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

Drug Class Update: Attention Deficit Hyperactivity Disorder

Date of Review: September 2017

Date of Last Review: March 2016
End Date of Literature Search: 06/30/2017

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
The purpose of this update is to evaluate new comparative evidence for efficacy and safety of treatements for attention deficit hyperactivity disorder (ADHD) published since the previous class update in March 2016. Evidence for 3 new Food and Drug Administratin (FDA)-approved stimulant formulations is also reviewed.

Research Questions:
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 comorbidities (e.g. tics, anxiety, substance use disorders, disruptive behavior disorders)?

Conclusions:
- This review includes new evidence from 3 systematic reviews,[1-3] 2 guidelines,[4,5] 2 randomized control trials (RCTs),[6,7] and 2 FDA safety updates.[8] Evidence for new, FDA-approved formulations of lisdexamfetamine chewable tablets, mixed amphetamine salts, and methylphenidate extended release orally disintegrating tablets is also included in this review.
- Overall, there is insufficient new evidence which evaluates comparative effectiveness of medications or formulations for treatment of ADHD in children or adults. A Cochrane review examining differences between agents found similar symptom improvement with dexamphetamine, lisdexamfetamine, and mixed amphetamine salts (standardized mean difference [SMD] of -0.44 to -0.72) indicating medium effect size compared to placebo.[2] Evidence was limited by use of indirect comparisons, high heterogeneity between trials, and unclear risk of bias for many trials included in the systematic review. In addition, few trials examined long-term use of stimulants (median duration 28 days).[2]
- Guidelines generally recommended non-pharmacological interventions as first-line treatment for children with ADHD, followed by pharmacological treatment in children with moderate symptoms who fail to respond to psychosocial or behavioral interventions.[4] Stimulants are recommended as initial

Author: Sarah Servid, PharmD

pharmacological treatment followed by non-stimulant medications such as atomoxetine, clonidine and guanfacine as second-line therapy if stimulants are not tolerated or ineffective.

- There is limited evidence in children with concurrent autism, Tourette's syndrome, or learning disabilities which suggest stimulants may help to improve symptoms of ADHD. There was low quality evidence that compared to methylphenidate, behavioral interventions were more effective at improving ADHD symptoms including motor activity, disruptive behavior and academic engagement in children with learning disabilities.[5] There is insufficient data which compares differences in efficacy or safety between drugs or formulations in these subpopulations.
- There is no new evidence which evaluates safety or efficacy of combination treatment with multiple stimulant medications for ADHD.

Recommendations:

- There is no new evidence which would change previous conclusions. Evaluate comparative costs in the executive session.

Previous Conclusions: March 2016

- There is insufficient evidence that directly compares general effectiveness outcomes of different drugs for ADHD in children or adults.
- In children, there is low to moderate quality evidence of no difference in improvement of ADHD symptoms between immediate-release (IR) and extended-release (ER) stimulants; between ER stimulants (including controlled delivery (CD), sustained-release (SR), and transdermal formulations); or between IR stimulants. Exceptions of studies that do show differences between stimulants are of low quality and further studies are needed to determine if true differences in efficacy between these drugs exist.
- In children, there is moderate quality evidence non-stimulant atomoxetine may be inferior to stimulants on most efficacy outcomes, such as response rates. Comparisons between stimulants and non-stimulants other than atomoxetine are either lacking or do not demonstrate differences in efficacy.
- In children, there is insufficient evidence that compares efficacy between non-stimulant ADHD drugs with the exception of guanfacine ER and atomoxetine, for which there is low quality evidence guanfacine ER may be superior to atomoxetine at reducing ADHD-RS scores at 6 weeks (difference -5.1; scale 0-54).
- In adolescents and adults, there is insufficient evidence to adequately compare differences in efficacy of stimulants and non-stimulant drugs for ADHD.
- The most common adverse effects from stimulants are appetite loss, abdominal pain, headaches and sleep disturbance; there is only low quality evidence to suggest any differences in harms between the agents.
- Insufficient evidence from survey data suggest lifetime non-medical use of methylphenidate IR and dextroamphetamine was more frequent compared to mixed amphetamine salts; the highest rate of diversion was with amphetamine/dextroamphetamine.

Previous Recommendations:

- No new evidence in the DERP report suggests changes should be made to the PDL based on clinical differences between agents.
- Designate QuilliChew ER™ and Adzenys XR-ODT™ as non-preferred based on limited evidence for safety and efficacy.
- Update the current safety edit.

