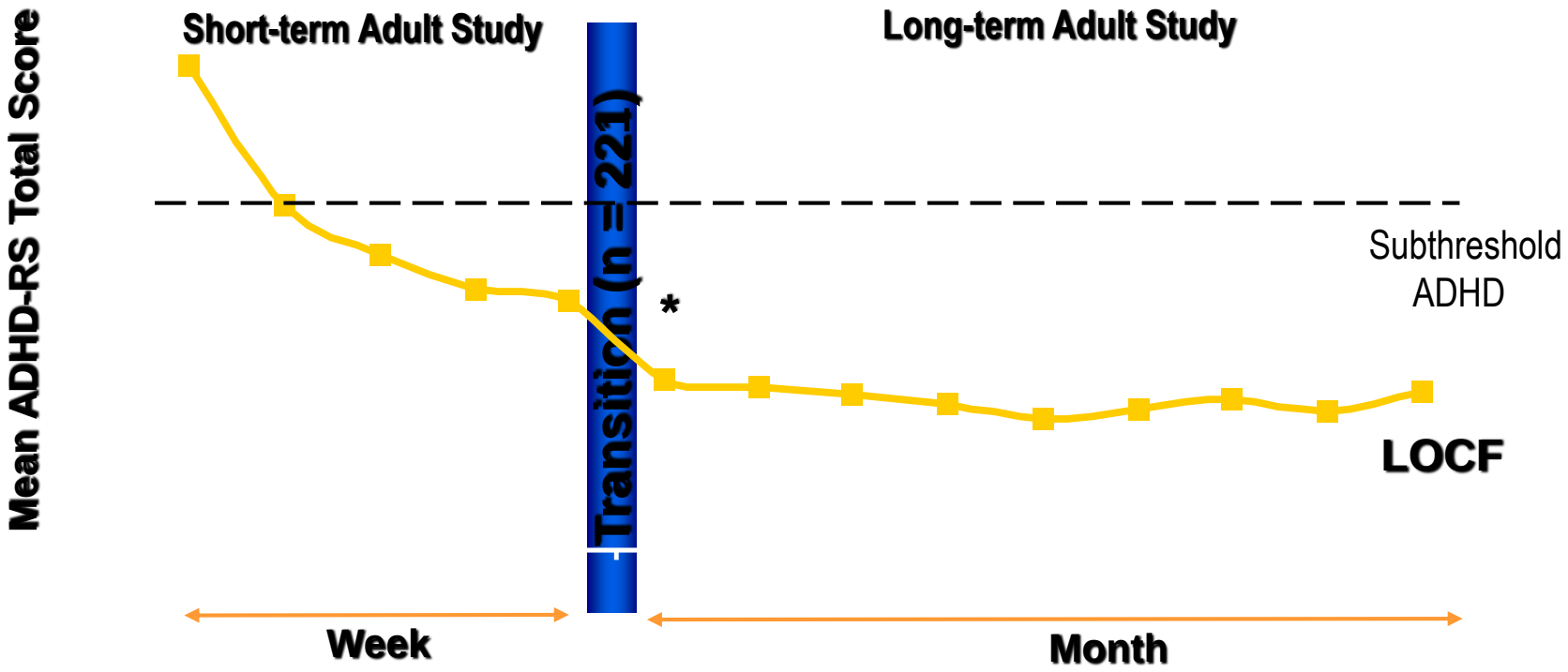
Medication	Formulation	Release % IR/ER	Isomers d,l	Duration
Dexedrine® Zenzedi®	Tablet	100/0	1:0	~ 4-6 hours
Dexedrine Spansules®	Capsules	unknown	1:0	~ 6 hours
Adderall® (IR)	Tablet	100/0	3:1	~ 4-6 hours
Evekeo®	Tablet	100/0	1:1	~ 4-6 hours
Evekeo ODT®	ODT	100/0	1:1	~ 4-6 hours
Procentra®	Oral Solution	100/0	1:0	~ 4-6 hours
Adzenys XR ODT®	ODT	50/50	3:1	~ 12 hours
Adzenys ER® Liquid	Oral Solution	50/50	3:1	~ 12 hours
Dyanavel XR®	Oral Solution	unknown	3.2:1	~ 13 hours
Adderall XR®	Capsule	50/50	3:1	~ 12 hours
Mydayis®	Capsule	33/33/33	3:1	~ 16 hours
Vyvanse®	Capsule	Prodrug	1:0	~ 13 hours
Vyvanse Chewable®	Tablet	Prodrug	1:0	~ 13 hours

