Drug Class Review
on
Pharmacologic Treatments for ADHD

Preliminary Scan Report #3
September 2014

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.

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OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with Participating Organizations’ consideration of allocating resources toward a full update of this topic, a summary review, an addendum or a new drug horizon scan. Comprehensive review, quality assessment, and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the U.S. Food and Drug Administration (FDA) since the last report. Other important studies could exist.

Date of Last Update Report
Update #4, December, 2011 (searches through July 2011)

Date of Last Preliminary Update Scan Report
December 2013

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 with input from a statewide panel of experts (pharmacists, primary care clinicians, pain care specialists, and representatives of the public). Subsequently, the key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The Participating Organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The Participating Organizations approved the following key questions to guide this review:

1. Evidence on Effectiveness and Efficacy
   a. What is the comparative or noncomparative evidence that pharmacologic treatments for attention deficit disorders improve effectiveness outcomes?
      i. Comparisons include individual drugs, as well as between stimulants and nonstimulants, and immediate-release compared with intermediate-release compared with long-acting formulations.
      ii. Noncomparative evidence will be considered for drugs with no comparative evidence.
   b. What is the comparative efficacy between any included pharmacologic treatment, between stimulants and nonstimulants, and between immediate-release compared with intermediate-release compared with long-acting formulations, for attention deficit disorders?
2. Tolerability, Serious Adverse Events, Misuse, and Diversion
   
a. What is the evidence of comparative tolerability of different pharmacologic treatments, between stimulants and nonstimulants, and between immediate-release compared with intermediate-release compared with long-acting formulations, for attention deficit disorders?

b. What is the evidence of serious adverse events or long-term adverse events associated with use of pharmacologic treatments for attention deficit disorders?

c. What is the comparative or noncomparative evidence that pharmacologic treatments for attention deficit disorders impact the risk of misuse or illicit diversion in patients with no history of misuse or diversion?
   
i. Comparisons include individual drugs, as well as between stimulants and nonstimulants, and immediate-release compared with intermediate-release compared with long-acting formulations.

   ii. Noncomparative evidence will be considered for drugs with no comparative evidence.

3. Evidence in Subgroups of Patients
   
a. What is the evidence of benefits and harms of pharmacologic treatments, between stimulants and nonstimulants, and between immediate-release compared with intermediate-release compared with long-acting formulations, for attention deficit disorders in subgroups of patients based on demographics (age, racial groups, gender), socioeconomic status, other medications or therapy, or comorbidities (e.g. tics, anxiety, substance use disorders, disruptive behavior disorders)?

b. What is the comparative or noncomparative evidence of misuse or illicit diversion of pharmacologic treatments for attention deficit disorders in patients with current or past substance use disorder comorbidities?
   
i. Comparisons include individual drugs, as well as between stimulants and nonstimulants, and immediate-release compared with intermediate-release compared with long-acting formulations.

   ii. Noncomparative evidence will be considered for drugs with no comparative evidence.

Inclusion Criteria

Populations

Pediatric (age <3, <6, and 6-17 years), and adult (age ≥18 years) outpatients with attention deficit disorders

- Attention deficit disorder
- Attention deficit hyperactivity disorder
### Interventions