Background:

ADHD is a neurobehavioral disorder which affects approximately 2-9% of children and adolescents characterized by hyperactivity, impulsivity, and inattention. According to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria, diagnosis is based on presence of at least 6 symptoms for greater than 6 months present in 2 different settings which interfere with function and are inappropriate for the patients developmental level (or at least 5 symptoms in patients greater than 16 years of age).[9] Comorbid conditions which can be associated with a diagnosis of ADHD include mood disorders, tic

disorders, developmental and learning disorders and anxiety disorders.[9] Recommendations from the American Academy of Pediatrics guidelines are based on age and disease severity. In children age 4-5 years, behavioral therapy is recommended as first-line treatment. Methylphenidate is recommended as a second-line therapy or in cases of moderate-to-severe functional impairment. In children older than 6 years of age, behavioral therapy and/or pharmacotherapy may be used. Evidence is strongest evidence for stimulant medications, although non-stimulant medications including atomoxetine, clonidine and guanfacine are recommended as second-line therapy if stimulants are not tolerated or ineffective.[9,10]

Goals of care include management of symptoms, functional improvement, and improved quality of life. Symptom and functional improvement can be evaluated using a variety of assessment scales and metrics. Assessment scales commonly used in randomized controlled trials (RCTs) include the ADHD rating scale, the Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale (SKAMP), Permanent Product Measure of Performance (PERMP), and Conners Parent Rating Scale (CPRS). The ADHD rating scale assesses symptoms of inattentiveness, hyperactivety, and impulsivity based on DSM criteria for diagnosis of ADHD. The range for this scale based on DSM-IV criteria is 0 to 54 with more higher scores indicating more severe symptoms.[11] The CPRS scale evaluates a variety of ADHD symptoms, each assessed on a 0 to 3 scale corresponding to symptoms which are not present (0), just a little present (1), pretty much present (2), and very much present (3).[11] The SKAMP rating scale is a teacher-rated scale which evaluates attention and behavior in a laboratory classroom setting. Scores assess 13 items including attention, quality of work, deportment and compliance. Each item is assessed on a 0 to 6 point scale with total score ranging from 0 to 78 and higher scores associated with more severe impairment.[12,13] The PERMP is another classroom assessment which evaluates attention using a skill-adjusted math test. The total PERMP score is a sum of the number of math problems attempted and the number answered correctly.[14] Because PERMP score is specific to the ability of the patient, the minimum clinically significant difference in PERMP score has not been determined.

In the Oregon Health Plan Fee-for-Service population, use of ADHD medications is restricted based on FDA approved age and dose. Use of duplicate therapy is permitted for the regimens listed in **Appendix 4,** and off-label use of these medications may be approved if the regimen is recommended by or in consultation with a specialist. Currently, patients receiving preferred or voluntary products in this class account for approximately 45% and 40% of claims, respectively. Of the non-preferred agents extended-release methylphenidate and extended-release dextroamphetamine-amphetamine are most commonly used. For patients requesting a non-preferred product, 64% of patients had a subsequent prior authorization approved. Only 9% of patients who initially request a non-preferred agent are switched to an alternate agent in the class.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated evidence-based clinical practice guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

