Pharmacological Therapies for Attention-Deficit/Hyperactivity Disorder (ADHD)

Surveillance Report 2

Washington P&T Committee Meeting

December 11, 2024

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EVIDENCE-BASED POLICY CENTER FOR

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Conflict of Interest Disclosures: No authors have conflicts of interest to disclose. All authors have completed and submitted the Oregon Health & Science University form for Disclosure of Potential Conflicts of Interest, and none were reported.

Funding and Support: This research was funded by the Center for Evidence-based Policy's Drug Effectiveness Review Project at Oregon Health & Science University.

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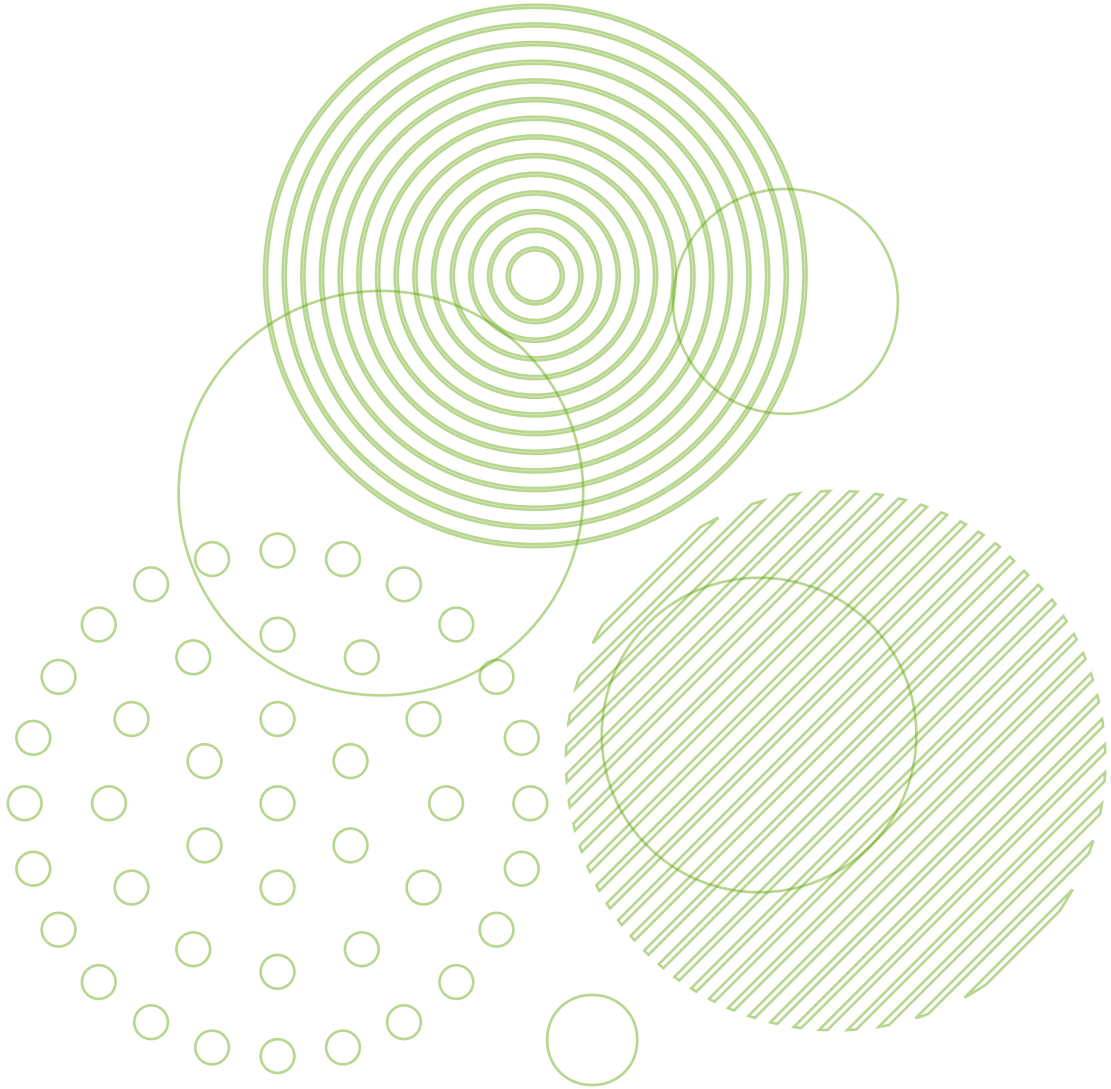
Overview

