# Drug Class Review

# Pharmacologic Treatments for Attention Deficit Hyperactivity Disorder

**Expanded Scan Report**

**January 2017**

Last Report: Update #5, July 2015

Last Preliminary Update Scan: Scan #1, June 2016

The purpose of Drug Effectiveness Review Project reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Brittany H. Lazur, MPH
Ian Blazina, MPH
Marian McDonagh, PharmD

Drug Effectiveness Review Project
Marian McDonagh, PharmD, Principal Investigator

Pacific Northwest Evidence-based Practice Center
Roger Chou, MD, Director
Marian McDonagh, PharmD, Associate Director

Oregon Health & Science University

# OBJECTIVE

The purpose of this expanded version of a preliminary updated literature scan process is to provide a preview of the volume and nature of new research that has emerged subsequent to the previous full review, with some additional features to allow more insight into the potential impact of the new evidence. This expanded scan builds on prior preliminary update scans. The expanded scan includes quality assessment of key trials that would fill a gap in evidence in the last full report update, with presentation of key results, and the study authors' conclusions. Comprehensive review and synthesis of the new research presented in this report along with previous evidence is not included, and would follow only if a full update of the report were commissioned. The literature search for this report focuses only on new randomized controlled trials, comparative effectiveness reviews, and actions taken by the U.S. Food and Drug Administration (FDA) since the last report. Other important studies could exist.

## Dates of Previous Reports

Update #5: July 2015 (searches through April 2015)
Update #4: December 2011
Update #3: October 2009
Update #2: November 2007
Update #1: May 2006
Original Report: September 2005

## Dates of Previous Preliminary Update Scans

Scan #1: June 2016 (searches through May 2016)

## Scope and Key Questions *(from last update report)*

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 *(from last update report)*

### *Populations*

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

- Attention deficit disorder

- Attention deficit hyperactivity disorder

### *Interventions*

| Generic Name | Trade name | Forms |
|---|---|---|
| Mixed amphetamine salts | Adderall XR® | Extended-release oral capsule |
| Amphetamine sulfate | Evekeo® | Oral tablet |
| Atomoxetine hydrochloride | Strattera® | Oral capsule |
| Clonidine hydrochloride | Catapres® | Oral tablet |
| | Catapres TTS® | Extended-release transdermal film |
| | Kapvay® | Extended-release oral tablet |
| Dexmethylphenidate hydrochloride | Focalin® | Oral tablet |
| | Focalin XR® | Extended-release oral capsule |
| Dextroamphetamine sulfate | Dexedrine® | Extended-release oral capsule |
| | Dexedrine Spansule® | Sustained-release oral capsule |
| Guanfacine hydrochloride | Intuniv® | Extended-release oral tablet |
| | Tenex® | Oral tablet |
| Lisdexamfetamine dimesylate | Vyvanse® | Oral capsule |
| Methamphetamine hydrochloride | Desoxyn® | Oral tablet |
| Methylphenidate | Daytrana® | Extended-release transdermal film |
| Methylphenidate hydrochloride | Concerta® | Extended-release oral tablet |
| | Metadate CD® | Extended-release oral capsule |
| | Metadate ER® | Extended-release oral tablet |
| | Methylin® | Chewable oral tablet and oral solution |
| | Methylin ER® | Extended-release oral tablet |
| | Quillivant XR® | Extended-release oral suspension |
| | Ritalin® | Oral tablet |
| | Ritalin LA® | Extended-release oral capsule |
| | Ritalin-SR® | Extended-release oral tablet |
| Modafinil | Provigil® | Oral tablet |
| Armodafinil | Nuvigil® | Oral tablet |

Abbreviations: CD, controlled delivery; ER or XR, extended release; LA, long acting; SR, sustained release; TTS, transdermal therapeutic system

### *Comparators*

Primary comparisons are included pharmacologic treatments (above) compared to each other.

- Comparisons by general mechanism of action (i.e. stimulants and nonstimulants) and by duration of formulation (i.e. short-, intermediate and long-acting) will also be made.

### *Effectiveness Outcomes*

1. Functional capacity (social, academic and occupational productivity)
2. Quality of life (patient, family members, caregivers, teachers)
3. Time to onset of effectiveness
4. Duration of effectiveness (length of therapy)

### *Efficacy Outcomes*

1. Symptom response (e.g., inattention, hyperactivity-impulsivity, global ratings, etc.), generally defined as the proportion of patients achieving a specific magnitude of improvement in scores on ADHD rating scales.