A Cochrane systematic review published in 2016 examined the efficacy of amphetamines for children and adolescents age 3 to 17 with ADHD.[2] The review included 19 parallel group or cross-over trials comparing amphetamines to placebo. Full data was not included from 4 of these studies as 2 studies were ongoing and 2 were non-English studies which were awaiting review at the time of publication to determine if they were randomized or included patients with a formal diagnosis of ADHD.[2] Of these trials, 20 were conducted in the United States.[2] Dosing regimen varied between trials with 12 studies which used a fixed dosing regimen, 5 studies which titrated dose based on response, and 7 studies which used weight based dosing.[2] The mean dose used in these studies was 34 mg/day for dextroamphetamine, 50 mg/day for lisdexamfetamine, and 20 mg/day for mixed amphetamine salts.[2] The median duration was 28 days, and only one study examined a duration longer than 63 days. Overall, most trials included in the meta-analysis failed to report adequate methodology and had unclear risk of bias. Only 3 trials described methods of randomization, 4 described methods of allocation concealment, 10 described blinding methods for patients and providers and 2 stated outcome assessors were blinded. Thirteen trials were rated as having low risk for attrition bias and only 4 trials had low risk of reporting bias.[2] Safety outcomes included the proportion of patients who withdrew due to adverse events, proportion of patients who completed the trial, and proportion of patients who experienced common adverse effects of stimulants. Due to a lack of direct comparative trials for ADHD drugs, subgroup analyses were conducted to estimate the treatment effects and relative safety based on the type of stimulant and formulation. Because trial outcomes were recorded with different scales and metrics, results were reported using standard mean difference (SMD) with lower numbers indicating a lower frequency of events and higher numbers associated with more events. The total ADHD symptom score based on parent ratings was similar between dexamphetamine (SMD -0.60, 95% CI -1.36 to 0.16), lisdexamfetamine (SMD -0.72, 95% CI -1.59 to 0.14), and mixed amphetamine salts (SMD -0.44, 95% CI -0.63 to -0.24).[2] Similar results were observed for other measures of efficacy and safety with no difference between stimulants. Only one subgroup analysis (the proportion of patients who experienced a decrease in appetite) demonstrated statistically significantly different results for formulations of dexamphetamine (RR 1.41, 95% CI 0.95 to 2.11), lisdexamfetamine (RR 9.83, 95% CI 5.08 to 19.02), and mixed amphetamine salts (RR 6.42, 95% CI 1.56 to 26.52) compared to placebo.[2] Analysis was limited by high heterogeneity between trials (I^2=86%).[2] Similarly, subgroup analysis between long- and short-acting formulations found no difference in academic performance, proportion of responders, and ADHD symptom score based on parent ratings. Analysis of patient retention was significantly different between long-acting (RR 1.11, 95% CI 1.00 to 1.24) and short-acting formulations (RR 0.98, 95% CI 0.95 to 1.01; p=0.03 for subgroup differences, I^2=0.78%).[2] The proportion of patients experiencing a decreased appetite was also higher for extended release formulations (RR 7.67, 95% CI 3.33 to 17.65) compared to short-acting formulations (RR 1.58, 95% CI 0.69 to 3.62; p=0.008 for subgroup differences, I^2=0.86%).[2] The absolute differences between formulations was not reported. Subgroup analyses for other safety outcomes demonstrated no differences between groups. Results from these analyses should be interpreted with caution due to use of indirect comparisons, high heterogeneity between trials, and unclear risk of bias for many trials.[2]

In 2017, AHRQ published a report of medications for children with autism spectrum disorder.[3] The review evaluated comparative studies of patients age 2 to 12 years of age with at least 10 participants. A total of 5 RCTs (n=265) assessing methylphenidate (n=2), atomoxetine (n=2) or guanfacine (n=1) were included in the review.[3] Overall, included trials had low to moderate risk of bias. Authors concluded that compared to placebo, methylphenidate and atomoxetine improved hyperactivity and other challenging behaviors in patients with autism spectrum disorder though strength of evidence was low.[3] Data was limited by small study size, short treatment duration, significant placebo effect, and inconsistency in results reported by parents and teachers. The most common adverse effects associated with treatment were irritability, gastrointestinal symptoms, drowsiness, and decreased appetite.[3] There was insufficient data to examine differences between agents or to evaluate outcomes for guanfacine.

A systematic review funded by the National Institute for Health Research in the United Kingdom evaluated 70 RCTs or controlled before-and-after studies which examined effectiveness of pharmacotherapy for tics in children and adolescents with Tourette's syndrome.[1] The review included 7 placebo-controlled studies examining efficacy of clonidine (as oral or patch formulations), 2 studies of guanfacine, and one study of atomoxetine.[1] Results were reported as standardized

mean differences (SMD) which allows for comparison of trials which use different scales or metrics to evaluate symptom severity. Authors conclude there was moderate-quality evidence suggesting oral clonidine had a medium to large effect on tic severity (SMD -0.71, 95% CI -1.10 to -0.31) and impairment (SMD -0.54, 95% CI -0.93 to -0.16) compared to placebo after 12 to 16 weeks of treatment.[1] However, results from one large study comparing clonidine patch to placebo over 4 weeks provided moderate quality evidence of no difference in tic improvement compared to placebo.[1] There was moderate quality evidence that guanfacine demonstrated a large impact on tic severity (SMD -0.73, 95% CI -1.26 to -0.20) compared to placebo with 4 to 8 weeks of treatment.[1] One trial (n=145) provided moderate quality evidence that atomoxetine given for 18 weeks was associated with small to moderate symptom improvement (SMD -0.54 to -0.63) but had higher rates of decreased appetite and nausea.[1] The efficacy and safety of stimulants in children with comorbid ADHD and tic disorders was also examined for methylphenidate (3 trials), combination methylphenidate and clonidine (1 trial), and dexmethylphenidate (1 trial).[1] The primary goal of these studies was to identify if use of stimulants worsened tic disorders. There was very low quality evidence suggesting stimulants did not significantly impact tic severity or impairment (SMD -0.30, 95% CI -0.76 to 0.15; p=0.83) compared to placebo.[1] Direct comparisons included 3 RCTs comparing clonidine to levetiracetam, risperidone, and haloperidol. No differences were noted in clinical efficacy of clonidine compared to these agents.[1] Evidence was of low or very low quality and limited by small population size, high risk of bias and imprecision.[1] Overall, due to the limited number of trials and low quality of evidence, authors conclude that further research is needed to assess differences in efficacy and safety of treatment options for treatment of tic disorders and Tourette's syndrome.[1]

