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OHSU Drug Effectiveness Review Project Summary Report – Pharmacological Therapies for Attention-Deficit/Hyperactivity Disorder (ADHD)

Date of Review: June 2022

Date of Last Review: August 2020

Literature Search: 09/01/2020-03/01/2022

Current Status of PDL Class:

See **Appendix 1**.

Research Questions:

1. For adults and children, what is the comparative effectiveness of the included interventions (see **Table 1**) for attention-deficit/hyperactivity disorder (ADHD)?
2. For adults and children, what are the comparative harms of the included interventions (see **Table 1**) for ADHD?

Conclusions:

- 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 this review.[1] Evidence for the following comparisons informed the DERP report:
    - Stimulant vs. Stimulant
    - Stimulant vs. Nonstimulant
    - Nonstimulant vs. Nonstimulant
    - Newer drug vs. Placebo
- Stimulant versus another stimulant medication: there was low quality evidence of rare serious adverse events (SAEs) for lisdexamfetamine and osmotic release oral system (OROS) methylphenidate groups compared to methylphenidate immediate-release based on 2 randomized controlled trials (RCTs) (N=611) with high risk of bias.[1] There were no high, moderate, or low-quality studies identified that reported any differences in the reduction of ADHD symptoms between various methylphenidate formulations and mixed amphetamine salts.
- Stimulant versus nonstimulant medications: there was moderate quality evidence of no differences in global measures in 11 of 12 studies; one trial (N=267) reported that lisdexamfetamine treatment resulted in statistically significant reductions of ADHD symptoms compared to atomoxetine based on

assessments with the ADHD-Rating Scale (RS)-IV (*P*<0.001) and Weiss Functional Impairment Rating Scale [WFIRS] Parent Form (*P* = 0.05). Low quality evidence from 3 RCTs reported slightly more discontinuations due to adverse events (AEs) for atomoxetine (8%; 31/381) compared to methylphenidate immediate release (6%; 14/246).[1] Risk of bias was high in 7 of the 12 RCTs and moderate in 5 of the 12 RCTs.[1]

- Nonstimulant versus another nonstimulant: there was low quality evidence from 1 RCT (N = 338) that extended-release guanfacine (guanfacine XR) resulted in statistically significant reductions of ADHD symptoms compared to atomoxetine based on assessments with the ADHD-RS-IV (least square mean difference (LSMD): −5.1 (95% CI, −8.2 to −2.0); *P*=0.001).[1] Although adverse events were rare in both groups, a slightly higher proportion of patients treated with guanfacine XR reported SAEs compared to atomoxetine (2% vs 0%, respectively), while discontinuations due to adverse events were slightly higher with guanfacine XR treatment compared to atomoxetine (7.8% vs 4.5%).[1]
- Newer drug vs. placebo: there was low quality evidence from 2 RCTs (N=535) of 8 weeks duration that reported viloxazine treatment resulted in a statistically significant reduction in ADHD symptoms at doses from 200 mg to 400 mg per day compared to placebo as measured across multiple instruments (least squares [LS] mean change ADHD-RS 5 = -17.5 to -17.6, p<0.05; LS mean total score Clinical Global Impressions-Illness (CGI-I) = 2.6 for both 200 mg and 400 mg doses, with p=0.003 and <0.01, respectively; ADHD-RS-IV, total score, LS mean change: 200 mg, 300 mg = -18.4 to -18.6 (p=0.03) and 400 mg = -19.0 (p= 0.02).[1]

Recommendations:

- No changes to the current Oregon Health Plan (OHP) Preferred Drug List (PDL).
- Evaluate costs in the executive session to inform PDL status.

Summary of Prior Reviews and Current Policy

Prior reviews have found evidence to support that both stimulant and non-stimulant pharmacologic agents are beneficial in ADHD treatment compared to placebo.[2] Comparisons between different formulations (immediate release [IR] vs. various extended-release [ER], XR, or long acting [LA] versions]) within this class have not demonstrated consistent differences.[2] 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.[2] The most frequent adverse effects from stimulants are appetite loss, abdominal pain, headaches and sleep disturbance; only low-quality evidence has been identified to suggest any differences in harms between various ADHD agents.[2]

To ensure safe and appropriate use within the OHP-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 are part of the mental health carve-out and are exempt from traditional prior authorization (PA) requirements: atomoxetine, clonidine ER, guanfacine ER, and the newest agent viloxazine. All medications, regardless of PDL status, may be subject to clinical PA criteria to address any safety concerns or to ensure medically appropriate use.

Background

Attention-deficit/hyperactivity disorder is a neurodevelopmental disorder which affects approximately 9% of children and adolescents in the United States (U.S.) and is characterized by hyperactivity, impulsivity, and inattention.[3] Although ADHD has been thought of as a childhood disorder, symptoms may persist into

adulthood in as many as 1% to 4% of US adults aged 18 to 44 years.[1,4] According to the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria, 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).[5] 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.[3-5]

ADHD may be classified into 3 general presentations: predominantly inattentive, hyperactive/impulsive, and combined.[6,7] ADHD that cannot be classified in one of the 3 main categories is referred to as ADHD other specified or unspecified type.[6,7] In predominantly inattentive ADHD, a child exhibits at least 6 months of 6 or more inattention symptoms (careless mistakes, lack of follow-through, loses things, forgetful, easily distracted, etc).[6,7] In hyperactive/impulsive type, a child shows 6 or more hyperactive or impulsive symptoms (fidgets, inappropriate running/climbing, difficulty with playing quietly, often interrupts/intrudes, etc.) for at least 6 months.[6,7] The third ADHD categorization is a combined presentation of inattentiveness and hyperactivity/impulsivity for at least 6 months or longer.[6,7] Predominantly hyperactive/impulsive- or combined type ADHD often becomes apparent from behavior problems as the child enters kindergarten/1st grade while predominantly inattentive ADHD generally has a later onset which is recognized by poor academic performance and organizational skills.[3,6-9] For adolescents older than 17 years old and adults, the DSM-5 ADHD Diagnostic Criteria is essentially identical but only requires that 5 or more symptoms of inattention and/or hyperactivity-impulsivity have persisted for at least 6 months and are inconsistent with the stage of development.[5]

Comorbid conditions which can be associated with a diagnosis of ADHD include mood disorders, tic disorders, developmental and learning disorders and anxiety disorders.[5] Many children and adults with ADHD have one or more comorbid psychiatric conditions with comparable symptoms that may hinder appropriate care and present unique challenges.[10,11] Some of the more common comorbidities in children and adolescents include anxiety, oppositional defiance disorder (ODD), learning disorders, and depression.[1,10,11] The presence of psychiatric disorders increases the risk of an ADHD diagnosis in adulthood.[10,11] Some common comorbidities present in adults also include anxiety and depression as well as other conditions such as substance use disorder (SUD) and bipolar disorder.[10]

