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DERP VI Surveillance 1: Pharmacological Treatments for ADHD

March 2019

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Objectives

The purpose of this Drug Effectiveness Review Project (DERP) surveillance report is to preview the volume and nature of new research and relevant clinical information that has emerged since the last scan[1] on pharmacological treatments for attention deficit hyperactivity disorder (ADHD). The literature search for this report focuses on new randomized controlled trials (RCTs), systematic reviews with and without meta-analyses, and actions taken by the U.S. Food and Drug Administration (FDA) since the last update review,[2] including approval of new drugs, formulations, or indications and identification of serious harms. Comprehensive searches, quality assessment, and synthesis of evidence would follow only if DERP participants commission an update review or another research product type for this topic. Comprehensive searches might identify additional eligible studies.

Topic History and Context

This report is the first surveillance document on this topic since the completion of scan 3 (June 2018).[1] The search strategy for scan 3 was through May 2018.

Key Questions

1. What is the comparative efficacy of pharmacological treatments for ADHD?
2. What are the comparative harms of pharmacological treatments for ADHD?
3. Are there subgroups of patients based on demographics (e.g., age, racial groups, gender), comorbidities (e.g., drug-disease interactions), or other medications for which pharmacological treatments for ADHD differ in efficacy, effectiveness, or frequency of adverse events?
4. What are the characteristics of ongoing studies of pharmacological treatments for ADHD?

Populations

- Pediatric outpatients with ADHD, including inattentive, hyperactive-impulsive, and combined subtypes
- Adult outpatients with ADHD, including inattentive, hyperactive-impulsive, and combined subtypes

Interventions

Table 1. Included Interventions

Generic Name	Brand Name	Date of FDA Approval
Stimulants		
Amphetamine	ADZENYS ER	September 15, 2017
Mixed amphetamine salts	Mydayis	June 20, 2017
Methylphenidate hydrochloride	Cotempla XR-ODT	June 19, 2017
Lisdexamfetamine dimesylate	Vyvanse Chewable	January 28, 2017

Generic Name	Brand Name	Date of FDA Approval
Amphetamine	ADZENYS XR-ODT	January 27, 2016
Methylphenidate hydrochloride	QuilliChew ER	December 4, 2015
Amphetamine	Dyanavel XR	October 19, 2015
Methylphenidate hydrochloride	Aptensio XR	April 17, 2015
Methylphenidate hydrochloride	Quillivant XR	September 27, 2012
Amphetamine	Evekeo	August 9, 2012
Armodafinil	Nuvigil	June 15, 2007
Lisdexamfetamine dimesylate	Vyvanse	February 23, 2007
Methylphenidate (patch)	Daytrana	April 6, 2006
Dexmethylphenidate hydrochloride	Focalin XR	May 26, 2005
Methylphenidate hydrochloride	Methylin	December 19, 2002
Methylphenidate hydrochloride	Ritalin LA	June 5, 2002
Dexmethylphenidate hydrochloride	Focalin	November 13, 2001
Mixed amphetamine salts	Adderall XR	October 11, 2001
Methylphenidate hydrochloride	Metadate CD	April 3, 2001
Methylphenidate hydrochloride	Concerta	August 1, 2000
Methylphenidate hydrochloride	Methylin ER	May 9, 2000
Modafinil	Provigil	December 24, 1998
Methylphenidate hydrochloride	Metadate ER	June 1, 1988
Methylphenidate hydrochloride	Ritalin-SR	March 30, 1982
Dextroamphetamine sulfate	Dexedrine Spansule	August 2, 1976
Methylphenidate hydrochloride	Ritalin	December 5, 1955
Methamphetamine hydrochloride	Desoxyn	December 31, 1943
Non-Stimulants		
Clonidine hydrochloride	Kapvay	September 29, 2009
Guanfacine hydrochloride	Intuniv	September 2, 2009
Atomoxetine hydrochloride	Strattera	November 26, 2002

Abbreviations. CD: continuous delivery; ER: extended release; FDA: U.S. Food and Drug Administration; LA: long-acting; ODT: oral disintegrating tablet; SR: sustained release; XR: extended release.

