Sleep Problems in ADHD

Mark A. Stein Ph.D.

Presenter's Disclosure: Mark A. Stein

	Consultant	Advisory	Stock	Speaker	Research
Medicie		X			
Supernus		x			
Maxis Health	x	X	X		

Learning Objectives

1. Recognize multi-directional associations between sleep and ADHD Symptoms
2. Summarize the effects of caffeine, stimulant medications, and nonstimulants on sleep
3. Describe the prevalence, risk and moderators of sleep as an adverse event in stimulant treatment
4. Discuss the impact on sleep based on drug, dose, baseline sleep difficulty, rate of titration, comorbidity and treatment duration.
5. Discuss treatment implications/recommendations for various ADHD symptom profiles and sleep problem phenotypes

“The awareness of a link between sleep disturbances and attention-deficit/hyperactivity disorder (ADHD) is not novel at all” Cortese (2014)

In 1957, Laufer and Denhoff wrote: “Generally the parents of hyperkinetic children are so desperate over the night problems that the daytime ones pale in significance”

DSM III (1980)- ‘restless sleep”

Warren Weinberg (1990)-Primary Disorder of Vigilance (inattention, daydreaming, restlessness, *sleepiness*)

Thanks to Dickens

Common Sleep Phenotypes

- Insomnia / Sleep-Onset Delay
  - Difficulty falling asleep; bedtime resistance, especially when symptoms are uncontrolled.
- Delayed Sleep–Wake Phase Disorder (DSWPD)
  - Late sleep timing, late dim-light melatonin onset; common in adolescents.
- Restless Legs Syndrome / Periodic Limb Movement Disorder
  - Consider iron deficiency; screen for urge to move legs, worse at night.
- Obstructive Sleep Apnea (OSA)
  - Snoring, witnessed apneas, daytime behavior problems; tonsillar hypertrophy risk.
- Daytime Sleepiness
  - From insufficient sleep, circadian delay, OSA, medication timing, or comorbidities.

TABLE 2. Prevalence of Specific Sleep Problems by Age Group (Percentage of Sample)*

Behavior	Don't Know/ Missing	Never	<1/Week	>1/Week	>7 Times/Week
Snores					
4–6 y old	4.5	55.3	17.3	10.6	12.3
7–10 y old	6.8	53.8	15.8	10.9	12.7
11–12 y old	5.6	56.9	19.4	11.1	6.9
Total sample	5.7	55.0	17.0	11.0	12.0
Takes >30 min to fall asleep					
4–6 y old	5.0	46.9	22.3	17.3	8.4
7–10 y old	6.4	44.8	27.6	13.1	8.1
11–12 y old	4.2	45.8	26.4	15.3	8.3
Total sample	5.5	46.0	25.0	15.0	8.3
Talks in sleep					

Sleep and Behavior Problems in School-Aged Children
Mark A. Stein, Janis Mendelsohn, William H. Obermeyer, Julie Amromin and Ruth Benca. *Pediatrics*. 2001

TABLE 7. Correlation of Sleep Factor Scores With CBCL Factor Scores

Variable	Sleep Factors				
	I, Parasomnias	II, Enuresis/Gags	III, Tiredness	IV, Noisy Sleep	V, Insomnia
Externalizing	0.31**	0.17**	0.31**	0.27**	0.40**
Internalizing	0.37**	0.12*	0.35**	0.26**	0.40**
Withdrawn	0.37**	0.05	0.26**	0.21**	0.27**
Somatic complaints	0.22**	0.05	0.28**	0.16**	0.26**
Anxious/depressed	0.41**	0.12*	0.26**	0.21**	0.39**
Social problem	0.36**	0.10*	0.34**	0.19**	0.37**
Thought problems	0.40**	0.20**	0.23**	0.20**	0.31**
Attention problem	0.31**	0.16**	0.31**	0.21**	0.38**
Delinquent behavior	0.25**	0.23**	0.08	0.09	0.22**
Aggressive behavior	0.36**	0.19**	0.30**	0.26**	0.38**

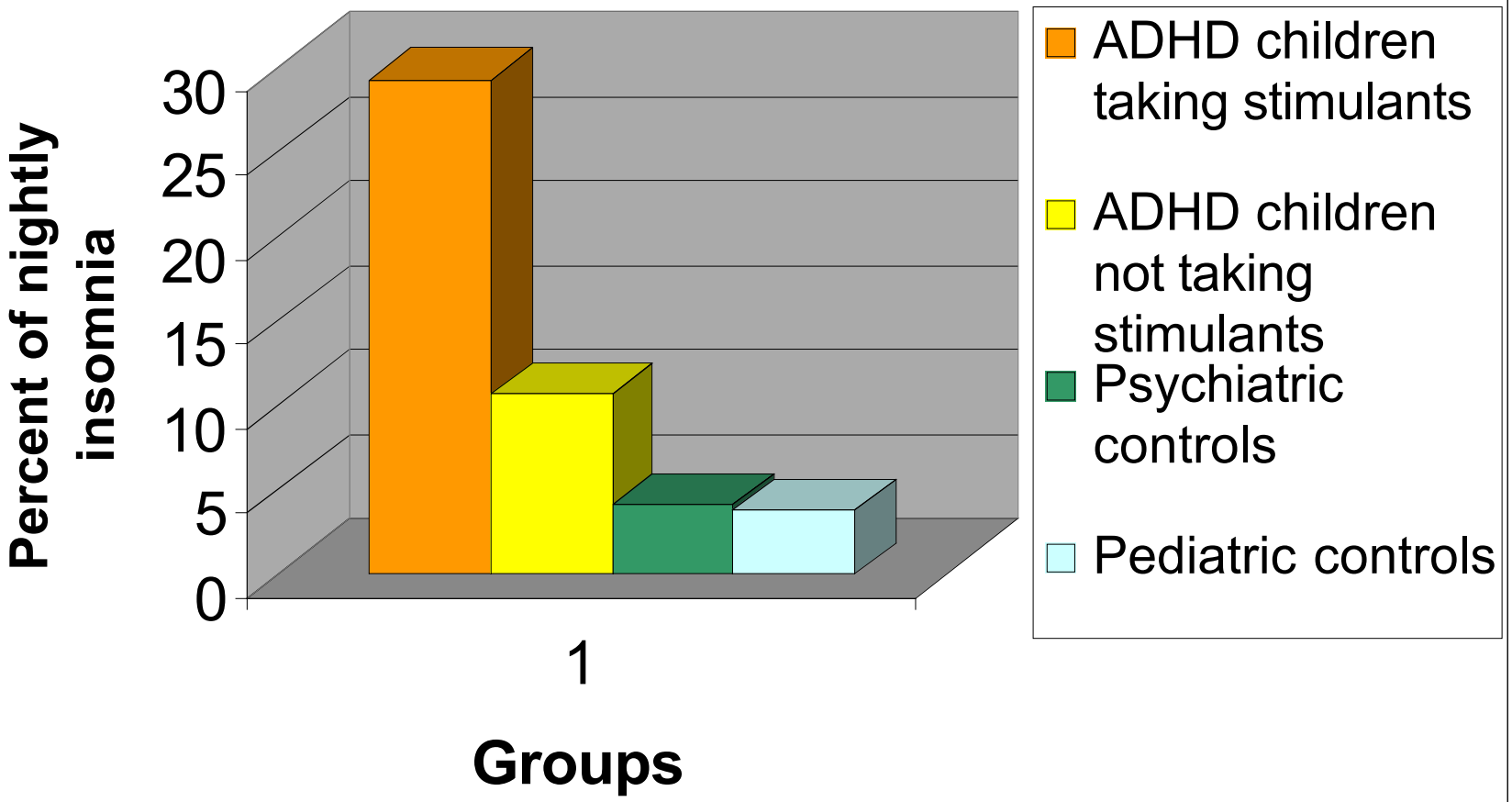
Sleep and Behavior Problems in School-Aged Children
Mark A. Stein, Janis Mendelsohn, William H. Obermeyer, Julie Amromin and Ruth Benca. *Pediatrics*. 2001

Multidirectiona, Mutually Exacerbating Conditions

- ADHD may cause sleep problems (chronic dysregulation hypothesis)
- Sleep problems may cause ADHD (Vigilance/ arousal hypothesis, OSA/SDB)
- Relationship may be artifactual (both caused by something else)
  - distress in general
  - bias in reporting (e.g., subjective/objective, parental depression)
  - Due to psychiatric comorbidity, especially anxiety/depression/ODD
  - Common disorders

Cortese S, Brown TE, Corkum P, et al. Assessment and management of sleep problems in youths with attention-deficit/hyperactivity disorder. *JAACAP.* 2013;52(8):784-796.

Comparisons of nightly insomnia according to parent report



Stein, 1999, J Child Adol. Psychopharm

ADHD Medication Treatments (2018)

Stimulants

Methylphenidate

Short Acting

Ritalin
Focalin*

Intermediate

Ritalin SR
Metadate ER
Journay (Delayed release)

Long Acting

Concerta
Metadate CD
Ritalin LA; **Focalin XR***
Daytrana (patch)
Aptensio XR;
Quillivant (liquid) Quillichew; Cotempla-XR-ODT

Amphetamine

Short Acting

Dextrostat†
Dexedrine tabs†

Intermediate

Dexedrine Spansule†
Adderall‡
Evekio ‡

Long Acting

Adderall XR‡
Lisdexamfetamine †
(tablets/chewable)
Adzenys XR-ODT ‡
Dyanavel (liquid) ‡
Mydayis ‡

*dexmethylphenidate
†dextroamphetamine sulfate
‡mixed amphetamine salts
¶atomoxetine

§tricyclic antidepressants
(many brands)
**modafinil
††bupropion
‡‡guanfacine
¶¶clonidine
§§venlafaxine

Non-Stimulant

Approved

Strattera¶
Viloxazine
Intuniv ‡‡
Kapvay¶

Not Approved

TCAs§
Provigil**
Wellbutrin, Zyban††
Tenex‡‡
Catapres¶¶
Effexor§§

Investigational

Dasotraline
Neurovance Drug
Mazindol
(Metadoxine)
(Vortioxetine)
(Edivoxetine)

