Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Month/Year of Review: July 2013
PDL Classes: ADHD

Date of Last Review: Drug December 2011
Source Document: Drug Effectiveness Review Project

Current Status of PDL Class:

- PREFERRED AGENTS: AMPHETAMINE ASPARTATE/AMPHETAMINE/D-AMPHETAMINE TABLET, DEXMETHYLPHENIDATE CPMP 50-50 (FOCALIN XR®), DEXTROAMPHETAMINE TABLETS (DEXEDRINE®), FOCALIN® (BRAND ONLY), LISDEXAMFETAMINE (VYVANSE®), METHYLPHENIDATE HCL TABLETS, methylphenidate ER
- NON-PREFERRED AGENTS: AMPHETAMINE ASPARTATE/AMPHETAMINE/D-AMPHETAMINE ER, DEXTROAMPHETAMINE ER, DEXTROAMPHETAMINE SOLUTION (PROCENTRA), METHAMPHETAMINE HCL TABLETS, METHYLPHENIDATE TRANSDERMAL (DAYTRANA®), METHYLPHENIDATE HCL CD CPMP 30-70, METHYLPHENIDATE ER CPMP 50-50, METHYLPHENIDATE HCL SOLUTION, METHYLPHENIDATE XR (QUILLIVANT XR®), METHYLPHENIDATE HCL CHEWABLE TABLET, METHYLPHENIDATE ER DESTROAMPHETAMINE/AMPHETAMINE, DEXTROAMPHEATMINE/AMPHETAMINE (ADDERALL XR®)
- NON-PREFERRED VOLUNTARY AGENTS: ATOMOXETINE (STRATTERA®), CLONIDINE HCL (KAPVAY®), GUANFACINE HCL (INTUNIV®)

Previous Recommendation:

- Due to a lack of comparative efficacy or effectiveness data, do not consider extended release formulations of clonidine and guanfacine as clinically superior to other stimulant and non-stimulant ADHD treatments.
- There is a lack of long term evidence to support any differences between stimulants and atomoxetine.

Current PA criteria:

Prior authorization is required for non-preferred drugs to ensure coverage only for OHP covered diagnoses and restrict to doses supported by the medical literature. This PA does not concern drugs in STC 07 or 11; however, these drugs are not to be encouraged. See specific criteria in Appendix 2.

Methods:

A Medline OVID search was conducted with the following search terms: amphetamine, amphetamines, d-amphetamine, dextroamphetamine, dexamphetamine, lisdexamfetamine, lisdexamphetamine, amphetamine salts, methylphenidate, dexmethylphenidate, dextromethylphenidate, Ritalin, Metadate, Concerta, Focalin, Adderall, Vyvanse, Quillivant, Daytrana, stimulants, central nervous system stimulants, guanfacine, clonidine, alpha adrenergic blockers, Intuniv, Kapvay, atomoxetine, Strattera, attention deficit and hyperactivity disorder, ADHD, and narcolepsy. The search was limited to English language articles of controlled trials conducted on humans published from 2011 to May week two 2013.

The Cochrane Collection, Dynamed and Medline OVID were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts. Finally, a search for new or updated guidelines was conducted at the AHRQ National Guideline Clearinghouse (NGC).

New Trials (Appendix 2):

A total of 245 citations resulted from the initial MEDLINE search. Articles were excluded due to the wrong study design (observational), comparator (placebo), or outcome (non-clinical). After a review of titles and abstracts for inclusion, seven relevant head-to-head clinical trials were identified and are discussed below. Please see Appendix 1 for the full abstracts.

Brams[1] et al studied the safety and efficacy of extended release dextromethylphenidate at different doses, 20 mg vs. 30 mg, in children with ADHD (n=157) aged 6 to 12 years old. This was a good quality, double-blind, randomized, cross-over study with subjects randomized to one of three treatments for three 7 day periods; all children received 20 mg, 30 mg of dexmethylphenidate and placebo. The setting was a classroom laboratory where children were observed for 12 hours. The primary efficacy outcome measure was change in the average Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP)-Combined score from pre-dose to (the average of 10, 11, and 12 hours' score) post-dose for 30 mg versus 20 mg. The SKAMP scale is a 13-item instrument designed to measure target classroom manifestations of ADHD. Dexmethylphenidate 30 mg was shown to have a significantly improved SKAMP score (difference in least mean square: -2.45, p=0.002) over the 20 mg dose and (-8.97, p<0.001) placebo. Safety was assessed by symptom questionnaires given to subjects and parents, as well as vital signs and measurements collected at visits. Most common adverse events were decreased appetite, headache, abdominal pain, and tachycardia. No significant difference was seen between the two treatment groups in adverse events.

