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Drug Class Literature Scan: Attention Deficit Hyperactivity Disorder (ADHD)

Date of Review: August 2020

Date of Last Review: May 2019
Literature Search: April 2018 – April 2020

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

Conclusions:

- This literature scan identified 2 systematic reviews [1-2], 3 new clinical practice guidelines [3-5], 3 new drug formulations [6-8], 1 expanded drug indication [9], 1 United States Food and Drug Administration (FDA) guidance document [10], and 1 FDA drug safety labeling update. [11] The identified literature supports current policy for attention deficit hyperactivity disorder (ADHD) drugs.
- A Cochrane systematic review of randomized controlled trials of amphetamine for ADHD in adults found an increased proportion of patients who withdrew from treatment due to any adverse events (e.g., insomnia, hypertension, or palpitations/tachycardia) compared to placebo (Relative Risk (RR) 2.69, 95% CI 1.64 to 4.42).[1]
- A Cochrane systematic review of randomized controlled trials (RCTs) of pharmacological treatments for ADHD in children with comorbid tic disorders found low quality evidence that ADHD drugs have not consistently been shown to reduce tic severity.[2] No difference was found in the effectiveness of ADHD agents for the reduction of ADHD symptom severity due to high heterogeneity among the studies.[2]
- The National Institute for Health and Care Excellence (NICE) amended their guideline on ADHD diagnosis and management to specify that an electrocardiogram is not needed before starting stimulants, atomoxetine or guanfacine if the patient's cardiovascular history and examination are normal and the person is not on any medication that increases cardiovascular risk.[3]
- The American Academy of Pediatrics updated guidelines for the management of ADHD in children ages 4 to 17 years made the following key recommendations: primary care clinicians should screen for comorbid conditions such as anxiety, depression, and substance use (Grade B, strong recommendation); management of ADHD should employ a chronic care model and medical home (Grade B, strong recommendation); evidence-based parent training in behavior management (PTBM) and/or behavioral classroom interventions should be used as first-line treatment for preschool-aged children (Grade A, strong recommendation for PTBM); use of FDA-approved medications combined with PTBM and behavioral interventions for elementary, middle school-aged children, and adolescents (Grade A, strong recommendation for medications; Grade A, strong recommendation for training and behavioral treatments for ADHD with family and school).[4]
- The Society for Developmental and Behavioral Pediatrics (SDBP) published guidelines to provide direction for assessment and treatment of children and adolescents with complex ADHD. Recommendations were similar in the American Academy of Pediatrics guideline, which emphasizes a comprehensive ADHD evaluation and management by a qualified specialist, use of evidence-based behavioral and educational interventions, and lifelong care and monitoring for ADHD and comorbidities (all quality of evidence grade B, strong recommendation), as well as use of appropriate evidence-based pharmacological treatments and strategies (evidence quality grade C to B, recommendation). [5]

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- 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.
- There is insufficient evidence that one ADHD drug is more effective or associated with fewer adverse events in specific subgroups of patients based on demographics (age, racial or ethnic groups and gender), other medications, or co-morbidities.

Recommendations:
- No changes to the current PDL.
- Review drug costs in the executive session.

Summary of Prior Reviews and Current Policy
Prior reviews have found evidence to support that stimulant and non-stimulant pharmacologic agents are beneficial in ADHD treatment compared to placebo. Comparisons between different formulations (immediate release [IR] vs. extended release [ER]) within this class have not demonstrated consistent differences. In addition, there is insufficient evidence to directly compare differences in efficacy or safety outcomes for different ADHD drugs in children or adults. The most frequent adverse effects from stimulants are appetite loss, abdominal pain, headaches and sleep disturbance; only low-quality evidence suggests any differences in harms between various ADHD agents.[12]

To ensure safe and appropriate use within the Oregon Health Plan (OHP) Fee-for-Service (FFS) population, all medications within the ADHD class have limits based on patient age and quantity prescribed. Safety edits are in place to ensure that medication use reflects best practices. Any request for a non-preferred agent or for an agent that exceeds the age or quantity limit requires consultation with a specialist prescriber such as a psychiatrist or other mental health specialist. Preferred agents within the ADHD class include atomoxetine, dexmethylphenidate, dextroamphetamine/amphetamine, lisdexamfetamine dimesylate, and methylphenidate. Three of the medications within the ADHD class are part of the mental health carve-out and are exempt from traditional prior authorization (PA) requirements: atomoxetine, clonidine, and guanfacine. All medications, regardless of PDL status, may be subject to clinical PA criteria to address any safety concerns or to ensure medically appropriate use.