Behavioral interventions such as cognitive behavioral therapy (CBT), skills training, and other supportive therapy is generally considered first-line therapy; however, a combination of psychosocial interventions and medications are increasingly employed and advocated by many guidelines.[6,12] It is estimated that 62% of children/adolescents and up to 80% of adults with ADHD use prescription medications to manage their symptoms.[3,6,10-12] In pediatric patients, recommendations from the American Academy of Pediatrics (AAP) are based on age and disease severity.[6] For pre-school aged children age 4-5 years, behavioral therapy is recommended as first-line treatment while methylphenidate may be used as a second-line therapy or in cases of moderate-to-severe functional impairment.[6] In children older than 6 years of age, either behavioral therapy or pharmacotherapy may be used as first-line therapy.[6] Evidence of efficacy is strongest for stimulant medications (e.g. methylphenidates, amphetamines) although non-stimulant medications including atomoxetine, clonidine ER and guanfacine ER are recommended as second-line therapy if stimulants are not tolerated or ineffective.[5,6] For adults, the National Institute for Health and Care Excellence (NICE) guidelines suggest lisdexamfetamine or methylphenidate as first-line pharmacological agents for adults with ADHD.[12] Atomoxetine is recommended as second line therapy for people that cannot tolerate stimulants or if they do not respond after 6 weeks of therapy.[12]

Researchers have investigated whether racial/ethnic disparities exist in ADHD diagnosis and medication use.[13] One longitudinal, multisite study of 5th-graders suggested an underdiagnosis and undertreatment of Black and Hispanic/Latino children compared to other races.[14] A study of children aged 6 to 17 years in Kentucky Medicaid also found that rates for receipt of an ADHD diagnosis were lowest for Hispanic/Latino and Asian children compared to other races.[15] In addition, racial/ethnic minority children were less likely to receive a stimulant medication, with Hispanic/Latino and Asian children having the lowest rates.[15]

However, the same study showed that non-Hispanic Black and Hispanic/Latino children had the highest rates of receiving psychosocial therapy interventions.[15] Most of the available studies are claims-based which are unable to determine the type or quality of services, whether the diagnosis/treatment was appropriate, or the accuracy of the optional fields in which race/ethnicity data are collected. More research is needed in this area to better understand whether differences in care are due to provider bias, child uniqueness, or cultural distinctions that impact treatment.

The goals of ADHD care may change as the patient matures, but generally, they focus on management of symptoms as well as improvements in function and quality of life.[6-8] Evaluation of symptom and functional improvement may employ a variety of behavior assessment scales and metrics which are usually completed by the parents, teacher, or patient with ADHD.[6-9,16,17] Assessment scales commonly used in clinical trials include the ADHD rating scale (ADHD-RS), the Weiss Functional Impairment Rating Scale (WFIRS), Permanent Product Measure of Performance (PERMP), the Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale (SKAMP), and Conners Parent Rating Scale (CPRS).[16,17] 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 54 with more higher scores indicating more severe symptoms.[17] 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.[16] Although the Clinical Global Impressions scale is not specific to ADHD, it has been paired with the ADHD-RS to assess ADHD symptom changes.[1,16] The CGI Symptoms (CGI-S) component is employed as a baseline measurement and is based on a scale of 1 (no symptoms) to 7 (very severe symptoms). A 1-point difference on CGI-S has been reported to correlate with 8 to 10 points on ADHD-RS.[16] 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.[16] It has been reported that a "much improved" (2-level improvement) on CGI-I correlates with 50 to 60% improvement on ADHD-RS.[16] Other scales such as the WFIRS is a 50-item instrument that assesses symptoms and degrees of impact on 6 clinically relevant functional areas.[17,18] WFIRS responses include "never or not at all", "sometimes or somewhat", "often or much", "very often or very much", and "N/A" (not applicable).[17,18] Any WFIRS item rating 2 or 3 within a section would indicate impairment.[17,18] The PERMP is a classroom assessment which evaluates attention using a skill-adjusted math test.[17,19] The total PERMP score is a sum of the number of math problems attempted and the number answered correctly.[17,19] Because PERMP score is specific to the ability of the patient, the minimum clinically significant difference (MCID) in PERMP score has not been determined. The SKAMP rating scale is another teacher-rated scale which evaluates attention and behavior in a laboratory classroom setting.[17] Scores assess 13 items including attention, quality of work, deportment and compliance.[17,20] Each item is assessed on a 0 to 6 point scale with total score ranging from 0 to 78 and higher scores associated with more severe impairment.[17,20] The CPRS scale evaluates a variety of ADHD symptoms, each assessed on a 0 to 3 scale corresponding to symptoms which are not present (0), just a little present (1), pretty much present (2), and very much present (3).[16] Minimal Clinically Important Differences (MCIDs) for ADHD outcomes related to the ADHD-RS, WFIRS, SKAMP, and CPRS scales are not presently well-defined.[1]

Methods:

The December 2021 drug class report by the DERP at the Center for Evidence Based Policy at the Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class. The original report is available to Oregon Pharmacy and Therapeutics Committee members upon request.

The purpose of the DERP report is to make available information regarding the comparative clinical effectiveness and harms of different drugs. DERP reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. OHSU does not recommend or endorse any guideline or recommendation developed by users of these reports.

Summary Findings:

The 2021 DERP report focused on the comparative efficacy and safety of drugs to treat ADHD and was an update of a previous DERP report completed in 2015.[1] The report focused on RCTs of FDA-approved stimulants and non-stimulants as well as off-label treatments.[1] DERP reviewers completed a systematic review

based on a literature search of studies published between January 1, 2015 and August 1, 2021.[1] Therapies were excluded if they were not RCTs, compared a branded agent to its generic equivalent, different doses of the same drug, placebo-controlled trials of older agents, trials that evaluated primarily multi-modal (non-drug) comparisons, and studies not published in English.[1]

Since the previous review, two new agents have received FDA approval for the treatment of ADHD.[1] Serdexmethylphenidate/dexmethylphenidate (AZSTARYS), an oral prodrug of the stimulant dexmethylphenidate, was approved in March 2021.[1,21] A new non-stimulant oral agent, viloxazine hydrochloride (QELBREE), was approved in April 2021.[1,22] Manufacturer's prescribing information for each of these products is presented in **Appendix 2**. Three ongoing head-to-head trials and 3 placebo-controlled RCTs for recently FDA- approved agents were identified but will not be discussed as results were pending.[1] The FDA approved drugs included in the ADHD DERP report are summarized by subclass and listed in **Table 1**.