Comparators

- Another listed intervention (head-to-head comparison)

Outcomes

- Symptom response (e.g., inattention, hyperactivity-impulsivity, global rating)
- Functional capacity (e.g., social, academic, and occupational activities)
- Quality of life (patient, family members, caregivers, teachers)

- Time to onset of effectiveness
- Duration of effectiveness (length of therapy)
- Tolerability
    - Overall adverse effects
    - Withdrawals due to adverse effects and overall withdrawal
    - Specific adverse events (e.g., 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

- Systematic reviews, with or without meta-analysis
- RCTs

Methods

Using the PICO outlined above, we searched for eligible RCTs in ClinicalTrials.gov, the ISRCTN Registry, and the FDA website. Using relevant clinical trial numbers and other identifiers, we then searched Ovid MEDLINE, Ovid MEDLINE In-Process & Other Non-Indexed Citations, and Ovid MEDLINE Epub Ahead of Print from May 2018 to January 2019 and used the Google search engine to identify studies published since the implementation of the search strategy in the last scan (May 2018).[1] We used limits for English language and human participants. We also searched the FDA website to identify newly approved drugs, formulations, indications, and new serious harms (e.g., boxed warnings) or warnings for included interventions. To identify new drugs, we used Google and searched CenterWatch, a privately owned database of clinical trials information.

Findings

New Drugs or Formulations

Since the searches in the last scan,[1] we identified 1 new formulation of methylphenidate hydrochloride approved by the FDA in August 2018.[3] JORNAY PM is an extended- and delayed-release capsule (20 mg, 40 mg, 60 mg, 80 mg, and 100 mg), approved for ADHD in patients aged 6 and older.[3] JORNAY PM is intended to be taken in the evening, with the timing adjusted to optimize tolerability and its efficacy the next morning and throughout the day.[3]

New Indications

No new indications were identified since the searches in the last scan.[1]

New Serious Harms or Warnings

Central nervous system (CNS) stimulators, including methylphenidate-containing products and amphetamines, have had a black box warning related to the high potential for abuse and dependence for decades. Prescribing labels for many products in this drug class display advice on assessing the risk of abuse before prescribing and on monitoring patients for signs of abuse and dependence while they are receiving the drug. In January 2019, prescribing labels for the following ADHD formulations were updated to include this known safety concern:

- Focalin[4]
- Focalin XR[5]
- Ritalin[6]
- Ritalin LA[7]
- Ritalin SR[8]

The black box warning also applies to the newly approved formulation, JORNAY PM.[3]

Randomized Controlled Trials

For this surveillance document, we identified 1 eligible head-to-head RCT (Table 2). The RCT compares different formulations of mixed amphetamine salts in adults with ADHD (see Appendix A for abstracts of included studies).

Table 2. Included Published Randomized Controlled Trials for ADHD Drugs

Author, Year NCT Number	Population Sample Size (N)	Active Treatment Groups	Outcomes
Wigal et al., 2018[9] NCT00928148	Adults with ADHD N = 86	• 50 mg/75 mg SHP465 MAS ER (MyDayis) • MAS IR	• PERMP score • Symptom frequency and severity • Safety • Tolerability

Abbreviations. ADHD: attention deficit hyperactivity disorder; ER: extended release; IR: immediate release; MAS: mixed amphetamine salts; PERMP: Permanent Product Measure of Performance.

Ongoing Studies

We identified 3 ongoing head-to-head comparisons of eligible interventions. Table 3 displays the registry number for the trial (NCT), treatment groups, eligible outcomes, estimated enrollment, and estimated primary completion date of these ongoing studies.

