

# Pharmacologic Treatments for ADD/ADHD

---

## Preliminary Scan Report #3

June 2018

Scan conducted by:  
Ian Blazina, MPH  
Marian McDonagh, PharmD  
Frances Hsu, MS

This report is intended only for state employees in states participating in the Drug Effectiveness Review Project (DERP). Do not distribute outside your state Medicaid agency and public agency partners.



Copyright © 2018  
Oregon Health & Science University  
Portland, Oregon 97239  
All rights reserved.

## Objective

The purpose of this literature scan is to preview the volume and nature of new research that has emerged since the last full review on this topic. The literature search for this scan focuses on new randomized controlled trials and comparative effectiveness reviews, as well as actions taken by the U.S. Food and Drug Administration (FDA) since the last report. Comprehensive searches, quality assessment, and synthesis of evidence would follow only if DERP Participating Organizations agreed to proceed with a full report update or other review product.

## Topic History

Update #5: July 2015, searches through April 2015

Scan #2: June 2017, searches through May 2017

## Scope and Key Questions

The scope of the review and key questions were originally developed and refined by the Pacific Northwest Evidence-based Practice Center (EPC) with input from DERP Participating Organizations, which ensure that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The EPC adapted the scope and key questions to guide this update scan:

1. What is the comparative evidence that pharmacologic treatments for attention deficit disorders differ in effectiveness or efficacy outcomes?
2. What is the comparative evidence that pharmacologic treatments for attention deficit disorders differ in harms (tolerability, serious adverse events, abuse/misuse/diversion) outcomes?
3. What is the comparative evidence that pharmacologic treatments for attention deficit disorders differ in effectiveness, efficacy or harms outcomes in subgroups of patients based on demographics, socioeconomic status, other medications or therapy, or co-morbidities (e.g. tics, anxiety, substance use disorders, disruptive behavior disorders)?

## Inclusion Criteria

### Populations

Pediatric (age <3, <6, and 6-17 years) and adult (≥18 years) outpatients with attention deficit disorder (ADD) or attention deficit hyperactivity disorder (ADHD), including inattentive, hyperactive-impulsive, and combined subtypes

### Interventions

Table 1. Included Interventions (Shaded = new since last full report)

Active Ingredient	Trade Name
<b>Stimulants</b>	
Amphetamine	Dyanavel™ SR
	ADZENYS XR-ODT
	ADZENY ER
	Evekeo®
Armodafinil	Nuvigil®
Lisdexamfetamine dimesylate	Vyvanse®
	Vyvanse® chewable tablet
Methylphenidate (patch)	Daytrana®
Dexmethylphenidate hydrochloride	Focalin®
	Focalin XR®
Mixed amphetamine salts	Adderall XR®
	Mydayis®
Modafinil	Provigil®
Methylphenidate hydrochloride	Ritalin®
	Ritalin LA®
	Ritalin-SR®
	Aptensio XR™
	Concerta®
	Cotempla XR-ODT
	Metadate CD®
	Methylin®
	Methylin ER®
	Quillivant™ XR
QuilliChew ER	
Methamphetamine hydrochloride	Desoxyn®
Dextroamphetamine sulfate	Dexedrine®
	Dexedrine Spansule®
<b>Non-stimulants</b>	
Atomoxetine hydrochloride	Strattera®
Guanfacine hydrochloride	Intuniv®
Clonidine hydrochloride	Kapvay™

Abbreviations: CD, controlled delivery; ER/XR, extended release; FDA, U.S. Food & Drug Administration; ODT, orally disintegrating tablet; LA, long acting; SR, sustained release

### **Comparators**

- Head-to-head comparisons of included interventions
- Comparisons by general mechanism of action (i.e., stimulants and nonstimulants) and by duration of formulation (i.e., short-, intermediate-, and long-acting)

### **Benefits Outcomes**

- Symptom response (e.g., inattention, hyperactivity-impulsivity, global ratings, etc.),
- Functional capacity (i.e., social, academic and occupational productivity)
- Quality of life (patient, family members, caregivers, teachers)
- Time to onset of effectiveness
- Duration of effectiveness (length of therapy)

### **Harms Outcomes**

- Tolerability
  - Overall adverse effect
  - Withdrawals due to adverse effects and overall withdrawal
  - Specific adverse events (i.e., abuse potential, anorexia, anxiety, insomnia, sexual dysfunction, tics)
- Serious and long-term (>12 months) adverse effects
  - Cardiovascular events
  - Growth effects
  - Hepatotoxicity
  - Suicide and suicidal behavior
- Misuse/diversion
  - Compliance, overdose
  - Development of substance abuse disorders
  - Trading, selling

### **Study Designs**

- Randomized controlled trials
- Comparative effectiveness reviews
  - Good-quality, covering topic scope, and with search dates ending in the last 2 years
- *Excluded* from preliminary update scan (included in reports): observational studies

## Methods for Scan

### Literature Search

To identify relevant citations, we searched Ovid MEDLINE<sup>®</sup>, Ovid MEDLINE<sup>®</sup> In-Process & Other Non-Indexed Citations, and the Cochrane Central Registry of Controlled Trials from April 2017 through May 21, 2018 using terms for specific included drugs and limits for English language and humans. Literature searches included any new drugs identified in the present scan (shaded in Table 1). We also searched the FDA website (<http://www.fda.gov/medwatch/safety.htm>) to identify new drugs, new populations, and new serious harms (i.e., boxed warnings). To identify new drugs, we also searched CenterWatch (<http://www.centerwatch.com>), a privately-owned database of clinical trials information, and conducted a limited internet search. To identify comparative effectiveness reviews, we searched the websites of the Agency for Healthcare Research and Quality (<http://www.ahrq.gov/>) (<http://www.effectivehealthcare.ahrq.gov/>), the Canadian Agency for Drugs and Technology in Health (<http://www.cadth.ca/>), and the VA Evidence-based Synthesis Program (<http://www.hsrd.research.va.gov/publications/esp/reports.cfm>). All citations were imported into an electronic database (EndNote X8) and duplicate citations were removed.

### Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

## Results

### New Drugs

Amphetamine mixed salts (Mydayis<sup>®</sup>) – approved on 06/20/2017 for adults and children (≥13 years) with ADHD. The new extended release formulation lasts up to 16 hours.

Methylphenidate (Cotempla XR-ODT) – first orally disintegrating tablet for methylphenidate and first once-daily oral dosage approved on 06/19/2017.

