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Drug Class Literature Scan: Attention Deficit Hyperactivity Disorder

Date of Review: September 2018

Date of Last Review: September 2017
Literature Search: 06/30/17 – 06/08/18

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

Conclusions:
- This literature scan identified 4 systematic reviews[1-4], 1 guideline[5], 1 new formulation (Adzenys ER™)[6], 1 United States Food and Drug Administration (FDA) safety update (rebound hypertension in guanfacine ER)[7], and 1 retrospective safety study[8]. The identified literature supports current policy for attention deficit hyperactivity disorder (ADHD) drugs.
- An Agency for Healthcare Research and Quality (AHRQ) review on ADHD treatment in children and adolescents found insufficient comparative evidence for all efficacy and safety outcomes except for gastrointestinal side effects (slightly higher with atomoxetine compared with methylphenidate; low strength of evidence).[4]
- A Cochrane systematic review on nonrandomized studies of methylphenidate for ADHD in children and adolescents found an increased risk of serious adverse events compared to no intervention (risk ratio 1.36; 95% confidence interval [CI] 1.17 to 1.57).[1]
- An update to the National Institute for Health and Care Excellence (NICE) guideline on ADHD diagnosis and management recommends methylphenidate as a first-line pharmacologic treatment option for both adults and children.[5] Lisdexamfetamine is also a first-line pharmacologic option for adults and a second-line option for children.[5]
- No significant trends were noted in diagnoses of ADHD, narcolepsy, or substance abuse/dependence for Oregon Health Plan (OHP) Fee-for-Service (FFS) patients prescribed ADHD medications listed in **Appendix 1**.

Recommendations:
- No further review or research needed.
- Update guanfacine extended-release dosing in Table 2 of the prior authorization criteria (**Appendix 6**) to clarify FDA-recommended maximum daily doses for monotherapy versus adjunctive therapy.
- No PDL changes recommended after evaluation of comparative costs in executive session.

Summary of Prior Reviews and Current Policy
Evidence summarized in prior reviews has demonstrated that compared to placebo, stimulants and non-stimulant medications have benefit for patients with ADHD. However, no consistent differences have been demonstrated between different formulations (immediate release [IR] vs. extended release [ER]) in this class of drugs. Additionally, there is insufficient evidence that directly compares general effectiveness outcomes for different drugs for ADHD in children or

adults.[9,10] The most common adverse effects from stimulants are appetite loss, abdominal pain, headaches and sleep disturbance; only low quality evidence suggests any differences in harms between the agents.[9]

In the Oregon Health Plan (OHP) Fee-for-Service (FFS) population, all medications in the ADHD class have age and quantity safety limits which ensure they are being used in the appropriate age range and within safe dosing parameters. If the request is for a non-preferred agent or any agent exceeding the age or quantity limits, a safety edit ensures that medication use is consistent with current best practices and also promotes care by a psychiatrist for patients requiring therapy outside of best-practice guidelines. Preferred medications in this class include atomoxetine, dexmethylphenidate, dextroamphetamine/amphetamine, lisdexamfetamine dimesylate, and methylphenidate. This class of the OHP FFS Preferred Drug List (PDL) contains three mental health carve-out medications: atomoxetine, clonidine, and guanfacine. These three medications are exempt from traditional PDL and prior authorization (PA) requirements. However, clinical PA criteria which address safety concerns or medically inappropriate use may be implemented.

OHP FFS Utilization Summary

In the OHP FFS population during the second quarter of 2018, utilization of preferred, voluntary, and non-preferred agents in this class was 48%, 48%, and 4%, respectively.

