Drug Class Review

Pharmacologic Treatments for Attention Deficit Hyperactivity Disorder

Final Update 5 Report

July 2015

The purpose of Drug Effectiveness Review Project 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. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Update 5 Authors:
Marian McDonagh, PharmD
Kim Peterson, MS
Brittany Holzhammer, MPH

Drug Effectiveness Review Project
Marian McDonagh, PharmD, Principal Investigator

Pacific Northwest Evidence-based Practice Center
Roger Chou, MD, Director
Marian McDonagh, PharmD, Associate Director

Copyright © 2015 by Oregon Health & Science University
Portland, Oregon 97239. All rights reserved.

Property of the Drug Effectiveness Review Project. For use by Idaho only.

Copyright Drug Effectiveness Review Project. All rights reserved.

STRUCTURED ABSTRACT

Purpose

Attention deficit hyperactivity disorder (ADHD) affects children and adults and is treated with both pharmacologic and nonpharmacologic interventions. Multiple drugs are used to treat ADHD. This review evaluates the evidence on how these drugs compare to each other in benefits and harms.

Data Sources

To identify published studies, we searched MEDLINE® the Cochrane Library databases, and reference lists of included studies. We also searched the U.S. Food and Drug Administration Center for Drug Evaluation and Research website for additional unpublished data and requested information from pharmaceutical manufacturers.

Review Methods

Study selection, data abstraction, validity assessment, grading the strength of the evidence, and data synthesis were all carried out according to our standard review methods.

Results and Conclusions

Evidence on the comparative effectiveness of drugs to treat ADHD was insufficient. Evidence on the comparative efficacy in children and adolescents was moderate- to low-strength with few differences among the drugs in improving symptoms or in adverse event rates in the short term. Comparisons of immediate-release and extended release stimulants found few differences; low-strength evidence suggested that lisdexamfetamine may be superior to methylphenidate OROS. Comparisons of sustained-release stimulant formulations showed differences at specific times of day depending on the pharmacokinetics, but overall differences were not found. Atomoxetine was not found superior to immediate-release methylphenidate, had lower efficacy than methylphenidate OROS, mixed amphetamine salts XR, lisdexamfetamine, and extended-release guanfacine, but resulted in higher rates of vomiting and somnolence, similar rates of nausea and anorexia, and lower rates of insomnia than stimulants. Immediate-release clonidine was similar to immediate-release methylphenidate. In adults, low-strength comparative evidence found similar efficacy for: immediate-release dextroamphetamine and modafinil or guanfacine; continuing immediate-release methylphenidate or switching to methylphenidate OROS; and immediate- versus extended-release mixed amphetamine salts. Differences in risk for sudden death and other cardiac events were not found among stimulants or between atomoxetine and stimulants. Dextroamphetamine immediate-release caused more inhibition of growth than other stimulants, with a dose-response, that resolved after 2 years. Comparative evidence on abuse, misuse, and diversion was limited and reported only on older stimulant drugs. Evidence of effects in subgroups of patients with anxiety or tic disorders indicated no differences among the stimulants.

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

TABLE OF CONTENTS

INTRODUCTION 6
Scope and Key Questions 6
Inclusion Criteria 7
Populations 7
Interventions 7
Comparators 7
Effectiveness Outcomes 7
Efficacy Outcomes 8
Harms 8
Tolerability 8
Serious and long-term (>12 months) adverse effects 8
Misuse/diversion 8
Study Designs 8
METHODS 8
Literature Search 8
Study Selection 9
Data Abstraction 9
Validity Assessment 9
Strength of Evidence 10
Effectiveness Compared With Efficacy 10
Data Synthesis 10
Peer Review 10
Public Comment 10
RESULTS 11
Overview 11
Key Findings 12
Efficacy and Tolerability 12
Young children (preschool age; 3-5 years) 12
Children (elementary school age; 6-12 years) 12
Stimulants 12
Nonstimulants 14
Adolescents 15
Adults 15
Long-Term Safety 15
Abuse/Misuse/Diversion 16
Subgroups 16
Key Question 1. Efficacy and Effectiveness for ADHD 16
Young children (preschool age; 3-5 years) 16
Children (elementary school age; 6-12 years and mixed populations up to 18 years) 17
Stimulants 17
Comparison of immediate-release and sustained-release formulations 18
Comparisons of sustained-release formulations 23
Comparisons of immediate-release formulations 24
Nonstimulants 27
Atomoxetine 27
Clonidine 28
Guanfacine 30
Adolescents (ages 13 to 17 - only) 30
Adults 31
Key Question 2. Harms 31
Short-term trial evidence in young children (preschool age; 3-5 years) 31

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

Short-term trial evidence in children (elementary school age; 6-12 years and mixed populations up to age 18 years) ... 32
Stimulants ... 32
Nonstimulants ... 33
Adults ... 34
Evidence on the long-term safety of drugs used to treat ADHD ... 35
Suicide ... 35
Cardiovascular deaths and events ... 35
Growth effects ... 37
Height ... 37
Weight ... 37
Insomnia, decreased appetite, and headaches ... 39
Tics ... 40
Seizures ... 40
Evidence on the risk of abuse, misuse or diversion of drugs used to treat ADHD in patients with no previous history of misuse/diversion ... 40
Key Question 3. Subgroups ... 41
Race or Ethnicity ... 41
Gender ... 42
Anxiety Disorders ... 42
Tic Disorders Including Tourette's Disorder ... 42

SUMMARY ... 43

Limitations of this Review ... 43
Applicability ... 43

CONCLUSIONS ... 48

REFERENCES ... 50

FIGURES

Figure 1. Results of Update 5 literature search ... 11

TABLES

Table 1. Attention deficit hyperactivity disorder drugs included in this review ... 7
Table 2. Numbers of head-to-head trials of drugs for attention deficit hyperactivity disorder ... 12
Table 3. Pharmacokinetic profiles of methylphenidate products ... 17
Table 4. Trials of immediate-release methylphenidate compared with methylphenidate OROS (Concerta®) ... 18
Table 5. Immediate-release dextroamphetamine compared with immediate-release methylphenidate study characteristics ... 25
Table 6. Change in Conners' Abbreviated Symptom Questionnaire Teacher scale ... 29
Table 7. Comparative effects on ADHD symptoms in head-to-head trials in adults ... 31
Table 8. Harms in head-to-head trials in adults ... 35
Table 9. Long-term height and weight outcomes with methylphenidate and other stimulants ... 38
Table 10. Summary of the evidence ... 44

APPENDIXES

Published in a separate document

EVIDENCE TABLES

Published in a separate document

Shading indicates new information for Update 5.

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

Acknowledgments
We thank Leah Williams, our publications editor, for putting this report into its present form for you to read. We also thank Ryan Stoner and Laura LaLonde for retrieval of articles and bibliographic assistance.

Authors of previous updates
Update 4 authors:
Marian S. McDonagh, PharmD
Kim Peterson, MS
Sujata Thakurta, MPA:HA
Allison Low, BA

Update 3 authors:
Marian S. McDonagh, PharmD
Vivian Christensen, PhD
Kim Peterson, MS
Sujata Thakurta, MPA:HA

Update 2 authors:
Marian S. McDonagh, PharmD
Kim Peterson, MS
Tracy Dana, MLS
Sujata Thakurta, MPA:HA

Original Report and Update 1 authors:
Marian S. McDonagh, PharmD
Kim Peterson, MS

Funding
The Drug Effectiveness Review Project, composed of 13 state Medicaid agencies, commissioned and funded this report. These organizations selected the topic of the report and had input into its Key Questions. The content and conclusions of the report were entirely determined by the Evidence-based Practice Center researchers. The authors of this report have no financial interest in any company that makes or distributes the products reviewed in this report.

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is considered the most commonly diagnosed childhood behavioral disorder. According to the most recent version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), ADHD symptoms are divided into two categories of inattention and hyperactivity and impulsivity that include behaviors such as failure to pay close attention to details, difficulty organizing tasks and activities, excessive talking, fidgeting, or an inability to remain seated in appropriate situations.[1] Symptoms can persist into adolescence in 80% of cases and into adulthood in 65% of cases.[2] Comorbid mood, anxiety, substance use, and/or impulse disorders also commonly occur in combination with ADHD in adults.[3] Historically, drug therapy for ADHD has consisted primarily of stimulant medications. More recently, nonstimulant medication treatment alternatives have been identified. Examples include atomoxetine, clonidine, and guanfacine. Nonstimulant treatment options *may* offer advantages for individuals (1) seeking medications that have not been identified as having potential for abuse, (2) with concern over the *potential* long-term effects of stimulants on growing children, (3) with a history of nonresponse to or poor tolerance of stimulants, and/or (4) in whom stimulants are contraindicated due to coexisting medical and/or behavioral disorders and/or concomitant medications.

Scope and Key Questions

The purpose of this review is to compare the benefits and harms of different pharmacologic treatments for ADHD. The Pacific Northwest Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project. The participating organizations of the Drug Effectiveness Review Project are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. What is the comparative evidence that pharmacologic treatments for attention deficit disorders differ in effectiveness or efficacy outcomes?
2. What is the comparative evidence that pharmacologic treatments for attention deficit disorders differ in harms (tolerability, serious adverse events, 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 co-morbidities (e.g. tics, anxiety, substance use disorders, disruptive behavior disorders)?

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

Inclusion Criteria

Populations

Pediatric (age <3, <6, and 6-17 years), and adult (age ≥18 years) outpatients with attention deficit disorders, including inattentive, hyperactive-impulsive, and combined subtypes

- Attention deficit disorder
- Attention deficit hyperactivity disorder

Interventions

Included drugs are described in Table 1.

Table 1. Attention deficit hyperactivity disorder drugs included in this review

Generic Name	Trade name	Forms
Mixed amphetamine salts	Adderall XR®	Extended-release oral capsule
Atomoxetine hydrochloride	Strattera®	Oral capsule
Clonidine hydrochloride	Catapres®, Catapres TTS	Oral tablet
	Kapvay™	Extended-release oral tablet
Dexmethylphenidate hydrochloride	Focalin®	Oral tablet
	Focalin XR®	Extended-release oral capsule
Dextroamphetamine sulfate	Dexedrine®	Oral tablet
	Dexedrine Spansule®	Sustained-release oral capsule
Guanfacine hydrochloride	Intuniv®	Extended-release oral tablet
	Tenex™	Oral tablet
Lisdexamfetamine dimesylate	Vyvanse®	Oral capsule
Methamphetamine hydrochloride	Desoxyn®	Oral tablet
Methylphenidate	Daytrana®	Extended-release transdermal film
Methylphenidate hydrochloride	Concerta®	Extended-release oral tablet
	Metadate CD®	Extended-release oral capsule
	Metadate ER®	Extended-release oral tablet
	Methylin®	Oral chewable tablet and solution
	Methylin ER®	Extended-release oral tablet
	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

Abbreviations: CD, controlled delivery; ER or XR, extended release; LA, long acting; SR, sustained release; TTS, transdermal therapeutic system

Comparators

Primary comparisons are included pharmacologic treatments (above) compared to each other.

- Comparisons by general mechanism of action (i.e. stimulants and nonstimulants) and by duration of formulation (i.e. short-, intermediate and long-acting) will also be made.

Effectiveness Outcomes

1. Functional capacity (social, academic and occupational productivity)
2. Quality of life (patient, family members, caregivers, teachers)

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

3. Time to onset of effectiveness
4. Duration of effectiveness (length of therapy)

Efficacy Outcomes

1. Symptom response (e.g., inattention, hyperactivity-impulsivity, global ratings, etc.), generally defined as the proportion of patients achieving a specific magnitude of improvement in scores on ADHD rating scales.

Numerous ADHD-specific and other psychiatric rating scales, as well as neuropsychological testing methods, are used to measure symptoms of ADHD. We limited our analyses to rating scales/tests for which we found published evidence of good reliability and validity.

Harms

Tolerability

1. Overall adverse effect reports
2. Withdrawals due to adverse effects and overall withdrawal
3. Specific adverse events (insomnia, anorexia, abuse potential, tics, anxiety and sexual dysfunction)

Serious and long-term (>12 months) adverse effects

1. Hepatotoxicity
2. Cardiovascular events
3. Growth effects
4. Suicide and suicidal behavior

Misuse/diversion

1. Trading, selling
2. Compliance, overdose
3. Development of substance abuse disorders

Study Designs

- Head-to-head randomized controlled trials
- Good-quality systematic reviews with similar scope and recent searches.
- Comparative observational studies (cohort studies including database studies, and case-control studies) to examine differences in effectiveness outcomes and serious and long-term harms and misuse/diversion outcomes.

METHODS

Literature Search

To identify relevant citations, we searched the Cochrane Central Register of Controlled Trials (February 2015), Cochrane Database of Systematic Reviews (2005 to February 2015), Ovid

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

MEDLINE® and Ovid OLDMEDLINE® (1946 to March Week 5 2015), Ovid MEDLINE® In-Process & Other Non-Indexed Citations (April 01, 2015) and PsycINFO (1806 to March Week 5 2015) using terms for included drugs, indications, and study designs (see Appendix B for complete search strategies). We attempted to identify additional studies through searches of reference lists of included studies and reviews, including the US Food and Drug Administration Center for Drug Evaluation and Research website for medical and statistical reviews of individual drug products. Finally, we requested dossiers of published and unpublished information from the relevant pharmaceutical companies for this review. All received dossiers were screened for studies or data not found through other searches. All citations were imported into an electronic database (Endnote® X7, Thomson Reuters).

Study Selection

Selection of included studies was based on the inclusion criteria created by the Drug Effectiveness Review Project participants. Two reviewers independently assessed titles and abstracts of citations identified through literature searches for inclusion using the criteria below. Full-text articles of potentially relevant citations were retrieved and again were assessed for inclusion by both reviewers. Disagreements were resolved by consensus. Results published *only* in abstract form were not included because inadequate details were available for quality assessment.

Data Abstraction

We abstracted information on population characteristics, interventions, subject enrollment, and discontinuation and results for efficacy, effectiveness, and harms outcomes for trials, observational studies, and systematic reviews. We recorded intent-to-treat results when reported. If true intent-to-treat results were not reported, but loss to follow-up was very small, we considered these results to be intent-to-treat results. In cases where only per-protocol results were reported, we calculated intent-to-treat results if the data for these calculations were available.

Validity Assessment

We assessed the internal validity (quality) of trials based on predefined DERP criteria based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intent-to-treat analysis for trials, and similar aspects for observational studies.[4] Studies were given an overall rating of good, fair or poor. Included systematic reviews were also rated for quality, based a clear statement of the review questions(s); reporting of inclusion criteria; methods used for identifying literature (the search strategy), validity assessment, and synthesis of evidence; and details provided about included studies.[4] These studies were categorized as good when all criteria were met. Study quality was first assessed by one reviewer and checked by another. All differences were resolved by consensus.

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

Strength of Evidence

The strength, or quality, of each body of evidence corresponding to a given drug-drug comparison for efficacy, effectiveness, harms or subgroups was assessed using the key domains of: methodological limitations (combines study designs, study sizes, and study quality), consistency, directness, and precision of the evidence. Earlier versions of this report used the U.S. Preventive Services Task Force methods, where the overall strength of evidence for a particular key question was assessed based on the quality, consistency, and power of the set of studies relevant to the question.

Effectiveness Compared With Efficacy

Throughout this report, we highlight *effectiveness* studies conducted in primary care or office-based settings that use less stringent eligibility criteria, assess health outcomes, and have longer follow-up periods than most *efficacy* studies. The results of effectiveness studies are more applicable to the "average" patient than results from highly selected populations in efficacy studies. Examples of "effectiveness" outcomes include quality of life, global measures of academic success, and the ability to work or function in social activities. These outcomes are more important to patients, family, and care providers than surrogate or intermediate measures such as scores based on psychometric scales.

Data Synthesis

We constructed evidence tables showing the study characteristics, quality ratings, and results for all included studies. We reviewed studies using a hierarchy of evidence approach, where the best evidence is the focus of our synthesis for each question, population, intervention, and outcome addressed. Quantitative analyses were conducted using meta-analyses of outcomes reported by a sufficient number of studies that were adequately homogeneous to allow pooling. In order to determine whether meta-analysis could be meaningfully performed, we considered the quality of the studies and the heterogeneity among studies in design, patient population, interventions, and outcomes. When meta-analysis could not be performed, the data were summarized qualitatively.

Peer Review

We requested and received peer review of the report from 1 methodology expert. Her comments were reviewed and, where possible, incorporated into the final document. All peer review and public comments and the authors' proposed actions were reviewed by representatives of the participating organizations of the Drug Effectiveness Review Project before finalization of the report.

Public Comment

This report was posted to the Drug Effectiveness Review Project website for public comment. We received comments from 2 people, both of them representing pharmaceutical companies.

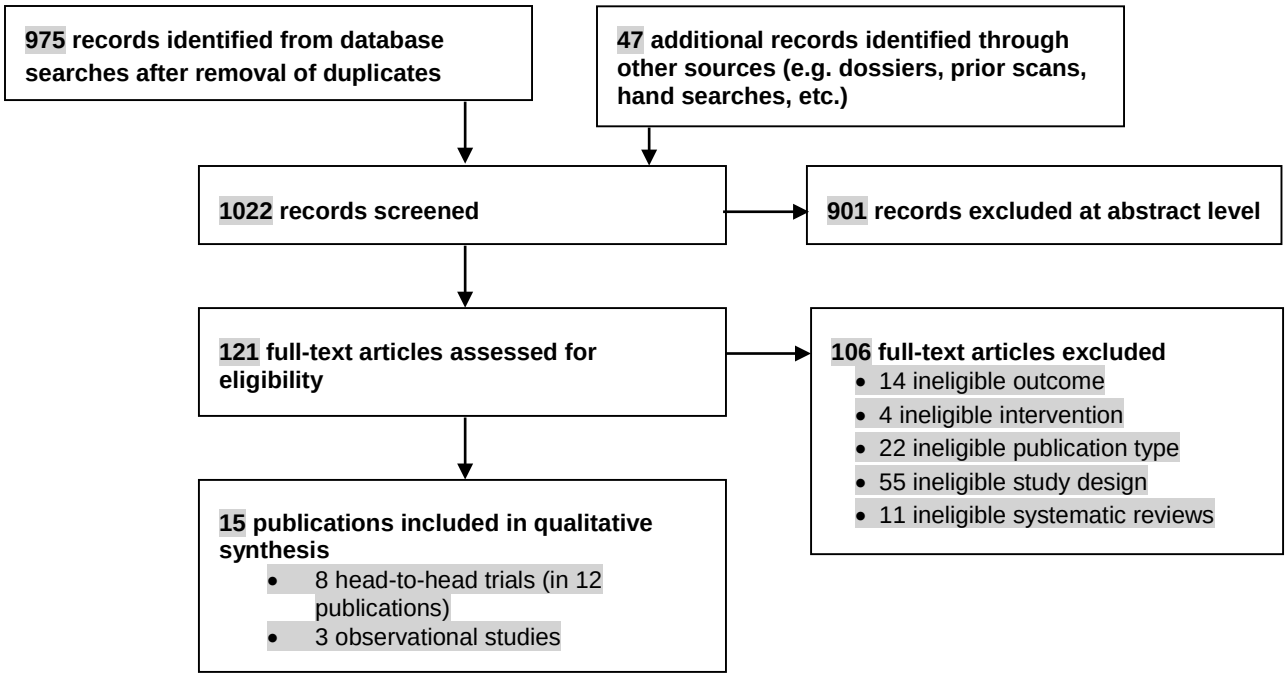
Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

RESULTS

Overview

Figure 1 details the results of our literature searches for Update 5. Overall, we identified a total of 1,022 citations from searching electronic databases, pharmaceutical manufacturer dossier submissions, reviews of reference lists, and hand searches. By applying the eligibility and exclusion criteria to titles and abstracts of all identified citations, we obtained full-text copies of 121 citations. After re-applying the criteria for inclusion, we ultimately included 15 publications, including 8 head-to-head trials[5-12] in 12 publications[5-16] and 3 observational studies.[17-19] A total of 126 publications are included in this review, reflecting studies identified in the current update and those identified in all prior reports in this drug class review. Dossiers were submitted by 5 pharmaceutical manufacturers for the original review: Eli Lilly (atomoxetine HCl), McNeil (methylphenidate OROS), Novartis (methylphenidate HCl, Ritalin LA®), Cephalon (modafinil), and Shire US (mixed amphetamine salts, mixed amphetamine salts XR). Additional dossiers were submitted for updates of this report as follows: Update 1, Eli Lilly (atomoxetine HCl) and McNeil (methylphenidate HCl, Concerta®); Update 2, Shire US (lisdexamfetamine dimesylate), McNeil (methylphenidate OROS), and Eli Lilly (atomoxetine HCl); Update 3, Eli Lilly (atomoxetine HCl), Shire US (lisdexamfetamine dimesylate and transdermal methylphenidate), and McNeil (methylphenidate OROS); Update 4, Shire US, Inc (guanfacine and lisdexamfetamine), UCB, Inc, (methylphenidate CD), Shionogi Inc (clonidine), and Ortho-McNeil Janssen Scientific Affairs, LLC (methylphenidate OROS); and Update 5, Boehringer-Ingelheim (clonidine, Catapres® and Catapres TTS®) and Janssen (methylphenidate HCl, Concerta®). A list of excluded studies and reasons for exclusion is available in Appendix C.

