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Drug Class Literature Scan: ADHD Drugs

Date of Review: October 2022

Date of Last Review: June 2022
Literature Search: 05/01/20 – 07/05/22

Plain Language Summary: Should the Oregon Health Authority change the current policy for medicines that treat attention deficit/hyperactivity disorder (ADHD) based on new evidence?

- The Food and Drug Administration (FDA) has already approved many medicines to treat attention deficit/hyperactivity disorder (ADHD). Since the last time the Pharmacy and Therapetuics Committee reviewed these medicines, the FDA has approved 2 new medicines for ADHD and approved 2 older medicines for new age groups. Evidence does not show that these new medicines are any better at improving ADHD symptoms than older medicines.
- The FDA has updated safety information for ADHD medicines since the last review:
  - Strattera™ (atomoxetine) now has a stronger warning for risk of worsening behaviors.
  - All amphetamine products may reduce blood supply to the gut.
- The Drug Use Research Management program does not recommend any policy changes to preferred products based on this new evidence.

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

Conclusions:

- No new high-quality systematic reviews or guidelines were published since the last ADHD class update.
- The Food and Drug Administration (FDA) approved a new formulation of amphetamine extended-release (ER) tablets (Dyanavel XR™) for the treatment of ADHD in patients 6 years of age and older.[1] Prior to this approval, Dynavel XR™ was only available as a 2.5 mg/mL ER oral suspension.[1]
- The FDA approved Xelstrym™ (dextroamphetamine transdermal system) for the treatment of ADHD in patients 6 years of age and older.[2] This is the first amphetamine-based medication formulated as a transdermal product for once daily use.[2-4]
- Evekeo ODT™ (amphetamine sulfate) received expanded FDA approval for the treatment of ADHD in children 3 to 5 years of age.[5] Previously it was approved for patients 6 to 17 years old.[5]
- Qelbree™ (viloxazine ER capsules) received expanded FDA approval for the treatment of ADHD in patients 18 years of age and older.[6] Previously it was approved for pediatric patients 6 to 17 years of age. [6]
- Two new FDA safety alerts have been identified since the last review. The medication guide labeling was updated to reflect a stronger warning for Strattera™ (atomoxetine) use and its association between risks of aggression and manic symptoms in all age groups (new psychotic/manic symptoms), increased risk in bipolar patients, and risk of aggressive behavior and hostility.[8] There was also an update to the labeling for all amphetamine products to include intestinal ischemia among documented adverse reactions.[9]

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Recommendations:

- Current evidence does not support changes to the Preferred Drug List (PDL).
- Revise prior authorization (PA) criteria to reflect maximum age and dose limits as specified in product labeling or supported compendia (see **Appendix 6**). To avoid disruption in care, patients initiated on an ADHD medication as a child should be excluded from PA if they age into a maximum age limit.
- After review comparative costs in the executive session, viloxazine (QELBREE) was made a preferred product.

Summary of Prior Reviews and Current Policy

Prior reviews have found evidence to support that stimulant and non-stimulant pharmacologic agents are beneficial in ADHD treatment compared to placebo. Comparisons between different formulations (immediate-release [IR] vs. ER) within this class have not demonstrated consistent differences. In addition, there is insufficient evidence to directly compare differences in efficacy or safety outcomes for different ADHD drugs in children or adults. The most frequent adverse effects from stimulants are appetite loss, abdominal pain, headache and sleep disturbance; only low-quality evidence suggests any differences in harms between various ADHD agents. There is insufficient evidence that one ADHD drug is more effective or associated with fewer adverse events in specific subgroups of patients based on demographics (age, racial or ethnic groups and gender), other medications, or co-morbidities.

To ensure safe and appropriate use within the Oregon Health Plan (OHP) Fee-for-Service (FFS) population, all medications within the ADHD class have limits based on patient age and quantity prescribed. Safety edits are in place to ensure that medication use reflects best practices. Any request for a non-preferred agent or for an agent that exceeds the age or quantity limit requires consultation with a specialist prescriber such as a psychiatrist or other mental health specialist. Preferred agents within the ADHD class are listed in **Appendix 1**. Note that three agents in **Appendix 1** are part of the mental health carve-out and are exempt from traditional PA requirements.