Numerous ADHD-specific and other psychiatric rating scales, as well as neuropsychological testing methods, are used to measure symptoms of ADHD. We limited our analyses to rating scales/tests for which we found published evidence of good reliability and validity.

### *Harms*

Tolerability

2. Overall adverse effect reports
3. Withdrawals due to adverse effects and overall withdrawal
4. Specific adverse events (insomnia, anorexia, abuse potential, tics, anxiety and sexual dysfunction)

Serious and long-term (>12 months) adverse effects

1. Hepatotoxicity
2. Cardiovascular events
3. Growth effects
4. Suicide and suicidal behavior

Misuse/diversion

1. Trading, selling
2. Compliance, overdose
3. Development of substance abuse disorders

### *Study Designs*

- Head-to-head randomized controlled trials
- Good-quality systematic reviews with similar scope and recent searches
- Comparative observational studies (cohort studies including database studies, and case-control studies) to examine differences in effectiveness outcomes and serious and long-term harms and misuse/diversion outcomes

## METHODS FOR EXPANDED SCAN

In consultation with DERP participating organization representatives, methods and scope for an expanded version of a scan of studies published since the last report or preliminary update scan were developed. The expanded scan focuses on evidence for new drugs and drugs with little or no evidence in the prior report, with emphasis placed on head-to-head comparisons.

### Literature Searches

To identify relevant citations, we searched Ovid MEDLINE® and Ovid MEDLINE® In-Process & Other Non-Indexed Citations from January 2015 through December 2016 using terms for included drugs. We limited results to randomized controlled trials and controlled clinical trials conducted in humans and published in English. 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/), the VA Evidence-based Synthesis Program (http://www.hsrd.research.va.gov/publications/esp/reports.cfm), and University of York Centre for Reviews and Dissemination (http://www.york.ac.uk/inst/crd/crdreports.htm - "Our Publications" and "Our Databases"). All citations were imported into an electronic database (EndNote X7) and duplicate citations were removed.

We also searched the FDA website (http://www.fda.gov/medwatch/safety.htm and http://www.accessdata.fda.gov/scripts/cder/drugsatfda/) for identification of new drugs and new

serious harms (e.g. 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.

## Study Selection

We first selected all trials that appeared to meet inclusion criteria for this report, as per usual DERP procedures for a preliminary update scan. We provided an accounting of all potentially eligible studies published since the last full report update.

From this set of trials, we then selected a subset for full-text review, data abstraction and quality assessment, focusing on evidence for drugs not included in the last report, or drugs with no head-to-head evidence in the last report. We prioritized primary publications of head-to-head randomized controlled trials, but for drugs without head-to-head evidence we included placebo-controlled trials. Secondary publications (e.g. subgroup analyses) were screened to identify any that resulted in strongly differing results compared to the overall trial; any such publications are noted. One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

## Quality Assessment

For those studies meeting the criteria for full-text review and data abstraction (above), a single reviewer assessed the quality of primary randomized controlled trials using the DERP methodology, resulting in ratings of good, fair, or poor. Any study rated poor-quality was reviewed by a second reviewer, and any differences in judgment resolved through consensus.

## Data Abstraction

For trials selected for additional assessment, we abstracted study identifiers (author, year, study name), study quality, study/patient characteristics (duration, number of participants, mean age), and 2 key benefit outcomes and 2 key harms outcomes determined a priori by discussion among the team. These outcomes were:

### *Benefit Outcomes*

- Symptom response (e.g., inattention, hyperactivity-impulsivity, global ratings, etc.), based on scales
- Functional capacity (social, academic and occupational productivity)

### *Harms Outcomes*

- Overall adverse effect reports
- Withdrawals due to adverse effects

We also abstracted the author's conclusion statement.