Jafarinia[2] et al compared ADHD symptom improvement in children (n=44) aged 6 to 17 years old treated with bupropion or methylphenidate for six weeks. Efficacy was measured by a change in the symptom measurement tool the Teacher and Parent Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) from baseline to week six. No significant difference was found between the two groups on the ADHD-RS-IV parent (mean difference -0.5, p = 0.609) and teacher (-1.4, p = 0.612) scores at week six. Adverse event frequency was not statistically different between the two groups in this fair quality study.

Weisler[3] et al conducted a study comparing a novel histamine H3 receptor antagonist (bavisant) with traditional ADHD medications for symptom control over 42 weeks. This good quality, randomized, double-blind, placebo-controlled, multi-center trial evaluated three dosages of bavisant (1 mg, 3 mg or 10 mg) with atomoxetine (80 mg), methylphenidate (54 mg) and placebo; 430 adult patients were randomized. The primary outcome was mean change from baseline in the total ADHD-RS-IV score at day 42. None of the bavisant groups showed a significance difference from placebo in their score difference; statistical analysis was performed only for the 10 mg strength (mean difference: -8.8 vs. -12.2, p = 0.161). Mean change from baseline in the total ADHD-RS-IV score at day 42 was superior to placebo in the atomoxetine (-15.3) and methylphenidate (-15.7) groups (both, p< 0.005). Methylphenidate and atomoxetine were not compared with each other.

Dopfner[4] et al compared the efficacy of two methylphenidate modified release formulations in a multi-center crossover trial. Children (n=113) with ADHD were randomized to two different 22% immediate release (IR) formulations of methylphenidate (Concerta or Medikinect), and a 50% IR formulation (Medikinect) in turn for three weeks. The primary endpoint was improvement from baseline in SKAMP score as measured during the first three hours of schooling by the kids' teachers. Medikinect 50% IR was found to be significantly superior to Concerta in improving SKAMP scores (p=0.0009). Medikinect 22% IR was found to be noninferior to Concerta. This was a poor quality trial with many discrepancies in allocation concealment, randomization and data collection.

Yildiz[5] et al conducted an open-label study to compare the efficacy and safety of atomoxetine and methylphenidate for ADHD. Children (n=25) aged 8 to 14 years old were randomized to 12 weeks of treatment with either medication. Efficacy was measured by the Clinical Global Impression Scales Severity and Improvement (CGI-S, CGI-I). These instruments are designed to record illness severity and the response to the intervention. Safety was assessed through parent observation of adverse effects and collection of results from physical examinations including vital signs, EKGs, and labs. At week twelve, 63.6% of atomoxetine and 83.3% of methylphenidate subjects were considered treatment responders on the CGI scale. This was not statistically significant (p=0.076). No difference was found between the two medications on a parent rated behavior assessment tool (T-DSM-IV), or in discontinuations due to adverse effects. Nervousness, nausea and anorexia were the most common reported adverse events for both medications. Both atomoxetine and methylphenidate groups had a significant decrease in weight from baseline but there was no statistical difference between treatments. This was a poor quality study with many opportunities for bias.

Date: July 2013

Spencer[6] et al compared the efficacy of extended release methylphenidate in patients currently on an immediate release formulation. Adults (n=53) with ADHD were randomized to receive equivalent doses of the ER preparation or to continue their IR regimen and were assessed for six weeks. The primary endpoint was improvement in the Adult ADHD Investigator System Symptom Report (AISRS) Scale. At the end of the study no difference was seen in the AISRS scores for the ER and IR groups (11.2 vs. 10.7, p= 0.8). This was a poor quality study with allocation, blinding and randomization all poorly explained or not performed.

Stein[7] et al conducted a fair quality, crossover study to compare the efficacy of extended release methylphenidate with extended release amphetamine salts in children with ADHD. For eight weeks, children (n=65) aged 9 to 17 years old were randomized to each medication for four weeks with a week of placebo use within the drug period. Change in the ADHD-RS-IV was the primary endpoint. Although both groups saw significant improvement in ADHD-RS-IV score ($p<0.001$), when compared there was no statistical difference between treatment groups ($p=0.855$).

New drugs:
None

New Formulations/Indications:
A new formulation of methylphenidate was approved in September 2012. Quillivant XR™ is an extended-release oral suspension indicated for adults and children aged six and older for the treatment of ADHD and is available as a 5mg/ml oral suspension.[8] This is the first liquid formulation of the drug that is available as once-daily. A short-acting oral solution is currently available (Methylin®).