#### Table 1. Attention deficit hyperactivity disorder drugs

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade name</th>
<th>Referred to in this report as</th>
<th>Forms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mixed amphetamine salts</strong></td>
<td>Adderall XR</td>
<td>Mixed amphetamine salts XR</td>
<td>Extended-release oral capsule</td>
</tr>
<tr>
<td><strong>Atomoxetine hydrochloride</strong></td>
<td>Strattera</td>
<td>Atomoxetine</td>
<td>Oral capsule</td>
</tr>
<tr>
<td><strong>Clonidine hydrochloride</strong></td>
<td>Catapres</td>
<td>Immediate-release clonidine</td>
<td>Oral tablet</td>
</tr>
<tr>
<td></td>
<td>Kapvay™</td>
<td>Extended-release clonidine</td>
<td>Extended-release oral tablet</td>
</tr>
<tr>
<td><strong>Dexmethylphenidate</strong></td>
<td>Focalin®</td>
<td>Immediate-release dexmethylphenidate</td>
<td>Oral tablet</td>
</tr>
<tr>
<td>hydrochloride</td>
<td>Focalin XR®</td>
<td>Extended-release dexmethylphenidate</td>
<td>Extended-release oral capsule</td>
</tr>
<tr>
<td><strong>Dextroamphetamine</strong></td>
<td>Dexedrine®</td>
<td>Immediate-release dextroamphetamine</td>
<td>Oral tablet</td>
</tr>
<tr>
<td>sulfate</td>
<td>Dexedrine Spansule®</td>
<td>Sustained-release dextroamphetamine</td>
<td>Sustained-release oral capsule</td>
</tr>
<tr>
<td><strong>Guanfacine hydrochloride</strong></td>
<td>Intuniv®</td>
<td>Extended-release guanfacine</td>
<td>Extended-release oral tablet</td>
</tr>
<tr>
<td></td>
<td>Tenex®</td>
<td>Immediate-release guanfacine</td>
<td>Oral tablet</td>
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<tr>
<td><strong>Lisdexamfetamine dimesylate</strong></td>
<td>Vyvanse®</td>
<td>Lisdexamfetamine</td>
<td>Oral capsule</td>
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<td><strong>Methamphetamine</strong></td>
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<td>Oral tablet</td>
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<td>hydrochloride</td>
<td>Daytrana®</td>
<td>Methylphenidate transdermal</td>
<td>Extended-release transdermal film</td>
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<td><strong>Methylphenidate</strong></td>
<td>Biphentin®</td>
<td>Multilayer-release methylphenidate</td>
<td>Extended-release oral capsule</td>
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<td>hydrochloride</td>
<td>Concerta®</td>
<td>Methylphenidate osmotic-release oral system</td>
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<td>Metadate CD®</td>
<td>Methylphenidate CD</td>
<td>Extended-release oral capsule</td>
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<tr>
<td></td>
<td>Metadate ER®</td>
<td>Methylphenidate ER</td>
<td>Extended-release oral tablet</td>
</tr>
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<td></td>
<td>Methylin®</td>
<td>Methylphenidate chewable Methylphenidate solution</td>
<td>Oral chewable tablet and Oral solution</td>
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<td>Methylin ER®</td>
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<td>Extended-release oral tablet</td>
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<td>Quillivant™ XR</td>
<td>Quillivant XR</td>
<td>Extended-release oral suspension</td>
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<td><strong>Methylphenidate hydrochloride</strong></td>
<td>Ritalin®</td>
<td>Immediate-release methylphenidate</td>
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<td>Ritalin LA®</td>
<td>Methylphenidate long acting</td>
<td>Extended-release oral capsule</td>
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<td>Ritalin-SR®</td>
<td>Methylphenidate sustained-release</td>
<td>Extended-release oral tablet</td>
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<td><strong>Modafinil</strong></td>
<td>Alertec®</td>
<td>Modafinil</td>
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<tr>
<td></td>
<td>Provigil®</td>
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<td>Oral tablet</td>
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</table>

Abbreviations: ER or XR, extended release; LA, long acting; SR, sustained release

*Active ingredients = Amphetamine mixture (amphetamine aspartate; amphetamine sulfate; dextroamphetamine saccharate; dextroamphetamine sulfate)
**Effectiveness outcomes**
- Functional capacity (social, academic, and occupational productivity)
- Caregiver satisfaction (parent, teacher, other)
- Quality of life (patient, family members, caregivers, teachers)
- Time to onset of effectiveness
- Duration of effectiveness (length of therapy)

**Efficacy outcomes**
- Symptom response (inattention, hyperactivity-impulsivity, aggression, global ratings, etc.)

**Harms**

**Tolerability**
- Overall adverse effect reports
- Withdrawals due to adverse effects and overall withdrawal
- Specific adverse events (insomnia, anorexia, abuse potential, tics, anxiety, and sexual dysfunction)

**Serious adverse effects**
- Hepatotoxicity
- Cardiovascular events
- Growth effects

**Misuse/diversion**
- Trading, selling
- Compliance, overdose
- Development of substance abuse disorders

**Study designs**
- Effectiveness: Controlled clinical trials, good-quality systematic reviews, and comparative observational studies (cohort studies including database studies and case-control studies).
- Efficacy and general adverse events: Controlled clinical trials and good-quality systematic reviews.
- Serious adverse events: Controlled clinical trials, good-quality systematic reviews, and comparative observational studies (cohort studies including database studies and case-control studies).
- Misuse/diversion: Controlled clinical trials, good-quality systematic reviews, comparative observational studies (cohort studies including database studies and case-control studies), and noncomparative observational studies (before-after, time-series).
- Subgroups: Controlled clinical trials, good-quality systematic reviews, and comparative observational studies (cohort studies including database studies and case-control studies).
METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE and Ovid MEDLINE In-Process & Other Non-Indexed Citations from December 2013 to August 13, 2014 using terms for included drugs. 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, indications, and safety alerts. 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 X4) 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

New drugs identified in this Preliminary Update Scan
No new drugs were identified in the present scan.

New drugs identified in previous Preliminary Update Scan(s)
Methylphenidate hydrochloride (Quillivant™ XR) approved in Sept 2012 for the treatment of ADHD in pediatric patients aged 6-17 years and available as 5mg/mL oral suspension.