Table 1. FDA-Approved and Selected Off-label Treatments for ADHD

Generic Name	Brand Name	Date of FDA Approval
Stimulants		
Serdexmethylphenidate dexmethylphenidate	AZSTARYS	March 2, 2021
Methylphenidate hydrochloride	ADHANSIA XR	February 27, 2019
Amphetamine sulfate	EVEKEO ODT	January 30, 2019
Methylphenidate hydrochloride	JORNAY PM	August 8, 2018
Amphetamine	ADZENYS ER	September 15, 2017
Mixed amphetamine salts	MYDAYIS	June 20, 2017
Methylphenidate	COTEMPLA XR-ODT	June 19, 2017
Lisdexamfetamine dimesylate	VYVANSE (CHEWABLE)	January 28, 2017
Amphetamine polistirex	ADZENYS XR-ODT	January 27, 2016
Methylphenidate hydrochloride	QUILLICHEW ER	December 4, 2015
Amphetamine	DYANAVEL XR	October 19, 2015
Methylphenidate hydrochloride	APTENSIO XR	April 17, 2015
Methylphenidate hydrochloride	QUILLIVANT XR	September 27, 2012
Amphetamine sulfate	EVEKEO	August 9, 2012
Lisdexamfetamine dimesylate	VYVANSE	February 23, 2007
Methylphenidate	DAYTRANA	April 6, 2006
Dexmethylphenidate hydrochloride	FOCALIN XR	May 26, 2005

Methylphenidate hydrochloride	METADATE CD	April 3, 2003
Methylphenidate hydrochloride	METHYLIN	December 19, 2002
Methylphenidate hydrochloride	RITALIN LA	June 5, 2002
Dexmethylphenidate hydrochloride	FOCALIN	November 13, 2001
Mixed amphetamine salts	ADDERALL XR	October 11, 2001
Methylphenidate hydrochloride (osmotic release)	CONCERTA	August 1, 2000
Methylphenidate hydrochloride	METHYLIN ER	May 9, 2000
Methylphenidate hydrochloride	RITALIN SR	March 30, 1982
Mixed amphetamine salts	ADDERALL	January 19, 1960
Methylphenidate hydrochloride	RITALIN	December 5, 1955
Nonstimulants		
Viloxazine hydrochloride	QELBREE	April 2, 2021
Clonidine hydrochloride (extended release)	KAPVAY	September 29, 2009
Guanfacine hydrochloride (extended release)	INTUNIV	September 2, 2009
Atomoxetine hydrochloride	STRATTERA	November 26, 2002
Off-Label treatment		
Armodafinil	NUVIGIL	June 15, 2007
Bupropion hydrochloride	WELLBUTRIN XL	August 28, 2003
Modafinil	PROVIGIL	December 24, 1998
Bupropion hydrochloride	WELLBUTRIN SR	October 4, 1996

Abbreviations. ADHD: attention deficit/hyperactivity disorder; CD: controlled dose; ER: extended release; LA: long acting; ODT: orally disintegrating tablet; SR: sustained release; XL/XR: extended release

There were 70 studies (N = 11,815) that met inclusion criteria. Of these trials, 50 involved populations from the United States that compared 2 active treatments.[1] Most participants were White between the ages of 6- and 12-years exhibiting ADHD symptoms of both inattention and hyperactivity or impulsiveness.[1] Fourteen studies had a moderate risk of bias while 56 studies had high risk.[1] The review compared findings for a stimulant versus another stimulant, a stimulant versus a nonstimulant, a nonstimulant versus another nonstimulant, and placebo compared to the new nonstimulant viloxazine.[1] **Table 2** is an overview of all the RCTs identified in the DERP review and the number of studies that met the minimum criteria for 8 weeks duration or longer.

Table 2: Overview of DERP Review Findings[1]

Comparators	Number of RCTs	Study Size Range	Total N	Study Duration (weeks)	Number of Studies 8 weeks or Longer
Stimulant vs. Stimulant	34	18 to 549	3,958	1 to 16	**3**
Stimulant vs. Nonstimulant	20	17 to 1,323	4,597	2 to 26	**13**
Nonstimulant vs. Nonstimulant	1	N/A	338	10 to 13	**1**
Newer drug vs. Placebo	11	59 to 477	2,786	1 to 8	**2**

Certainty of evidence was assessed using the GRADE criteria in RCTs that had a minimum of 8 weeks treatment (with or without follow-up) and was limited to 5 outcomes: symptom response, performance, quality-of-life (parent stress, parent satisfaction), discontinuations due to adverse events and SAEs.[1] Evidence certainty was assessed as "very low or moderate" for symptom response measures, "very low" for performance and quality of life measures, and "very low or low" for discontinuation due to AEs and SAEs.[1] All participants had ADHD symptom reduction compared to baseline without regard to what active treatment was employed and irrespective of age, race, gender, or ethnicity.[1] Studies comparing a stimulant to off-label treatment or placebo did not meet inclusion criteria.[1] In some cases, there were no eligible studies for a particular outcome or the included studies were rated as "Very low" certainty of evidence.[1] Only trials of 8-week or longer with High, Moderate, or Low quality of evidence for ADHD outcomes as will be highlighted in this DERP summary (see **Table 3** and **Table 4**).

Table 3: GRADE Criteria for Overall Quality of Evidence[1]

High	Raters are very confident that the estimate of the effect of the intervention on the outcome lies close to the true effect. Typical sets of studies are randomized controlled trials with few or no limitations, and the estimate of effect is likely stable.
Moderate	Raters are moderately confident in the estimate of the effect of the intervention on the outcome. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is different. Typical sets of studies are randomized controlled trials with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.
Low	Raters have little confidence in the estimate of the effect of the intervention on the outcome. The true effect may be substantially different from the estimate of the effect. Typical sets of studies are RCTs with serious limitations or nonrandomized studies without special strengths.
Very Low	Raters have no confidence in the estimate of the effect of the intervention on the outcome. The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.

Table 4: Overview and Certainty of Evidence for Select ADHD Outcomes in RCTs of at least 8 weeks[1]

Comparators	ADHD Outcomes Studied and Certainty of Evidence (Low, Moderate, High)				
	Symptom Response	Performance	Quality of Life	Discontinuations Due to AEs	Serious AEs
Stimulant vs. stimulant					Low (2 RCTs; N = 611)
Stimulant vs. nonstimulant	Moderate (12 RCTs; N = 1,991)			Low (10 RCTs; N=1,716)	Low (3 RCTs; N = 493)
Nonstimulant vs. nonstimulant	Low (1 RCT; N = 338)			Low (1 RCT; N = 338)	Low (1 RCT; N = 338)
Nonstimulant vs. placebo	Low (2 RCTs; N = 535)				

Abbreviations. ADHD = attention deficit/hyperactivity disorder; AE = adverse effects; RCT = randomized controlled trial
Note: Table 4 includes only those studies assessed with GRADE criteria that also met the minimum 8-weeks of treatment requirement. Gray row shading indicates there were no eligible studies for a particular outcome, or the included studies rated as "Very low" certainty of evidence, therefore those results will not be discussed in this DERP summary.

