Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Literature Scan: ADHD Drugs

Date of Review: December 2024

Date of Last Review: June 2022
Literature Search: 07/05/22 – 10/17/2024

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

Plain Language Summary:

- We looked at recent evidence for medicines that treat Attention Deficit Hyperactivity Disorder (ADHD).
- ADHD is a condition that is often identified in children and can continue into adulthood. Symptoms of ADHD include trouble focusing (inattention); inability to sit still for long periods (hyperactivity); or doing things without stopping to think (impulsivity). These symptoms can affect daily life, social relationships, school participation, or work performance.
- ADHD can be treated with medicines called stimulants such as methylphenidate, lisdexamfetamine, or dextroamphetamine or non-stimulant medicines such as atomoxetine, viloxazine, clonidine, or guanfacine.
- Professional organizations usually recommend stimulants such as methylphenidate or dextroamphetamine for most people with ADHD. In people who do not respond to stimulant therapy or if they have bothersome side effects from stimulant medicines, a non-stimulant medicine is usually recommended. Non-stimulant drugs take longer to start working than stimulants, but can also help improve focus, attention, and impulsivity in people with ADHD.
- Non-stimulant medicines (e.g., atomoxetine, viloxazine, clonidine, guanfacine) have different side effects than stimulants. Stimulants may cause unwanted headaches, stomachaches and problems sleeping. Sometimes causes serious unwanted effects like heart problems, hallucinations, or facial tics can develop with stimulants. Side effects from non-stimulant medicines include decreased heart rate and blood pressure, headache, and sleepiness.
- Evidence shows that compared with a sugar pill (placebo), methylphenidate may reduce symptoms of ADHD in children. There is less evidence to show that methylphenidate improves symptoms of ADHD in adults.
- Guanfacine improves symptoms of ADHD in children and adolescents better than a sugar pill, but it may also cause more side effects such as stomach pain and feeling tired.
- To ensure safe and appropriate use within the Oregon Health Plan Fee-for-Service (FFS) population, all medications within the ADHD class have limits based on patient age and quantity prescribed. Any request for an agent that exceeds the age or quantity limit requires consultation with a mental health provider before OHP will pay for the medicine. We do not recommend any changes to this policy.

Conclusions:

- A 2023 Cochrane review assessed the safety and efficacy of methylphenidate for children and adolescents with ADHD.[1] Low- to very low-quality evidence suggests that methylphenidate compared to placebo or no-intervention may improve teacher-rated ADHD symptoms and general behavior in children and adolescents with ADHD.[1] Compared with placebo, methylphenidate may have no effect on serious adverse events and quality of life, but may be associated

Author: Deanna Moretz, PharmD, BCPS

with an increased risk of non-serious adverse events, such as sleep problems and decreased appetite.[1] However, the certainty of the evidence for all outcomes is very low, and therefore, the true magnitude of effects remain unclear.[1]

- A 2024 systematic review developed in consultation with the Agency for Healthcare Research and Quality (AHRQ), the Patient-Centered Outcomes Research Institute, and the American Academy of Pediatrics (AAP) evaluated evidence for the safety and efficacy of Food and Drug Administration (FDA)-approved ADHD treatments in children and adolescents aged 18 years and younger.[2] High-quality evidence shows both stimulants and non-stimulants improve ADHD symptom severity in children and adolescents, compared with passive control (standardized mean difference [SMD] -0.61; 95% confidence interval [CI] -0.69 to -0.52; 49 studies, n = 7685).[2] There was no medication that significantly improved functional impairment or academic performance, though the latter was rarely assessed as a treatment outcome.[2] Pharmacologic treatment was associated with more adverse events compared with control (relative risk [RR] 1.29; 95% CI 1.23 to 1.35; 41 studies, n = 6926; high-quality evidence).[2] Stimulants and non-stimulants produced significantly more appetite suppression than control, with similar effect sizes for methylphenidate, amphetamine, and norepinephrine inhibitors (atomoxetine and viloxazine).[2] Non-stimulant alpha-agonists (specifically, guanfacine) did not suppress appetite.[2]
- A 2020 systematic review evaluated the comparative benefits and harms of pharmacologic treatments for adults with ADHD.[3] The interventions included methylphenidate, atomoxetine, mixed amphetamine salts, bupropion, dexamphetamine, lisdexamfetamine, and guanfacine.[3] Most of the RCTs were placebo-controlled studies.[3] As a class, ADHD pharmacotherapy improved patient and clinician-reported clinical response, quality of life, and executive function compared with placebo; however, these findings were not conserved when the analyses were restricted to studies at low risk of bias, and the certainty of the findings is very low.[3] There were few differences among individual medications, although atomoxetine was associated with improved patient-reported clinical response and quality of life compared with placebo.[3] There was no significant difference in the risk of serious adverse events or treatment discontinuation between ADHD pharmacotherapies and placebo; however, the proportion of participants who withdrew due to adverse events was significantly higher among participants who received any ADHD pharmacotherapy.[3] The certainty of the evidence was very low for all outcomes, and there was limited reporting of long-term adverse events.[3]
- A 2021 Cochrane Review evaluated evidence on the efficacy and harms of immediate-release (IR) methylphenidate in the treatment of adults with ADHD.[4] Very low- and low-quality evidence shows that IR methylphenidate compared with placebo can reduce symptoms of ADHD in adults.[4] Compared with placebo, adults treated with IR methylphenidate are at increased risk of gastrointestinal and metabolic-related harms.[4]
- A 2022 Cochrane review assessed the efficacy and harms of extended-release (ER) formulations of methylphenidate in adults diagnosed with ADHD.[5] Low-certainty evidence showed that ER methylphenidate compared to placebo improved ADHD symptoms in adults (with small-to-moderate effect sizes) measured on rating scales reported by participants, investigators, and peers such as family members.[5] Methylphenidate had no effect on number of days missed at work or serious adverse events. The effect on quality of life was small, and methylphenidate increased the risk of non-serious adverse events.[5] The evidence to support methylphenidate as a pharmacological treatment for ADHD in adults is low-quality, and treatment beyond 52 weeks is not supported by RCTs.[5] There is inadequate direct comparative evidence to guide clinical practice about ER methylphenidate compared to other ADHD medications.[5]
- In 2022 Canadian Agency for Drugs and Technologies in Health (CADTH) reviewed evidence for the use of guanfacine in autism spectrum disorder, ADHD, and/or oppositional defiance disorder.[6] Moderate-quality evidence from 4 systematic reviews and 2 RCTs suggests that guanfacine is more clinically effective than placebo for improving symptoms of ADHD, however it may be associated with increased adverse events such as abdominal pain and fatigue.[6] There is low-quality evidence from 2 systematic reviews that guanfacine may be equally effective in improving ADHD symptoms as other or non-stimulants, with the potential for more greater side effects, but the evidence is highly uncertain.[6] The 2018 National Institute for Health and Care Excellence (NICE guideline)[7] has a strong recommendation to offer guanfacine for use in children and adolescents when stimulants have failed, or they are not tolerable.[6]
- There was insufficient evidence to directly compare differences in efficacy or safety outcomes for different ADHD drugs in children or adults, or in specific subgroups of patients based on demographics (age, racial or ethnic groups and gender).

- In May 2024, the FDA approved a new ER suspension formulation of clonidine (ONYDA XR) to treat ADHD as monotherapy or as adjunctive therapy to stimulant medications in pediatric patients 6 years of age and older.[8] The safety and efficacy of ONYDA XR are based on 3 placebo-controlled studies of ER clonidine tablets.[8]
- The FDA issued a Drug Safety Communication in May 2023 regarding safety issues identified with stimulants. To address continuing concerns of misuse, abuse, addiction, and overdose of prescription stimulants, FDA is requiring updates to the Boxed Warning and other information to ensure the prescribing information is made consistent across the entire class of these medications.[9]

Recommendations:

- Based on review of recent evidence, no changes to the Preferred Drug List (PDL) are recommended at this time.
- Maintain the ER formulation of clonidine (ONYDA XR) as voluntary on the PDL.
- Review medication costs in executive session.
- After executive session dextroamphetamine ER capsules, amphetamine tablets, and methylphenidate tablets were made preferred on the PDL.