Figure 1. Results of Update 5 literature search[a]



[a] A modified PRISMA diagram was used.[20]

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

We identified the following numbers of primary head-to-head comparative trials of pharmacologic treatments for attention deficit hyperactivity disorder (Table 2).

Table 2. Numbers of head-to-head trials of drugs for attention deficit hyperactivity disorder

	MPH IR	MPH ER	MTS	CLON	DEX	DEX-MPH	DEX-MPH ER	GUAN	MAS IR	MAS XR	MODA	ATX	LIS DEX
MPH IR													
MPH ER	C: 13 A: 1	C: 2 T: 1											
MTS	C: 1	C: 1											
CLON	C: 4	--											
DEX	C: 11 A: 1	--											
DEX-MPH	C: 1	--	--	--	--								
DEX-MPH ER	--	C: 2 (1)	--	--	--	--							
GUAN	--	--	--	--	A: 1	--							
MAS IR	C: 5				C: 1								
MAS XR	--	T: 2	--	--	--	--	C: 1 (1)	--	A: 1 (1) C: 1				
MODA	C: 1	--	--	--	A: 1	--	--	--	--				
ATX	C: 3 (1)	C: 3 (1)	--	--	--	--	--	C: 1 (1)	C: 1	--	--		
LIS DEX	--	C: 1 (1)	--	--	--	--	--	--	--	C: 1	--	C: 1 (1)	

Abbreviations: A, adults; C, children; T, adolescents; ATX, atomoxetine; CLON, clonidine; DEX, dextroamphetamine; DEX-MPH, dexmethylphenidate; GUAN, guanfacine; LIS DEX, lisdexamphetamine; MODA, modafinil; MPH ER, methylphenidate extended release; MPH IR, methylphenidate immediate release; MTS, methylphenidate transdermal system.
Notes: Study counts reflect primary head-to-head trials (counts of companion publications are *not* included); Parentheses show primary head-to-head studies new to Update 5 (N=8).

Key Findings

Efficacy and Tolerability

Young children (preschool age; 3-5 years)

- Comparative evidence in young children was not found. Placebo-controlled evidence was mixed on efficacy outcomes.
- Adverse events occurred significantly more often with methylphenidate than with placebo. Over longer-term treatment, some resolved but others did not.

Children (elementary school age; 6-12 years)

Stimulants

- Immediate-release compared with extended-release formulations
  - The evidence regarding immediate-release methylphenidate compared with methylphenidate osmotic-release oral system (OROS) was conflicting, with 2 double-blind trials unable to identify differences, while 2 open-label studies found that methylphenidate OROS resulted in greater improvements on some but not all assessments.
  - Limited evidence was available for the comparisons of immediate-release methylphenidate to other extended-release formulations. Overall, the studies were

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

unable to identify differences between methylphenidate sustained-release (SR) and immediate-release methylphenidate, and methylphenidate controlled-delivery (CD) was found to be noninferior to immediate-release methylphenidate.
    - Significantly more children taking lisdexamfetamine achieved response (18% more) and had greater improvement in ADHD Rating Scale (ADHD-RS) scores at 7 weeks than those taking methylphenidate OROS (difference -5.6 points). Parent ratings found lisdexamfetamine had better scores in the morning, afternoon, and evening.
        - Overall adverse event rates did not differ, but there were slightly more discontinuations with lisdexamfetamine. More children had anorexia, decreased appetite, decreased weight, insomnia, and nausea with lisdexamfetamine, and headaches and nasopharyngitis with methylphenidate OROS.
- Sustained-release compared with 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. However, these results should be interpreted with caution until higher quality evidence is available.
    - Methylphenidate CD was better than methylphenidate OROS in the morning, similar in the afternoon, and methylphenidate OROS was superior in the evening. Methylphenidate OROS had statistically significantly higher rates of insomnia and decreased appetite than methylphenidate CD.
    - Limited evidence from 2 similar trials indicated that dexmethylphenidate extended-release (ER) resulted in better response from 0.5 to up to 6 hours post dose compared with methylphenidate OROS (primary outcome measure). Methylphenidate OROS resulted in better scores later in the day; from 10 to 12 hours post dose. Math scores followed a similar pattern.
    - 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. There was no evidence of a difference in adverse events between immediate-release and sustained-release formulations.
    - Differences were not found between lisdexamfetamine and mixed amphetamine salts XR using the Swanson, Kotkin, Agler, M-Flynn, and Pelham Deportment Scale (SKAMP-DS) scores in a simulated classroom setting, or using the Clinical Global Impressions – Improvement (CGI-I) response rates after 1 week. Adverse events were reported to not be different, but data were not reported.
- Immediate-release compared with immediate-release formulations
    - Dextroamphetamine compared with methylphenidate
        - The body of evidence clearly indicated no difference in efficacy between immediate-release dextroamphetamine and immediate-release methylphenidate. Evidence from short-term trials and observational studies suggested that weight loss is greater with immediate-release dextroamphetamine than immediate-release methylphenidate.
    - Mixed amphetamine salts compared with methylphenidate

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

        - Immediate-release mixed amphetamine salts were superior to immediate-release methylphenidate on a few efficacy outcome measures in 2 trials, but clear evidence of superiority was lacking.
    - Modafinil compared with methylphenidate
        - Differences were not found between modafinil and immediate-release methylphenidate over 6 weeks.
    - Dextroamphetamine compared with mixed amphetamine salts
        - Limited evidence suggested immediate-release dextroamphetamine was superior to dextroamphetamine SR in the morning, and dextroamphetamine SR was superior to mixed amphetamine salts in the afternoon. Transient weight loss was greater with mixed amphetamine salts and dextroamphetamine SR than with immediate-release dextroamphetamine.
- Transdermal methylphenidate compared with methylphenidate OROS
    - Methylphenidate transdermal system was found to have similar efficacy to methylphenidate OROS (over 7 weeks starting 4 hours after administration) and immediate-release methylphenidate (over 12 hours in a simulated classroom setting, starting 30 minutes after dosing).
    - Differences in adverse events were not found between methylphenidate transdermal system and immediate-release methylphenidate.

Nonstimulants

Atomoxetine

- Atomoxetine compared with methylphenidate
    - Evidence from 2 trials suggested that atomoxetine was associated with efficacy outcomes similar to immediate-release methylphenidate.
- Atomoxetine compared with methylphenidate OROS
    - Methylphenidate OROS had higher response rates; 56% methylphenidate OROS and 45% atomoxetine; P=0.02, and greater reduction in ADHD-RS scale score after 4 to 6 weeks.
- Atomoxetine compared with lisdexamfetamine
    - Lisdexamfetamine resulted in clinical improvement 9 days earlier and more patients had achieved clinical response (82% versus 64%), and had greater change in the ADHD-RS score (difference -6.5) at 9 weeks than atomoxetine.
- Atomoxetine compared with mixed amphetamine salts
    - Mixed amphetamine salts XR was found 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 approximately 3 times greater than immediate-release methylphenidate or mixed amphetamine salts XR. Incidence of somnolence (6% to 26%) was 3 to 4 times greater than methylphenidate OROS and mixed amphetamine salts XR.
- 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).

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

Clonidine

- Current evidence did not clearly identify a difference in improvement of ADHD symptoms between immediate-release clonidine and immediate-release methylphenidate in children with ADHD (both with comorbid Tourette's disorder and without). Caution is suggested in interpreting these results due to inconsistency in some outcomes.
- Immediate-release clonidine resulted in higher rates of sedation (42%) than immediate-release methylphenidate (14%), with 28% reporting the sedation to be moderate or severe. Somnolence may improve with time.
- No head-to-head evidence was available on extended-release clonidine

Guanfacine

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

Adolescents

- Methylphenidate OROS resulted in better simulated driving scores than immediate-release methylphenidate (only in the late evening or nighttime) and immediate-release 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 immediate-release dextroamphetamine and either modafinil or guanfacine, between continuing with immediate-release methylphenidate or switching to methylphenidate OROS, or between immediate-release compared with extended-release mixed amphetamine salts. Those same 4 trials provided low-strength evidence of no difference in harms, except for the comparison of immediate-release and extended-release mixed amphetamine salts, for which evidence was insufficient to draw conclusions on harms because there were no comparisons between drugs.

Long-Term Safety

- Cardiovascular deaths and events
  - For children, 2 retrospective cohort studies (in 3 publications) provided low-strength evidence of no significant differences 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
  - For adults, 2 retrospective cohort studies provided low-strength evidence of similar risk of stroke or transient ischemic attack (TIA) for atomoxetine compared

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

with stimulants and 1 retrospective cohort provided low-strength evidence of similar risk of sudden cardiac death for atomoxetine compared with stimulants

- Growth: There was moderate-strength evidence that immediate-release dextroamphetamine led to greater height and weight suppression than immediate-release methylphenidate within the first few years, but the differences resolved in later years. There was moderate-strength evidence that immediate-release methylphenidate and mixed amphetamine salts had similar effects on height and weight at 3 years.
- Evidence on longer-term insomnia, appetite suppression and headaches was low-strength. Insomnia and decreased appetite were not statistically significantly different among immediate-release methylphenidate, methylphenidate OROS, mixed amphetamine salts, mixed amphetamine salts XR, and atomoxetine.
    - Atomoxetine had lower rates of headache compared with mixed amphetamine salts XR (0% and 12%; P=0.001), immediate-release mixed amphetamine salts (0% and 11%; P=0.001), or methylphenidate OROS (0% and 10%; P=0.002).
- There was no comparative evidence on other long-term safety outcomes, including tics, seizures, cardiovascular adverse events, injury frequency, and hepatotoxicity.

Abuse/Misuse/Diversion

- Survey data suggested that lifetime nonmedical use was more frequent with immediate release methylphenidate or dextroamphetamine compared with mixed amphetamine salts and that amphetamine/dextroamphetamine had the highest rate of diversion

Subgroups

- No head-to-head evidence was found for demographic, socioeconomic, or co-intervention subgroups
- Differences in the rate of anxiety as an adverse event did not differ statistically significantly between immediate-release methylphenidate and immediate-release dextroamphetamine, mixed amphetamine salts, methylphenidate SR, methylphenidate OROS, or atomoxetine.
- In children with Tourette's disorder, immediate-release methylphenidate and immediate-release clonidine had similar effects on ADHD symptoms.

Key Question 1. Efficacy and Effectiveness for ADHD

Young children (preschool age; 3-5 years)

Evidence on pharmacotherapy for ADHD in young children was seriously lacking (Evidence Table 1) with no head-to-head evidence. Currently, the U.S. Food and Drug Administration approve no drugs for use in children less than 6 years old. The only randomized controlled trial (RCT) evidence available is summarized below.

A fair-quality trial, using an assessment tool with good validity (Children's Psychiatric Rating Scale-Revised; learning, conduct, and hyperactivity indices only), compared high dose (0.5 mg/kg twice daily) and low dose (0.3 mg/kg twice daily) immediate-release methylphenidate with placebo in preschool-aged children for 7 to 10 days.[21] Both doses resulted

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

in better scores than placebo. The high dose resulted in better scores than the low dose on only the learning component of the scale, with the low dose resulting in a mean of 8 points (10%) lower, and the high dose a mean of 14 points (18%) lower than the score while on placebo. The clinical importance of these differences is not known, and baseline scores are not reported or accounted for. Based on parental report, medication did not result in better compliance with tasks compared with placebo; although reports of time on task were better with the higher dose (mean 52 seconds longer compared with placebo).

The Preschool ADHD Treatment Study assessed immediate-release methylphenidate relative to placebo.[22,23] The study was a multi-center, multi-phase trial that included a crossover dose-titration phase (5 weeks; N=165), a parallel phase (4 weeks; N=114), and an open-label phase (10 months; N=140). In the publication describing the study design[22] the primary outcome measure of the crossover phase of the trial is described as a composite of scores from the Swanson, Conners, Milich, and Pelham scale and the Conners, Loney, and Milich Rating (CLAM) scale, while the publication of the results of the trial[23] state that the a priori primary outcome measure of the crossover phase is a composite of CLAM and Swanson, Kotlin, Agler, M-Flynn and Pelham (SKAMP) scale scores. The reason for or effect of this discrepancy is not stated. The primary outcome of the parallel phase was a derivative of the Swanson, Nolan and Pelham (SNAP-IV) scale ("excellent responder" criteria).[22]

The parallel phase of the study, in which 114 patients were randomized to either placebo or their optimal dose of immediate-release methylphenidate for 4 weeks, found no significant difference in the number of immediate-release methylphenidate patients that met the primary outcome measure of "excellent response" on the SNAP-IV score compared with placebo patients (immediate-release methylphenidate 13/61 [22%] compared with placebo 7/53 [13%; P<0.3]). Although a post-hoc analysis of overall SNAP scores found that immediate-release methylphenidate patients had a lower mean endpoint symptom score than placebo patients (immediate-release methylphenidate 1.49 compared with placebo 1.79; P<0.02), it is not clear how comparable the scores were at baseline. Overall patient withdrawal from this study was high (32%; N=36), with 45% of withdrawals on placebo and 15% on immediate-release methylphenidate.

Children (elementary school age; 6-12 years and mixed populations up to 18 years)

Stimulants

Table 3. Pharmacokinetic profiles of methylphenidate products[a]

Drug	Daily doses	Time to peak (hours)	Duration of action (hours)	Delivery system
Short-acting				
Immediate-release methylphenidate	2-3	1-2	3-4	Immediate-release tablet
Intermediate-acting				
Metadate ER®	2-3	~ 4-5	8	Wax-matrix vehicle tablet
Methylin ER®	2-3	~ 4-5	8	Wax-matrix vehicle tablet
Ritalin SR®	1-2	~ 3-4	8	Wax-matrix vehicle tablet
Focalin®	2	1-1.5	3-4	Immediate-release tablet
Long-acting (biphasic pharmacokinetic profiles)				
Biphentin®[b]	1	1st: 1.7-2.6 2nd: ~4.5	10-12	Multilayer-release system: 40% immediate; 60% delayed

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

Table 3. Pharmacokinetic profiles of methylphenidate products[a]

Drug	Daily doses	Time to peak (hours)	Duration of action (hours)	Delivery system
Metadate CD®, Equasym®	1	1st: 1.5 2nd: 4.5	8	Errand Diffucaps: 30% IR & 70% ER beads released from capsule
Ritalin LA®	1	1st: 1-3 2nd: 4-5	8-10	Spheroidal Oral Drug Absorption System (SODA): 50% IR; 50% delayed-release beads released from capsule
Concerta®	1	1st: 1-2 2nd: 6-8	12	Osmotic Release Oral System (OROS): 22% IR tablet coating; 78% released from tablet utilizing osmotic pressure
Focalin XR®	1	6.5	12	Spheroidal Oral Drug Absorption

[a] Information obtained from product labels.
[b] Not available in the United States.
Abbreviations: CD, controlled delivery; ER, extended release; IR, immediate release; LA, long acting; SR, sustained release

Comparison of immediate-release and sustained-release formulations

Immediate-release methylphenidate compared with methylphenidate OROS (Concerta®).

Efficacy Outcomes.

Five studies have compared immediate-release methylphenidate with methylphenidate OROS once daily, enrolling a total of 561 children with ADHD (Table 4).[24-28]

Table 4. Trials of immediate-release methylphenidate compared with methylphenidate OROS (Concerta®)

Study details	Mean dose	Mean *change* in IOWA Conners' MPH OROS vs. MPH IR	SNAP-IV MPH OROS vs. MPH IR	Response Rate
Wolraich, 2001 Double-blind RCT United States N=282 28 days	MPH IR 29.5 daily (TID dosing) Concerta® 34.3 daily	*Teacher ratings:* Inattention/overactivity –3.57 vs. –3.76 Oppositional/defiance –1.3 vs. –1.6 3 *Parent ratings:* Inattention/overactivity –3.73 vs. –4.79 Oppositional/defiance –2.36 vs. –3.24 *For all comparisons, P*=NS	*Teacher SNAP-IV:* Inattention –0.69 vs. –0.80 Hyperactivity/impulsivity –0.64 vs. –0.69 Oppositional/defiance –0.36 vs. –0.32 *Parent SNAP-IV:* Inattention –0.91 vs. –0.77 Hyperactivity/impulsivity –0.91 vs. –0.74 Oppositional/defiance –0.65 vs. –0.41 *For all comparisons, P*=NS	GI-I : 46.2 vs. 47.2 Global Effectiveness as "Good" or "Excellent" Parent: 54 vs. 46.5 Teacher: 42.9 vs. 46.9
Pelham, 2001 Double-blind Crossover[a] + Behavioral Treatment United States N=68 7 days	MPH IR 29 mg daily (TID dosing) Concerta® 35 daily	*Teacher ratings:* Inattention/overactivity 4.96 vs. 4.65 Oppositional/defiance 2.08 vs. 2.26 *P*=NS for both comparisons *Parent ratings:* Inattention/overactivity 4.49 vs. 5.64; *P*=0.05; Oppositional/defiance 2.02 vs. 2.46; *P*=NS		Global Effectiveness as "Good" or "Excellent" *Parent: 67.2 vs. 64.7* *Teacher: 67.2 vs. 57.4*
Swanson, 2003 Double-blind	MPH IR 5-15 mg daily (TID	*Teacher ratings:* *Reported as P=0.32 between active drug*	*Not measured.*	

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

Table 4. Trials of immediate-release methylphenidate compared with methylphenidate OROS (Concerta®)

Study details	Mean dose	Mean *change* in IOWA Conners' MPH OROS vs. MPH IR	SNAP-IV MPH OROS vs. MPH IR	Response Rate
RCT United States N=64 1 week	dosing) Concerta® 18-54 mg daily	*groups.*		
Steele, 2006 Open-label RCT Canada/United States N=147 8 weeks	MPH IR 33.3 mg daily (usual care; 61% TID, 38% BID) Concerta® 37.8 mg daily	*Teacher ratings:* NA *Parent ratings:* Inattention/overactivity –3.9 vs. –5.4; *P*=0.01; Oppositional/defiance NA	*Parent ratings:* SNAP-IV Remission[b] 16% vs. 44%; P 0.0002; NNT 3.6) Mean Change in SNAP-IV 26 (ADHD + ODD) –17.5 vs. –25.2; *P*=0.004 SNAP-IV-18 (ADHD only) –14.3 vs. –19.6; *P*=0.01	
Conners' Rating Scale Revised Short-Form				
Gau, 2006 Open-label RCT Taiwan N=64 28 days	NR	*Teacher ratings:* Inattention –1.90 vs. –1.44 Hyperactivity/impulsivity –4.94 vs. –4.00 Oppositional –3.03 vs. –1.91 *Parent ratings:* Inattention –5.63 vs. –4.19 Hyperactivity/impulsivity –7.53 vs. –5.84 Oppositional –3.87 vs. –3.41 Comparisons of slope (change in score over time) between treatments: *P*<0.0001 for all comparisons		

Abbreviations: ADHD, attention deficit hyperactivity disorder; BID, twice daily; NA, not applicable – scale not applied; NNT, number needed to treat; ODD, oppositional defiant disorder; RCT, randomized controlled trial; TID, 3 times daily.
[a] Simulated classroom setting and natural setting data collected; natural setting results reported here.
[b] 0 or 1 on all 18 ADHD items in SNAP-IV.