Lisdexamfetamine (Vyvanse<sup>®</sup>) – new chewable tablet formulation approved on 1/28/2017 for patients ≥6 years-old

Amphetamine (ADZENYS XR-ODT) – approved on 12/04/2015 for patients (≥6 years) with ADHD

Methylphenidate HCl (QuilliChew ER) – approved on 12/04/2015 for patients (≥6 years) with ADHD

Amphetamine (Dyanavel<sup>™</sup> XR) – approved on 10/19/2015 for patients (≥6 years) with ADHD

Methylphenidate HCl (Aptensio XR<sup>™</sup>) – approved on 4/17/2015 for patients (≥6 years) with ADHD

## New Serious Harms (i.e., Boxed Warnings)

None

## Comparative Effectiveness Reviews

We identified 1 new comparative effectiveness review update on ADHD. See Appendix A for abstract.

Kemper AR, et al. Attention Deficit Hyperactivity Disorder: Diagnosis and Treatment in Children and Adolescents. Comparative Effectiveness Review No. 203. (Prepared by the Duke University Evidence-based Practice Center under Contract No. 290-2015-00004-I.) AHRQ Publication No. 18-EHC005-EF. Rockville, MD: Agency for Healthcare Research and Quality; January 2018.

DOI: <https://doi.org/10.23970/AHRQEPCCER203>

## Randomized Controlled Trials

### *Trials identified since the most recent Full Report*

We reviewed 160 abstracts and identified 11 potentially relevant primary head-to-head trials comparing medications for ADHD. We did not identify any secondary publications of previously included studies.

Table 2. New head-to-head trials (N=14) **Shading indicates new studies found in this scan.**

Author, Year Trial name	N Duration	Population	Comparison
Bedard, 2015	N=102 8-12 weeks	Children with ADHD	Atomoxetine vs. methylphenidate
Kunju, 2017	N=80 8 weeks	Children with ADHD	Atomoxetine vs. methylphenidate
Park, 2016	N=86 12 weeks	Adolescents with ADHD and Internet gaming disorder	Atomoxetine vs. methylphenidate
Snircova, 2016	N=69 8 weeks	Children with ADHD	Atomoxetine vs. methylphenidate
Zhu, 2017	N=104 8 weeks	Children with ADHD	Atomoxetine vs. methylphenidate
Ni, 2016	N=52 8-10 weeks	Drug-naïve adults with ADHD	Atomoxetine vs. methylphenidate IR
Ni, 2017	N=63 8-10 weeks	Chinese adults with ADHD	Atomoxetine vs. methylphenidate IR
Newcorn, 2017	N=232 12 weeks	Children with ADHD	Atomoxetine vs. methylphenidate OROS
Shang, 2015	N=160 24 weeks	Children with ADHD	Atomoxetine vs. methylphenidate OROS

Su, 2016	N=237 5-8 weeks	Children and adolescents with ADHD	Atomoxetine vs. methylphenidate OROS
Loo, 2016	N=179 Duration NR	Children with ADHD	Guanfacine vs. d-methylphenidate
McCracken, 2016	N=207 8 weeks	Children with ADHD	Guanfacine vs. d-methylphenidate ER
Bilder, 2016	N=182 8 weeks	Children with ADHD	Guanfacine vs. methylphenidate
Sayer, 2016	N=207 8 weeks	Children with ADHD	Guanfacine vs. methylphenidate ER

Abbreviations: ADHD, attention deficit/hyperactivity disorder; ER, extended release; IR, immediate release; NR, not reported; OROS, osmotic release oral system.

**Table 3. Secondary analyses of included primary trial publications (N=3)**

**Shading indicates new studies found in this scan.**

Author, Year	N	Population	Comparison	Focus
Dittmann, 2014	N=267 9 weeks	Children or adolescents with ADHD	Atomoxetine vs. lisdexamfetamine	Response and Remission
Nagy, 2016	N=267 9 weeks	Children or adolescents with ADHD	Atomoxetine vs. lisdexamfetamine	Functional assessment
Santisteban, 2014	N=65 8 weeks	Children with ADHD	Mixed amphetamine salts ER vs. dexamethylphenidate ER	Sleep

Abbreviations: ADHD, attention deficit/hyperactivity disorder; ER, extended release.

## Summary

Cumulatively, there are 14 new RCTs since the last full report update (11 new this scan). Four studies assessed guanfacine and ten studies assessed atomoxetine. All atomoxetine studies compared with methylphenidate; 2 guanfacine studies compared with methylphenidate and 2 compared with dexmethylphenidate. We identified no trials of the newly approved drug formulations.

Conflict of Interest Disclosures: No authors have conflicts of interest to disclose. All authors have completed and submitted the Oregon Health & Science University form for Disclosure of Potential Conflicts of Interest, and none were reported.

# Pharmacologic Treatments for ADD/ADHD

---

## Preliminary Scan Report #3 Appendices

June 2018

Scan conducted by:  
Ian Blazina, MPH  
Frances Hsu, MS  
Marian McDonagh, PharmD

This report is intended only for state employees in states participating in the Drug Effectiveness Review Project (DERP). Do not distribute outside your state Medicaid agency and public agency partners.



Copyright © 2018  
Oregon Health & Science University  
Portland, Oregon 97239  
All rights reserved.



## APPENDIX A. New Comparative Effectiveness Reviews

Kemper AR, Maslow GR, Hill S, Namdari B, Allen LaPointe NM, Goode AP, Coeytaux RR, Befus D, Kosinski AS, Bowen SE, McBroom AJ, Lallinger KR, Sanders GD. Attention Deficit Hyperactivity Disorder: Diagnosis and Treatment in Children and Adolescents. Comparative Effectiveness Review No. 203. (Prepared by the Duke University Evidence-based Practice Center under Contract No. 290-2015-00004-I.) AHRQ Publication No. 18-EHC005-EF. Rockville, MD: Agency for Healthcare Research and Quality; January 2018. Posted final reports are located on the Effective Health Care Program [search page](#). DOI: <https://doi.org/10.23970/AHRQEPCCER203>

### Structured Abstract

**Objectives.** Attention deficit hyperactivity disorder (ADHD) is a common pediatric neurobehavioral disorder often treated in the primary care setting. This systematic review updates and extends two previous Agency for Healthcare Research and Quality (AHRQ) systematic evidence reviews and focuses on the comparative effectiveness of methods to establish the diagnosis of ADHD, updates the comparative effectiveness of pharmacologic and nonpharmacologic treatments, and evaluates different monitoring strategies in the primary care setting for individuals from birth through 17 years of age.