OHP FFS Utilization Summary
In the OHP FFS population during the third quarter of 2019, utilization of the preferred, voluntary, and non-preferred agents in this class were about 50%, 46%, and 4%, respectively.

In a previous review, medically appropriate use was analyzed in both children and adult patients with a paid FFS claim for at least one agent from the ADHD class from 7/1/2017 to 6/30/2018.[13] Patients were included if they had a minimum of 75% OHP eligibility in the year prior to the first ADHD claim and a diagnosis of interest present within the year prior to the ADHD claim.[14] The diagnoses of ADHD and narcolepsy were searched based on their FDA-approved indications while a diagnosis for substance abuse, substance dependence, or drug poisoning was also searched due to the high potential for abuse and dependence of ADHD drugs.[13] A recent search with the same inclusion criteria was conducted in OHP patients from 4/1/2019 to 3/31/2020. Results from the 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 (%)		% Change
			2017-2018[14]	2019-2020	
Patients <18 years			**7,161**	**8,032**	
	ADHD	F90.x	5,589 (78.0%)	6,298 (78.4%)	↑ 0.4%
	Narcolepsy	G47.41, G47.411, G47.419, G47.42, G47.421, or G47.429	2 (0.0%)	3 (0.0%)	No change
	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%)	1,731 (21.6%)	↓ 0.3%
	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%)	230 (2.9%)	↑ 0.3%
	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%)	19 (0.2%)	No change
Patients ≥18 years			**3,439**	**3,764**	
	ADHD	F90.x	2,197 (63.9%)	2,358 (62.6%)	↓ 1.3%
	Narcolepsy	G47.41, G47.411, G47.419, G47.42, G47.421, or G47.429	15 (0.4%)	27 (0.7%)	↑ 0.3%
	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%)	1,388 (36.9%)	↑ 1.1%
	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%)	1,039 (27.6%)	↓ 1.0%
	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%)	20 (0.5%)	No change

The 2019-2020 analysis showed a 12% increase in the number of unique patients with at least 1 paid FFS claim for an ADHD medication. However, the proportion of patients with a diagnosis of ADHD has remained consistent in both the adult and pediatric populations compared to the 2017-2018 claims data (about 78% and 64%, respectively). There were no meaningful changes in the number of patients diagnosed with narcolepsy, substance abuse or dependence, and poisonings. Since both reviews were based on claims data, there were limitations in the ability to directly connect the medical diagnosis with the ADHD medication pharmacy claims.

Methods:

A Medline literature search for new systematic reviews and 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, 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.

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:

In August 2018, the Cochrane Collaboration published a systematic review of the efficacy and safety of amphetamine in adults with ADHD.[1] The review included 19 studies (N=2521) of dexamphetamine, lisdexamphetamine, or mixed amphetamine salts at various strengths and doses compared to placebo or active intervention.[1] All studies had a length of treatment from 1 to 20 weeks (mean 5.3 weeks) with short-term follow-up and were considered to have unclear or high risk of bias.[1] Amphetamine efficacy was compared to other pharmacologic agents in 3 studies (n=137) and included either guanfacine, modafinil, or paroxetine.[1] Primary outcomes were measured with the standardized ADHD Rating Scale-IV by either clinicians or patients. The ADHD Rating Scale-IV is an 18-item questionnaire that uses a 4-point Likert scale to record the frequency and severity of ADHD symptoms based on DSM-IV criteria (0 to 54 points total; higher score=worse symptoms).[1] There were no head-to-head comparative studies identified to suggest differences between individual amphetamines or other active treatments in the ability to reduce ADHD symptom severity as measured by the ADHD Rating Scale-IV.[1] However, the authors found low to very low-quality evidence from 17 studies (n=2409) that amphetamines were associated with an increased proportion of patients who withdrew from treatment due to any adverse events such as insomnia, hypertension, or palpitations/tachycardia compared to placebo (RR 2.69, 95% CI 1.64 to 4.42).[1]

