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Drug Effectiveness Review Project Summary Report – ADHD

Date of Review: March 2016 **Date of Last Review:** January 2015

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

Research Questions:

1. What is the comparative evidence that pharmacologic treatments for attention deficit disorders differ in effectiveness outcomes (i.e., functional capacity as it relates to social, academic and occupational productivity; or quality of life for patients, family members, caregivers or teachers) or efficacy outcomes (symptom response assessing specific magnitude of improvement in scores on ADHD rating scales)?
2. What is the comparative evidence that pharmacologic treatments for attention deficit disorders differ in harms (i.e., tolerability, serious and long-term adverse events, and abuse/misuse/diversion) outcomes?
3. What is the comparative evidence that pharmacologic treatments for attention deficit disorders differ in effectiveness, efficacy or harms outcomes in subgroups of patients based on demographics, socioeconomic status, other medications or therapy, or comorbidities (e.g., tics, anxiety, substance use disorders, disruptive behavior disorders)?

Conclusions:

- There is insufficient evidence that directly compares general effectiveness outcomes of different drugs for ADHD in children or adults.
- In children, there is low to moderate quality evidence of no difference in improvement of ADHD symptoms between immediate-release (IR) and extended-release (ER) stimulants; between ER stimulants (including controlled delivery (CD), sustained-release (SR), and transdermal formulations); or between IR stimulants. Exceptions of studies that do show differences between stimulants are of low quality and further studies are needed to determine if true differences in efficacy between these drugs exist.
- In children, there is moderate quality evidence non-stimulant atomoxetine may be inferior to stimulants on most efficacy outcomes, such as response rates. Comparisons between stimulants and non-stimulants other than atomoxetine are either lacking or do not demonstrate differences in efficacy.
- In children, there is insufficient evidence that compares efficacy between non-stimulant ADHD drugs with the exception of guanfacine ER and atomoxetine, for which there is low quality evidence guanfacine ER may be superior to atomoxetine at reducing ADHD-RS scores at 6 weeks (difference -5.1; scale 0-54).
- In adolescents and adults, there is insufficient evidence to adequately compare differences in efficacy of stimulants and non-stimulant drugs for ADHD.
- The most common adverse effects from stimulants are appetite loss, abdominal pain, headaches and sleep disturbance; there is only low quality evidence to suggest any differences in harms between the agents.
- Insufficient evidence from survey data suggest lifetime non-medical use of methylphenidate IR and dextroamphetamine was more frequent compared to mixed amphetamine salts; the highest rate of diversion was with amphetamine/dextroamphetamine.

- Two medications for ADHD have been approved U.S. Food and Drug Administration (FDA) since the DERP report was published. However, evidence is insufficient to compared these medications to drugs already available for AHDH. The new formulation of extended-release methylphenidate (QuilliChew ER™) was approved based on low quality, placebo-controlled evidence. The new orally disintegrating, extended-release tablet formulation of mixed amphetamines (Adzenys XR-ODT™) was approved based on pharmacokinetic bioequivalence studies.

Recommendations:
- No new evidence in the DERP report suggests changes should be made to the PDL based on clinical differences between agents.
- Designate QuilliChew ER™ and Adzenys XR-ODT™ as non-preferred based on limited evidence for safety and efficacy.
- Update the current safety edit (**Appendix 3**).

Previous Conclusions:
- New clinical evidence suggests no changes to the PDL are needed.

Previous Recommendations:
- No changes to the PDL made. No further review or research needed.

Methods:
The July 2015 Drug Class Review on Pharmacologic Treatments for Attention Deficit Hyperactivity Disorder by the Drug Effectiveness Review Project (DERP) at the Pacific Northwest Evidence-based Practice Center at the Oregon Health & Science University (OHSU) was used to inform recommendations for the ADHD drug class.

The final original report is available to Oregon Pharmacy and Therapeutics Committee members upon request. An executive summary report is publically available in the agenda packet and on the DURM website.

The purpose of the DERP reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. 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.

In addition, new published evidence, approvals and safety alerts from the U.S. Food and Drug Administration (FDA) since the DERP report was published were identified. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used.

Summary Findings:
A total of 1,022 citations were identified. The ADHD drugs eligible to be included in the DERP drug review are listed in Table 1. After excluding sources that did not meet criteria for inclusion, 15 publications, including 8 head-to-head trials in 12 publications and 3 observational studies, were included in the DERP drug review.