There are currently no available head to head trials. Approval was based on a single double-blind crossover trial in 45 children aged 6-12 in a laboratory classroom setting.[9] The primary endpoint was the SKAMP rating system (evaluates school-related problems such as following class rules, interacting with classmates and teachers, and performance of classroom tasks). The primary endpoint measured at 4 hours post dose. Mean SKAMP scores were significantly better with the drug than with placebo at all post-dose assessment times (7.12 vs. 19.58, respectively; $p<0.0001$). Over the average 41 days, 93.3% experienced a treatment-emergent and 3 subjects experienced a severe treatment-emergent adverse event (affect lability, aggression, and initial insomnia).[9]

Lisdexamfetamine dimesylate (Vyvanse®) capsules were approved in January 2012 for maintenance treatment in Adults with ADHD.

New FDA safety alerts:
In November 2012, the FDA issued a drug safety communication regarding stimulant use in children and young adults with ADHD. Results from a large, recently completed study did not show any association between use of certain ADHD medications (amphetamine derivatives and methylphenidate) and adverse cardiovascular events (stroke, heart attack, and sudden cardiac death). The FDA recommends patients on these medications should still continue to be monitored for any abnormal increase in heart rate or blood pressure.[10]
In September 2011, the FDA updated the safety labeling for Vyvanse (lisdexamphfetamine) to include the psychiatric disorder dermatillomania as an adverse reaction.[11]

New Systematic Reviews: (Appendix 2)
Three new systematic reviews were identified. Please see Appendix 2 for the full abstracts.

Many patients with ADHD also have a diagnosis of oppositional defiant disorder (ODD) but little investigation has been focused on if comorbid ODD affects the efficacy of ADHD medication. Van Wyk[12] et al assessed how ODD, inattention, and hyperactivity-impulsivity affect the response to atomoxetine versus methylphenidate. Seven randomized control

trials (n=1,391) conducted on children with ADHD aged 6 to 16 years old were included in the systematic review. Trials were a mix of double-blinded and open label studies at least six weeks in length; a total of 42.7% of patients in the atomoxetine and 38.2% in the methylphenidate cohort had an ODD diagnosis. The primary outcome was a ≥ 40% reduction in the ADHD Rating Scale-IV (ADHD-RS-IV). For patients with ODD, the mean difference (atomoxetine minus methylphenidate) in response rates for patients with ODD was 0.6% (95% CI = −11.9% to 13.1%). Response rate differences for patients meeting the threshold for inattention or hyperactivity-impulsivity were −3.1% (95% CI = −11.5% to 5.3%) and −4.9% (95% CI = −14.3% to 4.4%), respectively. Comorbid ODD did not alter ADHD symptom response to atomoxetine or methylphenidate. Individual trial quality was rated as fair to good. For the most part randomization and blinding procedures were transparent, however two trials were open-label and not all trials explained procedures for allocation concealment.

Hanwella[13] et al performed a systematic review with head to head randomized clinical trials comparing the efficacy of atomoxetine versus methylphenidate for ADHD symptom improvement. The meta analysis combined nine double-blind and open label randomized control trials with children (n=2762) with ADHD aged 6 to 16 years old. Trials were at least 3 weeks in length. The outcome studied was a comparison in change in ADHD-RS-IV score. The standardized mean difference (SMD) was used as a measure of effect size. Analysis did not find a significant difference in efficacy between methylphenidate and atomoxetine (SMD = 0.09, 95% CI -0.08 to 0.26). Synthesis of data from eight trials found no significant difference in response rates (RR = 0.93 95% CI 0.76 to 1.14). Excluding open label trials did not significantly alter the effect size (SMD = 0.08, 95% CI -0.04 to 0.21). Individual trial quality was evaluated for the presence of randomization, description of outcome measures, inclusion and exclusion criteria; the authors found all included trials to rate more than 12 on the Detsky quality scale. However, because three of the included studies were open label and allocation concealment was not evaluated, the individual quality of the trials may be considered fair at best.

The Cochrane Collection[14] conducted a systematic review to examine the efficacy and safety of use of amphetamines in adults with ADHD. Randomized controlled trials comparing the efficacy of amphetamine derivatives (dextroamphetamine, lisdexamfetamine, and mixed amphetamine salts) against placebo or an active intervention were included. A total of seven studies were analyzed with 1091 adult subjects; all studies included a placebo as a comparator. Three studies had an additional active comparator: guanfacine, modafinil and paroxetine. The average trial length was 8.1 weeks. The primary efficacy outcome was measured as standard mean difference (SMD) in a composite proportion of patients achieving a reduction of ADHD symptom severity ≥30% on the ADHD-RS-IV, patients achieving a Clinical Global Impression-Improvement (CGI-I) score of 1 or 2, or Clinical Global Impression (CGI) at study end. Amphetamines improved ADHD symptom severity (SMD = -0.72; 95% CI -0.87 to -0.57). The three amphetamine derivatives investigated were all efficacious for reducing ADHD symptoms. Change in dose did not appear associated with differences in efficacy nor was there any difference between immediate and sustained drug release formulations. When amphetamines were compared to guanfacine, modafinil or paroxetine, they were not found to statistically superior. Amphetamines were associated with higher attrition due to adverse events. The quality of all trials was assessed as low to very low by the authors with high risk of bias likely for all outcomes.