Methods:

A Medline literature search for new systematic reviews, evidence-based guidelines, and randomized controlled trials (RCTs) assessing clinically relevant outcomes was conducted. 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.

A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

New Systematic Reviews:

No new high-quality systematic reviews were identified. Ten systematic reviews were excluded due to poor quality, wrong study design of included trials, comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[10-19]

New Guidelines:

No new high-quality guidelines were identified.

Additional Guidelines for Clinical Context:

Clinical Practice Guideline for the Assessment and Treatment of Children and Adolescents with Complex Attention-Deficit/Hyperactivity Disorder

The Society for Developmental and Behavioral Pediatrics (SDBP) created guidelines to assist primary care in the integrated interprofessional management of children and adolescents with complex ADHD, defined by the presence of coexisting conditions, moderate to severe functional impairment, diagnostic uncertainty, or inadequate response to treatment.[20] These guidelines were intended to complement general practice guidelines for ADHD management already published by the American Academy of Pediatrics (AAP).[20] The guideline did not report whether a systematic search of the literature had been performed but noted that literature was assembled and examined based on previously published evidence reviews and expert opinion. Each published study was organized into an evidence table under a key action statement (KAS) then evaluated/graded by 2 volunteer reviewers associated with SDBP and ADHD guideline panels.[20] Authors reported that evidence was graded based on the similar methods described in the 2011 AAP ADHD practice guideline, where classification was defined by level of policy (strong recommendation (S), recommendation (R), or option (O)) and based on the following levels of aggregate evidence quality: A (systematic review of RCTs), B (RCTs or observational studies with overwhelmingly consistent evidence), C (observational studies), and D (case reports or expert opinion).[20] Harm was assessed by a clear majority of benefit or a relative balance of benefits and harms.[20] There was also a category for recommendation under exceptional situations (X) in which evidence could not be obtained but clear benefits or harm are evident.[20] Treatment algorithms were based on consensus expert opinion of the Panel. There was no risk of bias assessment used as inclusion criteria for publications used for guideline development.[20] Other limitations to the guideline include the absence of the following: clearly defined target users, criteria specifics for evidence selection, diversity in representation from professional groups, patient and public input, external review by experts in the field, unambiguous and specific recommendations, and discussion on resource implications/barriers of recommendations.[20] Therefore, guideline recommendations for pharmaceutical management will be provided for clinical context but not relied upon for decisions regarding the PDL.[20]

The following description summarizes each of the KAS presented in the guideline[20]:

KAS 1: The clinician with specialized training or expertise should initiate a comprehensive assessment and develop an interprofessional, multimodal treatment plan for any child or adolescent through age 18 years with suspected or diagnosed complex attention-deficit/hyperactivity disorder (ADHD) upon referral from a primary care clinician.
(Strong Recommendation (S); Evidence Level B)

KAS 2: In the evaluation of a child or adolescent with complex ADHD, the clinician should verify any previous diagnoses and assess for coexisting conditions, employing an evidence-based approach that is developmentally appropriate, culturally sensitive, and inclusive of data from multiple settings and sources (home, school, community). The evaluation should include an appropriate, comprehensive medical history and physical examination, and psychological assessment based on the child's presenting problems and their severity, functional impairments, cognitive/developmental level, and the judgment of the treating clinician.
(Strong Recommendation (S); Evidence Level B)

KAS 3: Psychoeducation about ADHD and its coexisting conditions and evidence-based behavioral and educational interventions are foundational for the treatment of complex ADHD and should be implemented at the outset of treatment whenever possible. Evidence-based behavioral and educational interventions (e.g., behavioral parent training, behavioral classroom management, behavioral peer interventions, and, for older children, organizational skills training) should be provided to all children and adolescents with complex ADHD. These approaches address key functional domains (behavioral, educational, social) in home, school, and peer settings that are associated with long-term outcomes.
(Strong Recommendation (S); Evidence Level B)

KAS 4: Treatment of complex ADHD should include evidence-based approaches that address ADHD and account for coexisting conditions while respecting family background and preferences. It is often necessary to combine these approaches with pharmacological treatments. Treatment should focus on areas of functional impairment, not just symptom reduction, by incorporating developmentally appropriate strategies for self-management, skill building, and prevention of adverse outcomes (e.g., substance use, conduct problems, depression/anxiety, suicidal ideation, educational failure).
(Recommendation (R); Evidence Level C-B)