In the 3 double-blind trials submitted to the U.S. Food and Drug Administration, in which the primary comparison of interest was specified as methylphenidate OROS compared with placebo, methylphenidate OROS and immediate-release methylphenidate did not differ significantly on the majority of direct comparisons.[24,26,28] In contrast, the 2 newer, open-label studies did find a significant difference favoring methylphenidate OROS.[25,27] There is a potential risk of selection bias in that only 1 of the studies[26] reported the proportion of patients taking immediate-release methylphenidate or methylphenidate OROS prior to enrollment. The US Food and Drug Administration Statistical Review of the New Drug Application for methylphenidate OROS includes criticism of the trials submitted for product approval,[24,26,28] indicating that an assumption of equivalence should not be made based on these studies alone. (http://www.fda.gov/cder/foi/nda/2000/21-121_Concerta_statr.pdf - page 32).[29]

In the largest, highest-quality study, there were no significant differences between the formulations on the primary outcome measure (IOWA Conners' scale) or on 11 secondary measures in a randomized controlled trial of 312 children.[24] Similarly, a much smaller crossover trial (68 children) that was 7 days long and included behavioral treatment, found methylphenidate OROS to have lower scores on the Abbreviated Conners' Parents scale (total), and on the inattention/overactivity item (out of 16 items), however no differences were found

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

based on assessments made by teachers and counselors.[26] An additional study of 64 children was rated poor quality because it lacked adequate reporting on multiple measures.[28]

The study by Steele, et al.[25] was open-label, comparing usual care to switching to methylphenidate OROS. Based on a definition of remission as a score of 0 or 1 (none or just a little) on the 18 items relating to ADHD symptoms only (excluding the items pertaining to oppositional defiant disorder) of the parent assessed SNAP-IV scale, methylphenidate OROS treatment resulted in more patients being classified as in remission at 8 weeks, with a number needed to treat near 4 (see Table 4). Similar results were found using other measures of parental assessment. This study did not include teacher ratings. Because the study was open to patients currently receiving treatment, including immediate-release methylphenidate, and it was unblinded, it is potentially biased against immediate-release methylphenidate. The proportion of patients taking immediate-release methylphenidate, methylphenidate OROS, or who were not taking drug therapy prior to study enrollment was not reported.

We undertook an exploratory analysis, pooling the parent ratings of inattention/overactivity subscale items of the IOWA Conners' scale from these 3 studies, as it was the only item reported across all 3 (see Table 4). While the Wolraich and Pelham studies did not find significant differences in the mean change on this item, the pooled analysis with the Steele study does result in a statistically significant finding, favoring methylphenidate OROS (weighted mean difference, –1.19; 95% CI, –1.78 to –0.60). However, we did consider this an exploratory analysis because standard deviations were not provided in the Pelham and Wolraich studies and we made an assumption that the baseline and final scores were moderately correlated ($r^2 = 0.25$).

A fourth study conducted in Taiwan found methylphenidate OROS superior to immediate-release methylphenidate, assessing the change in Conners' Teacher Rating Scale Revised Short-Form score by either teacher or parent over 5 time points using a linear mixed model, $P<0.0001$ (see Table 4). The absolute difference in individual scores were not large (Table 4), with the largest difference in teacher ratings being 1.12 for oppositional defiant behaviors (out of 5 possible), and 1.69 for hyperactivity/impulsivity (out of 7 possible) in the parent ratings. This study had the same potential for bias as the unblinded study by Steele, except that in this case all patients had previously been taking some form of methylphenidate, but again the proportions taking immediate-release methylphenidate compared with methylphenidate OROS or other formulations prior to enrollment was not reported.

In contrast, findings from a retrospective study of 92 children from a "real-life clinical situation" in the United Kingdom suggested that 32% ($P<0.001$) were considered treatment failures when switched to an extended-release form of methylphenidate (Concerta XL®) from immediate-release methylphenidate of an unknown duration.[30] The validity and generalizability of these findings were unclear, however, as the study was retrospective in nature, physicians' use of personal case load to identify patients may have introduced a selection bias, treatment failure was not precisely defined, and it was unclear whether the United Kingdom formulation is comparable to methylphenidate OROS as included in this review.

Effectiveness Outcomes.

Integrated Health Care Information Services managed care claims data suggest that methylphenidate OROS was associated with fewer outpatient visits/hospitalization for accidents/injury than immediate-release methylphenidate over a 12-month follow-up period (odds ratio, 0.58; 95% CI, 0.353 to 0.945).[31] The study population (N=1,775) was 75% male,

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

with a mean age of 9.7 years; however no other information regarding ADHD subtypes, comorbidities, or race/ethnicity were provided. In a second study, reported in 2 publications,[32] that also used data from the Integrated Health Care Information Services database to derive a larger sample (N=5,939) of somewhat older children (mean age of 15 years) who were also mostly male (77%), findings also suggest that methylphenidate OROS was associated with a lower probability of an emergency room visit (odds ratio, 0.79; 95% CI, 0.60 to 0.95)[32] and a lower probability of being hospitalized (odds ratio, 0.67; 95% CI, 0.45 to 0.99) over a 12-month period.[33] This study also found that age, prior number of diagnoses, and drug or alcohol abuse were statistically significantly associated with the probability of being hospitalized[33] and that geographic region, total number of diagnoses, presence of drug or alcohol abuse, or accident or injury were statistically significantly associated with the probability of an emergency room visit and the number of visits.[32] However, the study also found that those taking immediate-release methylphenidate were statistically significantly younger (14 years compared with 17 years old), had more total diagnoses, and geographic differences in the proportions of patients taking methylphenidate OROS compared with immediate-release methylphenidate were present.

Immediate-release methylphenidate compared with methylphenidate SR (Ritalin SR®). A small 2-week randomized controlled trial (34 children) of immediate-release methylphenidate compared with methylphenidate SR found mixed results.[34] The outcome measures included questionnaires (not validated) completed by a physician, a teacher, and a parent. The teacher questionnaires indicated significant differences in final total score and the "Conduct Problem" scores favored immediate-release methylphenidate. Parent questionnaires indicated a significant difference favoring methylphenidate SR on the "Conduct Problem" item final score, and the physician scores showed no difference.

Immediate-release methylphenidate compared with methylphenidate ER (Metadate CD®, Equasym®). A 3-week study using over-encapsulation for blinding enrolled 327 children, comparing immediate-release methylphenidate to Equasym® (sold in the United States as Metadate CD®). The study analyzed only 87% of patients in the main per-protocol analysis with unclear description of those excluded.[35] The study included a non-inferiority analysis, assuming a difference of ≤ 1.5 points on the I/O score of the Conners' IOWA teachers rating scale to indicate equivalence (non-inferiority). At weeks 1, 2, and 3 immediate-release methylphenidate was found equivalent to Equasym®. Intent-to-treat analysis as well as subgroup analyses (country, dose, ADHD subtype) were reported in the discussion as supporting these results.

Immediate-release methylphenidate compared with methylphenidate transdermal system. In a very small (N=9) fair-quality crossover study, transdermal methylphenidate was compared with immediate-release methylphenidate in a 12-hour simulated classroom setting.[36] Starting at 7 AM, double-dummy doses were given or applied and assessment of classroom rule-breaking, math problems, and the teacher's IOWA was undertaken every 30 minutes. Statistically significant differences were not found between the active drugs. There was more variability in results in the immediate-release methylphenidate group depending on time of day relative to dosing, and the transdermal methylphenidate was only narrowly superior to placebo on math assessments. Unfortunately, no assessment of the effect of the order of randomization was undertaken.

Mixed amphetamine salts compared with mixed amphetamine salts XR (Adderall® compared with Adderall XR®). Fifty-one children were enrolled in a randomized crossover study of mixed

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

amphetamine salts XR at 10, 20, and 30 mg, immediate-release mixed amphetamine salts 10 mg, and placebo given once daily for 7 days with study assessments made in a simulated classroom setting.[37] Based on the SKAMP scale deportment and attention variables and a math test (Permanent Product Measure of Performance [PERMP]), the extended-release formulation had significantly better scores compared with placebo on all time points for the 30 mg dose. However, the 10 and 20 mg doses showed more variable benefits early (at 1.5 hours) and late (10.5 and 12 hours). Immediate-release mixed amphetamine salts showed a benefit over placebo early in the day, and more variable results as the day progressed. Direct comparisons were not undertaken, but scores were not largely different across the immediate-release and extended-release groups.

Lisdexamfetamine dimesylate compared with mixed amphetamine salts XR. We identified 1 small, fair-quality, randomized controlled trial of lisdexamfetamine, a 3-way crossover trial that compared 1-week treatment periods of lisdexamfetamine, mixed amphetamine salts XR, and placebo in 52 children (1 publication and data from FDA documents).[38,39] In this trial, 54% of patients were White, 24% were African American, 16% were Hispanic, 1% were Asian, 1% were Native Hawaiian/Pacific Islander, and 4% were Other. There were no significant differences between lisdexamfetamine and mixed amphetamine salts XR in LS-mean SKAMP-DS scores on the test day in a simulated classroom. Results of subgroup analyses suggested that lisdexamfetamine was similar in efficacy to mixed amphetamine salts XR, regardless of age, gender, race, or baseline illness severity as measured by the Clinical Global Impression Scale. A post-hoc analysis of physician perception of clinical improvement found that using the combined categories of 'much improved' and 'very much improved' on the Clinical Global Impression – Severity (CGI-S) scale (typical for assessing response) there was no difference between drugs (74% with lisdexamfetamine and 72% with mixed amphetamine salts XR).[15] When the analysis was limited to 'very much improved', significantly more met this criterion when taking lisdexamfetamine (32% versus 16%, P=0.0386).

Lisdexamfetamine dimesylate compared with methylphenidate OROS (Concerta®). A fair-quality RCT of 336 children aged 6 to 17 years evaluated lisdexamfetamine, methylphenidate OROS, and placebo for 7 weeks.[7] There were multiple publications based on this study,[13,14,16] with one focusing on the head-to-head comparison of the drugs.[16] After dose optimizations, most patients taking lisdexamfetamine were taking 50 mg or 70 mg, while most patients taking methylphenidate OROS were taking the highest dose (54 mg). Based on a 30% reduction in ADHD-RS score, there was a greater proportion responding to lisdexamfetamine than to methylphenidate OROS (18% more; RR 1.4; 95% CI, 1.09 to 1.80), with similar results using the CGI-I scores. The difference in reduction in ADHD-RS score between groups was -5.6 points (95% CI, -8.4 to -2.7). Using a marker of the mean ADHD-RS score for age, the difference is borderline significant (14%; RR 1.37; 95% CI, 1.01 to 1.85; P=0.05). Although there was a large attrition rate in this study (41%), the proportions were similar between drug groups (30% and 34%), and a last observation carried forward analysis was used. While quality of life was measured in this study, using the Child Health and Illness Profile; Child Edition and the Weiss Functional Impairment Rating Scale – Parent Report, direct comparisons between the drugs were not undertaken.[13] Each drug was superior to placebo, with effect sizes of 0.924 for lisdexamfetamine and 0.772 for methylphenidate OROS on the Weiss total score. Similarly, a post hoc analysis of change in the Conners' Parent Rating Scale throughout the day found that

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

lisdexamfetamine was superior to methylphenidate OROS at 1000, 1400, and 1800 hours (difference in scores -5.8, -6.8 and -6.1 respectively with baseline scores 49-54; $P<0.05$ for all).[14]

Comparisons of sustained-release formulations

Methylphenidate OROS (Concerta®) compared with methylphenidate CD (Metadate CD®). Results from the fair-quality COMACS crossover study of 184 children suggested that relative improvements in SKAMP deportment and attention scale scores differed for the comparison of methylphenidate OROS 18-54 mg and methylphenidate CD 20-60 mg (both given once daily) depending on time of assessment.[40,41] Methylphenidate CD was associated with significantly larger effect sizes than methylphenidate OROS in the morning, while treatment effects were similar in the afternoon, and methylphenidate OROS was superior in the evening. This study presented several problems, however, in that the SKAMP scale has been criticized for lack of sensitivity to change in symptoms, and that analysis of variance (ANOVA) analysis found the interaction of site x treatment x sequence (the order to randomization within patients) was found to be statistically significant. This finding resulted in the authors conducting additional analyses; however the effect of sequence was not included in these subsequent analyses. Therefore, these findings should be interpreted with caution.

Methylphenidate OROS (Concerta®) compared with methylphenidate SODAS (Ritalin LA®). Two small crossover studies have found methylphenidate spheroidal oral drug absorption system (SODAS) superior to methylphenidate OROS. A small 1-week crossover study of methylphenidate SODAS 20 mg compared with methylphenidate OROS 18 mg and 36 mg[42] found methylphenidate SODAS superior on the attention and deportment subscores of the SKAMP scale depending on the time-point and dose comparison. Secondary outcome assessment also found methylphenidate SODAS superior on 1 measure (proportion correct on math test). These limited differences were mitigated by concerns over the assessment tool (SKAMP) sensitivity, use of a simulated classroom, involvement of study sponsor in authorship, and differences in groups at baseline. A second crossover study of methylphenidate OROS (18 and 36 mg) and methylphenidate SODAS (20 and 40 mg) also assessed children in a simulated classroom setting after a single dose of the study medication using the SKAMP scale.[43] Here methylphenidate SODAS 40 mg was found superior to methylphenidate OROS 36 mg at all time points (0-4, 0-8, and 0-12 hours) based on the SKAMP attention subscale score area under the curve analyses, while methylphenidate SODAS 20 mg was not significantly different to either dose of methylphenidate OROS. Here, concerns over the clinical importance of the difference in area under the curve, involvement of study sponsor in authorship, and the impact of sequence of randomized treatment (analysis of treatment sequence was stated to be planned but results not reported) were present.

Methylphenidate OROS (Concerta®) compared with methylphenidate transdermal system. In a fair-quality trial (N=270), transdermal methylphenidate was not found to be significantly different to methylphenidate OROS after a 7-week period. Dose was titrated in a double blind fashion over 5 weeks.[44] Children applied the patch (placebo or active) and took the capsule (placebo or active) at 7 am each day. No difference was found between drugs in the mean change from baseline on the investigator's assessment of the ADHD-RS (difference in least squares mean change –2.6; 95% CI, –6.7 to 1.5). Similarly, differences were not found between drugs in ratings by teachers or parents using the Conners' scale. Measurements before 11 am were not taken, response rates were not reported. Although no difference was found between transdermal

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

methylphenidate and methylphenidate OROS, the study may not have been powered to detect such a difference, as the sample size was determined based on transdermal methylphenidate compared with placebo.

Dexmethylphenidate ER compared with methylphenidate OROS (Concerta®). Two very similar, fair quality crossover trials conducted by the same researchers compared 2 doses of dexmethylphenidate ER (20 mg or 30 mg daily) with 2 doses of methylphenidate OROS (36mg or 54 mg daily) or placebo using a simulated classroom assessment (total N=166)[11,45] Both studies were published in 2008, but neither cites the other study; overlap in children studied and potential duplication of data cannot be ruled out. Children were given the intervention for 7 days prior to the assessment. In the first study, the mean change in SKAMP combined scores was statistically significantly greater with dexmethylphenidate ER compared with methylphenidate OROS for time points from 0.5 hours up to 6 hours (lower doses compared and higher doses compared - *P* values ranged from <0.001 to =0.044). For example, at two-hours post-dose the adjusted mean change was –11 with dexmethylphenidate ER 20 mg compared with –6 for methylphenidate OROS 36 mg; *P*<0.001. However, at 10, 11, and 12 hours post dose) methylphenidate OROS had significantly greater change in SKAMP combined scores (*P* values ranged from <0.001 to <0.05). At hours 7, 8, and 9 there was no statistically significant difference between the drugs at either dose levels and analysis by Area Under the Curve from 0-6 and 6-12 hours was unable to identify statistically significant differences between the drugs. Analysis of attention and deportment subscale scores showed similar results. Assessments of math scores and problems attempted showed dexmethylphenidate ER superior up to 4 hours post dose and methylphenidate OROS superior at 11 and 12 hours post dose.

The second study found very similar results, with dexmethylphenidate ER superior to methylphenidate OROS from 0.5 to 5 hours post dose, no differences at 7 and 9 hours, and methylphenidate OROS superior at 10 and 11 hours post-dose.[11] This study, however did find that the Area Under the Curve analysis from 0-12 hours showed dexmethylphenidate ER 30 mg superior to methylphenidate OROS 54 mg. Math test scoring was also similar to the first study.

Dexmethylphenidate ER compared with mixed amphetamine salts XR. A single, small, fair-quality randomized, 8-week crossover trial of 56 children (mean age 12 years) examined low (10 mg), moderate (20 mg) and high (25 mg to 30 mg) doses of dexmethylphenidate ER and mixed amphetamine salts XR (10, 20, and 25-30 mg).[12] No differences were found between drugs at equivalent dose levels, based on the ADHD-RS or the CGI-S, but overall score and hyperactivity scores on the ADHD-RS improved with increasing dose of either drug. In this study, 37.5% had inadequate response to either drug and 37% responded similarly to both drugs. 14.3% responded only to dexmethylphenidate ER, and 12.5% responded only to mixed amphetamine salts XR. The reductions in ADHD-RS scores for responders were large with a mean change from baseline of 28 points.

Comparisons of immediate-release formulations

Immediate-release dextroamphetamine compared with immediate-release methylphenidate. We included 9 fair-quality studies (reported in 11 publications) of immediate-release dextroamphetamine compared with immediate-release methylphenidate.[46-56] Two poor-quality studies and 1 poor-quality subgroup analysis were found.[57-59] All 9 fair-quality studies were randomized, blinded crossover trials. Table 5 summarizes the study characteristics.

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

Table 5. Immediate-release dextroamphetamine compared with immediate-release methylphenidate study characteristics

Study, Date	Number Duration	Diagnosis criteria	Final dose[a]	Results
Efron, 1997	N=125 2 weeks	DSM-IV criteria for ADHD	DEX: 0.15 mg/kg MPH: 0.3 mg/kg	No differences found
Efron, 1998	N=102 2 weeks	DSM-IV criteria for ADHD	DEX: 0.15 mg/kg MPH: 0.3 mg/kg	No differences found
Elia, 1990	N=31 3 weeks	DSM-III criteria for attention deficit disorder with hyperactivity	< 30 kg/ > 30 kg: DEX: 40 mg/ 45 mg MPH: 70 mg/ 90 mg	No differences found
Elia, 1991	N=48 3 weeks	DSM-III criteria for attention deficit disorder with hyperactivity	< 30 kg/ > 30 kg: DEX: 40 mg/ 45 mg MPH: 70 mg/ 90 mg	No differences found
Elia, 1993	N=33 3 weeks	DSM-III criteria for attention deficit disorder with hyperactivity	< 30 kg/ > 30 kg: DEX: 40/ 45 mg MPH: 70 / 90 mg	No differences found
Sharp, 1999	N=32 3 weeks 100% girls	ADHD symptoms present in at least 2 settings; Conners' Hyperactivity factor scores at least 2 SD greater than age and sex norms	DEX: 0.64 mg/kg MPH: 1.28 mg/kg	No differences found
Arnold, 1978	N=29 3 weeks	Diagnosis of Minimal Brain Dysfunction; total score of 24 or more on the first 6 items of the David's Hyperkinetic Rating Scale	DEX: 15 mg MPH: 30 mg	No differences found
Kaufman, 1981	N=12 6 weeks	Children diagnosed as "hyperactive", according to a set of predetermined clinical criteria (NR)	DEX: 10-60 mg MPH: 5-30 mg	No differences found
Simpson, 1980	N=12 8 weeks	Hyperactivity that had been long term; complaints of hyperactivity by parents and teachers; at least average intellectual abilities as measured by the WISC-R	NR	Post-hoc analysis: DEX "the most effective drug, where a positive effect was seen"

Abbreviations: ADHD, attention deficit hyperactivity disorder; DEX, dextroamphetamine; DSM-III, Diagnostic and Statistical Manual of Mental Disorders - Third Edition; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition; MPH, methylphenidate; NR, not reported.
[a] All doses divided into morning/noon doses.