Guidelines:
The updated guidelines for ADHD from the American Academy of Pediatrics[15] and the American Academy of Family Physicians[16] were reviewed. No changes regarding the use of ADHD medications were found.

Recommendations:

- There is insufficient evidence that the new methylphenidate formulation (Quillivant XR®) has improved efficacy or safety or other formulations.
- There is no new clinical evidence to make changes to current PDL status.
- Evaluate comparative costs in executive session.

Date: July 2013

References:

1. Brams M, Turnbow J, Pestreich L, et al. A Randomized, Double-Blind Study of 30 Versus 20 mg Dexmethylphenidate Extended-Release in Children With Attention-Deficit/Hyperactivity Disorder. *Journal of Clinical Psychopharmacology*. 2012;32(5):637–644. doi:10.1097/JCP.0b013e3182677825.

2. Jafarinia M, Mohammadi M-R, Modabbernia A, et al. Bupropion versus methylphenidate in the treatment of children with attention-deficit/hyperactivity disorder: randomized double-blind study. *Human Psychopharmacology: Clinical and Experimental*. 2012;27(4):411–418. doi:10.1002/hup.2242.

3. Weisler RH, Pandina GJ, Daly EJ, Cooper K, Gassmann-Mayer C. Randomized Clinical Study of a Histamine H3 Receptor Antagonist for the Treatment of Adults with Attention-Deficit Hyperactivity Disorder. *CNS Drugs*. 2012;26(5):421–434. doi:10.2165/11631990-000000000-00000.

4. Döpfner M, Ose C, Fischer R, Ammer R, Scherag A. Comparison of the Efficacy of Two Different Modified Release Methylphenidate Preparations for Children and Adolescents with Attention-Deficit/Hyperactivity Disorder in a Natural Setting: Comparison of the Efficacy of Medikinect® Retard and Concerta® —a Randomized, Controlled, Double-Blind Multicenter Clinical Crossover Trial. *Journal of Child and Adolescent Psychopharmacology*. 2011;21(5):445–454. doi:10.1089/cap.2010.0082.

5. Yildiz O, Sismanlar SG, Memik NC, Karakaya I, Agaoglu B. Atomoxetine and Methylphenidate Treatment in Children with ADHD: The Efficacy, Tolerability and Effects on Executive Functions. *Child Psychiatry & Human Development*. 2010;42(3):257–269. doi:10.1007/s10578-010-0212-3.

6. Spencer TJ, Mick E, Surman CBH, et al. A Randomized, Single-Blind, Substitution Study of OROS Methylphenidate (Concerta) in ADHD Adults Receiving Immediate Release Methylphenidate. *Journal of Attention Disorders*. 2010;15(4):286–294. doi:10.1177/1087054710367880.

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 and Adolescent Psychopharmacology*. 2011;21(6):581–588. doi:10.1089/cap.2011.0018.

8. QUILLIVANT XR (methylphenidate hydrochloride) Label - 202100lbl.pdf. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202100lbl.pdf. Accessed May 28, 2013.

9. SB Wigal et al. NWP06, an extended release oral suspension of methylphenidate, improved attention-deficit/hyperactivity disorder symptoms compared with placebo in a laboratory classroom study. J Child Adolesc Psychopharmacol 2013 Jan 5 (epub).

10. Drug Safety and Availability > FDA Drug Safety Communication: Safety Review Update of Medications used to treat Attention-Deficit/Hyperactivity Disorder (ADHD) in adults. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm279858.htm. Accessed May 27, 2013.

11. Safety Information > Vyvanse (lisdexamfetamine dimesylate) Capsules. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm234015.htm. Accessed May 28, 2013.

12. Van Wyk GW, Hazell PL, Kohn MR, Granger RE, Walton RJ. How Oppositionality, Inattention, and Hyperactivity Affect Response to Atomoxetine Versus Methylphenidate: A Pooled Meta-Analysis. *Journal of Attention Disorders*. 2011;16(4):314–324. doi:10.1177/1087054710389989.

13. Hanwella R, Senanayake M, de Silva V. Comparative efficacy and acceptability of methylphenidate and atomoxetine in treatment of attention deficit hyperactivity disorder in children and adolescents: a meta-analysis. *BMC Psychiatry*. 2011;11(1):176. doi:10.1186/1471-244X-11-176.