**Data sources.** We searched PubMed®, Embase®, PsycINFO®, and the Cochrane Database of Systematic Reviews for relevant English-language studies published from January 1, 2011, through November 7, 2016.

**Review methods.** Two investigators screened each abstract and full-text article for inclusion, abstracted the data, and performed quality ratings and evidence grading. Random-effects models were used to compute summary estimates of effects when sufficient data were available for meta-analysis.

**Results.** Evidence was contributed from 103 articles describing 90 unique studies. Twenty-one studies related to diagnosis, 69 studies related to treatment, and no studies were identified on monitoring. The Attention and Executive Function Rating Inventory and Childhood Executive Functioning Inventory performed better than the Cambridge Neuropsychological Test Automated Battery for the diagnosis of ADHD for ages 7–17 years (strength of evidence [SOE]=low). Evidence was insufficient on the use of electroencephalography (EEG) or neuroimaging to establish the diagnosis of ADHD for ages 7–17 years. No studies directly assessed the harms to children labeled as having ADHD. Limited additional evidence published since the original 2011 report was available on ADHD medications approved by the Food and Drug Administration (FDA) compared with placebo or compared to different FDA-approved ADHD medications (SOE=insufficient). For atomoxetine and methylphenidate, the most commonly reported adverse events were somnolence and mild gastrointestinal problems.

Atomoxetine had slightly higher gastrointestinal effects than methylphenidate (SOE=low). Cognitive behavioral therapy improved ADHD symptoms (SOE=low). Child or parent training improved ADHD symptoms (SOE=moderate) but made no difference in academic performance (SOE=low). Omega-3/6 fatty acid supplementation made no difference in ADHD symptoms (SOE=moderate). Across all treatments, little evidence was reported on the risk of serious adverse events, including cardiovascular risk.

**Conclusions.** The 2011 AHRQ systematic review highlighted the benefit of psychostimulants for children 6–12 years of age with ADHD for up to 24 months and found that adding psychosocial/behavioral interventions to psychostimulants is more effective than psychosocial/behavioral interventions alone for children with ADHD and oppositional defiant disorder. This targeted update found insufficient evidence regarding new approaches to the diagnosis (e.g., EEGs, neuroimaging). Little is known about the impact of being labeled as having ADHD. Although cognitive behavioral therapy or child or parent training may decrease symptoms of ADHD, more information is needed regarding the relative benefit of these approaches compared to, or combined with, medication treatment. Omega-3/6 supplementation does not appear to improve ADHD outcomes. No information was identified regarding the optimal strategy for monitoring after diagnosis.

## Appendix B. Abstracts of Potentially Relevant New Active-Controlled Trials

### Primary Trials (N=14)

Bedard, A. C., et al. (2015). "Differential impact of methylphenidate and atomoxetine on sustained attention in youth with attention-deficit/hyperactivity disorder." Journal of Child Psychology & Psychiatry & Allied Disciplines **56**(1): 40-48.

**BACKGROUND:** This study examined the effects of atomoxetine (ATX) and OROS methylphenidate (MPH) on laboratory measures of inhibitory control and attention in youth with attention-deficit/hyperactivity disorder (ADHD). It was hypothesized that performance would be improved by both treatments, but response profiles would differ because the medications work via different mechanisms.

**METHODS:** One hundred and two youth (77 male; mean age = 10.5 +/- 2.7 years) with ADHD received ATX (1.4 +/- 0.5 mg/kg) and MPH (52.4 +/- 16.6 mg) in a randomized, double-blind, crossover design. Medication was titrated in 4-6-week blocks separated by a 2-week placebo washout. Inhibitory control and attention measures were obtained at baseline, following washout, and at the end of each treatment using Conners' Continuous Performance Test II (CPT-II), which provided age-adjusted T-scores for reaction time (RT), reaction time variability (RT variability), and errors. Repeated-measures analyses of variance were performed, with Time (premedication, postmedication) and Treatment type (ATX, MPH) entered as within-subject factors. Data from the two treatment blocks were checked for order effects and combined if order effects were not present.

**CLINICAL TRIAL REGISTRATION:** Clinicaltrials.gov: NCT00183391.

**RESULTS:** Main effects for Time on RT ( $p = .03$ ), RTSD ( $p = .001$ ), and omission errors ( $p = .01$ ) were significant. A significant Drug x Time interaction indicated that MPH improved RT, RTSD, and omission errors more than ATX ( $p < .05$ ). Changes in performance with treatment did not correlate with changes in ADHD symptoms.

**CONCLUSIONS:** MPH has greater effects than ATX on CPT measures of sustained attention in youth with ADHD. However, the dissociation of cognitive and behavioral change with treatment indicates that CPT measures cannot be considered proxies for symptomatic improvement. Further research on the dissociation of cognitive and behavioral endpoints for ADHD is indicated. Copyright © 2014 The Authors. Journal of Child Psychology and Psychiatry. © 2014 Association for Child and Adolescent Mental Health.

Bilder, R. M., et al. (2016). "Cognitive Effects of Stimulant, Guanfacine, and Combined Treatment in Child and Adolescent Attention-Deficit/Hyperactivity Disorder." Journal of the American Academy of Child & Adolescent Psychiatry **55**(8): 667-673.

**OBJECTIVE:** Psychostimulants are partially effective in reducing cognitive dysfunction associated with attention-deficit/hyperactivity disorder (ADHD). Cognitive effects of guanfacine, an alternative treatment, are poorly understood. Given its distinct action on alpha2A receptors, guanfacine may have different or complementary effects relative to

stimulants. This study tested stimulant and guanfacine monotherapies relative to combined treatment on cognitive functions important in ADHD.

**METHOD:** Children with ADHD (n = 182; aged 7-14 years) completed an 8-week, double blind, randomized, controlled trial with 3 arms: d-methylphenidate (DMPH), guanfacine (GUAN), or combination treatment with DMPH and GUAN (COMB). A nonclinical comparison group (n = 93) had baseline testing, and a subset was retested 8 weeks later (n = 38). Analyses examined treatment effects in 4 cognitive domains (working memory, response inhibition, reaction time, and reaction time variability) constructed from 20 variables.