KAS 5: Treatment of complex ADHD should include ongoing, scheduled monitoring of patients throughout the lifespan, commensurate with the individual patient's needs and profile, with particular emphasis on preparing for key developmental transitions (preschool to school, elementary to middle school, middle to high school, and high school to postsecondary education or employment).
(Strong Recommendation (S); Evidence Level B)

New Formulations:
In November 2021, the FDA approved a new formulation of Dyanavel XR® (amphetamine ER; Schedule II) tablets for the treatment of ADHD in patients 6 years of age and older.[1] Tablets are supplied 5 mg, 10 mg, 15 mg, and 20 mg strengths and taken once daily.[1] The FDA initially approved Dynavel XR® as a 2.5 mg/mL ER oral suspension in 2015.[1] Tablet and oral suspension formulations can be converted on a mg-per-mg basis; however, it should not be substituted for other amphetamine products on a mg-per-mg basis because of different amphetamine salt compositions and pharmacokinetic profiles.[1]

In March 2022, the FDA approved Xelstrym™ (dextroamphetamine transdermal system; Schedule II) for the treatment of ADHD in patients 6 years of age and older.[2] This is the first amphetamine-based transdermal product for once daily use.[2,3] Xelstrym™ is available as 4.5 mg, 9 mg, 13.5 mg, and 18 mg patches to be worn during a 9-hour period.[2] Xelstrym™ should not be substituted for other amphetamine products on a mg-per-mg basis, because of different amphetamine salt compositions and pharmacokinetic profiles.[2,3]

Approval of Xelstrym™ was based on a single phase 2, multi-center, modified analog classroom study in 106 pediatric patients aged 6 to 17 years with ADHD.[2-4] The study had a 4-week screening period followed by a 5-week, open-label, dose-optimization phase and a 2-week double-blind, randomized, placebo-controlled crossover treatment period with weekly classroom assessments and telephone-based safety follow-up 7-10 days after last dose of the study drug.[2-4] Patients were randomized by interactive response system in a 1:1 ratio to either their optimized dose of Xelstrym™ or placebo.[2-4] Patients at baseline must have had an ADHD-Rating Sacle (ADHD-RS-IV) total score 90% or greater of the general population of children by age and gender.[2-4] The ADHD-RS is an 18-item scale (range 0 to 54 points) that assesses symptoms of inattentiveness, hyperactivity, and impulsivity with higher scores indicative of more severe symptoms.[21] Patients were excluded if they had hypertension or a body mass index (BMI) outside of 95th percentile for age/gender, cardiovascular disease, history of substance use disorder (SUD), seizure history, other psychiatric disorder, or were a known non-responder to amphetamine treatment.[3,4] The demographics of the study participants were as follows: mean age 10.5 years; 69% male; 76% White, 14% Black or African American, 6% mixed race, 3% Asian, and 1% Caribbean Islander.[3,4]

The primary outcome measure was change from baseline in Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) total score.[2-4] The SKAMP total score assesses 13 items including attention, quality of work, deportment and compliance.[21] 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.[21] A minimal clinically important difference (MCID) for ADHD outcomes related to the SKAMP scale is not well defined. Over the 12-hour assessment period, treatment with Xelstrym™ resulted in a least-squares mean difference (LSMD) in SKAMP total score of -4.7 (95% CI, -8.0 to −1.4) compared to placebo.[2-4] No serious treatment-emergent adverse events were reported.[3] Adverse reactions with incidence of 5% or

greater that occurred during the dose-optimization phase of the clinical study included decreased appetite (54%), insomnia (32%), headache (21%), irritability (16%), abdominal pain (16%) affect lability (16%), application site pain (13%), nausea (9%), application site pruritus (7%), and fatigue (5%).[2,3] In the double-blind, placebo-controlled phase of the clinical study, adverse reactions that occurred in 5% or greater of Xelstrym™ patients and at least twice the rate of placebo, respectively, were decreased appetite (10% vs. 1%), insomnia (8% vs. 4%), and headache (6% vs. 2%).[2,3]

New Indications:
In April 2021, the FDA expanded the approval for Evekeo ODT® (amphetamine sulfate oral disintegrating tablets; Schedule II) to include patients 3 to 5 years of age for the treatment of ADHD.[5] Prior to the change, the labeled indication was for patients 6 to 17 years of age.[5]