Meta-analysis of Within-Subject Comparative Trials Evaluating Response to Stimulant Medications



18-Month Summary of Symptom Improvement With MAS XR 20, 40, and 60 mg/day

Results of Short-term and 18 Months of Long-term Open-Label Extension Study

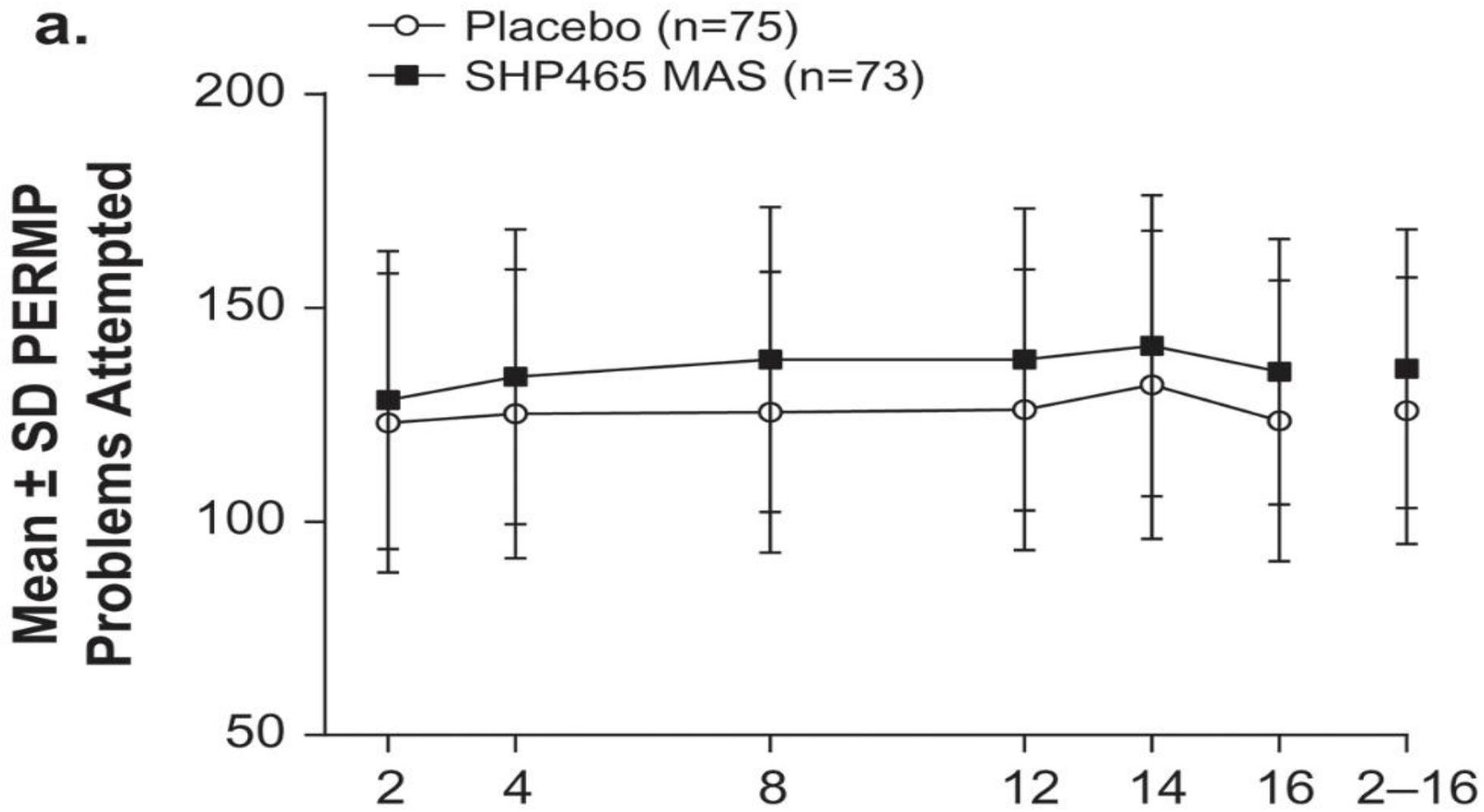


***P<.05 by 1-sample *t* test of mean change from baseline of long-term study.**

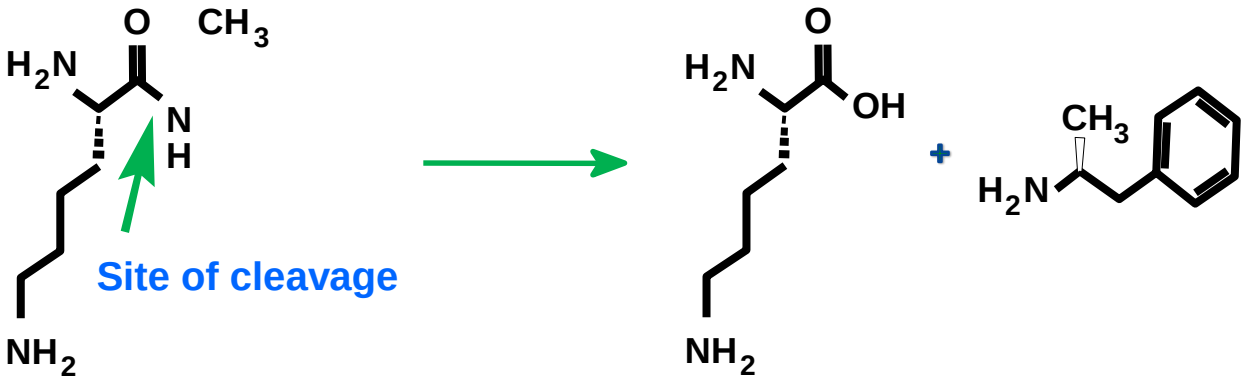
Wilens T. Presented at: 157th Annual APA Meeting; May 1-6, 2004; New York, NY.

Triple Bead MAS (Mydayis®)