**RESULTS:** The ADHD group showed impaired working memory relative to the nonclinical comparison group (effect size = -0.53 SD unit). The treatments differed in effects on working memory but not other cognitive domains. Combination treatment improved working memory more than GUAN but was not significantly better than DMPH alone. Treatment did not fully normalize the initial deficit in ADHD relative to the comparison group.

**CONCLUSION:** Combined treatment with DMPH and GUAN yielded greater improvements in working memory than placebo or GUAN alone, but the combined treatment was not superior to DMPH alone and did not extend to other cognitive domains. Although GUAN may be a useful add-on treatment to psychostimulants, additional strategies appear to be necessary to achieve normalization of cognitive function in ADHD.

**CLINICAL TRIAL REGISTRATION INFORMATION:** Single Versus Combination Medication Treatment for Children With Attention Deficit Hyperactivity Disorder; <http://clinicaltrials.gov/>; NCT00429273.

Kunju, M., et al. (2017). "A study on comparative efficacy and adverse effects of methylphenidate versus atomoxetine." *Journal of the Neurological Sciences* **Conference: 23rd world congress of neurology, WCN. 2017. Japan 381**(Supplement 1): 933.

**Background:** Methylphenidate and atomoxetine are used in children with Attention deficit hyperactivity disorder (ADHD) for control of core symptoms. As Methylphenidate is a restricted medicine availability is problematic. Atomoxetine which is available without restriction is useful but long term effect in ADHD in developing countries is not studied .  
**Objective:** To compare the comparative efficacy of methylphenidate and atomoxetine in children with Attention deficit hyperactivity disorder (ADHD). Patients and  
**Methods/Material and Methods:** Randomized controlled trial was conducted in 80 patients (age 6-12 y) with a diagnosis of ADHD, receiving methylphenidate or atomoxetine in pediatric neurology OPD of a tertiary care hospital-of-SAT hospital, medical college, Trivandrum. Children were randomized to open-label atomoxetine or methylphenidate group for 8 weeks. the baseline score of attention deficit hyperactivity disorder rating scale (ADHD-RS) and clinical global impression severity of illness(CGI-SI)are noted, efficacy is compared from the difference in mean score of ADHD -RS scale and CGI-SI scale after 8 weeks. **Results:** Most of the patients were of age 8-9 years, and more proportion were boys from rural area;duration of illness was 1-2 years,58.8%were below average in their current intellectual functioning, with poor school

performance. 7.5% were having family history of ADHD, 16.3% of patients were undergoing special education programmes. A greater proportion of children were having ADHD subtype combined: the mean efficacy index for methylphenidate was 2 and 1.7 for atomoxetine group. Majority patients were with medium or high medication adherence. Conclusion: Methylphenidate and atomoxetine are equally effective in treatment of ADHD.

Loo, S. K., et al. (2016). "Effects of d-Methylphenidate, Guanfacine, and Their Combination on Electroencephalogram Resting State Spectral Power in Attention-Deficit/Hyperactivity Disorder." *Journal of the American Academy of Child & Adolescent Psychiatry* **55**(8): 674-682.e671.

**OBJECTIVE:** Psychostimulant medications are the gold standard of treatment for attention-deficit/hyperactivity disorder (ADHD); however, a significant minority (~30%) of individuals with ADHD fail to respond favorably. Noradrenergic agents are increasingly used as ADHD monotherapies or adjuncts for suboptimal stimulant response, yet knowledge of their cortical effects is limited. This study is the first to examine comparative effects of guanfacine (an alpha adrenergic 2A agonist), psychostimulant, and their combination on resting state cortical activity in ADHD.

**METHOD:** The sample comprised 179 participants aged 7 to 14 years old with ADHD (113 boys, 55 girls). Participants were randomized to 1 of 3 blinded conditions: guanfacine (GUAN), d-methylphenidate (DMPH), or the combination (COMB). Electroencephalography (EEG) was performed pre-, mid-, and post-medication titration, with concomitant assessment of behavioral and cognitive functioning.

**RESULTS:** Analyses of spectral power measures during resting EEG suggested that each medication condition displayed a distinct profile of effects on cortical activity. Significant time effects suggested that GUAN decreased global alpha band (8-12 hertz [Hz]) power, DMPH and COMB increased centro-parietal beta band (13-21 Hz) power, and COMB resulted in decreased theta band (4-7 Hz) power. Relative to other medication groups, COMB was associated with significantly lower theta band power and DMPH with higher beta band power compared with those in the GUAN group. Medication-related changes in theta power were correlated with improvements in behavioral and cognitive functioning.

**CONCLUSION:** These data reveal distinct underlying medication-related effects on neural mechanisms. The COMB condition uniquely exhibited an EEG profile that was associated with improved behavioral and cognitive functioning. Clinical trial registration information-Single Versus Combination Medication Treatment for Children With Attention Deficit Hyperactivity Disorder; <http://clinicaltrials.gov/>; NCT00429273.

McCracken, J. T., et al. (2016). "Combined Stimulant and Guanfacine Administration in Attention-Deficit/Hyperactivity Disorder: A Controlled, Comparative Study." *Journal of the American Academy of Child & Adolescent Psychiatry* **55**(8): 657-666.e651.

**OBJECTIVE:** Because models of attention-deficit/hyperactivity disorder (ADHD) therapeutics emphasize benefits of both enhanced dopaminergic and noradrenergic signaling, strategies to enhance D1 and alpha2A agonism may yield enhanced clinical

and cognitive responses. This study tested the hypothesis that combined effects of a dopamine and noradrenergic agonist, d-methylphenidate extended-release (DMPH) with guanfacine (GUAN), an alpha2A receptor agonist, would be clinically superior to either monotherapy and would have equal tolerability.

**METHOD:** An 8-week, double-blind, 3-arm, comparative trial randomized 7- to 14-year-olds with DSM-IV ADHD to GUAN (1-3 mg/day), DMPH (5-20 mg/day), or a combination (COMB) with fixed-flexible dosing. Outcome measures were the ADHD Rating Scale IV (ADHD-RS-IV) and the Clinical Global Impression-Improvement (CGI-I) scale. Data on adverse events and safety measures were obtained.