14. Castells X, Ramos-Quiroga JA, Bosch R, Nogueira M, Casas M. Amphetamines for Attention Deficit Hyperactivity Disorder (ADHD) in adults. In: The Cochrane Collaboration, Castells X, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2011. Available at: http://doi.wiley.com/10.1002/14651858.CD007813.pub2. Accessed May 27, 2013.

15. Subcommittee on Attention-Deficit/Hyperactivity Disorder, Steering Committee on Quality Improvement and Management. ADHD: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. *PEDIATRICS*. 2011;128(5):1007–1022. doi:10.1542/peds.2011-2654.

16. Post RE, Kurlansik SL. Diagnosis and management of adult attention-deficit/hyperactivity disorder. *Am Fam Physician*. 2012; 85(9):890–896.

Date: July 2013

Appendix 1: Prior Authorization Criteria

Central Nervous System (CNS) Stimulatns

Goal(s):

- *Cover stimulants only for OHP covered diagnoses (e.g. ADHD, narcolepsy)*
- *Restrict to doses supported by medical literature and promote preferred drugs in class*
- *The long-term effects of stimulants are unknown. Adverse events are more frequently associated with high doses. However, effectiveness is not linearly associated with dose and promote preferred drugs in class.*

Initiative: CNS Stimulants (Non-PDL & Excessive Dose)

Length of Authorization: up to 12 months

Requires PA :

- Non-preferred drugs

Covered alternatives: See PDL list at http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

- PA does NOT concern drugs in STC 07 or 11 ; however, these drugs are not to be encouraged. The State is prohibited from prior authorizing Class 11 drugs by statute. These include :
  - Armodafinil (Nuvigil)
  - Atomoxetine (Strattera)
  - Modafanil (Provigil)

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code	
2. Is diagnosis one of the following?: ADHD (ICD9 314-314.01); Narcolepsy (ICD9 341);Drug-induced sedation (ICD9 292.89)?	Yes: Go to #4	No: Go to #3
3. Is the diagnosis above the line? Unspecified hypersomnia (ICD9 780.54) and Obesity treatment (278.0-278.1) are below the line.	Yes: Pass to RPH; Deny, (Not covered by OHP)	No: Go to #4
4. Is the drug requested preferred?	Yes: Go to #7	NO: Go to #5
5. Is this continuation of therapy (claim indicating prescription filled within prior 90 days)?	Yes: Document prior therapy in PA record. Go to #7	No: Go to #6
6. Will the provider consider a change to a preferred product? Message: - Preferred products do not require a PA - Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T Committee).	Yes: Inform provider of covered alternatives	No: Go to #7
7. Is the dose greater than limits in table below?	Yes: Go to #8	No: Approve for up to 1 year.

Date: July 2013

8. Is the prescriber a psychiatrist?	Yes: Approve for up to 1 year.	No: Go to #9
9. Is the patient <18 years old?	Yes: Go to #10	No: Pass to RPH; Deny, (Medical Appropriateness). Dose exceeds maximum recommended dose.
10. How much does the patient weight?	Document the patient's weight and continue to #11	
11. Is the patient receiving an accumulative dose that EXCEEDS 2mg/kg/day of methylphenidate products or EXCEEDS 0.5mg/kg/day of amphetamine products?	Yes: Pass to RPH; Deny. (Medical Appropriateness) – Dose exceeds maximum recommended dose. Consider switching to an alternative stimulant drug class or assessing compliance with the current therapy.	No: Approve for up to 1 year.

Appendix 2: RCT Abstracts

Brams M, Turnbow J, Pestreich L, et al. A Randomized, Double-Blind Study of 30 Versus 20 mg Dexmethylphenidate Extended-Release in Children With Attention-Deficit/Hyperactivity Disorder. *Journal of Clinical Psychopharmacology*. 2012; 32(5):637–644. doi:10.1097/JCP.0b013e3182677825.

The objective of this study was to evaluate the safety and efficacy of dexmethylphenidate extended-release (d-MPH-ER) 30 versus 20mg in children with attention-deficit/hyperactivity disorder (ADHD) in a 12-hour laboratory classroom setting. In a randomized, double-blind, 3-period _ 3-treatment, crossover study, children aged 6 to 12 years with Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition diagnosed ADHD previously stabilized on MPH (40Y60 mg/d) or D-MPH (Combined score from predose to 10, 11, and 12 hours postdose) compared with D-MPH-ER 20mg (2.02; P=0.002). Most common adverse events (Q3% in any group) were decreased appetite (6.1%, 4.9%, and 0%), headache (4.3%, 4.3%, and 1.9%), abdominal pain (3.7%, 3.1%, and 3.1%), and tachycardia (1.2%, 3.1%, and 0.6%) for D-MPH-ER 30 mg, D-MPH-ER 20 mg, and placebo, respectively). Significantly greater improvement in ADHD symptoms was noted with D-MPH-ER 30 mg compared with D-MPH-ER 20 mg at hours 10 through 12. Tolerability was comparable between doses. Dexmethylphenidate extended-release 30-mg dose may provide further benefit to patients who do not maintain optimal symptom control later in the day with D-MPH-ER 20 mg.