In June 2018, the Cochrane Collaboration published a systematic review of pharmacological treatments for ADHD in children with comorbid tic disorders.[2] Eight studies were included in the review (N=510) and included children 18 years of age or younger; 87% were male.[2] The trial sizes ranged from 22 to 148 patients and all had the diagnoses of ADHD and chronic tic disorder (Tourette syndrome, chronic motor tic disorder, or chronic vocal tic disorder).[2] Several ADHD medications were assessed which included atomoxetine, clonidine, desipramine, dextroamphetamine, guanfacine, and methylphenidate.[2] Most studies were deemed low risk of bias for performance bias (blinding), and low to unclear risk of bias for selection bias (allocation concealment), but two of the studies had high risk of bias in selective reporting.[2] Three of the 8 trials in the review assessed multiple agents while the rest assessed single agents compared to placebo.[2] Study duration was 3 to 22 weeks. All trials were graded as low quality. No meta-analysis was performed due to extensive heterogeneity among the studies.[2]

All studies except for one study of reported improvement in symptoms of ADHD compared to placebo. However, the symptom rating scales employed to measure ADHD severity varied and most trials failed to specify a primary outcome.[2] Therefore, the individual or comparative effectiveness of these agents for improvement of ADHD symptoms could not be adequately assessed. For measurement of tic severity, all included studies used the YGTSS, which is a summation of assessment scores of motor tic, vocal tic, and overall impairment (scale range 0 to 100; higher score=worse symptoms).[2] Three of the studies examined methylphenidate, 2 examined clonidine, and 2 examined desipramine.[2] One of the studies combined the use of 2 agents (methylphenidate plus clonidine).[2] For patients with ADHD and comorbid tic disorder, one study of clonidine monotherapy demonstrated a statistically significant decrease in the YGTSS versus placebo (10.9 points, 98.3% CI 2.1 to 19.7; P = 0.003) while a second study could not find a difference.[2] Of the 3 methylphenidate monotherapy studies, only 1 demonstrated YGTSS reduction at 16 weeks (11.0 points, 98.3%CI 2.1 to 19.8; P = 0.003), one study found no difference on the YGTSS, and the third study reported a worsening of tic severity in week 2 of one of the cohorts (P<0.01).[2] The combination of methylphenidate plus clonidine demonstrated YGTSS

improvements compared to placebo (11.0 points, 98.3% CI 2.1 to 19.8; P = 0.003). [2] Only one of the 2 studies with desipramine reported YGTSS score reductions (20 points; P < 0.001; low-quality evidence). [2]

After review, 29 systematic reviews were 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).

New Guidelines:

National Institute for Health and Care Excellence

In September 2019, NICE published an amendment to their 2018 guideline on ADHD diagnosis and management.[3] The initial recommendation to conduct a baseline assessment of physical health prior to starting medication for ADHD was amended to specify that an electrocardiogram is not needed before starting stimulants, atomoxetine or guanfacine if the patient's cardiovascular history and examination are normal and the person is not on any medication that increases cardiovascular risk.[3] No other updates to the guidelines were identified since the 2018 release.

In 2019, the American Academy of Pediatrics updated their 2011 guideline for the management of ADHD in children ages 4 to 17 years.[4] The update included a review of relevant clinical literature from 2011 through 2016. [4] The new Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) had been released within that timeframe and was reflected in the new guideline. [4] Recommendations were made for initial ADHD evaluation, diagnoses, referral guidance, screening for comorbid conditions, care coordination, and age-appropriate treatments. [4] Key recommendations from the guideline is summarized in Table 2.

Table 2. Summary of Key Action Statements for Diagnosing, Evaluating, and Treating ADHD in Children and Adolescents[4] (modified).