- Background and Topic History
- PICOS
- Key Questions
- Methods
- Findings
- Summary



Background and Context (1 of 2)

- Attention-deficit/hyperactivity disorder (ADHD) affects:
  - **~7 million (11.4%) US children and adolescents**
    - ~62% use medications (range across states, 38% to 81%)
  - **~11.7 million (4.5%) US adults**
    - ~75% receive some type of treatment (e.g., psychotherapy, medication)
      - Of those medicated, ~80% use stimulant medications (2018 estimate) to manage symptoms

- Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) diagnosis criteria require symptoms:
  - **Present by age 12**, regardless of age of diagnosis
  - **Present in 2 or more settings** (e.g., work, school)
  - **Interfere with functioning** in school, work, or social settings
  - **Not be better explained** by another mental health disorder

Background and Context (2 of 2)

- **3 symptomatic presentations of ADHD**
  - Predominantly inattentive
  - Predominantly hyperactive-impulsive
  - Combined
- **Psychiatric comorbidities are common**
  - Learning disorders, oppositional-defiant disorders, and anxiety in children
  - Depression, anxiety, and substance use disorder in adults
- **Treatments**
  - Pharmacological (e.g., stimulants, non-stimulants)
    - 31 treatments approved by US Food and Drug Administration (FDA)
  - Behavioral interventions (e.g., skills training)
  - Setting-specific interventions (e.g., workplace accommodation)
  - Combined therapies

Prevalence and Treatment in Medicaid

- **13% of Medicaid-enrolled children have an ADHD diagnosis**
  - National average across private insurers is ~5%
- Children identified as:
  - **African American are less likely** to receive follow-up and more likely to discontinue and disengage
  - **White, male, and living in a 2-parent household are more likely** to be assessed and treated, especially within Medicaid
- In Medicaid-enrolled adults, African Americans follow similar pattern as in children; **males and those living rurally less likely to initiate treatment**
- Medication **initiation in adults across states highly varied**
  - 8% in New Jersey to 48% in Tennessee

Topic History

Research Product Type	Date Presented	Search Dates
Surveillance Report 1	October 2023	July 1, 2021 to July 31, 2023
Systematic Review	December 2021	January 1, 2015 to August 1, 2021

- The **2021 systematic review included 70 studies**:
  - 34 randomized controlled trials (RCTs) comparing a stimulant vs. another stimulant
  - 20 RCTs comparing a stimulant vs. a nonstimulant
  - 4 RCTs comparing a stimulant vs. bupropion
  - 6 placebo-controlled RCTs comparing stimulants approved between 2015 and 2021
  - 5 placebo-controlled RCTs comparing nonstimulants approved between 2015 and 2021
  - 1 post hoc analysis comparing a nonstimulant vs. another nonstimulant

PICOS

- Populations
  - Pediatric or adult patients with ADHD of any presentation
- Comparators[a]
  - Another listed intervention (head-to-head comparison)
  - Standard of care or placebo
    - For treatments approved since January 2015 (e.g., viloxazine [Qelbree])
    - For studies that enrolled individuals aged 18 years or older
- Study design
  - RCTs

Note. [a] *We excluded studies that compared a brand name with a generic equivalent, compared different doses of the same medication, or explicitly included multimodal treatments.*

PICOS: Pharmacological Therapies (1 of 4)