New Indications

New indications identified in this Preliminary Update Scan
No new indications were identified in the present scan.

Identified in previous Preliminary Update Scan(s)
Lisdexamfetamine dimesylate (Vyvanse®) capsules, approved in April 2013 for maintenance treatment in children with ADHD, ages 6-17 years.
Lisdexamfetamine dimesylate (Vyvanse®) capsules, approved in January 2012 for maintenance treatment in Adults with ADHD.
New Safety Alerts

Identified in this Preliminary Update Scan
No new boxed warnings were identified in the present scan.

Identified in previous Preliminary Update Scan(s)
December 2013: Methylphenidate products may in rare instances cause prolonged and sometimes painful erections known as priapism. New labeling under the Warnings sections of all methylphenidate products is:

Priapism
Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate products in both pediatric and adult patients. Priapism was not reported with drug initiation but developed after some time on the drug, often subsequent to an increase in dose. Priapism has also appeared during a period of drug withdrawal (drug holidays or during discontinuation). Patients who develop abnormally sustained or frequent and painful erections should seek immediate medical attention

Focalin® (dexamphetamine hydrochloride) and Focalin XR® (dexamphetamine hydrochloride) Extended-Release Capsules: as of May 2012, the following labeling revision:

Serious side effects include:

- Serious allergic reactions (symptoms can be difficulty breathing, swelling of the face, neck and throat, rashes and hives, fever)
- slowing of growth (height and weight) in children
- seizures, mainly in patients with a history of seizures
- eyesight changes or blurred vision

Strattera® (atomoxetine hydrochloride) capsule: as of August 2012, the following labeling revision:

Severe Liver Injury
Postmarketing reports indicate that Strattera can cause severe liver injury. Although no evidence of liver injury was detected in clinical trials of about 6000 patients, there have been rare cases of clinically significant liver injury that were considered probably or possibly related to Strattera use in postmarketing experience…

Strattera® (atomoxetine hydrochloride) capsule: as of June, 2012, the following labeling revision

Severe Cardiovascular Disorder
Strattera® should not be used in patients with severe cardiovascular disorders whose condition would be expected to deteriorate if they experience increases in blood pressure or heart rate that could be clinically important (for example, 15 to 20 mm Hg in blood pressure or 20 beats per minute in heart rate).
Comparative Effectiveness Reviews

Reviews identified in this Preliminary Update Scan
No new relevant comparative effectiveness reviews were identified in the present scan.

Reviews identified in previous Preliminary Update Scan(s)
None.

Randomized Controlled Trials

Trials identified in this Preliminary Update Scan
Medline searches for the present scan resulted in 118 citations. Of these, 17 were potentially relevant new trials consisting of 5 new head-to-head trials and 12 new placebo-control trials. Of the new head-to-head trial publications identified in this scan, one was a post-hoc analysis. New head-to-head trials identified in the present scan are shaded in Table 2. New placebo-controlled trials identified in the present scan are shaded and listed by drug of study below.

Trials identified since the most recent Full Report
Since the last complete report update, we identified 53 new publications of trial results. Of these, 9 are head-to-head comparisons (2 in adults) and 44 are placebo-controlled trials (23 in adults). Of the head-to-head trial publications, one is a post-hoc analysis of a published trial involving the comparison of lisdexamfetamine dimesylate and OROS methylphenidate in children and adolescents. Of the placebo-controlled trial publications, 17 trials (12 in adults) are post-hoc or secondary analyses of published trials.

While many trials report efficacy and harms, some focus on subgroups with comorbid disorders, concomitant treatments, quality of life measures, or other subgroup analyses. Characteristics of the new head-to-head trials are shown in Table 2 below and the corresponding abstracts are available in Appendix A. Placebo-controlled trials are listed below by drug of study. Abstracts for placebo-controlled trials are available upon request.

Table 2. Cumulative list of new trials since last report update

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Drug</th>
<th>Population</th>
<th>Focus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weisler, 2012</td>
<td>Atomoxetine versus OROS MPH (versus bivisant, H-3 antagonist)</td>
<td>Adults</td>
<td>6 weeks, efficacy (ADHD-RS-IV), harms</td>
</tr>
<tr>
<td>Stein, 2011</td>
<td>Dexmethylphenidate extended-release versus mixed amphetamine salts XR</td>
<td>Children and adolescents</td>
<td>8-weeks, efficacy (ADHD-RS-IV) – dose effects</td>
</tr>
<tr>
<td>Silva, 2008</td>
<td>Dexmethylphenidate extended-release versus MPH-IR</td>
<td>Children</td>
<td>Academic efficacy</td>
</tr>
<tr>
<td>Banaschewski, 2013</td>
<td>Lisdexamfetamine dimesylate versus placebo versus OROS MPH as reference treatment</td>
<td>Children and adolescents</td>
<td>Health-related quality of life, functional impairment</td>
</tr>
<tr>
<td>Coghill, 2013</td>
<td>Lisdexamfetamine dimesylate versus placebo versus OROS MPH as reference arm</td>
<td>Children and adolescents</td>
<td>7 weeks, efficacy (ADHD-RS-IV), safety</td>
</tr>
<tr>
<td>Coghill, 2014</td>
<td>Lisdexamfetamine dimesylate versus placebo versus OROS MPH as reference arm</td>
<td>Children and adolescents</td>
<td>Efficacy (Conners’ Parent Rating Scale-Revised)</td>
</tr>
</tbody>
</table>
### Placebo-controlled trials