Amphetamine sulfate oral disintegrating tablets contains a 1:1 racemic mixture of dextroamphetamine sulfate and levoamphetamine sulfate.[5] The expanded approval was based on amendments to the originally submitted study with amphetamine sulfate IR tablets (Evekeo®) for the treatment of ADHD in patients 6 years of age and older.[5] Evekeo ODT® should not be substituted with other amphetamine sulfate products due to different salt compositions and pharmacokinetic profiles.[5] Evekeo ODT® is supplied in 2.5 mg tablets for use in 3 to 5-year-old patients which may be titrated in 2.5 mg increments at weekly intervals.[5] Evekeo ODT® is also available as 5 mg, 10 mg, 15 mg, and 20 mg tablets in 30-count blister cards.[5]

In May 2022, the FDA granted expanded approval for Qelbree® (viloxazine ER capsules) for the treatment of ADHD in patients 18 years of age and older.[6] Viloxazine, a selective norepinephrine reuptake inhibitor, which was initially approved in April in pediatric patients 6 to 17 years of age. It was the first novel, non-stimulant medication for ADHD approved by the FDA since 2002.[6] The maximum dose for the adults is 600 mg per day.[6]

Expanded approval for adults with ADHD was based on one multicenter, randomized, double-blind, placebo-controlled, flexible-dose, parallel-group monotherapy trial in 374 patients aged 18 to 65 years.[6] The patients were randomized to receive either dose-adjusted viloxazine ER capsules (n=175) or placebo (n=179) once daily for 6 weeks.[6] The viloxazine group was given 200 mg once daily in Week 1, followed by 400 mg once daily in Week 2, then individually adjusted by 200 mg per day once a week (range 200mg to 600 mg once per day).[6] Eligible patients had an adult ADHD Investigator Symptom Rating Scale (AISRS) total score of 26 or higher at baseline and a BMI classified as normal or overweight (18 to 35 kg/m^2).[6] Patients were excluded if they had a history of moderate or severe head trauma or other neurological disorder (e.g. seizures, encephalopathy, etc.), SUD, Hamilton Anxiety Rating Scale (HAM-A) score of > 21, organic mental disorder, a known or self-identified current habitual/chronic cannabis user, any clinically significant medical condition (including, but not limited to cardiovascular, metabolic, endocrine, gastrointestinal, hepatic, infectious, hematological, immunological or dermatological disorders), or history or risk of suicide.[6] The ADHD population treated with viloxazine ER was 56% male, 81% White, 12% Black, 3% Asian, 3% other races and 1% multiracial.[6]

The primary endpoint for the study was the change from baseline in the adult AISRS total score at Week 6.[6] The AISRS is an 18-item scale that corresponds to the 18 DSM-IV symptoms of ADHD where 9 inattentive items alternate with 9 hyperactive-impulsive items.[6] Each item has 4 numerical values and is scored as follows: 0 (none), 1 (mild), 2 (moderate), 3 (severe); the maximum total score for the scale is 54 points, with 27 points for each subscale.[6] The AISRS total score is the sum of the inattentive and hyperactive-impulsive subscales.[6] A higher AISRS score correlates with more severe symptoms.[6] A MCID related to the AISRS score is not defined. At week 6, the AISRS was reported to result in a LSMD from baseline of -15.5 points for the viloxazine ER group compared to a -11.7-point decline from baseline for placebo patients (LSMD -3.7; 95% CI, -6.2 to -1.2; P=0.004).[6] Seventeen out of 189 (9%) of patients receiving viloxazine ER discontinued treatment due to an adverse reaction.[6] The most commonly reported adverse reactions associated with discontinuation of viloxazine ER were fatigue (n=4), insomnia (n=3), constipation (n=3), and headache (n=2).[6] The most common adverse reactions occurring in 5% or more of viloxazine ER-treated patients and at

least twice the rate of placebo, respectively, were insomnia (23% vs. 7%), headache (17% vs. 7%), nausea (12% vs. 3%), fatigue (12% vs. 3%), decreased appetite (10% vs. 3%), dry mouth (10% vs. 2%), somnolence (6% vs. 2%) and constipation (6% vs. 1%).[6]