Daytime Treatments

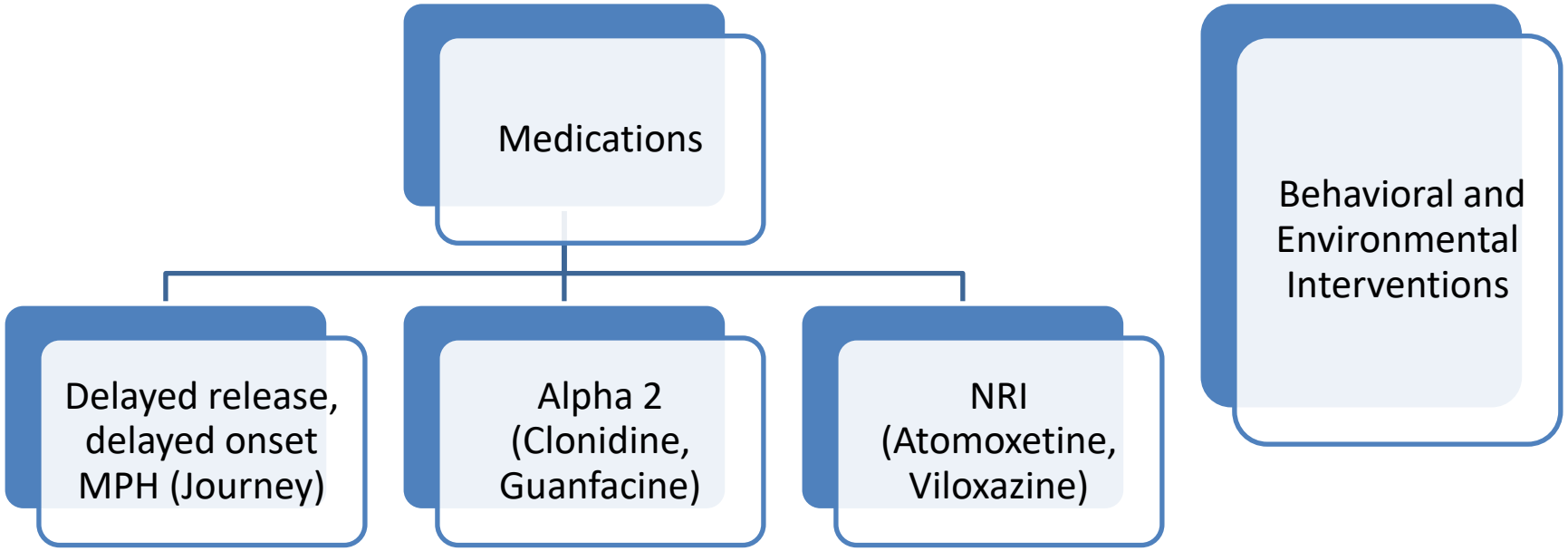
Medications

- Stimulants –IR, SR
- Atomoxetine
- Viloxazine
- Clonidine and Guanfacine

Environmental and Behavioral Interventions

- Parent, teacher, and peer delivered
- Summer Treatment Programs
- Physical activity, sleep (LEAP)

Interventions that can also be delivered at day or night



How do daytime administered medications effect ADHD and Sleep?

Dose, Formulation/Class, Timing of Administration

Effects of caffeine on sleep quality and daytime functioning

Frances O'Callaghan[1]
Olav Muurlink[2,3]
Natasha Reid[4]

[1]School of Applied Psychology, Griffith Health, Griffith University, Southport, QLD, Australia; [2]School of Business and Law, Central Queensland University, Brisbane, QLD, Australia; [3]Griffith Institute for Educational Research, Griffith University, Southport, QLD, Australia; [4]Child Health Research Centre, Faculty of Medicine, University of Queensland, Brisbane, QLD, Australia

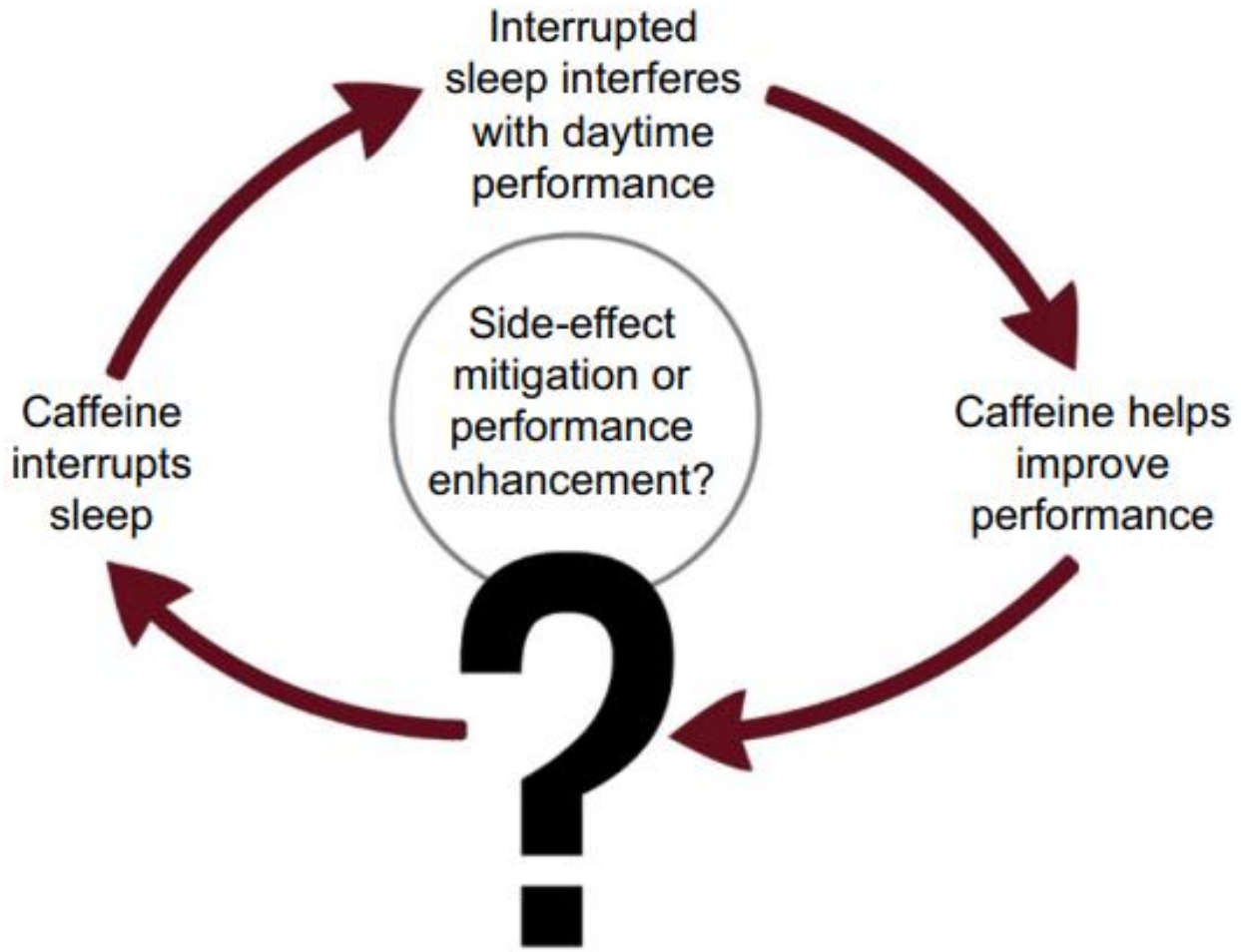


Figure 1 The cycle of benefits/disbenefits in caffeine consumption.

JCSM
Journal of Clinical Sleep Medicine

Caffeine Effects on Sleep Taken 0, 3, or 6 Hours before Going to Bed

Christopher Drake, Ph.D., F.A.A.S.M.[1,2]; Timothy Roehrs, Ph.D., F.A.A.S.M.[1,2]; John Shambroom, B.S.[3]; Thomas Roth, Ph.D.[1]

[1]Sleep Disorders & Research Center, Henry Ford Hospital, Detroit, MI; [2]Department of Psychiatry and Behavioral Neurosciences, Wayne State College of Medicine, Detroit, MI; [3]Zeo Inc, Newton, MA

Table 2—Means ± SD of sleep diary-based measures for each condition

Sleep Measure	Placebo	Caffeine at bedtime	Caffeine 3 hours before bed	Caffeine 6 hours before bed	F (3,33)	p
Latency to sleep (min)	21.00 ± 8.99	56.67 ± 74.23	62.50 ± 66.18*	44.17 ± 44.56^	3.06	0.04
Total sleep time (h)	7.82 ± 0.54	6.92 ± 1.10*	6.77 ± 0.95*	7.13 ± 0.93^	4.14	0.01
Wake time during sleep (min)	11.00 ± 11.24	9.18 ± 9.41	17.67 ± 33.99	9.27 ± 14.01	0.71	0.55
Sleep efficiency %	93.60 ± 3.47	86.43 ± 13.87	83.98 ± 12.68	89.05 ± 9.22	2.65	0.07
Sleep quality	6.20 ± 2.04	5.83 ± 2.33	5.17 ± 1.53	5.67 ± 2.19	0.63	0.60

Follow-up pairwise compairsons, where omnibus F-values are significant : *p < 0.05 vs. placebo, ^p < 0.10.