# RESULTS

## New Drugs

### *Identified since the last update report*

**Table 1. Newly approved drugs and formulations to treat ADHD since last DERP report**

| Generic Name | Trade name | FDA Approval Date | Forms |
|---|---|---|---|
| Amphetamine | Adzenys XR-ODT™ | 1/27/2016 | Extended-release orally disintegrating tablet |
| | Dyanavel™ XR | 10/19/2015 | Extended-release oral suspension |
| Methylphenidate hydrochloride | Aptensio XR® | 4/17/2015 | Extended-release oral capsule |
| | QuilliChew ER™ | 12/4/2015 | Extended-release chewable tablet |

Abbreviations: ER, extended-release; ODT, orally disintegrating tablet; XR, extended-release.

## New Serious Harms (Boxed Warnings)

### *Identified since the last update report*

We have identified no new serious harms (e.g. boxed warnings) since the last update report on this topic.

## New Comparative Effectiveness Reviews

### *Identified since the last update report*

We have identified no potentially relevant new comparative effectiveness reviews published since the last update report that are completed at this time. There is an ongoing AHRQ comparative effectiveness review entitled "Diagnosis and Treatment of Attention Deficit Hyperactivity Disorder (ADHD) in Children and Adolescents". This is an update to the 2011 AHRQ review on effectiveness of ADHD treatment in at-risk preschoolers, the long-term effectiveness of ADHD treatment in all ages, and the variability in ADHD prevalence, diagnosis and treatment. The protocol indicates that a wide range of drug treatments will be compared to each other (see https://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=2148). The draft report was posted in November 2016, such that the final report is expected by spring 2017.

## Randomized Controlled Trials

### *Identified since the last update report*

Medline searches conducted since the last update report yielded 95 new citations, of which 2 head-to-head trials and 3 secondary analyses of head-to-head trials included in the last update report met inclusion criteria (Table 2). None of these trials included the new drug formulations. Key study characteristics and findings of the primary head-to-head studies are available in Table 3, and those of the secondary analyses are available in Table 4. Quality assessments of the included studies are available in Appendix A and descriptions of the scales used in these studies are available in Appendix B.

**Table 2. New head-to-head trials of pharmacologic treatments for ADHD**

| Author, Year | N | Comparison | Population |
|---|---|---|---|
| ***New Primary Trials*** | | | |
| Shang, 2015[1] | 160 | Atomoxetine vs. OROS methylphenidate | Children with ADHD |
| Bedard, 2015[2] | 143 | Atomoxetine vs. OROS methylphenidate | Youth with ADHD |
| ***New Secondary Analyses*** | | | |
| Dittmann, 2014[3] Nagy, 2016[4] | 267 | Atomoxetine vs. lisdexamfetamine | Children and adolescents with ADHD |
| Santisteban, 2014[5] | 65 | Mixed amphetamine salts ER vs. dexmethylphenidate ER | Youth with ADHD |

Abbreviations: ADHD, attention deficit hyperactivity disorder; ER, extended release; OROS, osmotic release oral system.

### *New Primary Studies*

The 2 primary head-to-head randomized controlled trials[1,2] compared atomoxetine with OROS methylphenidate in children with ADHD. Sample sizes ranged from 143 to 160 patients, duration of treatment ranged from 8 to 24 weeks, and mean participant age ranged from 9.8 to 10.5 years. One trial[2] was rated poor-quality due to unclear randomization and allocation concealment techniques, differences between groups at baseline, and >20% overall attrition. This study's primary objective was to compare the drugs on surrogate measures of attention and reaction time, outcomes not included in DERP reports. The other trial[1] was rated fair-quality.

Based on the total ADHD Rating Scale-IV (ADHD-RS-IV) score, both studies found that atomoxetine and OROS methylphenidate showed statistically significant reductions in ADHD symptoms from baseline to 8 weeks and 24 weeks treatment duration, but there were no statistically significant differences in ADHD symptoms between treatment groups.[1,2] In the fair-quality study by Shang,[1] both atomoxetine and OROS methylphenidate also showed significant decreases in global ADHD symptoms severity, as measured by the Clinical Global Impressions-ADHD Severity Scale (CGI-ADHD-S), but again there were no significant differences between atomoxetine and OROS methylphenidate in mean change of CGI-ADHD-S scores at week 8 (-2.34 vs. -2.45, P=0.465) or week 24 (-2.40 vs. -2.57, P=0.308). There were also no significant differences between groups in mean reductions in Swanson, Nolan and Pelman-IV scale (SNAP-IV) total score from baseline to weeks 8 and 24 in this study. Withdrawals due to adverse events were the same between groups in this study, and no adverse event outcomes were reported in the other study.

