MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Stimulant Treatment of Pediatric ADHD

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Disclosures

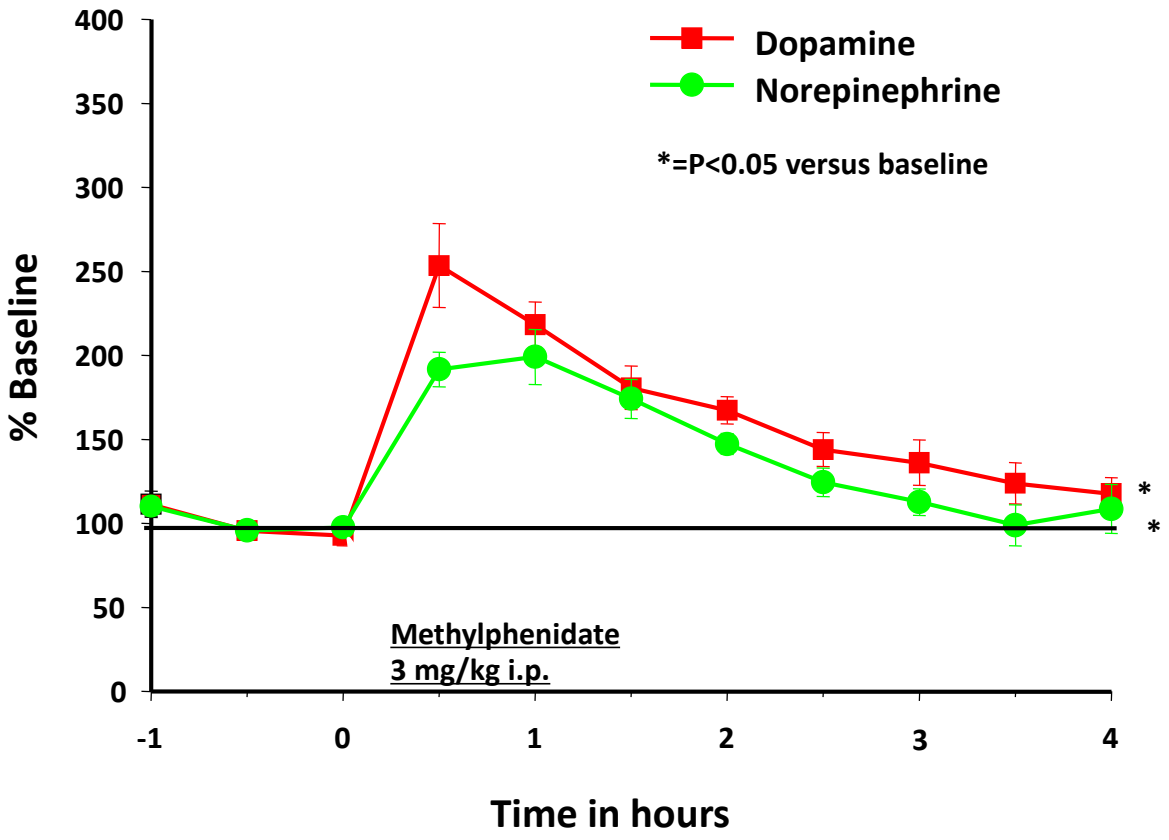
FDA	Research Support
Department of Defense	Research Support
Avekshan	Consultant
Sunovion	Research Support

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

Effects of Methylphenidate (3 mg/kg i.p.) on Extracellular Levels of Monoamines in the Rat Prefrontal Cortex



From Bymaster et al., Neuropsychopharmacology, 2002

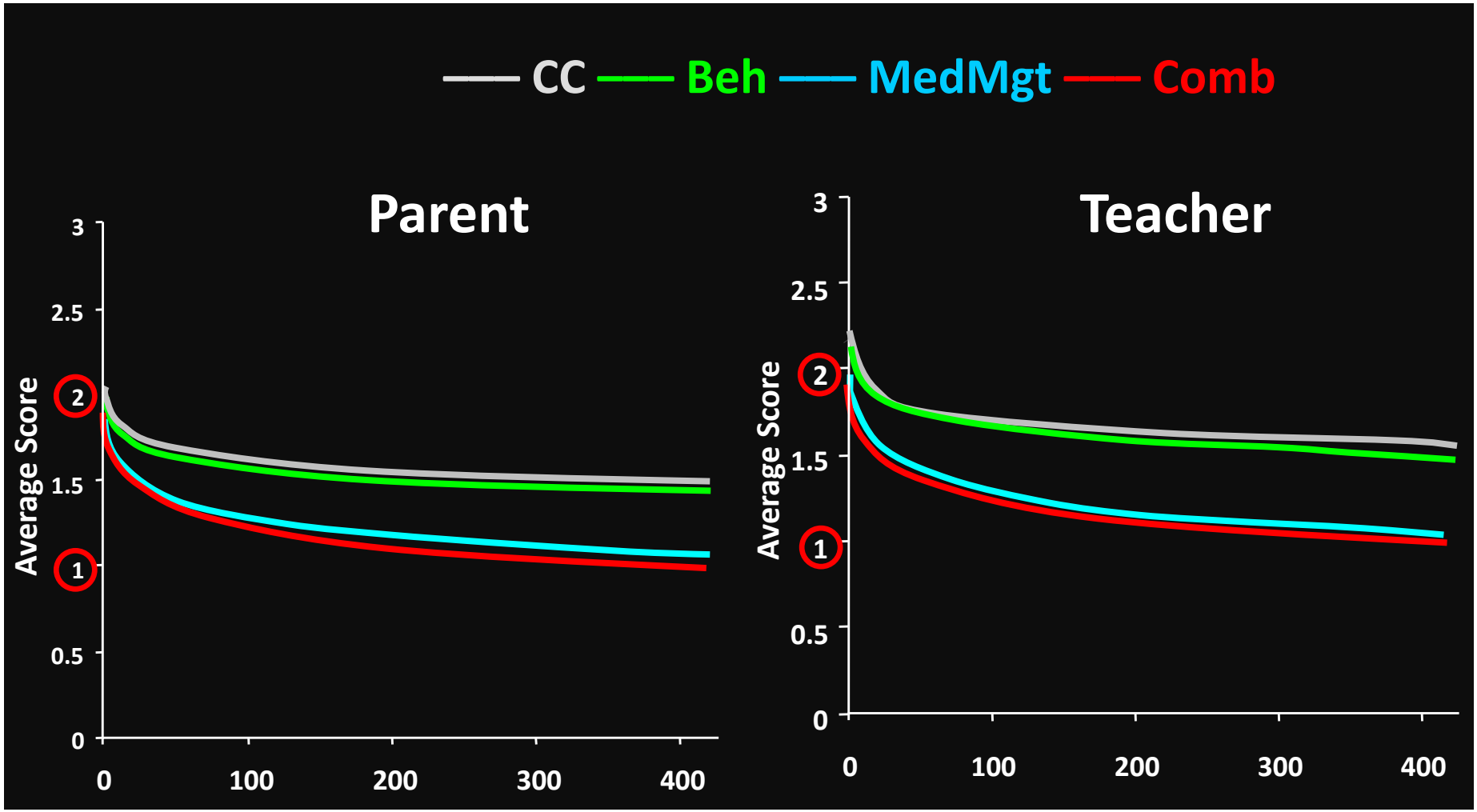
Mechanism of Action MPH: Insights from PET Imaging Studies

(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

MTA: Treatment Effects on Inattention Scores (SNAP)