Time effect, less effect at 6 hours vs bedtime or 3 hours
Marked individual variability

Table 3—Objective sleep measures for each condition (mean ± SD)

Sleep Measure	Placebo	Caffeine at bedtime	Caffeine 3 hours before bed	Caffeine 6 hours before bed	F (3,33)	P
Latency to persistent sleep (min)	20.59 ± 9.79	43.0 ± 38.93	37.82 ± 29.91	44.68 ± 54.60	2.05	0.13
Total sleep time (h)	7.68 ± 0.85	6.60 ± 1.10*	6.54 ± 1.36*	6.50 ± 1.32*	3.43	0.03
Wake time during sleep (min)	9.55 ± 14.73	27.04 ± 40.06	37.18 ± 43.0*	17.59 ± 22.28*	3.29	0.03
Sleep efficiency %	91 ± 5.71	83.1 ± 12.11*	82.51 ± 12.73*	82.33 ± 12.15*	7.50	0.058#
Stage 1 & 2 (min)	266.77 ± 40.15	226.17 ± 57.75*	222.68 ± 62.24*	222.82 ± 48.83*	3.66	0.02
Stage 1 & 2 (%)	58.02 ± 7.37	56.47 ± 7.77	56.77 ± 10.48	57.28 ± 6.26	0.22	0.88
Slow wave sleep (min)	71.45 ± 26.48	56.67 ± 21.48*	57.0 ± 16.78	48.91 ± 15.81*	4.26	0.01
Slow wave sleep (%)	15.47 ± 5.28	14.47 ± 4.85	14.84 ± 3.87	12.71 ± 3.88	1.22	0.32
REM (min)	123.27 ± 33.89	114.36 28.53	112.5 ± 46.57	118.73 ± 39.75	0.30	0.83
REM (%)	26.62 ± 6.35	29.21 ± 7.19	28.39 ± 11.25	29.99 ± 6.54	0.88	0.46

*$p < 0.05$ pairwise comparisons vs. placebo; #Nonparametric related samples test of Friedman two-way analysis of variance by ranks was performed as data was not normally disturbed following transformation.

CAFFEINE IN ENERGY DRINKS

INCLUDING CALORIES & SUGAR CONTENT

cheatdaydesign.com

3D
200mg Caffeine
15 Calories
7g Carbs
0g Sugar

5 HOUR ENERGY SHOT
200mg Caffeine
4 Calories
1g Carbs
0g Sugar

ALANI NU
200mg Caffeine
10 Calories
6g Carbs
0g Sugar

BANG
300mg Caffeine
0 Calories
0g Carbs
0g Sugar

BEYOND RAW LIT
250mg Caffeine
20 Calories
4g Carbs
0g Sugar

C4 ENERGY
200mg Caffeine
0 Calories
0g Carbs
0g Sugar

CELSIUS
200mg Caffeine
10 Calories
2g Carbs
0g Sugar

GHOST
200mg Caffeine
5 Calories
1g Carbs
0g Sugar

MTN DEW RISE
180mg Caffeine
25 Calories
5g Carbs
3g Sugar

MONSTER
160mg Caffeine
230 Calories
58g Carbs
54g Sugar

MONSTER ZERO SUGAR
140mg Caffeine
10 Calories
3g Carbs
0g Sugar

NOCCO
180mg Caffeine
12 Calories
0g Carbs
0g Sugar

NOS
160mg Caffeine
200 Calories
54g Carbs
54g Sugar

REIGN
300mg Caffeine
10 Calories
3g Carbs
0g Sugar

RED BULL
80mg Caffeine
110 Calories
29g Carbs
27g Sugar

RED BULL SUGARFREE
80mg Caffeine
10 Calories
2g Carbs
0g Sugar

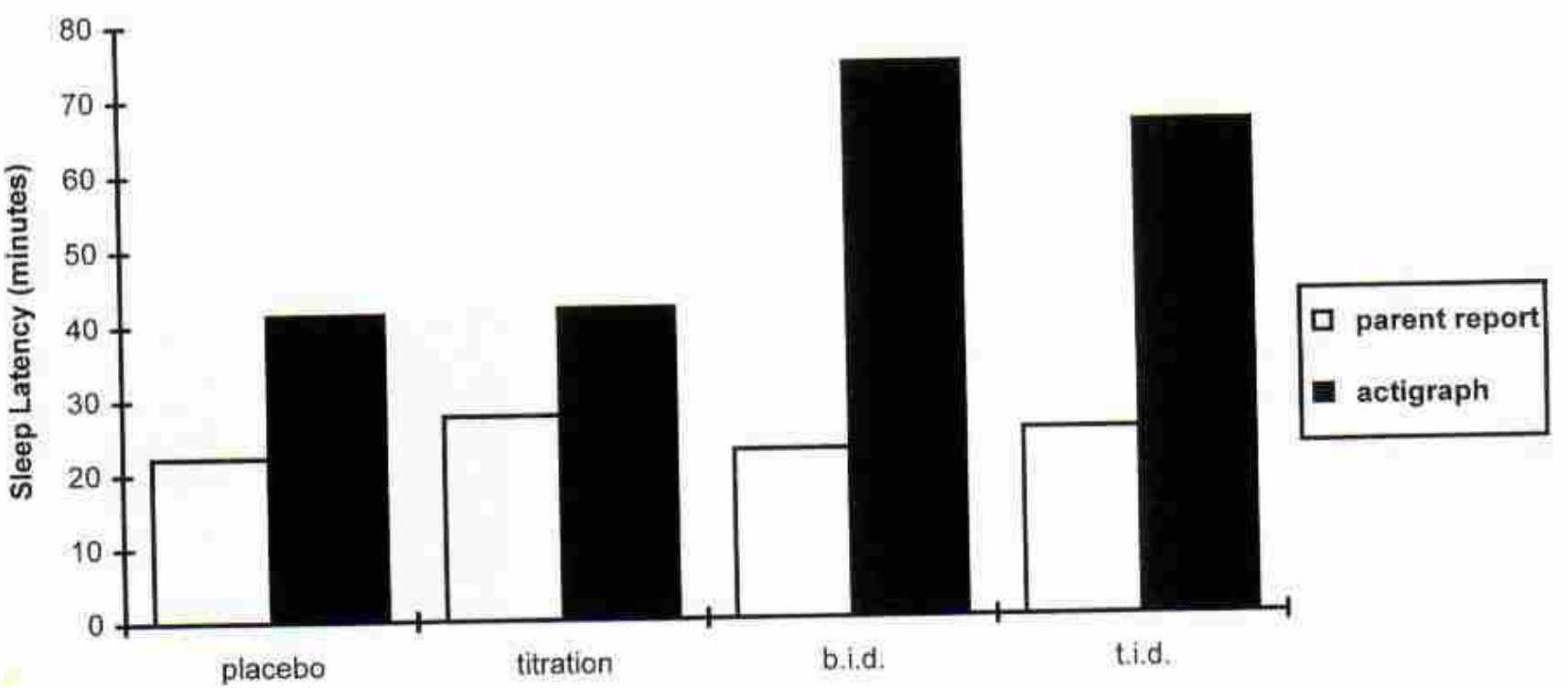
ROCKSTAR
160mg Caffeine
250 Calories
63g Carbs
63g Sugar

ROCKSTAR SUGAR-FREE
160mg Caffeine
25 Calories
1g Carbs
0g Sugar

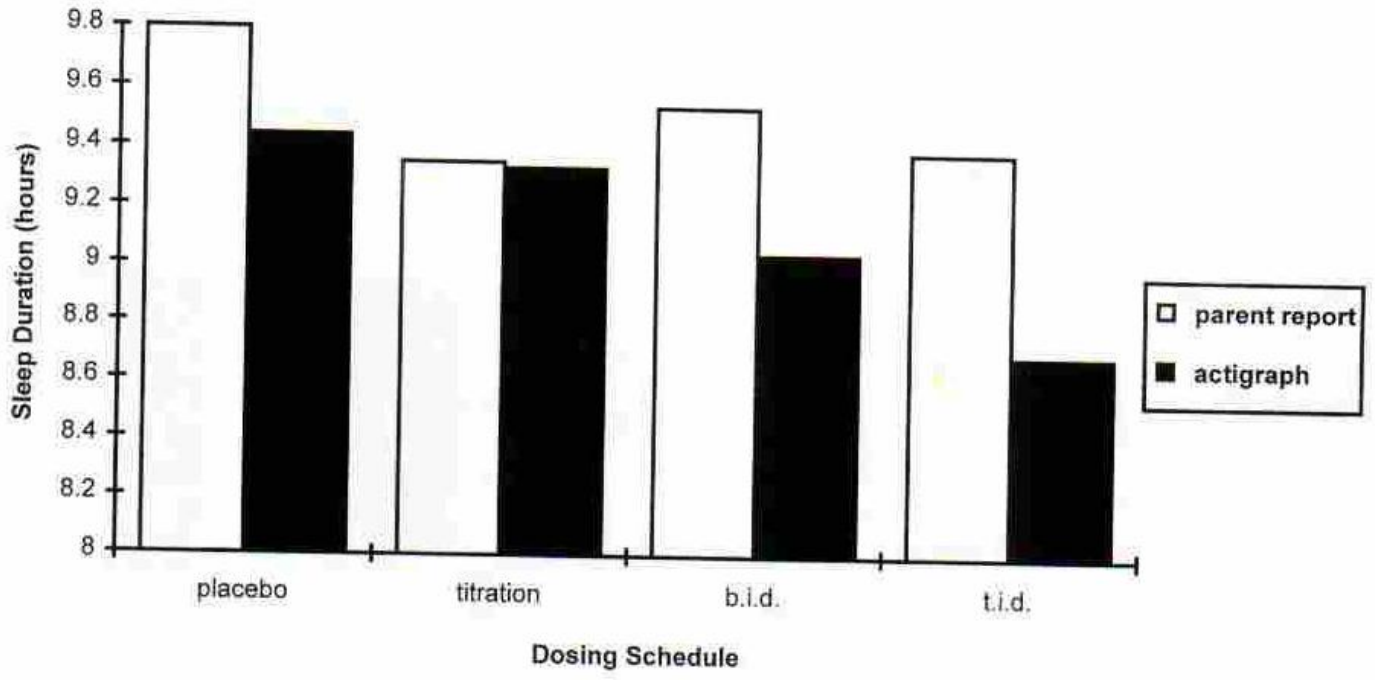
ZEVIA
120mg Caffeine
0 Calories
0g Carbs
0g Sugar

ZOA
160mg Caffeine
15 Calories
3g Carbs
0g Sugar

Sleep Onset Latency by Dose (Subjective and Objective) n = 25 (Stein et al, Pediatrics 1995)