### *New Secondary Analyses*

Two publications[3,4] were secondary analyses of a head-to-head randomized controlled trial included in the last update report.[6] This fair-quality study compared atomoxetine with lisdexamfetamine in children or adolescents with ADHD who had a previous inadequate response to methylphenidate. The sample size for the primary study and the secondary analyses was 267 patients, the duration of treatment was 9 weeks, and the mean age of participants was approximately 10.7 years. The secondary analyses agree with the overall findings of the primary study, but provide data on sustained response and functioning using validated measures.

The first of these secondary analyses did not add much to the previous findings for response. The primary publication reported response defined as a Clinical Global Impressions-Improvement (CGI-I) score of 1 (very much improved) or 2 (much improved), and found lisdexamfetamine to be superior (Table 4). This publication reported additional response outcomes, using definitions of 25%, 30% or 50% reduction in the ADHD-RS-IV score. Again, compared with atomoxetine, significantly more patients taking lisdexamfetamine met response criteria of 25% (90.5% vs. 76.7%), 30% (88.1% vs. 73.7%), or 50% reductions (73.0% vs.

50.4%) by week 9 (P-values <0.001).[3] This publication also reported "sustained response", where the response was maintained from week 4 through week 9. Again, significantly more patients taking lisdexamfetamine compared with atomoxetine exhibited sustained response, when defined as an ADHD-RS-IV reduction of ≥25% (66.1% vs. 51.1%), ≥30% (61.4% vs. 47.4%), and ≥50% (41.7% vs. 23.7%) (P-values <0.05). They also reported scores on the CGI-Severity scale as a proxy for remission, and found significantly more patients taking lisdexamfetamine (52.0% vs. 39.3%) meeting criteria of a CGI-S score of 1 (normal, not at all ill) or 2 (borderline mentally ill) from weeks 4 through 9.

Evidence from the other secondary analysis[4] of the same trial indicated that parents rated their children treated with lisdexamfetamine to have better improvement in functioning than parents of children assigned to atomoxetine. This was quantified by a greater increase in least-squares mean change in Weiss Functional Impairment Rating Scale-Parent Report (WFIRS-P) total score from baseline to endpoint compared with patients treated with atomoxetine (-0.35, 95% CI -0.42 to -0.29 vs. -0.27, 95% CI -0.33 to -0.20), with a significant difference between lisdexamfetamine and atomoxetine treatment (P=0.046, effect size=0.27). It is not clear whether these changes from baseline or the difference between them are clinically important.

The last publication[5] was a secondary analysis of a head-to-head randomized controlled crossover trial also included in the last update report.[7] This study compared extended-release mixed amphetamine salts with extended-release dexmethylphenidate in children with ADHD and was also rated fair-quality. Each drug was given for 4 weeks, with 1 week of placebo randomly inserted. The sample size for the primary study was 65, but only 37 participants had sufficient sleep data and were included in the secondary analysis. The mean age of participants was 11.8 years. This secondary analysis added data on sleep duration, sleep start time, sleep end time, and nocturnal awakenings that were not already included in the primary trial publication. There were no significant differences in sleep duration, sleep start time, nocturnal awakenings or sleep end time in children taking extended-release mixed amphetamine salts compared with those taking extended-release dexmethylphenidate. While the analysis comparing the drugs was not affected by dose, there was a significant reduction in minutes of sleep duration with 25 mg or 30 mg doses compared with 10 mg doses of either stimulant (mean 21 minutes, P <0.05). No new adverse event data were reported.