In 2016, CADTH conducted a systematic review to examine the clinical effectiveness of combination treatment (ie a long-acting stimulant or non-stimulant medication combined with a short-acting stimulant) for adults with ADHD.[15] Systematic reviews, meta-analyses, non-randomized studies, and RCTs were considered for the review. No studies were identified which compared combination treatment to placebo or monotherapy with a long-acting or short-acting stimulant in adults with ADHD.

New Guidelines:

A 2016 CADTH rapid response review examined recommendations from evidence based guidelines for the pharmacological treatment of ADHD in children, adolescents or adults.[4] Three guidelines from the British Association for Psychopharmacology, American Academy of Pediatrics, and Academy of Medicine/Singapore/Ministry of Health met inclusion criteria and were assessed for quality using the AGREE II tool.[4] All 3 guidelines addressed treatment in children and adolescents, and comparisons included both pharmacologic and non-pharmacologic interventions. Pharmacological treatments were broadly defined as stimulant and non-stimulant treatment options. All 3 guidelines recommended non-pharmacological interventions as first-line treatment for children with ADHD, followed by pharmacological treatment in children with moderate symptoms who fail to respond to psychosocial or behavioral interventions.[4] Overall, guidelines recommend stimulant medications as first-line therapy for children and adolescents with ADHD (strong recommendation).[4] Only one guideline addressed treatment of ADHD in adults, recommending stimulants as first-line treatment in adults with ADHD.[4] Guidelines recommend atomoxetine as an initial treatment in patient with a risk of abuse or misuse (strong recommendation) and patients for whom stimulants are contraindicated, ineffective, or not tolerated.[4] Two guidelines also had recommendations for extended-release stimulant formulations instead of immediate-release formulations in patients with a history of abuse of misuse (based on weak evidence).[4] All guidelines also noted that there was insufficient evidence for simultaneous use of stimulant and non-stimulant medication in patients with ADHD.[4] Guidelines included in this review were limited as one guideline (Academy of Medicine/Singapore/Ministry of Health) did not provide adequate description of the development process, sources of evidence, or conflicts of interest for participating members involved in the guideline development.[4] Members involved in development for the other guidelines declared consultation fees, honoraria for speaking, research grants, or conference support from pharmaceutical companies.[4]

In 2016, NICE updated guidelines for prevention, assessment and management of mental health problems in people with learning disabilities.[5] Pharmacologic therapy is commonly used in patients with learning disabilities and concomitant psychiatric diagnosis and/or challenging behavior (defined as behavior with intensity, frequency, or duration which threatens the safety of the patient or threatens other people, or restricts access to community facilities).[5] Very few RCTs examined efficacy of ADHD medications in this population and evidence was limited by small sample sizes, imprecision, and high risk of bias. Moderate quality evidence from a single RCT demonstrated that methylphenidate improved ADHD symptoms and hyperactivity score after 16 weeks of treatment.[5] Adverse effects from treatment included poor appetite, weight loss and difficulty sleeping. There was low quality evidence that compared to methylphenidate, behavioral interventions were more effective at improving ADHD symptoms including motor activity, disruptive behavior and academic engagement.[5] There was insufficient evidence to draw conclusions for other drugs or for other outcomes. The guideline committee concluded that behavior modification was likely more effective than pharmacotherapy and that the available evidence in patients with learning disabilities supported recommendations regarding treatment of ADHD.[5] No specific recommendations were made for this subpopulation of patients.[5]

New Formulations or Indications:
In January 2017, lisdexamfetamine (Vyvanse®) chewable tablets were FDA approved for treatment moderate to severe binge eating disorder (BED) in adults and ADHD in adult and pediatric patients.[16] Approval was based on bioequivalence studies compared to lisdexamfetamine capsules.