Stimulant vs. Another Stimulant

A total of 34 RCTs (N=3958) were identified that compared one stimulant versus another that ranged from 3 to 16 weeks; however, only 3 studies were 8 weeks or longer.[1,23-25] Thirty-one studies involved children and adolescents with a mean age range of 7 to 18 years while 3 studies included adults up to 60 years of age (mean age range 33 – 36 years).[1] Thirty of the studies were rated as high risk of bias due to poor reporting and industry conflicts while 4 were moderate risk of bias due to inadequate methods reporting, lack of blinding, high (>20%) attrition, and other factors.[1] Adverse events were reported in only 13 of 33 studies.[1] Overall, there were no significant differences found in the reduction of ADHD symptoms between different methylphenidate formulations and mixed amphetamine salts.[1] There was low quality evidence from 2 RCTs (N=611) of rare SAEs, with one SAE reported in both the osmotic-release oral system methylphenidate and the lisdexamfetamine groups, and none in the immediate-release amphetamine group.[1,24,25] An overview of study characteristics for each trial is provided in **Table 5**.

Table 5: Overview of Study Characteristics for RCTs of at least 8-weeks Duration

Study Details						Population Eligibility			Outcomes				
Author, Year	Study Design	Duration + Follow-up (weeks)	Included United States	N Enrolled	Interventions	Ages or Other Criteria	ADHD Presentation	Other Comorbidities Allowed	Symptom Response	Performance	Quality of Life	AEs	Risk of Bias
Stimulant vs Another Stimulant													
Cikili Uytun, 2019[23]	RCT	16	No	103	ER-MPH OROS-MPH	6 to 16	Any	ODD	Yes	NR	NR	Yes	High
Steele, 2006[24]	RCT	8	No	147	IR-MPH OROS-MPH	6 to 12	Any	NR	Yes	NR	No	Yes	High
Newcorn, 2017[25] (flexi-dose)	RCT	8 + 1	Yes	464	LDX OROS-MPH PBO	13 to 17	Any	ODD	Yes	NR	NR	Yes	High
Newcorn, 2017[25] (forced dose)	RCT	6 + 1	Yes	549	LDX OROS-MPH PBO	13 to 17	Any	ODD	Yes	NR	NR	Yes	Mod
Stimulant vs Non-stimulant													
ÇEtİN, 2015[26]	RCT	26	No	145	ATX OROS-MPH	7 to 16	Any	None	Yes	NR	NR	Yes	Mod
Dittmann, 2013[27]	RCT	9	Yes	267	ATX LDX	6 to 17	Any	NR	Yes	Yes	NR	Yes	High
Garg, 2014[28]	RCT	8	No	84	ATX IR-MPH	6 to 14	Any	ODD	Yes	NR	NR	Yes	High
Kratochvil, 2002[29]	RCT	10	Yes	228	ATX MPH	Males, 7 to 15 Females, 7 to 9	Any	NR	Yes	NR	NR	Yes	High
Ni, 2017[30]	RCT	8 to 10	No	71	ATX IR-MPH	18 to 50 Drug naïve	Any	None	Yes	NR	NR	NR	Mod
Palumbo, 2008[31]	RCT	16	Yes	122	CLON +/-MPH MPH PBO	7 to 12	Any	NR	Yes	NR	NR	Yes	Mod

Shang, 2015[32]	RCT	24	No	160	ATX OROS-MPH	7 to 16 Drug naïve	Any	NR	Yes	NR	NR	Yes	Mod
Snircova, 2016[33]	RCT	8	No	78	ATX XR-MPH	5 to 16 Drug naïve	CM	None	Yes	NR	NR	NR	High
Su, 2016[34]	RCT	8	No	262	ATX OROS-MPH	6 to 16 Drug naïve	Any	NR	Yes	NR	NR	Yes	High
Tas Torun, 2020[35]	RCT	18	No	140	ATX OROS-MPH	6 to 12	Any	NR	Yes	NR	NR	Yes	High
Wang, 2007[36]	RCT	8	No	330	ATX MPH	6 to 16	Any	NR	Yes	NR	NR	Yes	High
Zhu, 2017[37]	RCT	8	No	104	ATX MPH	6 to 14	Any	NR	Yes	NR	NR	Yes	Mod
Tourette's Syndrome Study Group, 2002[38]	RCT	16	Yes	136	CLON MPH MPH + CLON PBO	6 to 14	Any	Tourette's	Yes	NR	NR	Yes	High
Non-stimulant vs Non-stimulant													
Hervas, 2014[39]	RCT	10 to 13	Yes	338	ATX GXR PBO	6 to 17	Any	ODD	Yes	NR	NR	Yes	Mod
Non-stimulant vs Placebo													
Nasser, 2021[40]	RCT	8	Yes	313	VLX	6 to 11	Any	None	Yes	NR	Yes	Yes	High
Johnson, 2017[41]	RCT	8	Yes	222	VLX	6 to 12	Any	None	Yes	NR	NR	Yes	High

Note: Table includes those studies of 8 weeks or longer and applicable new studies which were assessed with GRADE criteria.
Abbreviations. ADHD: attention deficit/hyperactivity disorder; AE: adverse event; ER: extended release; IR: immediate release; LA: long acting; LDX: lisdexamfetamine; MPH: methylphenidate; NR: not reported; ODD: oppositional deviance disorder; OROS: osmotic-release oral system; PBO: placebo; RCT: randomized controlled trial; SAE: serious adverse event; XR: extended release