#### Atomoxetine
- Young, 2011†
- Sotherland, 2012‡
- Wilens, 2011‡

#### Clonidine extended-release
- Kollins, 2011a

#### Guanfacine extended-release
- Kollins, 2011b
- Wilens, 2012

#### Immediate-release methylphenidate
- Gadow, 2011
- Simonoff, 2013

#### Lisdexamfetamine dimesylate
- Adler, 2013a†
- Adler, 2013b‡
- Biederman, 2012‡
- Brans, 2011‡
- Brans, 2012‡
- Childress, 2014‡
- Faraone, 2012†
- Findling, 2011
- Findling, 2013
- Giblin, 2011
- Ginsberg, 2011†‡
- Jain, 2013
- Kollins, 2014‡

#### Methylphenidate extended-release
- Cox, 2012†
- Retz, 2012†
- Pearson, 2013
- Wigal, 2013

#### Methylphenidate transdermal
- Reimherr, 2013‡

#### Modafinil
- Arnold, 2014†

#### OROS methylphenidate
- Biederman, 2010†
- Biederman, 2012‡
- Buitelaar, 2011†‡
- Casas, 2013†
- Ginsberg, 2012†‡
- Gray, 2011‡
- Heffner, 2013‡
- Murray, 2011
- Nunes, 2013†
- Riggs, 2011∗
- Tam, 2013†
- Warden, 2012∗
- Westover, 2013†‡
- Wigal, 2011
Williamson, 2014

*Duplicate data in two publications
†Indicates placebo-controlled trials in adult populations
‡Indicates post-hoc or secondary analyses
Shading indicates trials found in present scan

Summary and Recommendations

The present preliminary update scan identified no new drugs, indications, or boxed warnings pertaining to drugs to treat ADHD. Previous scans identified only one new drug, Quillivant XR, an extended release oral liquid formulation of methylphenidate. Previous scans identified few new indications or boxed warnings, and none that would alter the review conclusions. There have been no comprehensive comparative effectiveness reviews of drugs to treat ADHD in children and adults published that would update or replace the DERP report.

Since the last full report update, we have identified 9 new head to head trials (5 this scan) and 44 new placebo-controlled trials (12 this scan). New head to head evidence in adults is limited to 2 trials of methylphenidate immediate release or atomoxetine compared with MPH OROS. New head to head trials in children include 3 of lisdexamfetamine vs MPH OROS (+1 post hoc analysis) reporting on quality of life and efficacy throughout the day, and 2 of dexmethylphenidate ER vs mixed amphetamine salts or MPH IR. Placebo-controlled trial evidence is largely in children and involves mainly lisdexamfetamine dimesylate and MPH OROS, with a few new studies of extended release guanfacine or clonidine.
Appendix A. Abstracts of Potentially Relevant Trials

Shading indicates trials found in present scan

**Head-to-head Trials (N = 8)**


**BACKGROUND:** Optimal management of attention deficit hyperactivity disorder (ADHD) aims not only to ameliorate patients' symptoms, but also to improve health-related quality of life (HRQL) and functioning. A pivotal, 7-week, randomized, double-blind, placebo-controlled, phase III study in children and adolescents in ten European countries demonstrated that the stimulant prodrug lisdexamfetamine dimesylate (LDX) is an effective and generally well-tolerated treatment for symptoms of ADHD.

**OBJECTIVE:** The aim of this study was to assess HRQL and functional impairment outcomes in this clinical trial, using the Child Health and Illness Profile-Profile-Child Edition: Parent Report Form (CHIP-CE:PRF) and the Weiss Functional Impairment Rating Scale-Parent Report (WFIRS-P), respectively.

**METHODS:** Patients (aged 6-17 years) with diagnosed ADHD and a baseline ADHD Rating Scale IV total score >28 were randomized (1:1:1) to 7 weeks of double-blind treatment with once-daily LDX, placebo or the reference treatment, osmotic-release oral system methylphenidate (OROS-MPH). Participants' parents (or legally authorized representatives) completed the CHIP-CE:PRF and WFIRS-P questionnaires at baseline, at weeks 4 and 7, and/or at early termination. Endpoint was defined as the last on-treatment visit with valid data (<30 % missing items). The CHIP-CE:PRF Achievement domain was pre-specified as the primary HRQL outcome.