## Table 3. New randomized controlled trials of pharmacologic agents for ADHD

| Author, Year<br>Country<br>Trial Name/#<br>(Quality) | Drug Comparison | N<br>Duration of treatment<br>Mean Age<br>Population | Benefit Outcome | Harms Outcome | Author's Conclusions |
|---|---|---|---|---|---|
| ***Atomoxetine vs. OROS methylphenidate*** | | | | | |
| Shang, 2015[1]<br>Taiwan<br>NCT00916786<br>(Fair) | Atomoxetine 0.5 mg/kg to 1.2 mg/kg daily<br>vs.<br>OROS methylphenidate 18 mg to 54 mg daily<br><br>(Drug doses titrated depending on clinical response and adverse effects) | 160<br>24 weeks<br>9.8 years old | Atomoxetine vs. OROS methylphenidate<br><br>Symptoms<br>ADHD-RS-IV: both ATX and OROS MPH showed statistically significant reductions in ADHD symptoms at each time point (weeks 8 and 24), but no significant differences between the groups at each time point. No significant differences in mean changes from baseline to week 8 between ATX and OROS MPH groups.<br><br>CGI-ADHD-S: both ATX and OROS MPH showed significant decreases in global ADHD symptoms severity (weeks 2 to endpoint).<br>Mean change from baseline to week 8, points: 2.34 vs. 2.45<br>Mean change from baseline to endpoint (week 24), points: 2.40 vs. 2.57<br>No significant group differences in mean reductions from baseline to week 8 (P=0.465) and to endpoint (P=0.308) were found between ATX and OROS MPH.<br><br>SNAP-IV: no significant differences between groups in mean reductions in total score from baseline to week 8 and endpoint. | Atomoxetine vs. OROS methylphenidate<br><br>Withdrawals due to adverse events, n: 3 vs. 3 | "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." |

## Table 3. New randomized controlled trials of pharmacologic agents for ADHD

| Author, Year<br>Country<br>Trial Name/#<br>(Quality) | Drug Comparison | N<br>Duration of treatment<br>Mean Age<br>Population | Benefit Outcome | Harms Outcome | Author's Conclusions |
|---|---|---|---|---|---|
| Bedard, 2015[2]<br>US<br>NCT00183391<br>(Poor) | Atomoxetine 0.5 mg/kg, 1.0 mg/kg, 1.4 mg/kg, 1.8 mg/kg<br>vs.<br>OROS methylphenidate 18 mg, 36 mg, 54 mg, 72 mg<br><br>(both drugs titrated to most effective dose) | 143<br>8-12 weeks (crossover study with 2 4-6 week treatment periods)<br>10.5 years old | <u>Symptom response (ADHD-RS)</u><br>Both MPH and ATX produced significant improvement in ADHD symptoms from pre- to post-treatment (P<0.001 for both).<br><br>Changes from baseline in ADHD-RS were not significantly associated with changes in any CPT measure for MPH or ATX.<br><br>Surrogate measures of attention and response time were also reported. | NR | "MPH [methylphenidate] has greater effects than ATX [atomoxetine] 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." (refers to surrogate measures; CPT II = Conners' Continuous Performance Test II) |

Abbreviations: ADHD, attention deficit hyperactivity disorder; ADHD-RS, ADHD Rating Scale; ATX, atomoxetine; CGI-ADHD-S, Clinical Global Impressions-ADHD Severity Scale; CPT-II, Conners' Continuous Performance Test II; ER, extended-release; LDX, lisdexamfetamine; MPH, methylphenidate; NR, not reported; NS, not significant; OROS, osmotic-release oral system; SNAP-IV, Swanson, Nolan and Pelman-IV (scale).

## Table 4. New secondary analyses of a randomized controlled trial of pharmacologic agents for ADHD included in the last update report