At the time of a recent OHP FFS drug use evaluation (DUE) completed in July 2016, it was recommended to continue to monitor use of ADHD medications in the adult populations and to evaluate trends in adults.[11]

An analysis of patients with a paid FFS claim for at least one medication in the ADHD class from 7/1/2017 to 6/30/2018 and their associated medical diagnoses was completed to evaluate for medically appropriate use. Patients included in the analysis had at least 75% OHP eligibility in the year prior to the first ADHD claim and the presence of diagnoses were evaluated in the year prior to the first ADHD claim. Diagnoses of ADHD and narcolepsy were specifically searched due to their FDA-approved indications in the drugs of the ADHD class. Additionally, substance abuse, substance dependence, and poisoning diagnoses were searched due to safety concerns. Results for this query are outlined in **Table 1**.

Table 1. OHP FFS Utilization of ADHD Drugs by Selected Diagnoses

Patient Age	Diagnosis	ICD-10 codes	Number of unique patients with a paid FFS claim for ≥1 medication in the ADHD class	Percent of patients based on total in age group
Patients <18 years			**7,161**	
	ADHD	F90.x	5,589	78.0%
	Narcolepsy	G47.41, G47.411, G47.419, G47.42, G47.421, or G47.429	2	0.0%
	No diagnosis of ADHD or narcolepsy	Absence of F90.x AND absence of G47.41, G47.411, G47.419, G47.42, G47.421, and G47.429	1,571	21.9%
	Substance abuse or dependence (including alcohol, opioid, cocaine, cannabis, other stimulant, other psychoactive substance, or non-psychoactive substances)	F10.1x, F10.2x, F15.1x, F15.2x, F11.1x, F11.2x, F19.1x, F19.2x, F12.1x, F12.2x, F14.1x, F14.2x, or F55.x	185	2.6%

	Poisoning by unspecified psychostimulants, amphetamines, methylphenidate, or other psychostimulants (accidental [unintentional], intentional self-harm, or undetermined)	T43.601x, T43.602x, T43.604x, T43.621x, T43.622x, T43.624x, T43.631x, T43.632x, T43.634x, T43.691x, T43.692x, or T43.694x	13	0.2%
Patients ≥18 years			**3,439**	
	ADHD	F90.x	2,197	63.9%
	Narcolepsy	G47.41, G47.411, G47.419, G47.42, G47.421, or G47.429	15	0.4%
	No diagnosis of ADHD or narcolepsy	Absence of F90.x AND absence of G47.41, G47.411, G47.419, G47.42, G47.421, and G47.429	1,232	35.8%
	Substance abuse or dependence (including alcohol, opioid, cocaine, cannabis, other stimulant, other psychoactive substance, or non-psychoactive substances)	F10.1x, F10.2x, F15.1x, F15.2x, F11.1x, F11.2x, F19.1x, F19.2x, F12.1x, F12.2x, F14.1x, F14.2x, or F55.x	985	28.6%
	Poisoning by unspecified psychostimulants, amphetamines, methylphenidate, or other psychostimulants (accidental [unintentional], intentional self-harm, or undetermined)	T43.601x, T43.602x, T43.604x, T43.621x, T43.622x, T43.624x, T43.631x, T43.632x, T43.634x, T43.691x, T43.692x, or T43.694x	17	0.5%

Compared to the DUE completed in July 2016, this data shows slightly higher proportions of patients in both pediatric (78.0% vs. 63.9%, respectively) and adult (63.9% vs. 55.7%, respectively) groups with a diagnosis of ADHD.[11] There are also slightly lower proportions of patients with a diagnosis of substance abuse or dependence who have a paid claim for a medication in the ADHD class in this data compared to the 2016 DUE in children (2.6% vs. 4.4%, respectively) and adult (28.6% vs. 33.4%, respectively).[11] A small percentage of patients also had a diagnosis of poisoning by stimulants; this data was not evaluated in the 2016 DUE and was instead evaluated by ED visits and hospitalization counts.

As a full analysis similar to the previous DUE was not completed, there may be differences in populations which may impact these results. Claims data may also be limited by incomplete reporting of diagnoses. Furthermore, differences between the ICD-9 codes utilized in the DUE and the ICD-10 codes in this analysis may impact results.