Wigal et al. 2018

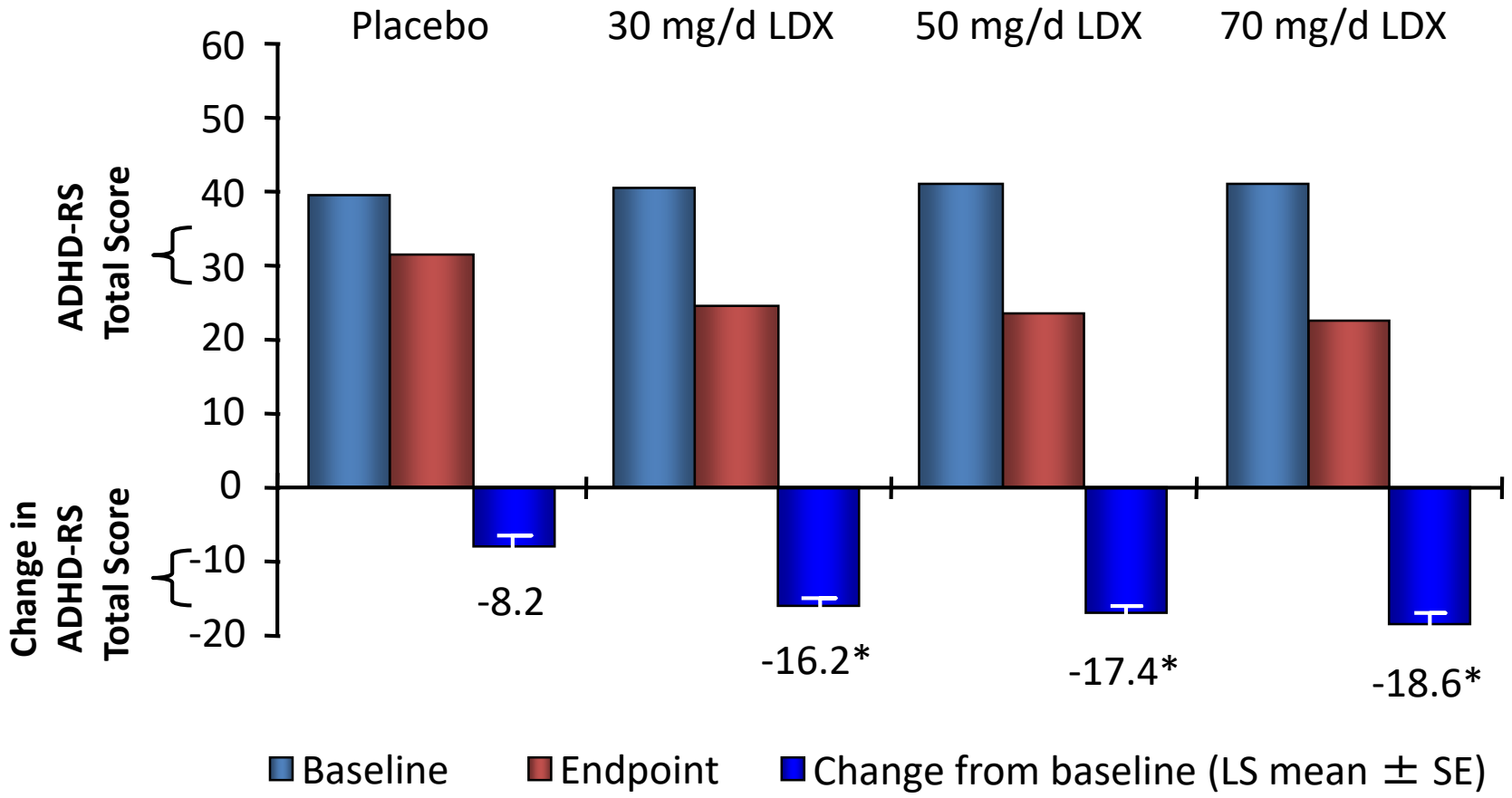


LDX Chemistry



LDX **_l_-lysine** **_d_-amphetamine**