Summary of Prior Reviews and Current Policy

- This topic was last reviewed by the Pharmacy and Therapeutics (P & T) Committee at the June 2022 meeting. The December 2021 drug class report on ADHD by the Drug Effectiveness Review Project (DERP) at the Center for Evidence Based Policy at the Oregon Health & Science University (OHSU) was used to inform recommendations for the review. No changes were recommended to the Oregon Health Plan (OHP) PDL based on clinical evidence. After review of costs in executive session, ER methylphenidate tablet-24 was designated as preferred on the PDL.
- Prior reviews have found evidence to support both stimulant and non-stimulant pharmacologic agents for ADHD treatment compared to placebo. Comparisons between different formulations (IR vs. various ER, or long-acting [LA] versions]) within this class have not demonstrated consistent differences. There has been insufficient evidence to directly compare differences in efficacy or safety outcomes for different ADHD drugs in children or adults, or in specific subgroups of patients based on demographics (age, racial or ethnic groups and gender), when taken with other medications, or when co-morbidities are present. The most frequent adverse effects from stimulants are appetite suppression, abdominal pain, headaches and sleep disturbance; only low-quality evidence has been identified to suggest any differences in harms between various ADHD agents.
- To ensure safe and appropriate use within the 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 (see **Appendix 1**). Four of the medications within the ADHD class (atomoxetine, clonidine ER, guanfacine ER, and viloxazine), are part of the mental health carve-out and are exempt from traditional prior authorization requirements.
- In the OHP FFS population during the third quarter of 2024 (July 1 to September 30), 89% of claims in this class were for voluntary medications (guanfacine, atomoxetine, clonidine, and viloxazine). Preferred medications (dextroamphetamine, methylphenidate, and lisdexamfetamine) comprised 8% of claims. The remaining claims were for a mix of preferred and nonpreferred agents.

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 literature scan 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), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Oregon Mental Health Clinical Advisory Group (MHCAG), the Scottish Intercollegiate Guidelines Network (SIGN), and the Canada's Drug Agency (CDA-AMA) 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.

ADHD Diagnosis and Assessments

According to the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria, ADHD diagnosis is confirmed based on presence of at least 6 symptoms for greater than 6 months 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).[10] For adults, the Center for Disease Control (CDC) recommends the following criteria are met in adults for diagnosis of ADHD: 1) More than one symptom of ADHD has been present prior to 12 years of age; 2) several symptoms are present in 2 or more settings (i.e. home, school or work; with friends or relatives; in other activities); 3) evidence that the symptoms interfere with, or reduce the quality of work functioning, and 4) the symptoms are not explained by another mental disorder and do not happen only during the course of another psychotic disorder.[11]

A variety of behavior assessment scales completed by clinicians, parents, teachers, or patients with ADHD can be used to evaluate symptom and functional improvement. Assessment scales commonly used in clinical trials include the ADHD Rating Scale (ADHD-RS) and Conners Parent Rating Scale.[12,13] The ADHD-RS is based on DSM criteria for ADHD diagnosis which assesses symptoms of inattentiveness, hyperactivity, and impulsivity.[17] This 18-item scale has a range of 0 to 72 with higher scores indicating more severe symptoms.[13] There has been some research to suggest that a 30% mean total score change difference between treatment groups (5.2 to 7.7 points) on the ADHD-RS represents a clinically meaningful change.[12] Although the Clinical Global Impression (CGI) scales are not specific to ADHD, they have been paired with the ADHD-RS to assess ADHD symptom changes.[12] The CGI Severity (CGI-S) scale is based on a scale of 1 (no symptoms) to 7 (very severe symptoms).[12] A 1-point difference on CGI-S has been reported to correlate with 8 to 10 points on ADHD-RS.[12] The CGI Improvement (CGI-I) scores follow changes from baseline where 1 to 3 means improvement, 4 means no change, and 5 to 7 means worsening symptoms.[12] It has been reported that a "much improved" (2-level improvement) on CGI-I correlates with 50 to 60% improvement on ADHD-RS.[12] The Conners' Parent Rating Scale evaluates a variety of ADHD symptoms, each assessed on a 0 to 3-point scale corresponding to symptoms which are not present (0), just a little present (1), pretty much present (2), and very much present (3).[12] Minimal Clinically Important Differences (MCIDs) for ADHD outcomes related to the Conners' scales are not presently well-defined.[14] **Table 1** summarizes the assessments described in the systematic reviews presented below.

Table 1. ADHD Assessments Used In Clinical Trials

Outcome	Assessor	Age Range	Description	Scale
Revised Conners' Parent Rating Scale (CPRS-R)[15] (Modified version of original CPRS, a 93-item assessment)	Parents	Children and Adolescents	Parental reports of childhood behavior problems including sleep, problems with eating, temper, keeping friends, and in school.	48 items on a 4-point scale of symptoms 0 = not present 1 = just a little present 2 = pretty much present 3 = very much present Range 0 to 144 points

				Higher score indicates more symptoms
Conners' Teacher Rating Scale (CTRS)[16]	Teacher	Children and Adolescents	Assess children's classroom behavior before and after medication	39 items on a 4-point scale of behavior 1 = not at all 2 = just a little 3 = quite 5a bit 4 = very much Range 0 to 156 points Higher score indicates more symptoms
ADHD Rating Scale (ADHD-RS)[13]	Clinician	Children and Adults	Frequency and severity of ADHD symptoms	18 items on a 4-point scale of symptoms 0 = never or rarely 1 = sometimes 2 = often 3 =very often Range 0 to 72 points Higher score indicates more symptoms A 30% mean total score change difference between treatment groups (5.2 to 7.7 points) on the ADHD-RS represents a clinically meaningful change.[12]
Clinical Global Impression (CGI)-Severity scale[16]	Clinician	Children and Adults	Symptom severity	1 = not ill 2 – borderline ill 3 = mildly ill 4 = moderately ill 5 = markedly ill 6 = severely ill 7 = extremely ill A 1-point difference on CGI-S has been reported to correlate with 8 to 10 points on the ADHD-Rating Scale.[16]
Clinical Global Impression (CGI)-Improvement scale[16]	Clinician	Children and Adults	Assess how much patient's illness has improved or worsened relative to baseline state	1 = very much improved 2 = much improved 3 = minimally improved 4 = no change 5= minimally worse 6 = much worse 7= very much worse Much improved (2-level improvement) on CGI-I correlates with 50 to 60% improvement on ADHD-Rating Scale.[16]
Conners' Adult ADHD Rating Scale-Observer-Short Version (CAARS-O-SV)[17]	Clinician	Adults	• Inattention/memory problems • Impulsivity/emotional lability • Hyperactivity/restlessness • Problems with self-concept	20 items on a 4-point scale Score range: 0 to 78 Higher scores indicate an increase in symptoms or illness severity
Conners' Adult ADHD Rating Scale (CAARS)[17]	Clinician	Adults	• Inattention/memory problems • Impulsivity/emotional lability	66 items rated on a 4-point scale (0-3) 0 = not at all true to 3 = very much true

			• Hyperactivity/restlessness • Problems with self-concept	Score range: 0 to 198 Higher scores indicate an increase in symptoms or illness severity
Adult Quality of Life Score[18]	Patient	Adults	• Life Productivity • Psychological Health • Relationships • Life Outlook	29 item questionnaire rated on a 5-point Likert scale ranging from 1 (not at all/never) to 5 (extremely/very often). Scores range from 29 to 145 with higher scores indicating greater quality of life
Adult ADHD Self Report Scale (ASRS)[19]	Patient	Adults	• Inattention • Hyperactivity • Impulsivity	18 items on a 5-point scale 0 = never/seldom to 4 = very often Score range: 0 to 72