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. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), 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 and recent evidence-based 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:

Agency for Healthcare Research and Quality: ADHD Diagnosis and Treatment in Children and Adolescents

In January 2018, AHRQ published a comparative effectiveness review on ADHD diagnosis and treatment in children and adolescents as a targeted update to a 2011 AHRQ systematic review.[4] Trials published between January 1, 2009 and November 7, 2016 of children 17 years of age and younger with any pharmacologic treatment of ADHD, alone or in combination, were included.[4] The focus of this summary is on evidence from high quality trials or outcomes with high to moderate quality evidence. Trials reporting only placebo comparisons, and comparisons to non-pharmacologic treatments are excluded from this summary.[4]

For comparative pharmacologic efficacy evidence, only one fair quality trial was identified.[4] This trial compared atomoxetine versus osmotic release oral system methylphenidate and found no difference at 6 months in the proportion of patients achieving at least a 40% reduction from baseline in the Conners Comprehensive Behavior Rating Scale-Teacher hyperactive, inattentive, and behavior subscales (insufficient strength of evidence).[4] Other identified trials were of poor quality.[4] For safety outcomes, there was low strength of evidence that the proportion of patients reporting gastrointestinal side effects was slightly higher with atomoxetine compared with methylphenidate (3 observational studies; n=1,966).[4] Other findings related to safety outcomes were all insufficient strength of evidence and are listed below in **Table 2**.

The report concluded that there was limited comparative pharmacologic evidence since the time of the initial report in 2011 and insufficient evidence for all comparative pharmacologic efficacy and safety outcomes except for gastrointestinal effects.[4]

Table 2. AHRQ Comparative Pharmacologic Clinical Safety Outcomes Findings[4]

Outcome	Comparators	Quality of Trial(s)	Result	Strength of Evidence
Gastrointestinal AEs	Atomoxetine vs. methylphenidate	Fair to good	Higher incidence with atomoxetine*: Rate ratio 4.56; 95% CI 2.0 to 10.43	Low
Adverse reactions	Atomoxetine vs. methylphenidate	Fair to good	Higher incidence with atomoxetine*: Relative risk 3.57; 95% CI 1.92 to 6.64	Insufficient
Cardiovascular AEs	Atomoxetine vs. methylphenidate	Fair to good	Higher incidence with atomoxetine*: Rate ratio 3.43; 95% CI 1.21 to 9.76	Insufficient
Neuropsychiatric AEs	Atomoxetine vs. methylphenidate	Fair to good	Higher incidence with atomoxetine*: Rate ratio 2.54; 95% CI 1.34 to 4.74	Insufficient

Abbreviations: AE = adverse event; CI = confidence interval; ER = extended-release; IR = immediate-release

*Absolute rates not reported

Cochrane Collaboration: Adverse Events in Non-Randomized Studies of Methylphenidate

In May 2018, the Cochrane Collaboration published a systematic review of adverse events in non-randomized, observational studies (n=260 studies) of methylphenidate for ADHD in children and adolescents.[1] The primary outcomes were serious adverse events, withdrawal of methylphenidate due to serious adverse events, and withdrawal of methylphenidate due to adverse events of unknown severity.[1] Patients ranged from 3 to 20 years of age and were predominantly