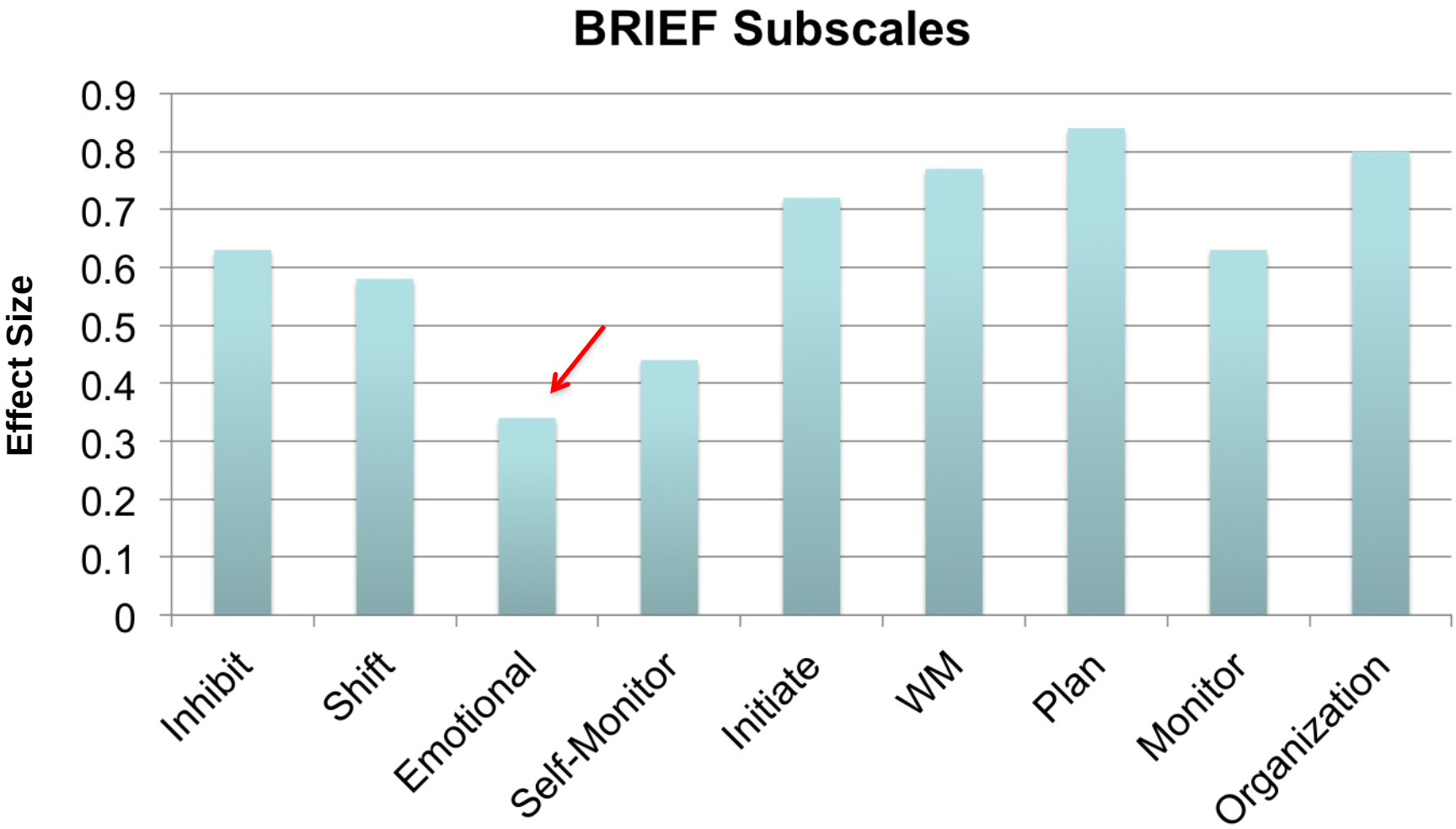
LDX in Adult ADHD: ADHD-RS Total Scores (ITT Population)