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

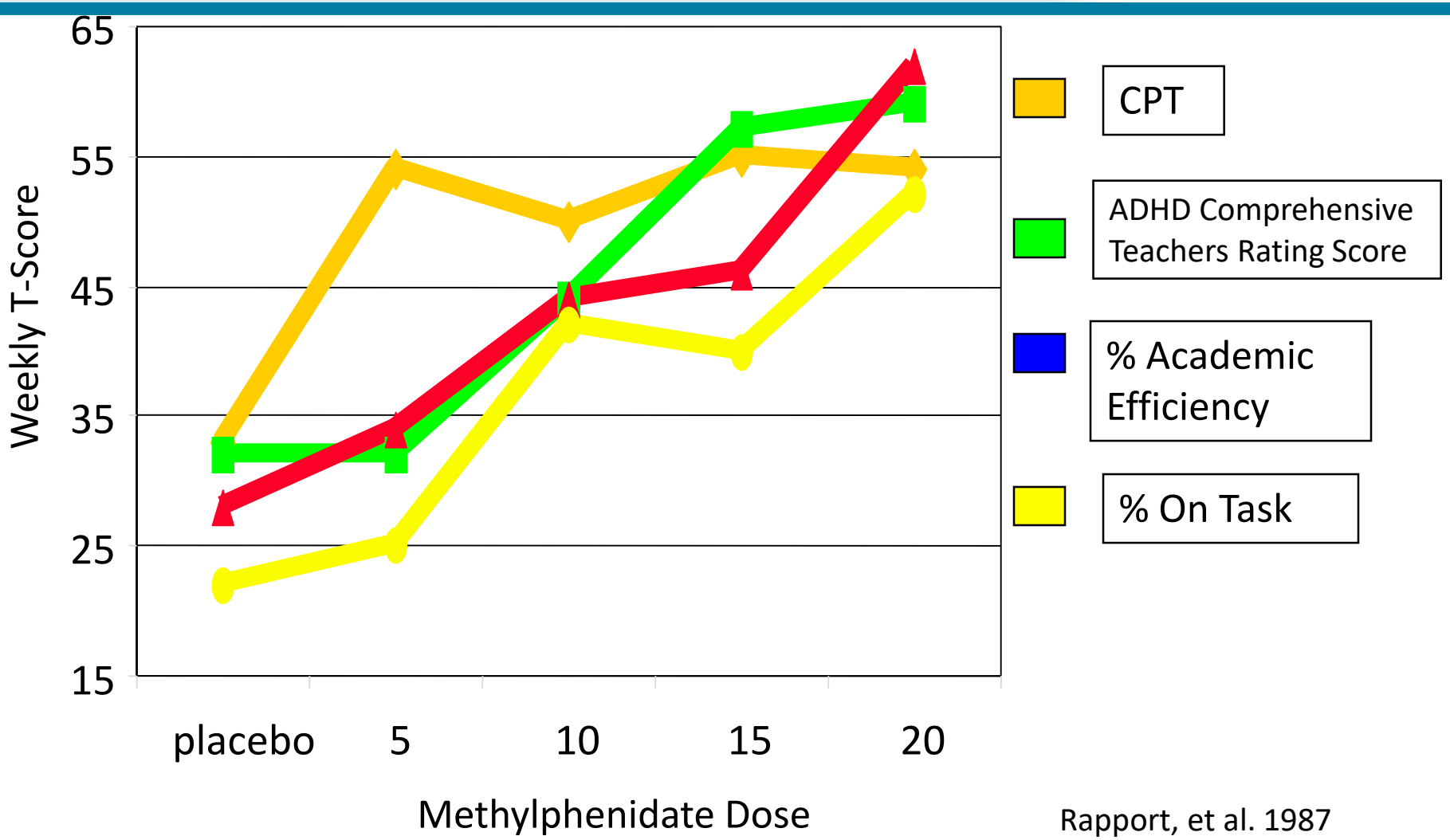


Indirect Effects of Medication on Parents, Teachers and Peers

(Barkley et al., Cunningham et al.)

- *Social changes in Parents and Teachers*
  - *(Barkley et al., Pelham et al., Whalen et al.)*
  - Decreased rate of commands and degree of supervision
  - Increased praise and positive responsiveness
- *Social changes in Peers*
  - *(Cunningham et al., Whalen et al.)*
  - Decreased negative and aggressive behavior on stimulants
  - Leads to greater acceptance by peers
  - Leads to further positive benefit to the child

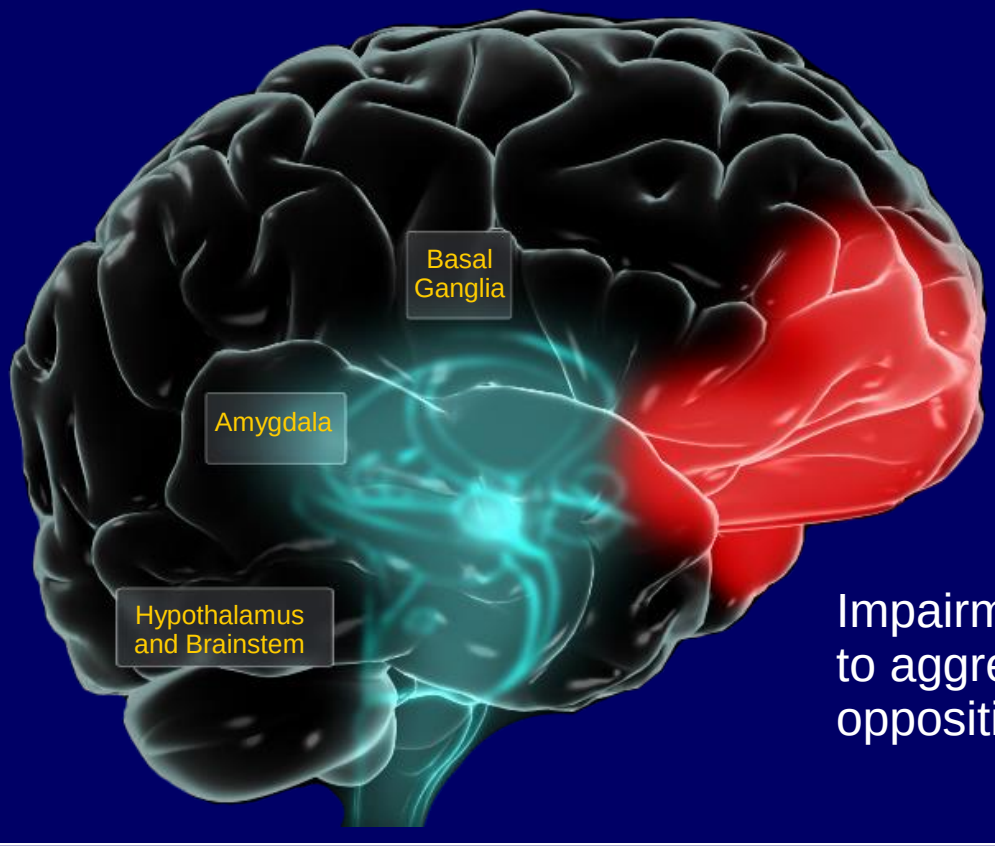
ADHD and Methylphenidate: Dose Effects on Attention in Clinic and Classroom



Rapport, et al. 1987

The Ventromedial PFC: Emotional Regulation

Ventromedial PFC is thought to regulate emotion[1–3]



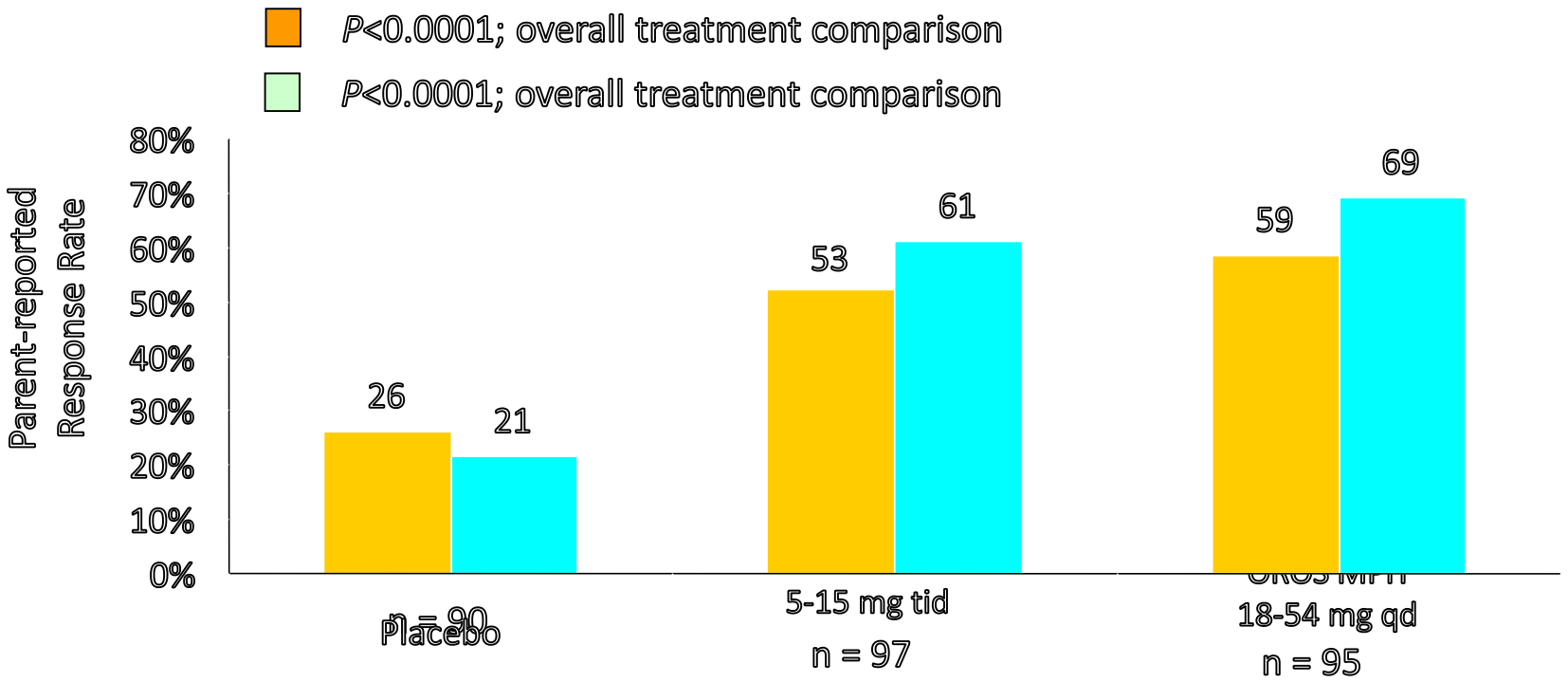
Ventromedial PFC

Impairment may lead to aggressive and oppositional behavior

[1]Anderson SW, et al. *Nat Neurosci.* 1999;2:1032-1037.
[2]Arnsten AFT, et al. *J Child Adolesc Psychopharmacol.* 2007;17:393-406.
[3]Price JL, et al. *Prog Brain Res*. 1996;107:523-536.