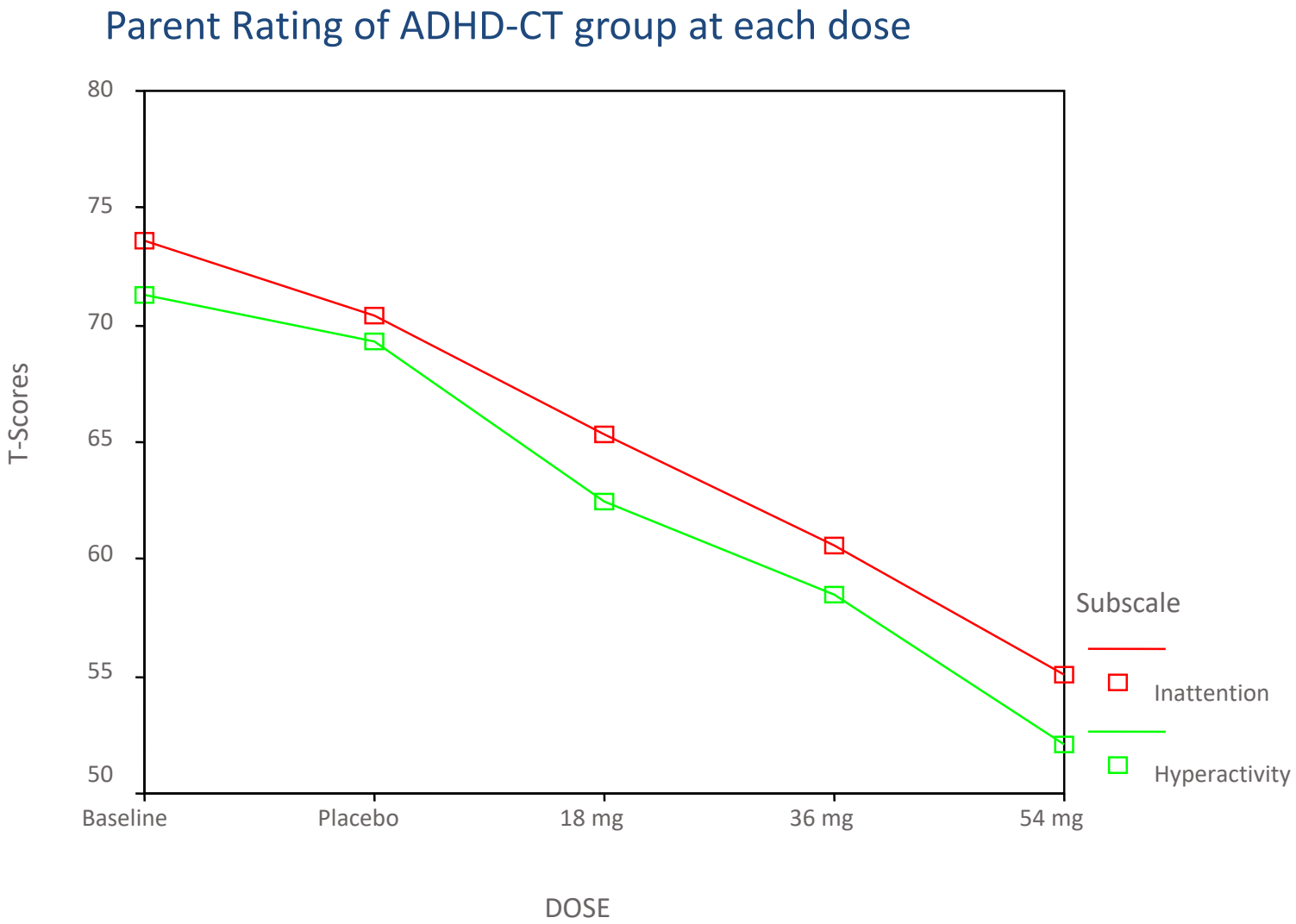


Sleep Duration (Subjective and Objective) and Dosing Schedule

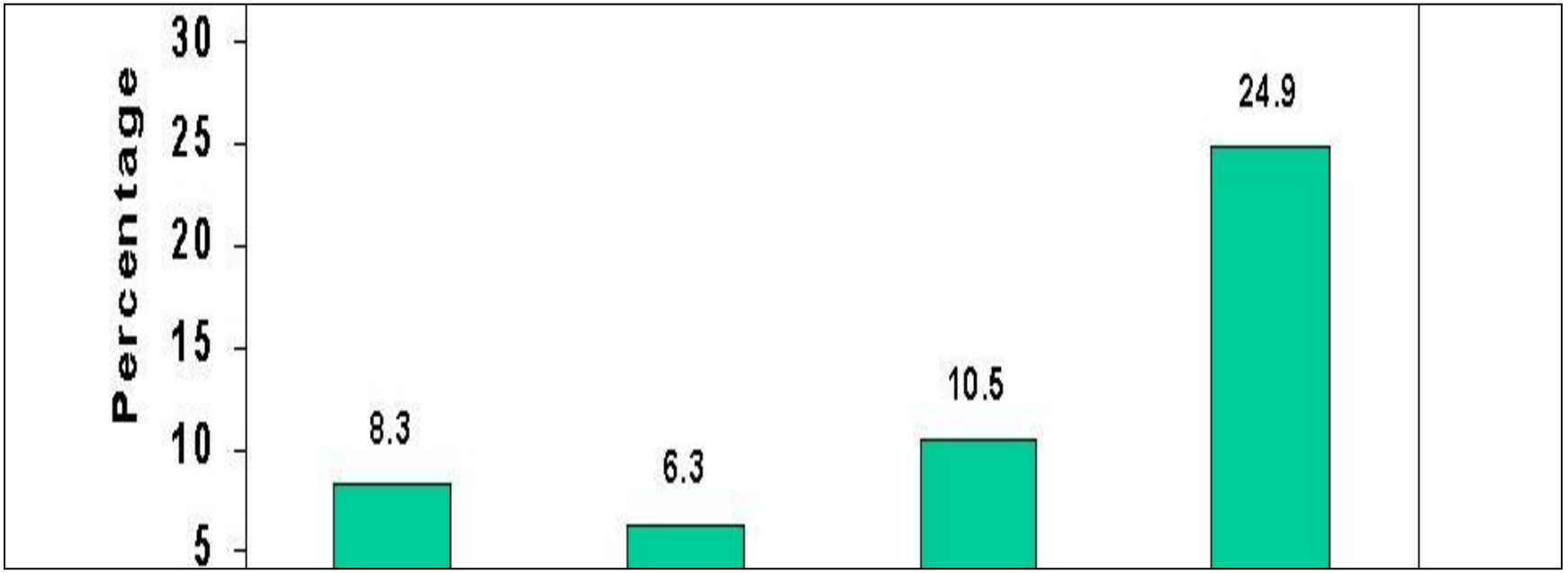


Linear Dose Response Effect for ADHD Symptoms

(Stein et al., *Pediatrics*, 2003)



Dose Effects of OROS MPH on Insomnia (*K-24, Primary Care a Lab for Basic and Clinical Research in ADHD*)



Stein et al., Pediatrics, 2004

ER MAS vs. ER D-MPH

ADHD-RS Score by Drug (JCAP, 2011)