New Systematic Reviews:

Methylphenidate For Children and Adolescents With ADHD

A 2023 Cochrane review assessed the safety and efficacy of methylphenidate for children and adolescents with ADHD.[1] Literature was searched through March 2022 for RCTs that compared methylphenidate to either placebo or no intervention in children and adolescents aged 18 years and younger.[1] Two hundred twelve RCTs (n = 16,302) met inclusion criteria.[1] Only 165 of the 212 trials included usable data on one or more outcomes from 14,271 participants.[1] The 2 primary outcomes were improvement in ADHD symptoms and incidence of serious adverse events. ADHD symptoms (attention, hyperactivity and impulsivity), were measured over the short term (within 6 months) and over the long term (longer than 6 months) by psychometric instruments or by observations of behavior.[1] Raters could be teachers, the children, independent assessors, or parents. The results of teacher-rated outcomes were selected as the primary assessment for change in ADHD symptoms.[1] Serious adverse events were defined as any event that led to death, hospitalization, or disability.[1] All other adverse events were considered non-serious.[1] Secondary outcomes included general behavior, quality of life, and adverse events such as sleep problems, growth retardation, decreased appetite, and gastrointestinal effects.[1] Most trials were carried out in high-income countries, and 86 of the 212 included trials (41%) were funded or partly funded by the pharmaceutical industry.[1] Of the 212 trials, 191 had high risk of bias and 21 had low risk of bias.[1] If unblinding of methylphenidate due to typical adverse events is considered, then all 212 trials were at high risk of bias.[1]

The mean age of participants was 9.8 years ranging from 3 to 18 years (2 trials enrolled patients aged 3 to 21 years).[1] The male-female ratio was 3:1 (with the percentage of girls ranging from 0% to 41% [mean across studies 23.8%]).[1] Methylphenidate treatment duration ranged from 1 to 425 days, with a mean duration of 28.8 days.[1] Only 4 trials were long-term trials (conducted longer than 6 months).[1] Sixty-one trials used ER methylphenidate tablets, while 101 trials used IR methylphenidate.[1] Five trials used transdermal methylphenidate patches.[1] The type of methylphenidate used in 32 trials was unclear.[1] Forty-eight trials used placebo as control, and 8 trials used no intervention as control.[1] Eight trials used clonidine, omega fatty acids, atomoxetine, guanfacine or lisdexamfetamine as a co-intervention in both the intervention and control groups.[1] In 3 trials parent training was used as cognitive-behavioral therapy, and 6 trials used other behavioral therapies as co-interventions for the intervention and control groups.[1] One trial used neurofeedback as co-intervention in both the intervention and control group.[1]

Conners' questionnaires were most frequently used to measure ADHD symptoms.[1] A meta-analysis showed a difference in effects between methylphenidate and placebo on teacher-rated ADHD symptoms (SMD −0.74, 95% CI −0.88 to −0.61; I^2 = 38%; 21 trials; 1728 participants; very low-certainty evidence).[1] The SMD of -0.74 for ADHD symptoms corresponds to a mean difference (MD) of −10.58% (95% CI −12.58 to −8.72) on the ADHD-RS (range 0 to 72 points).[1] The MCID on the ADHD-RS is a change ranging between 5.2 and 7.7 points.[1] Methylphenidate may improve teacher-rated general behavior versus placebo (SMD −0.62, 95% CI

−0.91 to −0.33; I^2 = 68%; 7 trials 792 participants; very low-certainty evidence), but may not affect quality of life (SMD 0.40, 95% CI −0.03 to 0.83; I^2 = 81%; 4 trials, 608 participants; very low-certainty evidence).[1]

There was no difference in serious adverse effects between methylphenidate and the control group (RR 0.80, 95% CI 0.39 to 1.67; I^2 = 0%; 26 trials, 3673 participants; very low-certainty evidence).[1] Participants receiving methylphenidate were more likely to experience non-serious adverse events overall (RR 1.23, 95% CI 1.11 to 1.37; I^2 = 72%; 35 trials, 5342 participants; very low-certainty evidence).[1]

Treatments for ADHD in Children and Adolescents

A 2024 systematic review developed in consultation with AHRQ, AAP, and the Patient-Centered Outcomes Research Institute evaluated evidence for effective treatment of ADHD in children and adolescents aged 18 years and younger.[2] The interventions included any FDA-approved ADHD treatment alone or in combination taken over 4 weeks or longer.[2] Interventions included stimulants (methylphenidate and amphetamine), and non-stimulants (norepinephrine reuptake inhibitors [NRIs] and alpha agonists). Different methylphenidate formulations, including immediate, extended, and multilayer release formulations, methylphenidate osmotic-release oral system, and methylphenidate transdermal patch were evaluated in the included studies. Amphetamine formulations included amphetamine, dextroamphetamine mixed salts, and lisdexamfetamine. The NRI studies evaluated atomoxetine or extended-release viloxazine. The alpha agonist studies evaluated extended-release clonidine or extended-release guanfacine. The comparators included no treatment, placebo, or other pharmacologic agents. Other treatment components included delivery of youth-directed psychotherapies, parent support, neurofeedback, and dietary supplements.[2] Literature was searched from 1980 to June 2023 and 312 studies met inclusion criteria.[2] Only a very small number of studies (33 of 312) reported on outcomes at or beyond 12 months of follow-up.[2] One hundred six studies evaluated pharmacologic interventions.[2] For the purposes of this literature scan, only the data supporting pharmacotherapeutic interventions will be summarized.

Across all 106 studies, only 4 studies included young children 3 to 5 years old.[2] Studies varied in whether they required participants to be drug naïve at study initiation, while others allowed concomitant medication during the study.[2] Most studies reported on the comparison to a control group not receiving the evaluated pharmacological treatment (passive control).[2] Half of the studies reported on the effects of an alternative intervention, for example a different dose of the same medication, or a different medication.[2]

As a class, high-quality evidence showed that stimulants (methylphenidate, amphetamines) significantly improved ADHD symptom severity (SMD, −0.88; 95% CI, −1.13 to −0.63; studies = 12; n = 1620) compared to passive control.[2] Changes in functional impairment were not observed (SMD, 1.00; 95% CI, −0.25 to 2.26; studies = 4; n = 540) with stimulants compared to passive control.[2] Methylphenidate formulations improved ADHD symptoms (SMD, −0.68; 95% CI, −0.91 to −0.46; studies = 7; n = 863; high-quality evidence) compared to control.[2] Only 1 study assessed academic performance, reporting large improvements compared with a passive control group (SMD, −1.37; 95% CI, −1.72 to −1.03; n = 156; low-quality evidence).[2] High-quality evidence showed methylphenidate suppressed appetite (RR, 2.80; 95% CI, 1.47 to 5.32; studies = 8; n = 1110), and more patients reported adverse events (RR, 1.32; 95% CI, 1.25 to 1.40; studies = 6; n = 945), compared to passive control.[2] Compared to control, amphetamine formulations significantly improved ADHD symptoms (SMD, −1.16; 95% CI, −1.64 to −0.67; studies = 5; n = 757; high-quality evidence).[2] High-quality evidence showed amphetamines significantly suppressed appetite (RR, 7.08; 95% CI, 2.72 to 18.42; studies = 8; n = 1229), and more patients reported adverse events (RR, 1.41; 95% CI, 1.25 to 1.58; studies = 8; n = 1151), compared to passive control.[2]