Generic Name	Brand Name	Date of FDA Approval
Stimulants		
Methylphenidate HCL	Relexxii	June 23, 2022
Dextroamphetamine	Xelstrym (transdermal)	March 22, 2022
Amphetamine, amphetamine aspartate/dextroamphetamine sulfate	Dyanavel XR (tablet)	November 4, 2021
Serdexmethylphenidate dexmethylphenidate	Azstarys	March 2, 2021
Methylphenidate HCL	**Adhansia XR**	**Discontinued[a]**
Amphetamine sulfate	**Evekeo ODT**	**Discontinued[a]**
Methylphenidate HCL	Jornay PM	August 8, 2018
Amphetamine	**Adzenys ER**	**Discontinued[a]**
Mixed amphetamine salts	Mydayis	June 20, 2017
Methylphenidate	Cotempla XR-ODT	June 19, 2017

*Notes. Shaded rows indicate treatments approved since 2021 systematic review. **Bold text** indicates a change in availability. [a] Date not provided. Abbreviations. ER: extended release; FDA: US Food and Drug Administration; HCL: hydrochloride; ODT: oral disintegrating tablet; PM: extended release; XR: extended release.*

PICOS: Pharmacological Therapies (2 of 4)

Generic Name	Brand Name	Date of FDA Approval
Stimulants		
Lisdexamfetamine dimesylate	Vyvanse (chewable)	January 28, 2017
Amphetamine polistirex	Adzenys XR-ODT	January 27, 2016
Methylphenidate HCL	Quillichew ER	December 4, 2015
Amphetamine sulfate	Dyanavel XR (suspension)	October 19, 2015
Methylphenidate HCL	Aptensio XR	April 17, 2015
Methylphenidate HCL	Quillivant XR (suspension)	September 27, 2012
Amphetamine sulfate	Evekeo	August 9, 2012
Lisdexamfetamine dimesylate	Vyvanse (capsule)	February 23, 2007
Methylphenidate	Daytrana (transdermal patch)	April 6, 2006
Dexmethylphenidate HCL	Focalin XR	May 26, 2005

Abbreviations. ER: extended release; FDA: US Food and Drug Administration; HCL: *hydrochloride; ODT: oral disintegrating tablet; XR: extended release.*

PICOS: Pharmacological Therapies (3 of 4)

Generic Name	Brand Name	Date of FDA Approval
Stimulants		
Methylphenidate HCL	Methylin (oral solution)	December 19, 2002
Methylphenidate HCL	Ritalin LA (capsule)	June 5, 2002
Dexmethylphenidate HCL	Focalin	November 13, 2001
Mixed amphetamine salts	Adderall XR	October 11, 2001
Methylphenidate HCL	Metadate CD	April 3, 2001
Methylphenidate HCL	Concerta-XL	August 1, 2000
Methylphenidate HCL	Methylin ER (tablet)	May 9, 2000
Methylphenidate HCL	Ritalin-SR	March 30, 1982
Mixed amphetamine salts	Adderall	January 19, 1960
Methylphenidate HCL	Ritalin (tablet)	December 5, 1955

Abbreviations. CD: continued delivery; ER: extended release; FDA: US Food and Drug Administration; HCL: *hydrochloride; LA: long-acting; SR: sustained release; XL: extended release; XR: extended release.*

PICOS: Pharmacological Therapies (4 of 4)

Generic Name	Brand Name	Date of FDA Approval
Nonstimulants		
Clonidine HCL	Ondya XR	May 24, 2024
Viloxazine HCL	Qelbree	April 2, 2021
Clonidine HCL	**Kapvay**	**Discontinued[a]**
Guanfacine HCL	Intuniv	September 2, 2009
Atomoxetine HCL	Strattera	November 26, 2002
Off-label treatment		
Armodafinil	Nuvigil	June 15, 2007
Bupropion HCL	Wellbutrin XL	August 28, 2003
Modafinil	Provigil	December 24, 1998
Bupropion HCL	Wellbutrin SR	October 4, 1996