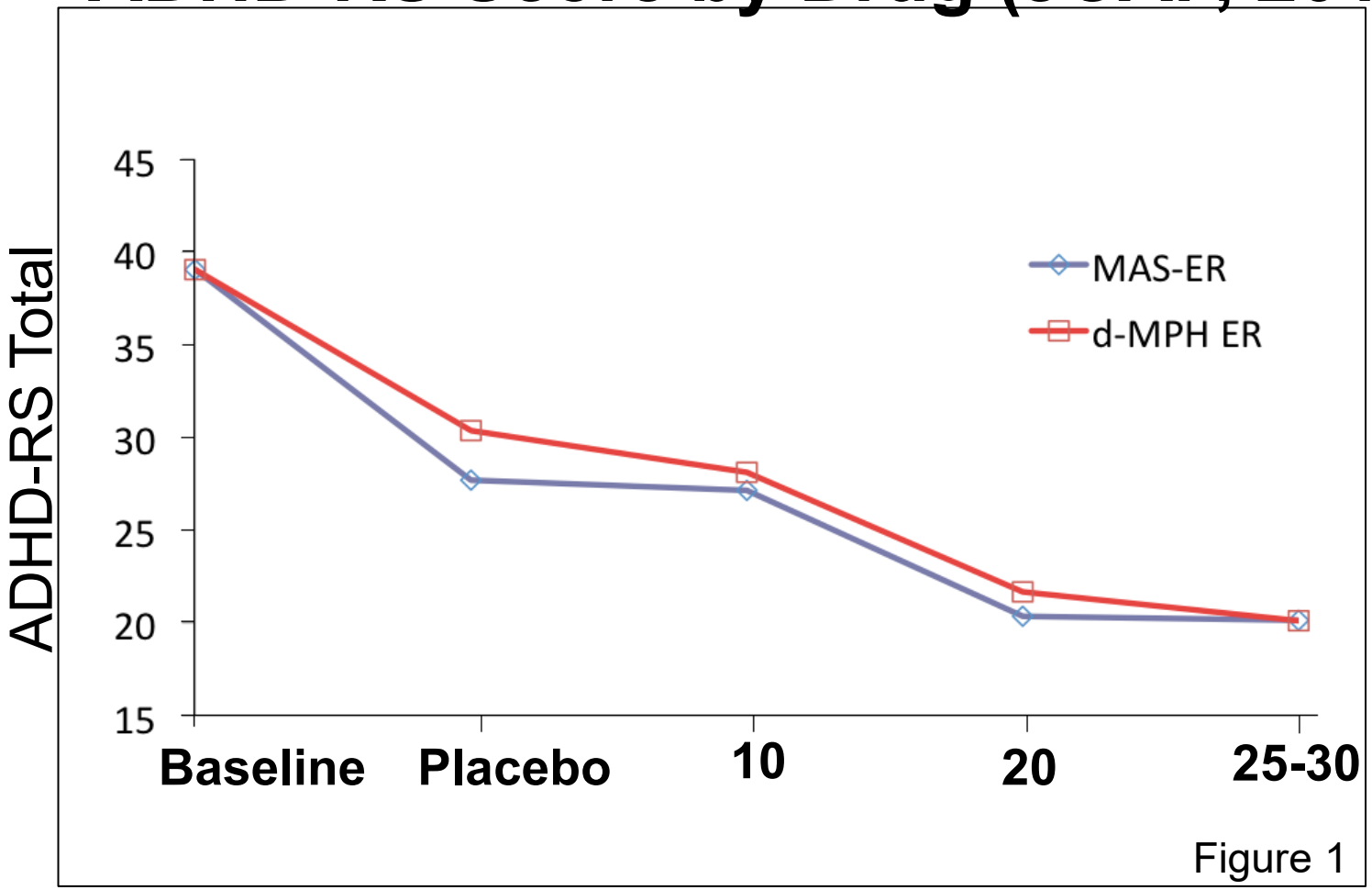
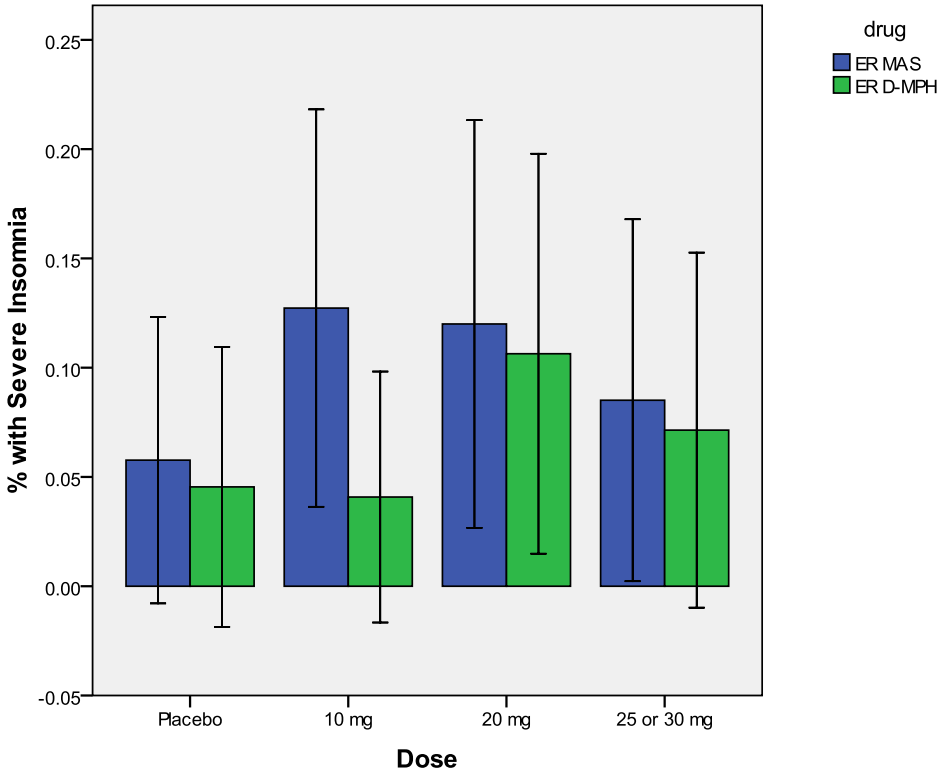
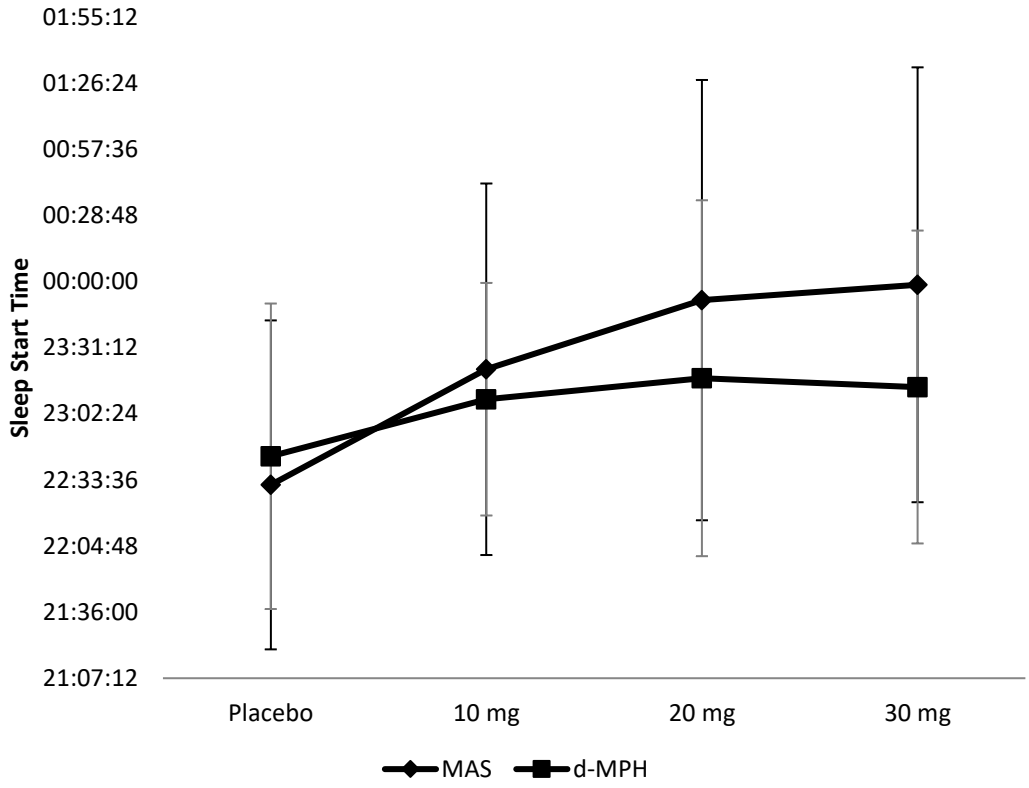


Figure 1

Dose Response Effects on Severe Insomnia by Type of Stimulant (n = 56) (Stein et al. 2013, Child and Adolescent Psychopharmacology)

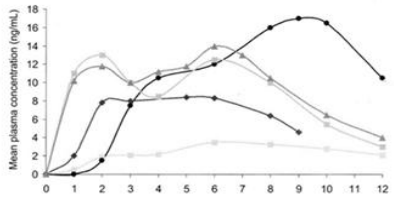


Sleep Schedule: Sleep start time for MAS and d-MPH at all dosages. Mean sleep start time occurs later with higher dosages for both medications. There are significant differences in mean sleep start time during placebo compared to 20mg and 30mg treatment ($p < 0.05$).



- Effect of Extended-Release Dexmethylphenidate and Mixed Amphetamine Salts on Sleep: A
- Double-Blind, Randomized, Crossover Study in Youth with Attention-Deficit Hyperactivity Disorder J. A. Santisteban • M. A. Stein • L. Bergmame • R. Gruber (2014), CNS Drugs

Long-acting Methylphenidate Dosage Forms



*These products differ only in their release profile of the same drug, racemic methylphenidate over time.

Clinical Questions:

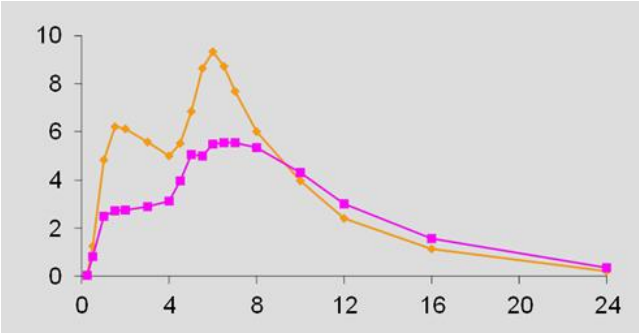
*Which dosage form for which patient?

Is their significant variability between patients?

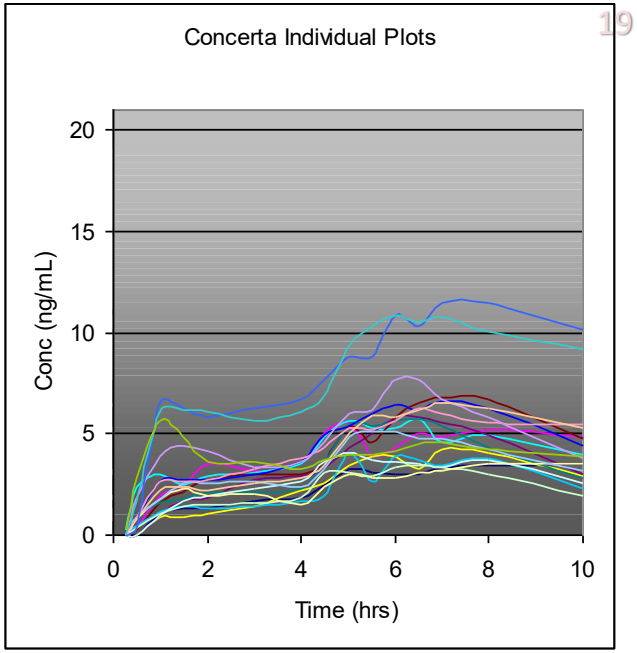
Product	Delivery Mechanism	Dosing Frequency	Duration of Effect (hrs)	Dosage Strengths	Sprinkle/ Dividing
Ritalin®	Immediate-release (IR)	3 times daily	3-4	5, 10, 20mg	Can split/crush
Ritalin SR®	Tablet / matrix	Once Daily	8	20mg	No
Metadate ER®	Tablet / wax matrix	Once Daily	8-12	20mg	No
Methylin ER®	Tablet, dissolution polymer ER	Once Daily	8	10, 20mg	No
Quillichew ER™	Chewable tablet delivering 30% IR MPH and 70% ER MPH	Once Daily	8-12	20, 30, 40mg	No
Concerta®	Non-deformable tablet, osmotic release, OROS™	Once daily	10-12	18, 27, 36, 54mg	No
Ritalin LA®	Capsule, biphasic beaded delivery, 50% IR, 50% ER	Once Daily	8	10, 20, 30, 40, 60mg	Can be sprinkled
Metadate CD®	Capsule, beaded delivery with 30% IR, 70% ER	Once Daily	8	10, 20, 30, 40 50, 60mg	Can be sprinkled
Daytrana®	Transdermal Patch	Once Daily	10-12	10, 15, 20 30mg	No
Quillivant XR®	Suspension, reconstituted powder contains 20% IR and 80% ER	Once Daily	8, 10, 12	10 mg/2ml, 20 mg/4ml 30 mg/6ml, 40 mg/8 ml 50 mg/10 ml, 60 mg/12ml	No
Adhansia XR™	Capsule, multilayer release beads, 20% IR and 80% ER	Once Daily	12+	25, 35, 45, 55 70, 85mg	Can be sprinkled
Aptensio XR™	Capsule, outer IR layer 40% and inner CR layer providing 60% ER	Once Daily	7-8	10, 15, 20, 30, 40, 50, 60mg	Can be sprinkled
Cotempla™XR-ODT	Orally disintegrating tablet, contains 25% IR MPH and 75% ER MPH	Once Daily	8-12	8.6, 17.3, 25.9mg	No
Jornay PM™	Capsule, microbeads with outer delayed-release layer, inner ER layer, surrounding an IR core	Once in evening	12+	20, 40, 60, 80, 100mg	Can be sprinkled
Focalin XR®	Capsule, biphasic beaded delivery, 50% IR, 50% ER	Once daily	12	5, 10, 15, 20, 25, 30, 35, and 40 mg	Can be sprinkled