As a class, non-stimulants significantly improved ADHD symptoms (SMD, −0.52; 95% CI, −0.59 to −0.46; studies = 37; n = 6065; high-quality evidence) and disruptive behaviors (SMD, 0.66; 95% CI, 0.22 to 1.10; studies = 4; n = 523), but not functional impairment (SMD, 0.20; 95% CI, −0.05 to 0.44; studies = 6; n = 1163; low-quality evidence).[2] Compared to passive control, norepinephrine reuptake inhibitors improved ADHD symptoms (SMD, −0.55; 95% CI, −0.62 to −0.47;

studies=28; n = 4493) but suppressed appetite (RR, 3.23; 95% CI, 2.40 to 4.34; studies = 27; n = 4176), and more patients reported adverse events (RR, 1.31; 95% CI, 1.18 to 1.46; studies = 15; n = 2600).[2] Guanfacine and clonidine improved ADHD symptoms (SMD, −0.52; 95% CI, −0.67 to −0.37; studies = 11; *n* = 1885) without significantly suppressing appetite (RR, 1.49; 95% CI, 0.94 to 2.37; studies = 4 of guanfacine; n = 919), but more patients reported adverse events (RR, 1.21; 95% CI, 1.11 to 1.31; studies = 14, n = 2544).[2]

One study directly compared amphetamine versus methylphenidate finding more improvement in ADHD symptoms (SMD, −0.46; 95% CI, −0.73 to −0.19; n = 222) but not functional impairment (SMD, 0.16; 95% CI, −0.11 to 0.43; n = 211) with lisdexamfetamine compared to osmotic-release oral system methylphenidate.[2] No difference was found in appetite suppression (RR, 1.01; 95% CI, 0.72 to 1.42; studies = 2, n = 414) or adverse events (RR, 1.11; 95% CI, 0.93 to 1.33; study = 1, n = 222).[2]

One study directly compared guanfacine with atomoxetine finding significantly greater improvement in ADHD symptoms with guanfacine (SMD, −0.47; 95% CI, −0.73 to −0.2; n = 226). [2] This study reported less appetite suppression for guanfacine (RR, 0.48; 95% CI, 0.27 to 0.83; n = 226) but no difference in adverse events (RR, 1.14; 9% CI, 0.97 to 1.34; n = 226) compared to atomoxetine.[2]

Studies directly comparing non-stimulants versus stimulants (atomoxetine vs. methylphenidate in all but 1 study) tended to favor stimulants but did not yield significance for changes in ADHD symptom severity (SMD, 0.23; 95% CI, −0.03 to 0.49; studies = 7; n = 1611).[2] Atomoxetine produced slightly greater improvements in disruptive behaviors compared with methylphenidate (SMD, −0.08; 95% CI, −0.14 to −0.03; studies = 4; n = 608).[2] The 2 classes of medications did not significantly differ in appetite suppression (RR, 0.82; 95% CI, 0.53 to 1.26; studies = 8; n = 1463) or incidence of adverse events (RR, 1.11; 95% CI, 0.90 to 1.37; studies = 4; n = 756).[2]

Several studies assessed whether adding a non-stimulant to a stimulant medication improved outcomes compared with stimulant medication alone. All trials evaluated alpha-agonists added to different stimulants. Combination therapy had a small but significant additional improvement in ADHD symptoms compared to monotherapy (SMD, −0.36; 95% CI, −0.52 to −0.19; studies = 5; n = 724; low-quality of evidence).[2]

In summary, the body of evidence shows that FDA-approved pharmacotherapeutic interventions significantly improve ADHD symptom severity in children and adolescents.[2] This includes large but variable effects for amphetamines and moderate-sized effects for methylphenidate, NRIs, and alpha-agonists (high-quality evidence).[2] For disruptive behaviors, non-stimulant medications (high-quality evidence) produced significant improvement with medium effect.[2] No treatment modality significantly improved functional impairment or academic performance, though the latter was rarely assessed as a treatment outcome.[2] Stimulants and non-stimulant NRIs produced significantly more appetite suppression than placebo, with similar effect sizes for methylphenidate, amphetamine, and NRIs.[2] Non-stimulant alpha-agonists (specifically, guanfacine) did not suppress appetite.[2] Rates of other adverse events were similar between NRIs and alpha-agonists.[2]

Pharmacologic Treatment of ADHD in Adults

A 2020 systematic review and network meta-analysis (NMA) evaluated pharmacologic treatments for adults with ADHD.[3] For the purposes of this review only the results from pair wise meta-analyses will be presented, as results from NMAs are based on indirect comparisons.[20] A literature search through December 2018 identified 81 RCTs (n = 12,423) that reported at least one outcome of interest.[3] The primary outcome for this report was patient or clinician-reported clinical response.[3] Secondary outcomes included changes in quality of life and executive function, withdrawals due to adverse events, treatment discontinuation, serious adverse events, and emergency department visits.[3]

Most studies were at high or unclear risk of at least one important source of bias.[3] Only 5 RCTs had an overall low risk of bias.[3] The RCTs enrolled between 16 and 725 participants.[3] The mean age of participants was between 30 and 40 years of age, although 6 RCTs involved participants with a mean age of less than 30 years and 6 RCTs involved participants with a mean age of 41 years and older.[3] The interventions and comparators were varied among the included RCTs, with 98% involving a placebo control.[3] The interventions included methylphenidate (36 RCTs), atomoxetine (20 RCTs), mixed amphetamine salts (9 RCTs), bupropion (6 RCTs), dexamphetamine (6 RCTs), lisdexamfetamine (6 RCTs), and guanfacine (2 RCTs).[3] Funding from a pharmaceutical company was reported by 57 trials (49 studies fully funded by pharmaceutical industry sources and 8 studies with mixed industry and non-industry sources).[3] Treatment periods ranged from one day to 52 weeks, and about 75% of studies involved treatment for less than 12 weeks.[3] Most studies were conducted in the United States (72%).[3]

Clinician-Reported Clinical Response: Among RCTs with a treatment duration of at least 12 weeks, clinical response was assessed by a clinician as a continuous measure in 15 RCTs (n = 3365) and as a dichotomous measure in 8 RCTs (n = 1902).[3] Only half of the trials contributing data to the analysis of clinician-reported clinical response as a dichotomous measure were judged to be at low risk of bias for blinding compared to 40% of studies contributing data to the analysis of continuous data for this outcome.[3] Only one study was at low risk of bias across all risk of bias domains, which reported a significant improvement in clinician-reported clinical response among men (n = 25) who received 16 weeks of methylphenidate treatment but not among those who received placebo (n = 24).[3] The results of pairwise meta-analysis showed that compared with placebo, the number of patients who showed a clinical response was higher among those using any ADHD pharmacotherapy (RR 1.32, 95% CI 1.05 to 1.66, I^2 = 58%).[3] The use of any ADHD pharmacotherapy revealed a moderate improvement in clinical response compared to placebo on the Conners' Adult ADHD Rating Scale-Observer-Short Version scale (MD –3.89, 95% CI –4.49 to –2.76), although the I^2 value associated with this analysis was 78%, which indicates a considerable amount of heterogeneity between studies.[3]

Executive Function: No studies with a treatment duration of 12 weeks or longer assessed executive function.[3] Data from 12 RCTs (n = 3024) that assessed executive function on a continuous scale after treatment for 2 to 10 weeks were analyzed by pair-wise meta-analysis.[3] Compared with placebo, use of any ADHD pharmacotherapy was associated with a moderate improvement in executive function using the Brief Rating Inventory of Executive Function for Adults (MD –5.72, 95% CI –7.15 to –4.29; I^2 = 58%).[3] Negative differences on this scale indicate improvement in clinical response and executive function.[3]

Quality of Life: Quality of life was assessed in 5 RCTs with a treatment duration of 12 weeks or longer.[3] Of these, all involved the use of standard-dose atomoxetine compared with placebo or no treatment (n = 1862).[3] Pair-wise meta-analysis showed that atomoxetine was associated with a small favorable improvement response when compared to placebo using the Adult ADHD Quality of Life Scale which ranges from 29 to 145 points (MD 4.21, 95% CI 2.04 to 6.38).[3,18] Positive differences on this scale indicate improvement in quality of life.[3]