Table 1. Drugs for ADHD Included in DERP Review.

Generic Name	Trade Name	Formulation
Mixed amphetamine salts*	Adderall XR®	Extended-release oral capsule
Atomoxetine	Straterra®	Oral capsule
Clonidine	Catapres®, Catapres TTS®	Oral tablet
	Kapvay™	Extended-release oral tablet
Dexmethylphenidate HCl	Focalin®	Oral tablet
	Focalin XR®	Extended-release oral capsule
Dextroamphetamine sulfate	Dexedrine®	Oral tablet
	Dexedrine Spansule®	Sustained-release oral capsule
Guanfacine HCl	Intuniv®	Extended-release oral tablet
	Tenex™	Oral tablet
Lisdexamfetamine dimesylate	Vyvanse®	Oral capsule
Methamphetamine HCl	Desoxyn®	Oral tablet
Methylphenidate	Daytrana®	Extended-release transdermal film
Methylphenidate HCl	Concerta®	Extended-release oral tablet
	Metadate CD®	Extended-release oral capsule
	Metadate ER®	Extended-release oral tablet
	Methylin®	Oral chewable tablet and solution
	Quillivant™ XR	Extended-release oral suspension
	Ritalin®	Oral tablet
	Ritalin LA®	Extended-release oral capsule
	Ritalin-SR®	Extended-release oral tablet
Modafinil^	Provigil®	Oral tablet
Armodafinil^	Nuvigil®	Oral tablet

* Active ingredients = amphetamine aspartate; amphetamine sulfate; dextroamphetamine saccharate; dextroamphetamine sulfate.

^Modafinil and armodafinil are not approved by the FDA for ADHD. Though these drugs are included in the DERP report, they belong to a separate drug class on the OHP PMPDP and are subject to prior authorization to restrict use to funded conditions with evidence of efficacy.

EFFICACY/EFFECTIVENESS AND SAFETY OF ADHD DRUGS

Note: each item on the ADHD-RS 18-item measure is scored on a 4-point scale ranging from 0 (no symptoms) to 3 (severe symptoms), yielding a possible total score of 0-54].

Young children (preschool age; 3-5 years)

- Comparative evidence was not found; placebo-controlled evidence had mixed efficacy outcomes.
- Adverse events occurred significantly more often with methylphenidate than with placebo. Over long-term treatment, some adverse events resolved but others did not.

Children (elementary school age; 6-12 years)

Stimulants

- Immediate-release vs. Extended-release Formulations
    - There was conflicting evidence that compared methylphenidate IR and methylphenidate ER OROS formulation. Two double-blind trials were unable to identify differences between the IR and OROS formulations and 2 open-label studies found the OROS formulation was associated with greater improvements in some, but not all, assessments.
    - Limited evidence was available to adequately compare IR and ER methylphenidate formulations. Overall, the studies were unable to identify differences between methylphenidate sustained-release (SR) and IR methylphenidate; and methylphenidate CD was non-inferior to IR methylphenidate.
    - Response to treatment was 18% higher in children who took lisdexamfetamine compared to children who took methylphenidate OROS. A greater improvement in the ADHD-RS scores at 7 weeks was also found with lisdexamfetamine, with a difference of 5.6 points. Parent rating scores were also better for lisdexamfetamine. Overall, adverse event rates did not differ between lisdexamfetamine and methylphenidate OROS: more children had anorexia, decreased appetite, decreased weight, insomnia and nausea with lisdexamfetamine; headaches and nasopharyngitis were more common with methylphenidate OROS.
- Sustained-release vs. Sustained-release Formulations
    - Limited evidence from 2 small crossover studies suggested that methylphenidate long-acting (LA) was superior to methylphenidate OROS on some, but not all efficacy outcomes.
    - Methylphenidate CD was superior to methylphenidate OROS in the morning, but inferior in the evening; both formulations were similarly effective in the afternoon. Methylphenidate OROS had statistically higher rates of insomnia and decreased appetite than methylphenidate CD.
    - Limited evidence indicates dexmethylphenidate extended-release (ER) resulted in a better response from 0.5 to up to 6 hours post-dose compared to methylphenidate OROS; however, methylphenidate OROS resulted in better scores later in the day, from 10 to 12 hours post-dose.
    - Limited evidence of no difference in response rates or symptom improvement was found between dexmethylphenidate ER and mixed amphetamine salts extended-release (XR) after 8 weeks.
    - Differences were not found between lisdexamfetamine and mixed amphetamine salts XR using the Swanson, Kotkin, Agler, M-Flynn, and Perlham Deportment Scale (SKAMP-DS) scores in a simulated classroom setting , or using the Clinical Global Impressions – Improvement (CGI-I) response rates after 1 week.