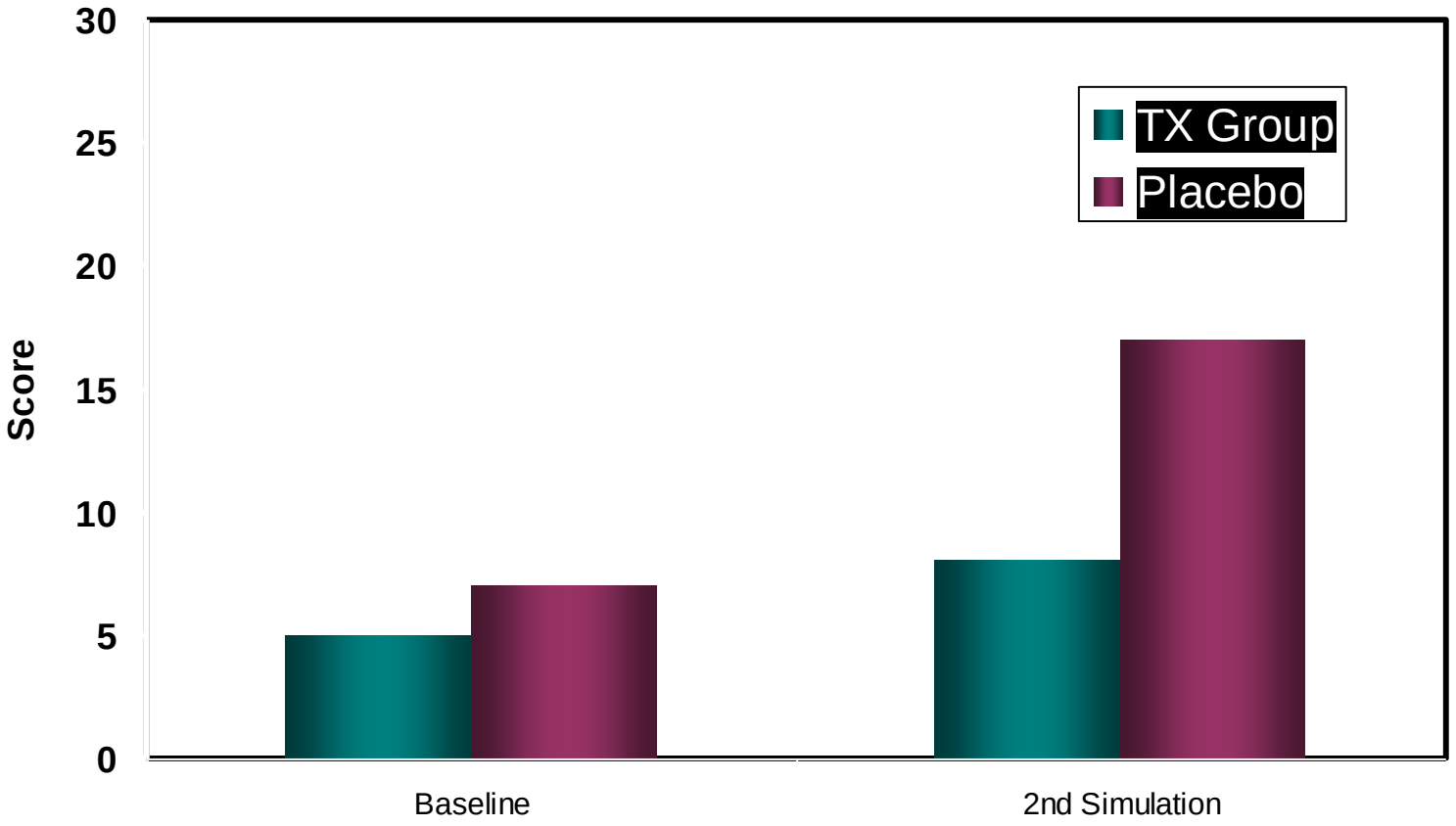
A more negative change in ADHD-RS total score indicates greater improvement.
LS=least squares; SE=standard error of the mean.
*P<.0001 (adjusted Dunnett's test compared with placebo following ANCOVA with baseline score as covariate).