The 2 largest studies[47,48] enrolled children with ADHD and used clear criteria for diagnosis. One tested the hypothesis that some adverse events associated with stimulants are actually characteristics of ADHD and would be improved by drug treatment in 1 study,[47] and the other tested the differences between child and parent assessment of therapy in the other.[48] Neither study provided details on the efficacy results, other than summary statements that there were no differences between the 2 drugs based on children's self-assessment[48] and based on parent and teacher ratings.[47] These 2 studies had similar populations, primarily children with the mixed subtype (82%), however comorbidities and ethnicity were not reported.

Of the 7 small studies (N=12 to 48), only 1 found a difference between the drugs.[55] This study assessed attention to task and deviant behavior in the usual classroom settings using a modified version of the Werry-Quay Direct Observational System.[55] The text of the paper reported that in a post-hoc analysis, immediate-release dextroamphetamine was the most effective drug *in instances where a positive effect was seen.* Because this study did not use a

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

standardized tool for diagnosis, and ADHD subtypes, comorbidities, or ethnicity were not reported, it could be assumed that significant heterogeneity in the population may have led to the discordant results.

Immediate-release methylphenidate compared with mixed amphetamine salts. Three small, fair-quality studies of mixed amphetamine salts compared with immediate-release methylphenidate were found.[60-63] One was a parallel group randomized controlled trial[63] while the other 2 were randomized crossover trials.[60-62] Two additional studies were rated poor quality[64,65] due to no description of randomization or concealment of randomization code, no intent to treat analysis, high discontinuation rates or no randomization (clinician selected drug), and no blinding of patients or outcome assessors.

The parallel group randomized controlled trial enrolled 58 children with ADHD and randomized them to 3 weeks of mixed amphetamine salts, immediate-release methylphenidate, or placebo.[63] The mean doses at the end of study were mixed amphetamine salts 12.5 mg daily and immediate-release methylphenidate 25.2 mg daily (divided into morning +/- noon doses for both drugs). No differences were found in the mean IOWA Conners' Teacher Rating Scale scores (Inattention/Overactivity and Aggression/Defiance subscales) rated by teachers 4 mornings and afternoons a week, but children taking mixed amphetamine salts scored significantly better on both subscales when morning and afternoon scores were combined. No differences were found in parent ratings. The mean Clinical Global Impression-Improvement Scale score (rated by a blinded psychiatrist) was also significantly lower (better) in the mixed amphetamine salts group than the immediate-release methylphenidate group (final score 1.6 compared with 2.35; $P<0.05$), but the difference in the proportions of responders (90% compared with 65%, respectively) did not reach statistical significance. No differences were found on the Conners' Global Index.

The 2 crossover studies were conducted in the same manner by the same authors and were conducted in a summer treatment program.[60-62] These short-term studies (6 to 8 weeks) enrolled 21 and 25 children with a higher prevalence of comorbid oppositional defiant disorder (67% and 52%) than the general population of children with ADHD. The first study found mixed amphetamine salts to be superior to immediate-release methylphenidate given once daily, while few or no differences were found when comparing to immediate-release methylphenidate given twice daily, based on counselor and teacher ratings. Ratings of after school behavior indicated that the addition of a third 0.3 mg/kg dose of immediate-release methylphenidate or the mixed amphetamine salts 0.3 mg/kg once daily dose lead to the best results based on combinations of parent ratings and child task completion. The results of the second study indicated that on a few measures the low dose (10 mg twice daily) of immediate-release methylphenidate was not as effective as the higher dose (17.5 mg twice daily) or either dose of mixed amphetamine salts (7.5 or 12.5 mg twice daily). Measures where this difference was seen were interruption, conduct problems, negative verbalizations, the daily report card score, and counselor ratings of oppositional defiant scores. No difference in response was seen between the 2 doses of mixed amphetamine salts and the higher dose of immediate-release methylphenidate.

Modafinil compared with immediate-release methylphenidate. In a fair-quality randomized controlled trial of 60 children and teens, modafinil was found to be similar to immediate-release methylphenidate after 3 and 6 weeks of treatment with 200 to 300 mg of modafinil or 20 to 30 mg daily of immediate-release methylphenidate (based on a weight cut-off of 30 kg).[66] Using the ADHD parent and teacher rating scale, significant differences were seen compared with baseline,

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

but not between groups (*P*=0.74 for parents; *P*=0.60 for teachers). Similarly, no statistically significant differences were seen in the proportion of responders (>40% reduction in score; 73% compared with 70% for parents rating of modafinil and immediate-release methylphenidate, respectively; 73% in both groups based on teachers ratings). Although the study was well conducted, details about children at baseline were too limited to guide generalization of the results.

Nonstimulants

Atomoxetine

Atomoxetine compared with methylphenidate. Four studies compared atomoxetine to immediate release methylphenidate were included.[9,67-69] In a fair-quality, 8-week, noninferiority trial (N=330), atomoxetine was found noninferior to immediate-release methylphenidate based on ADHD rating scale response rates (>40% reduction in score; atomoxetine, 77%; immediate-release methylphenidate, 82%; *P*=0.4, assuming a margin [delta] of 18%).[68] The mean final doses of drug were somewhat imbalanced, with 44 mg daily of atomoxetine and 18 mg daily for immediate-release methylphenidate. Differences were not found between groups using other measures or through logistic regression controlling for multiple factors. Another study comparing atomoxetine and immediate-release methylphenidate found no differences between the drugs based on changes in the ADHD rating scale, the Conners' Parent Rating Scale Revised hyperactivity item, and the Clinical Global Impression-Severity Scale.[67]

Two other studies, one evaluating the impact of each drug on sleep and the other ADHD symptoms, were rated poor quality due to a high attrition rate, differences at baseline and other concerns.[9,69]

Atomoxetine compared with methylphenidate OROS. Low strength evidence from 3 RCTs of atomoxetine compared with methylphenidate OROS found methylphenidate to reduce ADHD symptoms or result in response more than atomoxetine.[6,70,71] In a 6-week fair-quality noninferiority trial, atomoxetine was not found noninferior to methylphenidate OROS.[70] Using response (40% or more reduction of ADHD–RS) as the primary outcome, and a margin of 15%, methylphenidate OROS was found superior to atomoxetine with an overall 56% response rate with methylphenidate OROS compared with 45% with atomoxetine (number needed to treat, 9; *P*=0.02). Analysis of the subgroup with prior stimulant exposure (n=310) found again a statistically significantly higher rate of response with methylphenidate OROS (51%) compared with atomoxetine (37%) (number needed to treat, 8; *P*=0.03). However, in the smaller subgroup without prior stimulant exposure, (n=191) the 2 drugs were not found to be statistically significantly different in response rates (57% atomoxetine compared with 64% methylphenidate OROS). Secondary outcome measures, such as the mean change in ADHD rating scale total and subscale scores, resulted in similar findings. This study used over-encapsulation of methylphenidate OROS. The authors reported that dissolution studies indicated no alteration in drug release. Also, atomoxetine was administered in a divided dose rather than given once daily.

In a fair-quality randomized crossover trial, 102 children aged 6-17 years (mean age 10.5) received atomoxetine or methylphenidate OROS for 4 to 6 weeks. The doses were titrated to best effect and adverse event profile, with resulting mean doses of 1.4 mg/kg and 52 mg, respectively.[6] Changes from baseline on the ADHD-RS scale were statistically significant in both groups, but comparisons across groups were not made on this outcome measure. The

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

starting scores were similar for each drug (36.5 and 37.0), but the final scores favored methylphenidate slightly (20.54 atomoxetine versus 17.37 methylphenidate OROS) 4-6 weeks.

The Formal Observation of Concerta® compared with Strattera® (FOCUS) trial was rated poor quality, based on a combination of flaws including undescribed methods of randomization and allocation concealment, significant between-groups baseline differences in ADHD severity, and lack of information about attrition and number of patients included in analyses (Evidence Table 2).[71]

Atomoxetine compared with mixed amphetamine salts XR (Adderall SR®). The extended-release form of mixed amphetamine salts (Adderall SR®) 10-30 mg was superior to atomoxetine 0.5-1.2 mg/kg daily on most efficacy outcomes after 3 weeks in a fair-quality trial of 215 children (mean age, 8.7 years).[72] This trial, also known as Strattera®/Adderall XR® Randomized Trial, was conducted in a simulated classroom setting which involved 12 hours of observation daily. Participants were mostly male (71.9%) who were diagnosed with ADHD of either the hyperactive/impulsive or combined subtypes. Mixed amphetamine salts XR was associated with significantly greater reductions in the mean SKAMP deportment scale scores, which was prespecified as the primary outcome (–0.56 compared with –0.13; $P<0.0001$). Mixed amphetamine salts XR was also associated with superior outcomes on multiple secondary outcome measures including mean change in SKAMP Attention scale scores, proportions of SKAMP scale "responders" (≥ 25% improvement on deportment and/or attention scales), and numbers of math problems attempted and/or completed correctly.

Atomoxetine compared with lisdexamfetamine. A fair quality, 9-week parallel design RCT (N=267) compared atomoxetine (weight-based dosing for < 70 kg, 40, 80 or 100 mg daily for over 70 kg) and lisdexamfetamine (30, 50, or 70mg daily) for the time to first onset first clinical response (defined as CGI-I score of 'much improved or 'very much improved').[8] Patients taking lisdexamfetamine achieved the outcome at a median of 12 days, compared with 21 days for atomoxetine ($P=0.001$). At week 9, 82% in the lisdexamfetamine group met the response criteria, compared with 64% on atomoxetine ($P=0.001$), and the difference in change in ADHD-RS score from baseline was also significant (-6.5; $P<0.001$). This study suffered from a high attrition rate (25%), with 9.7% withdrawing from atomoxetine due to lack of efficacy, compared with 1.5% on lisdexamfetamine.

Clonidine

Immediate-release clonidine compared with methylphenidate. Four parallel group randomized controlled trials of immediate-release clonidine compared with immediate-release methylphenidate were found.[73-76] Two small randomized controlled trials of immediate-release clonidine compared with immediate-release methylphenidate measured outcomes using scales or tests that have either been shown to have low validity (e.g., Home/School Situations Questionnaire [HSQ and SSQ] and Gordon Diagnostic System), or which validity could not be verified (e.g., Disruptive Behavior Scale and Grooved Pegboard) and were rated poor quality.[74,76] ClinicalTrials.gov lists 1 additional study of immediate-release clonidine and immediate-release methylphenidate that is completed but not yet published.

The remaining small trials (N=122 and 132) reported no statistically significant differences in Conners' Abbreviated Symptom Questionnaire Teacher scale from baseline to endpoint (16 weeks) between immediate-release methylphenidate and clonidine. However, this

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

comparison was not the primary aim of either study, and the studies have conflicting findings outside of this comparison. While the studies had similar 2 x 2 factorial designs, 1 enrolled children with both ADHD and Tourette's disorder and evaluated the effect of drugs on tics, while the other enrolled children without Tourette's disorder. The study of children with Tourette's disorder and ADHD enrolled 136 children (mean age 10.2 years) and assigned them to immediate-release methylphenidate, immediate-release clonidine, both drugs, or placebo for 8 weeks.[75] Mean doses at the end of study were 0.25 mg clonidine and 26 mg immediate-release methylphenidate daily. All analyses made comparisons of each drug group to placebo, although it is stated that there was no difference between the immediate-release methylphenidate and immediate-release clonidine groups on the primary outcome measure of the Conners' Abbreviated Symptom Questionnaire Teacher scale (Table 6). Immediate-release clonidine was significantly better than placebo on more Tourette's outcome measures than immediate-release methylphenidate, and immediate-release methylphenidate was significantly better than placebo on more ADHD outcome measures than clonidine.

The second trial enrolled 122 children with ADHD (mean age 8 years) and also randomized them to immediate-release methylphenidate, immediate-release clonidine, both drugs, or placebo for 8 weeks.[73] Mean doses at the end of study were 0.24 mg clonidine and 30 mg immediate-release methylphenidate daily. Based on the primary outcome measure of mean change in the Conners' Abbreviated Symptom Questionnaire Teacher scale no difference was found between groups receiving clonidine and those receiving methylphenidate although the change was greater with methylphenidate (–3.35 vs. –5.07; *P*=0.16). Similar results were found with secondary outcome measures for the direct comparison of the drugs.

The difference in results of these 2 studies is shown in Table 6 below. Using the 2 x 2 factorial designs, the analysis of treatment effect in groups receiving methylphenidate (alone or with clonidine) was statistically significant compared with groups not receiving methylphenidate (clonidine or placebo groups) in both studies. However, the treatment effect of clonidine (alone or with methylphenidate) was statistically significant only in the Tourette's syndrome study, and not in the Palumbo 2008 trial. The parent ratings in the Palumbo trial conflict with the results based on teacher ratings – showing methylphenidate to have no effect and clonidine to have an effect. In the Tourette's syndrome study, the parent and teacher ratings results were similar, finding both drugs beneficial. The reasons for the differences were not clear, but may have been related to differential attrition rates across groups in the Palumbo study, and while both studies allowed psychological interventions, important variation across the studies may have occurred. Taken together, and considering all efficacy outcomes, we were not able to currently identify a difference in effect between immediate-release clonidine and immediate-release methylphenidate.

Table 6. Change in Conners' Abbreviated Symptom Questionnaire Teacher scale

Treatment effects	Immediate-release clonidine vs. no clonidine *P* value		Immediate-release methylphenidate vs. no methylphenidate *P* value	
	Teacher ratings[a]	Parent ratings	Teacher ratings[a]	Parent ratings
Tourette's Syndrome Study, 2002	3.2 *P*=0.002	2.5 *P*=0.05	3.2 *P*=0.003	3.3 *P*=0.01
Palumbo, 2008	-2.9 *P*=0.008	7.5 *P*=0.0002	-1.4 *P*=0.19	3.7 *P*=0.06

[a]Primary outcome measure

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

Guanfacine

Extended-release guanfacine compared with atomoxetine. A good quality trial of 338 children aged 6 to 17 years with at least moderate severity ADHD (ADHD-RS score ≥32) compared atomoxetine with guanfacine ER for 6 weeks, following a 4-7 week dose-optimization period.[10] A placebo arm was included, and the primary analysis compared guanfacine ER to placebo. The difference in unadjusted mean change from baseline favored guanfacine ER over atomoxetine; difference in mean change -5.1 (95% CI, -8.2 to -2.0). The placebo-adjusted mean change from baseline in the guanfacine ER group was -8.9 (P=0.0017), and for atomoxetine was -3.8 (P<0.001). There was no statistical difference in the proportion of patients who were 'much improved' or 'very much improved' using the CGI-S; EPC calculated RR 1.15 (95% CI, 0.93 to 1.43).

Adolescents (ages 13 to 17 - only)

Immediate-release methylphenidate compared with methylphenidate OROS (Concerta®). A single, very small, *single blinded* crossover study of 6 adolescent boys showed methylphenidate OROS superior to immediate-release methylphenidate on some simulated measures of driving skills, dependent on the time of day of testing.[77] ADHD was confirmed using the DePaul ADHD Rating Scale IV (parents completed), the Diagnostic Interview Schedule for Children (DISC-IV), and the Standardized Interview for Adult ADHD. Four of the 6 had inattentive type ADHD. After 7 days of dosing, the teens performed significantly better while taking methylphenidate OROS on 3 of 9 measures (inappropriate braking, missed stop signals, and speed control) at each testing time (2 PM, 5 PM, 8 PM, and 11 PM). Because only F- and P values were reported, it is not possible to interpret the magnitude of differences found. An analysis of a combined score of 7 (of 9) measures at each of the 4 time points indicated that there were no differences between the formulations at the 2 PM and 5 PM test times, but the scores were significantly lower with the immediate-release formulation at the 8 PM and 11 PM times (P<0.01). Self-evaluations of risky driving behavior did not show any differences between the formulations. Adverse events were not measured. Since 2 teens were previously on methylphenidate OROS, 2 had been taking immediate-release methylphenidate, and the only person blinded was an observer in the driving simulator, it would be important to know the effect of prior medication and order of randomization. These were not assessed.

Methylphenidate OROS compared with mixed amphetamine salts XR. A 17-day, small (N=35) crossover study compared the effect of stimulant use on the driving ability of adolescents with ADHD.[78] There was no significant difference between methylphenidate OROS 72 mg once daily and mixed amphetamine salts XR 30 mg once daily in self-reported symptom improvement among participants (P=0.55) although both interventions appeared to improve symptoms compared with baseline (no further data provided). Methylphenidate OROS was associated with significantly better overall driving performance relative to mixed amphetamine salts based on testing in a driving simulator (P=0.03). However, subjective ratings of driving performance by participants failed to detect a difference between the 2 study drugs.

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

Adults

Four small short-term trials provide low-strength evidence of similar effects on ADHD symptoms after two to six weeks for the comparisons between immediate-release dextroamphetamine and either modafinil[79] or guanfacine, [80] between continuing with immediate-release methylphenidate or switching to methylphenidate OROS,[81] or between immediate-release compared with extended-release mixed amphetamine salts (Table 7).[5] There were no apparent differences, but limitations of these comparisons were that their consistency was unknown because they were each supported by only a single, fair-quality trial and their effect estimates were imprecise due to the very small sample sizes.

Table 7. Comparative effects on ADHD symptoms in head-to-head trials in adults

Intervention comparison	Trial quality, design, duration and sample size	ADHD symptoms
Modafinil 206.8 mg vs immediate-release dextroamphetamine 21.8 mg	Fair-quality, double-blind, crossover trial with 2-week treatment periods[79] N=22	≥30% reduction ADHD Rating Scale total scores: 48% in both groups
Immediate-release guanfacine 1.10 mg vs immediate-release dextroamphetamine 10.2 mg, administered once daily	Fair-quality, double-blind crossover trial with 2-week treatment periods[80] N=17	DSM-IV ADHD Behavior Checklist for Adults mean total symptom score at endpoint: 23.3 vs 24.2; baseline NR
Continuing with immediate-release methylphenidate vs switching to methylphenidate OROS; mean dosage NR, but not to exceed 1.3 mg/kg/day or 144 mg/day total	Fair-quality, single-blind parallel trial[81] 6 weeks N=53	Much or very much improved on the Clinical Global Impression Scale-I: 63% vs 58%; *P*=0.8
Immediate-release (26.7 mg to 37.5 mg) vs extended-release (26.3 to 34.3 mg) mixed amphetamine salts	Fair-quality, open, crossover trial with 3-week treatment periods[5] N=62	ADHD Rating Scale Response rate (threshold NR): rates NR; $X^2[1]=0.2$; *P*=0.63

Abbreviations: OROS, osmotic-release oral system; NR, not reported

Key Question 2. Harms

Short-term trial evidence in young children (preschool age; 3-5 years)

One fair-quality placebo-controlled trial of immediate-release methylphenidate reported results of adverse event assessments.[21] Immediate-release methylphenidate (at 0.3 to 0.5 mg/kg/day) was associated with higher rates of adverse events (e.g. increased sadness, decreased appetite, and sociability impairments) than placebo after 7-10 days in 31 preschoolers ($P<0.001$). Based on the Side Effects Rating Scale, the mean severity was greater in the methylphenidate groups as well ($P<0.01$). For both the number and severity of adverse events, the higher dose of methylphenidate resulted in numerically greater values than the lower dose, although statistical analysis of this comparison was not undertaken.