male.[1] Risk of bias ranged from moderate to critical in the studies (primarily due to their non-randomized design) and the GRADE quality rating of the evidence was insufficient for all outcomes.[1] However, this information may still be beneficial to assist providers in evaluating risks versus benefits of therapy. In comparative studies, methylphenidate had a higher incidence of serious adverse events compared to no intervention (risk ratio 1.36; 95% CI 1.17 to 1.57; 2 studies, n=72,005).[1] In non-comparative cohort studies, 1.2% of methylphenidate-treated patients experienced a serious adverse event (95% CI 0.70% to 2.00%; 51 studies, n=162,422).[1] Withdrawal from methylphenidate due to any serious event was also 1.2% (95% CI 0.60% to 2.30%; 7 studies, n=1,173) and withdrawal due to adverse events of unknown severity occurred in 7.30% of patients (95% CI 5.30% to 10.0%; 22 studies; n=3,708).[1] Also in non-comparative cohort studies, 51.2% of patients treated with methylphenidate experienced a non-serious adverse event (95% CI 41.2% to 61.1%; 49 studies; n=13,978), 6.20% of patients discontinued methylphenidate due to non-serious adverse events (95% CI 4.80% to 7.90%; 37 studies; n=7,142), and 16.2% of patients withdrew from the study for unknown reasons (95% CI 13.0% to 19.9%; 57 studies; n=8,340).[1] The specific types of serious adverse events experienced were not described, but frequently reported categories of serious adverse events included central nervous system, cardiovascular, and respiratory system events.[1] The authors concluded that methylphenidate may be associated with a number of serious adverse events and monitoring adverse events is of high importance.[1]

Canadian Agency for Drugs and Technologies in Health: Guanfacine HCl ER for ADHD

In March 2018, CADTH published a rapid response report on guanfacine hydrochloride extended-release for ADHD.[2] Efficacy results focused on low quality indirect network meta-analyses and one poor quality RCT.[2,12] Therefore, efficacy results will not be discussed. Direct comparative safety evidence was limited to guanfacine extended-release (ER) versus placebo which came from four systematic reviews of RCT data.[2] Discontinuations due to treatment-emergent adverse events was significantly greater in the guanfacine ER groups compared to placebo (odds ratio [OR] range: 2.94-4.49; 3 meta-analyses; absolute numbers not reported).[2] Abdominal pain and fatigue were also significantly greater with guanfacine ER compared to placebo (abdominal pain: OR 2.04, 95% CI 1.37 to 3.13; fatigue: OR 2.70, 95% CI 1.89 to 3.85; 3 meta-analyses; absolute numbers not reported).[2]

Canadian Agency for Drugs and Technologies in Health: Clonidine for Psychiatric Conditions and Symptoms

In February 2018, CADTH published a rapid response report on clonidine for the treatment of psychiatric conditions and symptoms.[3] One randomized controlled trial and 3 non-randomized studies (2 retrospective chart reviews; 1 retrospective post-hoc analysis cohort study) provided clinical evidence for the report.[3] Retrospective analyses and poor quality RCT efficacy data will not be discussed due to the low quality of evidence.[3,13] In regards to harms, one retrospective chart review (quality not graded by CADTH; limited by analysis not adjusting for confounders) evaluated potential misuse and abuse of clonidine and found that harms associated with clonidine overdose include impaired consciousness, miosis, hypothermia, bradycardia, hypotension, and severe hypertension.[3] Frequency of clonidine overdose overall was not reported.[3]

After review, 1 systematic review was excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[14]

New Guidelines:

National Institute for Health and Care Excellence

In March 2018, NICE published an update to their 2008 guideline on ADHD diagnosis and management.[5] In this update, new recommendations were made for medication treatment, review of medication, and discontinuation, among other topics.[5] Selected recommendations regarding pharmacologic treatment are reported below. This guidance is limited in that several medications in the ADHD class, including dexmethylphenidate, dextroamphetamine/amphetamine, methamphetamine, and amphetamine were not included in the literature search for the evidence as they are not licensed for the treatment in ADHD in the United Kingdom.[15]

Medication Choice:

Recommendations based on costs in the United Kingdom are excluded from the summary below.