Treating ADHD and ODD With OROS MPH

Randomized, double-blind, placebo-controlled, 28-day trial (N = 282; all with ADHD; Mean Baseline Parent-Rated IOWA Conners O/D Score = 7.89)



Response defined as achieving a ≥30% reduction from baseline IOWA Conners subscale score; Oppositional/Defiant (O/D); Inattention/Overactivity (I/O)

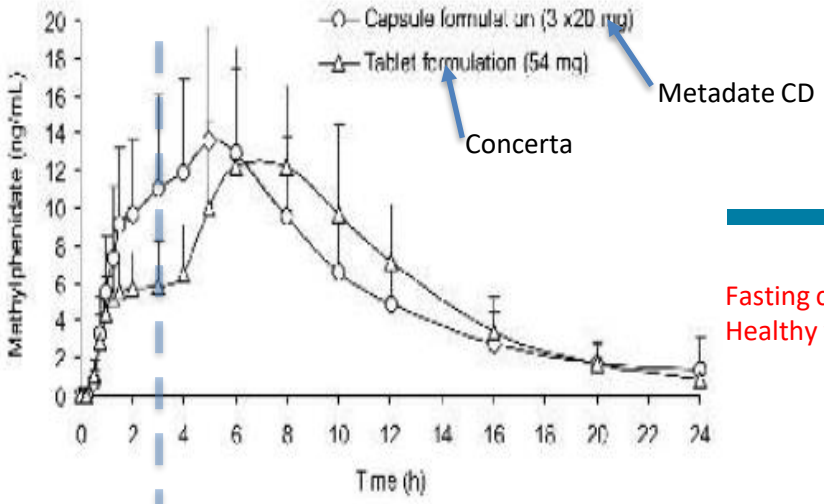
Wan et al. Presented at: 17th Annual US Psychiatric and Mental Health Congress; November 18-21, 2004; San Diego, Calif.

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.



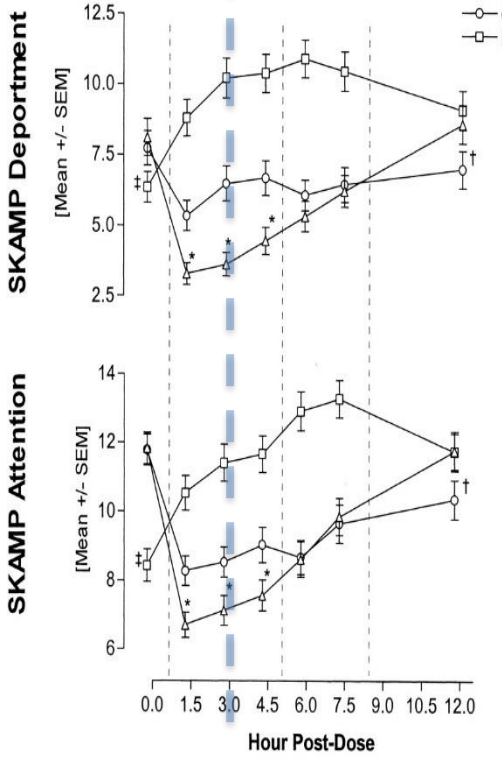
Metadate CD

Concerta

Fasting conditions, Healthy volunteers

MCD = Metadate CD
CON = Concerta
PLA = placebo

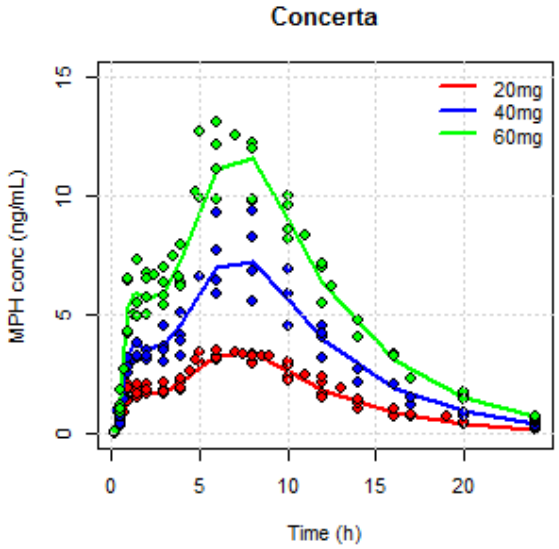
Swanson, James M., et al. "A comparison of once-daily extended-release methylphenidate formulations in children with attention-deficit/hyperactivity disorder in the laboratory school (the Comacs Study)." *Pediatrics* 113.3 (2004): e206-e216.

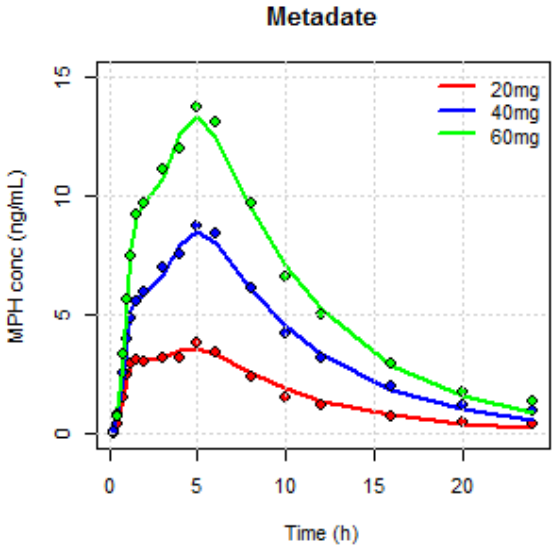


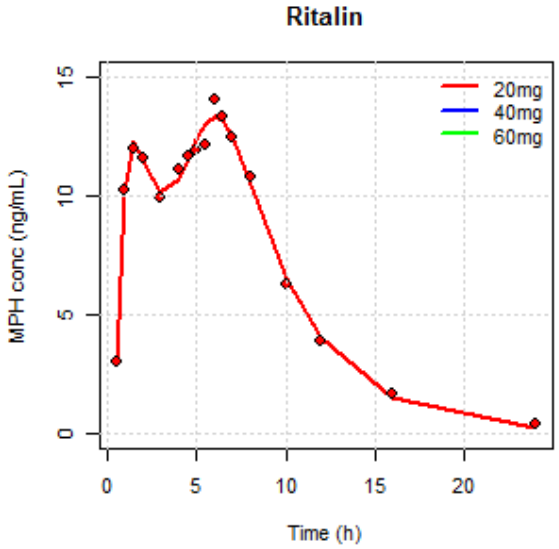
For doses of MPH, differences in PK from 0-3 hours is reflected in the SKAMP ratings

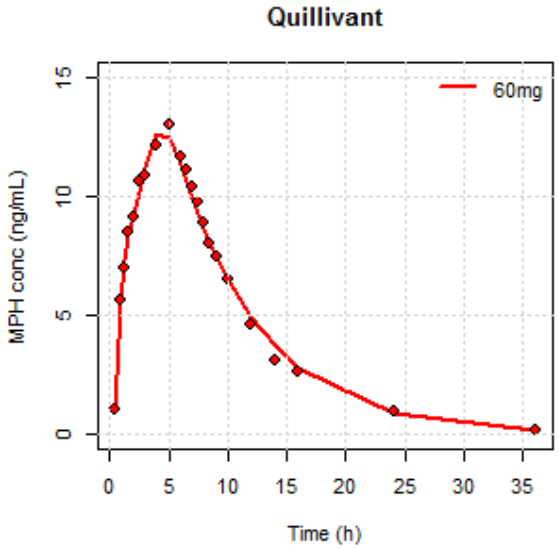
* and †: statistically significance between active treatments