In the Preschool ADHD Treatment Study 21/183 (11%) of patients taking methylphenidate withdrew due to adverse events.[23,82] One serious adverse event, a suspected seizure, was potentially linked to methylphenidate use. Moderate to severe adverse events were reported in 16% to 30% in methylphenidate groups and 16% to 21% in placebo groups. Parents

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

identified significantly more adverse events with methylphenidate than placebo during the crossover titration phase of the study, including trouble sleeping ($P \leq 0.005$), appetite loss ($P \leq 0.003$), stomachache ($P \leq 0.03$), dull/tired/listless behavior ($P \leq 0.02$), social withdrawal ($P \leq 0.03$), and buccal-lingual movements ($P \leq 0.01$). In the 10-month open-label phase of the study rates of some adverse events significantly decreased (irritability, crying, sadness/depression, listless/tired behavior; $P \leq 0.03$) while others remained stable (appetite loss, picking, trouble sleeping, anxiety, social withdrawal, stomachache, headache, abnormal movements, and buccal-lingual movements). In this study, children (N=140; mean age 4.4 years) were larger than average at baseline, based on Centers for Disease Control growth charts (73.1% for height; 79.7% for weight). Methylphenidate (mean 337 days) was associated with a reduction in growth rate, with a mean loss of –6.35 percentiles in height and –14.42 percentiles in weight. Subgroup analysis found that sex, initial height, and initial methylphenidate dose did not affect the growth reductions.

Short-term trial evidence in children (elementary school age; 6-12 years and mixed populations up to age 18 years)

Stimulants

Four of 6 trials of immediate-release dextroamphetamine compared with immediate-release methylphenidate reported no differences between the drugs in adverse events.[46,47,50,51] However, 2 short-term crossover trials found immediate-release dextroamphetamine to cause greater weight loss than immediate-release methylphenidate with mean weight change differences of 0.7 kg to 0.97 kg.[53,54] One of 3 trials of mixed amphetamine salts compared with immediate-release methylphenidate found no difference in adverse event rates,[63] but 2 other studies found differences.[60,61] Limitations in study design and lack of description of analysis methods made results from these 2 studies less reliable. These studies found that adding additional doses to the daily regimen of either drug increased the reports of loss of appetite and sleep problems,[60] and that mixed amphetamine salts given twice daily caused the highest rates of these adverse events.[61] In a small study, modafinil had similar rates of adverse events as immediate-release methylphenidate, with the exception of decreased appetite and insomnia, where immediate-release methylphenidate resulted in statistically significantly higher rates.[66]

All 3 studies of immediate-release methylphenidate compared with extended-release formulations (methylphenidate OROS, SODAS, and SR) reported no significant differences in the incidence of side effects.[24,26,34] Mixed amphetamine salts and dextroamphetamine SR were found to cause more weight loss than immediate-release dextroamphetamine during the first week of treatment, but weight gain during the second week was greater with these drugs than with immediate-release dextroamphetamine.[83] Since this was such a short-term trial, no conclusions about differential effects on weight can be made from these data. No differences in adverse event rates were found between methylphenidate SR (Ritalin LA®) and methylphenidate OROS (Concerta®).[42]

In the COMACS study, methylphenidate OROS was found to have higher rates of insomnia/trouble sleeping (P=0.005) and decreased appetite (P=0.001) compared with methylphenidate CD, using the Barkley Stimulant Side Effect Rating Scale scores.[84]

A trial of transdermal methylphenidate compared with methylphenidate OROS reported higher percentages of adverse events and discontinuations due to adverse events with the transdermal, but these differences were not found to be statistically significant in post-hoc

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

analyses.[44] In a very small (N=9) fair-quality crossover trial of transdermal methylphenidate compared with immediate-release methylphenidate, reports of adverse events were not found to be statistically significantly different between groups, with 33% in both groups reporting appetite suppression, and no difference in time to fall asleep (within subject variance assessed). While the transdermal patch (placebo or active) was reported to be well tolerated, there were 3 "moderate" reactions (not defined) that lasted "under 12 hours" reported. [36]

Two small studies of dexmethylphenidate ER versus methylphenidate OROS found no differences in the rate of overall adverse events, serious adverse events or discontinuations due to adverse events.[11,45]

A single, small, fair-quality randomized, 8-week crossover trial of 56 children (mean age 12 years) examined low (10 mg), moderate (20 mg) and high (25 mg to 30 mg) doses of dexmethylphenidate ER and mixed amphetamine salts XR (10, 20, and 25-30 mg).[12] This study found that rates of adverse events increased with increased dose of either stimulant, but that there were not differences between the drugs with the exception of slightly increased rate of insomnia with 10 mg mixed amphetamine salts compared with 10 mg dexmethylphenidate (7% versus 2%, *P*=0.058). While 6 patients discontinued the study due to adverse events, the study did not report which drug or dose they were taking when they stopped. One serious adverse event occurred, a possible seizure and abnormal electrocardiogram (ECG) requiring overnight observation, in the dexmethylphenidate ER group.

In a fair-quality trial of lisdexamfetamine, methylphenidate OROS and placebo (N=366), rates of overall adverse events were similar across groups.[7,16] Discontinuations due to adverse events occurred more frequently with lisdexamfetamine (4.5%) than with methylphenidate OROS (1.8%). The lisdexamfetamine group experienced more frequent anorexia, decreased appetite, decreased weight, insomnia, and nausea than those taking methylphenidate OROS, while those taking methylphenidate OROS experienced more frequent headaches and nasopharyngitis. Few patients reported serious adverse events in either group (2.7% lisdexamfetamine and 1.8% methylphenidate OROS).

Nonstimulants

Atomoxetine. Atomoxetine (doses ranging from 0.5 mg/kg to 1.2 mg/kg per day) consistently caused more vomiting and somnolence than the stimulant comparators in 4 trials and all differences were statistically significant.[67,68,70,72] Rates of vomiting were 12% to 13% for atomoxetine, approximately 3 times greater than rates for immediate-release methylphenidate[72,85] or amphetamine salts XR.[68,70,72] Rates of somnolence ranged from 6% to 26% with atomoxetine, which was 3 to 4 times greater than rates with methylphenidate OROS[70,72] and mixed amphetamine salts XR [68,70,72] and over 7 times greater than rates with immediate-release methylphenidate.[67,68] 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).[67,68,70,72] Rates of nausea and anorexia were greater with atomoxetine compared with immediate-release methylphenidate in 1 trial, however the dose comparison (atomoxetine at recommended doses, immediate-release methylphenidate at lower end of recommended) may have contributed to this finding.[68] Overall rates of adverse events and study discontinuations due to adverse events were similar between lisdexamfetamine and atomoxetine in a study of 267 children.[8] Rates of insomnia were higher with lisdexamfetamine (11.7% versus 6%), whereas somnolence was more frequent with atomoxetine (11.9% versus 3.1%).

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

Two trials have compared clonidine to methylphenidate and reported adverse events.[75,86] Compared with immediate-release methylphenidate, clonidine was found to have significantly higher rates of overall adverse events and specifically sedation, with greater severity of sedation. In a fair-quality, 16-week study (N=122) the proportion of children reporting any adverse events was higher with clonidine (84% vs. 59%; *P*=0.006 for all groups taking clonidine vs. all those not taking clonidine). The rate of sedation reported as an adverse event was 42% with clonidine and 7% with immediate-release methylphenidate (*P*<0.001 for all groups taking clonidine vs. all those not taking clonidine).[86] The rate of sedation reported as an adverse event decreased over time, as did the proportion rating their sedation as moderate or severe. Over 16 weeks, children taking clonidine averaged a 2 kg weight gain compared with 0.3 kg for immediate-release methylphenidate. Several changes in blood pressure, heart rate, or electrocardiogram parameters were reported to be significantly greater with one or the other drug (no consistent pattern) but the changes were small and clinical significance was not clear. Methylphenidate was found to have a small negative weight change compared with a weight increase with clonidine.

In a 16-week crossover trial of children with ADHD and Tourette's disorder, 42% in the clonidine groups reported sedation (28% reported moderate or severe sedation) compared with 14% in the methylphenidate alone group.[75] Reporting of other adverse events was minimal, other than stating that the drugs were well tolerated and there were no cardiac toxicities. There were no differences in the severity of tics between the groups.

A good quality study of atomoxetine versus guanfacine ER included 336 children age 6-17 years,[10] with dose-titration over 4 to 7 weeks and 6 weeks at maintenance doses. A placebo arm was included as the primary comparator for guanfacine ER. Overall, adverse events were reported by 77% on guanfacine ER and 68% on atomoxetine, with 7.9% and 4.5% withdrawing from study due to an adverse event. Differences were not statistically significant. Two serious adverse events occurred in the guanfacine ER group (syncope) and none in the atomoxetine group. Assessments of suicidal thoughts and behaviors did not find differences among the three groups. This evidence is insufficient to draw conclusions about differences in adverse events with guanfacine ER and atomoxetine.

Adults

Four small short-term trials provide low-strength evidence of similar effects on harms after two to six weeks for the comparisons between immediate-release dextroamphetamine and either modafinil[79] or guanfacine, [80] or between continuing with immediate-release methylphenidate or switching to methylphenidate OROS,[81] but insufficient evidence for the comparison of immediate-release compared with extended-release mixed amphetamine salts (Table 8).[5] The trial of immediate-release and extended-release mixed amphetamine salts provided no between-groups comparisons of harms.[5] Limitations of the remaining comparisons were that their consistency was unknown because they were supported by only a single, fair-quality trial and their effect estimates were imprecise due to the very small sample sizes.

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

Table 8. Harms in head-to-head trials in adults

Intervention comparison	Trial quality, design, duration and sample size	Harms
Modafinil 206.8 mg vs immediate-release dextroamphetamine 21.8 mg	Fair-quality, double-blind, crossover trial with 2-week treatment periods[79] N=22	Insomnia: 38% vs 19%, *P*=NS Muscle tension: 24% vs 19%; *P*=NS Appetite suppression: 24% vs 19%, *P*=NS Withdrawals due to adverse events: None
Immediate-release guanfacine 1.10 mg vs immediate-release dextroamphetamine 10.2 mg, administered once daily	Fair-quality, double-blind crossover trial with 2-week treatment periods[80] N=17	Number of adverse events: 1.00 compared with 0.70, *P* not reported Withdrawals due to adverse events: NR
Continuing with immediate-release methylphenidate vs switching to methylphenidate OROS; mean dosage NR, but not to exceed 1.3 mg/kg/day or 144 mg/day total	Fair-quality, single-blind parallel trial[81] 6 weeks N=53	Proportion with no adverse events: fewer with IR MPH at baseline=33% vs 51% and at endpoint= -7% vs +25%; statistical significance NR
Immediate-release (26.7 mg to 37.5 mg) vs extended-release (26.3 to 34.3 mg) mixed amphetamine salts	Fair-quality, open, crossover trial with 3-week treatment periods[5] N=62	Adverse event withdrawals: 9.7% overall; no between-group comparison

Abbreviations: IR, immediate release; MPH, methylphenidate; OROS, osmotic-release oral system; NR, not reported; NS, not significant

Evidence on the long-term safety of drugs used to treat ADHD

We included observational studies for analysis of long-term safety parameters.[87-118] The studies were 1 to 5 years in duration. All but 2 involved elementary school-aged children.

Suicide

Although placebo- and uncontrolled evidence suggests in increase in risk for suicidal behavior with stimulants and atomoxetine, no head-to-head evidence was found.

Cardiovascular deaths and events

In children, 2 retrospective cohort studies (in 3 publications) provided low-strength evidence of no significant differences between methylphenidate or amphetamine products in the rate of emergency department visits for cardiac reasons or between methylphenidate, amphetamines or atomoxetine in sudden death, ventricular arrhythmia.[93,117,118] In adults, 2 retrospective cohort studies provided low-strength evidence of similar risk of stroke or TIA for atomoxetine compared with stimulants[18,114] and 1 retrospective cohort provided low-strength evidence of similar risk of sudden cardiac death for atomoxetine compared with stimulants.[18]

Children. One study evaluated the rate of serious cardiovascular events in children for amphetamines, methylphenidate, and atomoxetine compared with nonuse.[117] Unfortunately, this study did not make direct comparisons among the different drugs. But, we indirectly assessed between-drug comparisons by comparing the point estimates and overlap of their confidence intervals for their comparison to nonuse. Cardiac death was evaluated in children for 241,417 incident (new) users of ADHD medications (specifically, amphetamines, methylphenidate, and atomoxetine) and evaluated only validated cases of sudden death or ventricular arrhythmia.[117]

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

Compared to nonuse, there were no differences between taking methylphenidate, amphetamines or atomixetine in risk of sudden death or ventricular arrhythmia (hazard ratio, 0.16; 95% CI, 0.00 to 0.89l; 0.00; 95% CIs, 0.00 to 0.79 and 0.00 to 5.8, respectively), because indirect comparison of their effects versus nonuse found considerable overlap in the 95% confidence intervals. This study also examined cardiovascular outcomes such as stroke, myocardial infarction and composite outcomes. For all of these outcomes the hazard ratios were less than 1, indicated a reduced risk with exposure to the ADHD medication, but again the confidence intervals indicated a nonstatistically significant finding. Only "nonaccidental death" resulted in a (barely) statistically significant lower risk among users of any ADHD medication compared with nonusers (hazard ratio, 0.53; 95% CI, 0.29 to 0.99).

A good-quality retrospective cohort study based on 10 years of Florida Medicaid claims data and the Vital Statistics Death Registry data identified 55,383 patients with newly diagnosed ADHD.[93,118] Of these, 32,807 had used a stimulant (either currently or formerly) and 22,576 had never used a stimulant medication. Of 73 children who died over the study period, 5 died of circulatory causes (4 per 100,000 person-years); none of these were sudden cardiac death and numbers were too small to make reliable comparisons among groups. Emergency department and physician office visits due to cardiac causes occurred significantly more often in the group currently using a stimulant compared with non-users (hazard ratio, 1.20; 95% CI, 1.04 to 1.38 and hazard ratio, 1.21; 95% CI, 1.06 to 1.39, respectively). Former use of stimulants was not significantly associated. Comparison of current users of methylphenidate products to those currently using amphetamine products showed no statistically significant difference in the rate of emergency department visits for cardiac reasons (hazard ratio, 1.01; 95% CI, 0.80 to 1.28). Comparison of former use of these products also resulted in a nonsignificant finding.

Adults. One fair-quality retrospective, population-based cohort study used Optum Insight Epidemiology, Tennessee Medicaid, Kaiser Permanente California, and the HMO Research Network electronic health care records to evaluate rate of serious cardiovascular events in 443,198 young and middle-aged adults using amphetamines, methylphenidate, and atomoxetine compared with nonuse.[18] Because this study did not make direct comparisons among the different drugs, we indirectly assessed between-drug comparisons by comparing the point estimates and overlap of their confidence intervals for their comparison to nonuse. Based on indirect comparison, risk of sudden cardiac death appears similar for methylphenidate users (adjusted rate ratio, 0.89; 95% CI, 0.71-1.13), amphetamine (adjusted rate ratio 0.92; 95% CI, 0.70 to 1.19), or atomoxetine (adjusted rate ratio 0.87; 95% CI, 0.48 to 1.57). This study also examined stroke, myocardial infarction and composite outcomes. For all of these outcomes the adjusted rate ratios were around or below 1.0, suggesting similar or lower risk for use versus nonuse. This study also found no significant differences in cardiovascular event risk for current use of amphetamines, methylphenidate, and atomoxetine versus remote use or for new use (no use in past year) versus nonuse or remote use.

In a smaller fair-quality retrospective cohort database study, the risk of stroke or transient ischemic attack was compared in adults taking initiating atomoxetine or stimulant therapy for ADHD/ADD (N=42,993). Using propensity score matching and only validated cases of stroke or transient ischemic attack, no statistically significant difference was found between the drugs for either outcome (relative risks, 1.38; 95% CI, 0.42 to 4.54 for stroke, and 0.31; 95% CI, 0.04 to 2.63 for transient ischemic attack).[114] Overall the numbers of cases were small, limiting the ability to determine statistically significant differences if they were to exist.

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

Growth effects

A non-systematic review, using estimation techniques, graphing, and qualitative synthesis, found that stimulants (amphetamines and methylphenidate) caused growth delays in both height and weight but that these were attenuated over time.[88] The qualitative analysis indicated that there may be a dose effect, that there are no important differences between amphetamines and methylphenidate, and that discontinuing treatment results in resumption of normal growth. Because this review was not systematic and pooled data from a wide variety of study designs, we suggest caution in interpreting these findings.

A frequently cited nonsystematic review concluded that effects on weight and height associated with immediate-release methylphenidate vary across short-term clinical trials and long-term observational studies and are mostly transient.[119] We reached similar conclusions based on our analysis of a larger number of primarily long-term observational studies that compared immediate-release methylphenidate to immediate-release dextroamphetamine.[100,101,108]

We did not analyze results from 2 poor-quality, comparative studies.[17,110] Limitations of the study of growth rebound in methylphenidate and immediate-release dextroamphetamine include the lack of sufficient detail to rule out between-groups differences in baseline characteristics and the potential for confounding by time and other relevant factors.[110] Limitations of the study of methylphenidate and atomoxetine included the exclusion of large proportion of patients from the 12 and 24-month analyses (42% to 47% and 84% to 86%) and the lack of control for any confounding variables.[17]

Height

Immediate-release methylphenidate and immediate-release dextroamphetamine. The only comparative evidence came from 2 studies of immediate-release dextroamphetamine and methylphenidate[100,108] and 1 of methylphenidate and mixed amphetamine salts.[113] Results were mixed across the methylphenidate compared with immediate-release dextroamphetamine studies (Table 9). Both reported changes in height percentiles using the outdated Iowa City norms. Immediate-release dextroamphetamine and methylphenidate were both associated with similar height *increases* at final follow-up (mean 6 years) in 1 study[100] and immediate-release dextroamphetamine was associated with significantly greater height *decreases* than methylphenidate after at least 2 years in the other.[108] It is impossible to establish whether heterogeneity in group characteristics across studies may possibly contribute to the contradictory findings, as 1 of the studies did not report mean age, dosage, or duration.[108]

Immediate-release methylphenidate and mixed amphetamine salts. A study of methylphenidate (any formulation) compared with mixed amphetamine salts (any formulation) did not find statistically significant differences in the z-score for height change over 3 years of continuous treatment.[113] Mixed amphetamine salts appeared to have a small negative impact at year 1, but this difference was not statistically significant. The authors found that the adjusted cumulative dose showed a statistically significant negative relationship to height (both drugs combined) ($r=-0.26$, $P=0.001$), but when 3 outlier values were removed from the regression the findings were no longer statistically significant.