| Author, Year<br>Country<br>Trial Name/#<br>(Quality) | Drug<br>Comparison | N<br>Duration of treatment<br>Mean Age<br>Population | Benefit Outcome | Harms Outcome | Author's Conclusions |
|---|---|---|---|---|---|
| ***Atomoxetine vs. lisdexamfetamine*** | | | | | |
| Dittmann, 2013[6]<br>**Dittmann, 2014[3]**<br>**Nagy, 2016[4]**<br>US, Canada, 7 European countries<br>NCT01106430<br>(Fair) | Lisdexamfeta-mine 30 mg, 50 mg, 70 mg vs. Atomoxetine 0.5 to 1.2 mg/ kg (<70 kg) 40 mg, 80 mg or 100 mg (≥70 kg) | 267<br>9 weeks<br>10.7 years old | Lisdexamfetamine vs. atomoxetine<br><br><u>Dittmann, 2013 (primary study included previously)</u><br>Median time to first clinical response (CGI-I 1 or 2): 12.0 days (95% CI, 8.0–16.0) vs 21.0 days (95% CI, 15.0–23.0), p=0.001<br><br>% responding to treatment by week 9: 81.7 % (95% CI, 75.0–88.5) vs 63.6 % (95% CI, 55.4–71.8), p=0.001 using a definition of clinical response as a Clinical Global Impressions-Improvement (CGI-I) score of 1 (very much improved) or 2 (much improved).<br><br>Change from baseline in ADHD-RS-IV total score by visit 9, mean (SD): -26.3 (11.94) vs -19.4 (12.82)<br><br>ADHD-RS-IV total score LDX and ATX difference in least-squares mean change from baseline: -6.5 (95% CI, -9.3 to -3.6); p<0.001; effect size 0.56<br><br>**<u>Dittmann, 2014 (new)</u>**<br>**Patients meeting response criteria by week 9[a]:**<br>**25% reduction, %: 90.5 vs. 76.7, P<0.01**<br>**30% reduction, %: 88.1 vs. 73.7, P<0.01**<br>**50% reduction, %: 73.0 vs. 50.4, P<0.01**<br><br>**Patients with sustained response[b]:**<br>**ADHD-RS-IV ≥25%, %: 66.1 vs. 51.1, P<0.05**<br>**ADHD-RS-IV ≥30%, %: 61.4 vs. 47.4, P<0.05**<br>**ADHD-RS-IV ≥50%, %: 41.7 vs. 23.7, P<0.05**<br>**CGI-I score 1 or 2, %: 52.0 vs. 39.3, P<0.05** | Lisdexamfetamine vs. atomoxetine<br><br><u>Dittmann, 2013 (primary study included previously)</u><br>Any treatment-emergent adverse events (TEAEs), %: 71.9 vs 70.9<br>Any TEAE leading to discontinuation of study drug, %: 6.3 vs 7.5 | **<u>Dittmann, 2014</u>**<br>**"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."**<br><br>**<u>Nagy, 2016</u>**<br>**"In conclusion, this study has shown that both LDX and ATX treatment can improve functioning, as measured by the WFIRS-P, in children and adolescents with ADHD who have experienced a clinically inadequate response to MPH (as judged by investigators). Improvements overall and in certain domains were statistically significantly greater in magnitude with LDX treatment than with ATX treatment, within the time frame of the study."** |

## Table 4. New secondary analyses of a randomized controlled trial of pharmacologic agents for ADHD included in the last update report

| Author, Year<br>Country<br>Trial Name/#<br>(Quality) | Drug<br>Comparison | N<br>Duration of treatment<br>Mean Age<br>Population | Benefit Outcome | Harms Outcome | Author's Conclusions |
|---|---|---|---|---|---|
| | | | **Remission: CGI-S score of 1[c] or 2[d] at week 9, %: 60.7 vs. 46.3 (P-value calculated to be 0.024)**<br><br>**<u>Nagy, 2016 (new)</u>**<br>**WFIRS-P total score, LS mean change from baseline to endpoint:**<br>**-0.35 (95% CI -0.42 to -0.29) vs.**<br>**-0.27 (95% CI -0.33 to -0.20)**<br><br>**Difference in WFIRS-P total score LS mean change (LDX vs. ATX): P=0.046, effect size=0.27** | | |
| ***Mixed amphetamine salts ER vs. dexmethylphenidate ER*** | | | | | |
| Stein, 2011[7]<br>**Santisteban, 2014[5]**<br>US<br>NCT00393042<br>(Fair) | Mixed amphetamine salts ER 10 mg, 20 mg, 30 mg<br>vs.<br>Dexmethylphe-nidate ER 10 mg, 20 mg, 30 mg | 65 (37 had sufficient sleep data)<br>8 weeks (crossover study with 4 week treatment periods)<br>11.8 years old | Mixed amphetamine salts ER vs. Dexmethylphenidate ER<br><br><u>Stein, 2011 (primary study included previously)</u><br>% of participants at highest dose rated as "much" or "very much" improved on the ADHD RS using the Reliable Change Index (RCI): 80 vs 79, p=0.855<br><br>% achieving Clinical Global Impressions-Improvement "much" or "very much" improved:<br>10 mg vs 20 mg vs 25 -30 mg ER MAS vs placebo: 15 vs 23 vs 25 vs 13<br>10 mg vs 20 mg vs 25 -30 mg ER d-MPH vs placebo: 9 vs 23 vs 24 vs 9<br><br>Dose-related decreases in Total symptom scores: p < 0.001<br><br>Dose-related decreases in CGI-S scores: p <0.001 | <u>Stein, 2011 (primary study included previously)</u><br>Withdrawals due to adverse events: 6 total | **<u>Santisteban, 2014</u>**<br>**"Overall, both ER MAS and ER d-MPH were associated with significant, dose-dependent reductions in sleep duration. Higher doses were associated with shorter sleep durations due to later sleep initiation times. There were no differences between the two long-acting MPH and amphetamine medications."** |