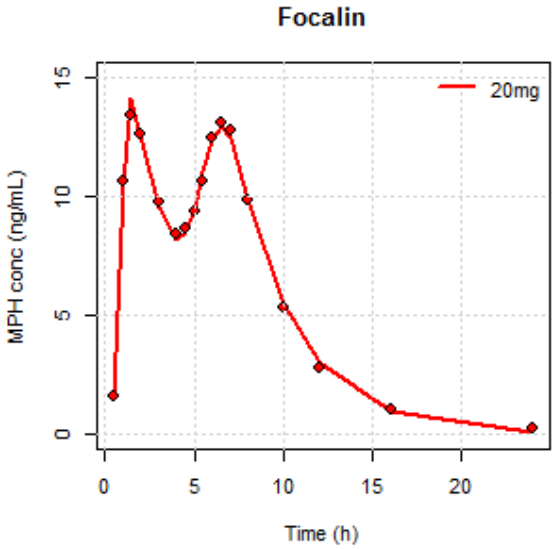
Long Acting MPH formulations

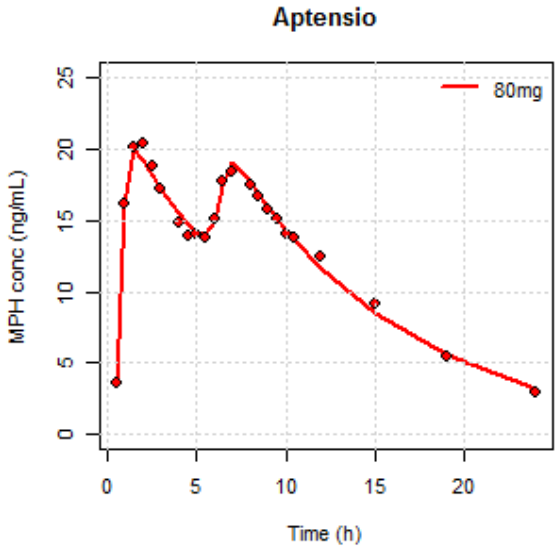




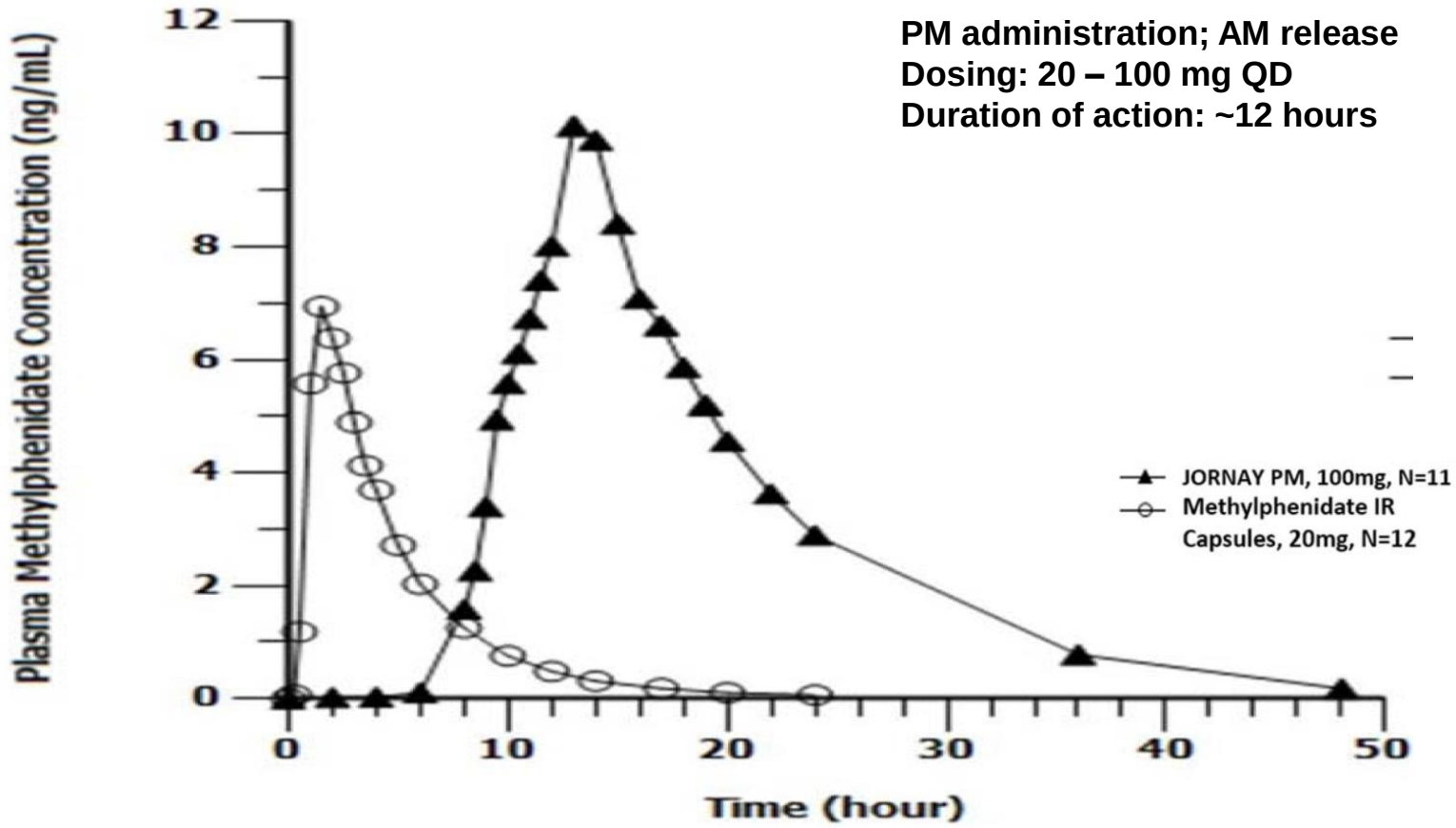






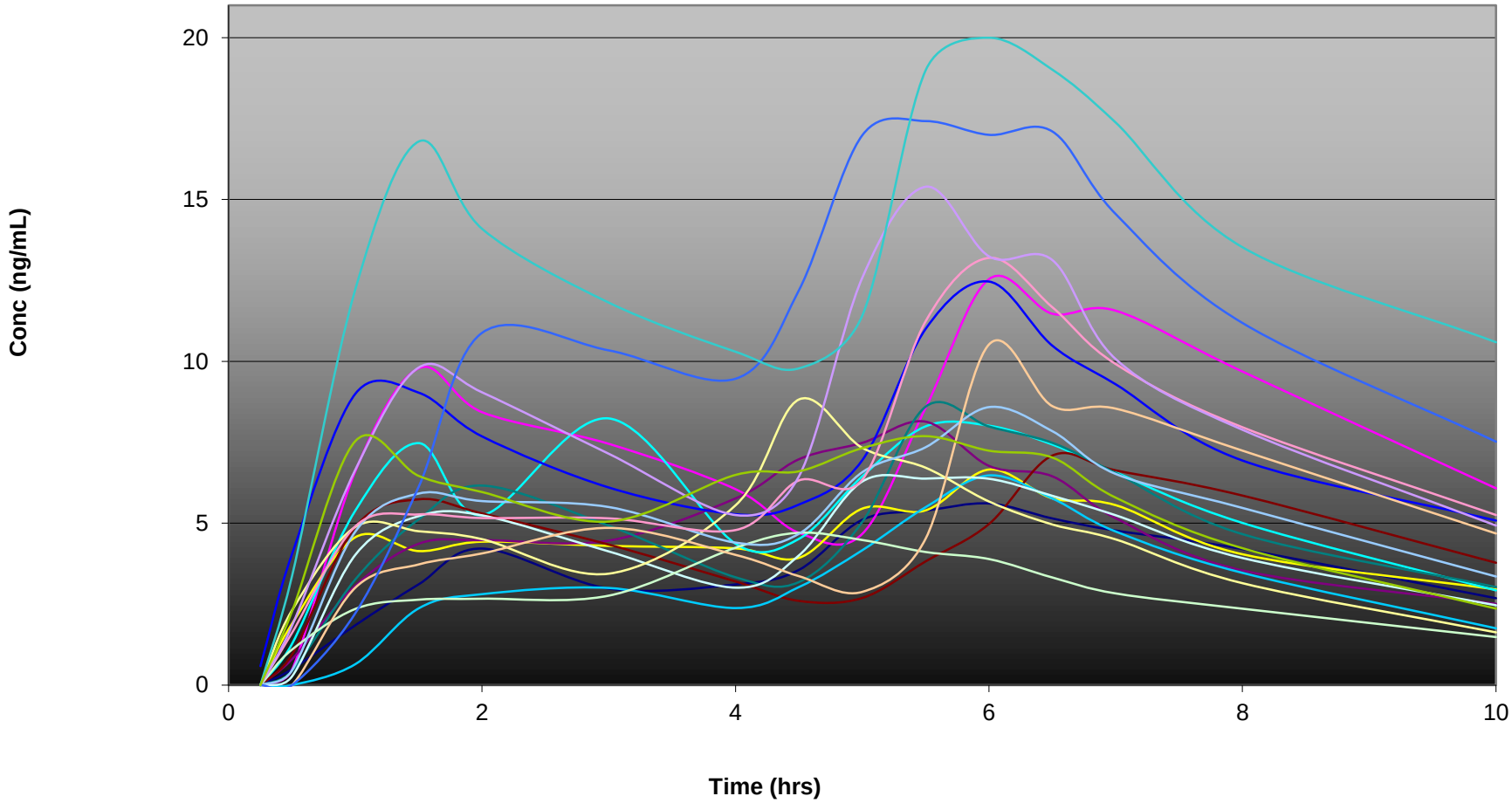


Jornay PM® Delayed Release Methylphenidate

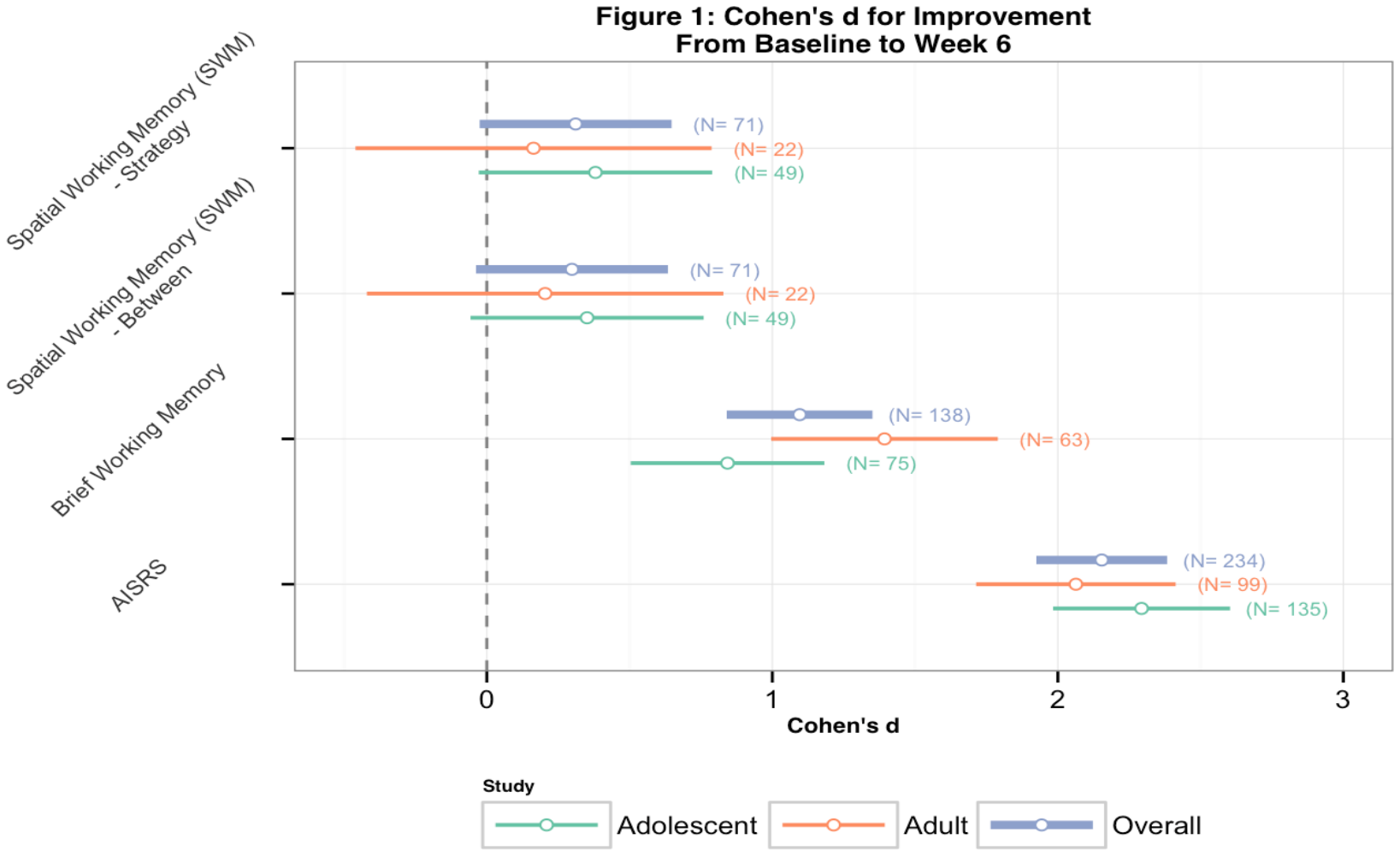


PM administration; AM release
Dosing: 20 – 100 mg QD
Duration of action: ~12 hours