Table 3. Included Ongoing Randomized Controlled Trials for ADHD Drugs

NCT Number	Participants	Active Treatment Groups	Eligible Outcomes	Enrollment	Primary Completion Date
Head-to-Head Comparisons					
NCT02555150	Adults with ADHD	• Methylphenidate XR (PRC-063) • Lisdexamfetamine	• Driving performance • Adverse events • Suicide risk	40	January 2017
NCT01678209	Children aged 7 to 17 with ADHD (also healthy controls)	• Methylphenidate (Concerta) • Atomoxetine	• Task performance • Symptom frequency and severity	127	March 2018
NCT03153488	Adults with ADHD	• Methylphenidate LA (Ritalin) • MAS XR (Adderall)	• Condition severity • Symptom severity	60	July 2020

Abbreviations. ADHD: attention deficit hyperactivity disorder; LA: long-acting; XR: extended release.

Summary

Since the completion of the DERP update report in July 2015,[2] we identified the following:

- No new drugs
- 9 new formulations (*1 during this surveillance period*)
    - Amphetamine
        - ADZENYS ER
        - ADZENYS XR-ODT
        - Dyanavel XR
    - Lisdexamfetamine
        - Vyvanse Chewable
    - Methylphenidate
        - Aptensio XR
        - Cotempla XR-ODT
        - JORNAY PM (*identified during this surveillance period*)
        - QuilliChew ER
    - Mixed amphetamine salts
        - Mydayis
- No new indications
- 1 known FDA black box warning added to product labels (*during this surveillance period*)
    - Some CNS stimulators, including methylphenidate-containing products, were updated to include a known warning related to the high potential for abuse and dependence
- 8 head-to-head RCTs (*1 during this surveillance period*)
- 7 secondary analyses

- 3 ongoing head-to-head studies

Using the *Is There a There There Scale* (ITS) for new RCTs and FDA actions since the update report in 2015[2] (Table 4), we rated this topic as *Maybe* (see Appendix B for ratings and definitions).

Table 4. Summary and ITS Rating

Clinical Evidence	**Yes** **How many?**	**No**
New Comparative Trial	☑ 8	
New Meaningful[a] Study	☑ • 1 RCT comparing atomoxetine and methylphenidate in 63 adults (new population) • 1 RCT comparing guanfacine with dexmethylphenidate ER in 207 children and adolescents (new comparison)	
Ongoing Study Likely to be Published in the Next Year	☑ • 1 RCT comparing methylphenidate XR and lisdexamfetamine in 40 adults • 1 RCT comparing atomoxetine and methylphenidate ER in 127 children and adolescents	
FDA Actions	**Yes** **Description**	**No**
New Drug or Formulation	☑ JORNAY PM	
New Indication		☒
New Serious Harm or Warning	☑ A known black box warning on the risk of abuse and dependence for CNS stimulants added to some ADHD formulations	
ITS Rating: *Maybe*		

Abbreviations. ER: extended release; ITS: Is There a There There Scale; XR: extended release. Note. a Large studies (> 400 participants), studies that have long-term follow-up (> 12 months), studies that compare one drug with another that is considered the standard of care or has not been reported and is clinically important, and studies that include an intervention or outcome that is not previously reported in the literature or is clinically important (e.g., mortality) and adds to the body of literature.

References

1. Blazina I, McDonagh M, Hsu F. Pharmacologic treatment for ADD/ADHD. Preliminary scan report #3. 2018; https://www.derpclearinghouse.org/topicfiles/attention_deficit_hyperactivity_disorder_add_adhd_drugs/scans/. Accessed February 1, 2019.

2. McDonagh M, Peterson K, Holzhammer B. Drug class review. Pharmacologic treatments for attention deficit hyperactivity disorder. Final update 5 report. 2015; https://www.derpclearinghouse.org/topicfiles/attention_deficit_hyperactivity_disorder_add_adhd_drugs/update_5/. Accessed February 1, 2019.

3. U.S. Food and Drug Administration. JORNAY PM (methylphenidate hydrochloride) extended-release capsules, for oral use. 2018; https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/209311s000lbl.pdf. Accessed January 29, 2019.

4. U.S. Food and Drug Administration. Focalin (dexmethylphenidate hydrochloride) tablets, for oral use. 2019; https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021278s011s019lbl.pdf. Accessed January 29, 2019.