Harms: Pair-wise meta-analyses were performed for serious adverse effects, withdrawals due to adverse effects, and treatment discontinuations.[3] No studies reported on emergency room visits during the study period.[3] In total, 33 studies reported serious adverse effects; of these, 5 involved a treatment duration of at least 12 weeks.[3] A total of 16 RCTs reported the occurrence of serious adverse effects, while an additional 17 RCTs reported that no serious adverse effects had occurred during the study.[3] Compared with placebo, there was no significant difference in the risk of a serious adverse effects with use of an ADHD pharmacotherapy (RR 1.21, 95% CI 0.67 to 2.18; I^2 = 0%).[3] Studies involving treatment for at least 12 weeks had similar results with no difference compared to placebo.[3]

Seventeen RCTs with a treatment duration of at least 12 weeks reported withdrawals due to adverse events (n = 3650).[3] Compared with placebo, there was a significant increase in withdrawals due to adverse events among participants who received an ADHD medication, with moderate heterogeneity between trials (RR 2.30, 95% CI 1.62 to 3.25; I^2 = 37%).[3] Similar results were seen in the 52 RCTs (n = 10,726) evaluating any treatment duration, (RR 2.54, 95% CI 2.14 to 3.03; I^2

= 0%).[3] Sixteen RCTs with a treatment duration of at least 12 weeks reported treatment discontinuations (n = 3568).[3] There was no significant difference in the number of discontinuations between participants who received an ADHD pharmacotherapy and those who received placebo with moderate heterogeneity between trials (RR 1.04, 95% CI 0.91 to 1.20; I^2 = 63%).[3] The effect estimate was similar among 52 RCTs (n = 9959) with any treatment duration (RR 1.10, 95% CI 1.00 to 1.21; I^2 = 46%).[3]

Conclusions: As a class, ADHD pharmacotherapy improved patient and clinician-reported clinical response, quality of life, and executive function compared with placebo (range: 4 to 15 RCTs per outcome); however, these findings were not conserved when the analyses were restricted to studies at low risk of bias, and the certainty of the finding is very low.[3] There were few differences among individual medications, although atomoxetine was associated with improved patient-reported clinical response and quality of life compared with placebo.[3] There was no significant difference in the risk of serious adverse events or treatment discontinuation between ADHD pharmacotherapies and placebo; however, the proportion of participants who withdrew due to adverse events was significantly higher among participants who received any ADHD pharmacotherapy.[3] Few RCTs reported on the occurrence of adverse events over a long treatment duration.[3]

Immediate-Release Methylphenidate for ADHD in Adults

A 2021 Cochrane Review evaluated the efficacy and harms of IR methylphenidate for adults with ADHD.[4] Literature was searched through January 2020 for RCTs that compared IR methylphenidate with placebo or other pharmacologic interventions (i.e. ER methylphenidate).[4] Primary outcomes included changes in the symptoms of ADHD and harms. Secondary outcomes included changes in the clinical impression of severity and improvement, level of functioning, depression, anxiety and quality of life.[4] Outcomes were rated by investigators or participants.[4] Ten RCTs in 497 adults with ADHD met inclusion criteria.[4] Three trials were conducted in Europe and one in Argentina; the remaining trials did not report their location.[4] Six RCTs compared IR methylphenidate with placebo.[4] In the other RCTs, bupropion, lithium, an ER form of methylphenidate, and Pycnogenol® (a medicine derived from the bark of a pine tree) were the comparators.[4] Participants included outpatients, inpatients in addiction treatment, and adults willing to attend an intensive outpatient program for cocaine dependence.[4] The duration of the follow-up ranged from 6 to 18 weeks.[4] Most of the included trials were at unclear risk of selection, performance and detection bias.[4] Most trials had a high risk of attrition and reporting bias for both the efficacy and harms outcomes.[4] For harms, all the included trials had a high risk of reporting bias.[4]

Low-certainty evidence showed that, compared with placebo, IR methylphenidate may reduce symptoms of ADHD when measured with the Adult ADHD Investigator Symptom Report Scale, (scored from 0 to 54), (MD = −20.70; 95% CI −23.97 to −17.43; 1 RCT, 146 participants) but the evidence is uncertain.[4] There is low-certainty evidence that, compared with placebo, IR methylphenidate may slightly impact the clinical impression of an improvement in symptoms of ADHD using the CGI-Improvement scale (scored from 1 [very much improved] to 7 [very much worse], (MD = −0.94, 95% CI −1.37 to −0.51; 1 trial, 49 participants). There is no clear evidence of an effect on anxiety using the Hamilton Anxiety Scale (HAM-A; scored from 0 to 56; MD −0.20, 95% CI −4.84 to 4.44; 1 trial, 19 participants; very low-certainty evidence) or depression using the Hamilton Depression Scale (HAM-D; scored from 0 to 52; MD 2.80, 95% CI −0.09 to 5.69; 1 trial, 19 participants; very low-certainty evidence) in analyses comparing IR methylphenidate with placebo.[4]

IR methylphenidate increased the risk of gastrointestinal complications (RR 1.96, 95% CI 1.13 to 2.95) and loss of appetite (RR 1.77, 95% CI 1.06 to 2.96) in 4 trials reporting harms compared to placebo (n=344).[4] Cardiovascular adverse events were reported inconsistently, preventing a comprehensive analysis.[4] Four trials had notable concerns of vested interests influencing the evidence, and authors from 2 trials did not report information related to the sources of funding and conflicts of interest.[4]

In summary, the evidence identified to show that IR methylphenidate compared with placebo can reduce symptoms of ADHD in adults was low and very low-quality.[4] Adults treated with IR methylphenidate are at increased risk of gastrointestinal and metabolic-related harms compared with placebo.[4]

Extended-Release Methylphenidate for ADHD in Adults

A 2022 Cochrane review assessed the efficacy and harms of ER formulations of methylphenidate in adults diagnosed with ADHD.[5] Literature was searched through February 2021 for RCTs that compared methylphenidate to placebo or other pharmacologic agents.[5] Twenty-four studies (n = 5066) met inclusion criteria; 21 trials were conducted in an outpatient setting and 3 were conducted in prisons.[5] Studies were primarily conducted in North America and Europe.[5] All 24 trials compared ER methylphenidate with placebo, and 2 RCTs also included active comparators, bupropion and atomoxetine respectively.[5] The median participant age was 36 years.[5] Twelve trials (76% of participants) were industry-sponsored, four (14% of participants) were publicly funded with industry involvement, seven (10% of participants) were publicly funded, and one had unclear funding.[5] The median trial duration was 8 weeks.[5]

One RCT had unclear risk of bias and 20 RCTs had high risk of bias, primarily related to blinding of participants and investigators, attrition bias, and selective outcome reporting.[5] The pre-specified primary outcomes were functional outcomes such as academic and job adherence (measured as days of lost work or study activities), self-rated ADHD symptoms measured using the Conners' Adult ADHD Rating Scale, and serious adverse events.[5] Secondary outcomes included quality of life, ADHD symptoms rated by investigators and by peers such as family members, cardiovascular adverse events, severe psychiatric adverse events, and other adverse events.[5]

ER methylphenidate had no effect on the number of days missed at work at 13-week follow-up (MD −0.15 days, CI −2.11 to 1.81; 1 trial, n = 409) or serious adverse events (RR 1.43, CI 95% CI 0.85 to 2.43; 14 trials, n = 4078) when compared to placebo (very low-certainty evidence).[5] Compared to placebo, ER methylphenidate did improve:

- self-rated ADHD symptoms (small-to-moderate effect; SMD −0.37, 95% CI −0.43 to −0.30; 16 trials, n = 3799).[5]
- self-rated quality of life (small effect; SMD −0.15, 95% CI −0.25 to −0.05; 6 trials, n = 1888),
- investigator-rated ADHD symptoms (small-to-moderate effect; SMD −0.42, 95% CI −0.49 to −0.36; 18 trials, n = 4183), and
- ADHD symptoms rated by peers such as family members (small-to-moderate effect; SMD −0.31, 95% CI −0.48 to −0.14; 3 trials, n = 1005).