**RESULTS:** A total of 207 participants were randomized and received drug. Analyses showed significant treatment group main effects for ADHD-RS-IV ADHD total ( $p = .0001$ ) and inattentive symptoms ( $p = .0001$ ). COMB demonstrated small but consistently greater reductions in ADHD-RS-IV Inattentive subscale scores versus monotherapies (DMPH:  $p = .05$ ;  $f(2) = .02$ ; and GUAN:  $p = .02$ ;  $f(2) = .02$ ), and was associated with a greater positive response rate by CGI-I ( $p = .01$ ). No serious cardiovascular events occurred. Sedation, somnolence, lethargy, and fatigue were greater in both guanfacine groups. All treatments were well tolerated.

**CONCLUSION:** COMB showed consistent evidence of clinical benefits over monotherapies, possibly reflecting advantages of greater combined dopaminergic and alpha2A agonism. Adverse events were generally mild to moderate, and COMB treatment showed no differences in safety or tolerability.

**CLINICAL TRIAL REGISTRATION INFORMATION:** Single Versus Combination Medication Treatment for Children With Attention Deficit Hyperactivity Disorder (Project1); <http://clinicaltrials.gov/>; NCT00429273.

Newcorn, J., et al. (2017). "Methylphenidate vs. atomoxetine in youth with ADHD: comparative effectiveness and preference following treatment with both medications." *Biological Psychiatry Conference: 72nd annual scientific convention and meeting of the society of biological psychiatry, SOBP. 2017. United states 81*(10 Supplement 1): S346-S347.

**Background:** The majority of youth with ADHD treated with psychostimulant medication experience significant improvement, but a smaller number achieve normalized function. The availability of FDA-approved non-stimulants offers therapeutic alternatives, but more information is needed to guide treatment selection and algorithm development. We compared OROS methylphenidate (MPH) (long-acting stimulant) and atomoxetine (ATX) (nonstimulant) in a randomized, double-blind, crossover study (~6 weeks each, separated by a two week placebo washout) **Methods:** Multiple-group latent growth curve models were used to estimate the effects of drug (ATX vs. MPH) on block 1 and block 2 changes in ADHD symptoms. Latent transition analyses examined the effect of order on responder status. Preference was determined under blinded conditions by a combination of direct query, ratings, and chart review. **Results:** 232 children ages 7-17 were randomized; 199 completed both treatments. Mean doses were: MPH: 54 mg (18.02); ATX: 1.35 mg/kg (0.47). MPH was associated with nominally greater symptomatic response, which reached significance in block 2 ( $d_{50.17}$  (block 1); 0.34 (block 2)). MPH

was preferred by more families (51%), but a large minority (34%) preferred ATX. Preference was greater for the medication given first, and when there was excellent  
Conclusions: Response to both medications was good to excellent, with a small effect size favoring MPH. The relatively large number of families who preferred ATX, and the fact that ATX did substantially better when given first, have important implications for the development of treatment algorithms.

Ni, H. C., et al. (2016). "Atomoxetine could improve intra-individual variability in drug-naive adults with attention-deficit/hyperactivity disorder comparably with methylphenidate: A head-to-head randomized clinical trial." Journal of Psychopharmacology **30**(5): 459-467.

OBJECTIVE: Intra-individual variability in reaction time (IIV-RT) is common in individuals with attention-deficit/hyperactivity disorder (ADHD). It can be improved by stimulants. However, the effects of atomoxetine on IIV-RT are inconclusive. We aimed to investigate the effects of atomoxetine on IIV-RT, and directly compared its efficacy with methylphenidate in adults with ADHD.

METHODS: An 8-10 week, open-label, head-to-head, randomized clinical trial was conducted in 52 drug-naive adults with ADHD, who were randomly assigned to two treatment groups: immediate-release methylphenidate (n=26) thrice daily (10-20 mg per dose) and atomoxetine once daily (n=26) (0.5-1.2 mg/kg/day). IIV-RT, derived from the Conners' continuous performance test (CCPT), was represented by the Gaussian (reaction time standard error, RTSE) and ex-Gaussian models (sigma and tau). Other neuropsychological functions, including response errors and mean of reaction time, were also measured. Participants received CCPT assessments at baseline and week 8-10 (60.4+/-6.3 days).

RESULTS: We found comparable improvements in performances of CCPT between the immediate-release methylphenidate- and atomoxetine-treated groups. Both medications significantly improved IIV-RT in terms of reducing tau values with comparable efficacy. In addition, both medications significantly improved inhibitory control by reducing commission errors.

CONCLUSION: Our results provide evidence to support that atomoxetine could improve IIV-RT and inhibitory control, of comparable efficacy with immediate-release methylphenidate, in drug-naive adults with ADHD. Shared and unique mechanisms underpinning these medication effects on IIV-RT awaits further investigation.

Ni, H. C., et al. (2017). "An Open-Label, Randomized Trial of Methylphenidate and Atomoxetine Treatment in Adults With ADHD." Journal of Attention Disorders **21**(1): 27-39.

OBJECTIVE: To directly compare the efficacy of methylphenidate and atomoxetine in improving symptoms, social functions, and quality of life among adults with ADHD.

METHOD: This was an 8-to-10-week, open-label, head-to-head, randomized clinical trial with two treatment arms: immediate-release methylphenidate (IR-methylphenidate; n = 31) and atomoxetine once daily ( n = 32). The outcome measures included ADHD symptom severity, quality of life, and functional impairments.

RESULTS: We found a significant reduction in overall ADHD symptoms and improvement in social functions and quality of life for both groups at Weeks 4 to 5 and Weeks 8 to 10.

There was no significant difference in the slope of improvements over time except that atomoxetine was superior to IR-methylphenidate in reducing hyperactive/impulsive symptoms at Weeks 4 to 5. There was no significant group difference in the rates of adverse effects.

**CONCLUSION:** Both IR-methylphenidate and atomoxetine are well tolerated and efficacious in ethnic Chinese adults with ADHD.

Park, J. H., et al. (2016). "Effectiveness of atomoxetine and methylphenidate for problematic online gaming in adolescents with attention deficit hyperactivity disorder." Human Psychopharmacology **31**(6): 427-432.

**OBJECTIVE:** There is a high prevalence of problematic online gaming in adolescents with attention deficit hyperactivity disorder (ADHD). In the current study, we compared the effectiveness of atomoxetine (ATM) and methylphenidate (MPH) on problematic online gaming in adolescents with ADHD.

**METHODS:** We recruited 86 adolescents diagnosed with ADHD together with Internet gaming disorder. These participants were divided into two treatment groups: 44 participants were treated with MPH for 12 weeks, and 42 participants were treated with ATM for 12 weeks.