Notes. Shaded rows indicate treatments approved since 2021 systematic review. ***Bold text*** *indicates a change in availability.*
[a] *Date not provided.*
Abbreviations. FDA: US Food and Drug Administration; HCL*: hydrochloride; SR: sustained release; XL: extended release; XR: extended release.*

PICOS

Outcomes:* *Efficacy and Effectiveness

- **Symptom response** (e.g., inattention, hyperactivity-impulsivity, global rating)
- **Functional capacity** (e.g., social, academic, and occupational activities)
- **Quality of life** (patient, family members, caregivers, teachers, employability)
- **Time to onset of effectiveness**
- **Duration of effectiveness**

Image source. AIA Malaysia

Outcomes:* *Harms

- **Tolerability**
  - Overall adverse events (AEs), including side effects (e.g., loss of appetite, palpitations)
  - Withdrawals due to AEs
  - Specific AEs (e.g., anorexia, insomnia, tics)
- **Serious and long-term (≥ 12 months) AEs**
  - Cardiovascular events
  - Growth effects
  - Hepatotoxicity
  - Suicide and suicidal behavior
- **Misuse/diversion**
  - Compliance, overdose
  - Development of substance use disorders
  - Trading, selling

Key Questions

1. **Effectiveness** of FDA-approved pharmacological treatments
2. **Harms** of FDA-approved pharmacological treatments
3. **Subgroup differences** in effectiveness or harms
4. **Ongoing studies**

Methods

REGISTERED TRIALS

- ClinicalTrials.gov
- ScanMedicine
- FDA website

PUBLISHED EVIDENCE

Using clinical trial numbers or other identifiers (e.g., trial name):

- Ovid MEDLINE
- Google Scholar

FDA ACTIONS

- FDA website
- IPD Analytics

- All searches covered July 1, 2021 through July 29, 2024

Findings

Clinical Landscape

New FDA Actions and Pipeline Therapies

New Drugs and Formulations for ADHD (1 of 2)

Generic Name	Brand Name	Indication	Date of FDA Approval
Stimulants			
MPH	Relexxii	Ages 6 to 65 years	June 23, 2022
d-AMPH	Xelstrym (transdermal)	Ages ≥ 6 years	March 22, 2022
AMPH/d-AMPH	Dyanavel XR (tablet)	Ages ≥ 6 years	November 4, 2021
Nonstimulants			
Clonidine	Ondya XR	Ages ≥ 6 years	May 24, 2024

Abbreviations. ADHD: attention-deficit/hyperactivity disorder; AMPH: amphetamine; d-AMPH: dextroamphetamine; FDA: US Food and Drug Administration; MPH: methylphenidate; XR: extended release.

New Drugs and Formulations for ADHD (2 of 2)

Drugs and Formulations No Longer Available:

- Adhansia XR (methylphenidate; approved February 2019)
- Adzenys ER (amphetamine; approved September 2017)
  - Adzenys XR-ODT (oral disintegrating tablet) remains available
- Evekeo ODT (approved January 2019)
  - Evekeo (oral tablet) remains available
- Kapvay (extended-release clonidine; approved September 2009)

New Indications

- **Evekeo** (amphetamine)
  - September 2022: now **excludes use in children aged 3 to 5** years
    - Use in patients aged 6 to 17 years remains approved by the FDA
- **Qelbree** (viloxazine)
  - April 2022: **expanded for use in all patients aged ≥ 6 years** (originally approved April 2021 for ages 6 to 17 years)

Pipeline Therapies for ADHD

Generic Name	Development or Brand Name	Mechanism of Action	Status
AMPH	AR19	Stimulant	PDUFA pending[a]
d-MPH	CTx-1301	Stimulant	Phase 3
LDX	Vyvanse (capsule, new dose)	Stimulant	Phase 3
MPH	ORADUR-MPH	Stimulant	Phase 3
Centanafadine	EB-1020	SNDRI	Phase 3
TBD	NRCT-101SR	Glutamate modulator	Phase 3
MPH	Jornay PM	Stimulant	Phase 3
Solriamfetol	Sunosi	NDRI	Phase 3

Note. [a] *No date provided.*
Abbreviations. ADHD: attention-deficit/hyperactivity disorder; AMPH: amphetamine; d-MPH: dexmethylphenidate; LDX: lisdexamfetamine; MPH: methylphenidate; NDRI: norepinephrine and dopamine reuptake inhibitor; PDUFA: Prescription Drug User Fee Act; PM: extended release; SNDRI: serotonin, norepinephrine, and dopamine reuptake inhibitor; TBD: to be determined.