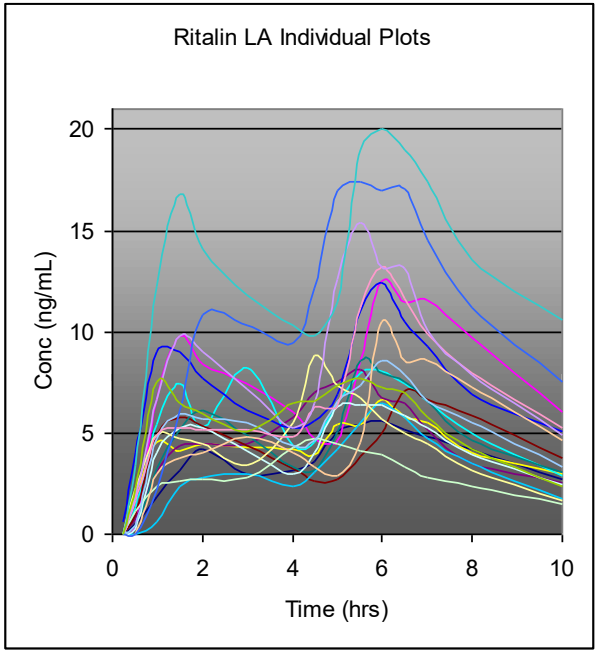
Courtesy J. Markowitz

Variable PK



N= 19





Nonstimulants vs. Stimulants: Effects on Sleep

Effects of Atomoxetine and Methylphenidate on Sleep in Children With ADHD

R. Bart Sangal, MD[1]; Judith Owens, MD[2]; Albert J. Allen, MD[3]; Virginia Sutton, PhD[3]; Kory Schuh, PhD[3]; Douglas Kelsey, MD[3]

[1]Clinical Neurophysiology Services, PC, Troy, MI; [2]Child and Family Psychiatry, Rhode Island Hospital, Providence, RI; [3]Lilly Research Laboratories, Indianapolis, IN

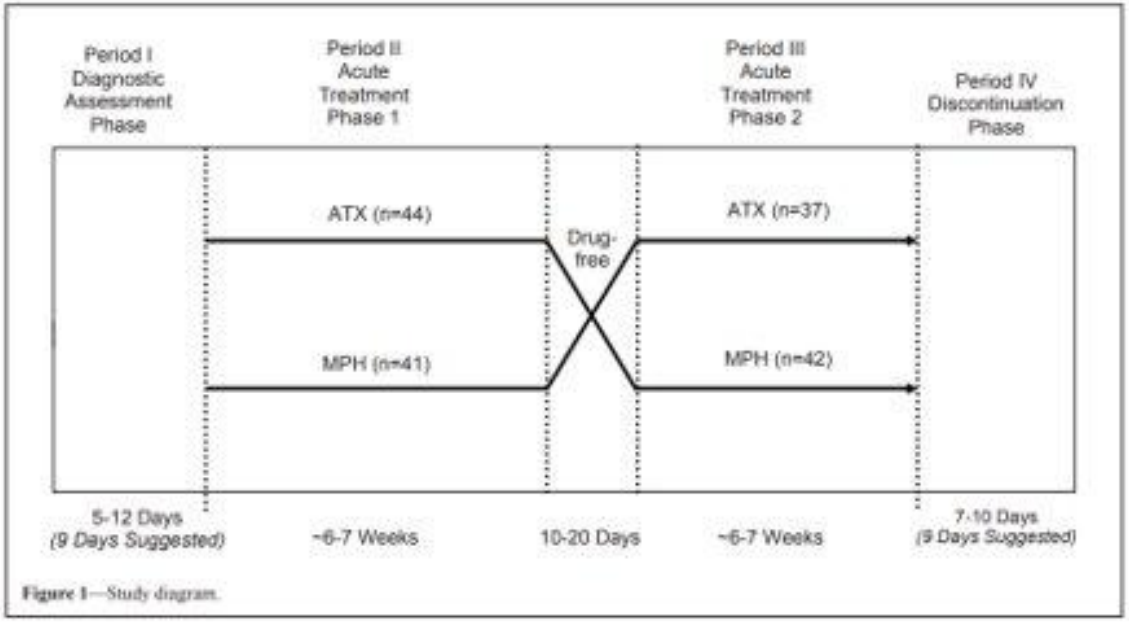


Figure 1—Study diagram.

Table 1—Atomoxetine and Methylphenidate Dosing Schedules[a]

	Atomoxetine Doses divided and given twice daily with placebo given as the noontime dose	Methylphenidate Doses divided into thirds and given thrice daily
Visit 3	0.5 then increased to 0.8	0.45
Visit 4	1.0	0.9
Visit 5	1.5	1.35
Visit 6	Can be decreased to 1.0 for patients with tolerability problems or increased to 1.8 for patients with residual ADHD symptoms with an absolute upper limit of 120 mg/day	Can be decreased to 0.9 for patients with tolerability problems or increased to 1.8 for patients with residual ADHD symptoms with an absolute upper limit of 60 mg/day

[a]All doses are in mg/kg per day. ADHD refers to attention-deficit/hyperactivity disorder.

Similar efficacy on ADHD RS, Better Evenings

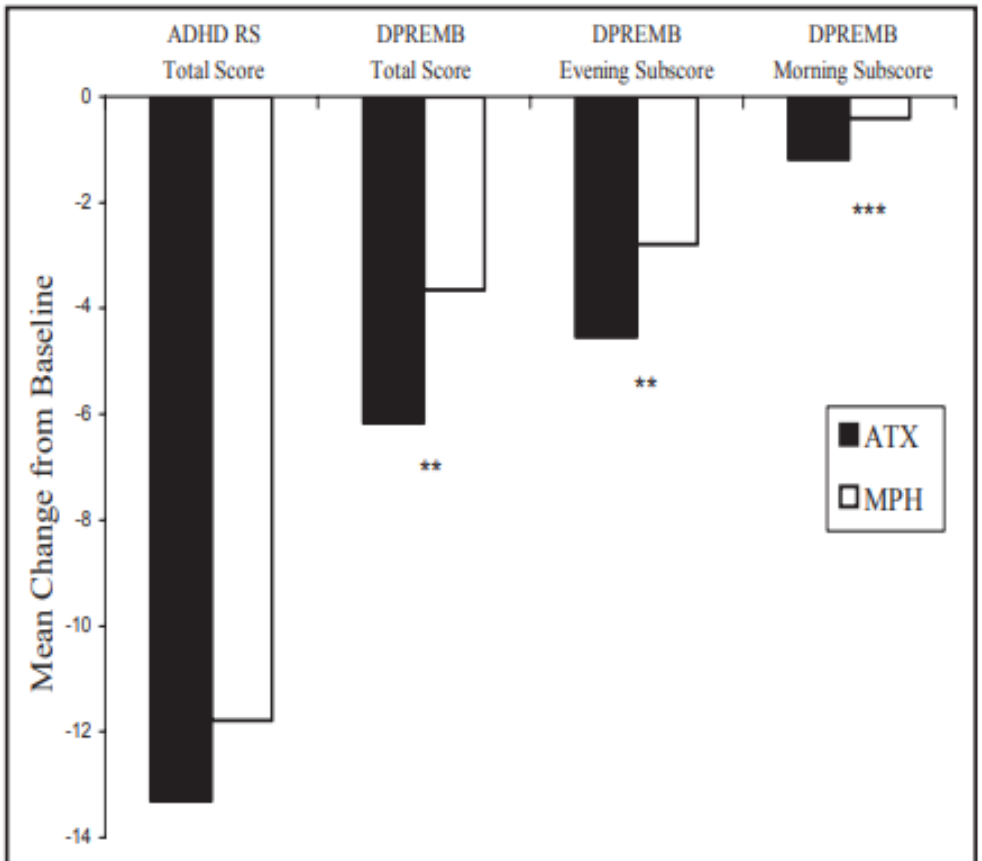


Figure 4—Effects of atomoxetine (ATX) and methylphenidate (MPH) on mean change from baseline scores from the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored (ADHD RS) Total score, and from the Daily Parent Ratings of Evening and Morning Behavior (DPREMB) Total score and subscores. The numbers for ATX and MPH, respectively, are 41 and 34 for the ADHD RS Total score, 21 and 13 for the DPREMB Total score, 28 and 17 for the DPREMB evening subscore, and 34 and 23 for the DPREMB morning subscore. ** = $p < .01$, *** = $p < .001$