In June 2017, a new formulation of methylphenidate extended release orally disintegrating tablet (Cotempla XR-ODT®) was FDA approved for treatment of ADHD in pediatric patients 6 to 17 years of age.[12] Cotempla XR-ODT is available as 8.6, 17.3 and 25.9 mg orally disintegrating tablets and was approved on the basis of a single double-blind, placebo-controlled RCT.[12] The trial included an open-label dose optimization period before randomization in which all patients were initially started on 17.3 mg of methylphenidate-XR-ODT and titrated to an optimal dose (maximum 51.8 mg).[12] After the dose-optimization period (5 weeks total), patients were randomized to the individually optimized dose of Cotempla or placebo for a 1 week period.[12] The primary endpoint for this study was the average of the SKAMP-Combined rating scale over the course of the testing day (from 1 to 13 hours post-dose).[12] The SKAMP rating scale is a teacher-rated scale which evaluates attention and behavior in a laboratory classroom setting. Scores assess 13-items and range from 0 to 78 with higher scores indicating more severe impairment.[12] Baseline scores at randomization were 21.1 and 20.4 points for methylphenidate and placebo groups, respectively.[12] Compared to placebo, patients randomized to methylphenidate had an average SKAMP-combined score of 14.3 points which was statistically significant compared to placebo (25.3 points; mean difference [MD] -11.0; 95% CI-13.9 to -8.2).[12] Largest differences in score were apparent at 3 hours post-dose and were no longer statistically significant compared to placebo by 13 hours post-dose.[12]

A new formulation of mixed amphetamine salts (Mydayis®) was FDA approved in June 2017 for ADHD in patients greater than 13 years of age.[14] In clinical trials, patients younger than 13 years of age had higher plasma concentrations and experienced more adverse effects than older adolescents when given the same dose.[14] Mydayis extended release capsules include amphetamine aspartate, amphetamine sulfate, dextroamphetamine saccharate, and dextroamphetamine sulfate and are available as 12.5 mg, 25 mg, 37.5mg and 50 mg capsules.[14] This new formulation was approved on the basis of 2 short-term, multicenter, placebo-controlled, double-blind, RCTs in adult (n=275) and pediatric patients age 13 to 17 years (n=157).[14] The primary endpoint for these trials was change in the ADHD-rating scale from baseline to 4 weeks. Adult patients meeting DSM-5 criteria for ADHD were randomized in a 1:1:1 ratio to 12.5 mg daily, initial 12.5 mg daily with forced-titration to 37.5 mg daily, or placebo.[14] Mean baseline score for adult patients was 40 points indicating relatively severe symptoms (total possible range of 0 to 54 points). In patients randomized to mixed amphetamine salts, the mean change in the ADHD rating scale from baseline was -18.5 and -23.8 points compared to placebo (-10.4 points).[14] The mean difference compared to placebo was -8.1 points (95% CI -11.7 to -4.4) in patients given 12.5 mg and -13.4 points (95% CI -17.1 to -9.7) in patients titrated to 37.5 mg daily.[14] Pediatric patients who met DSM-4 TR criteria for ADHD were randomized to placebo or 12.5 mg of mixed amphetamine salts with titration to an optimal dose (maximum 25 mg daily).[14] The mean baseline score for the ADHD-rating scale-IV was 36-

37 points.[14] Patients randomized to mixed amphetamine salts had a mean improvement of 20.3 points compared to a mean 11.6 point improvement with placebo (MD compared to placebo of -8.7 points [95% CI -12.6 to -4.8]).[14] Results were statistically significant compared to placebo, though p-values were not reported. Supporting evidence also included 3 single-dose, double-blind, placebo-controlled, crossover RCTs in adult (n=2) and pediatric (n=1) patients.[14] The primary endpoint for these studies was the Permanent Product Measure of Performance (PERMP) which evaluates attention using a skill-adjusted math test. The total PERMP score is a sum of the number of math problems attempted and the number answered correctly. Assessments were evaluated at 2, 4, 8, 14 and 16 hours post-dose.[14] In adult patients, PERMP scores were statistically significant compared to placebo at 4 to 16 hours in patients given 25 mg and at 2 to 16 hours in patients given 50 mg (MD compared to placebo of 19.3 points [95% CI 10.9 to 27.6] and 18.4 [95% CI 11.3 to 25.5] for 25 and 50 mg, respectively).[14] In pediatric patients, patients randomized to amphetamine salts had a mean change from baseline of 272.7 points compared to 231.4 points in patients randomized to placebo (MD 41.3 points, 95% CI 32.2 to 50.3).[14]

New FDA Safety Alerts:

In 2017, product labeling for stimulants including lisdexamfetamine, amphetamine, methamphetamine, dextroamphetamine, and mixed amphetamine salts was updated to specify that these product are contraindicated in patients taking concomitant monoamine oxidase inhibitors (MAOI) or within 14 days of stopping a MAOI due to an increased risk of hypertensive crisis.[8] Warnings included risk for serotonin syndrome when taken in combination with other serotonergic medications. Labeling for mixed amphetamine salts, amphetamine, and dextroamphetamine were also updated to include contraindications in patients with previous hypersensitivity reactions to other amphetamine products.[8]