- Immediate-release vs. Immediate-release Formulations
    - Evidence clearly indicates no difference in efficacy between dextroamphetamine IR and methylphenidate IR, though weight loss may be greater with dextroamphetamine IR than with methylphenidate IR.
    - Mixed amphetamine salts IR were superior to methylphenidate IR on a few efficacy outcomes evaluated in 2 trials, but clear evidence of superiority is lacking.
    - No differences were found between modafinil and methylphenidate IR over 6 weeks.
    - Limited evidence suggests dextroamphetamine IR is superior to dextroamphetamine SR in the morning, and dextroamphetamine SR is superior to amphetamine salts in the afternoon. Transient weight loss was greater with mixed amphetamine salts and dextroamphetamine SR than with dextroamphetamine IR.
- Transdermal Methylphenidate vs. Methylphenidate OROS or Methylphenidate IR
    - Methylphenidate transdermal system has similar efficacy to methylphenidate OROS (over 7 weeks starting 4 hours after administration) and methylphenidate IR (over 12 hours in a simulated classroom setting, starting 30 minutes after dosing). No differences in adverse events were observed.

Nonstimulants

Atomoxetine

- Atomoxetine vs. Methylphenidate IR
    - Evidence from 2 trials suggests atomoxetine and methylphenidate IR result in similar efficacy.
- Atomoxetine vs. Methylphenidate OROS
    - Methylphenidate OROS had higher response rates; 56% methylphenidate OROS and 45% atomoxetine (p=0.02) and greater reduction in ADHD-RS scale scores after 4 to 6 weeks.
- Atomoxetine vs. Lisdexamfetamine
    - Lisdexamfetamine resulted in clinical improvement 9 days earlier and more patients had achieved clinical response (82% vs. 64%) than atomoxetine; similarly, lisdexamfetamine had greater change in the ADHD-RS score (difference -6.5) at 9 weeks than atomoxetine.
- Atomoxetine vs. Mixed Amphetamine Salts
    - Mixed amphetamine salts XR was found to be superior to atomoxetine on most measures of efficacy in a simulated classroom study.
- Atomoxetine was associated with significantly higher rates of vomiting, somnolence, nausea, and anorexia than stimulants, depending on the specific drug comparison. Incidence of vomiting (12-13%) was about 3-times greater than methylphenidate IR or mixed amphetamine salts XR. Incidence of somnolence (6-26%) was 3- to 4-times greater than methylphenidate OROS and mixed amphetamine salts XR. However, methylphenidate OROS and mixed amphetamine salts XR caused higher rates of insomnia than atomoxetine in 2 trials (7% atomoxetine, 13% methylphenidate OROS, 28% mixed amphetamine salts XR).

Clonidine

- Current evidence does not clearly identify a difference in improvement of ADHD symptoms between clonidine IR and methylphenidate IR (both with and without comorbid Tourette's disorder); however, these results should be interpreted with caution due to inconsistency in some outcomes.
- Clonidine IR resulted in higher rates of sedation (42%) than methylphenidate IR (14%), with 28% reporting the sedation to be moderate or severe.
- No head-to-head evidence is available on clonidine ER.

Guanfacine

- No head-to-head evidence was available on guanfacine IR.
- Guanfacine ER had superior reduction in ADHD-RS scores at 6 weeks compared with atomoxetine (difference of 5.1), but no difference in the proportion of patients who clinically improved (RR 1.15; 95% CI, 0.93 to 1.43) based on a single study. Adverse event rates did not differ.

Adolescents

- Methylphenidate OROS resulted in better simulated driving scores only in the late evening or nighttime than methylphenidate IR and mixed amphetamine salts.