**RESULTS:** The full analysis set comprised 317 patients (LDX, n = 104; placebo, n = 106; OROS-MPH, n = 107), the majority of whom completed the study (LDX, n = 77; placebo, n = 42; OROS-MPH, n = 72). Baseline CHIP-CE:PRF T-scores in four of the five domains were >1 standard deviation below norms (US community samples). Compared with placebo, LDX was associated with statistically significantly improved T-scores from baseline to endpoint in these four domains, with effect sizes of 1.280 (p < 0.001) in Achievement, 1.079 (p < 0.001) in Risk Avoidance, 0.421 (p < 0.01) in Resilience and 0.365 (p < 0.05) in Satisfaction. In LDX-treated patients, placebo-adjusted improvements from baseline to endpoint in WFIRS-P scores were statistically significant (p < 0.001) for total score and four of the six domains, with effect sizes of 0.924 (total score), 1.249 (Learning and School), 0.730 (Family), 0.643 (Social Activities) and 0.640 (Risky Activities). OROS-MPH treatment showed similar patterns of improvement from baseline to endpoint in both CHIP-CE:PRF and WFIRS-P scores.

**CONCLUSIONS:** Baseline HRQL and functional impairment scores reflect the burden of untreated ADHD. The benefits of short-term stimulant treatment in children and adolescents with ADHD extend beyond symptomatic relief and impact positively on HRQL and daily functioning.

This study evaluated the efficacy and safety of lisdexamfetamine dimesylate (LDX) compared with placebo in children and adolescents with attention-deficit/hyperactivity disorder (ADHD) in Europe. Osmotic-release oral system methylphenidate (OROS-MPH) was included as a reference arm. Patients (6-17 years old) with a baseline ADHD Rating Scale version IV (ADHD-RS-IV) total score > 28 were randomized (1:1:1) to dose-optimized LDX (30, 50, or 70 mg/day), OROS-MPH (18, 36, or 54 mg/day) or placebo for 7 weeks. Primary and key secondary efficacy measures were the investigator-rated ADHD-RS-IV and the Clinical Global Impressions-Improvement (CGI-I) rating, respectively. Safety assessments included treatment-emergent adverse events (TEAEs), electrocardiograms, and vital signs. Of 336 patients randomized, 196 completed the study. The difference between LDX and placebo in least squares mean change in ADHD-RS-IV total score from baseline to endpoint was -18.6 (95% confidence interval [CI]: -21.5 to -15.7) (p<0.001; effect size, 1.80). The difference between OROS-MPH and placebo in least squares mean change in ADHD-RS-IV total score from baseline to endpoint was -13.0 (95% CI: -15.9 to -10.2) (p<0.001; effect size, 1.26). The proportions (95% CI) of patients showing improvement (CGI-I of 1 or 2) at endpoint were 78% (70-86), 14% (8-21), and 61% (51-70) for LDX, placebo, and OROS-MPH. The most common TEAEs for LDX were decreased appetite, headache, and insomnia. Mean changes in vital signs were modest and consistent with the known profile of LDX. LDX was effective and generally well tolerated in children and adolescents with ADHD.


Lisdexamfetamine dimesylate (LDX) is a long-acting, prodrug stimulant therapy for patients with attention-deficit/hyperactivity disorder (ADHD). This randomized placebo-controlled trial of an optimized daily dose of LDX (30, 50 or 70 mg) was conducted in children and adolescents (aged 6-17 years) with ADHD. To evaluate the efficacy of LDX throughout the day, symptoms and behaviors of ADHD were evaluated using an abbreviated version of the Conners' Parent Rating Scale-Revised (CPRS-R) at 1000, 1400 and 1800 hours following early morning dosing (0700 hours). Osmotic-release oral system methylphenidate (OROS-MPH) was included as a reference treatment, but the study was not designed to support a statistical comparison between LDX and OROS-MPH. The full analysis set comprised 317 patients (LDX, n = 104; placebo, n = 106; OROS-MPH, n = 107). At baseline, CPRS-R total scores were similar across treatment groups. At endpoint, differences (active treatment - placebo) in least squares (LS) mean change from baseline CPRS-R total scores were statistically significant (P < 0.001) throughout the day for LDX (effect sizes: 1000 hours, 1.42; 1400 hours, 1.41; 1800 hours, 1.30) and OROS-MPH (effect sizes: 1000 hours, 1.04; 1400 hours, 0.98; 1800 hours, 0.92). Differences in LS mean change from baseline to endpoint were statistically significant (P < 0.001) for both active treatments in all four subscales of the CPRS-R (ADHD index, oppositional, hyperactivity and cognitive). In conclusion, improvements relative to placebo in ADHD-related symptoms and behaviors in children and adolescents...
receiving a single morning dose of LDX or OROS-MPH were maintained throughout the day and were ongoing at the last measurement in the evening (1800 hours).