Stimulant Tx of Executive Function Lisdexamfetamine in Adult ADHD + GEC > 65

Adler et al. JCP 2013



Controlled Trial of Lisdexamfetamine Collisions



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

Adverse Reactions Mydayis®
FDA Approved Labeling

Black Box

Drug Abuse Dependence

Contraindications

- Hypersensitivity to amphetamine
- Monoamine Oxidase Inhibitors

Warnings and Precautions

- Serious Cardiovascular Events
- Increase blood pressure
- Psychiatric Adverse Events
- Seizures
- Peripheral Vasculopathy, including Raynaud's phenomenon
- Long-Term Suppression of Growth
- Serotonin Syndrome

ONLINE FIRST

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

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William O. Cooper, MD, MPH
Colin M. Sox, MD, MS
K. Arnold Chan, MD, ScD
Bruce H. Fireman, MA
Patrick G. Arbogast, PhD
T. Craig Cheetham, PharmD, MS
Virginia P. Quinn, PhD, MPH
Sascha Dublin, MD, PhD
Denise M. Boudreau, PhD, RPh
Susan E. Andrade, ScD
Pamala A. Pawloski, PharmD
Marsha A. Raebel, PharmD
David H. Smith, RPh, PhD
Ninah Achacoso, MS
Connie Uratsu, RN
Alan S. Go, MD
Steve Sidney, MD, MPH
Mai N. Nguyen-Huynh, MD, MAS
Wayne A. Ray, PhD
Joe V. Selby, MD, MPH