ER methylphenidate increased the risk of experiencing any adverse event compared to placebo (RR 1.27, 95% CI 1.19 to 1.37; 14 trials, n = 4214).[5] The certainty of the evidence was rated as very low for all outcomes, primarily due to high risk of bias and indirectness of the evidence.[5] Only one trial (n = 419) had follow-up at 52 weeks, and 2 trials (n = 314) included active comparators, so long-term and comparative evidence is limited.[5]

In conclusion, low-certainty evidence showed that ER methylphenidate compared to placebo improved ADHD symptoms in adults (small-to-moderate effects) measured on rating scales reported by participants, investigators, and peers such as family members.[5] Methylphenidate had no effect on number of days missed at work or serious adverse events, had a small effect on quality of life, and increased the risk of several adverse events.[5] The benefits and harms of ER methylphenidate remain uncertain.[5] Clinical guidelines and consensus documents, such as the European Consensus Statement,[21] the World Federation of ADHD International Consensus Statement,[22] and the NICE ADHD guideline,[7] reflect the very low certainty of the evidence.[5] The evidence to support methylphenidate as a pharmacological treatment for ADHD in adults is low-quality, and treatment beyond 52 weeks is not supported by RCTs.[5] There is inadequate direct comparative evidence to guide clinical practice about ER methylphenidate against other ADHD medications.[5]

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

A 2022 CADTH report reviewed evidence for guanfacine in autism spectrum disorder, ADHD, and/or oppositional defiance disorder.[6] Literature was searched through May 31, 2022.[6] Seven publications met the inclusion criteria: 4 systematic reviews, 2 RCTs, and 1 evidence-based guideline from NICE.[6] The systematic reviews included both adults and children with ADHD and compared guanfacine to placebo, amphetamines, atomoxetine, bupropion, clonidine, lisdexamfetamine, methylphenidate and modafinil given as oral therapy, alone or in combination with other drugs.[6] One of the RCTs enrolled children 6 to 12

years of age with ADHD who were taking a stable methylphenidate or amphetamine regimen for at least 30 days and had ongoing executive function difficulties.[6] The other trial was conducted in adults at least 18 years old with ADHD.[6] The NICE guideline was published in 2018 and updated in 2019.[7]

All the systematic reviews reported change in ADHD symptoms outcomes, assessed by any validated scales and reported the finding using standardized mean difference.[6] However, specific outcome measures and rating scales varied between reviews. For example, one systematic review only evaluated the ADHD-RS.[6] If they were included, parent, teacher and clinician ratings were analyzed separately.[6] Safety outcomes in both trials included adverse events, vital sign measurements, and physical examinations (weight and height). The adult trial additionally collected electrocardiogram parameters, while the pediatric study also measured safety using the used the Columbia Suicide Severity Rating Scale, which asks a series of 'yes' or 'no' questions to assess suicide risk.[6]

In the 2 systematic reviews that compared the effectiveness of guanfacine to psychostimulant drugs, low-quality evidence showed guanfacine was not different than methylphenidate in clinician-rated symptoms, parent-rated symptoms, or teacher-rated symptoms.[6] Similarly, guanfacine was not different than methylphenidate on the ADHD-RS.[6] In terms of safety, the tolerability of guanfacine was similar to methylphenidate and amphetamines in one systematic review.[6] However, another systematic review found that guanfacine was associated with greater odds of withdrawals due to adverse events compared to methylphenidate.[6] This systematic review also found that guanfacine had higher risk for withdrawal due to lack of efficacy and increased abdominal pain compared to lisdexamfetamine.[6]

Two systematic reviews and one RCT compared guanfacine to placebo. In the data analyses, guanfacine was associated with improved symptoms compared to placebo on the CGI-I score and clinician rating scales but not in the teacher or parent-rated scales.[6] In addition to symptoms, guanfacine was more effective for improvements in executive function compared to placebo in both RCTs.[6] Executive function was evaluated using the Behavior Rating Inventory of Executive Function-Parent (BRIEF-P) scale in pediatric patients or BRIFF-Adult (BRIEF-A) scale in adults. In the RCT in children, BRIEF-P scores improved more in the guanfacine group than the placebo group.[6] Similarly, the RCT in adults found statistically significant improvements on the Inhibit, Initiate, and Plan/Organize dimensions of the BRIEF-A scales, but not the other dimensions.[6]

In safety assessments, guanfacine was associated with increased odds of sedation, fatigue, abdominal pain, total adverse events, and dropouts due to adverse events compared to placebo.[6] One systematic review found no difference in laboratory test results, weight, or cardiovascular tests, although one person dropped out of the study due to sedation.[6] In the RCT conducted in adults, 19.8% (n = 19) of adverse events led to discontinuation in the guanfacine group versus 3% (n = 3) in the placebo group, and 81% (n = 82) of people treated with guanfacine versus 62% (n = 62) of people treated with placebo experienced an adverse event.[6] In the RCT among children, adverse events occurred in 41 children (87%) in the guanfacine group and 41 children (85%) in the placebo group.[6]

Most of the evidence in this review has substantial indirectness and uncertainty in head-to-head comparisons, limiting the confidence in relative effects of guanfacine versus other non-psychostimulants and stimulant medications.[6] The systematic reviews and included studies were generally of sufficient quality.[6] However, the number of primary studies with head-to-head comparisons and in subpopulations is limited.[6] One systematic review concluded that the evidence quality for the guanfacine comparisons was moderate versus placebo, low versus atomoxetine and very low for comparisons to clonidine, methylphenidate and modafinil.[6] Two other systematic reviews concluded that the quality of evidence was low for the population with autism spectrum disorder due to indirectness and imprecision, and very low for children with ADHD and tics.[6] Finally, the included RCTs were funded by the manufacturer of guanfacine (INTUNIV) which may affect interpretation of findings and increase risk for reporting bias.[6]

In summary, moderate-quality evidence from 4 systematic reviews and 2 RCTs suggest that guanfacine is more clinically effective than placebo for improving symptoms of ADHD, however it may be associated with increased adverse events such as abdominal pain and fatigue.[6] There is low-quality evidence from 2 systematic reviews that guanfacine may be equally effective as other psychostimulants or non-psychostimulants, with the potential for more side effects, but the evidence is highly uncertain.[6] The 2018 NICE guideline[7] has a strong recommendation to offer guanfacine for use in children and adolescents when psychostimulants have failed, or they are not tolerable.[6]

After review, 21 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:
High Quality Guidelines: No new high-quality guidelines have been published since the last P & T Committee review.