Jafarinia M, Mohammadi M-R, Modabbernia A, et al. Bupropion versus methylphenidate in the treatment of children with attention-deficit/hyperactivity disorder: randomized double-blind study. *Human Psychopharmacology: Clinical and Experimental*. 2012; 27(4):411–418. doi:10.1002/hup.2242.

Objective To compare the safety and efficacy of bupropion with methylphenidate in children and adolescents with attention-deficit/ hyperactivity disorder (ADHD).
Methods In a 6-week randomized double-blind study, 44 patients with a DSM-IV-TR diagnosis of ADHD were randomly assigned to receive bupropion 100–150 mg/day (100 mg/day for <30 kg and 150 mg/day for >30 kg) or methylphenidate 20–30 mg/day. Symptoms were assessed using Teacher and Parent Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) at baseline and weeks 3 and 6.
Results Forty patients had at least one post-baseline measurement, and 38 patients completed the trial. No significant difference was found between the two groups on the Parent and Teacher ADHD-RS-IV scores ([F(1, 38) = 0.266, p = 0.609] and [F(1, 38) = 0.001, p = 0.972], respectively). By week 6, 18 patients (90%) in each group achieved response on the Parent scale (Fisher's exact test p-value = 1.0). With the Teacher ADHD-RS-IV used, eight (40%) patients in the bupropion group and 12 (60%) patients in the methylphenidate group achieved response by week 6 (w2(1) = 1.600, p = 0.206). Headache was observed more frequently in the methylphenidate group. Frequency of other side effects was not significantly different between the two groups.
Conclusions Bupropion has a comparable safety and efficacy profile with methylphenidate in children and adolescents with ADHD

Weisler RH, Pandina GJ, Daly EJ, Cooper K, Gassmann-Mayer C. Randomized Clinical Study of a Histamine H3 Receptor Antagonist for the Treatment of Adults with Attention-Deficit Hyperactivity Disorder. *CNS Drugs*. 2012;26(5):421–434. doi:10.2165/11631990-000000000-00000.

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 (1 mg/day, 3 mg/day or 10 mg/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 1 mg/day, 3 mg/day or 10 mg/day, atomoxetine hydrochloride 80 mg/day or osmotic-release oral system (OROS) methylphenidate hydrochloride 54 mg/day.
Main outcome measure: The primary efficacy endpoint was the change in the Attention Deficit Hyperactivity Disorder Rating Scale, Version IV (ADHDRS-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 1 mg/day, 3 mg/day and 10 mg/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 1 mg/day and 3 mg/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 1 mg/day, 3 mg/day and 10 mg/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.

Döpfner M, Ose C, Fischer R, Ammer R, Scherag A. Comparison of the Efficacy of Two Different Modified Release Methylphenidate Preparations for Children and Adolescents with Attention-Deficit/Hyperactivity Disorder in a Natural Setting: Comparison of the Efficacy of Medikinet® Retard and Concerta® —a Randomized, Controlled, Double-Blind Multicenter Clinical Crossover Trial. *Journal of Child and Adolescent Psychopharmacology*. 2011;21(5):445–454. doi:10.1089/cap.2010.0082.

Objective: The comparison of the efficacy of Medikinect_ retard and Concerta_ trial was a multisite, randomized, double-blind, crossover trial that aimed at comparing the effects of two different modified release methylphenidate preparations (Medikinect retard: 50% immediate release (IR); Concerta: 22% IR) in a natural setting across the day in 113 randomized children and adolescents with attention-deficit/hyperactivity disorder (age range 6–16 years). The duration of the study per patient was 3 weeks.

Methods: The primary outcome variable was the German version of the ''Swanson, Kotkin, Agler, M-Flynn, and Pelham scale'' in the first 3 hours of school as assessed by teachers.
Results: Medikinect retard with a higher IR component than Concerta (and an equivalent daily dose) was superior to Concerta (p = 0.0009), and Medikinect retard with similar IR components in the morning as Concerta (but a lower daily dose) was noninferior to Concerta with regard to the primary outcome. Further, exploratory analyses on teacher and parent ratings on attention-deficit/hyperactivity disorder and on externalizing symptoms during the day revealed no evidence for the superiority of Concerta over Medikinect retard in an equivalent daily dosage throughout the day.
Conclusion: Children and adolescents may be treated with a lower daily dose of Medikinect retard (which has a similar IR component as Concerta) without resulting in a clinically relevant worse effect during school time.