Adults

- Four small short-term trials provide low-strength evidence of similar effects on ADHD symptoms after 2 to 6 weeks for the comparisons between dextroamphetamine IR and either modafinil or guanfacine, between continuing with methylphenidate IR or switching to methylphenidate OROS, or between IR and ER mixed amphetamine salts. Those same 4 trials provided low-strength evidence of no difference in harms, except for the comparison of IR and ER mixed amphetamine salts, for which there was insufficient evidence to draw conclusions on harms.

Long-term Safety

- Cardiovascular Deaths and Events
    - Two retrospective cohort studies in children provide low-strength evidence that there is no difference between methylphenidate or amphetamine products in the rate of emergency department visits for cardiac reasons or between methylphenidate, amphetamines or atomoxetine in sudden death or ventricular arrhythmia.
    - Two retrospective cohort studies in adults provide low-strength evidence of similar risk of stroke or transient ischemic attack (TIA) for atomoxetine compared with stimulants; similarly, one retrospective cohort provided low-strength evidence of similar risk of sudden cardiac death for atomoxetine compared with stimulants.
- Growth
    - There is moderate-strength evidence that dextroamphetamine IR was associated with more suppression of height and weight compared to methylphenidate IR within the first few years, but the differences resolved in later years. There is moderate-strength evidence that methylphenidate IR and mixed amphetamine salts had similar effects on height and weight at 3 years.
- Only low-strength evidence is available on difference between ADHD drugs on long-term insomnia, appetite suppression and headaches. No comparative evidence is available on long-term outcomes such as tics, seizures, cardiovascular events, injury frequency and hepatotoxicity.

ABUSE/MISUSE/DIVERSION

- Survey data suggest lifetime non-medical use of methylphenidate IR and dextroamphetamine was more frequent compared to mixed amphetamine salts; the highest rate of diversion was with amphetamine/dextroamphetamine.

SUBGROUPS

- No head-to-head evidence was found for demographic, socioeconomic, or co-intervention subgroups.
- In children with Tourette's disorder, methylphenidate IR and clonidine IR had similar effects on ADHD symptoms.

New Safety Alerts:
None identified.

New Formulations or Indications:
The FDA approved a chewable tablet formulation of extended-release methylphenidate (QuilliChew ER™) for ADHD in children aged 6 years and older in December 2015. The drug, specifically dosed for each child, statistically significantly improved attention and behavior compared to placebo in a blinded, controlled laboratory classroom study that involved 90 children aged 6 to 12 years who had a diagnosis of ADHD. At the end of the double-blind treatment period, raters and teachers evaluated the attention and behavior of the students throughout the day using the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) rating scale. The SKAMP scale measures behaviors of ADHD using observations of the student's impairment in the classroom. SKAMP combined score is comprised of 13 items (including subscales: attention with items 1-4, deportment with items 5-8, quality of work with items 9-11 and compliance with items 12-13). The SKAMP composite score was obtained by summing up each item score where each item is rated on a 7-point impairment scale (0=normal to 6=maximal impairment) for a total possible combined score of 0 to 78; where higher score signified worst impairment. The combined SKAMP score, which was measured at 7 time points on the last day of the pre-determined treatment period, was used to assess the primary and secondary efficacy endpoints. The primary efficacy endpoint was the average treatment effect across all time points on the last day of the treatment period. QuilliChew ER was statistically significantly superior to placebo with respect to the primary endpoint by a difference of -7.0 points (95% CI, -10.9 to -3.1). A publication of this trial could not be identified through a Medline search.

Reference: Quillichew ER™ (methylphenidate hydrochloride extended-release), CII [product information]. Monmouth Junction, NJ: Tris Pharma, Inc., December 2015

The FDA approved an orally disintegrating extended-release tablet formulation of amphetamine (Adzenys XR-ODT™) for ADHD in patients 6 years of age and older in January 2016. The formulation was approved on the basis of pharmacokinetic data demonstrating that the drug was bioequivalent to Adderall XR (mixed amphetamine salts) extended-release capsule. It is the first orally disintegrating drug formulation for the management of ADHD.