New FDA Safety Alerts:

Table 1. FDA Drug Safety-related Labeling Changes[7-9]

Generic Name	Brand Name	Month/Year of Change	Location of Change	Addition or Change and Mitigation Principles (if applicable)
Atomoxetine[8]	Strattera™	January 2022	Warning	**Emergence of New Psychotic or Manic Symptoms** Psychotic or manic symptoms (e.g., hallucinations, delusional thinking, or mania) in patients without a prior history of psychotic illness or mania can be caused by STRATTERA at usual doses. If such symptoms occur, consider discontinuing STRATTERA. **Screening Patients for Bipolar Disorder** Patients with bipolar disorder or risk factors for bipolar disorder may be at increased risk of developing mania or mixed episodes during treatment with STRATTERA. It may not be possible to determine whether a manic or mixed episode that appears during treatment with STRATTERA is due to an adverse reaction to STRATTERA or a patient's underlying bipolar disorder. Before initiating treatment with STRATTERA, patients should be adequately screened for risk factors for bipolar disorder such as a personal or family history of mania and depression. **Aggressive Behavior or Hostility** Patients beginning treatment with STRATTERA should be monitored for the appearance or worsening of aggressive behavior or hostility. There is evidence that STRATTERA may cause the emergence or worsening of aggressive behavior or hostility. ADHD and other mental illnesses can be associated with irritability, which can make it difficult to determine if the drug or the underlying psychiatric condition is causing the emergence or worsening of aggressive behavior or hostility in specific patients. If such symptoms occur during treatment, consider a possible causal role of STRATTERA.
Amphetamine products (all)[7,9]	Adderall™ Adzenys ER™ Adzenys XR-ODT™ Desoxyn™ Dexedrine™ Dynavel XR™	February 2022	Adverse Reactions	Gastrointestinal: intestinal ischemia

	Evekeo ODT™ Mydayis™ Vyvanse™			

References:

1. Dyanavel XR™ Prescribing Information. Monmouth Junction, NJ: Tris Pharma, Inc; June 2022.
2. Xelstrym™ Prescribing Information. Miami, FL: Noven Therapeutics, Inc; March 2022.
3. Xelstrym Multi-Discipline Review. Center for Drug Evaluation and Research. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/215401Orig1s000MultidisciplineR.pdf. Accessed July 1, 2022.
4. Cutler AJ, Suzuki K, Starling B, et al. Efficacy and Safety of Dextroamphetamine Transdermal System for the Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents: Results from a Pivotal Phase 2 Study. *J Child Adolesc Psychopharmacol* 2022; 32(2):89-97.
5. Evekeo ODT™[prescribing information], Atlanta, GA: Arbor Pharmaceuticals, LLC; April 2021.
6. Product Information: QELBREE™ oral extended-release capsules. Rockville, MD: Supernus Pharmaceuticals Inc; April 2022.
7. Food and Drug Administration. Drug Safety-related Labeling Changes (SrLC): Vyvanse™ https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=472. Accessed July 1, 2022.
8. Food and Drug Administration. Drug Safety-related Labeling Changes (SrLC): Strattera™ https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=1079. Accessed July 1, 2022
9. Food and Drug Administration. Drug Safety-related Labeling Changes (SrLC): amphetamine https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchResult.page. Accessed July 1, 2022
10. Candido RCF, Menezes de Padua CA, Golder S, et al. Immediate-release methylphenidate for attention deficit hyperactivity disorder (ADHD) in adults. *Cochrane Database Syst Rev*. 2021;1(1):CD013011. Published 2021 Jan 18.
11. Castells X, Ramon M, Cunill R, et al. Relationship Between Treatment Duration and Efficacy of Pharmacological Treatment for ADHD: A Meta-Analysis and Meta-Regression of 87 Randomized Controlled Clinical Trials. *Journal of Attention Disorders*.25(10):1352-1361.
12. Farhat LC, Flores JM, Behling E, et al. The effects of stimulant dose and dosing strategy on treatment outcomes in attention-deficit/hyperactivity disorder in children and adolescents: a meta-analysis. *Molecular Psychiatry*.27(3):1562-1572.
13. Hulsbosch AK, De Meyer H, Beckers T, et al. Systematic Review: Attention-Deficit/Hyperactivity Disorder and Instrumental Learning. *Journal of the American Academy of Child & Adolescent Psychiatry*.60(11):1367-1381.
14. Joshi G, Wilens T, Firmin ES, et al. Pharmacotherapy of attention deficit/hyperactivity disorder in individuals with autism spectrum disorder: A systematic review of the literature. *Journal of Psychopharmacology*.35(3):203-210.
15. McKenzie A, Meshkat S, Lui LMW, et al. The effects of psychostimulants on cognitive functions in individuals with attention-deficit hyperactivity disorder: A systematic review. *Journal of Psychiatric Research*.149:252-259.
16. Rodrigues R, Lai MC, Beswick A, et al. Practitioner Review: Pharmacological treatment of attention-deficit/hyperactivity disorder symptoms in children and youth with autism spectrum disorder: a systematic review and meta-analysis. *Journal of Child Psychology & Psychiatry & Allied Disciplines*.62(6):680-700.