In February 2017, product labeling for methylphenidate hydrochloride products, QuilliChew ER and Quillivant XR, was revised to emphasize serious cardiovascular reactions including stroke and myocardial infarction in children and adolescents with structural cardiac abnormalities or in adults taking CNS stimulants at doses recommended for ADHD.[8]

Randomized Controlled Trials:

A total of 105 citations were manually reviewed from the initial literature search. After further review, 103 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining 2 trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Outcome	Results
Snircova E, et al. 2016.[6] AC, RCT N=78 Duration: 8 weeks	1. Atomoxetine - For <70kg: 0.5 mg/kg/day titrated to 0.8-1.2 mg/kg/day - For ≤70 kg: 40 mg titrated to 80 mg daily 2. Methylphenidate ER 5 mg titrated to 40 mg daily if needed	Patients 5-16 years of age with ADHD	ADHD rating scale IV at 8 weeks (range 0-54 with larger numbers indicating more severe disease) Conners Parent Rating Scale for anxiety at 8 weeks	ADHD rating scale-IV (mean, SD) 1. 20.44 (11.86) 2. 22.73 (9.80) p=0.389 Conners Parent Rating Scale for anxiety 1. 3.22 (3.49) 2. 5.54 (4.26) p=0.015

Nagy P, et al. 2016.[7] DB, AC, PG, RCT N=267 Duration: 9 weeks	1. Lisdexamphetamine 30 mg/day titrated to 70 mg as needed 2. Atomoxetine - For ≤70 kg: 40 mg/day titrated to 100 mg as needed - For <70kg: 1.2 mg/kg/day titrated to 1.4 mg/kg/day if needed	Patients 6-17 years of AGE with ADHD and inadequate response to methylphenidate	Mean change in Weiss Functional Impairment Rating Scale-Parent Report (range 0-3) at 9 weeks	1. -0.37 (95% CI -0.44 to -0.30) 2. -0.30 (95% CI -0.36 to -0.23) p-value NR

Abbreviations: AC = active-controlled; DB = double-blind, NR = not reported; PG = parallel group; RCT = randomized clinical trial; SD = standard deviation.

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Appendix 1: Current Preferred Drug List

FormDesc	Brand	Generic	PDL
CAPSULE	STRATTERA	ATOMOXETINE HCL	Y
CAPSULE	VYVANSE	LISDEXAMFETAMINE DIMESYLATE	Y
CPBP 50-50	DEXMETHYLPHENIDATE HCL ER	DEXMETHYLPHENIDATE HCL	Y
CPBP 50-50	FOCALIN XR	DEXMETHYLPHENIDATE HCL	Y
PATCH TD24	DAYTRANA	METHYLPHENIDATE	Y
TABLET	ADDERALL	DEXTROAMPHETAMINE/AMPHETAMINE	Y
TABLET	DEXTROAMPHETAMINE-AMPHETAMINE	DEXTROAMPHETAMINE/AMPHETAMINE	Y
TABLET	FOCALIN	DEXMETHYLPHENIDATE HCL	Y
TABLET	METHYLPHENIDATE HCL	METHYLPHENIDATE HCL	Y
TABLET	RITALIN	METHYLPHENIDATE HCL	Y
TAB ER 12H	CLONIDINE HCL ER	CLONIDINE HCL	Carve-out
TAB ER 12H	KAPVAY	CLONIDINE HCL	Carve-out
TAB ER 24H	GUANFACINE HCL ER	GUANFACINE HCL	Carve-out
TAB ER 24H	INTUNIV	GUANFACINE HCL	Carve-out
CAP ER 24H	ADDERALL XR	DEXTROAMPHETAMINE/AMPHETAMINE	N
CAP ER 24H	DEXTROAMPHETAMINE-AMPHET ER	DEXTROAMPHETAMINE/AMPHETAMINE	N
CAPSULE ER	DEXEDRINE	DEXTROAMPHETAMINE SULFATE	N
CAPSULE ER	DEXTROAMPHETAMINE SULFATE ER	DEXTROAMPHETAMINE SULFATE	N
CPBP 30-70	METHYLPHENIDATE HCL CD	METHYLPHENIDATE HCL	N
CPBP 30-70	METHYLPHENIDATE HCL ER	METHYLPHENIDATE HCL	N
CPBP 50-50	METHYLPHENIDATE ER	METHYLPHENIDATE HCL	N
CPBP 50-50	METHYLPHENIDATE LA	METHYLPHENIDATE HCL	N
CPBP 50-50	RITALIN LA	METHYLPHENIDATE HCL	N
CSBP 40-60	APTENSIO XR	METHYLPHENIDATE HCL	N
SOLUTION	DEXTROAMPHETAMINE SULFATE	DEXTROAMPHETAMINE SULFATE	N
SOLUTION	METHYLIN	METHYLPHENIDATE HCL	N
SOLUTION	METHYLPHENIDATE HCL	METHYLPHENIDATE HCL	N
SOLUTION	PROCENTRA	DEXTROAMPHETAMINE SULFATE	N
SU ER RC24	QUILLIVANT XR	METHYLPHENIDATE HCL	N
SUS BP 24H	DYANAVEL XR	AMPHETAMINE	N
TAB CBP24H	QUILLICHEW ER	METHYLPHENIDATE HCL	N
TAB CHEW	METHYLPHENIDATE HCL	METHYLPHENIDATE HCL	N
TAB CHEW	VYVANSE	LISDEXAMFETAMINE DIMESYLATE	N
TAB ER 24	CONCERTA	METHYLPHENIDATE HCL	N
TAB ER 24	METHYLPHENIDATE ER	METHYLPHENIDATE HCL	N
TAB RAP BP	ADZENYS XR-ODT	AMPHETAMINE	N