Yildiz O, Sismanlar SG, Memik NC, Karakaya I, Agaoglu B. Atomoxetine and Methylphenidate Treatment in Children with ADHD: The Efficacy, Tolerability and Effects on Executive Functions. *Child Psychiatry & Human Development*. 2010;42(3):257–269. doi:10.1007/s10578-010-0212-3.
The aim of this study was to compare the safety, efficacy, tolerability, and the effects of atomoxetine and OROS-MPH on executive functions in children with ADHD. This study was an open-label study that only included two medication groups. Children were randomized to open-label atomoxetine or OROS-MPH for 12 weeks. Primary efficacy measures were T-DSM-IV-S, CGI-I and neuropsychological tests battery. Safety assessments included electrocardiogram, adverse events checklist and laboratory tests. According to the endpoint improvement scores of CGI and parents T-DSM-IV-S, treatment responses were not significantly different between the two study groups. OROS-MPH led to a significantly greater reduction in teacher T-DSM-IV-S scale scores. OROS-MPH was more effective than atomoxetine on Stroop-5 time and number of corrections. Significant decrease in the percentage of perseverative errors on WCST in the OROS-MPH group was seen (p = 0.005). The most frequently reported adverse events in the atomoxetine group were anorexia, nausea, nervousness, weight loss, abdominal pain, and somnolence. In the OROS-MPH group, patients most frequently reported anorexia, nervousness, insomnia, headache, nausea, and weight loss. When all these results are considered, although both drugs can be considered effective in ADHD treatment, more remarkable improvement is provided by OROS-MPH based on the rates across informant (i.e., teachers, clinicians) and neuropsychological evaluation.

Spencer TJ, Mick E, Surman CBH, et al. A Randomized, Single-Blind, Substitution Study of OROS Methylphenidate (Concerta) in ADHD Adults Receiving Immediate Release Methylphenidate. *Journal of Attention Disorders*. 2010;15(4):286–294. doi:10.1177/1087054710367880.
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.

Stein MA, Waldman ID, Charney E, et al. Dose Effects and Comparative Effectiveness of Extended Release Dexmethylphenidate and Mixed Amphetamine Salts. *Journal of Child and Adolescent Psychopharmacology*. 2011;21(6):581–588. doi:10.1089/cap.2011.0018.
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 ERMAS 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.

Appendix 3: Abstracts of Meta Analyses

Van Wyk GW, Hazell PL, Kohn MR, Granger RE, Walton RJ. How Oppositionality, Inattention, and Hyperactivity Affect Response to Atomoxetine Versus Methylphenidate: A Pooled Meta-Analysis. *Journal of Attention Disorders*. 2011;16(4):314–324. doi:10.1177/1087054710389989.
Objective: To assess how threshold oppositional defiant disorder (ODD), inattention, and hyperactivity-impulsivity affect the response to atomoxetine versus methylphenidate.
Method: Systematic review of randomized controlled trials (RCTs; ≥6 weeks follow-up). The primary measure was core symptom response—≥40% reduction in ADHD Rating Scale-IV–Parent Version: investigator administered and scored total or domain subscores, as appropriate.
Results: Data from 1,391 children and adolescents (823 atomoxetine, 568 methylphenidate; 7 RCTs) were meta-analyzed. The mean difference in response rates for patients with ODD was 0.6% (95% confidence interval [CI] = −11.9%-13.1%). The "without ODD" patient group showed significant between-trial heterogeneity (p < .001). Response rate differences for patients meeting the threshold for inattention or hyperactivity-impulsivity were −3.1% (95% CI = −11.5%-5.3%) and −4.9% (95% CI = −14.3%-4.4%), respectively.
Conclusions: Meeting the threshold criteria for oppositionality, inattention, or hyperactivity-impulsivity did not alter core ADHD symptom response to atomoxetine versus methylphenidate, which was equivalent.

Hanwella R, Senanayake M, de Silva V. Comparative efficacy and acceptability of methylphenidate and atomoxetine in treatment of attention deficit hyperactivity disorder in children and adolescents: a meta-analysis. *BMC Psychiatry*. 2011;11(1):176. doi:10.1186/1471-244X-11-176.