New Boxed Warnings

- As of October 2023, all **ADHD stimulant medications** have a boxed warning that states these medications **have a high potential for abuse and misuse**
- **Viloxazine** received a boxed warning to monitor patients for **emergence or worsening of suicidal thoughts and behaviors**

New Harms

- Numerous new warnings were added to or expanded for ADHD stimulant medications including:
  - Acute angle closure glaucoma
  - Increased blood pressure and heart rate
  - Increased intraocular pressure and glaucoma
  - Increased risk of serotonin syndrome (Dyanavel XR only)
  - Long-term suppression of growth in pediatric patients
  - Motor and verbal tics, and worsening of Tourette syndrome
  - Peripheral vasculopathy, including Raynaud phenomenon (newer amphetamine medications only)
  - Psychiatric adverse reactions
  - Risks to patients with serious cardiac disease

Research Landscape

New Published Studies and Ongoing Studies

Findings: Characteristics of New RCTs

Comparators	Number of RCTs	Study Size Range	Total N	Study Duration, (weeks)
Stimulant vs. nonstimulant	1	n/a	60	12
Stimulant vs. mindfulness	1	n/a	91	8
Stimulant vs. PBO (adults only)	5	38 to 433	834	5 to 52
Newer stimulant vs. PBO	2	110 and 155	265	1 to 5
Nonstimulant vs. PBO	3	44 to 374	619	6 to 12
Nonstimulant vs. CBT	1	n/a	59	16
Total	**13** in 17 publications	**38 to 433**	**1,928**	1 to 52

Abbreviations. CBT: cognitive behavioral therapy; n/a: not applicable; PBO: placebo; RCT: randomized controlled trial.

Characteristics of New RCTs in Adults (Part 1 of 2)

First Author, Year	Duration (weeks)	N Enrolled	Interventions	Mean Age (years); Other Criteria	% Female	% Non-White
Head-to-head						
Shim, 2022	12	60	ATX vs. OROS-MPH	23.2; MDD	20	*NR*
Stimulants vs. placebo						
Adler, 2021	10	38	LDX vs. PBO	34.6	66	47
Asherson, 2022	8	200	OROS-MPH vs. PBO	20.7	0	37
Cutler, 2022	5	130	AMPH-ER vs. PBO	32.4	40	18
Levin, 2024	12	33	MAS-ER vs. PBO	32.9; CUD	31	*NR*
Lopez-Pinar, 2024	52 + 78	433	MPH vs. PBO	34.2	50	*NR*

Abbreviations. AMPH: amphetamine; ATX: atomoxetine; CUD: cannabis use disorder; ER: extended release; LDX: lisdexamfetamine; MAS: mixed amphetamine salts; MDD: major depressive disorder; MPH: methylphenidate; NR: not reported; OROS: osmotic-release oral system; PBO: placebo; RCT: randomized controlled trial.

Characteristics of New RCTs in Adults (Part 2 of 2)

First Author, Year	Duration (weeks)	N Enrolled	Interventions	Mean Age (years); Other Criteria	% Female	% Non-White
Nonstimulants						
Iwanami, 2020	12	201	GXR vs. PBO	32.5	36	100
Nasser, 2022	6	374	VLX vs. PBO	34.8	45	21
Wang, 2022	10	44	ATX vs. PBO	41.1; PTSD	17	50

Abbreviations. ATX: atomoxetine; GXR: guanfacine; PBO: placebo; PTSD: post-traumatic stress disorder; RCT: randomized controlled trial; VLX: viloxazine.