Weight

Immediate-release methylphenidate and immediate-release dextroamphetamine. Results from 3 comparative studies suggested that immediate-release dextroamphetamine is associated with

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

significantly greater suppression of weight gain than methylphenidate, at least in the first 1 to 2 years (Table 9).[100,101,108] Immediate-release dextroamphetamine was associated with a significantly lower mean weight gain (kg) than methylphenidate after 9 months in 1 study,[101] significantly greater declines in weight percentiles after the first of 5 years another study,[100] and at end of treatment (≥2 years) in yet another.[108] In the 5-year, partly retrospective and partly prospective study that involved 84 children (mean age at initiation of drug therapy, 9 years; 82% male), however, differences in decreased weight percentiles between immediate-release dextroamphetamine and methylphenidate resolved by the second year and resulted in significantly greater than expected mean increases in weight percentiles at final follow-up (+10.9; $P<0.01$ and +12.8; $P<0.001$, respectively).[100]

The 9-month study also reported subgroup analyses.[101] The first suggests that comparison of mean weight gain between immediate-release dextroamphetamine and methylphenidate may have been confounded by dosage disparities. Apparently, the difference between immediate-release dextroamphetamine and methylphenidate resolved when 4 patients taking lower-dose methylphenidate (20 mg daily) were removed from the analysis (0.13 kg compared with 0.12 kg per month). Weight gain in children who continued medication over the summer compared with those who discontinued medication during the summer was also reported. In patients taking immediate-release dextroamphetamine, medication continuation was associated with significantly lower mean weight gain than in children who discontinued medication (0.14 compared with 0.47 kg per month, $P<0.01$). Medication continuation status did not have an effect on weight gain in the group of patients taking methylphenidate.

Immediate-release methylphenidate and mixed amphetamine salts. A study of methylphenidate compared with mixed amphetamine salts (any formulation) found no statistically significant differences in z-scores for weight change over a 3 year period between the 2 drugs, but did find a significant negative association of duration of treatment with mixed amphetamine salts and z-score ($P=0.029$), indicating a greater impact on weight over time.[113] Overall, the children in the study were heavier than average, such that the mean final weights were not below average for age.

Table 9. Long-term height and weight outcomes with methylphenidate and other stimulants

Study	Interventions (mean dose) Duration Sample size	Age Gender Population	Height	Weight
Gross, 1976[100]	DEX 16.5 mg, n=12 6.8 years follow-up MPH 34 mg, n=60 5.8 years follow-up	Mean age=9 82% male Children/adolescents with hyperkinetic syndrome or minimal brain dysfunction	Change in percentile: +10.9, $P<0.01$ vs. +12.8, $P<0.001$	Change in percentile: +16.0, $P<0.02$ vs. +11.4, $P<0.001$

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

Table 9. Long-term height and weight outcomes with methylphenidate and other stimulants

Study	Interventions (mean dose) Duration Sample size	Age Gender Population	Height	Weight
Safer, 1972[101]	DEX 11.7 mg, n=3 11.8 mg, n=8 MPH 37.5 mg, n=4 24.0 mg, n=5 9 months follow-up	Mean age=9.8 Gender NR	NR	Weight gain (kg): 0.23 vs. 0.12, t=1.8, *P*<0.05 Weight gain (excluding patients taking low-dose MPH, n=16) (kg): 0.13 vs. 0.12, t=0.137, NS ON vs. OFF Weight gain (kg) over a 3-month summer period: MPH= 0.29 vs. 0.41, t=0.526, *P*=NS; DEX= 0.14 vs. 0.47, t=2.523, *P*<0.01
Safer, 1973[108]	DEX, n=29 MPH, n=20 Unmedicated controls, n=14 ≥ 2 years follow-up Mean dosages NR	Mean age NR 89.8% male in children on medication; 100% male in unmedicated control group 100% White	Change in percentile: DEX: –13.45 MPH > 20 mg: –9.40 All MPH: –5.20 MPH ≤ 20 mg: –1.00 Controls: +1.29 DEX > MPH all-dose, low-dose and control groups DEX=MPH high-dose group MPH high-dose > controls MPH all-dose and low-dose=controls	DEX; MPH: high-dose (> 20 mg), all, low-dose (≤ 20 mg); controls Percentile changes in: Weight: –20.38; –10.0, –6.35, –2.7, +6.79 DEX > all MPH dosage groups and controls; MPH high-dose and all doses > controls; MPH low-dose=controls
Pliszka, 2006[113]	MPH, n=113 2.7 years follow-up MAS, n=66 2.4 years follow-up Mean dose NR	Mean age 9 81% male	Change in z-score: MPH 0.1 MAS 0.1	Change in z-score: MPH 0 MAS 0.3

Abbreviations: DEX, dextroamphetamine; MAS, mixed amphetamine salts; MPH, methylphenidate; NR, not reported; NS, not significant.

Insomnia, decreased appetite, and headaches

A small (N=150), 24-month, retrospective cohort study examined rates of insomnia, decreased appetite, and headache reported by children attending a single clinic.[90] Using a one-way ANOVA analysis, the rates of insomnia across immediate-release methylphenidate, methylphenidate OROS, mixed amphetamine salts, mixed amphetamine salts XR, and atomoxetine were not statistically significantly different, although the crude rate in the mixed amphetamine salts group (22%) was numerically greater than in the other groups (range 4% to 13%). Similarly, rates of decreased appetite were not found to be different, although the rates in the immediate-release mixed amphetamine salts, mixed amphetamine salts XR, and methylphenidate OROS groups (range 15% to 22%) were also higher than the atomoxetine and immediate-release methylphenidate groups (range 9% to 10%). Atomoxetine had lower rates of headache compared with mixed amphetamine salts XR (0% and 12%, *P*=0.001), immediate-release mixed amphetamine salts (0% and 11%, *P*=0.001), or methylphenidate OROS (0% and

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

10%, P=0.002). Dose was not controlled for in these analyses, and because the data were sparse a Bonferroni correction was used, thus we suggest caution in interpreting these findings.

Tics

One observational study and 2 meta-analyses reported tic-related outcomes. A meta-analysis of data from 3 short-term trials found similar rates of tics reported as an adverse event among immediate-release methylphenidate, methylphenidate OROS and placebo.[120] A meta-analysis of 9 trials found that tic severity was improved with clonidine or guanfacine (effect size 0.74, 95% CI, 0.44 to 1.04; 3 trials) and atomoxetine (effect size 0.32, 95% CI, 0.09 to 0.56), but that methylphenidate had no significant impact (effect size 0.28, 95% CI, -0.03 to 0.58; 4 trials).[121] An observational study (N=150) of immediate-release methylphenidate, methylphenidate OROS, and immediate-release mixed amphetamine salts XR found no difference in tic prevalence over 2 years using one-way ANOVA analysis.[90]

Seizures

In an analysis of post marketing data and clinical trials data, the manufacturer of atomoxetine found that the rate of seizure was 0.1% to 0.2%, with no statistically significant difference in rate between atomoxetine, methylphenidate, and placebo, although the comparative data were limited.[92] In a good-quality retrospective cohort study of claims data for 34,727 children (age 6 to 17) with at least 2 codes for ADHD diagnosis, the risk of new onset seizure was higher with atomoxetine (relative risk, 2.5; 95% CI, 0.9 to 7.1) than “other ADHD therapy” (stimulants and bupropion combined, relative risk, 0.7; 95% CI, 0.2 to 2.0) compared with “nonuse”, although neither were statically significant.[115]

Evidence on the risk of abuse, misuse or diversion of drugs used to treat ADHD in patients with no previous history of misuse/diversion

Because the potential for misuse and/or diversion crosses the lines of childhood to adulthood, the evidence is considered as 1 body here. Also, because development of abuse and diversion are longer-term issues, we did not examine short-term trial evidence regarding apparent misuse based on tablet counts. We did not include studies of abuse potential in persons who did not have ADHD.[122]

We identified only 5 comparative studies of abuse, misuse or diversion outcomes.[19,123-126] Two studies that used data collected as part of the National Survey on Drug Use and Health in 2002[123] and in 2009,[19] respectively, consistently found more frequent lifetime nonmedical use of immediate release methylphenidate or dextroamphetamine compared with mixed amphetamine salts. The 2002 survey of over 7.3 million respondents found that the estimated number of lifetime users, in thousands was 4,524 for immediate release methylphenidate, 3,361 for dextroamphetamine, 593 for mixed amphetamine salts and 3 for OROS methylphenidate.[123] The 2009 survey of 55,646 respondents found that lifetime nonmedical use of immediate-release methylphenidate was 40% compared with 1.2% for mixed amphetamine salts.[19] No psychiatric diagnosis information is available from these surveys, so it is not known what proportion of respondents had ADHD.

Another survey study of college students evaluated responses of 483 students with a prescription for any medication. Of these, 81 were taking an ADHD medication.[124] This group of students had the highest rate of diverting ADHD medication at 61.7%. The highest rate of

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

diversion was reported with amphetamine/dextroamphetamine (70.5%, N=31). Rates did not differ much between methylphenidate and extended-release methylphenidate (no formulation specified, 37% compared with 39.1% respectively).

Two additional studies compared rates of misuse and abuse of drugs used to treat ADHD.[125,126] But, because of numerous major deficiencies, findings from these studies do not add anything to the National Survey on Drug Use and Health evidence. One study used combinations of data from the Drug Abuse Warning Network, Drug Enforcement Administration claims of theft or losses, and the US Food and Drug Administration Adverse Event Warning System to evaluate the risk of abuse or diversion with methylphenidate OROS for years 2000 (the year of its US Food and Drug Administration approval) to 2003 in comparison with other formulations of methylphenidate. The study was based on groups of cross-sectional data, each of which had flaws. For example, the Drug Abuse Warning Network data do not report product specific information, but the authors report small numbers of cases from Drug Abuse Warning Network where methylphenidate OROS is specifically mentioned, and then use this in part as a basis for their conclusions. The second study used a survey of poison control centers used as proxy for estimating level of abuse of various stimulants, with final outcome determined in 64% of calls; no info on other missing data and no control for confounders in analysis of trends, data were extrapolated from a sample of physicians to all prescriptions in the United States.

Key Question 3. Subgroups

Race or Ethnicity

Only one-half of all studies of elementary school-aged children reported race or ethnicity among the baseline characteristics. Study populations were made up primarily of White participants, with a few exceptions. The scales used in the trials included may not perform well in all ethnic groups, or when translated into languages other than English. Since the majority of trials were performed in English speaking populations, with primarily White participants, these issues were not explored in the studies.

A subgroup analysis conducted specifically to evaluate the comparative efficacy and safety of open-label methylphenidate OROS and atomoxetine in 183 Black children with ADHD (out of 1,323 children that participated in the overall trial) found treatment outcomes to be similar to those for the overall study population.[127] Main findings from the subgroup analysis are summarized in Evidence Table 1, but will not be discussed in detail here due to concerns about study quality. This trial (the FOCUS trial) was rated poor quality based on a combination of flaws including undescribed methods of randomization and allocation concealment, significant between-groups baseline differences in ADHD severity, and lack of information about attrition and number of patients included in analyses (Evidence Table 2).

Lisdexamfetamine. Subgroup analyses of ethnic origin (Caucasian compared with Non-Caucasian) were performed using data from 1 double-blind, randomized controlled trial of lisdexamfetamine and results were reported in the Center for Drug Evaluation and Research Medical Review[128] In the 1-week, crossover study, average Swanson, Kotlin, Agler, M-Flynn and Pelham - Deportment Subscale scores for lisdexamfetamine were similar to mixed amphetamine salts XR, regardless of ethnic origin.

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

Gender

The average SKAMP-DS scores for lisdexamfetamine were similar to mixed amphetamine salts XR regardless of gender in a small (N=88) 1-week, crossover study. [128] In a study of mixed amphetamine salts XR and atomoxetine, similar to the overall study analysis, mixed amphetamine salts XR was found to have greater improvements in symptoms compared with atomoxetine in a subgroup analysis of 57 girls.[129] A post-hoc analysis of data from the COMACS study, comparing methylphenidate OROS and methylphenidate CD, found differences between boys and girls, but not between drugs. At baseline, more girls had comorbid anxiety disorder and girls had superior response rates at 1.5 hours post dose, but inferior response rates at 12 hours post dose compared with boys.[130] A post-hoc analysis of a small crossover study of 35 adolescents with ADHD comparing methylphenidate OROS and mixed amphetamine salts XR (and placebo) found that while females had lower symptoms scores, statistically significant interaction between drug and sex were not found based on self-report, parent report, or simulated driving skill.[131] This study was small, and may have not had adequate statistical power (Type II error).

Anxiety Disorders

Overall, 7 head-to-head trials in children reported symptoms of anxiety or nervousness as an adverse event and 1 head-to-head comparison reported it as a symptom of ADHD or comorbidity. In head-to-head comparisons no statistically significant differences in the rate of reporting anxiety as an adverse event were found between immediate-release methylphenidate compared with immediate-release dextroamphetamine, mixed amphetamine salts, methylphenidate SR, methylphenidate OROS, or atomoxetine, although for some comparisons numerical differences were apparent.[25,27,34,37,63,67,132] For example, compared with immediate-release methylphenidate, rates were higher with atomoxetine (15.8% compared with 10% nervousness) and immediate-release dextroamphetamine (68% compared with 61%), but lower compared with mixed amphetamine salts (10% compared with 5%) or methylphenidate OROS (31.3% compared with 18.7% in 1 study, 12% compared with 13% in another). Two trials assessing anxiety symptoms as part of ADHD did not find a difference in anxiety between immediate-release methylphenidate and methylphenidate SR in children with minimal brain dysfunction[34]

Tic Disorders Including Tourette's Disorder

In a fair-quality randomized, double-blind, double-dummy trial of 136 children (mean ages 9.7 to 10.7 years) with preexisting tic disorders, mainly Tourette's disorder, children were assessed for improvement in ADHD symptoms and worsening tics in response to immediate-release methylphenidate, clonidine, and the combination over 16 weeks.[75] Mean doses at the end of study were 0.25 mg clonidine and 26 mg immediate-release methylphenidate daily. All analyses made comparisons of each drug group to placebo; although it was stated that there was no difference between the immediate-release methylphenidate and clonidine groups on the primary outcome measure of the Conner-ASQ-Teacher scale and the combination therapy provided the largest effect size compared with placebo. It was also noted that immediate-release methylphenidate resulted in better scores than clonidine on attentiveness, while clonidine had

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

better scores on improving more emotional items (e.g. “demands must be met immediately, easily frustrated”). The rate of worsening tics was similar between the drug groups: 22% with immediate-release methylphenidate alone, 26% with clonidine, 18% with the combination, and 22% with placebo. However, 35% assigned to methylphenidate alone had to limit dosage increases due to tics, compared with 18% with clonidine alone or 15% with the combination. After a small worsening in score with methylphenidate alone at 8 weeks on the Yale Global Tic Severity Scale, scores on 3 scales assessing tic symptoms were significantly reduced at endpoint in all drug groups with no direct comparisons across groups presented.

SUMMARY

Limitations of this Review

The results of this review are summarized in Table 10, below. As with other types of research, it is important to recognize the limitations of this systematic review. These can be divided into those relating to generalizability of the results and those relating to methodology within the scope of this review. The generalizability of the results is limited by the scope of the key questions and inclusion criteria, and the generalizability of the studies included. The great majority of studies included narrowly defined patient populations who met strict criteria for case definition, had few comorbidities, and used few or no concomitant medications. One concern about this group of studies is the variation in diagnostic criteria, particularly comparing studies conducted recently to those conducted in previous decades. Another concern is the handling of subtypes of ADHD in these studies. While many studies identify the proportions of patients diagnosed with various subtypes, stratification or analysis of the results based on these is lacking. Similarly, common comorbid conditions are not well addressed by the studies. In large part, the failure to address either subtypes or comorbidities may be due to small sample sizes involved in most studies, but these are serious shortcomings that should not be ignored. The failure of these studies to assess the effect of prior medication exposure or concurrent treatment with other psychoactive medications on outcomes is another serious issue, particularly when comparing older studies where very few patients had prior exposure to newer studies where large proportions did have exposure. Minorities and the most seriously ill patients were underrepresented.

Methodological limitations of the review within the defined scope include the exclusion of studies published in languages other than English, and the lack of a specific search for unpublished studies.

Applicability

The evidence in preschool-age children is most applicable to White boys, ages 4 to 5, with moderately severe symptoms. The evidence base is very small such that characterization of the studies beyond this is not possible, most do not report the proportions with specific subtypes of ADHD or comorbidities.

Studies of elementary school age children with ADHD were characterized by under-reporting of baseline subtype classifications, race or ethnicity, co-occurring disorders, and illness severity, although ore recent studies report these data more consistently. Only one-quarter of all studies of school-aged children reported ADHD subtype prevalence rates. The mixed subtype

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

was most common, occurring in 58% to 100% of participants across most study populations. The inattentive subtype was generally observed less frequently (prevalence rate range: 9% to 40%) and the hyperactive subtype was relatively rare (prevalence rate range: 1% to 8%). Only one-half of all studies of elementary school-aged children reported race or ethnicity among the baseline characteristics. The racial/ethnic make-up of the majority of these study populations was consistent with the current United States Census Bureau Estimates (White = 80.4%; Black = 12.8%; Asian = 4.2%; and of Hispanic/Latino origin = 14.1%).[133] However, the prevalence of ADHD among ethnic groups may not correlate with these data. The evidence applies best to children 8 to 9 years old.

Just over half of studies reported prevalence rates of co-occurring disorders, including oppositional defiant disorder (19% to 66.7%), conduct disorder (9% to 38.5%), anxiety (1.4% to 42%), and depression (0.7% to 6.6%). With the exception of depression, the ranges of comorbidities reported in these trials encompass the American Academy of Pediatrics estimates on prevalence of common comorbidities: oppositional defiant disorder, 35%; conduct disorder, 26%; anxiety disorder, 26%; and depressive disorder, 18%.[134] Illness severity was not presented as a baseline characteristic in most studies, and comparisons across studies based on scales used to assess symptoms are hampered by variation in scale choice and method of reporting. Diagnostic processes also varied across studies. Seventy-two percent of studies used either the DSM III, DSM III-R, or DSM IV criteria to diagnose ADHD, however many used additional criteria and the clinical comparability of patients enrolled is not clear.

The evidence in adolescents, although limited, is more diverse. While many studies reflect populations that are mainly White boys (mean age of 14 years) with moderate to severe symptoms, a few studies included populations with close to 50% girls and 50% boys, and higher percentages of non-White teens. The combined type of ADHD was more prevalent; however few studies reported this characteristic.

In adults, studies generally included populations in their mid-thirties that were fairly balanced in terms of sex. However, studies in adults were also characterized by under-reporting of baseline ADHD subtype classifications, race or ethnicity, and co-occurring disorders. In the small number of trials that reported these data, race was predominantly white, but prevalence varied widely for the inattentive and combined subtypes of ADHD and for co-occurring disorders.