Recommendation	Evidence Quality, Strength of Recommendation
Clinician should start ADHD evaluations for children from ages 4 through 17 with academic or behavioral problems and symptoms of inattention, hyperactivity, or impulsivity	Grade B, strong recommendation
Diagnosis of ADHD should meet DSM-5 criteria, including documentation of symptoms and impairment in at least 1 major setting (social, academic, or occupational) by gathering information from parents, guardians, teachers, other school personnel, and mental health clinicians involved in the child's care	Grade B, strong recommendation
The PCC should screen for comorbid conditions, including emotional or behavior types (eg, anxiety, depression, oppositional defiant disorder, conduct disorders, substance use), developmental conditions (eg, learning and language disorders, autism spectrum disorders), and physical conditions (eg, tics, sleep apnea) PCC should initiate treatment of comorbid conditions if experienced; if not, refer patient to an appropriate specialist	Grade B, strong recommendation Grade C, recommendation
Patient management should involve a long-term chronic care/medical home model	Grade B, strong recommendation
Treatment for children ages 4 to 5 years: • Use evidence-based PTBM and/or behavioral classroom interventions as first-line therapy, if available	Grade A, strong recommendation

• Methylphenidate may be considered if PTBM does not show improvement or if a disturbance in functioning is observed but risks of therapy before age 6 should be weighed against harms of treatment delay	Grade B, strong recommendation
Treatment for children ages 6 to 11 years: • Use FDA-approved medications, along with PTBM and/or behavioral classroom intervention	Grade A, strong recommendation
Treatment for children ages 12 to 17 years: • Use FDA-approved medications with the adolescent's assent, along with PTBM and/or behavioral classroom intervention	Grade A, strong recommendation
Clinician should titrate medication doses to achieve maximum benefits with tolerable side effects	Grade B, strong recommendation

Evidence Quality	Evidence Grade	Evidence Interpretation
Level A - well-designed randomized controlled trials or diagnostic studies on relevant population Level B - randomized controlled trials with minor limitations; overwhelmingly consistent evidence from observational studies Level C - observational studies (case-control and cohort design)	Grade A: consistent level A evidence Grade B: consistent level B or extrapolations from level A evidence Grade C: level C evidence or extrapolations from level B or level C evidence	"Strong Recommendation" = benefits of the approach clearly exceed the harms of that approach "Recommendation" = benefits exceed the harms, but the quality of the evidence is not as strong

Abbreviations: PCC = primary care clinician; PTBM = parent training in behavioral management.

A new guideline was released in 2020 by the SDBP to provide direction for assessment and treatment of children and adolescents with complex ADHD.[5] Complex ADHD was defined by age (<4 years or presentation at age >12 years), presence of comorbidities, moderate to severe functional impairment, diagnostic uncertainty, or inadequate response to treatment. [5] The SDBP followed the same methodology as the AAP to develop their practice guidelines in order to keep cohesion and consistency with current standards. [5] The recommendations were condensed into 5 key action statements and were assigned an evidence grade:

- implementation of a comprehensive evaluation by a clinician with specialized training (quality of evidence grade B, strong recommendation) [5]
- use of appropriate, comprehensive assessments with verification of pre-existing comorbidities, functional impairments, and developmental deficiencies (quality of evidence grade B, strong recommendation) [5]
- evidence-based behavioral and educational interventions to build knowledge and skills in complex ADHD management (quality of evidence grade B, strong recommendation) [5]
- use evidence-based pharmacological treatments and strategies for management of complex ADHD and associated comorbidities to improve symptoms, function, encourage self-management, and avoid adverse outcomes (quality of evidence grade C to B, recommendation) [5]
- include lifetime patient management and monitoring especially during key developmental transition periods (quality of evidence grade B, strong recommendation). [5]

New Formulations or Indications:

In August 2018, the FDA approved an extended-release (ER) capsule formulation of methylphenidate (Jornay PM®) to treat ADHD in patients 6 years of age and older. The approval was based on 2 clinical trials of pediatric patients 6 to 12 years of age.[6] A full risk of bias and applicability evaluation was unclear as studies used for FDA-approval were not published. Study 1 was as 7-week, phase 3 randomized withdrawal trial. All patients (n=117) received Jornay PM® at flexible doses between 20 mg and 100 mg once each evening for 6 weeks. The open-label phase was followed by a 1-week, double blind, placebo-controlled phase in which patients were randomized to remain on optimized doses of Jornay PM (n=64) or change to placebo (n=53).[6] After the 1 week double-blinded treatment phase, patient response was assessed over 12 hours with the Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale (SKAMP). SKAMP is a 13-item, 78-point observer-rated scale (0=normal, 78=maximal impairment) used to evaluate ADHD indicators in the classroom environment such as attention, deportment, work quality, and rule compliance.[6] The study used a model-adjusted average of all post-dose SKAMP-combined scores (SKAMP-C) measured during the 12-hour testing period as the primary endpoint.[6] A statistically significant reduction in the SKAMP-C average score was reported for Jornay PM® compared to placebo (least squares mean difference -5.9 [95% CI -9.1 to -2.7]).[6] Mean baseline scores were not available for comparison.