Reference: Adzenys XR-ODT™ (amphetamine extended-release orally disintegrating tablets), CII [prescribing information]. Grand Prairie, TX: Neos Therapeutics, Inc., January 2016

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	TRADE NAME	GENERIC NAME	PDL
ORAL	TABLET	EVEKEO	AMPHETAMINE SULFATE	Y
ORAL	CAPSULE	STRATTERA	ATOMOXETINE HCL	Y
ORAL	TABLET	FOCALIN	DEXMETHYLPHENIDATE HCL	Y
ORAL	CPBP 50-50	FOCALIN XR	DEXMETHYLPHENIDATE HCL	Y
ORAL	CPBP 50-50	DEXMETHYLPHENIDATE HCL ER	DEXMETHYLPHENIDATE HCL	Y
ORAL	TABLET	ADDERALL	DEXTROAMPHETAMINE/AMPHETAMINE	Y
ORAL	TABLET	AMPHETAMINE SALT COMBO	DEXTROAMPHETAMINE/AMPHETAMINE	Y
ORAL	CAPSULE	VYVANSE	LISDEXAMFETAMINE DIMESYLATE	Y
ORAL	CPBP 30-70	METADATE CD	METHYLPHENIDATE HCL	Y
ORAL	TABLET	METHYLPHENIDATE HCL	METHYLPHENIDATE HCL	Y
ORAL	TABLET	RITALIN	METHYLPHENIDATE HCL	Y
TRANSDERM	PATCH TD24	DAYTRANA	METHYLPHENIDATE	Y
ORAL	TAB ER 12H	CLONIDINE HCL ER	CLONIDINE HCL	CARVE-OUT
ORAL	TAB ER 12H	KAPVAY	CLONIDINE HCL	CARVE-OUT
ORAL	TAB ER 24H	GUANFACINE HCL ER	GUANFACINE HCL	CARVE-OUT
ORAL	TAB ER 24H	INTUNIV	GUANFACINE HCL	CARVE-OUT
ORAL	TABLET	EVEKEO	AMPHETAMINE SULFATE	N
ORAL	CAPSULE ER	DEXEDRINE	DEXTROAMPHETAMINE SULFATE	N
ORAL	CAPSULE ER	DEXTROAMPHETAMINE SULFATE ER	DEXTROAMPHETAMINE SULFATE	N
ORAL	TABLET	DEXTROAMPHETAMINE SULFATE	DEXTROAMPHETAMINE SULFATE	N
ORAL	SOLUTION	DEXTROAMPHETAMINE SULFATE	DEXTROAMPHETAMINE SULFATE	N
ORAL	SOLUTION	PROCENTRA	DEXTROAMPHETAMINE SULFATE	N
ORAL	TABLET	ZENZEDI	DEXTROAMPHETAMINE SULFATE	N
ORAL	CAP ER 24H	ADDERALL XR	DEXTROAMPHETAMINE/AMPHETAMINE	N
ORAL	CAP ER 24H	DEXTROAMPHETAMINE-AMPHET ER	DEXTROAMPHETAMINE/AMPHETAMINE	N
ORAL	TABLET	DEXMETHYLPHENIDATE HCL	DEXMETHYLPHENIDATE HCL	N
ORAL	TABLET	METHAMPHETAMINE HCL	METHAMPHETAMINE HCL	N
ORAL	TABLET	DESOXYN	METHAMPHETAMINE HCL	N
ORAL	CPBP 30-70	METHYLPHENIDATE HCL CD	METHYLPHENIDATE HCL	N
ORAL	CPBP 50-50	METHYLPHENIDATE ER	METHYLPHENIDATE HCL	N
ORAL	CPBP 50-50	METHYLPHENIDATE LA	METHYLPHENIDATE HCL	N
ORAL	CPBP 50-50	RITALIN LA	METHYLPHENIDATE HCL	N
ORAL	SOLUTION	METHYLIN	METHYLPHENIDATE HCL	N
ORAL	SOLUTION	METHYLPHENIDATE HCL	METHYLPHENIDATE HCL	N

ORAL	SU ER RC24	QUILLIVANT XR	METHYLPHENIDATE HCL	N
ORAL	TAB CHEW	METHYLIN	METHYLPHENIDATE HCL	N
ORAL	TAB CHEW	METHYLPHENIDATE HCL	METHYLPHENIDATE HCL	N
ORAL	TAB ER 24	CONCERTA	METHYLPHENIDATE HCL	N
ORAL	TAB ER 24	METHYLPHENIDATE ER	METHYLPHENIDATE HCL	N
ORAL	TABLET ER	METADATE ER	METHYLPHENIDATE HCL	N
ORAL	TABLET ER	METHYLPHENIDATE ER	METHYLPHENIDATE HCL	N
ORAL	CPBP 50-50	RITALIN LA	METHYLPHENIDATE HCL	N