**RESULTS:** During the 3-month study period, the MPH group showed greater improvement in Korean ADHD rating scale scores than the ATM group. The ATM group showed greater improvement in Child Depression Inventory scores than the MPH group. However, Young Internet Addiction Scale and Behavioral Inhibition & Activation Scales score changes did not differ significantly between the MPH and ATM groups. In both groups, changes in Young Internet Addiction Scale scores were positively correlated with the changes in Behavioral Inhibition & Activation Scales scores.

**CONCLUSIONS:** Both MPH and ATM reduced the severity of Internet gaming disorder symptoms, and this reduction was correlated with impulsivity reduction, which also resulted from both ADHD medications. These findings suggest impulsivity plays a critical role in the development of problematic online gaming.

Sayer, G. R., et al. (2016). "Acute and Long-Term Cardiovascular Effects of Stimulant, Guanfacine, and Combination Therapy for Attention-Deficit/Hyperactivity Disorder." Journal of Child & Adolescent Psychopharmacology **26**(10): 882-888.

**OBJECTIVES:** This study examines cardiovascular (CV) effects of guanfacine immediate-release (GUAN-IR), dexamethylphenidate extended-release (DMPH), and their combination (COMB) during acute and long-term treatment of youth with attention-deficit/hyperactivity disorder.

**METHODS:** Two hundred seven participants aged 7-14 years enrolled in an 8-week double-blind randomized trial of GUAN-IR (1-3 milligrams (mg)/day), DMPH (5-20mg/day), or COMB with fixed-flexible dosing and titrated to optimal behavioral response. Heart rate, systolic blood pressure (BP), diastolic BP, and electrocardiograms were assessed at baseline, end of blinded optimization, and over a 1-year open-label maintenance phase.



**RESULTS:** During acute titration, GUAN-IR decreased heart rate, systolic BP, and diastolic BP; DMPH increased heart rate, systolic BP, diastolic BP, and corrected QT (QTc) interval; COMB increased diastolic BP, but had no effects on heart rate, systolic BP, or QTc. During maintenance, GUAN-IR-associated decreases in heart rate and DMPH-associated increases in systolic BP returned to baseline values. Other variables across the three groups remained unchanged from the end of blinded titration. There were no discontinuations due to CV adverse events.

**CONCLUSION:** GUAN-IR, DMPH, and COMB were well tolerated and safe. Expected changes in CV parameters during acute titration were seen in GUAN-IR and DMPH groups, with COMB values falling intermediately between the two other treatment groups. No serious CV events occurred in any participant. GUAN-IR- and DMPH-associated CV changes generally returned to baseline with sustained therapy. These data suggest that COMB treatment might attenuate long-term CV effects of GUAN-IR and stimulant monotherapy, possibly reducing risk of the small but statistically significant changes associated with either single treatment. Clinicaltrials.gov Identifier: NCT00429273.

Shang, C. Y., et al. (2015). "An Open-Label, Randomized Trial of Methylphenidate and Atomoxetine Treatment in Children with Attention-Deficit/Hyperactivity Disorder." Journal of Child & Adolescent Psychopharmacology **25**(7): 566-573.

**OBJECTIVE:** The efficacy of both methylphenidate and atomoxetine has been established in placebo-controlled trials. The present study aimed to directly compare the efficacy of methylphenidate and atomoxetine in improving symptoms among children with attention-deficit/hyperactivity disorder (ADHD).

**METHODS:** The study sample included 160 drug-naive children and adolescents 7-16 years of age, with DSM-IV-defined ADHD, randomly assigned to osmotic-release oral system methylphenidate (OROS-methylphenidate) (n=80) and atomoxetine (n=80) in a 24 week, open-label, head-to-head clinical trial. The primary efficacy measure was the score of the ADHD Rating Scale-IV Parents Version: Investigator Administered and Scored (ADHD-RS-IV). The secondary efficacy measures included the Clinical Global Impressions-ADHD-Severity (CGI-ADHD-S) and Chinese Swanson, Nolan, and Pelham IV scale (SNAP-IV), based on the ratings of investigators, parents, teachers, and subjects.

**RESULTS:** At week 24, mean changes in ADHD-RS-IV Inattention scores were 13.58 points (Cohen's d, -3.08) for OROS-methylphenidate and 12.65 points (Cohen's d, -3.05) for atomoxetine; and mean changes in ADHD-RS-IV Hyperactivity-Impulsivity scores were 10.16 points (Cohen's d, -1.75) for OROS-methylphenidate and 10.68 points (Cohen's d, -1.87) for atomoxetine. In terms of parent-, teacher-, and self-ratings on behavioral symptoms, both of the two treatment groups significantly decreased on the SNAP-IV scores at the end-point, with effect sizes ranging from 0.9 to 0.96 on the Inattention subscale and from 0.61 to 0.8 on the Hyperactivity/Impulsivity subscale for OROS-methylphenidate; and from 0.51 to 0.88 on the Inattention subscale and from 0.29 to 0.57 on the Hyperactivity/Impulsivity subscale for atomoxetine. No statistically significant differences between treatment groups were observed on the outcome measures. Vomiting, somnolence, and dizziness were reported more often for atomoxetine than for

OROS-methylphenidate, whereas insomnia was reported more often for OROS-methylphenidate than for atomoxetine.

**CONCLUSIONS:** After 24 weeks of treatment, OROS-methylphenidate and atomoxetine had comparable efficacy in reducing core ADHD symptoms in drug-naïve children and adolescents with ADHD.

Snircova, E., et al. (2016). Anxiety reduction on atomoxetine and methylphenidate medication in children with ADHD. *Pediatrics International*. **58**: 476-481.

**BACKGROUND:** Atomoxetine and methylphenidate are widely used to treat attention-deficit-hyperactivity disorder (ADHD) with similar effectiveness after 8 weeks of treatment, when atomoxetine has reached its a full effect. Both drugs have also been shown to have an effect on comorbid anxiety. To the best of our knowledge, no study has compared their effect on the dynamics of anxiety symptom reduction. The aim of this study was to compare the medication effect on core and comorbid anxiety symptom dynamics in children with ADHD.

**METHODS:** Sixty-nine patients participated in the study: 36 patients were taking atomoxetine and 33 patients, methylphenidate. Therapeutic effect on core symptoms of ADHD was measured on the ADHD-rating scale IV, and symptoms of anxiety were measured using the Conners Parent Rating Scale (CPRS). Symptoms were measured prior to and every 2 weeks during 8 weeks of treatment.