- Children aged 5 years and over and young people:
  - Offer methylphenidate (either short or long acting) as the first-line pharmacological treatment.[5]
  - Consider switching to lisdexamfetamine in patients who have had a 6 week methylphenidate trial and have not derived enough benefit in ADHD symptoms and associated impairment.[5]
  - Offer atomoxetine or guanfacine if patients cannot tolerate methylphenidate or lisdexamfetamine or their symptoms have not responded to separate 6 week trials of lisdexamfetamine and methylphenidate, having considered alternative preparations and adequate doses.[5]
- Adults:
  - Lisdexamfetamine or methylphenidate are recommended as first-line pharmacological treatment options. Trials of each medication are recommended if the patient has not derived enough benefit in ADHD symptoms and associated impairment from one of the medications.[5]
  - Offer atomoxetine if patients cannot tolerate lisdexamfetamine or methylphenidate or their symptoms have not responded to separate 6 week trials of lisdexamfetamine and methylphenidate, having considered alternative preparations and adequate doses.[5]
- Further medication choices:
  - Obtain second opinion or refer to tertiary service if ADHD symptoms are unresponsive to one or more stimulants and one non-stimulant.[5]
  - Do not offer the following medications without advice from tertiary ADHD service:
    - Guanfacine: for adults[5]
    - Clonidine: for children with ADHD and sleep disturbance, rages or tics[5]
    - Atypical antipsychotics in addition to stimulants: for patients with ADHD and coexisting pervasive aggression, rage or irritability[5]
    - Medications not listed in the previously described recommendations[5]
- Patients with coexisting conditions:
  - Offer the same medication choices to patients with ADHD and anxiety disorder, tic disorder or autism spectrum disorder as other patients with ADHD.[5]
  - For patients experiencing an acute psychotic or manic episode: stop any ADHD medication and consider restarting or starting new ADHD medication after the episode has resolved.[5]

Considerations When Prescribing ADHD Medication:

- Modified-release once daily preparation considerations: convenience, improving adherence, reducing stigma (reduced need for doses during school or work), reducing problems of storing and administering controlled drugs at school, the risk of stimulant misuse and diversion with immediate-release preparations, and pharmacokinetic profiles.[5]
- Immediate-release and modified-release preparations combinations may be used to optimize effect.[5]
- Be cautious about prescribing stimulants for ADHD if there is a risk of diversion for cognitive enhancement or appetite suppression.[5]
- Do not offer immediate or modified-release stimulants that can be easily injected or insufflated if there is a risk of stimulant misuse.[5]

Monitoring and Discontinuation

- Monitor effectiveness of medication and adverse effects.[5]

- Depending on age and other patient characteristics, monitoring may include: height and weight, cardiovascular, tics, sexual dysfunction, seizures, sleep, worsening behavior, and stimulant diversion.[5]
- ADHD medication should be reviewed at least once a year to discuss with the patient whether the medication should be discontinued.[5]
- Consider trial periods of stopping medication or reducing the dose when assessment of the overall balance of benefits and harms suggests this may be appropriate.[5]

New Formulations:

In September 2017, a new formulation of amphetamine extended-release oral suspension (Adzenys ER™) was approved by the FDA for the treatment of ADHD in patients 6 years and older.[6] This formulation was approved based on studies of mixed salts of a single-entity amphetamine product extended-release capsules (MAS ER) for the treatment of ADHD.[6] No clinical trials specific to this new formulation were completed and MAS ER study details on results were not reported in depth in the FDA package labeling. The first MAS ER study included pediatric patients age 6-12 years with ADHD.[6] Patients received 10, 20, or 30 mg of the MAS ER capsules or placebo once daily in the morning for three weeks.[6] The primary outcome was the Attention Deficit Hyperactivity Disorder-Rating Scale IV (ADHD-RS-IV; 18 item symptom scale) total score, and patients who received MAS ER showed statistically significant improvements in this outcome for both morning and afternoon assessments compared to patients taking placebo.[6] In a classroom analogue study, pediatric patients showed statistically significant improvements on the teacher-rated Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) scale Attention and Deportment variables as well as the Permanent Product Measure of Performance (PERMP) scale compared to those treated with placebo.[6] In a third pediatric study, patients age 13-17 years showed statistically significantly greater improvements with MAS ER 10 mg, 20 mg, 30 mg, and 40 mg, compared to those treated with placebo.[6] However, there was inadequate evidence that doses greater than 20 mg/day provided additional benefit.[6] One study was also completed in adults receiving 20, 40, or 60 mg of MAS ER or placebo once daily for four weeks.[6] Improvements in the ADHD-RS were seen for all MAS ER doses but doses over 20 mg/day did not provide additional benefit.[6]