Table 10. Summary of the evidence

Key Question Category	Comparison: Overall strength of the evidence	Conclusion
Key Question 1. Benefits		
General: Effectiveness		
	No trials found: Insufficient	No conclusions about comparative effectiveness of different pharmacotherapies for ADHD could be made.
Young children: Efficacy		
MPH IR and Atomoxetine	Insufficient	Only placebo-controlled trials found. No comparative evidence.
Children: Efficacy		
Stimulants		

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

Table 10. Summary of the evidence

Key Question Category	Comparison: Overall strength of the evidence	Conclusion
IR vs. SR formulations	MPH IR vs. MPH SR: Low	Studies of MPH IR vs. extended-release formulations in children generally were unable to identify significant differences in symptom improvement. Studies of MPH IR and MPH OROS were conflicting; a difference was not found in double-blind studies while open-label studies indicated greater improvement with MPH OROS on some measures. Lisdexamfetamine was comparable to MAS XR on average SKAMP-DS scores in simulated classroom, and clinician perception of improvement. Lisdexamfetamine superior to MPH-OROS in response and change in symptom scores and parent scores (morning, afternoon, evening).
SR vs. SR formulations	MPH SR vs. MPH SR formulations: Low	Limited evidence that MPH LA was superior to MPH OROS on some, but not all efficacy outcomes. Limited evidence that MPH CD was superior to MPH OROS on outcomes in the morning; similar effects in the afternoon; and MPH OROS was superior in the evening. d-MPH ER was superior to MPH OROS at 0.5 to 6 hours post dose and MPH OROS was superior at 10 to 12 hours (2 small trials). d-MPH-ER was no found different to MAS XR in efficacy at 8 weeks.
IR vs. IR	DEX IR vs. MPH IR: Moderate	The body of evidence clearly indicated no difference in efficacy between DEX and MPH IR.
	MAS IR vs. MPH IR: Low	MAS IR was superior to MPH IR on a few efficacy outcome measures in 2 trials but clear evidence of superiority was lacking.
	DEX IR vs. DEX ER vs. MAS: Low	Evidence on the comparison of DEX IR vs. DEX SR vs. MAS may suggest that measures made in the morning show DEX IR superior to DEX SR, and afternoon measures show DEX SR superior to MAS.
	Modafinil vs. MPH IR: Low	Based on 1 trial, modafinil was similar to MPH IR in efficacy
	Dexmethylphenidate: Insufficient	Only placebo-controlled evidence was found.
Transdermal MPH	MTS vs. MPH OROS: Low MTS vs. MPH IR: Low	Based on 1 trial each, MTS had similar efficacy compared with MPH OROS or MPH IR.
Nonstimulants		
Atomoxetine	Atomoxetine vs. MPH IR: Low	Limited evidence suggested a lack of a difference in efficacy compared with MPH IR.
	Atomoxetine vs. MAS XR: Low	Limited evidence suggested that MAS XR was superior to atomoxetine on most efficacy measures.
	Atomoxetine vs. MPH OROS: Moderate	MPH OROS was superior to atomoxetine in response rates.
	Atomoxetine vs. lisdexamfetamine: Low	Lisdexamfetamine resulted in clinical improvement 9 days earlier, more patients had achieved response at 9 weeks (82% versus 64%), and had greater change in the ADHD-RS score (difference -6.5) than atomoxetine.
Clonidine	Clonidine IR vs. MPH IR: Moderate	Clonidine IR was found to be similar to MPH IR on teacher assessment of ADHD symptoms, but other findings were inconsistent.
	Clonidine ER: Insufficient	No head-to-head evidence.
Guanfacine	Guanfacine IR: Insufficient	No head-to-head evidence.

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

Table 10. Summary of the evidence

Key Question Category	Comparison: Overall strength of the evidence	Conclusion
	Guanfacine XR: Low	Guanfacine had superior reduction in ADHD-RS scores at 6 weeks, compared with atomoxetine (difference -5.1), but no difference in the proportion clinically improved (RR 1.15; 95% CI, 0.93 to 1.43).
Adolescents: Efficacy		
	MPH OROS vs. MAS IR: Moderate	Effectiveness outcomes: NR Short-term improvements in core ADHD symptoms: No differences. Other: MPH OROS > MAS IR on overall simulator driving performance.
	MPH IR vs. MPH OROS: Low	Short-term improvements of core ADHD symptoms: NR. Driving performance: MPH OROS > MPH IR in evening and at night.
Adults: Efficacy		
	Immediate-release dextroamphetamine vs. either modafinil or guanfacine; continuing with immediate-release methylphenidate or switching to methylphenidate OROS; immediate-release compared with extended-release mixed amphetamine salts: Low	Similar effects on ADHD symptoms after 2 to 6 weeks.
Key Question 2. Harms		
Young children		
	MPH: Insufficient	No head-to-head evidence.
Children		
	MPH IR vs. MPH SR	There was no evidence of a difference in adverse events between IR and SR formulations for any comparison.
	MPH SR vs. MPH SR formulations	No differences in adverse events, except that MPH OROS had higher rates of insomnia and decreased appetite than MPH CD.
	MTS vs. MPH IR or OROS	No differences found in overall adverse events.
	DEX vs. MPH IR	Limited evidence from short-term trials suggested that weight loss is greater with DEX than MPH IR.
	MAS vs. MPH IR	Limited evidence that twice daily dosing of MAS led to higher rates of loss of appetite and sleep trouble.
	DEX IR vs. DEX ER vs. MAS	Transient weight loss greater with MAS and DEX SR.
	Lisdexamfetamine vs. MPH OROS	More discontinuations due to adverse events with lisdexamfetamine (4.5% vs. 1.8%) than with methylphenidate OROS. More insomnia, nausea and decreased appetite and weight with lisdexamfetamine; more headaches and nasopharyngitis with MPH OROS.
	Atomoxetine vs. MPH IR, MPH OROS, MAS XR, lisdexamfetamine	Vomiting: atomoxetine rates 12% to 13%, approximately 3 times > MPH IR or MAS XR. Somnolence: atomoxetine rates 6% to 26%, 3 to 4 times > lisdexamfetamine, MPH OROS and MPH XR. Nausea and anorexia: > atomoxetine than MPH IR in 1 trial. Insomnia: 13% MPH OROS, 28% MAS XR, 12% lisdexamfetamine vs. 6-7% atomoxetine.

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

Table 10. Summary of the evidence

Key Question Category	Comparison: Overall strength of the evidence	Conclusion
	Clonidine IR vs. MPH IR: Moderate	Sedation: 42% with clonidine, 14% MPH IR. 28% reported as moderate to severe, may improve over time.
	Clonidine ER: Insufficient	No head-to-head evidence.
	Guanfacine ER vs atomoxetine: Low	No differences in overall, serious or discontinuations due to adverse events. One case of syncope with guanfacine ER.
Adults		
	Immediate-release dextroamphetamine vs either modafinil or guanfacine; continuing with immediate-release methylphenidate or switching to methylphenidate OROS: Low Immediate-release compared with extended-release mixed amphetamine salts: Insufficient due to lack of direct comparison	Similar effects on AE outcomes after 2 to 6 weeks.
Long-term safety: Observational studies		
Mixed populations, primarily children		
	Sudden cardiac death: Low	In children, similar risk of sudden death or ventricular arrhythmia for atomoxetine and stimulants. In adults, similar risk of sudden cardiac death for atomoxetine compared with stimulants.
	Cardiac events: Low	Emergency room visits for cardiac causes were similar in current users of methylphenidate products and amphetamine products. Former use of these products also resulted in a nonsignificant finding. In adults, similar risk of stroke or TIA for atomoxetine and stimulants
	Height: Moderate	Evidence on DEX IR compared with MPH IR was inconsistent. Evidence suggested that MPH IR and MPH OROS adversely impacts expected height gain at least during the first 12 months of treatment.
	Weight: Moderate	DEX IR was associated with significantly greater suppression of weight gain than MPH IR in the first 1-2 years, but the difference resolved by the second year. Higher relative doses of DEX IR may have influenced findings.
	Tics, seizures, injuries, and suicidal behavior	No comparative evidence.
Abuse/Misuse/Diversion		
Abuse, misuse, diversion	Low	Survey data suggested that lifetime nonmedical use was more frequent with immediate release methylphenidate or dextroamphetamine compared with mixed amphetamine salts and that amphetamine/dextroamphetamine had the highest rate of diversion

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

Table 10. Summary of the evidence

Key Question Category	Comparison: Overall strength of the evidence	Conclusion
Key Question 3. Subgroups		
	ADHD subtypes or severity: insufficient	No head-to-head evidence
	Demographics: insufficient	No head-to-head evidence
Common comorbidities	Anxiety: Low	Children: The rate of anxiety being reported as an adverse event did not differ statistically significantly in head-to-head comparisons of: MPH IR compared with IR DEX, MAS, MPH SR, MPH OROS, or atomoxetine.
	Tic disorders: Low	Children: MPH IR and IR clonidine both improved ADHD symptom scores and were not found to significantly differ from each other in children with Tourette's disorder.

Abbreviations: ADHD, attention deficit hyperactivity disorder; d-MPH, dexmethylphenidate; DEX, dextroamphetamine; ER, extended release; IR, immediate release; LA, long acting; MAS, mixed amphetamine salts; MPH, methylphenidate; NR, not reported; SR, sustained release; SUD, substance abuse disorder; TIA, transient ischemic attack.

CONCLUSIONS

Evidence on the comparative effectiveness of drugs to treat ADHD was insufficient. Evidence on the comparative efficacy in children and adolescents was moderate- to low-strength and indicated very few differences among the drugs in improving symptoms or in adverse event rates. Sustained-release formulations of stimulants showed benefit over comparators at specific times of day depending on the pharmacokinetics of the specific formulation, but overall differences were not found. Atomoxetine (a nonstimulant) was not found superior to some extended-release stimulant products. Atomoxetine resulted in higher rates of vomiting and somnolence, similar rates of nausea and anorexia, and lower rates of insomnia than stimulants. Extended-release guanfacine was found superior to atomoxetine. Extended-release clonidine had no comparative evidence to date. Immediate-release clonidine was similar to immediate-release methylphenidate.

Comparative evidence in adults was limited and provided low-strength evidence of no significant differences in efficacy between switching to methylphenidate OROS compared with continuing with immediate-release methylphenidate or between immediate-release guanfacine or modafinil compared with immediate-release dextroamphetamine. Evidence was insufficient to assess the comparability of adverse events between switching to methylphenidate OROS or continuing with immediate-release methylphenidate, but low-strength evidence found no significant differences between immediate-release guanfacine or modafinil compared with immediate-release dextroamphetamine.

Evidence on the risk of serious harms was primarily indirect, and indicated atomoxetine had increased risk of suicidal behavior compared with placebo. Differences in risk for sudden death was unclear, cardiac adverse events were not different between stimulants, and cerebrovascular adverse events in adults did not differ between stimulants and atomoxetine. Dextroamphetamine immediate-release caused more inhibition of growth than other stimulants, but the difference was influenced by dose and resolved after 2 years of treatment. Atomoxetine caused similar inhibition of weight gain that lasted up to 5 years. Evidence on abuse, misuse, and diversion was limited, but indicated that stimulant use during childhood is not associated with increased risk of substance use later. Misuse and diversion rates varied by age and were highest

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

among college students, and rates of diversion were highest with amphetamine-based products but similar among methylphenidate products. Evidence of effects in important subgroups of patients with ADHD (e.g. comorbid anxiety) was not comparative.

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5): Attention Deficit/Hyperactivity Disorder Fact Sheet. 2013. http://www.dsm5.org/Documents/ADHD%20Fact%20Sheet.pdf.
2. Dunne JE, Arnold V, Benson S, et al. Summary of the practice parameters for the assessment and treatment of children, adolescents, and adults with ADHD. *J Am Acad Child Adolesc Psychiatry.* 1997;36(9):1311-1318.
3. Kessler RC, Adler L, Barkley RA, et al. The prevalence and correlates of adult ADHD in the United States: results from the national comorbidity survey replication. *Am J Psychiatry.* 2006;163:716-723.
4. McDonagh MS, Jonas DE, Gartlehner G, et al. Methods for the drug effectiveness review project. *BMC Med Res Methodol.* 2012;12:140.
5. Adler LA, Lynch LR, Shaw DM, et al. Medication adherence and symptom reduction in adults treated with mixed amphetamine salts in a randomized crossover study. *Postgrad Med.* Sep 2011;123(5):71-79.
6. Bedard A-CV, Stein MA, Halperin JM, Krone B, Rajwan E, Newcorn JH. Differential impact of methylphenidate and atomoxetine on sustained attention in youth with attention-deficit/hyperactivity disorder. *J Child Psychol Psychiatry.* Jan 2015;56(1):40-48.
7. Coghill D, Banaschewski T, Lecendreux M, et al. European, randomized, phase 3 study of lisdexamfetamine dimesylate in children and adolescents with attention-deficit/hyperactivity disorder. *Eur Neuropsychopharmacol.* Oct 2013;23(10):1208-1218.
8. 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-to-head, randomized, double-blind, phase IIIb study. *CNS Drugs.* Dec 2013;27(12):1081-1092.
9. 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.
10. 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):1861-1872.
11. Silva R, Muniz R, McCague K, Childress A, Brams M, Mao A. Treatment of children with attention-deficit/hyperactivity disorder: results of a randomized, multicenter, double-blind, crossover study of extended-release dexmethylphenidate and D,L-methylphenidate and placebo in a laboratory classroom setting. *Psychopharmacol Bull.* 2008;41(1):19-33.
12. Stein MA, Waldman ID, Charney E, et al. Dose effects and comparative effectiveness of extended release dexmethylphenidate and mixed amphetamine salts. *J Child Adolesc Psychopharmacol.* Dec 2011;21(6):581-588.
13. Banaschewski T, Soutullo C, Lecendreux M, et al. Health-related quality of life and functional outcomes from a randomized, controlled study of lisdexamfetamine dimesylate in children and adolescents with attention deficit hyperactivity disorder. *CNS Drugs.* Oct 2013;27(10):829-840.

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

14. Coghill DR, Banaschewski T, Lecendreux M, et al. Efficacy of lisdexamfetamine dimesylate throughout the day in children and adolescents with attention-deficit/hyperactivity disorder: results from a randomized, controlled trial. *Eur Child Adolesc Psychiatry.* Feb 2014;23(2):61-68.
15. Lopez FA, Scheckner B, Childress AC. Physician perception of clinical improvement in children with attention-deficit/hyperactivity disorder: A post hoc comparison of lisdexamfetamine dimesylate and mixed amphetamine salts extended release in a crossover analog classroom study. *Neuropsychiatric Disease and Treatment Vol 7(1), May 2011, ArtID 267-273.* May 2011;7(1).
16. Soutullo C, Banaschewski T, Lecendreux M, et al. A post hoc comparison of the effects of lisdexamfetamine dimesylate and osmotic-release oral system methylphenidate on symptoms of attention-deficit hyperactivity disorder in children and adolescents. *CNS Drugs.* Sep 2013;27(9):743-751.
17. Germinario EA, Arcieri R, Bonati M, et al. Attention-deficit/hyperactivity disorder drugs and growth: an Italian prospective observational study. *J Child Adolesc Psychopharmacol.* Sep 2013;23(7):440-447.
18. Habel LA, Cooper WO, Sox CM, et al. ADHD medications and risk of serious cardiovascular events in young and middle-aged adults. *JAMA.* Dec 28 2011;306(24):2673-2683.
19. Pilkinton M, Cannatella A. Nonmedical use of prescription stimulants: Age, race, gender, and educational attainment patterns. *J Hum Behav Soc Environ.* Apr 2012;22(4):409-420.
20. Liberati A, Altman D, Tetzlaff J, Mulrow C, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med.* 2009;151(4):W65-W94.
21. Musten LM, Firestone P, Pisterman S, Bennett S, Mercer J. Effects of methylphenidate on preschool children with ADHD: cognitive and behavioral functions. *J Am Acad Child Adolesc Psychiatry.* 1997;36(10):1407-1415.
22. Kollins S, Greenhill L, Swanson J, et al. Rationale, Design, and Methods of the Preschool ADHD Treatment Study (PATS). *J Am Acad Child Adolesc Psychiatry.* Nov 2006;45(11):1275-1283.
23. Greenhill L, Kollins S, Abikoff H, et al. Efficacy and Safety of Immediate-Release Methylphenidate Treatment for Preschoolers With ADHD. *J Am Acad Child Adolesc Psychiatry.* Nov 2006;45(11):1284-1293.
24. Wolraich ML, Greenhill LL, Pelham W, et al. Randomized, controlled trial of OROS methylphenidate once a day in children with attention-deficit/hyperactivity disorder. *Pediatrics.* 2001;108(4):883-892.
25. 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 immediate-release methylphenidate in attention deficit-hyperactivity disorder. *Can J Clin Pharmacol.* 2006;13(1):e50-62.
26. Pelham WE, Gnagy EM, Burrows-Maclean L, et al. Once-a-day Concerta methylphenidate versus three-times-daily methylphenidate in laboratory and natural settings. *Pediatrics.* 2001;107(6).
27. Gau SS-F, Shen H-Y, Soong W-T, Gau C-S. An open-label, randomized, active-controlled equivalent trial of osmotic release oral system methylphenidate in children

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

with attention-deficit/hyperactivity disorder in Taiwan. *J Child Adolesc Psychopharmacol.* Aug 2006;16(4):441-455.
28. Swanson J, Gupta S, Lam A, et al. Development of a new once-a-day formulation of methylphenidate for the treatment of attention-deficit/hyperactivity disorder: proof-of-concept and proof-of-product studies. *Arch Gen Psychiatry.* 2003;60(2):204-211.
29. Anonymous. Sustained-release methylphenidate: new preparations. New pharmaceutical forms: a slight advantage for a small number of children. *Prescrire Int.* 2004;13(74):203-206.
30. Thompson AE, Nazir SA, Abbas MJ, Clarke J. Switching from immediate- to sustained-release psychostimulants in routine treatment of children with attention-deficit hyperactivity disorder. *Psychiatr Bull.* Jul 2006;30(7):247-250.
31. Lage M, Hwang P. Effect of methylphenidate formulation for attention deficit hyperactivity disorder on patterns and outcomes of treatment. *J Child Adolesc Psychopharmacol.* 2004;14(4):575-581.
32. Kemner JE, Lage MJ. Effect of methylphenidate formulation on treatment patterns and use of emergency room services. *Am J Health Syst Pharm.* Feb 15 2006;63(4):317-322.
33. Kemner J, Lage M, et al. Impact of methylphenidate formulation on treatment patterns and hospitalizations: a retrospective analysis. *Ann Gen Psychiatry.* 2006;5(5).
34. Whitehouse D, Shah U, Palmer FB. Comparison of sustained-release and standard methylphenidate in the treatment of minimal brain dysfunction. *J Clin Psychiatry.* 1980;41(8):282-285.
35. Findling RL, Quinn D, Hatch SJ, Cameron SJ, DeCory HH, McDowell M. Comparison of the clinical efficacy of twice-daily Ritalin and once-daily Equasym XL with placebo in children with Attention Deficit/Hyperactivity Disorder. *Eur Child Adolesc Psychiatry.* Dec 2006;15(8):450-459.
36. Pelham WE, Waxmonsky JG, Schentag J, et al. Efficacy of a methylphenidate transdermal system versus t.i.d. methylphenidate in a laboratory setting. *J Atten Disord.* Jan 2011;15(1):28-35.
37. McCracken JT, Biederman J, Greenhill LL, et al. Analog classroom assessment of a once-daily mixed amphetamine formulation, SLI381 (Adderall XR), in children with ADHD. *J Am Acad Child Adolesc Psychiatry.* 2003;42(6):673-683.
38. Biederman J, Boellner S, Childress A, Lopez FA, Krishnan S, Zhang Y. Lisdexamfetamine Dimesylate and Mixed Amphetamine Salts Extended Release in Children with ADHD: A Double-Blind Placebo Controlled, Crossover, Analog, Classroom Study. *Biol Psychiatry.* 2007.
39. Eli Lilly and Company. Strattera Product Label. *http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021411s029s030lbl.pdf*. 2007.
40. Sonuga-Barke EJ, Swanson JM, Coghill D, DeCory HH, Hatch SJ. Efficacy of two once-daily methylphenidate formulations compared across dose levels at different times of the day: preliminary indications from a secondary analysis of the COMACS study data. *BMC Psychiatry.* 2004;4(1):28.
41. Swanson JM, Wigal SB, Wigal T, et al. A comparison of once-daily extended-release methylphenidate formulations in children with attention-deficit/hyperactivity disorder in the laboratory school (the COMACS Study). *Pediatrics.* 2004;113(3 Pt 1):e206-216.