## Table 4. New secondary analyses of a randomized controlled trial of pharmacologic agents for ADHD included in the last update report

| Author, Year<br>Country<br>Trial Name/#<br>(Quality) | Drug<br>Comparison | N<br>Duration of treatment<br>Mean Age<br>Population | Benefit Outcome | Harms Outcome | Author's Conclusions |
|---|---|---|---|---|---|
| | | | WFIRS Total Score: p = 0.008<br><br>**<u>Santisteban, 2014 (new)</u>**<br>**Reduction in minutes of sleep duration for different stimulant doses (head-to-head comparison only):**<br>**25 mg or 30 mg vs. 10 mg, mean (SD): 21.14 (29.15)**<br><br>**No significant differences between ER MAS and ER d-MPH on sleep duration, sleep start time, and sleep end time.**<br><br>**No significant interactions between stimulant medication and dose were found for sleep duration, sleep start time, and sleep end time.**<br><br>**No significant differences in number of nocturnal awakenings between ER MAS and ER d-MPH, and no significant interactions between dose and medication.** | | |

Abbreviations: ADHD, attention deficit hyperactivity disorder; ADHD-RS, ADHD Rating Scale; ATX, atomoxetine; ER, extended-release; LDX, lisdexamfetamine; MPH, methylphenidate; NR, not reported; NS, not significant; WFIRS-P, Weiss Functional Impairment Rating Scale-Parent Report.

**Bolding indicates data from the new secondary analyses identified in the Medline searches for this expanded scan.**

[a] Reduction from baseline in ADHD-RS-IV total score of at least 25%. 30%, or 50%.

[b] Meeting response criteria during weeks 4 through 9.

[c] CGI-S score of 1 = normal, not at all ill

[d] CGI-S score of 2 = borderline mentally ill

## SUMMARY

Since the last update report in 2015, there has been 4 new drug formulations approved by the FDA, no new boxed safety warnings, and no new comparative effectiveness reviews on this topic. There are 5 new publications regarding head-to-head trials, of which 2 are new primary trials comparing atomoxetine with OROS methylphenidate and 3 are new secondary analyses of 2 trials included in the last update report (1 comparing atomoxetine with lisdexamfetamine and 1 comparing extended-release mixed amphetamine salts with extended-release dexmethylphenidate). The secondary analyses provide additional data not included in the primary trials.

In 2 new primary head-to-head trials, both atomoxetine and OROS methylphenidate were shown to significantly decrease ADHD symptom-related outcomes from baseline, however there were no significant differences between the treatment groups in these outcomes or withdrawals due to adverse events.

In secondary analyses of trials included in the last update report, more children taking lisdexamfetamine achieved response according to multiple criteria, and achieved remission, than those taking atomoxetine over 9 weeks. Additionally, more patients experienced sustained response over 4 to 9 weeks of treatment. Another secondary analysis from this trial reported greater improvements in family, social, and school functioning according to parent assessment with lisdexamfetamine, but the change and the difference were very small.

A secondary analysis of a crossover trial of extended-release mixed amphetamine salts compared with extended-release dexmethylphenidate included in the last update report found no significant differences in sleep duration, sleep start time, nocturnal awakenings, or sleep end time between the drugs. When considered together, higher doses (25 mg or 30 mg per day) of extended-release mixed amphetamine salts or extended-release dexmethylphenidate resulted in shorter sleep duration compared with lower daily doses (10 mg per day). This secondary analysis added data on sleep outcomes that were not included in the primary trial publication.