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



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

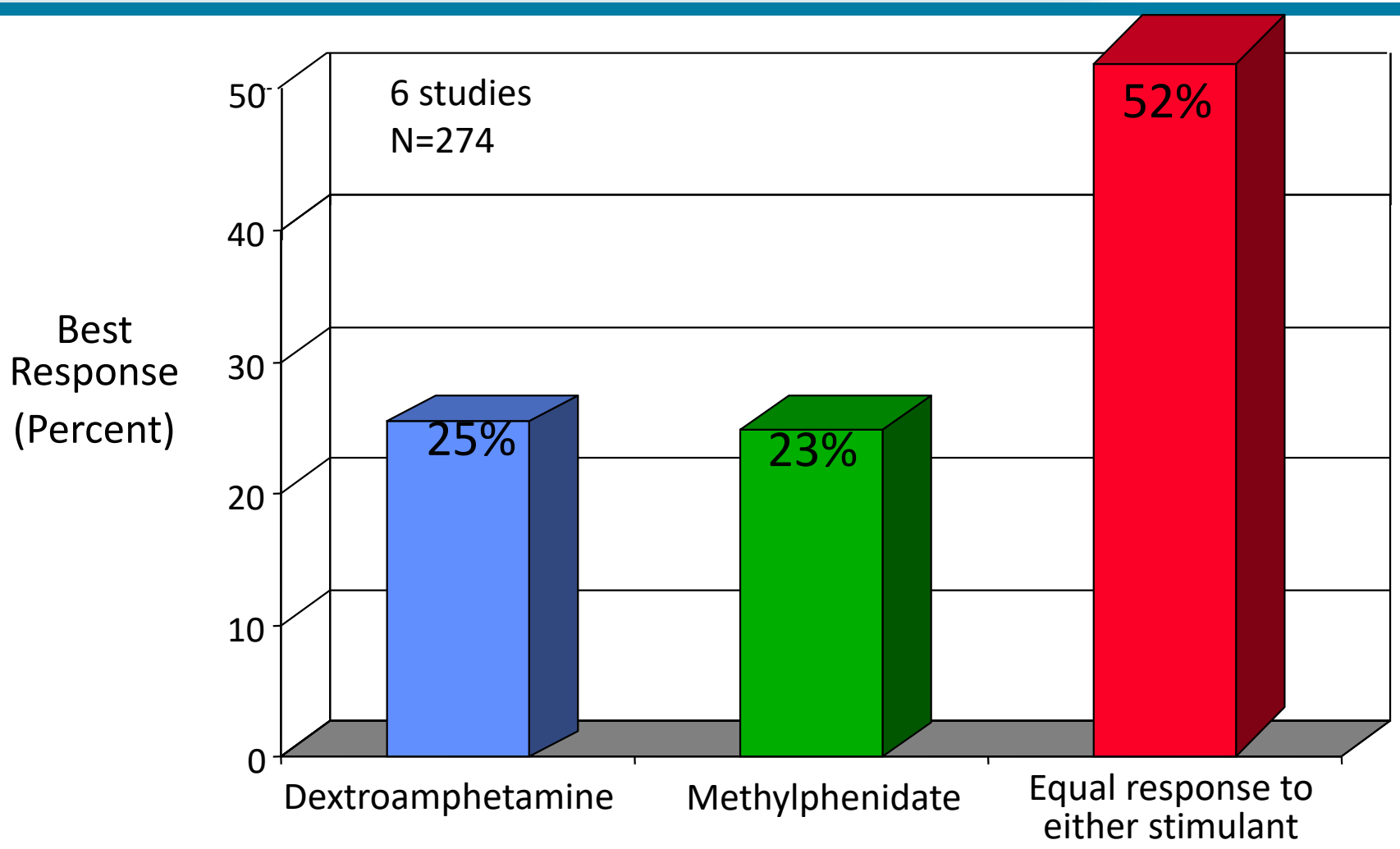


Amphetamine Formulations

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

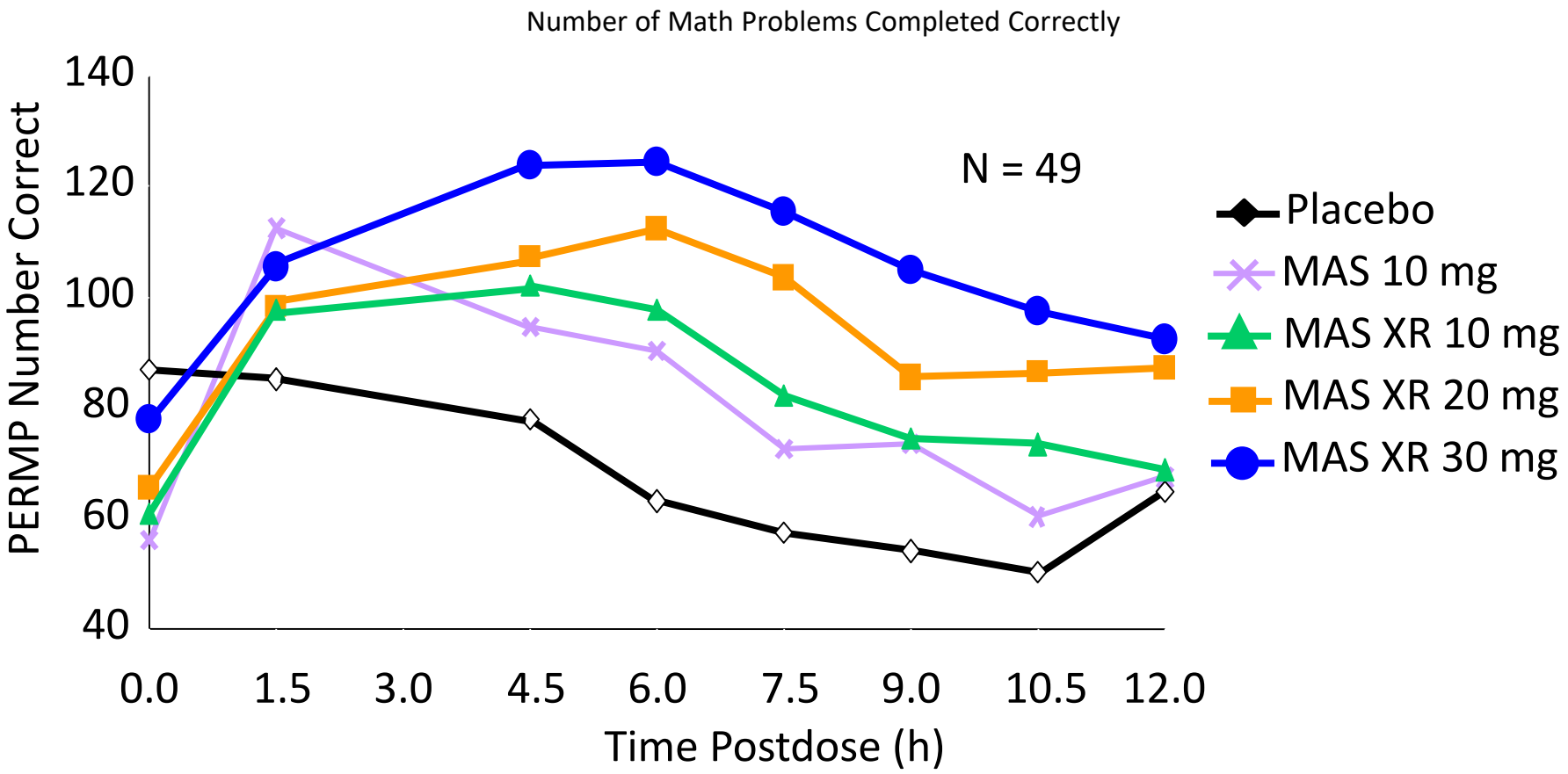
Meta-analysis of Within-Subject Comparative Trials Evaluating Response to Stimulant Medications

Spencer et al. Arch of Gen Psych 2001



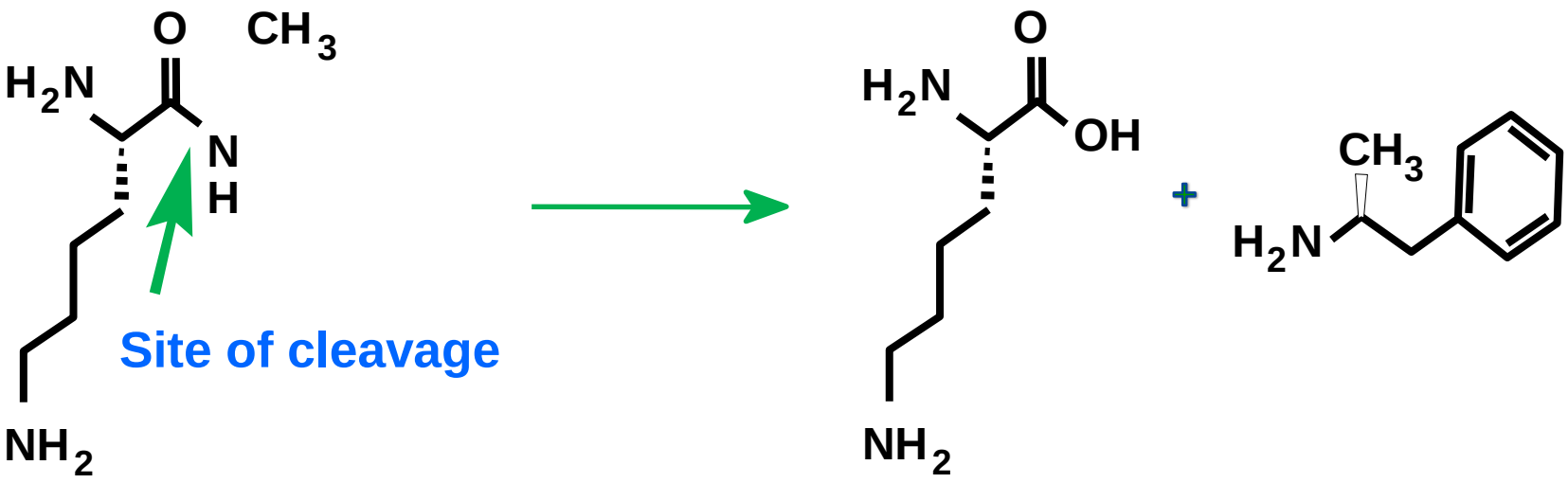
MAS XR Efficacy:

Academic Productivity
Randomized, Double-Blind, Placebo-Controlled Study



McCracken JT, et al. *J Am Acad Child Adolesc Psychiatry.* 2003;42(6):673-683.

LDX Chemistry



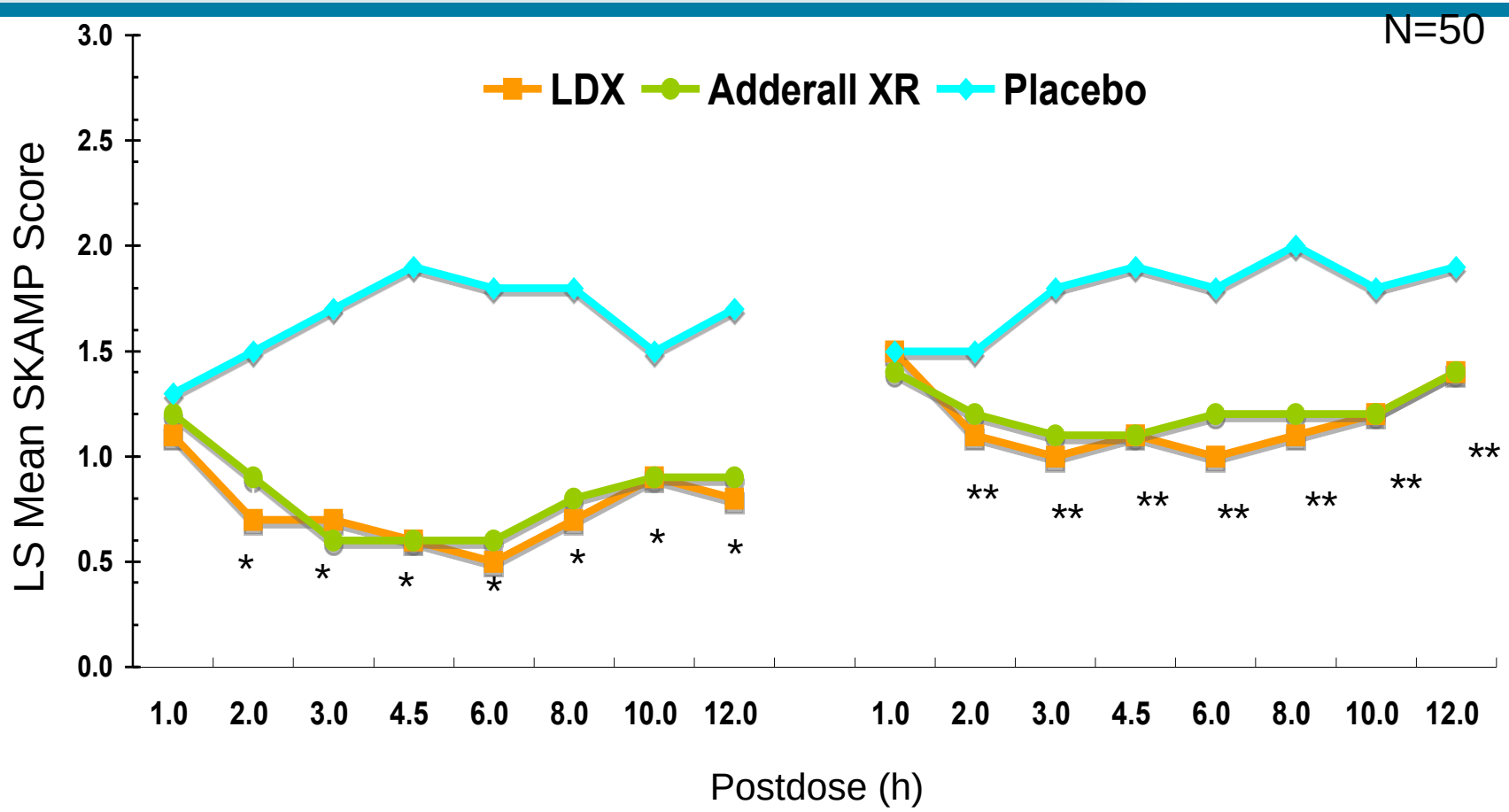
LDX **_l_-lysine** **_d_-amphetamine**

LDX Extraction, Pharmacokinetic and Abuse Liability Studies: Results

- Amphetamine is very difficult to extract from LDX prodrug
- Intravenous administration does not result in appreciable serum amphetamine levels in rat and human studies
- Intranasal administration does not result in appreciable serum amphetamine levels in rat and human studies
- Apparent "saturation" of LDX in gut limits ultimate serum amphetamine levels (e.g., overdose implications)
- Marginally less likeability in human studies

Jasinski D, et al. Posters presented at CPDD Meeting, June, 2006, Scottsdale, AZ.;
Biederman J, et al. Poster presented at Annual APA Meeting, May 24, 2006, Toronto, Ontario, Canada.
Boyle L, et al. Presented at NCDEU, June 12-15, 2006, Boca Raton, FL.