New FDA Safety Alerts:

Table 3. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Guanfacine extended-release[7]	Intuniv®	11/2017	Warnings and Precautions	In post marketing experience, abrupt discontinuation has resulted in clinically significant and persistent rebound hypertension above baseline levels and increases in heart rate.[7] To minimize risk of rebound hypertension upon discontinuation, total daily dose should be tapered in increments of no more than 1 mg every 3-7 days.[7] Blood pressure and heart rate should be monitored when reducing the dose or discontinuing.[7]

References:

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2. Guanfacine hy drochloride extended-release f or attention def icit hy peractivity disorder: a rev iew of clinical ef f ectiveness, cost-effectiveness, and guidelines. CADTH Rapid Response Report. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2018 Mar 7. https://www.cadth.ca/guanfacine-hydrochloride-extended-release-attention-deficit-hyperactivity-disorder-review-clinical-0. Accessed June 19, 2018.
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14. Sturman N, Deckx L, van Driel ML. Methylphenidate for children and adolescents with autism spectrum disorder. *Cochrane Database Syst Rev.* 2017;11:CD011144.
15. Attention deficit hyperactivity disorder (ADHD): Treatment. National Health Service Choices. Last reviewed 30 May 2018. https://www.nhs.uk/conditions/attention-deficit-hyperactivity-disorder-adhd/treatment/#medication. Accessed 17 July 2018.

Appendix 1: Current Preferred Drug List

Route	Formulation	Brand	Generic	PDL	Carveout
ORAL	TABLET	METHYLPHENIDATE HCL	methylphenidate HCl	Y	
ORAL	TABLET	RITALIN	methylphenidate HCl	Y	
ORAL	CPBP 30-70	METADATE CD	methylphenidate HCl	Y	
ORAL	CPBP 30-70	METHYLPHENIDATE HCL CD	methylphenidate HCl	Y	
ORAL	CPBP 30-70	METHYLPHENIDATE HCL ER	methylphenidate HCl	Y	
ORAL	TABLET	DEXMETHYLPHENIDATE HCL	dexmethylphenidate HCl	Y	
ORAL	TABLET	FOCALIN	dexmethylphenidate HCl	Y	
ORAL	CPBP 50-50	DEXMETHYLPHENIDATE HCL ER	dexmethylphenidate HCl	Y	
ORAL	CPBP 50-50	FOCALIN XR	dexmethylphenidate HCl	Y	
TRANSDERM	PATCH TD24	DAYTRANA	methylphenidate	Y	
ORAL	CAPSULE	ATOMOXETINE HCL	atomoxetine HCl	Y	Y
ORAL	CAPSULE	STRATTERA	atomoxetine HCl	Y	Y
ORAL	TABLET	ADDERALL	dextroamphetamine/amphetamine	Y	
ORAL	TABLET	DEXTROAMPHETAMINE-AMPHETAMINE	dextroamphetamine/amphetamine	Y	
ORAL	CAP ER 24H	ADDERALL XR	dextroamphetamine/amphetamine	Y	
ORAL	CAP ER 24H	DEXTROAMPHETAMINE-AMPHET ER	dextroamphetamine/amphetamine	Y	
ORAL	CAPSULE	VYVANSE	lisdexamfetamine dimesylate	Y	
ORAL	TAB ER 12H	CLONIDINE HCL ER	clonidine HCl	V	Y
ORAL	TAB ER 12H	KAPVAY	clonidine HCl	V	Y
ORAL	TAB ER 24H	GUANFACINE HCL ER	guanfacine HCl	V	Y
ORAL	TAB ER 24H	INTUNIV	guanfacine HCl	V	Y
ORAL	TABLET ER	METADATE ER	methylphenidate HCl	N	
ORAL	TABLET ER	METHYLPHENIDATE ER	methylphenidate HCl	N	
ORAL	TAB ER 24	CONCERTA	methylphenidate HCl	N	
ORAL	TAB ER 24	METHYLPHENIDATE ER	methylphenidate HCl	N	
ORAL	CPBP 50-50	METHYLPHENIDATE ER	methylphenidate HCl	N	
ORAL	CPBP 50-50	METHYLPHENIDATE LA	methylphenidate HCl	N	
ORAL	CPBP 50-50	RITALIN LA	methylphenidate HCl	N	
ORAL	TAB CHEW	METHYLIN	methylphenidate HCl	N	
ORAL	TAB CHEW	METHYLPHENIDATE HCL	methylphenidate HCl	N	
ORAL	SOLUTION	METHYLIN	methylphenidate HCl	N	
ORAL	SOLUTION	METHYLPHENIDATE HCL	methylphenidate HCl	N	
ORAL	CSBP 40-60	APTENSIO XR	methylphenidate HCl	N	
ORAL	SU ER RC24	QUILLIVANT XR	methylphenidate HCl	N	
ORAL	TAB CBP24H	QUILLICHEW ER	methylphenidate HCl	N	
ORAL	TAB RAP BP	COTEMPLA XR-ODT	methylphenidate	N	
ORAL	TABLET	EVEKEO	amphetamine sulfate	N	