17. Vertessen K, Luman M, Staff A, et al. Meta-analysis: Dose-Dependent Effects of Methylphenidate on Neurocognitive Functioning in Children With Attention-Deficit/Hyperactivity Disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*.61(5):626-646.
18. Yuan D, Zhang M, Huang Y, et al. Noradrenergic genes polymorphisms and response to methylphenidate in children with ADHD: A systematic review and meta-analysis. Medicine.100(46):e27858.
19. Bahji A, Mesbah-Oskui L. Comparative efficacy and safety of stimulant-type medications for depression: A systematic review and network meta-analysis. *Journal of Affective Disorders*.292:416-423.
20. Barbaresi WJ, Campbell L, Diekroger EA, et al. Society for Developmental and Behavioral Pediatrics Clinical Practice Guideline for the Assessment and Treatment of Children and Adolescents with Complex Attention-Deficit/Hyperactivity Disorder. *J Dev Behav Pediatr*. 2020;41 Suppl 2S:S35-S57.
21. Markowitz JT, Oberdhan D, Ciesluk A, et al. Review of Clinical Outcome Assessments in Pediatric Attention-Deficit/Hyperactivity Disorder. *Neuropsychiatr Dis Treat*. 2020;16:1619-1643.

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
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	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
serdexmethylphen/dexmethylphen	AZSTARYS	CAPSULE	N

Appendix 2: New Comparative Clinical Trials

A total of 89 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical).

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to July 05, 2022

1	*serdexmethylphenidate.mp.*	*5*
2	*methylphenidate hydrochloride.mp. or Methylphenidate/*	*7681*
3	*Amphetamine sulfate.mp. or Amphetamine/*	*13078*
4	*mixed amphetamine salts.mp.*	*150*
5	*lisdexamfetamine.mp. or Lisdexamfetamine Dimesylate/*	*479*
6	*dexmethylphenidate.mp. or Dexmethylphenidate Hydrochloride/*	*99*
7	*viloxazine.mp. or Viloxazine/*	*366*
8	*clonidine.mp. or Clonidine/*	*18643*
9	*Guanfacine/ or guanfacine.mp.*	*1147*
10	*atomoxetine.mp. or Atomoxetine Hydrochloride/*	*1977*
11	*attention deficit disorder.mp. or Attention Deficit Disorder with Hyperactivity/*	*33939*
12	*adhd.mp.*	*29597*
13	*1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10*	*41512*
14	*10 or 11 or 12*	*41928*
15	*13 and 14*	*6507*
16	*limit 15 to (english language and humans and yr="2020 -Current" and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or pragmatic clinical trial or randomized controlled trial or "systematic review"))*	*151*
17	*limit 16 to yr="2021 -Current"*	*89*

Appendix 5: Key Inclusion Criteria

Population	Adult and pediatric patients with attention deficit hyperactivity disorder (ADHD) or attention deficit disorder (ADD)
Intervention	Drugs in ADHD class (Appendix 1)
Comparator	Drugs in ADHD class (Appendix 1) or placebo if clinically important safety outcomes
Outcomes	Efficacy: symptom improvement, functional capacity, quality of life, time to onset of effectiveness, duration of effectiveness. Safety: withdrawals due to adverse events, serious and long-term (>12 months) adverse events, misuse/diversion
Timing	Literature from 05/01/20 – 07/05/22
Setting	Outpatient