TABLET	DEXEDRINE	DEXTROAMPHETAMINE SULFATE	N
TABLET	DEXMETHYLPHENIDATE HCL	DEXMETHYLPHENIDATE HCL	N
TABLET	DEXTROAMPHETAMINE SULFATE	DEXTROAMPHETAMINE SULFATE	N
TABLET	EVEKEO	AMPHETAMINE SULFATE	N
TABLET	METHAMPHETAMINE HCL	METHAMPHETAMINE HCL	N
TABLET	ZENZEDI	DEXTROAMPHETAMINE SULFATE	N
TABLET ER	METADATE ER	METHYLPHENIDATE HCL	N
TABLET ER	METHYLPHENIDATE ER	METHYLPHENIDATE HCL	N

Appendix 2: Abstracts of Comparative Clinical Trials

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

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

Snircova E, Marcincakova-Husarova V, Hrtanek I, Kulhan T, Ondrejka I, Nosalova G. Anxiety reduction on atomoxetine and methylphenidate medication in children with ADHD. *Pediatr Int.* 2016;58(6):476-481.

BACKGROUND: Atomoxetine and methylphenidate are widely used to treat attention-deficit-hyperactivity disorder (ADHD) with similar effectiveness after 8 weeks of treatment, when atomoxetine has reached its a full effect. Both drugs have also been shown to have an effect on comorbid anxiety. To the best of our knowledge, no study has compared their effect on the dynamics of anxiety symptom reduction. The aim of this study was to compare the medication effect on core and comorbid anxiety symptom dynamics in children with ADHD.
METHODS: Sixty-nine patients participated in the study: 36 patients were taking atomoxetine and 33 patients, methylphenidate. Therapeutic effect on core symptoms of ADHD was measured on the ADHD-rating scale IV, and symptoms of anxiety were measured using the Conners Parent Rating Scale (CPRS). Symptoms were measured prior to and every 2 weeks during 8 weeks of treatment.
RESULTS: There was a significant decrease in CPRS anxiety subscale score in both medication groups. Anxiety subscale score was significantly lower in the atomoxetine group in the fourth week, and lasted through to 8 weeks of medication.
CONCLUSION: Both atomoxetine and methylphenidate reduced the symptoms of ADHD and anxiety. Atomoxetine was more effective in anxiety symptom reduction from the fourth week of treatment.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) 1946 to June Week 4 2017**, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 2013 to Daily Update**

1	exp Atomoxetine Hydrochloride/	1402
2	exp methylphenidate/ or dexmethylphenidate hydrochloride/	7918
3	Amphetamines/	6843
4	exp Methylphenidate/ or exp Amphetamines/ or exp Dextroamphetamine/ or exp Lisdexamfetamine Dimesylate/	46290
5	exp Clonidine/	13809
6	Guanfacine/	745
7	exp Methamphetamine/	10178
8	1 or 2 or 3 or 4 or 5 or 6 or 7	16210
9	limit 8 to (english language and humans)	28312
10	limit 9 to yr="2016 -Current"	1341
11	limit 10 to (clinical study or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or pragmatic clinical trial or randomized controlled trial or systematic reviews)	352
12	exp Attention Deficit Disorder with Hyperactivity/	31902
13	adhd.mp.	26773
14	exp "Attention Deficit and Disruptive Behavior Disorders"/	36480
15	12 or 13 or 14	42845
16	11 and 15	105

Attention Deficit Hyperactivity Disorder (ADHD) Safety Edit

Goals:

- Cover ADHD medications only for diagnoses funded by the OHP and medications consistent with current best practices.
- Promote care by a psychiatrist for patients requiring therapy outside of best-practice guidelines.
- Promote preferred drugs in class.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred drugs on the enforceable preferred drug list.
- Regimens prescribed outside of standard doses and age range (Tables 1 and 2)
- Non-standard polypharmacy (Table 3)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. FDA-approved and OHP-funded Indications.