ORAL	CAPSULE ER	DEXEDRINE	dextroamphetamine sulfate	N
ORAL	CAPSULE ER	DEXTROAMPHETAMINE SULFATE ER	dextroamphetamine sulfate	N
ORAL	TABLET	DEXEDRINE	dextroamphetamine sulfate	N
ORAL	TABLET	DEXTROAMPHETAMINE SULFATE	dextroamphetamine sulfate	N
ORAL	TABLET	ZENZEDI	dextroamphetamine sulfate	N
ORAL	SOLUTION	DEXTROAMPHETAMINE SULFATE	dextroamphetamine sulfate	N
ORAL	SOLUTION	PROCENTRA	dextroamphetamine sulfate	N
ORAL	TABLET	DESOXYN	methamphetamine HCl	N
ORAL	TABLET	METHAMPHETAMINE HCL	methamphetamine HCl	N
ORAL	CPTP 24HR	MYDAYIS	dextroamphetamine/amphetamine	N
ORAL	TAB CHEW	VYVANSE	lisdexamfetamine dimesylate	N
ORAL	SUS BP 24H	DYANAVEL XR	amphetamine	N
ORAL	TAB RAP BP	ADZENYS XR-ODT	amphetamine	N
ORAL	SUS BP 24H	ADZENYS ER	amphetamine	N

Appendix 2: New Comparative Clinical Trials

A total of 89 citations were manually reviewed from the initial literature search. After further review, 88 citations were excluded because of wrong study design (e.g., observational studies except for in the case of clinically important safety outcomes), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 1 trial is summarized in the table below. The full abstract is included in **Appendix 3**.

Table 1. Description of Comparative Clinical Trials or Observational Trials for Clinically Important Safety Outcomes.

Study	Comparison	Population	Primary Outcome	Results
Quinn PD, et al[8] Retrospective claims study N=2,993,887 Claims from 2005-2014	1. Stimulant* or atomoxetine 2. No medication	Patients 13 years of age and older with ADHD	Risk of substance-related events (i.e., emergency department visits related to substance use disorders) during months in which patients received prescribed stimulant medication or atomoxetine relative to risk during months in which they did not	*Males* 1. 3.1% 2. 4.0% OR 0.76; 95% CI 0.75 to 0.78 *Females* 1. 2.6% 2. 2.8% OR 0.94; 95% CI 0.91 to 0.97

Abbreviations: CI = confidence interval; OR = odds ratio

*Stimulant = amphetamine salt combination, dexmethylphenidate hydrochloride, dextroamphetamine sulfate, lisdexamfetamine dimesylate, methamphetamine hydrochloride, methylphenidate, or methylphenidate hydrochloride

Appendix 3: Abstracts of Comparative Clinical Trials

1. Quinn PD, Chang Z, Hur K, et al. ADHD Medication and Substance-Related Problems. Am J Psychiatry. 2017;174(9):877-885.