**OBJECTIVE:** The purpose of this study was to investigate clinical gains from including both dextroamphetamine and methylphenidate in stimulant trials.

**METHOD:** Thirty-six medication-naive children ages 9-14 years diagnosed with attention-deficit/hyperactivity disorder (ADHD) were enrolled for 6 weeks in a crossover trial, with 2 weeks of methylphenidate, dextroamphetamine, and placebo, in a randomly assigned, counterbalanced sequence. Outcome measures constituted a computer-based continuous performance test combined with a motion tracking system (Qb Test) and an ADHD questionnaire rated by parents and teachers.

**RESULTS:** Group analyses found significant treatment effects of similar size for the two stimulants on both outcome measures. Single-subject analyses revealed that each stimulant produced a favourable response in 26 children; however, an individual child frequently responded qualitatively or quantitatively differently to the two stimulants. By including both stimulants in the trial, the number of favorable responders increased from 26 (72%) to 33 (92%). In children with favorable responses of unequal strength to the two stimulants, a shift from inferior drug to best drug was associated with a 64% mean increase in the overall response strength score, as measured by the ADHD questionnaire.

**CONCLUSIONS:** The likelihood of a favorable response and optimal response strength is increased by including both stimulants in the stimulant trial. The study was first registered in clinical trials 28 September 2010. Clinical Trials.gov Identifier: NCT01220440.


The purpose of this study was to compare the efficacy and safety of extended-release dexmethylphenidate (d-MPH-ER) to that of d,l-MPH-ER and placebo in children with attention-deficit/hyperactivity disorder (ADHD) in a laboratory classroom setting. This multicenter, double-blind, crossover study randomized 82 children, 6 to 12 years of age, stabilized on a total daily dose to the nearest equivalent of 40 to 60 mg of d,l-MPH or 20 or 30 mg/day of d-MPH. Patients participated in a screening day and practice day, and were randomized to 1 of 10 sequences of all five treatments in five separate periods. Treatments included d-MPH-ER (20 mg/day), d-MPH-ER (30 mg/day), d,l-MPH-ER (36 mg/day), d,l-MPH-ER (54 mg/day), and placebo. Primary efficacy was measured by the change from predose on the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) Rating Scale-Combined scores at 2-h postdose during the 12-h laboratory assessment (d-MPH-ER 20 mg/day vs. d,l-MPH-ER 36 mg/day). Adverse events were monitored throughout the study period. d-MPH-ER (20 mg/day) was significantly more effective than d,l-MPH-ER (36 mg/day) in the primary efficacy variable, change from predose to 2-h postdose in SKAMP-combined score. In general, d-MPH-ER had an earlier onset of action than d,l-MPH-ER, while d,l-MPH-ER had a stronger effect at 12-h postdose. No
serious adverse events were reported. Treatment with either agent was associated with significant improvements in ADHD symptoms. d-MPH-ER and d,l-MPH-ER can be differentiated on what part of the day each is more effective.


OBJECTIVE: The main aim of this study was to examine the efficacy, tolerability, and compliance of an extended-release formulation of methylphenidate (OROS-MPH) in adults with ADHD receiving immediate-release methylphenidate (IR-MPH).

METHOD: Participants were outpatient adults with ADHD who were stable on IR-MPH-administered TID. Participants were randomized (4:1) to equipotent doses of OROS-MPH or to continue IR-MPH and were assessed weekly for 6 weeks with the Adult ADHD Investigator System Symptom Report Scale (AISRS).

RESULTS: Randomization of 53 IR-MPH responders to IR- or OROS-MPH had no effect on AISRS score at endpoint (11.2 +/- 6.9 vs. 10.7 +/- 5.1, p = .8). Participants stabilized on IR-MPH and switched to OROS-MPH remained satisfied over 71% of the time. However, the IR-MPH group missed more doses (7.3 +/- 6.8 vs. 3.3 +/- 4.2, p = .02) than the OROS-MPH group.

CONCLUSION: Findings showed that adults with ADHD can be successfully switched from an effective regimen of IR-MPH TID to once-daily OROS-MPH. Results also demonstrated better compliance with OROS-MPH than with IR-MPH treatment.