In study 2, Jornay PM® was evaluated in a 3-week, multicentered, randomized, double-blind, placebo-controlled, parallel-group study in 6 to 12-year old pediatric patients.[6] Patients were randomized to receive Jornay PM® (n=81) at variable doses (40 mg, 60 mg, 80 mg) or placebo (n=80) administered once daily in the evening.[6] Dose and administration times were adjusted by subjects based on tolerability and control of ADHD symptoms. The primary efficacy endpoint was measured with the ADHD-RS-IV (54 points total; 0=no ADHD symptoms, 54=severe symptoms).[6] The intention-to-treat population used for the primary endpoint consisted of all randomized patients who received at least 1 dose of the study drug and at least 1 post-baseline evaluation with the ADHD-RS-IV.[6] At 3 weeks, a statistically significant difference was reported on the ADHD-RS-IV symptom score in the Jornay PM® group compared to the placebo group (24.1 vs 31.2 points, respectively; least-squares mean ADHD RS-IV -7.0 [95% CI -11.4 to -2.7]).[6] Mean baseline ADHD RS-IV scores for Jornay PM® and placebo were 43.5 and 43.1, respectively. Jornay PM® was not studied in this trial at the 20 mg or 100 mg doses.[6]

Treatment emergent adverse events were collected from the start of study treatment up to the safety follow-up assessment (35 days).[6] Adverse reactions that occurred in at least 5% of Jornay PM®-treated pediatric patients and occurred at a greater frequency than placebo are listed in Table 3.[6]

Table 3. Adverse Reactions Reported in the Jornay PM® 3-Week ADHD Study (Study 2).[6]

Adverse Reaction	Jornay PM® (N=81)	Placebo (N=80)
Insomnia	33%	9%
Decreased appetite	19%	4%
Headache	10%	5%
Vomiting	9%	0%
Blood pressure diastolic increased	7%	4%
Nausea	6%	0%
Affect lability/mood swings	6%	1%
Psychomotor hyperactivity	5%	1%

In January 2019, the FDA approved Evekeo ODT®, a new formulation of amphetamine sulfate.[7] The safety and effectiveness of Evekeo ODT® in the treatment of ADHD was established based on the studies of the reference product, immediate-release amphetamine sulfate (Evekeo), under the 505(b)(2) regulatory pathway.[7] Evekeo ODT® is a short-acting orally disintegrating tablet indicated for the treatment of ADHD in pediatric patients 6 to 17 years of age.[7]

The FDA also approved Adhansia XR® (methylphenidate ER) capsules in February 2019 for the treatment of ADHD in patients 6 years and older.[8] Adhansia XR® labeling identified 4 studies used for FDA approval, but a full risk of bias and applicability evaluation was unclear as studies used for FDA-approval were not yet published. Adhansia XR® was first evaluated in 2 double-blind, randomized placebo controlled trials of adult patients between the ages of 18 and 72 years who met the DSM-5 criteria.[8] Study 1 (n=375) evaluated methylphenidate ER at 25 mg, 45 mg, 70 mg, and 100 mg once daily compared to placebo.[8] Patients were titrated over 2 weeks and then assigned a maintenance dose over 2 more weeks.[8] The primary efficacy endpoint was change from baseline in the ADHD-RS-5 (visit 2, week 1) to visit 6 in week 5.[8] Adhansia XR® demonstrated statistically significant improvements only at the 45 mg and 100 mg doses compared to placebo (-7.1 [95% CI -10.8 to -3.4] and -7.9 [95% CI, -11.6 to -4.1], respectively).[8]