5. U.S. Food and Drug Administration. Focalin XR (dexmethylphenidate hydrochloride) extended-release tablets, for oral use. 2019; https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021802s019s029lbl.pdf. Accessed January 29, 2019.

6. U.S. Food and Drug Administration. Ritalin (methylphenidate hydrochloride) tablets, for oral use. 2019; https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/010187s071s082,018029s041s051lbl.pdf. Accessed January 29, 2019.

7. U.S. Food and Drug Administration. Ritalin LA (methylphenidate hydrochloride) extended-release capsules, for oral use. 2019; https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021284s016s029lbl.pdf. Accessed January 29, 2019.

8. U.S. Food and Drug Administration. Ritalin-SR (methylphenidate hydrochloride) extended-release tablets, for oral use. 2019; https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/010187s071s082,018029s041s051lbl.pdf. Accessed January 29, 2019.

9. Wigal T, Brams M, Frick G, Yan B, Madhoo M. A randomized, double-blind study of SHP465 mixed amphetamine salts extended-release in adults with ADHD using a simulated adult workplace design. *Postgrad Med*. 2018;130(5):481-493. doi: 10.1080/00325481.2018.1481712.

Appendix A. Abstracts of Eligible Studies

Head-to-Head RCTs

McCracken JT, McGough JJ, Loo SK, et al. Combined stimulant and guanfacine administration in attention-deficit/hyperactivity disorder: a controlled, comparative study. *J Am Acad Child Adolesc Psychiatry*. 2016;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. Copyright © 2016 American Academy of Child and Adolescent Psychiatry. Published by Elsevier Inc. All rights reserved.

Ni H-C, Lin Y-J, Gau SS-F, Huang H-C, Yang L-K. An open-label, randomized trial of methylphenidate and atomoxetine treatment in adults with ADHD. *J Atten Disord*. 2017;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 JH, Lee YS, Sohn JH, Han DH. Effectiveness of atomoxetine and methylphenidate for problematic online gaming in adolescents with attention deficit hyperactivity disorder. *Hum Psychopharmacol.* 2016;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.

Shang C-Y, Pan Y-L, Lin H-Y, Huang L-W, Gau SS-F. An open-label, randomized trial of methylphenidate and atomoxetine treatment in children with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol.* 2015;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-naive children and adolescents with ADHD.

Snircova E, Marcincakova-Husarova V, Hrtanek I, Kulhan T, Ondrejka I, Nosalova G. Anxiety reduction on atomoxetine and methylphenidate medication in children with ADHD. *Pediatr Int*. 2016;58(6):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.

Su Y, Yang L, Stein MA, Cao Q, Wang Y. 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. *J Child Adolesc Psychopharmacol.* 2016;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 <=1), robust improvement (ADHD-RS-IV >=40% decrease in total score), or improvement (>= 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.

Wigal T, Brams M, Frick G, Yan B, Madhoo M. A randomized, double-blind study of SHP465 mixed amphetamine salts extended-release in adults with ADHD using a simulated adult workplace design. *Postgrad Med.* 2018;130(5):481-493.

OBJECTIVES: The objective of this paper was to evaluate the efficacy, duration of effect, and tolerability of SHP465 mixed amphetamine salts (MAS) extended-release versus placebo and immediate-release MAS (MAS IR) in adults with attention-deficit/hyperactivity disorder (ADHD). METHODS: Adults with ADHD Rating Scale, Version IV (ADHD-RS-IV) scores >/=24 were randomized to SHP465 MAS (50 or 75 mg),