**RESULTS:** There was a significant decrease in CPRS anxiety subscale score in both medication groups. Anxiety subscale score was significantly lower in the atomoxetine group in the fourth week, and lasted through to 8 weeks of medication.

**CONCLUSION:** Both atomoxetine and methylphenidate reduced the symptoms of ADHD and anxiety. Atomoxetine was more effective in anxiety symptom reduction from the fourth week of treatment.

Copyright © 2015 Japan Pediatric Society.

Su, Y., et al. (2016). "Osmotic Release Oral System Methylphenidate Versus Atomoxetine for the Treatment of Attention-Deficit/Hyperactivity Disorder in Chinese Youth: 8-Week Comparative Efficacy and 1-Year Follow-Up." *Journal of Child & Adolescent Psychopharmacology* **26**(4): 362-371.

**OBJECTIVE:** The purpose of this study was to compare the short-term efficacy, tolerability, and 1-year adherence in Chinese children and adolescents with attention-deficit/hyperactivity disorder (ADHD) treated with either osmotic release oral system methylphenidate (OROS MPH) or atomoxetine (ATX).

**METHODS:** Children and adolescents meeting Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV) criteria for ADHD were randomly assigned to receive either OROS MPH (n=119) or ATX (n=118). Participants underwent a 1-4 week dose titration period to determine optimal dose, and then were maintained on that dose for 4 weeks (maintenance period). Assessment for efficacy was conducted every week over the titration period and at the end of the maintenance period. The primary efficacy measure was the investigator-rated total ADHD Rating Scale-IV (ADHD-RS-IV) score. Response

was further classified as remission (ADHD-RS-IV [18 or 9 items] average score  $\leq 1$ ), robust improvement (ADHD-RS-IV  $\geq 40\%$  decrease in total score), or improvement ( $\geq 25\%$  decrease in total score) at the end of maintenance period. Medication adherence (taking medication at least 5 days in 1 week) and reasons for nonadherence were evaluated every week over the titration period, at the end of maintenance period, and then at 3, 6, and 12 months.

**RESULTS:** At the end of maintenance period, both OROS MPH and ATX were associated with significant and similar reductions from baseline in ADHD symptoms. Percentages achieving remission, robust improvement, and improvement were comparable for OROS MPH and ATX treatment (35.3% vs. 37.1%, 45.4% vs. 44.8%, 65.5% vs. 66.4%). Medication use decreased over time for both treatments; however, at end of maintenance period, 3 month, 6 month, and 1 year follow-ups, subjects in the OROS MPH group were more likely to be compliant with treatment (74.8%, 50.4%, 38.7%, and 21.8% for OROS MPH vs. 52.5%, 33.9%, 12.7%, and 3.4% for ATX) ( $p < 0.05$ ). The most common reasons for nonadherence were adverse events and lack of efficacy.

**CONCLUSIONS:** Both OROS MPH and ATX resulted in similar reductions in ADHD symptoms in Chinese children and adolescents with ADHD. Long-term adherence with medication was poor in general, although somewhat better with OROS MPH than with ATX.

**CLINICAL TRIAL REGISTRATION:** ClinicalTrials.gov , Identifier: NCT01065259.

Zhu, X., et al. (2017). "A randomized parallel-controlled study of curative effect and safety of atomoxetine and methylphenidate in treatment of ADHD in children." International Journal of Clinical and Experimental Medicine **10**(6): 9576-9582.

**Objective:** To compare the curative effect and safety of atomoxetine and methylphenidate in treatment of attention deficit hyperactivity disorder (ADHD) in children. **Methods:** One hundred and four children with ADHD treated in our hospital from February 2014 to January 2016 were included in this study. They were divided into atomoxetine group (52 cases) and methylphenidate group (52 cases) according to the design method of the randomized single-blind parallel controlled trial. Both groups were respectively treated with atomoxetine and methylphenidate for 8 weeks. Curative efficacy was evaluated through the changes of recorded scores of ADHD Rating Scale-IV: Parent Version (ADHDRS-IV-Parent: Inv), Conners' Parent Rating Scale-Revised: Short Form (CPRS-R: S) and Clinical Global Impression of ADHD Severity (CGI-ADHD-S) before and after treatments. Cohen's d, an effect size index, and the Treatment Emergent Symptom Scale (TESS) were used to evaluate and compare the safety of the two treatments.

**Results:** The response rates of atomoxetine group and methylphenidate group were 71.2% and 78.8% ( $P=0.365$ ), respectively; and the dropout rates were 11.5% and 7.7% ( $P=0.506$ ), which were not significantly different. A statistically significant decrease from baseline was observed in the postoperative scores of both groups in comparison with the preoperative ones ( $P < 0.001$ ). It had significant clinical significance, but there was no significant difference in curative effect between the two treatments. No serious adverse event occurred during the treatment, and the most common adverse events in two groups were loss of appetite, lethargy and nausea. The incidence of lethargy of

atomoxetine group was significantly higher than that of methylphenidate group (P=0.027). Conclusion: The short-term efficacy and safety of atomoxetine in the treatment of ADHD in children is similar to that of methylphenidate, and the long-term efficacy and safety of the two treatments need to be further verified by more randomized controlled trials. Copyright (C) 2017, E-Century Publishing Corporation. All rights reserved.

### Secondary Analyses (N=3)

Dittmann, R. W., et al. (2014). "Treatment response and remission in a double-blind, randomized, head-to-head study of lisdexamfetamine dimesylate and atomoxetine in children and adolescents with attention-deficit hyperactivity disorder." *CNS Drugs* **28**(11): 1059-1069.

**OBJECTIVES:** A secondary objective of this head-to-head study of lisdexamfetamine dimesylate (LDX) and atomoxetine (ATX) was to assess treatment response rates in children and adolescents with attention-deficit hyperactivity disorder (ADHD) and an inadequate response to methylphenidate (MPH). The primary efficacy and safety outcomes of the study, SPD489-317 (ClinicalTrials.gov NCT01106430), have been published previously.