	STIMULANTS		NON-STIMULANTS		
Indication	**Methylphenidate and derivatives**	**Amphetamine and derivatives**	**Atomoxetine**	**Clonidine ER**	**Guanfacine ER**
ADHD	Age ≥6 years	Age ≥3 years	Age ≥6 years	Children age 6-17 years only	Children age 6-17 years only
Narcolepsy	Age ≥6 years	Age ≥6 years	Not approved	Not approved	Not approved

Table 2. Standard Age and Maximum Daily Doses.

Drug Type	Generic Name	Minimum Age	Maximum Age	Maximum Daily Dose (adults or children <18 years of age unless otherwise noted)
CNS Stimulant	amphetamine/dextroamphetamine salts IR	3		40 mg
CNS Stimulant	amphetamine/dextroamphetamine salts ER	6		60 mg
CNS Stimulant	dexmethylphenidate IR	6		20 mg
CNS Stimulant	dexmethylphenidate LA	6		40 mg for adults or 30 mg if age <18 years

CNS Stimulant	dextroamphetamine IR	6		40 mg
CNS Stimulant	dextroamphetamine LA	6		60 mg
CNS Stimulant	lisdexamfetamine	6		70 mg
CNS Stimulant	methamphetamine	6	17	not established
CNS Stimulant	methylphenidate IR	4		60 mg
CNS Stimulant	methylphenidate LA	6		72 mg
CNS Stimulant	methylphenidate transdermal	6	17	30 mg
Non-Stimulant	atomoxetine	6		100 mg
Non-Stimulant	clonidine LA	6	17	0.4 mg
Non-Stimulant	guanfacine LA	6	17	4 mg

Abbreviations: IR = immediate-release formulation; LA = long-acting formulation (extended-release, sustained-release, etc.)

Table 3. Standard Combination Therapy for ADHD

Age Group	Standard Combination Therapy
Age <6 years*	Combination therapy not recommended
Age 6-17 years*	1 CNS Stimulant Formulation (LA or IR) + Guanfacine LA 1 CNS Stimulant Formulation (LA or IR) + Clonidine LA
Age ≥18 years**	Combination therapy not recommended

Abbreviations: IR = immediate-release formulation; LA = long-acting formulation (extended-release, sustained-release, etc.)
* As recommended by the American Academy of Pediatrics 2011 Guidelines www.pediatrics.org/cgi/doi/10.1542/peds.2011-2654
**As identified by Drug Class Review: Pharmacologic Treatments for Attention Deficit Hyperactivity Disorder: Drug Effectiveness Review Project, 2011.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the treated diagnosis an OHP-funded condition?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by OHP.
3. Is the requested drug on the PDL?	**Yes:** Go to #5	**No:** Go to #4

Approval Criteria		
4. Will the prescriber consider a change to a preferred agent? Message: • Preferred drugs are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of preferred alternatives	**No:** Go to #5
5. Is the request for an approved FDA indication defined in Table 1?	**Yes:** Go to #6	**No:** Go to #9
6. Are the patient's age and the prescribed dose within the limits defined in Table 2?	**Yes:** Go to #7	**No:** Go to #9
7. Is the prescribed drug the only stimulant or non-stimulant filled in the last 30 days?	**Yes:** Approve for up to 12 months	**No:** Go to #8
8. Is the multi-drug regimen considered a standard combination as defined in Table 3?	**Yes:** Approve for up to 12 months	**No:** Go to #9
9. Was the drug regimen developed by, or in consultation with, a psychiatrist, developmental pediatrician, psychiatric nurse practitioner, sleep specialist or neurologist?	**Yes:** Document name and contact information of consulting provider and approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness. Doses exceeding defined limits or non-recommended multi-drug regimens of stimulants and/or non-stimulants are only approved when prescribed by a psychiatrist or in consultation with a mental health specialist. May approve continuation of existing therapy once up to 90 days to allow time to consult with a mental health specialist.

P&T Review: *9/17 (SS); 5/16; 3/16 (AG); 5/14; 9/09; 12/08; 2/06; 11/05; 9/05; 5/05; 2/01; 9/00; 5/00*
Implementation: *10/13/16; 7/1/16; 10/9/14; 1/1/15; 9/27/14; 1/1/10; 7/1/06; 2/23/06; 11/15/05*