Background: Psychostimulants and non-stimulants are effective in the treatment of ADHD. Efficacy of both methylphenidate and atomoxetine has been established in placebo controlled trials. Direct comparison of efficacy is now possible due to availability of results from several head-to-head trials of these two medications.
Methods: All published, randomized, open label or double blind trials, comparing efficacy of methylphenidate with atomoxetine, in treatment of ADHD in children, diagnosed using DSM-IV™ criteria were included. The outcome studied was ADHDRS-IV Parent score. The standardized mean difference (SMD) was used as a measure of effect size.
Results: Nine randomized trials comparing methylphenidate and atomoxetine, with a total of 2762 participants were included. Meta-analysis did not find a significant difference in efficacy between methylphenidate and atomoxetine (SMD = 0.09, 95% CI -0.08-0.26) (Z = 1.06, p = 0.29). Synthesis of data from eight trials found no significant difference in response rates (RR = 0.93 95% CI 0.76-1.14, p = 0.49). Sub group analysis showed a significant standardized mean difference favouring OROS methylphenidate (SMD = 0.32, 95% CI 0.12-0.53 (Z = 3.05,p < 0.002). Immediate release methylphenidate was not superior to atomoxetine (SMD = -0.04, 95% CI -0.19-0.12) (Z = 0.46, p = 0.64). Excluding open label trials did not significantly alter the effect size (SMD = 0.08, 95% CI -0.04- 0.21) (Z = 1.27, p = 0.20). All-cause discontinuation was used as a measure of acceptability. There was no significant difference in all cause discontinuation between atomoxetine and methylphenidate (RR 1.22, 95% CI 0.87- 1.71). There was significant heterogeneity among the studies (p = 0.002, I2 = 67%). Subgroup analysis demonstrated the heterogeneity to be due to the open label trials (p = 0.001, I2 = 81%).
Conclusions: In general atomoxetine and methylphenidate have comparable efficacy and equal acceptability in treatment of ADHD in children and adolescents. However OROS methylphenidate is more effective than atomoxetine and may be considered as first line treatment in treatment of ADHD in children and adolescents.

Castells X, Ramos-Quiroga JA, Bosch R, Nogueira M, Casas M. Amphetamines for Attention Deficit Hyperactivity Disorder (ADHD) in adults. In: The Cochrane Collaboration, Castells X, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2011. Available at: http://doi.wiley.com/10.1002/14651858.CD007813.pub2. Accessed May 27, 2013.

Background Attention Deficit Hyperactivity Disorder (ADHD) is a childhood onset disorder that can persist into adulthood. Amphetamines are used to treat adult ADHD, but uncertainties persist about their efficacy and safety.
Objectives To examine the efficacy and safety of amphetamines for adults with ADHD, as well as the influence of dose, drug type and release formulation type.
Search methods We searched CENTRAL, PubMed, EMBASE, CINAHL, PsycINFO, clinicaltrials.gov, UK Clinical Trials Gateway and references obtained from articles and experts in the field. We conducted the electronic searches on 25 February 2010.
Selection criteria Randomized controlled trials comparing the efficacy of amphetamine derivatives against placebo or an active intervention.
Data collection and analysis Two authors extracted data from each included study. We used the standardized mean difference (SMD) and the risk ratio (RR) to assess continuous and dichotomous outcomes, respectively. We conducted a stratified analysis to determine the influence of moderating variables. We assessed the trials for risk of bias and drew a funnel plot to investigate the possibility of publication bias.
Main results We included seven studies, which enrolled 1091 participants. All studies were placebo-controlled and three included an active comparator: guanfacine, modafinil and paroxetine. Most studies had short-term follow-up, with a mean study length of 8.1 weeks. Amphetamines improved ADHD symptom severity (SMD = -0.72; 95% CI -0.87 to -0.57) but did not improve retention in treatment overall and were associated with increased dropout due to adverse events (RR 3.03; 95% CI 1.52 to 6.05). The three amphetamine derivatives investigated dextroamphetamine, lisdexamphetamine and mixed amphetamine salts (MAS)) were all efficacious for reducing ADHD symptoms, but MAS also increased retention in treatment. Different doses did not appear associated with differences in efficacy. We investigated immediate and sustained drug release formulations but found no difference between them on any outcome. When amphetamines were compared to other drug interventions, no differences were found. We did not find any study to be at low risk of bias overall, mainly because amphetamines have powerful subjective effects that may reveal the assigned treatment.
Authors' conclusions Amphetamines improved short-term ADHD symptom severity. MAS also increased retention in treatment. Amphetamines were associated with higher attrition due to adverse events. The short study length and the restrictive inclusion criteria limit the external validity of these findings. Furthermore, the possibility that the results of the included studies were biased was high, which could have led to an overestimation of amphetamine efficacy.

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