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

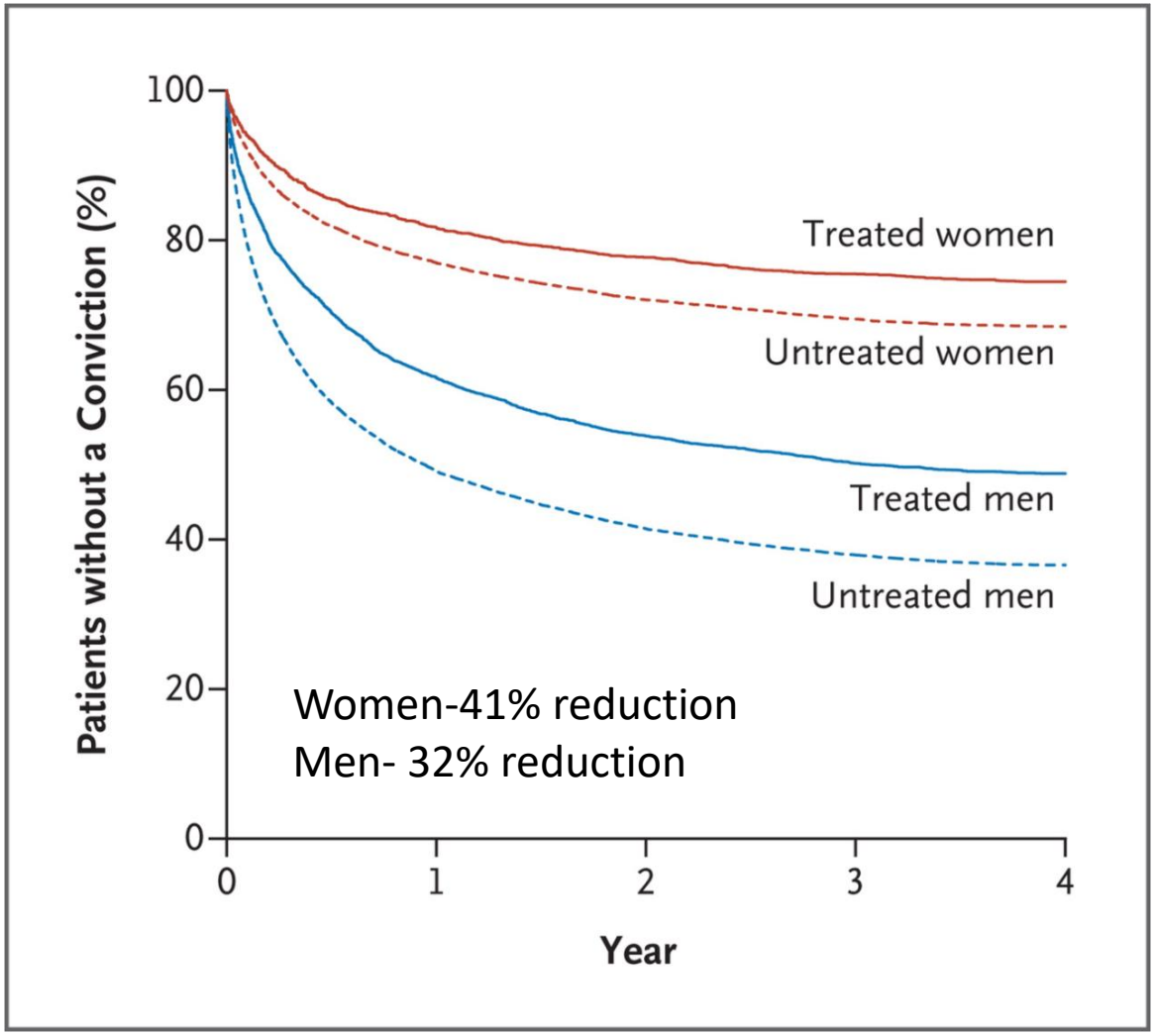
Screening for Cardiac Risk: AHA Guidelines

- Medical history
  - Personal congenital or acquired cardiac disease history
  - Family history of cardiac disease (<50 years of age)
  - Palpitations, chest pain, fainting, seizures, post-exercise symptoms
  - Ask about other medications (including OTC)
- Routine medical exam
- Monitor BP and pulse at baseline and follow-up, especially in adults
- ECG is reasonable but not mandatory
- Routine check of Holter, ECHO is not necessary

Gutgesell H, et al. *Circulation.* 1999:99:979-982.
Schubiner H, et al. *J Atten Disord*. 2006;10:205-211.

Medication for ADHD and Criminality

(Lichtenstein et al. NEJM 2012: 367:2006-2014)



Swedish national registers (N= 25,656 with ADHD-about 50% on medications)
Ca. 40% of convictions related to drug offenses (Tx OR=0.6). No difference in type of ADHD medication (stimulants, nonstimulants) or level of crime.