12.5 SOL increase with ATX: 69 min SOL with MPH , double variability. 30 minutes less total sleep on MPH,

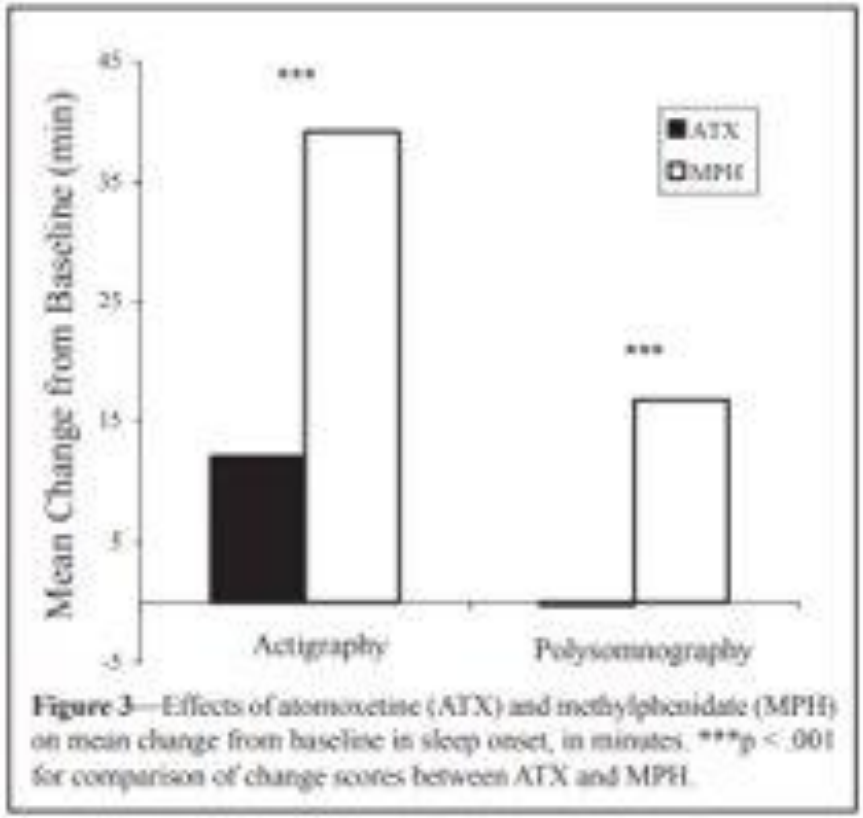


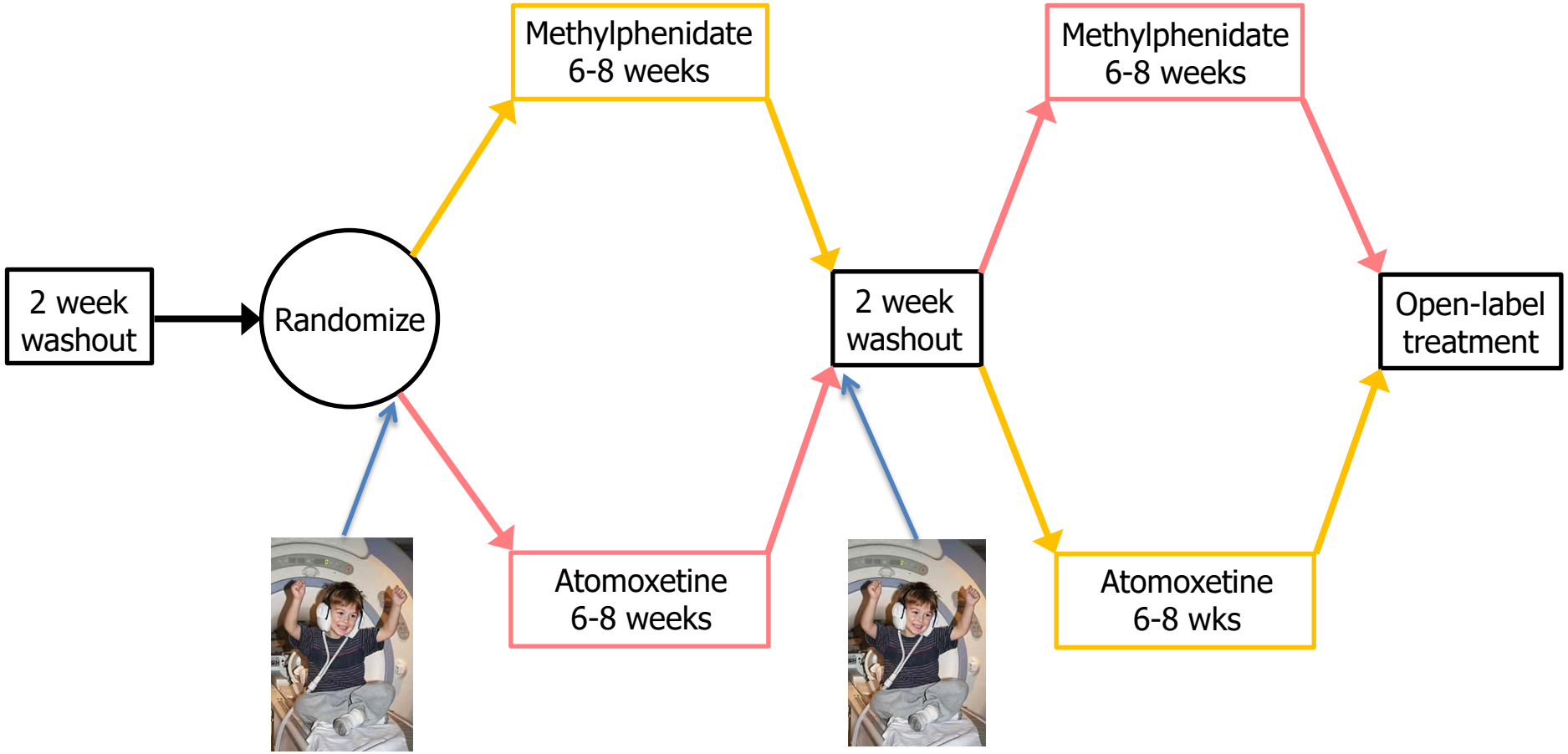
Figure 3—Effects of atomoxetine (ATX) and methylphenidate (MPH) on mean change from baseline in sleep onset, in minutes. ***p < .001 for comparison of change scores between ATX and MPH.

Table 3—Actigraphic Sleep Measures During Atomoxetine and Methylphenidate Treatment[a]

Sleep Measure	Baseline	Atomoxetine		Methylphenidate		Atomoxetine vs Methylphenidate		
		Endpoint	Change	Endpoint	Change	p Value	Effect Size	95% CI
Sleep-onset latency, min	30.11 ± 24.84	42.17 ± 31.61	12.06 ± 27.07	69.35 ± 43.86	39.24 ± 40.77	< .001[b]	-.79	-12.82, -6.49
Total nap time, min	3.47 ± 5.32	7.97 ± 10.11	4.49 ± 10.41	6.51 ± 7.30	3.04 ± 7.92	.475	.16	-1.68, 3.55
Total sleep interval, min	518.82 ± 44.13	503.82 ± 50.97	-15.00 ± 45.10	482.93 ± 62.64	-35.89 ± 56.10	.004[b]	.41	6.81, 34.15
Assumed sleep time, min	457.41 ± 47.34	442.14 ± 50.63	-15.26 ± 44.25	427.80 ± 57.20	-29.61 ± 53.00	.016	.29	2.73, 25.73
Interrupted sleep time, min	61.41 ± 20.85	61.67 ± 20.00	0.26 ± 15.04	55.13 ± 20.61	-6.28 ± 17.48	.025	.40	0.80, 11.69
Sleep interruptions, no.	31.78 ± 7.79	30.47 ± 10.42	-1.31 ± 6.83	27.42 ± 9.62	-4.36 ± 6.33	.011	.46	0.70, 5.19

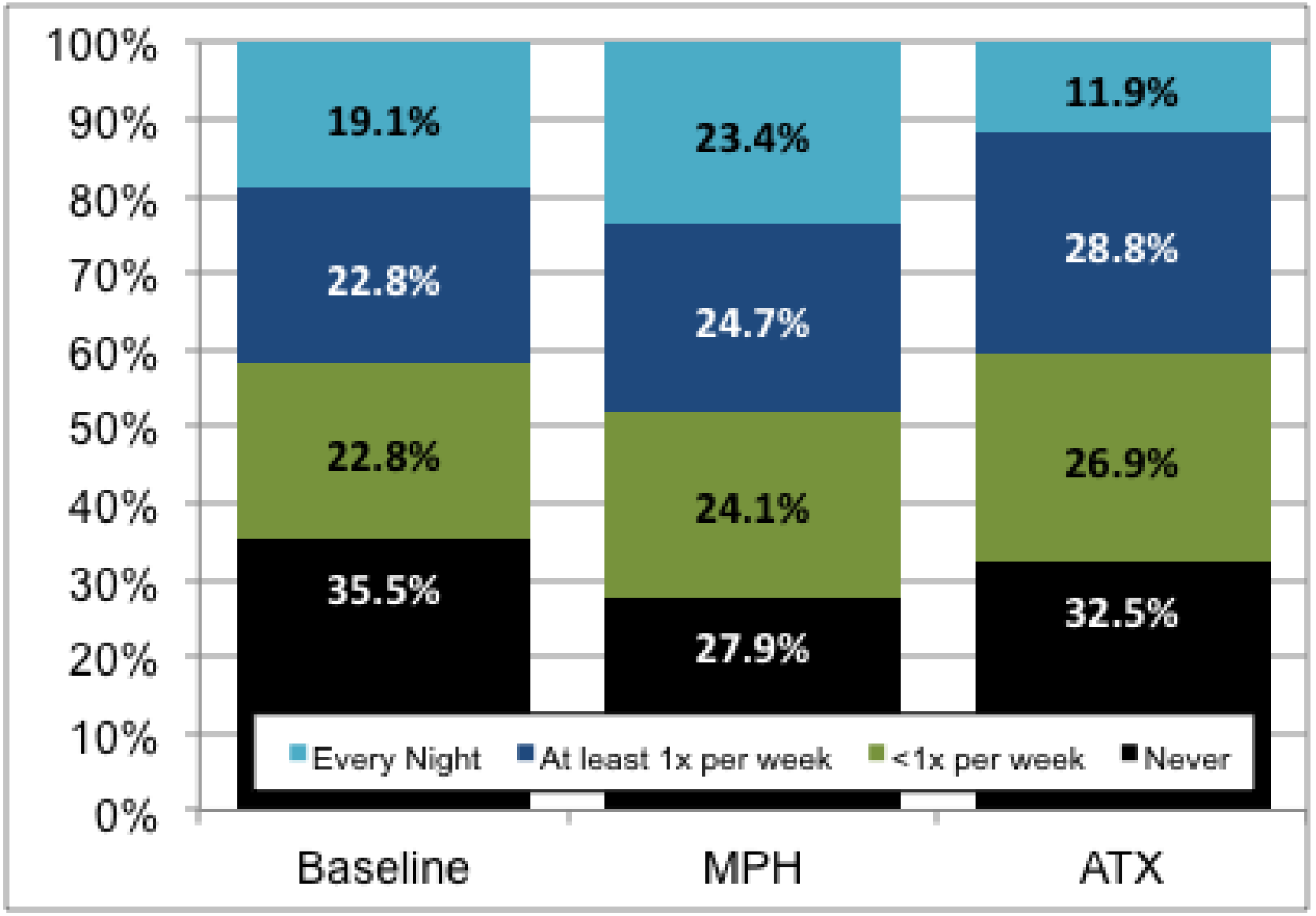
[a]Data are from 50 subjects, except sleep interruptions, which were from 48 subjects both effect sizes; 95% confidence intervals computed based on methylphenidate subtracted from atomoxetine. Baseline, endpoint, and change data are presented as mean ± SD. CI refers to confidence interval.
[b]p Value remained significant after a Bonferroni adjustment for multiple comparisons.