# REFERENCES


1. Shang CY, Pan YL, Lin HY, Huang LW, Gau SS. An Open-Label, Randomized Trial of Methylphenidate and Atomoxetine Treatment in Children with Attention-Deficit/Hyperactivity Disorder. *Journal of Child & Adolescent Psychopharmacology.* 2015;25(7):566-573.
2. Bedard AC, Stein MA, Halperin JM, Krone B, Rajwan E, Newcorn JH. Differential impact of methylphenidate and atomoxetine on sustained attention in youth with attention-deficit/hyperactivity disorder. *Journal of Child Psychology & Psychiatry & Allied Disciplines.* 2015;56(1):40-48.
3. 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.
4. 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. *European Child & Adolescent Psychiatry.* 2016;25(2):141-149.
5. 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.
6. Dittmann RW, Cardo E, Nagy P, et al. Efficacy and safety of lisdexamfetamine dimesylate and atomoxetine in the treatment of attention-deficit/hyperactivity disorder: a head-to-head, randomized, double-blind, phase IIIb study. *CNS Drugs.* 2013;27(12):1081-1092.
7. Stein MA, Waldman ID, Charney E, et al. Dose effects and comparative effectiveness of extended release dexmethylphenidate and mixed amphetamine salts. *Journal of Child & Adolescent Psychopharmacology.* 2011;21(6):581-588.

# APPENDIX A. QUALITY RATINGS FOR INCLUDED RANDOMIZED CONTROLLED TRIALS

| Author, Year Trial Name | Randomization adequate? | Allocation concealment adequate? | Groups similar at baseline? | Outcome assessors blinded? | Clinician blinded? | Patient blinded? | Intention to treat? | Acceptable level of overall attrition (≤20%)? | Acceptable level of differential attrition (<10%)? | Overall quality |
|---|---|---|---|---|---|---|---|---|---|---|
| Bedard, 2015 | Unclear | Unclear | Unclear | Yes | Yes | Yes | No | No | Yes | Poor |
| Dittmann, 2014<br>Nagy, 2016 (secondary publications to Dittmann, 2013; QA for primary publication shown) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No; 23% overall | Yes; equal between groups | Fair |
| Santisteban, 2014 (companion to Stein, 2011; QA for primary publication shown) | Unclear | Unclear | Unclear. Higher % with no prior stimulant use in those not completing the crossover. | Yes | Yes | Yes | No | Yes | Unclear | Fair |
| Shang, 2015 | Yes | Unclear | Yes | No | No | No | Yes | Yes | Yes | Fair |

# APPENDIX B. SCALES USED IN NEW INCLUDED STUDIES

ADHD-RS-IV: ADHD Rating Scale-IV

- Validated 18-item scale (1 item for each DSM-IV diagnostic criteria)
- Semistructured interviews with patient's parent
- Assesses symptom severity over past week
- Four point scale for each item: 0=never or rarely, 1=sometimes, 2=often, 3=very often

CGI-ADHD-S: Clinical Global Impressions-ADHD Severity Scale

- Validated, single item rating of the clinician's assessment of global severity of ADHD symptoms in relation to the clinician's total experience with other ADHD patients
- Severity rated on 7-point scale from 1=normal, not at all ill, to 7=among the most extremely ill

CPT-II: Connor's Continuous Performance Test II

- Validated, computer-administered task
- Participants respond to 360 letters which appear on the monitor, one at a time, for 250 ms
- Participants press space bar for all letters except 'X', which happens on 10% of trials
- Interstimulus interval varies among 1, 2, or 4-s across 18 blocks of 20 trials each
- Evaluates indices of sustained attention including omission errors, reaction time for correct responses, reaction time variability, and commission errors

SNAP-IV: Swanson, Nolan and Pelman-IV scale

- 26-item scale; good validity and reliability
- Inattention (items 1-9), hyperactivity/impulsivity (items 10-18), oppositionality (items 19-26)
- Items rated on 4 point Likert scale: 0=not at all, 1=just a little, 2=quite a bit, 3=very much

WFIRS-P: Weiss Functional Impairment Rating Scale-Parent Report

- Provides a disorder-specific measure of functioning in children and adolescents with ADHD
- Good internal consistency; moderate convergent validity with other instruments
- 50-item questionnaire grouped into 6 domains (Family, Learning and School, Life Skills, Child's Self-Concept, Social Activities, and Risky Activities)
- Each item relates to previous month; scored on a 4-point Likert scale: 0=never or not at all; 1=sometimes or somewhat; 2=often or much; 3=very often or very much) or recorded as not applicable
- Higher scores indicate more severe functional impairment