Additional Guidelines for Clinical Context:
Canadian Agency for Drugs and Technologies in Health: Clonidine for Management of ADHD in Adults
In 2024, CADTH reviewed guidelines on clonidine for various indications including hypertension, substance use disorders, menopause, restless leg syndrome, migraine, Tourette syndrome, and ADHD.[23] No evidence-based guidelines for the use of clonidine in the treatment of adults with ADHD were identified.[23]

After review, 2 guidelines were excluded due to poor quality.[24,25]

New Formulations:
In May 2024 the FDA approved a new ER suspension formulation of clonidine (ONYDA XR) for to treat ADHD as monotherapy or as adjunctive therapy to central nervous system stimulant medications in pediatric patients 6 years of age and older.[8] The starting dose is 0.1 mg once daily at bedtime.[8] The maximum recommended dose is 0.4 mg once daily.[8] The safety and efficacy of ONYDA XR are based on 3 placebo-controlled studies (2 studies conducted over 8 weeks and one study conducted over 40 weeks) of ER clonidine tablets.[8]

New FDA Safety Alerts:
May 2023: Drug Safety Communication: To address continuing concerns of misuse, abuse, addiction, and overdose of prescription stimulants, FDA is requiring updates to the Boxed Warning and other information to ensure the prescribing information is made consistent across the entire class of these medications.[9] Prescription stimulants can be an important treatment option for disorders for which they are indicated.[9] However, even when prescribed to treat an indicated disorder, their use can lead to misuse or abuse.[9] The FDA reviewed the medical literature published from January 2006 to May 2020 on misuse and abuse, also called nonmedical use, of prescription stimulants and associated adverse events.[9] Overall, the most common source of prescription stimulants for nonmedical use in the general population came from friends or family members, with estimates generally ranging from 56 percent to 80 percent, usually provided for free.[9] Nonmedical use from their own prescription accounted for approximately 10 percent to 20 percent of people who report having used stimulants nonmedically in the past year. Less commonly reported sources included drug dealers or strangers accounting for 4 percent to 7 percent of people who report having used stimulants nonmedically in the past year, and the internet accounting for 1 percent to 2 percent.[9] FDA is requiring manufacturers of amphetamine and methylphenidate products to update and standardize their prescribing information to clearly inform patients, caregivers and health care professionals of risks associated with their medications.[9]

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
dextroamphetamine/amphetamine	ADDERALL XR	ORAL	CAP ER 24H	Y
dextroamphetamine/amphetamine	DEXTROAMPHETAMINE-AMPHET ER	ORAL	CAP ER 24H	Y
viloxazine HCl	QELBREE	ORAL	CAP ER 24H	Y
atomoxetine HCl	ATOMOXETINE HCL	ORAL	CAPSULE	Y
lisdexamfetamine dimesylate	LISDEXAMFETAMINE DIMESYLATE	ORAL	CAPSULE	Y
atomoxetine HCl	STRATTERA	ORAL	CAPSULE	Y
lisdexamfetamine dimesylate	VYVANSE	ORAL	CAPSULE	Y
methylphenidate HCl	METHYLPHENIDATE HCL CD	ORAL	CPBP 30-70	Y
methylphenidate HCl	METHYLPHENIDATE HCL ER (CD)	ORAL	CPBP 30-70	Y
dexmethylphenidate HCl	DEXMETHYLPHENIDATE HCL ER	ORAL	CPBP 50-50	Y
dexmethylphenidate HCl	FOCALIN XR	ORAL	CPBP 50-50	Y
lisdexamfetamine dimesylate	LISDEXAMFETAMINE DIMESYLATE	ORAL	TAB CHEW	Y
lisdexamfetamine dimesylate	VYVANSE	ORAL	TAB CHEW	Y
clonidine HCl	CLONIDINE HCL ER	ORAL	TAB ER 12H	Y
methylphenidate HCl	CONCERTA	ORAL	TAB ER 24	Y
methylphenidate HCl	METHYLPHENIDATE ER	ORAL	TAB ER 24	Y
methylphenidate HCl	RELEXXII	ORAL	TAB ER 24	Y
guanfacine HCl	GUANFACINE HCL ER	ORAL	TAB ER 24H	Y
guanfacine HCl	INTUNIV	ORAL	TAB ER 24H	Y
dextroamphetamine/amphetamine	ADDERALL	ORAL	TABLET	Y
dexmethylphenidate HCl	DEXMETHYLPHENIDATE HCL	ORAL	TABLET	Y
dextroamphetamine/amphetamine	DEXTROAMPHETAMINE-AMPHETAMINE	ORAL	TABLET	Y
dexmethylphenidate HCl	FOCALIN	ORAL	TABLET	Y
methylphenidate HCl	METHYLPHENIDATE HCL	ORAL	TABLET	Y
methylphenidate HCl	RITALIN	ORAL	TABLET	Y
methylphenidate	DAYTRANA	TRANSDERM	PATCH TD24	Y
methylphenidate	METHYLPHENIDATE	TRANSDERM	PATCH TD24	Y
clonidine HCl	ONYDA XR	ORAL	SUS ER 24H	V
serdexmethylphen/dexmethylphen	AZSTARYS	ORAL	CAPSULE	N
dextroamphetamine sulfate	DEXEDRINE	ORAL	CAPSULE ER	N
dextroamphetamine sulfate	DEXTROAMPHETAMINE SULFATE ER	ORAL	CAPSULE ER	N
methylphenidate HCl	METHYLPHENIDATE ER (LA)	ORAL	CPBP 50-50	N
methylphenidate HCl	METHYLPHENIDATE LA	ORAL	CPBP 50-50	N
methylphenidate HCl	RITALIN LA	ORAL	CPBP 50-50	N
methylphenidate HCl	JORNAY PM	ORAL	CPDR ER SP	N
dextroamphetamine/amphetamine	DEXTROAMPHETAMINE-AMPHET ER	ORAL	CPTP 24HR	N
dextroamphetamine/amphetamine	MYDAYIS	ORAL	CPTP 24HR	N
methylphenidate HCl	APTENSIO XR	ORAL	CSBP 40-60	N

methylphenidate HCl	METHYLPHENIDATE ER	ORAL	CSBP 40-60	N
dextroamphetamine sulfate	DEXTROAMPHETAMINE SULFATE	ORAL	SOLUTION	N
methylphenidate HCl	METHYLIN	ORAL	SOLUTION	N
methylphenidate HCl	METHYLPHENIDATE HCL	ORAL	SOLUTION	N
dextroamphetamine sulfate	PROCENTRA	ORAL	SOLUTION	N
methylphenidate HCl	QUILLIVANT XR	ORAL	SU ER RC24	N
amphetamine	DYANAVEL XR	ORAL	SUS BP 24H	N
amphetamine	DYANAVEL XR	ORAL	TAB BP 24H	N
methylphenidate HCl	QUILLICHEW ER	ORAL	TAB CBP24H	N
methylphenidate HCl	METHYLPHENIDATE HCL	ORAL	TAB CHEW	N
methylphenidate HCl	METHYLPHENIDATE ER	ORAL	TAB ER 24	N
methylphenidate HCl	RELEXXII	ORAL	TAB ER 24	N
amphetamine	ADZENYS XR-ODT	ORAL	TAB RAP BP	N
methylphenidate	COTEMPLA XR-ODT	ORAL	TAB RAP BP	N
amphetamine sulfate	EVEKEO ODT	ORAL	TAB RAPDIS	N
amphetamine sulfate	AMPHETAMINE SULFATE	ORAL	TABLET	N
dextroamphetamine sulfate	DEXTROAMPHETAMINE SULFATE	ORAL	TABLET	N
amphetamine sulfate	EVEKEO	ORAL	TABLET	N
methamphetamine HCl	METHAMPHETAMINE HCL	ORAL	TABLET	N
dextroamphetamine sulfate	ZENZEDI	ORAL	TABLET	N
methylphenidate HCl	METHYLPHENIDATE ER	ORAL	TABLET ER	N
dextroamphetamine	XELSTRYM	TRANSDERM	PATCH TD24	N

Appendix 2: New Comparative Clinical Trials

A total of 137 citations were manually reviewed from the initial literature search. After further review, 137 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to October 17, 2024

1	attention deficit disorder.mp. or exp Attention Deficit Disorder with Hyperactivity/	37515
2	exp Atomoxetine Hydrochloride/	1447
3	exp Viloxazine/	254
4	exp Central Nervous System Stimulants/	105037
5	exp Dextroamphetamine/	7221
6	exp Dexmethylphenidate Hydrochloride/	67
7	exp Amphetamine/	19813
8	exp Lisdexamfetamine Dimesylate/	350
9	exp Methylphenidate/	8019
10	serdexmethylphenidate.mp.	15
11	exp Methamphetamine/	11640
12	exp Clonidine/	13597
13	exp Guanfacine/	789
14	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	119713
15	1 and 14	7480
16	limit 15 to (english language and humans and yr="2022 -Current")	580
17	limit 16 to (clinical trial, phase iii or clinical trial or comparative study or controlled clinical trial or guideline or meta-analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	137

Appendix 4: 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 07/05/22 – 10/17/2024
Setting	Outpatient

Attention Deficit Hyperactivity Disorder (ADHD) Safety Edit

Goals:

- Cover medications used for ADHD and narcolepsy if diagnosis is funded by the OHP, and medication use is consistent with best practices.
- Promote care by a psychiatrist for patients requiring therapy outside of best practices.
- 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. Age Range and Maximum Daily Doses for Drugs Approved for ADHD.