Stimulant vs. Nonstimulant

A total of 20 RCTs (N=4,597) were identified that compared a stimulant to a non-stimulant and the studies ranged in length from 2 to 26 weeks.[1] Eighteen studies involved children and adolescents with a mean range of 9 to 11 years while only 2 studies involved adults (mean range of 31 to 41 years).[1] Twelve studies were rated as high risk of bias due to poor reporting of methods, short treatment and follow-up periods, and industry involvement while 8 studies were rated as moderate risk of bias.[1] Only 13 of the 20 studies met the minimum 8-week treatment requirement.[1,26-38] The MCIDs were not well defined for various outcomes. In children and adolescents, one 9-week trial (N=267) reported that lisdexamfetamine treatment resulted in statistically significant reductions of ADHD

symptoms compared to atomoxetine based on assessments with the ADHD-RS-IV (p<0.001) and the WFIRS (p = .05).[1,27] In participants who received a combination of methylphenidate and clonidine, there was a statistically significant reduction in ADHD symptoms compared with those who received clonidine alone based on the Conners Abbreviated Symptoms Questionnaire [ASQ] Teacher version (p = 0.03).[1,31] No differences were found in the reduction of ADHD symptoms among standard formulations of methylphenidate and atomoxetine or guanfacine XR.[1] There was low quality evidence of no difference in SAEs based on 3 RCTs (N=493) with methylphenidate versus clonidine, lisdexamfetamine versus atomoxetine, or methylphenidate versus atomoxetine.[1] Ten trials (N=1,716) of 8 weeks or longer reported discontinuations due to adverse events (AEs). In 4 of the studies (N=729) with standard methylphenidate versus atomoxetine, there were 49 total discontinuations reported.[1] Low quality evidence from 3 of these RCTs reported 8% discontinuations due to AEs for atomoxetine (31/381) compared to 6% for standard methylphenidate or immediate-release methylphenidate (14/246).[1,28,29,36] Similar results were observed in a trial of atomoxetine versus lisdexamfetamine.[1,27] Although specific frequencies of individual AEs were not consistently reported, the most common AEs that led to discontinuation highlighted by the authors are listed in **Table 6**.

Table 6: Reported Adverse Events Leading to Discontinuation for Atomoxetine versus Lisdexamfetamine or Methylphenidate[1,27-29,36]

	Atomoxetine (N = 518)	**Lisdexamfetamine** (N = 133)	**Methylphenidate** (N = 243)
Total Discontinuations (%)	41 (8%)	8 (6%)	14 (6%)
Daytime drowsiness/somnolence	X	X	
Decreased appetite /decreased weight/anorexia	X	X	X
Nausea/abdominal pain	X	X	X
Tachycardia/palpitations/chest pain	X		X
Headache	X		X
Agitation and/or irritability	X	X	
Other	skin-related issues	tic	mania

Nonstimulant vs. Another Nonstimulant

One 13-week RCT (N=338) compared a non-stimulant to another non-stimulant.[1,39] The study involved children and adolescents with a range of 6 to 17 years and 56% of participants also had a comorbid diagnosis of ODD.[1,39] The study was rated as moderate risk of bias due to poor reporting of methods, short treatment and follow-up periods, and industry involvement.[1,39] The MCIDs were not well defined for various outcomes. The study reported that guanfacine XR treatment resulted in statistically significant reductions of ADHD symptoms compared to atomoxetine based on assessments with the ADHD-RS-IV (LSMD: −5.1 (95% CI, −8.2 to −2.0; p=0.001).[1,39] In patients treated with guanfacine XR compared to atomoxetine, there was low quality evidence that found a slightly higher proportion of patients with discontinuations due to AEs (7.8% vs 4.5%, respectively).[1,39] In the same trial, serious AEs were rare with 2 (1.7%) reported in guanfacine XR-treated patients and none in those treated with atomoxetine (low quality evidence).[1,39]

Recently Approved Nonstimulant vs. Placebo

Two 8-week RCTs (N=535) compared a newer nonstimulant to placebo.[1,40,41] The studies included children and adolescents between 6 and 12 years of age without comorbidities.[1,40,41] The studies reported viloxazine treatment resulted in a statistically significant reduction in ADHD symptoms at doses from 200 mg to 400 mg per day compared to placebo as measured across multiple instruments (LS mean change ADHD-RS 5 = -17.5 to -17.6, p<0.05; LS mean total score Clinical Global Impressions-Illness (CGI-I) = 2.6 for both 200 mg and 400 mg doses, with p=0.003 and <0.01, respectively; ADHD-RS-IV, total score, LS mean change: 200 mg, 300 mg = -18.4 to -18.6 (p=0.03) and 400 mg = -19.0 (p= 0.02).[1,40,41] A dose-response effect was reported as larger reductions of symptoms were noted at the 200 mg and 400 mg doses.[1,40,41] No significant differences were found in symptom improvement with any other clinical instrument (e.g. Conners PS or WFIRS-Parent).[1,40,41] **Table 7** summarizes the participant characteristics and outcomes studied for viloxazine.

Table 7: Participant Characteristics and Outcomes for RCTs: Recently Approved Nonstimulant vs. Placebo for ADHD Treatment[1,40,41]

First Author, Year Duration + Follow-up N Randomized n of N Reported	Participant Characteristics	Mean Dose Symptom Response	AEs Quality of Life
Nasser, 2021[40] 8 weeks N = 313 • VLX: 204 of 301 PBO: 97 of 301	Participant characteristics, n of 301 (%) • Age, mean years (SD): 8.5 (1.7) • Male: 191 (63.4) • Race or ethnicity AI/AN: 3 (1.0) Asian: 1 (0.3) Black: 125 (41.5) Multiple: 13 (4.3) White: 159 (52.8) • ADHD presentation, NR Comorbidities, NR	Mean dose, NR **Symptom Response, vs. PBO** ADHD-RS−5, total score LS mean change (SE) • 200 mg, −17.6 (1.4); *P* <0.05 • 400 mg, −17.5 (1.5); *P* < 0.05 CGI-I, total score, LS mean (SE) • 200 mg, 2.6 (0.12); *P* = 0.003 • 400 mg, 2.6 (0.12); *P* < 0.01 Conners 3-PS, composite score, difference of LS means (SE) • 200 mg, −3.8 (1.39; 95% CI, −6.5 to −1.1); *P* = .006 • 400 mg, no difference WFIRS-Parent, no difference	AEs • AEs: VLX, 114 of 207 (55.1) vs. PBO, 47 of 103 (45.6) • SAEs: VLX, 7 of 207 (3.4) vs. PBO, 4 of 103 (3.9) • Discontinuation: VLX, 10 of 207 (4.8) vs. PBO, 3 of 107 (2.9) **Quality of Life, vs. PBO** PSI-4-SF, total score 200 mg, no difference 400 mg, LS mean (SD): −11.6 (2.01); *P* = 0.04
Johnson, 2017[41] weeks N = 222 • VLX: 182 of 206 PBO: 24 of 206	Participant characteristics, n of 206 (%) • Age, median years (range) 9.0 (6 to 12) • Male: 138 (67.0) Race or ethnicity AI/AN: 2 (1.0) Asian: 2 (1.0) Black/AA: 79 (38.3) Multiple: 6 (2.9) White: 117 (56.8) ADHD presentation, NR	Mean dose, NR **Symptom response, vs. PBO** ADHD-RS-IV, total score, LS mean change: • 100 mg, no difference • 200 mg, −18.4 (*P* = 0.03) • 300 mg, −18.6 (*P* = 0.03) • 400 mg, −19.0 (*P* = 0.02)	AEs • Any AE: VLX, 132 of 182 (72.5) vs. PBO, 11 of 24 (45.8) • SAEs: 0 for all groups Discontinuation: VLX, 13 of 182 (7.1) vs. PBO, 0