**METHODS:** In this 9-week, double-blind, active-controlled study, patients aged 6-17 years with a previous inadequate response to MPH were randomized (1:1) to dose-optimized LDX (30, 50 or 70 mg/day) or ATX (patients <70 kg: 0.5-1.2 mg/kg/day, not to exceed 1.4 mg/kg/day; patients >70 kg: 40, 80 or 100 mg/day). Treatment response was a secondary efficacy outcome and was predefined as a reduction from baseline in ADHD Rating Scale IV (ADHD-RS-IV) total score of at least 25, 30 or 50 %. Sustained response was predefined as a reduction from baseline in ADHD-RS-IV total score (>25, >30 or >50 %) or a Clinical Global Impressions (CGI)-Improvement (CGI-I) score of 1 or 2 throughout weeks 4-9. CGI-Severity (CGI-S) scores were also assessed, as an indicator of remission.

**RESULTS:** A total of 267 patients were enrolled (LDX, n = 133; ATX, n = 134) and 200 completed the study (LDX, n = 99; ATX, n = 101). By week 9, significantly ( $p < 0.01$ ) greater proportions of patients receiving LDX than ATX met the response criteria of a reduction from baseline in ADHD-RS-IV total score of at least 25 % (90.5 vs. 76.7 %), 30 % (88.1 vs. 73.7 %) or 50 % (73.0 vs. 50.4 %). Sustained response rates were also significantly ( $p < 0.05$ ) higher among LDX-treated patients (ADHD-RS-IV >25, 66.1 %; ADHD-RS-IV >30, 61.4 %; ADHD-RS-IV >50, 41.7 %; CGI-I, 52.0 %) than among ATX-treated individuals (ADHD-RS-IV >25, 51.1 %; ADHD-RS-IV >30, 47.4 %; ADHD-RS-IV >50, 23.7 %; CGI-I, 39.3 %). Finally, by week 9, 60.7 % of patients receiving LDX and 46.3 % of those receiving ATX had a CGI-S score of 1 (normal, not at all ill) or 2 (borderline mentally ill), and greater proportions of patients in the LDX group than the ATX group experienced a reduction from baseline of at least one CGI-S category.

**CONCLUSIONS:** Both LDX and ATX treatment were associated with high levels of treatment response in children and adolescents with ADHD and a previous inadequate response to MPH. However, within the parameters of the study, LDX was associated with significantly higher treatment response rates than ATX across all response criteria examined. In addition, higher proportions of patients in the LDX group than the ATX group had a CGI-

S score of 1 or 2 by week 9, indicating remission of symptoms. Both treatments were generally well tolerated, with safety profiles consistent with those observed in previous studies.

Nagy, P., et al. (2016). "Functional outcomes from a head-to-head, randomized, double-blind trial of lisdexamfetamine dimesylate and atomoxetine in children and adolescents with attention-deficit/hyperactivity disorder and an inadequate response to methylphenidate." European Child & Adolescent Psychiatry **25**(2): 141-149.

Attention-deficit/hyperactivity disorder (ADHD) is associated with functional impairments in multiple domains of patients' lives. A secondary objective of this randomized, active-controlled, head-to-head, double-blind, dose-optimized clinical trial was to compare the effects of lisdexamfetamine dimesylate (LDX) and atomoxetine (ATX) on functional impairment in children and adolescents with ADHD. Patients aged 6-17 years with an ADHD Rating Scale IV total score > 28 and an inadequate response to methylphenidate treatment (judged by investigators) were randomized (1:1) to once-daily LDX or ATX for 9 weeks. Parents/guardians completed the Weiss Functional Impairment Rating Scale-Parent Report (WFIRS-P) at baseline and at week 9 or early termination. p values were nominal and not corrected for multiple comparisons. Of 267 randomized patients, 200 completed the study (LDX 99, ATX 101). At baseline, mean WFIRS-P total score in the LDX group was 0.95 [standard deviation (SD) 0.474; 95% confidence interval (CI) 0.87, 1.03] and in the ATX group was 0.91 (0.513; 0.82, 1.00). Scores in all WFIRS-P domains improved from baseline to endpoint in both groups, with least-squares mean changes in total score of -0.35 (95% CI -0.42, -0.29) for LDX and -0.27 (-0.33, -0.20) for ATX. The difference between LDX and ATX was statistically significant ( $p < 0.05$ ) for the Learning and School (effect size of LDX vs ATX, 0.43) and Social Activities (0.34) domains and for total score (0.27). Both treatments reduced functional impairment in children and adolescents with ADHD; LDX was statistically significantly more effective than ATX in two of six domains and in total score.

Santisteban, J. A., et al. (2014). "Effect of extended-release dexamethylphenidate and mixed amphetamine salts on sleep: a double-blind, randomized, crossover study in youth with attention-deficit hyperactivity disorder." CNS Drugs **28**(9): 825-833.

OBJECTIVE: We sought to determine the dose-response effects of extended-release (ER) dexamethylphenidate (d-MPH) and ER mixed amphetamine salts (MAS) on objective measures of sleep.

METHODS: This was an 8-week, double-blind, placebo-controlled, randomized, two period, crossover study of youth with attention-deficit hyperactivity disorder (ADHD) as confirmed by the Kiddie Schedule for Affective Disorders for School-Age Children-Present and Lifetime version (K-SADS-PL). Children aged 10-17 years were recruited from clinical practice, colleague referrals, and flyers. Participants were randomized to initially receive either d-MPH or MAS. During each 4-week drug period, children received three dose levels (10, 20, and 25/30 mg) in ascending order, with placebo substituted for active medication in a randomized fashion during 1 week of the study. After 4 weeks,

participants were switched to the alternative medication for another 4 weeks of treatment. The main outcome measure was sleep duration as measured by actigraphy. Children, parents, and researchers were blinded to drug, dose, and placebo status.

**RESULTS:** Sixty-five participants met the inclusion criteria and were enrolled in the study. Of these, 37 participants with sufficient sleep data for analysis were included. Sleep schedule measures showed a significant effect for dose on sleep start time ( $F(1,36) = 6.284$ ;  $p < 0.05$ ), with a significantly later sleep start time when children were receiving 20- or 30-mg doses, compared with placebo ( $p < 0.05$ ). A significant dose effect was found on actual sleep duration ( $F(1,36) = 8.112$ ;  $p < 0.05$ ), with significantly shorter actual sleep duration for subjects receiving 30 mg compared with those receiving placebo ( $p < 0.05$ ). There were no significant differences on sleep duration or sleep schedule between the two stimulant medications. The trial is complete and closed to follow-up.

**CONCLUSIONS:** Higher stimulant doses were associated with reduced sleep duration and later sleep start times, regardless of medication class.

**TRIAL REGISTRATION:** ClinicalTrials.gov: NCT00393042.