Mechanisms of Action and Predictors of Response to Methylphenidate (Stimulant) and Atomoxetine (Non-Stimulant) Medications



The MACRO Study (PI's: Newcorn, Stein)

Frequency of Sleep Onset Latency >30 min



Delayed Release, Delayed Onset MPH (HLD200-107; NCT02493777

- 125 children aged 6 to 12 years with ADHD
- 45% of the subjects had preexisting sleep disturbances
- mean Jornay-PM dose in study 1 was 66.2mg
- insomnia was reported in 8% of participants who received JORNAY PM and 9% of those who received placebo during the one-week double-blind phase.
- During the open-label phase, most insomnia treatment-emergent adverse events (TEAEs) were mild or moderate in severity
- 7 participants experienced severe insomnia.
- Sleep related events resolved within 11 days and 90% resolved without dose adjustments.
- None of the participants in the open-label or double-blind phases withdrew from the study due to insomnia.

From: **α_2-Adrenergic Agonists or Stimulants for Preschool-Age Children With Attention-Deficit/Hyperactivity Disorder**

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Table 4. Adverse Effects in a Study of α_2-Adrenergic Agonists vs Stimulants for Preschool-Age Children With Attention-Deficit/Hyperactivity Disorder

Adverse effect[a]	No. (%) [95% CI]	
	α_2-Adrenergic agonist (n = 175)	Stimulants (n = 321)[b]
Daytime sleepiness	66 (38) [30-45]	9 (3) [1-5]
Moodiness/irritability	50 (29) [21-36]	161 (50) [43-57]
Disruptive behavior	49 (28) [19-37]	72 (22) [16-29]
Difficulty with sleep	19 (11) [6-15]	67 (21) [17-25]
Headaches	16 (9) [5-13]	16 (5) [3-7]
Appetite suppression	13 (7) [3-12]	123 (38) [33-44]
Stomachaches	8 (5) [1-8]	42 (13) [9-17]
Skin picking or other repetitive behaviors	8 (5) [1-8]	36 (11) [7-15]

[a] The data abstraction form listed many known adverse effects and an "other" category, and the presence or absence of each was abstracted from the medical records.

[b] One child who was treated with stimulant medication (methylphenidate) did not have the clinician identification number available and thus was excluded from these results because the 95% CIs provided were adjusted for clustering by clinician.

Randomized, Double-Blind Trial of Guanfacine Extended Release in Children With Attention-Deficit/Hyperactivity Disorder: Morning or Evening Administration

Jeffrey H. Newcorn, M.D., Mark A. Stein, Ph.D., Ann C. Childress, M.D., Sharon Youcha, M.D., Carla White, B.Sc., C.Stat., Gail Enright, M.Ed., Jonathan Rubin, M.D., M.B.A.

Objective: To examine the efficacy and tolerability of guanfacine extended release (GXR) administered in the morning or evening in children with attention-deficit/hyperactivity disorder (ADHD). **Method:** In this multicenter, double-blind, placebo-controlled, dose-optimization study, children 6 to 12 years of age with ADHD were randomized to receive GXR (1–4 mg/d) in the morning and placebo in the evening (GXR AM), placebo in the morning and GXR in the evening (GXR PM), or twice-daily placebo. The primary efficacy measure was the ADHD Rating Scale–IV (ADHD-RS-IV). **Results:** A total of 333 child participants received study drug in the following cohorts: GXR AM (n = 107), GXR PM (n = 114), or placebo (n = 112). Mean (standard deviation) changes from baseline to week 8 (visit 10 or last observation carried forward) in ADHD-RS-IV total scores were significant for both GXR treatment groups combined (GXR all-active: –20.0 [12.97]) and separately (GXR AM: –19.8 [12.95]; GXR PM: –20.1 [13.04]) compared with placebo (–11.0 [12.93]; $p < .001$ for all). Most spontaneously-elicited treatment-emergent adverse events were mild or moderate in severity; the most common was somnolence (GXR all-active: 44.3%; GXR AM: 46.7%; GXR PM: 42.1%; placebo: 12.5%). **Conclusions:** GXR administered either in the morning or evening was associated with significant and clinically meaningful improvements in ADHD symptoms. The levels of response and tolerability observed with GXR were similar regardless of time of dosing (morning versus evening), indicating that once-daily GXR monotherapy is effective whether

Table 2. Treatment-Emergent Adverse Events Occurring in ≥5% of Subjects

Adverse event, n (%) of subjects	All-Active (n= 221)	GXR AM (n= 107)	GXR PM (n= 114)	Placebo (n= 112)
Somnolence	98 (44.3)	50 (46.7)	48 (42.1)	14 (12.5)
Headache	37 (16.7)	19 (17.8)	18 (15.8)	12 (10.7)
Sedation	32 (14.5)	15 (14.0)	17 (14.9)	3 (2.7)
Abdominal pain upper	27 (12.2)	7 (6.5)	20 (17.5)	8 (7.1)
Fatigue	24 (10.9)	11 (10.3)	13 (11.4)	3 (2.7)
Irritability	16 (7.2)	8 (7.5)	8 (7.0)	3 (2.7)
Nausea	12 (5.4)	6 (5.6)	6 (5.3)	1 (0.9)
Upper respiratory tract infection	12 (5.4)	8 (7.5)	4 (3.5)	11 (9.8)
Diarrhea	11 (5.0)	4 (3.7)	7 (6.1)	4 (3.6)
Dizziness	11 (5.0)	6 (5.6)	5 (4.4)	3 (2.7)
Vomiting	11 (5.0)	7 (6.5)	4 (3.5)	2 (1.8)
Insomnia	9 (4.1)	6 (5.6)	3 (2.6)	4 (3.6)
Decreased appetite	9 (4.1)	6 (5.6)	3 (2.6)	3 (2.7)
Enuresis	7 (3.2)	1 (0.9)	6 (5.3)	1 (0.9)
Increased appetite	2 (0.9)	0	2 (1.8)	6 (5.4)

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Take Aways

- 6-10% ADHD youth have sleep onset difficulties/insomnia at baseline
- In short term, stimulants are associated with increased SOL, difficulty waking up in the morning.
- Marked individual variability in sensitivity: *both* insomnia and improvement in sleep are possible outcomes.
- Alpha 2's are associated with tiredness, fatigue, lethargy during the day
  - if given at night can promote sleep
- Atomoxetine, Viloxazine are not associated , on average, not associated with increased sleep onset latency
- Effects of ADHD medications on sleep and daytime tiredness tend to occur when initiating medication trial, during escalating dose titration, or with multiple doses used to extend the stimulant duration of action
- Chronic sleep deprivation can also occur, and night-to-night variability (e.g, medication on school days) can adversely affect circadian rhythms, especially in adolescents.

Assessment

- Screening
  - Ask every ADHD visit about sleep onset latency, snoring, restless legs, daytime sleepiness.
- Tools
  - Sleep diary (2 weeks), actigraphy when helpful; consider rating scales (e.g., BEARS).
- When to order PSG
  - Suspected OSA, parasomnias with injury risk, unclear PLMD/RLS, treatment-resistant cases.
- Medical contributors
  - Check concurrent meds, caffeine, iron status (ferritin), allergies/asthma, anxiety/depression, ASD.

Recommended strategies for sleep problems in children with ADHD and medication

1.Obtain thorough sleep history and rule out a primary sleep disorder
2.Treat primary sleep disorder if present (restless legs syndrome, obstructive sleep apnea (ENT eval, CPAP/adenotonsillectomy),)
3.Monitor sleep with sleep diaries or actigraphy at baseline and throughout medication trial
4.Encourage sleep hygiene
5.If sleep-onset latency problems, insomnia, difficulty waking up, or daytime sleepiness persists, consider reducing the dose/timing of stimulants and observe
6.Consider adding melatonin, switching formulations, or combining or switching to a nonstimulant
7.Behavioral sleep interventions at any time

Treatment: Pharmacologic Pearls

- Melatonin
  - Start low (e.g., 1–3 mg, 30–60 min before desired bedtime; adolescents/adults 1–5 mg). Time earlier (3–5 h before DLMO) for phase advance in DSWPD.
- Iron for RLS/PLMD
  - If ferritin is low/low-normal (e.g., <50–75 ng/mL), consider iron after discussing with pediatrician; recheck ferritin and avoid overload.
- Stimulant timing
  - Prefer morning/early afternoon dosing; avoid late-day doses that push sleep later.
- Alpha-2 agonists
  - Low-dose clonidine/guanfacine at bedtime can aid sleep; monitor blood pressure and next-day sedation.

The New Sleep Paradigm (M. Weiss)

- When sleep is measured as an outcome in all participants rather than as a side effect in a subset of patients, group data shows overall improvement in children, adolescents and adults. Weiss MD, *CNS Drugs, J Child Adolesc Psychopharmacol;* 2021; Owens J,*2016*
- Clinicians are NOT choosing between *either* better management of ADHD with higher doses of stimulant and poor sleep OR limited management of ADHD and better sleep: optimal patient outcome requires optimization of ***both*** ADHD and sleep.
- More patients will switch from poor to good sleep than from good to poor sleep.

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