Drug	Brand Name (or generic equivalents)	Min Age	Max Age	Max Daily Dose
STIMULANTS				
Amphetamine IR	Evekeo (tab)	3	NA	40 mg
	Evekeo ODT (dist tab)	3	NA	40 mg
Amphetamine ER	Adsensys ER (susp) and XR-ODT (tab)	6	12	18.8
		13	NA	12.5 mg
	Dyanavel XR (susp, tab)	6	NA	20 mg
Dextroamphetamine IR	ProCentra (sol)	3	16	40 mg
	Zenzedi (tab)	3	16	40 mg
Dextroamphetamine ER	Dexedrine Spansule (cap)	6	16	40 mg
	Xelstrym (transdermal patch)	6	NA	18 mg/9 hour

Dextroamphetamine/ amphetamine salts IR	Adderall (tab)	3	NA	40 mg
Dextroamphetamine/ amphetamine salts ER	Adderall XR (cap)	6	12	30 mg
		13	NA	60 mg
	Mydayis (cap)	13	17	25 mg
		18	55	50 mg
Dexmethylphenidate IR	Focalin (tab)	6	17	20 mg
Dexmethylphenidate ER	Focalin XR (cap)	6	17	30 mg
		18	NA	40 mg
Lisdexamfetamine	Vyvanse (cap; chew tab)	6	NA	70 mg
Methamphetamine IR	Desoxyn (tab)	6	17	25 mg
Methylphenidate IR	Methylin (sol)	6	NA	60 mg
	Ritalin (tab)	6	NA	60 mg
Methylphenidate ER	Adhansia XR (cap)	6	17	85 mg
		18	NA	100 mg
	Aptensio XR (cap)	6	NA	60 mg
	Concerta (tab)	6	12	54 mg
		13	65	72 mg
	Cotempla XR-ODT (tab)	6	17	51.8 mg
	Daytrana (transdermal patch)	6	17	30 mg/9 hour
	Jornay PM (cap)	6	NA	100 mg
	Metadate CD (tab)	6	NA	60 mg
	QuilliChew ER (chew tab)	6	NA	60 mg
	Quillivant XR (susp)	6	NA	60 mg
	Relexxi (tab)	6	12	54 mg
		13	65	72 mg
	Ritalin LA (cap)	6	NA	60 mg
Serdexmethylphenidate/ dexmethylphenidate	Azstarys (cap)	6	NA	52.3 mg/ 10.4 mg
NON-STIMULANTS				
Atomoxetine	Strattera (cap)	6	17	≤70 kg: lesser of 1.4 mg/kg or 100 mg >70 kg: 100 mg
		18	NA	100 mg
Clonidine ER	Kapvay (tab)	NA	NA	NA

Guanfacine ER	Intuniv (tab)	NA	NA	NA
Viloxazine ER	Qelbree (cap)	6	17	400 mg
		18	NA	600 mg
Abbreviations: cap = capsule; chew = chewable; dist = disintegrating; ER = extended-release formulation; IR = immediate-release formulation; NA = not applicable; sol = solution; susp = suspension; tab = tablet.				

Table 2. Age Range and Maximum Daily Doses for Drugs Approved for Narcolepsy.

Drug	Brand Name (or generic equivalents)	Min Age	Max Age	Max Daily Dose
STIMULANTS				
Amphetamine IR	Evekeo (tab)	6	12	40 mg
		13	NA	60 mg
Dextroamphetamine IR	ProCentra (sol)	3	17	40 mg
		18	NA	60 mg
	Zenzedi (tab)	3	17	40 mg
		18	NA	60 mg
Dextroamphetamine ER	Dexedrine (cap)	6	17	40 mg
		18	NA	60 mg
Dextroamphetamine/amphetamine salts IR	Adderall (tab)	6	17	40 mg
		18	NA	60 mg
Methylphenidate IR	Methylin (sol)	6	NA	60 mg
	Ritalin (tab)	6	NA	60 mg
Methylphenidate ER	Ritalin LA (cap)	6	12	60 mg
Abbreviations: cap = capsule; ER = extended-release formulation; IR = immediate-release formulation; NA = not applicable; sol = solution; tab = tablet.				

Table 3. Standard Combination Therapy for ADHD

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

Abbreviations: ER = extended-release; IR = immediate-release formulation.

* Recommended by the American Academy of Pediatrics. Wolraich ML, Hagan JF, Jr., Allan C, et al. Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. Pediatrics. 2019;144(4).
**Identified by: Pharmacologic Treatments for Attention Deficit Hyperactivity Disorder: Drug Effectiveness Review Project, 2015.

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:** Current Age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP Current age < 21 years: go to #13.
3. Is the requested for a preferred drug?	**Yes:** Go to #5	**No:** Go to #4
4. Will the prescriber consider a change to a preferred agent? Preferred drugs reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	**Yes:** Inform prescriber of preferred alternatives	**No:** Go to #5
5. Is the request for an ADHD diagnosis?	**Yes:** Go to #6	**No:** Go to #9
6. Are the patient's age and the prescribed dose within the limits defined in Table 1?	**Yes:** Go to #7	**No:** Go to #11
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 a standard combination therapy, as defined in Table 3?	**Yes:** Approve for up to 12 months	**No:** Go to #11
9. Is the request for a narcolepsy diagnosis?	**Yes:** Go to #10	**No**: Pass to RPh. Deny; medical appropriateness.
10. Are the patient's age and the prescribed dose within the limits defined in Table 2?	**Yes:** Approve for up to 12 months	**No:** Go to #11

Approval Criteria		
11. Was the drug regimen developed by or in consultation with a relevant specialist (e.g., psychiatrist, developmental pediatrician, psychiatric nurse practitioner, sleep specialist, pulmonologist, or neurologist)?	**Yes:** Document name and contact information of consulting provider and approve for up to 12 months	**No:** Go to #12
12. Was the current drug regimen *initiated* at doses and ages recommended in Tables 1-3 and has the provider assessed ongoing need for treatment in the past year?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness. Ages or doses exceeding defined limits, or non-recommended multi-drug regimens, are only approved when prescribed by or in consultation with a mental health specialist. Specialist consultation is not required if patients age into a maximum age limit. May approve continuation of existing therapy once up to 90 days to allow time to consult with a mental health specialist.
13. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	**Yes:** Go to #14	**No:** Pass to RPh. Deny; medical necessity.
14. Is the request for an FDA-approved indication?	**Yes:** Go to #15	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
15. Is the request for a preferred product OR has the patient failed to have benefit with, or have contraindications or intolerance to, at least 2 preferred products? Message: Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	**Yes:** Approve for 12 months.	**No:** Pass to RPh. Deny; medical appropriateness. Inform prescriber of covered alternatives in class and process appropriate PA.

P&T Review: 12/24 (DM); 6/24 (SS); 10/22 (DE);6/22; 8/20; 5/19; 9/18; 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: 7/1/24; 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