	Comorbidities, NR		

Abbreviations. AA: African American; ADHD: attention deficit/hyperactivity disorder; ADHD-RS-IV: ADHD Rating Scale IV; ADHD-SRS: ADHD Self-Rating Scale; AE: adverse event; AI: American Indian; AN: Native American; CGI-S: Clinical Global Impressions-Improvement; CI: confidence interval; C(3)PRS: Conners Parents Rating Scale; LS: least square; NR: not reported; PBO: placebo; PSI(4)SF: Parenting Stress Index, Short Form; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation; VLX: viloxazine; WFIRS: Weiss Functional Impairment Rating Scale

Limitations

There were several limitations conveyed by the DERP review authors. Roughly 1/3 of the trials (25/70) were RCTs between 1 and 7 weeks in length, however, guidelines including those from the American Academy of Pediatrics (AAP) recommend a minimum of 6 weeks of therapy for adequate assessment of therapy. A similar proportion of included RCTs (26/70) were crossover design with 1 to 3-week phases and no washout period. In addition, many of the trials titrated the medication doses over several weeks so the target or optimal dose was only maintained for 1 to 2 weeks. There were numerous cases where performance was measured in a single day after a short treatment period which may have resulted in uncertainty of evidence. Lastly, most of the studies overtly excluded patients with comorbidities.

References:

1. Robalino S, Vintro A, Harrod C. Pharmacological therapies for attention deficit/hyperactivity disorder. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2021.
2. OSU Drug Use Research & Management Program. Drug Literature Scan: Attention Deficit Hyperactivity Disorder. August 2020. http://www.orpdl.org/durm/meetings/meetingdocs/2020_08_06/archives/2020_08_06_ADHD_LitScan.pdf. Accessed April 1, 2022.
3. Centers for Disease Control and Prevention. Attention-deficit/hyperactivity disorder (ADHD): data and statistics. 2020; https://www.cdc.gov/ncbddd/adhd/data.html. Accessed March 12, 2022.
4. Danielson ML, Bitsko RH, Ghandour RM, et al. Prevalence of Parent-Reported ADHD Diagnosis and Associated Treatment Among U.S. Children and Adolescents. *Journal of Clinical Child & Adolescent Psychology*, 2016; 47:2, 199-212
5. American Psychiatric Association. Neurodevelopmental Disorders. In: Diagnostic and Statistical Manual of Mental Disorders, 5th edition. Arlington, VA., American Psychiatric Association, 2013.
6. 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 [published correction appears in *Pediatrics*. 2020 Mar;145(3):]. *Pediatrics*. 2019;144(4):e20192528.
7. Felt BT, Biermann B, Christner JG, Kochhar P, Harrison RV. Diagnosis and management of ADHD in children. *Am Fam Physician.* 2014 Oct 1;90(7):456-64
8. Feldman HM, Reiff MI. Clinical practice. Attention deficit-hyperactivity disorder in children and adolescents. *N Engl J Med.* 2014 Feb 27;370(9):838-46
9. Ryan-Krause P; American Psychiatric Association. Attention deficit hyperactivity disorder: part I. *J Pediatr Health Care*. 2010;24(3):194-198.
10. Gnanavel S, Sharma P, Kaushal P, Hussain S. Attention deficit hyperactivity disorder and comorbidity: a review of literature. *World J Clin Cases.* 2019;7(17):2420-2426.
11. Katzman MA, Bilkey TS, Chokka PR, Fallu A, Klassen LJ. Adult ADHD and comorbid disorders: clinical implications of a dimensional approach. *BMC Psychiatry*. 2017;17(1):302.
12. National Institute for Health and Care Excellence. Attention deficit hyperactivity disorder: diagnosis and management (NG87). 2018. nice.org.uk/guidance/ng87. Accessed March 15, 2022.
13. Wong AWWA, Landes SD. Expanding Understanding of Racial-Ethnic Differences in ADHD Prevalence Rates among Children to Include Asians and Alaskan Natives/American Indians. *Journal of Attention Disorders*. 2022;26(5):747-754.