OBJECTIVE: To compare the dose effects of long-acting extended-release dexmethylphenidate (ER d-MPH) and ER mixed amphetamine salts (ER MAS) on attention-deficit/hyperactivity disorder (ADHD) symptom dimensions, global and specific impairments, and common adverse events associated with stimulants. METHODS: Fifty-six children and adolescents with ADHD participated in an 8-week, double-blind, crossover study comparing ER d-MPH (10, 20, 25-30 mg) and ER MAS (10, 20, 25-30) with a week of randomized placebo within each drug period. Efficacy was assessed with the ADHD Rating Scale-IV (ADHD-RS-IV), whereas global and specific domains of impairment were assessed with the Clinical Global Impressions Severity and Improvement Scales and the parent-completed Weiss Functional Impairment Scale, respectively. Insomnia and decreased appetite, common stimulant-related adverse events, were measured with the parent-completed Stimulant Side Effects Rating Scale.

RESULTS: Both ER d-MPH and ER MAS were associated with significant reductions in ADHD symptoms. Improvement in Total ADHD and Hyperactivity/Impulsivity symptoms were strongly associated with increasing dose, whereas improvements in Inattentive symptoms were only moderately associated with dose. About 80% demonstrated reliable change on ADHD-RS-IV at the highest dose level of ER MAS compared with 79% when receiving ER d-MPH. Decreased appetite and insomnia were more common at higher dose levels for both stimulants. Approximately 43% of the responders were preferential responders to only one of the stimulant formulations. CONCLUSIONS: Dose level, rather than stimulant class, was strongly related to medication response.

BACKGROUND: Psychostimulants, including methylphenidate and amphetamine preparations, are commonly prescribed for the treatment of attention-deficit hyperactivity disorder (ADHD) in children and adults. Histamine H3 receptors reside on non-histamine neurons and regulate other neurotransmitters (e.g. acetylcholine, noradrenaline [norepinephrine]) suggesting that H3 antagonists have the potential to improve attention and impulsivity. Research indicates that H3 receptor antagonists due to their novel mechanism of action may have a unique treatment effect offering an important alternative for the treatment of ADHD. Bavisant (JNJ-31001074) is a highly selective, orally active antagonist of the human H3 receptor with a novel mechanism of action, involving wakefulness and cognition, with potential as a treatment for ADHD.

OBJECTIVE: The objective of this study was to evaluate the efficacy, safety and tolerability of three dosages of bavisant compared with placebo in adults with ADHD.

STUDY DESIGN: This randomized, double-blind, placebo- and active-controlled, parallel-group, multicentre study evaluated three dosages of bavisant (1mg/day, 3mg/day or 10mg/day) and two active controls in adults with ADHD. The study consisted of a screening phase of up to 14 days, a 42-day double-blind treatment phase and a 7-day post-treatment follow-up phase. Efficacy and safety assessments were performed.

SETTING: The study was conducted at 37 study centres in the US from April 2009 through January 2010.

PARTICIPANTS: Men and women aged 18-55 years with an established diagnosis of ADHD as confirmed by clinician and self-report diagnostic measures were enrolled.

INTERVENTION: Participants were randomly assigned equally to one of six treatment groups: placebo, bavisant 1mg/day, 3mg/day or 10mg/day, atomoxetine hydrochloride 80mg/day or osmotic-release oral system (OROS) methylphenidate hydrochloride 54mg/day.

MAIN OUTCOME MEASURE: The primary efficacy endpoint was the change in the Attention Deficit Hyperactivity Disorder Rating Scale, Version IV (ADHD-RS-IV) total score from baseline (day 1) to the end of the treatment phase (day 42), and included all randomized participants who received one or more doses of study drug and had baseline and one or more post-baseline assessments (intent-to-treat [ITT] population). Safety assessments included treatment-emergent adverse events (TEAEs), laboratory tests and ECG readings.

RESULTS: 430 participants were randomized, 424 received one or more doses of study medication and 335 (78%) of those randomized completed the study. Study participants had a mean age of 33.9 years and were predominantly White men. Mean treatment duration ranged from 31.4 to 38.8 days across groups. Mean change from baseline in the total ADHD-RS-IV score at day 42 (primary efficacy endpoint) was -8.8 in the placebo group versus -9.3, -11.2 and -12.2 in the bavisant 1mg/day, 3 mg/day and 10mg/day groups, respectively; the change in the 10 mg/day group was not statistically superior to placebo (p=0.161), and hence statistical comparisons of the 1mg/day and 3mg/day groups with placebo based on a step-down closed testing procedure were not performed. Mean change from baseline in the total ADHD-RS-IV score at day 42 was superior to placebo in the atomoxetine (-15.3) and OROS methylphenidate (-15.7) groups (p<0.005). Secondary efficacy assessments demonstrated a similar pattern with a non-significant trend towards improvement in the bavisant groups. The two lower dosages showed a good tolerability profile, but the higher dosage of bavisant was less well tolerated, as evidenced by the incidence of total TEAEs (61.8%, 82.4%, 89.0%), and discontinuations due to TEAEs (4.4%, 7.4%, 19.2%) in the bavisant 1mg/day, 3 mg/day and 10mg/day groups, respectively, compared with 58.9% and 2.7%, respectively on placebo. In the atomoxetine and
OROS methylphenidate groups, the incidence of total TEAEs was 83.8% and 82.4% and discontinuations due to TEAEs was 10.8% and 8.8%, respectively. CONCLUSION: Bavisant, a highly selective, wakefulness-promoting H3 antagonist, did not display significant clinical effectiveness in the treatment of adults with ADHD. Clinical Trial Registration Number: NCT00880217.