In a second Adhansia XR® study, adult patients aged 18 to 58 with ADHD were titrated over 2 to 7 weeks to methylphenidate ER 25 mg, 35 mg, 45 mg, 55 mg, 70 mg, 85 mg, or 100 mg given orally once daily in an open-label phase.[8] In the second crossover phase, patients were randomized to either 1 week of study drug followed by placebo or 1 week of placebo followed by study drug.[8] The primary efficacy endpoint studied was the change in the Permanent Product Measure of Performance Total (PERMP-T) averaged across all timepoints in a simulated adult workplace environment (AWE). The PERMP-T score measures the number of correctly answered math problems attempted and answered correctly.[8] Higher PERMP scores indicate less severe ADHD symptoms. Efficacy assessments were calculated at pre-dose, and 1, 2, 5, 8, 11, 14, and 16 hours post-dose during the AWE sessions.[8] The full analysis population (N=46) included all randomized subjects who received any amount of study medication for at least one post dose time point. Adhansia XR demonstrated a statistically significant improvement in PERMP-T score compared to placebo at most post-dose time points (mean difference 26.8 [95% CI, 15.2 to 38.4]) but not at 14 hours post-dose.[8]

Adhansia XR® was also studied in 2 additional RCTs of pediatric patients with ADHD (n=354).[8] Study 3 was a 4-week, randomized, double-blind, placebo-controlled study in pediatric patients aged 12-17 years who met DSM-5 ADHD criteria.[8] Patients were randomized to once-daily methylphenidate ER 25 mg, 45 mg, 70 mg, 85 mg, or placebo groups.[8] As in study 1, the primary efficacy endpoint was change from baseline in the ADHD-RS-5 total score from baseline (week 1) to Visit 6. At visit 6, Week 5, Adhansia XR demonstrated statistically significant changes from baseline on the ADHD-RS-5 total score only for the 45 mg and 70 mg doses compared to placebo (-5.4 [95% CI, -9.2 to -1.6] and -5.2 [95% CI, -9 to -1.4] respectively), but not at the other doses.[8]

In study 4, Adhansia XR® was evaluated in 6 to 12-year old patients with ADHD (n=147).[8] Patients were randomized to either methylphenidate ER 25 mg, 35 mg, 45 mg, 55 mg, 70 mg, 85 mg, or placebo.[8] The trial consisted of a 6-week, open-label, flexible dosing period with a 1-week randomized treatment phase with an optimized patient dose.[8] Most patients were optimized to a dose between 45 and 55 mg.[8] After the randomized phase, patients were evaluated at pre-dose and 1, 2, 4, 6, 8, 10, 12, and 13 hours post-dose on simulated classroom day using the SKAMP-C.[8] The primary efficacy endpoint measured was change in the mean SKAMP-CS, averaged across the 8 timepoints on the analog classroom day.[8] Through all post-dose laboratory classroom hours, Adhansia XR was reported to show a statistically significant improvement in SKAMP-C score compared to placebo (Placebo-subtracted difference, -8.6 [95% CI, -10.6 to -6.6]).[8]

The most common adverse reactions, with incidence greater than or equal to 5% and at rate at least twice the frequency of placebo, reported in Adhansia XR-treated pediatric patients (6 to 12 years of age) were decreased appetite (35%), insomnia (10%), upper abdominal pain (15%), affect lability (13%), nausea or vomiting (13%), decreased weight (12%), insomnia (10%), irritability (10%), and headache (10%).[8] In patients 12 to 17 year of age, the most common adverse reactions for Adhansia XR®-treated patients compared to placebo were decreased appetite (20% vs. 0%, respectively), decreased weight (7% vs. 0%,

respectively), and insomnia (6% vs. 1%, respectively).[8] Similar adverse effects and rates were observed in Adhansia XR®-treated adults compared to placebo, but with additional reports of dry mouth (9% vs 4%, respectively).[8] Adhansia XR® has an FDA boxed warning for risk of abuse and dependence.[8]

In February 2019, a formulation of amphetamine 2.5 mg/ml oral suspension (Dyanavel XR®) received FDA approval for an expanded indication in patients 6 years of age and older.[9] Previously, the FDA labeling authorized use of Dyanavel XR® for the treatment of ADHD in children ages 6 to 17 years old.[9] The FDA, however, deferred the submission of a pediatric study for ages 4 to 5 years until additional safety or effectiveness data have been collected.[9]