14. Coker TR, Elliott MN, Toomey SL, et al. Racial and ethnic disparities in ADHD diagnosis and treatment. *Pediatrics.* 2016;138(3).
15. Davis DW, Jawad K, Feygin Y, et al. Disparities in ADHD diagnosis and treatment by race/ethnicity in youth receiving Kentucky Medicaid in 2017. *Ethn Dis.* 2021;31(1):67-76.
16. Goodman D, Faraone SV, Adler LA, et al. Interpreting ADHD Rating Scale Scores: Linking ADHD Rating Scale Scores and CGI Levels in Two Randomized Controlled Trials of Lisdexamfetamine Dimesylate in ADHD. *Primary Psychiatry*. 2010; 17(3):44-52.
17. Markowitz JT, Oberdhan D, Ciesluk A, Rams A, Wigal SB. Review of Clinical Outcome Assessments in Pediatric Attention-Deficit/Hyperactivity Disorder. *Neuropsychiatr Dis Treat*. 2020;16:1619-1643.
18. Thompson T, Lloyd A, Joseph A, Weiss M. The Weiss Functional Impairment Rating Scale-Parent Form for assessing ADHD: evaluating diagnostic accuracy and determining optimal thresholds using ROC analysis. *Quality of life research: an international journal of quality of life aspects of treatment, care and rehabilitation.* 2017;26(7):1879-1885.
19. ClinicalTrials.gov https://clinicaltrials.gov/ct2/show/NCT00697515. Accessed March 15, 2022.
20. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT00904670. Accessed March 15, 2022.
21. Azstarys™ oral capsules, serdexmethylphenidate dexmethylphenidate oral capsules. Corium Inc, Grand Rapids, MI, 2021.
22. Qelbree™ oral extended-release capsules, viloxazine oral extended-release capsules. Supernus Pharmaceuticals Inc, Rockville, MD, 2021.
23. Cikili Uytun M, Çetin FH, Babadağı Z. Parent-reported social problems and clinician evaluated adverse effects may be differentially affected by differing extended release methylphenidate formulations: a prospective, naturalistic study from Turkey. Psychiatr Clin Psychopharmacol. 2019;29(4):722-729.
24. Steele M, Weiss M, Swanson J, Wang J, Prinzo RS, Binder CE. A randomized, controlled effectiveness trial of OROS-methylphenidate compared to usual care with immediaterelease methylphenidate in attention deficit-hyperactivity disorder. *Can J Clin Pharmacol.* 2006;13(1):e50-62.
25. Newcorn JH, Nagy P, Childress AC, Frick G, Yan B, Pliszka S. Randomized, double-blind, placebo-controlled acute comparator trials of lisdexamfetamine and extended-release methylphenidate in adolescents with attention-deficit/hyperactivity disorder. *CNS Drugs.* 2017;31(11):999-1014.
26. ÇEtİN FH, TaŞ Torun Y, IŞIk Taner Y. Atomoxetine versus OROS methylphenidate in attention deficit hyperactivity disorder: a six-month follow up study for efficacy and adverse effects. *Turk Klin J Med Sci.* 2015;35(2):88-96.
27. Dittmann RW, Cardo E, Nagy P, et al. Efficacy and safety of lisdexamfetamine dimesylate and atomoxetine in the treatment of attention-deficit/hyperactivity disorder: a head-tohead, randomized, double-blind, phase IIIb study. *CNS Drugs.* 2013;27(12):1081-1092.
28. Garg J, Arun P, Chavan BS. Comparative short term efficacy and tolerability of methylphenidate and atomoxetine in attention deficit hyperactivity disorder. *Indian Pediatr.* 2014;51(7):550-554.
29. Kratochvil CJ, Heiligenstein JH, Dittmann R, et al. Atomoxetine and methylphenidate treatment in children with ADHD: a prospective, randomized, open-label trial. *J Am Acad Child Adolesc Psychiatry*. 2002;41(7):776-784.
30. Ni HC, Hwang Gu SL, Lin HY, et al. Atomoxetine could improve intra-individual variability in drug-naive adults with attention-deficit/hyperactivity disorder comparably with methylphenidate: a head-to-head randomized clinical trial. *J Psychopharmacol.* 2016;30(5):459-467.
31. Palumbo DR, Sallee FR, Pelham WE, Jr., et al. Clonidine for attention-deficit/hyperactivity disorder: I. Efficacy and tolerability outcomes. J *Am Acad Child Adolesc Psychiatry*. 2008;47(2):180-188.
32. Shang CY, Pan YL, Lin HY, Huang LW, Gau SS. An open-label, randomized trial of methylphenidate and atomoxetine treatment in children with attentiondeficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol.* 2015;25(7):566-573.
33. Snircova E, Marcincakova-Husarova V, Hrtanek I, Kulhan T, Ondrejka I, Nosalova G. Anxiety reduction on atomoxetine and methylphenidate medication in children with ADHD. *Pediatr Int*. 2016;58(6):476-481.

34. Su Y, Yang L, Stein MA, Cao Q, Wang Y. Osmotic release oral system methylphenidate versus atomoxetine for the treatment of attention-deficit/hyperactivity disorder in Chinese youth: 8-week comparative efficacy and 1-year follow-up. *J Child Adolesc Psychopharmacol.* 2016;26(4):362-371.
35. Tas Torun Y, Isik Taner Y, Guney E, Iseri E. Osmotic release oral system-methylphenidate hydrochloride (OROS-MPH) versus atomoxetine on executive function improvement and clinical effectiveness in ADHD: a randomized controlled trial. Appl Neuropsychol Child. 2020:1-12.
36. Wang Y, Zheng Y, Du Y, et al. Atomoxetine versus methylphenidate in paediatric outpatients with attention deficit hyperactivity disorder: a randomized, double-blind comparison trial. *Aust N Z J Psychiatry.* 2007;41(3):222-230.
37. Zhu X, Sun X, Zhang Y, Liu K, Zhao L. A randomized parallel-controlled study of curative effect and safety of atomoxetine and methylphenidate in treatment of ADHD in children. *Int J Clin Exp Med*. 2017;10(6):9576-9582.
38. Tourette's Syndrome Study, Group. Treatment of ADHD in children with tics: a randomized controlled trial. *Neurology.* 2002;58(4):527-536.
39. Hervas A, Huss M, Johnson M, et al. Efficacy and safety of extended-release guanfacine hydrochloride in children and adolescents with attention-deficit/hyperactivity disorder: a randomized, controlled, phase III trial. *Eur Neuropsychopharmacol.* 2014;24(12):18611872.
40. Nasser A, Liranso T, Adewole T, et al. Once-daily SPN-812 200 and 400 mg in the treatment of ADHD in school-aged children: a phase III randomized, controlled trial. *Clin Ther*. 2021;43(4):684-700.
41. Johnson JK, Liranso T, Saylor K, et al. A phase II double-blind, placebo-controlled, efficacy and safety study of SPN-812 (extended-release viloxazine) in children with ADHD. *J Atten Disord.* 2020;24(2):348-358.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL	Carveout
atomoxetine HCl	ATOMOXETINE HCL	CAPSULE	Y	Y
atomoxetine HCl	STRATTERA	CAPSULE	Y	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	
lisdexamfetamine dimesylate	VYVANSE	TAB CHEW	Y	
methylphenidate	DAYTRANA	PATCH TD24	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	Y
clonidine HCl	KAPVAY	TAB ER 12H	V	Y
guanfacine HCl	GUANFACINE HCL ER	TAB ER 24H	V	Y
guanfacine HCl	INTUNIV	TAB ER 24H	V	Y
viloxazine HCl	QELBREE	CAP ER 24H	V	Y
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
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	METHYLPHENIDATE ER	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
serdexmethylphen/dexmethylphen	AZSTARYS	CAPSULE	N

Appendix 2: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use AZSTARYS safely and effectively. See full prescribing information for AZSTARYS.

AZSTARYS (serdexmethylphenidate and dexmethylphenidate) capsules, for oral use, CII [controlled substance schedule pending for serdexmethylphenidate]
Initial U.S. Approval: [pending controlled substance scheduling]

WARNING: ABUSE AND DEPENDENCE
See full prescribing information for complete boxed warning.