**Post-hoc Analyses of Head-to-Head Trials (N = 1)**


**INTRODUCTION:** There are limited head-to-head data comparing the efficacy of long-acting amphetamine- and methylphenidate-based psychostimulants as treatments for individuals with attention-deficit hyperactivity disorder (ADHD). This post hoc analysis provides the first parallel-group comparison of the effect of lisdexamfetamine dimesylate (lisdexamfetamine) and osmotic-release oral system methylphenidate (OROS-MPH) on symptoms of ADHD in children and adolescents.

**STUDY DESIGN:** This was a post hoc analysis of a randomized, double-blind, parallel-group, dose-optimized, placebo-controlled, phase III study.

**SETTING:** The phase III study was carried out in 48 centres across ten European countries.

**PATIENTS:** The phase III study enrolled children and adolescents (aged 6-17 years) who met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision criteria for a primary diagnosis of ADHD and who had a baseline ADHD Rating Scale IV (ADHD-RS-IV) total score of 28 or higher.

**INTERVENTION:** Eligible patients were randomized (1:1:1) to receive a once-daily, optimized dose of lisdexamfetamine (30, 50 or 70 mg/day), placebo or OROS-MPH (18, 36 or 54 mg/day) for 7 weeks.

**MAIN OUTCOME MEASURES:** In this post hoc analysis, efficacy was assessed using the ADHD-RS-IV and Clinical Global Impressions-Improvement (CGI-I) scale. Responders were defined as those achieving at least a 30% reduction from baseline in ADHD-RS-IV total score and a CGI-I score of 1 (very much improved) or 2 (much improved). The proportion of patients achieving an ADHD-RS-IV total score less than or equal to the mean for their age (based on normative data) was also determined. Endpoint was the last on-treatment visit with a valid assessment. Safety assessments included treatment-emergent adverse events (TEAEs) and vital signs.

**RESULTS:** Of the 336 patients randomized, 332 were included in the safety population, 317 were included in the full analysis set and 196 completed the study. The mean (standard deviation) ADHD-RS-IV total score at baseline was 40.7 (7.31) for lisdexamfetamine, 41.0 (7.14) for placebo and 40.5 (6.72) for OROS-MPH. The least-squares (LS) mean change (standard error) in ADHD-RS-IV total score from baseline to endpoint was -24.3 (1.16) for lisdexamfetamine, -5.7 (1.13) for placebo and -18.7 (1.14) for OROS-MPH. The difference between lisdexamfetamine and OROS-MPH in LS mean change (95% confidence interval [CI]) in ADHD-RS-IV total score from baseline to endpoint was statistically significant in favour of lisdexamfetamine (-5.6 [-8.4 to -2.7]; p < 0.001). The difference between lisdexamfetamine and OROS-MPH in the percentage of patients (95% CI) with a CGI-I score of 1 or 2 at endpoint was 17.4 (5.0-29.8; p < 0.05; number needed to treat [NNT] 6), and the difference in the percentage of patients (95% CI) achieving at least a 30% reduction in ADHD-RS-IV total score and a CGI-I score of 1 or
2 was 18.3 (5.4-31.3; p < 0.05; NNT 6). The difference between lisdexamfetamine and OROS-MPH in the percentage of patients (95% CI) with an ADHD-RS-IV total score less than or equal to the mean for their age at endpoint was 14.0 (0.6-27.4; p = 0.050).

The overall frequency of TEAEs and the frequencies of decreased appetite, insomnia, decreased weight, nausea and anorexia TEAEs were greater in patients treated with lisdexamfetamine than in those treated with OROS-MPH, whereas headache and nasopharyngitis were more frequently reported in patients receiving OROS-MPH.

CONCLUSIONS: This post hoc analysis showed that, at the doses tested, patients treated with lisdexamfetamine showed statistically significantly greater improvement in symptoms of ADHD than those receiving OROS-MPH, as assessed using the ADHD-RS-IV and CGI-I. The safety profiles of lisdexamfetamine and OROS-MPH were consistent with the known effects of stimulant medications.