Characteristics of New RCTs in Children

First Author, Year	Duration (weeks)	N Enrolled	Interventions	Mean Age (years)	% Female	% Non-White
Head-to-head						
David, 2021	16	59	ATX vs. ATX + CBT or CBT alone	8.5	20	*NR*
Stimulants						
Cutler, 2022	5	110	d-AMPH (Xelstrym) vs. PBO	10.5	31	*NR*
Kollins, 2021	1	155	SDX/d-MPH (Azstarys) vs. PBO	9.6	39	49
Meppelink, 2024	8	91	MPH vs. mindfulness	11.3	29	*NR*

Abbreviations. ATX: atomoxetine; d-AMPH: dextroamphetamine; CBT: cognitive behavioral therapy; d-MPH: dexmethylphenidate; NR: not reported; PBO: placebo; RCT: randomized controlled trial; SDX: serdexmethylphenidate.

Findings: Ongoing Head-to-Head Studies

3 ongoing head-to-head studies

- Adults
  - 1 comparing a stimulant vs. a nonstimulant (N = 648) in ages 18 to 64 years with a **history of psychosis or bipolar disorder** (October 2025)
- Children
  - 1 comparing a stimulant vs. a nonstimulant or clonidine (N = 500) in ages 4 to 17 years with **comorbid autism** (March 2027)
  - 1 comparing a nonstimulant vs. another nonstimulant or placebo (N = 288) in ages 6 to 17 years (June 2027)

Findings: Ongoing Placebo-Controlled Studies

7 ongoing placebo-controlled studies

- Adults
  Completion dates in September 2022 and September 2026
  - 2 studies comparing a stimulant to placebo (total N = 110); 1 requires **half of the participants to have a diagnosed anxiety disorder** (N =60)
- Children
  Completion dates range from May 2024 to July 2026
  - 4 studies comparing a stimulant to placebo (total N = 564); 1 is enrolling **participants with Down Syndrome** (N = 100)
  - 1 study comparing the nonstimulant viloxazine (Qelbree) in **ages 4 to 5 years** (N = 286)

Summary

New FDA Actions and Clinical Evidence Since the 2021 Review

New FDA Actions and Clinical Evidence (1 of 3)

- **4 new drugs or formulations** (3 stimulants, 1 nonstimulant)
- **2 new indications**
  - Qelbree (viloxazine) is now available for use in adults
  - Evekeo (an amphetamine sulfate) is no longer approved for use in children ages 3 to 5 years
- **4 brand-name treatments no longer available**
  - Adhansia XR, Adzenys ER, Evekeo ODT, and Kapvay
- **8 pipeline therapies in phase 3 trials**
  - 1 pipeline therapy has a pending Prescription Drug User Fee Act (PDUFA) date (date not given)

New FDA Actions and Clinical Evidence (2 of 3)

- **2 new boxed warnings**
  - All stimulant medications: high potential for abuse or misuse
  - Viloxazine: new or worsening suicidal thoughts and behaviors
- **9 new harms across stimulant treatments**
  - Risks to patients with serious cardiac disease; acute angle closure glaucoma; increased blood pressure and heart rate; increased intraocular pressure and glaucoma; psychiatric adverse reactions; motor and verbal tics, and worsening of Tourette syndrome; peripheral vasculopathy, including Raynaud phenomenon; long-term suppression of growth in pediatric patients; risk of serotonin syndrome

New FDA Actions and Clinical Evidence (1 of 3)

- **13 new RCTs**
  - 3 head-to-head study (1 in adults; 2 in children)
  - 5 comparing a stimulant vs. placebo (all in adults)
  - 5 comparing a nonstimulant vs. placebo (3 in adults; 2 in children)
- **10 ongoing RCTs**
  - 3 head-to-head (1 in adults; 2 in children)
  - 6 comparing a stimulant vs. placebo (2 in adults; 4 in children)
  - 1 comparing a nonstimulant vs. placebo in children

Questions?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