LDX : Duration of Action
SKAMP Time Course



*P < .0001, **P < .01, LDX and Adderall XR vs placebo;
LS = Least Square.

Adverse Effects of Stimulants

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

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

Adverse Reactions Concerta®
FDA Approved Labeling

Black Box

- Drug Dependence

Contraindications

- Hypersensitivity to methylphenidate
- Marked anxiety, tension or agitation
- Glaucoma
- Tics
- Monoamine Oxidase Inhibitors

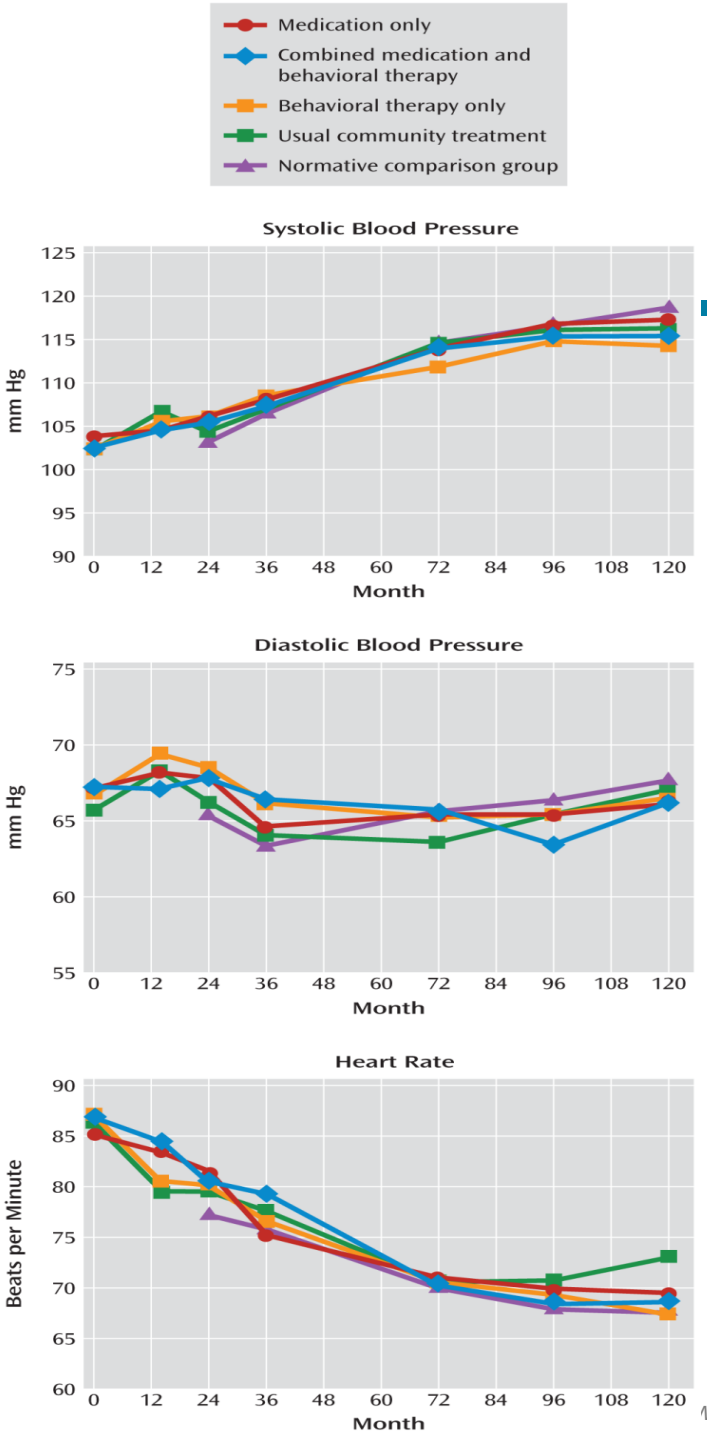
Warnings and Precautions

- Serious Cardiovascular Events
- Increase blood pressure
- Psychiatric Adverse Events
- Seizures
- Priapism
- Peripheral Vasculopathy, including Raynaud's Phenomenon
- Long-Term Suppression of Growth
- Visual Disturbance
- Hematologic Monitoring

Blood Pressure and Heart Rate Over 10 Years in the MTA

No significant treatment-by-time effect was observed on systolic or diastolic blood pressure.

A significant treatment-by-time effect was observed on heart rate (p=0.02), with significantly higher mean heart rates in the groups receiving medication at 14 months, but not afterward.



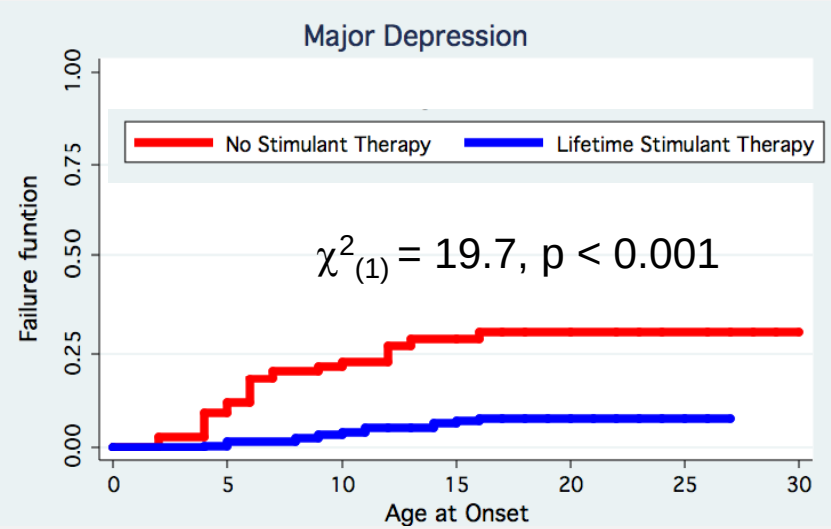
(Vitiello et al. JAMA 2012)

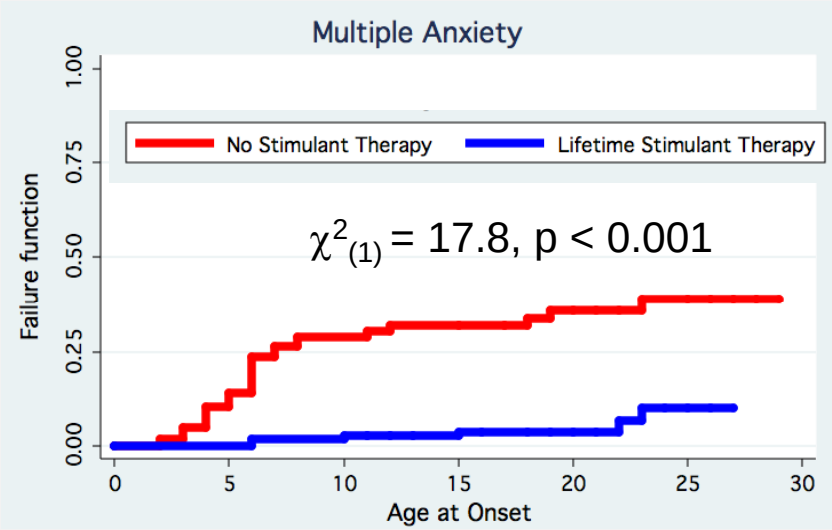
Screening for Cardiac Risk: AHA Guidelines

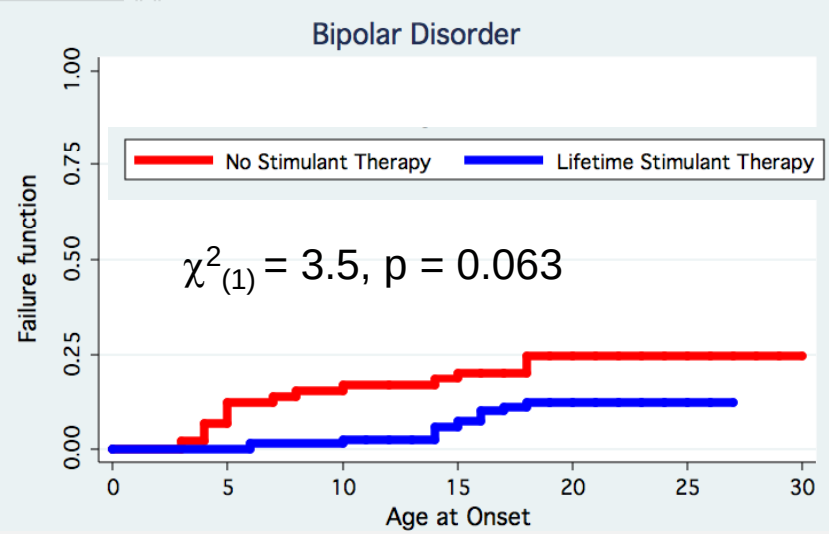
- Medical history
  - Personal congenital or acquired cardiac disease history
  - Family history of cardiac disease (<50 years of age)
  - Palpitations, chest pain, fainting, seizures, post-exercise symptoms
  - Ask about other medications (including OTC)
- Routine medical exam
- Monitor BP and pulse 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.