New FDA News:

In May 2019, the FDA released a draft guidance document to provide a general framework of recommendations to sponsors for the streamlined development of stimulant drugs for treatment of ADHD in pediatric and adult patients.[10] The guidance did not address development programs for nonstimulant drugs.[10] The guidance specifically provided advice for drug manufacturers to identify mechanisms to help reduce patient exposure to potential harms in methylphenidate and amphetamine 505(b)(2) drug development programs through extrapolation of data from safety and efficacy studies.[10] The recommendations also include criteria to determine when extrapolation of pharmacokinetic data is appropriate and when clinical trials would be necessary, especially in pediatric populations.[10] Guidance was given regarding safety monitoring parameters to track adverse reactions such as increased blood pressure and heart rate, appetite suppression, delayed growth, and insomnia.[10] The draft guidance document was distributed for comment purposes only.[10]

New FDA Safety Alerts:

Table 4. Description of New FDA Safety Alerts[11]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Methylphenidate hydrochloride	Aptensio XR®	6/14/2019	Use in Specific Populations	Due to high rates of adverse reactions, most notably weight loss, the benefits of using APTENSIO XR do not outweigh the risks in pediatric patients 4 to <6 years of age.

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11. Food and Drug Administration. Drug Safety-related Labeling Changes (SrLC): Aptensio XR®
https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=686 Accessed April 5, 2020.
12. OSU Drug Use Research & Management Program. Drug Class Update: Attention Deficit Hyperactivity Disorder. September 2017.
http://www.orpdl.org/durm/meetings/meetingdocs/2017_09_28/archives/2017_09_28_ADHD_ClassUpdate.pdf. Accessed April 10, 2020.
13. OSU Drug Use Research & Management Program. Drug Literature Scan: Attention Deficit Hyperactivity Disorder. September 2018.
http://www.orpdl.org/durm/meetings/meetingdocs/2018_09_27/archives/2018_09_27_ADHD_LitScan.pdf. Accessed April 10, 2020.

Appendix 1: Current Preferred Drug List

Generic	Brand	FormDesc	PDL
atomoxetine HCl	ATOMOXETINE HCL	CAPSULE	Y
atomoxetine HCl	STRATTERA	CAPSULE	Y
dexmethylphenidate HCl	DEXMETHYLPHENIDATE HCL ER	CPBP 50-50	Y
dexmethylphenidate HCl	FOCALIN XR	CPBP 50-50	Y
dexmethylphenidate HCl	DEXMETHYLPHENIDATE HCL	TABLET	Y
dexmethylphenidate HCl	FOCALIN	TABLET	Y
dextroamphetamine/amphetamine	ADDERALL XR	CAP ER 24H	Y
dextroamphetamine/amphetamine	DEXTROAMPHETAMINE-AMPHET ER	CAP ER 24H	Y
dextroamphetamine/amphetamine	ADDERALL	TABLET	Y
dextroamphetamine/amphetamine	DEXTROAMPHETAMINE-AMPHETAMINE	TABLET	Y
lisdexamfetamine dimesylate	VYVANSE	CAPSULE	Y
methylphenidate	DAYTRANA	PATCH TD24	Y
methylphenidate HCl	METADATE CD	CPBP 30-70	Y
methylphenidate HCl	METHYLPHENIDATE HCL CD	CPBP 30-70	Y
methylphenidate HCl	METHYLPHENIDATE HCL ER (CD)	CPBP 30-70	Y
methylphenidate HCl	METHYLPHENIDATE HCL	TABLET	Y
methylphenidate HCl	RITALIN	TABLET	Y
clonidine HCl	CLONIDINE HCL ER	TAB ER 12H	V
clonidine HCl	KAPVAY	TAB ER 12H	V
guanfacine HCl	GUANFACINE HCL ER	TAB ER 24H	V
guanfacine HCl	INTUNIV	TAB ER 24H	V