OBJECTIVE: Substance use disorders are major contributors to excess mortality among individuals with attention deficit hyperactivity disorder (ADHD), yet associations between pharmacological ADHD treatment and substance-related problems remain unclear. This study investigated concurrent and long-term associations between ADHD medication treatment and substance-related events. METHOD: The authors analyzed 2005–2014 commercial health care claims from 2,993,887 (47.2% female) adolescent and adult ADHD patients. Within-individual analyses compared the risk of substance-related events (i.e., emergency department visits related to substance use disorders) during months in which patients received prescribed stimulant medication or atomoxetine relative to the risk during months in which they did not. RESULTS: In adjusted within-individual comparisons, relative to periods in which patients did not receive ADHD medication, male patients had 35% lower odds of concurrent substance-related events when receiving medication (odds ratio=0.65, 95% CI=0.64–0.67), and female patients had 31% lower odds of concurrent substance-related events (odds ratio=0.69, 95% CI=0.67–0.71). Moreover, male patients had 19% lower odds of substance-related events 2 years after medication periods (odds ratio=0.81, 95% CI=0.78–0.85), and female patientshad14%lowerodds of substance-related events2years after medication periods (odds ratio=0.86, 95% CI= 0.82–0.91). Sensitivity analyses supported most findings but were less consistent for long-term associations among women. CONCLUSIONS: These results provide evidence that receiving ADHD medication is unlikely to be associated with greater risk of substance-related problems in adolescence or adulthood. Rather, medication was associated with lower concurrent risk of substance-related events and, at least among men, lower long-term risk of future substance-related events.

Appendix 4: Medline Search Strategy on 06/08/2018

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

1 exp Atomoxetine Hydrochloride/	*1069*
2 exp Dexmethylphenidate Hydrochloride/	*54*
3 exp DEXTROAMPHETAMINE/	*6918*
4 exp AMPHETAMINES/	*36198*
5 exp Lisdexamfetamine Dimesylate/	*221*
6 exp METHYLPHENIDATE/	*6698*
7 exp CLONIDINE/	*13009*
8 exp GUANFACINE/	*649*
9 Methamphetamine/	*8493*
10 exp Attention Deficit Disorder with Hyperactivity/	*25633*
11 adhd.mp	*21653*
12 exp "Attention Deficit and Disruptive Behavior Disorders"/	*29288*
13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	*35206*
14 10 or 11 or 12	*34988*
15 13 and 14	*4585*
16 limit 15 to (English language and humans)	*3931*
17 limit 16 to (clinical trial, all 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)	*1745*
18 limit 17 to yr="2017-Current"	*78*

Appendix 5: Key Inclusion Criteria

Population	Adult and pediatric patients with attention deficit hyperactivity disorder (ADHD) or attention deficit disorder (ADD)
Intervention	Drugs in ADHD class (**Appendix 1**)
Comparator	Drugs in ADHD class (**Appendix 1**) or placebo if clinically important safety outcomes
Outcomes	Efficacy: symptom improvement, functional capacity, quality of life, time to onset of effectiveness, duration of effectiveness Safety: withdrawals due to adverse events, serious and long term (>12 months) adverse events, misuse/diversion
Timing	Literature from 06/30/17 (end of literature search from last review in 7/2018) – 06/08/18
Setting	Outpatient

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

See **Table 2 for off-label methylphenidate IR dosing for age ≥ 4 years

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 for adjunctive therapy in ages 6-17 years and for monotherapy in ages 6-12 years 7 mg for monotherapy in ages 13-17 years

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 drug being used to treat 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 diagnosis 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: *9/18 (JP); 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: *TBD; 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*