placebo, or 25 mg MAS IR in a double-blind, three-period, crossover study using a simulated adult workplace environment. On the final day of each 7-day treatment period, efficacy was assessed for 16 h postdose. Primary efficacy analyses for Permanent Product Measure of Performance (PERMP) total score averaged across all postdose assessments and each postdose time point were conducted in the intent-to-treat population using a mixed linear model. Secondary end-points included PERMP problems attempted and answered correctly and ADHD-RS-IV scores based on clinician ratings of counselor observations using the Time Segment Rating System and participant self-report. Tolerability assessments included treatment-emergent adverse events (TEAEs) and vital signs. RESULTS: Least squares mean (95% CI) treatment differences (combined 50/75 mg SHP465 MAS-placebo) significantly favored SHP465 MAS over placebo for PERMP total score averaged across all postdose assessments (18.38 [11.28, 25.47]; P < .0001) and at each postdose assessment (all P < .02). Nominal superiority of MAS IR over placebo for PERMP total score averaged across all postdose assessments was observed (nominal P = .0001); treatment differences between SHP465 MAS and MAS IR were not significant (nominal P = .2443). The two most frequently reported TEAEs associated with SHP465 MAS were insomnia (36.5%) and anorexia (21.2%). Mean increases in pulse and blood pressure with SHP465 MAS exceeded those of placebo. CONCLUSIONS: SHP465 MAS (combined 50/75 mg) significantly improved PERMP total score versus placebo, with superiority observed from 2 to 16 h postdose. The tolerability profile of SHP465 MAS was similar to previous reports of SHP465 MAS in adults with ADHD. CLINICAL TRIAL REGISTRATION: https://clinicaltrials.gov/ct2/show/NCT00928148 identifier is NCT00928148.

Zhu X, Sun X, Zhang Y, Liu K, Zhao L. A randomized parallel-controlled study of curative effect and safety of atomoxetine and methylphenidate in treatment of ADHD in children. *Int J Clin Exp Med.* 2017;10:9576-9582.

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 ADHDSeverity (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.

Secondary Analyses

Bilder RM, Loo SK, McGough JJ, et al. Cognitive effects of stimulant, guanfacine, and combined treatment in child and adolescent attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2016;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.

Dittmann RW, Cardo E, Nagy P, et al. 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. **2014;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.

Loo SK, Bilder RM, Cho AL, et al. Effects of d-methylphenidate, guanfacine, and their combination on electroencephalogram resting state spectral power in attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2016;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.

Nagy P, Hage A, Coghill DR, et al. 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. *Eur Child Adolesc Psychiatry*. 2016;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.

Ni H-C, Hwang Gu S-L, Lin H-Y, et al. 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. *J Psychopharmaco.* 2016;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.

Santisteban JA, Stein MA, Bergmame L, Gruber R. Effect of extended-release dexmethylphenidate and mixed amphetamine salts on sleep: a double-blind, randomized, crossover study in youth with attention-deficit hyperactivity disorder. *CNS Drugs*. 2014;28(9):825-833.

OBJECTIVE: We sought to determine the dose-response effects of extended-release (ER) dexmethylphenidate (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.

Sayer GR, McGough JJ, Levitt J, et al. Acute and long-term cardiovascular effects of stimulant, guanfacine, and combination therapy for attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol*. 2016;26(10):882-888.

OBJECTIVES: This study examines cardiovascular (CV) effects of guanfacine immediate-release (GUAN-IR), dexmethylphenidate 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 (5-20 mg/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.

Appendix B. ITS Ratings and Definitions

The *Is There a There There Scale* (ITS) consists of 3 ratings: *no*, *maybe,* and *yes*. The definitions of these ratings and methods for selection are described below. Center for Evidence-based Policy (Center) researchers will use these definitions to rate each surveillance topic. The assigned rating does not require Drug Effectiveness Review Project (DERP) participants to follow this guidance. Each rating is strictly based on the identified new research and clinical information and is not comprehensive to all aspects of policy decision making, such as competing priorities, budget, and internal and external state agency needs.

No

- We did not find evidence or information that would indicate a need to update the report or develop a derivative research product.
- A rating of *No* is typically given when there are few new studies and/or no new meaningful studies, and no new serious harms.

Maybe

- We found some evidence or information that might suggest a need to update the report or develop a derivative research product.
- A rating of *Maybe* is typically given when there are multiple new comparative trials or at least 1 new meaningful study or serious harm.

Yes

- We found evidence or information that suggests a need to update the report or develop a derivative research product.
- A rating of *Yes* is typically given when there are multiple new comparative trials and meaningful studies and new serious harms, drugs, formulations, or indications.