- **CNS stimulants, including AZSTARYS, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence (5.1, 9.2, 9.3)**
- **Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy (5.1, 9.2)**

----------INDICATIONS AND USAGE----------
AZSTARYS is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years of age and older. (1)

---------- DOSAGE AND ADMINISTRATION ----------
- Pediatric Patients 6 to 12 years: Recommended starting dosage is 39.2 mg/7.8 mg orally once daily in the morning. Dosage may be increased to 52.3 mg/10.4 mg daily or decreased to 26.1 mg/5.2 mg daily after one week. Maximum recommended dosage is 52.3 mg/10.4 mg once daily. (2.2)
- Adults and Pediatric Patients 13 to 17 years: Recommended starting dosage is 39.2 mg/7.8 mg orally once daily in the morning. Increase the dosage after one week to 52.3 mg/10.4 mg once daily. (2.2)
- Administer with or without food. (2.3)
- Swallow capsules whole or open and sprinkle onto applesauce or add to water. (2.3)
- To avoid substitution errors and overdosage, do not substitute for other methylphenidate products on a milligram-per-milligram basis. (2.4)

---------- DOSAGE FORMS AND STRENGTHS ----------
- Capsules (serdexmethylphenidate/dexmethylphenidate): 26.1 mg/5.2 mg, 39.2 mg/7.8 mg, 52.3 mg/10.4 mg. (3)

----------CONTRAINDICATIONS----------
- Known hypersensitivity to serdexmethylphenidate, methylphenidate, or product components. (4)
- Concurrent treatment with a monoamine oxidase inhibitor (MAOI), or use of an MAOI within the preceding 14 days. (4)

---------- WARNINGS AND PRECAUTIONS ----------
- *Serious Cardiovascular Reactions*: Sudden death has been reported in association with CNS stimulant treatment at recommended doses in pediatric patients with structural cardiac abnormalities or other serious heart problems. In adults, sudden death, stroke, and myocardial infarction have been reported. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmias, or coronary artery disease. (5.2)
- *Blood Pressure and Heart Rate Increases*: Monitor blood pressure and pulse. Consider the benefits and risks in patients for whom an increase in blood pressure or heart rate would be problematic. (5.3)
- *Psychiatric Adverse Reactions*: Use of stimulants may cause psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychiatric illness. Evaluate for bipolar disorder prior to AZSTARYS use. (5.4)
- *Priapism*: Cases of painful and prolonged penile erections and priapism have been reported with methylphenidate products. Immediate medical attention should be sought if signs or symptoms of prolonged penile erections or priapism are observed. (5.5)
- *Peripheral Vasculopathy, including Raynaud's Phenomenon*: Stimulants used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment with ADHD stimulants. (5.6)
- *Long-Term Suppression of Growth*: Monitor height and weight at appropriate intervals in pediatric patients. (5.7)

---------- ADVERSE REACTIONS ----------
Based on accumulated data from other methylphenidate products, the most common (>5% and twice the rate of placebo) adverse reactions are appetite decreased, insomnia, nausea, vomiting, dyspepsia, abdominal pain, weight decreased, anxiety, dizziness, irritability, affect lability, tachycardia, and blood pressure increased. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Corium, Inc. at 1-616-656-4563 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Antihypertensive Drugs: Monitor blood pressure. Adjust dosage of antihypertensive drug as needed. (7.1)
- Halogenated Anesthetics: Avoid use of AZSTARYS on the day of surgery if halogenated anesthetics will be used. (7.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 3/2021

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use QELBREE™ safely and effectively. See full prescribing information for QELBREE™.

QELBREE™ (viloxazine extended-release capsules), for oral use
Initial U.S. Approval: 2021

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning.

In clinical trials, higher rates of suicidal thoughts and behavior were reported in pediatric patients treated with Qelbree than in patients treated with placebo. Closely monitor for worsening and emergence of suicidal thoughts and behaviors (5.1).

----------INDICATIONS AND USAGE----------

Qelbree is a selective norepinephrine reuptake inhibitor indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in pediatric patients 6 to 17 years of age (1)

----------DOSAGE AND ADMINISTRATION----------

- *Pediatric patients 6 to 11 years of age*: Recommended starting dosage is 100 mg once daily. May titrate in increments of 100 mg weekly to the maximum recommended dosage of 400 mg once daily (2.2)
- *Pediatric patients 12 to 17 years of age*: Recommended starting dosage is 200 mg once daily. May titrate after 1 week, by an increment of 200mg, to the maximum recommended dosage of 400 mg once daily (2.2)
- Capsules may be swallowed whole or opened and the entire contents sprinkled onto applesauce (2.3)
- Severe Renal Impairment: Initial dosage is 100 mg once daily. Titrate in weekly increments of 50 mg to 100 mg to a maximum recommended dosage of 200 mg once daily (2.4, 8.6)

----------DOSAGE FORMS AND STRENGTHS----------

Extended-release capsules: 100 mg, 150 mg and 200 mg (3)

----------CONTRAINDICATIONS----------

- Concomitant administration of monoamine oxidase inhibitors (MAOI), or dosing within 14 days after discontinuing an MAOI (4, 7.1)
- Concomitant administration of sensitive CYP1A2 substrates or CYP1A2 substrates with a narrow therapeutic range (4, 7.1)

----------WARNINGS AND PRECAUTIONS----------

- Blood Pressure and Heart Rate Increases: Assess heart rate and blood pressure prior to initiating treatment, following increases in dosage, and periodically while on therapy (5.2)
- Activation of Mania or Hypomania: Screen patients for bipolar disorder (5.3)
- Somnolence and Fatigue: Advise patients to use caution when driving or operating hazardous machinery due to potential somnolence (including sedation and lethargy) and fatigue (5.4)

----------ADVERSE REACTIONS----------

Most commonly observed adverse reactions (≥5% and at least twice the rate of placebo) were: somnolence, decreased appetite, fatigue, nausea, vomiting, insomnia, and irritability (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Supernus Pharmaceuticals at 1-866-398-0833 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Moderate sensitive CYP1A2 substrates: Not recommended for coadministration with Qelbree. Dose reduction may be warranted (7.1)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: May cause maternal harm; discontinue when pregnancy is recognized (8.1)
- Hepatic Impairment: Not recommended (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised:4/2021

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**	**Viloxazine**
ADHD	**Age ≥6 years**	**Age ≥3 years**	**Age ≥6 years**	**Children age 6-17 years only**	**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**	**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 ER	3		20 mg
CNS Stimulant	amphetamine/dextroamphetamine salts IR	3		40 mg
CNS Stimulant	amphetamine/dextroamphetamine salts ER	6		60 mg
CNS Stimulant	amphetamine/dextroamphetamine ER (Mydayis®)	13		25 mg for children 13-17 years 50 mg for adults 18-55 years
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	4		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
CNS Stimulant	serdexmethylphenidate/dexmethylphenidate	6		52.3 mg/ 10.4 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
Non-Stimulant	viloxazine	6	17	400 mg

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

Table 3. Standard Combination Therapy for ADHD

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

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

* As recommended by the American Academy of Pediatrics 2019 Guidelines 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).

**As identified by Drug Class Review: 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:** 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
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

Approval Criteria		
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: *6/22 (DE); 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: *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*