amphetamine	ADZENYS ER	SUS BP 24H	N
amphetamine	AMPHETAMINE	SUS BP 24H	N
amphetamine	DYANAVEL XR	SUS BP 24H	N
amphetamine	ADZENYS XR-ODT	TAB RAP BP	N
amphetamine sulfate	EVEKEO ODT	TAB RAPDIS	N
amphetamine sulfate	AMPHETAMINE SULFATE	TABLET	N
amphetamine sulfate	EVEKEO	TABLET	N
dextroamphetamine sulfate	DEXEDRINE	CAPSULE ER	N
dextroamphetamine sulfate	DEXTROAMPHETAMINE SULFATE ER	CAPSULE ER	N
dextroamphetamine sulfate	DEXTROAMPHETAMINE SULFATE	SOLUTION	N
dextroamphetamine sulfate	PROCENTRA	SOLUTION	N
dextroamphetamine sulfate	DEXEDRINE	TABLET	N
dextroamphetamine sulfate	DEXTROAMPHETAMINE SULFATE	TABLET	N
dextroamphetamine sulfate	ZENZEDI	TABLET	N
dextroamphetamine/amphetamine	MYDAYIS	CPTP 24HR	N
lisdexamfetamine dimesylate	VYVANSE	TAB CHEW	N
methamphetamine HCl	DESOXYN	TABLET	N
methamphetamine HCl	METHAMPHETAMINE HCL	TABLET	N
methylphenidate	COTEMPLA XR-ODT	TAB RAP BP	N
methylphenidate HCl	ADHANSIA XR	CPBP 20-80	N
methylphenidate HCl	METHYLPHENIDATE ER (LA)	CPBP 50-50	N
methylphenidate HCl	METHYLPHENIDATE LA	CPBP 50-50	N
methylphenidate HCl	RITALIN LA	CPBP 50-50	N
methylphenidate HCl	JORNAY PM	CPDR ER SP	N
methylphenidate HCl	APTENSIO XR	CSBP 40-60	N
methylphenidate HCl	METHYLIN	SOLUTION	N
methylphenidate HCl	METHYLPHENIDATE HCL	SOLUTION	N
methylphenidate HCl	QUILLIVANT XR	SU ER RC24	N
methylphenidate HCl	QUILLICHEW ER	TAB CBP24H	N
methylphenidate HCl	METHYLPHENIDATE HCL	TAB CHEW	N
methylphenidate HCl	CONCERTA	TAB ER 24	N
methylphenidate HCl	METHYLPHENIDATE ER	TAB ER 24	N
methylphenidate HCl	RELEXXII	TAB ER 24	N
methylphenidate HCl	METHYLPHENIDATE ER	TABLET ER	N
methylphenidate HCl	METHYLPHENIDATE HCL	TABLET ER	N

Appendix 2: New Comparative Clinical Trials

A total of 110 citations were manually reviewed from the initial literature search. After further review, all were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical).

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to April 06, 2020
1 atomoxetine.mp. or Atomoxetine Hydrochloride/ 1769
2 dexmethylphenidate.mp. or Dexmethylphenidate Hydrochloride/ 89
3 dextroamphetamine.mp. or Dextroamphetamine/ 7133
4 amphetamines.mp. or Amphetamines/ 9374
5 Lisdexamfetamine Dimesylate/ or lisdexamphetamine.mp. /272
6 methylphenidate.mp. or Methylphenidate/ 9138
7 clonidine.mp. or Clonidine/ 18205
8 guanfacine.mp. or Guanfacine/ 1053
9 methamphetamine.mp. or Methamphetamine/ 13302
10 Attention Deficit Disorder with Hyperactivity/ 28208
11 adhd.mp. /24847
12 "Attention Deficit and Disruptive Behavior Disorders"/ 2822
13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 /55408
14 10 or 11 or 12 /36855
15 13 and 14 /6213
16 limit 15 to english language /5830
17 limit 16 to humans /4813
18 limit 17 to (yr="2018 -Current" and 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 randomized controlled trial or "systematic review") /110

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 4/1/18 to 4/1/20
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
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

Approval Criteria		
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: *6/20; 5/19; 9/18 (JP); 5/16; 3/16; 5/14; 9/09; 12/08; 2/06; 11/05; 9/05; 5/05; 2/01; 9/00; 5/00*
Implementation: *11/1/2018; 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*