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to January Week 3 2016

1 exp Amphetamine/ 5569
2 exp Amphetamines/ 15803
3 exp Atomoxetine Hydrochloride/ 873
4 exp Clonidine/ 4155
5 exp Dexmethylphenidate Hydrochloride/ 48
6 exp Dextroamphetamine/ 1682
7 exp Guanfacine/ 265
8 exp Lisdexamfetamine Dimesylate/ 146
9 exp Methamphetamine/ 5275
10 exp Methylphenidate/ 3768
11 exp Attention Deficit Disorder with Hyperactivity/ or adhd.mp. or exp "Attention Deficit and Disruptive Behavior Disorders"/ 22396
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 23821
13 11 and 12 3478
14 limit 13 to (english language and (clinical study or 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 practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews) and last year) 22

No high-quality systematic reviews or guidelines were identified. In addition, no randomized, controlled clinical trials assessing clinically relevant health outcomes were identified.

Attention Deficit Hyperactivity Disorder (ADHD) Safety Edit

Goals:

- Cover ADHD medications only for diagnoses funded by the OHP and medications consistent with current best practices.
- Promote care by a psychiatrist for patients requiring therapy outside of best-practice guidelines.
- Promote preferred drugs in class.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred drugs on the enforceable preferred drug list.
- Regimens prescribed outside of standard doses and age range (Tables 1 and 2)
- Non-standard polypharmacy (Table 3)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. FDA-approved and OHP-funded Indications.

	STIMULANTS		NON-STIMULANTS	
Indication	**Methylphenidate and derivatives**	**Amphetamine and derivatives**	**Atomoxetine**	**Clonidine ER**	**Guanfacine ER**
ADHD	Age ≥6 years	Age ≥3 years	Age ≥6 years	Children age 6-17 years only	Children age 6-17 years only
Narcolepsy	Age ≥6 years	Age ≥6 years	Not approved	Not approved	Not approved

Table 2. Standard Age and Maximum Daily Doses.

Drug Type	Generic Name	Minimum Age	Maximum Age	Maximum Daily Dose (adults or children <18 years of age unless otherwise noted)
CNS Stimulant	amphetamine/dextroamphetamine salts IR	3		60 mg
CNS Stimulant	amphetamine/dextroamphetamine salts ER	6		30 mg
CNS Stimulant	dexmethylphenidate IR	6		20 mg
CNS Stimulant	dexmethylphenidate LA	6		40 mg for adults or 30 mg if age <18 years
CNS Stimulant	dextroamphetamine IR	6		40 mg
CNS Stimulant	dextroamphetamine LA	6		60 mg
CNS Stimulant	lisdexamfetamine	6		70 mg
CNS Stimulant	methamphetamine	6	17	not established
CNS Stimulant	methylphenidate IR	4		60 mg
CNS Stimulant	methylphenidate LA	6		72 mg
CNS Stimulant	methylphenidate transdermal	6	17	30 mg
Non-Stimulant	atomoxetine	6		100 mg
Non-Stimulant	clonidine LA	6	17	0.4 mg
Non-Stimulant	guanfacine LA	6	17	4 mg

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

Table 3. Standard Combination Therapy for ADHD

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

Abbreviations: IR = immediate-release formulation; LA = long-acting formulation (extended-release, sustained-release, etc.)
* As recommended by the American Academy of Pediatrics 2011 Guidelines www.pediatrics.org/cgi/doi/10.1542/peds.2011-2654
**As identified by Drug Class Review: Pharmacologic Treatments for Attention Deficit Hyperactivity Disorder: Drug Effectiveness Review Project, 2011.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the treated diagnosis an OHP-funded condition?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by OHP.

Approval Criteria		
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 do not require co-pay and 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 indication 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 for 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: *3/16 (AG); 5/14; 9/09; 12/08; 2/06; 11/05; 9/05; 5/05; 2/01; 9/00; 5/00*
Implementation: *TBD; 10/9/14; 1/1/15; 9/27/14; 1/1/10; 7/1/06; 2/23/06; 11/15/05*