Protective Effect of Stimulants on Comorbidity

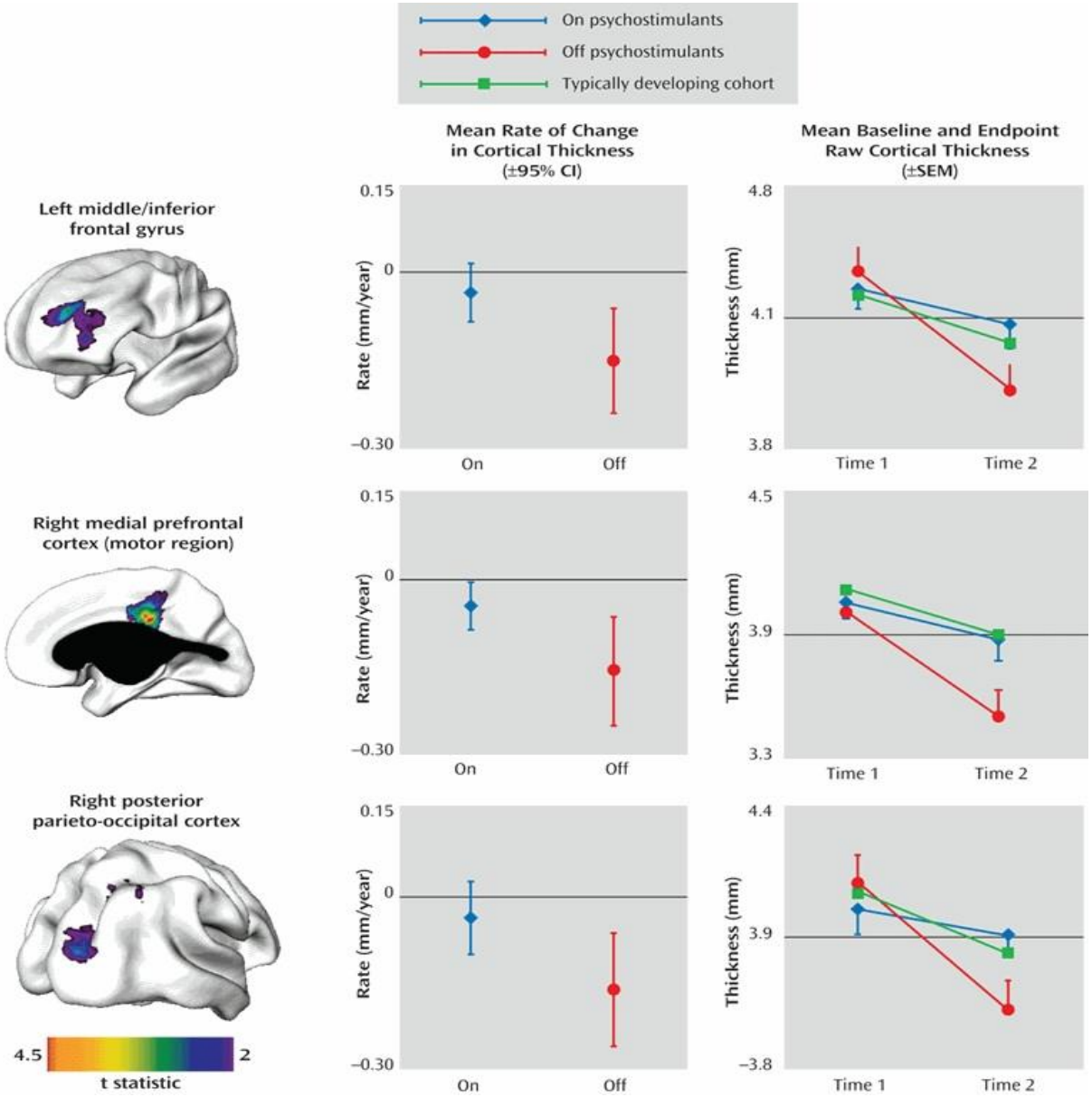






Biederman et al. Pediatrics. 2009.

Psychostimulant Treatment and the Developing Cortex in ADHD



Shaw et al 2009

Onset of Tic Disorders in ADHD Probands Stratified by Stimulant Treatment

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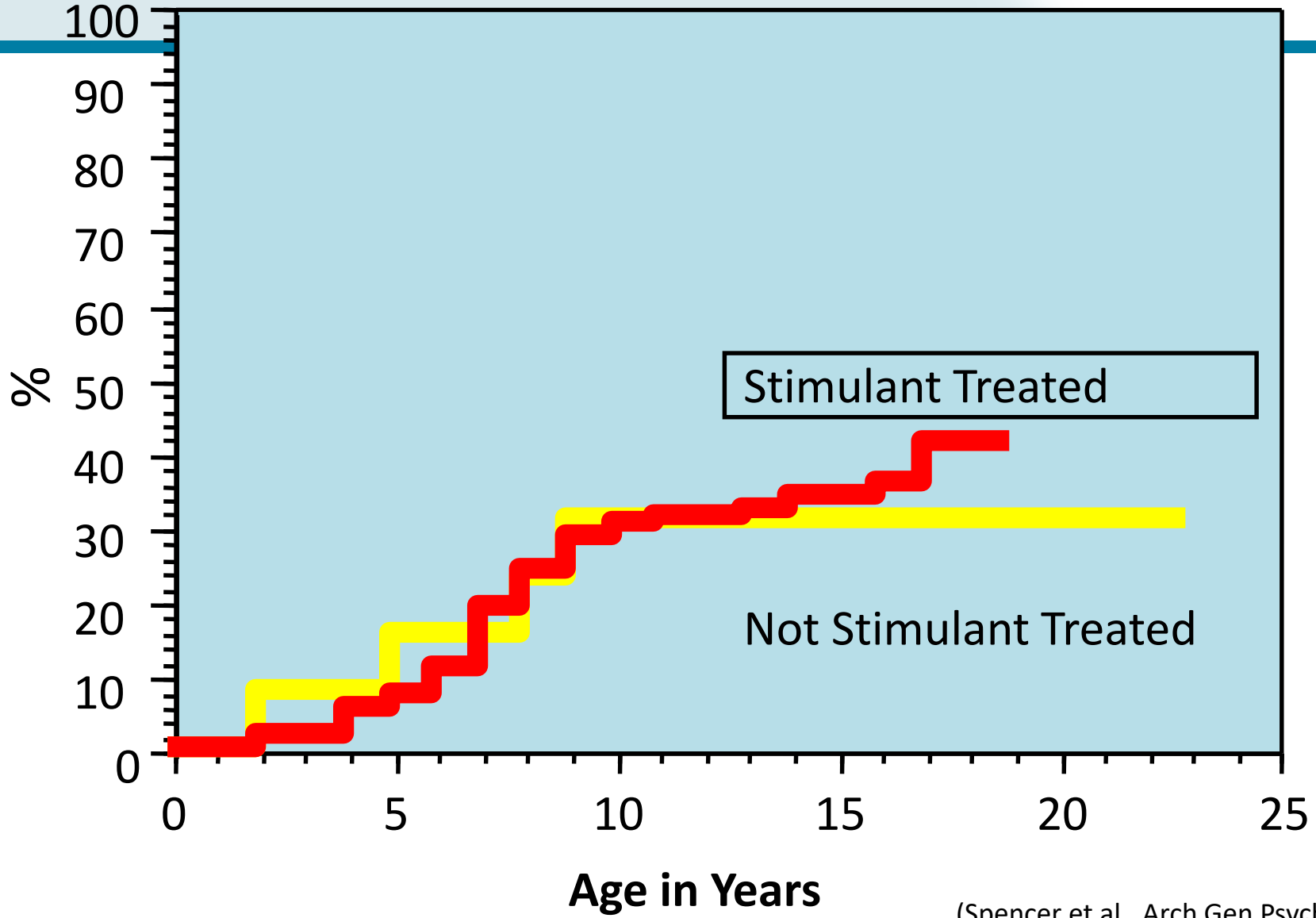

(Spencer et al., Arch Gen Psych, 1999)

Effect of Stimulants on Height and Weight: A Review of the Literature

SV FARAONE, PH.D., J BIEDERMAN, M.D., C MORLEY, M.A., TJ SPENCER, M.D.

J. Am. Acad. Child Adolesc. Psychiatry, 2008;47(9)

Conclusions

Treatment with stimulants in childhood modestly reduced expected height and weight. Although these effects attenuate over time and some data suggest that ultimate adult growth parameters are not affected, more work is needed to clarify the effects of continuous treatment from childhood to adulthood. Although physicians should monitor height, deficits in height and weight do not appear to be a clinical concern for most children treated with stimulants.