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

42. Lopez F, Silva R, Pestreich L, Muniz R. Comparative efficacy of two once daily methylphenidate formulations (Ritalin LA and Concerta) and placebo in children with attention deficit hyperactivity disorder across the school day. *Paediatr Drugs.* 2003;5(8):545-555.
43. Silva R, Muniz R, Pestreich LK, Brams M, Childress A, Lopez FA. Efficacy of two long-acting methylphenidate formulations in children with attention-deficit/hyperactivity disorder in a laboratory classroom setting. *J Child Adolesc Psychopharmacol.* Aug 2005;15(4):637-654.
44. Findling RL, Bukstein OG, Melmed RD, et al. A randomized, double-blind, placebo-controlled, parallel-group study of methylphenidate transdermal system in pediatric patients with attention-deficit/hyperactivity disorder. *J Clin Psychiatry.* Jan 2008;69(1):149-159.
45. Muniz R, Brams M, Mao A, McCague K, Pestreich L, Silva R. Efficacy and safety of extended-release dexmethylphenidate compared with d,l-methylphenidate and placebo in the treatment of children with attention-deficit/hyperactivity disorder: A 12-hour laboratory classroom study. *J Child Adolesc Psychopharmacol.* Jun 2008;18(3):248-256.
46. Arnold LE, Christopher J, Huestis R, Smeltzer DJ. Methylphenidate vs dextroamphetamine vs caffeine in minimal brain dysfunction: controlled comparison by placebo washout design with Bayes' analysis. *Arch Gen Psychiatry.* 1978;35(4):463-473.
47. Efron D, Jarman F, Barker M. Side effects of methylphenidate and dexamphetamine in children with attention deficit hyperactivity disorder: a double-blind, crossover trial. *Pediatrics.* 1997a;100(4):662-666.
48. Efron D, Jarman FC, Barker MJ. Child and parent perceptions of stimulant medication treatment in attention deficit hyperactivity disorder. *J Paediatr Child Health.* 1998;34(3):288-292.
49. Elia J, Borcherding BG, Potter WZ, Mefford IN, Rapoport JL, Keysor CS. Stimulant drug treatment of hyperactivity: biochemical correlates. *Clin Pharmacol Ther.* 1990;48(1):57-66.
50. Elia J, Borcherding BG, Rapoport JL, Keysor CS. Methylphenidate and dextroamphetamine treatments of hyperactivity: are there true nonresponders? *Psychiatry Res.* 1991;36(2):141-155.
51. Elia J, Welsh PA, Gullotta CS, Rapoport JL. Classroom academic performance: improvement with both methylphenidate and dextroamphetamine in ADHD boys. *J Child Psychol Psychiatry.* 1993;34(5):785-804.
52. Huestis RD, Arnold LE, Smeltzer DJ. Caffeine versus methylphenidate and d-amphetamine in minimal brain dysfunction: a double-blind comparison. *Am J Psychiatry.* 1975;132(8):868-870.
53. Kauffman RE, Smith-Wright D, Reese CA, Simpson R, Jones F. Medication compliance in hyperactive children. *Pediatr Pharmacol.* 1981;1(3):231-237.
54. Sharp WS, Walter JM, Marsh WL, Ritchie GF, Hamburger SD, Castellanos FX. ADHD in girls: clinical comparability of a research sample. *J Am Acad Child Adolesc Psychiatry.* 1999;38(1):40-47.
55. Simpson RL, Reece CA, Kauffman R, Jones F. Stimulant medications and the classroom attention-to-task and deviant social behaviors of twelve hyperactive males. *Learn Disabil Q.* 1980;3(1):19-27.

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

56. Schmidt ME, Kruesi MJ, Elia J, et al. Effect of dextroamphetamine and methylphenidate on calcium and magnesium concentration in hyperactive boys. *Psychiatry Res.* 1994;54(2):199-210.
57. Gross MD. A comparison of dextro-amphetamine and racemic-amphetamine in the treatment of the hyperkinetic syndrome or minimal brain dysfunction. *Dis Nerv Syst.* 1976;37(1):14-16.
58. Borcherding BG, Keysor CS, Rapoport JL, Elia J, Amass J. Motor/vocal tics and compulsive behaviors on stimulant drugs: is there a common vulnerability? *Psychiatry Res.* 1990;33(1):83-94.
59. Castellanos FX, Giedd JN, Elia J, et al. Controlled stimulant treatment of ADHD and comorbid Tourette's syndrome: effects of stimulant and dose. *J Am Acad Child Adolesc Psychiatry.* 1997;36(5):589-596.
60. Pelham WE, Gnagy EM, Chronis AM, et al. A comparison of morning-only and morning/late afternoon Adderall to morning-only, twice-daily, and three times-daily methylphenidate in children with attention-deficit/hyperactivity disorder. *Pediatrics.* 1999a;104(6):1300-1311.
61. Pelham WE, Aronoff HR, Midlam JK, et al. A comparison of Ritalin and Adderall: efficacy and time-course in children with attention-deficit/hyperactivity disorder. *Pediatrics.* 1999b;103(4):e43.
62. Chronis AM, Pelham WE, Gnagy EM, Roberts JE, Aronoff HR. The impact of late-afternoon stimulant dosing for children with ADHD on parent and parent-child domains. *J Clin Child Adolesc Psychol.* Mar 2003;32(1):118-126.
63. Pliszka SR, Browne RG, Olvera RL, Wynne SK. A double-blind, placebo-controlled study of Adderall and methylphenidate in the treatment of attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry.* 2000;39(5):619-626.
64. Barkley RA, Connor DF, Kwasnik D. Challenges to determining adolescent medication response in an outpatient clinical setting: Comparing Adderall and methylphenidate for ADHD. *J Atten Disord.* Aug 2000;4(2):102-113.
65. Manos MJ, Short EJ, Findling RL. Differential effectiveness of methylphenidate and Adderall in school-age youths with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry.* 1999;38(7):813-819.
66. Amiri S, Mohammadi M-R, Mohammadi M, Nouroozinejad G-H, Kahbazi M, Akhondzadeh S. Modafinil as a treatment for Attention-Deficit/Hyperactivity Disorder in children and adolescents: a double blind, randomized clinical trial. *Prog Neuropsychopharmacol Biol Psychiatry.* Jan 1 2008;32(1):145-149.
67. 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.
68. 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.* Mar 2007;41(3):222-230.
69. Sangal RB, Owens J, Allen AJ, Sutton V, Schuh K, Kelsey D. Effects of atomoxetine and methylphenidate on sleep in children with ADHD. *Sleep.* Dec 1 2006;29(12):1573-1585.
70. Newcorn JH, Kratochvil CJ, Allen AJ, et al. Atomoxetine and osmotically released methylphenidate for the treatment of attention deficit hyperactivity disorder: acute

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

comparison and differential response.[see comment]. *Am J Psychiatry.* Jun 2008;165(6):721-730.
71. Kemner JE, Starr HL, Ciccone PE, Hooper-Wood CG, Crockett RS. Outcomes of OROS methylphenidate compared with atomoxetine in children with ADHD: a multicenter, randomized prospective study. *Adv Ther.* Sep-Oct 2005;22(5):498-512.
72. Wigal SB, Wigal TL, McGough JJ, et al. A laboratory school comparison of mixed amphetamine salts extended release (Adderall XR) and atomoxetine (Strattera) in school-aged children with attention deficit/hyperactivity disorder. *J Atten Disord.* Aug 2005;9(1):275-289.
73. Palumbo DR, Sallee FR, Pelham WE, Jr., Bukstein OG, Daviss WB, McDermott MP. Clonidine for attention-deficit/hyperactivity disorder: I. Efficacy and tolerability outcomes. *J Am Acad Child Adolesc Psychiatry.* Feb 2008;47(2):180-188.
74. van der Meere J, Gunning B, Stemerdink N. The effect of methylphenidate and clonidine on response inhibition and state regulation in children with ADHD. *J Child Psychol Psychiatry.* 1999;40(2):291-298.
75. The Tourette's Syndrome Study Group. Treatment of ADHD in children with tics: a randomized controlled trial. *Neurology.* 2002;58(4):527-536.
76. Connor DF, Barkley RA, Davis HT. A pilot study of methylphenidate, clonidine, or the combination in ADHD comorbid with aggressive oppositional defiant or conduct disorder. *Clin Pediatr.* 2000;39(1):15-25.
77. Cox DJ, Merkel RL, Penberthy JK, Kovatchev B, Hankin CS. Impact of methylphenidate delivery profiles on driving performance of adolescents with attention-deficit/hyperactivity disorder: a pilot study. *J Am Acad Child Adolesc Psychiatry* 2004;43(3):269-275.
78. Cox DJ, Merkel RL, Moore M, Thorndike F, Muller C, Kovatchev B. Relative benefits of stimulant therapy with OROS methylphenidate versus mixed amphetamine salts extended release in improving the driving performance of adolescent drivers with attention-deficit/hyperactivity disorder. *Pediatrics.* Sep 2006;118(3):e704-710.
79. Taylor FB, Russo J. Efficacy of modafinil compared to dextroamphetamine for the treatment of attention deficit hyperactivity disorder in adults. *J Child Adolesc Psychopharmacol.* 2000;10(4):311-320.
80. Taylor FB, Russo J. Comparing guanfacine and dextroamphetamine for the treatment of adult attention-deficit/hyperactivity disorder. *J Clin Psychopharmacol.* 2001;21(2):223-228.
81. Spencer TJ, Mick E, Surman CB, et al. A randomized, single-blind, substitution study of OROS methylphenidate (Concerta) in ADHD adults receiving immediate release methylphenidate. *J Atten Disord.* May 2011;15(4):286-294.
82. Wigal T, Greenhill L, Chuang S, et al. Safety and Tolerability of Methylphenidate in Preschool Children With ADHD. *J Am Acad Child Adolesc Psychiatry.* Nov 2006;45(11):1294-1303.
83. James RS, Sharp WS, Bastain TM, et al. Double-blind, placebo-controlled study of single-dose amphetamine formulations in ADHD. *J Am Acad Child Adolesc Psychiatry.* 2001;40(11):1268-1276.
84. Sonuga-Barke EJ, Coghill D, Wigal T, DeBacker M, Swanson J. Adverse reactions to methylphenidate treatment for attention-deficit/hyperactivity disorder: Structure and

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

associations with clinical characteristics and symptom control. *J Child Adolesc Psychopharmacol.* Dec 2009;19(6):683-690.
85. Prasad S, Harpin V, Poole L, et al. A multi-centre, randomised, open-label study of atomoxetine compared with standard current therapy in UK children and adolescents with attention-deficit/hyperactivity disorder (ADHD). *Curr Med Res Opin.* Feb 2007;23(2):379-394.
86. Daviss WB, Patel NC, Robb AS, et al. Clonidine for attention-deficit/hyperactivity disorder: II. ECG changes and adverse events analysis. *J Am Acad Child Adolesc Psychiatry.* Feb 2008;47(2):189-198.
87. Bangs ME, Tauscher-Wisniewski S, Polzer J, et al. Meta-analysis of suicide-related behavior events in patients treated with atomoxetine. *J Am Acad Child Adolesc Psychiatry.* Feb 2008;47(2):209-218.
88. Faraone SV, Biederman J, Morley CP, Spencer TJ. Effect of stimulants on height and weight: A review of the literature. *J Am Acad Child Adolesc Psychiatry.* Sep 2008;47(9):994-1009.
89. Goldman W, Seltzer R, Reuman P. Association between treatment with central nervous system stimulants and Raynaud's syndrome in children: a retrospective case-control study of rheumatology patients. *Arthritis Rheum.* Feb 2008;58(2):563-566.
90. Miller-Horn JW, Kaleyias J, Valencia I, et al. Efficacy and tolerability of ADHD medications in a clinical practice. *J Pediatr Neurol.* 2008;6(1):5-10.
91. Spencer TJ, Kratochvil CJ, Sangal RB, et al. Effects of atomoxetine on growth in children with attention-deficit/hyperactivity disorder following up to five years of treatment. *J Child Adolesc Psychopharmacol.* Oct 2007;17(5):689-700.
92. Wernicke JF, Holdridge KC, Jin L, et al. Seizure risk in patients with attention-deficit-hyperactivity disorder treated with atomoxetine. *Dev Med Child Neurol.* Jul 2007;49(7):498-502.
93. Winterstein AG, Gerhard T, Shuster J, Johnson M, Zito JM, Saidi A. Cardiac safety of central nervous system stimulants in children and adolescents with attention-deficit/hyperactivity disorder. *Pediatrics.* Dec 2007;120(6):e1494-1501.
94. Spencer TJ, Newcorn JH, Kratochvil CJ, Ruff D, Michelson D, Biederman J. Effects of Atomoxetine on Growth After 2-Year Treatment Among Pediatric Patients With Attention-Deficit/Hyperactivity Disorder. *Pediatrics.* 2005;116(1):e74-80.
95. Brehaut JC, Miller A, Raina P, McGrail KM. Childhood behavior disorders and injuries among children and youth: a population-based study. *Pediatrics.* 2003;111(2):262-269.
96. Gadow KD, Sverd J, Sprafkin J, Nolan EE, Ezor SN. Efficacy of methylphenidate for attention-deficit hyperactivity disorder in children with tic disorder. *Arch Gen Psychiatry.* 1995;52(6):444-455.
97. Quinn PO, Rapoport JL. One-year follow-up of hyperactive boys treated with imipramine or methylphenidate. *Am J Psychiatry.* 1975;132(3):241-245.
98. Mattes JA, Gittelman R. Growth of hyperactive children on maintenance regimen of methylphenidate. *Arch Gen Psychiatry.* 1983;40(3):317-321.
99. Wernicke JF, Faries D, Girod D, et al. Cardiovascular effects of atomoxetine in children, adolescents, and adults. *Drug Saf.* 2003;26(10):729-740.
100. Gross MD. Growth of hyperkinetic children taking methylphenidate, dextroamphetamine, or imipramine/desipramine. *Pediatrics.* 1976;58:423-431.

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

101. Safer D, Allen R, Barr E. Depression of growth in hyperactive children on stimulant drugs. *N Engl J Med.* 1972;287(5):217-220.
102. Satterfield JH. Growth of hyperactive children treated with methylphendiate. *Arch Gen Psychiatry.* 1979;36:212-217.
103. McNutt BA, Ballard JE, Boileau RA. The effects of long-term stimulant medication on growth and body composition of hyperactive children. *Psychopharmacol Bull.* 1976;12(2):13-15.
104. Wilens T, Pelham W, Stein M, et al. ADHD Treatment With Once-Daily OROS Methylphenidate: Interim 12-Month Results From a Long-Term Open-Label Study. *J Am Acad Child Adolesc Psychiatry.* 2003;42(4):424-433.
105. Millichap JG. Growth of hyperactive children treated with methylphendiate: A possible growth stimulant effect. In: Millichap JG, ed. *Learning Disabilities and Related Disorders*. Chicago: Year Book Medical Publishers Inc.; 1977:151-154.
106. Gualtieri CT. Attention Deficit Disorder in Adults. *Clin Neuropharmacol.* 1985;8(4):343-356.
107. Horrigan JP, Barnhill LJ. Low-dose amphetamine salts and adult attention-deficit/hyperactivity disorder. *J Clin Psychiatry.* 2000;61(6):414-417.
108. Safer D, Allen R. Factors influencing the suppressant effects of two stimulant drugs on the growth of hyperactive children. *Pediatrics.* 1973;51(4):660-667.
109. Zeiner P. Body Growth and Cardiovascular Function after Extended Treatment (1.75 Years) with Methylphenidate in Boys with Attention-Deficit Hyperactivity Disorder. *J Child Adolesc Psychopharmacol.* 1995;5(2):129-138.
110. Safer DJ, Allen RP, Barr E. Growth rebound after termination of stimulant drugs. *Pediatrics.* 1975;86(1):113-116.
111. Kratochvil CJ, Bohac D, Harrington M, Baker N, May D, Burke WJ. An open-label trial of tomoxetine in pediatric attention deficit hyperactivity disorder. *J Child Adolesc Psychopharmacol.* 2001;11(2):167-170.
112. Charach A, Figueroa M, Chen S, Ickowicz A, Schachar R. Stimulant treatment over 5 years: effects on growth. *J Am Acad Child Adolesc Psychiatry.* Apr 2006;45(4):415-421.
113. Pliszka SR, Matthews TL, Braslow KJ, Watson MA. Comparative effects of methylphenidate and mixed salts amphetamine on height and weight in children with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry.* May 2006;45(5):520-526.
114. Holick CN, Turnbull BR, Jones ME, Chaudhry S, Bangs ME, Seeger JD. Atomoxetine and cerebrovascular outcomes in adults. *J Clin Psychopharmacol.* Oct 2009;29(5):453-460.
115. McAfee AT, Holdridge KC, Johannes CB, Hornbuckle K, Walker AM. The effect of pharmacotherapy for attention deficit hyperactivity disorder on risk of seizures in pediatric patients as assessed in an insurance claims database. *Curr Drug Saf.* May 2008;3(2):123-131.
116. McCarthy S, Cranswick N, Potts L, Taylor E, Wong ICK. Mortality associated with attention-deficit hyperactivity disorder (ADHD) drug treatment: a retrospective cohort study of children, adolescents and young adults using the general practice research database. *Drug Saf.* 2009;32(11):1089-1096.
117. Schelleman H, Bilker WB, Strom BL, et al. Cardiovascular Events and Death in Children Exposed and Unexposed to ADHD Agents. *Pediatrics.* 2011;127:1102–1110.

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

118. Winterstein AG, Gerhard T, Shuster J, Saidi A. Cardiac safety of methylphenidate versus amphetamine salts in the treatment of ADHD. *Pediatrics.* Jul 2009;124(1):e75-80.
119. Rapport MD, Moffitt C. Attention deficit/hyperactivity disorder and methylphenidate. A review of height/weight, cardiovascular, and somatic complaint side effects. *Clin Psychol Rev.* 2002;22:1107-1131.
120. Palumbo D, Spencer T, Lynch J, Co-Chien H, Faraone SV. Emergence of tics in children with ADHD: impact of once-daily OROS methylphenidate therapy. *J Child Adolesc Psychopharmacol.* 2004;14(2):185-194.
121. Bloch MH, Panza KE, Landeros-Weisenberger A, Leckman JF. Meta-analysis: treatment of attention-deficit/hyperactivity disorder in children with comorbid tic disorders. *J Am Acad Child Adolesc Psychiatry.* Sep 2009;48(9):884-893.
122. Parasrampuria D, Schoedel KA, Schuller R, et al. Do Formulation Differences Alter Abuse Liability of Methylphenidate? A Placebo controlled, Randomized, Double blind, Crossover Study in Recreational Drug Users. *J Clin Psychopharmacol.* 2007;27(5):459-467.
123. Kroutil LA, Van Brunt DL, Herman-Stahl MA, Heller DC, Bray RM, Penne MA. Nonmedical use of prescription stimulants in the United States. *Drug Alcohol Depend.* Sep 2006;84(2):135-143.
124. Garnier LM, Arria AM, Caldeira KM, Vincent KB, O'Grady KE, Wish ED. Sharing and selling of prescription medications in a college student sample. *J Clin Psychiatry.* Mar 2010;71(3):262-269.
125. Coleman JJ, Bensinger PB, Gold MS, Smith DE, Bianchi RP, DuPont RL. Can Drug Design Inhibit Abuse. *J Psychoactive Drugs.* 2005;37(4):343-362.
126. Setlik J, Bond G, Ho M. Adolescent prescription ADHD medication abuse is rising along with prescriptions for these medications. *Pediatrics.* Sep 2009;124(3):875-880.
127. Starr HL, Kemner J. Multicenter, randomized, open-label study of OROS methylphenidate versus atomoxetine: treatment outcomes in African-American children with ADHD. *J Natl Med Assoc.* 2005;97(10 Suppl):11S-16S.
128. Centre for Drug Evaluation and Research. Medical Review: NRP104 (lisdexamphetamine dimesylate) NDA #21-977. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/021977s000_MedR.pdf. 2007. Accessed August 21, 2007.
129. Biederman J, Wigal SB, Spencer TJ, McGough JJ, Mays DA. A post hoc subgroup analysis of an 18-day randomized controlled trial comparing the tolerability and efficacy of mixed amphetamine salts extended release and atomoxetine in school-age girls with attention-deficit/hyperactivity disorder. *Clin Ther.* Feb 2006;28(2):280-293.
130. Sonuga-Barke EJS, Coghill D, Markowitz JS, Swanson JM, Vandenberghe M, Hatch SJ. Sex differences in the response of children with ADHD to once-daily formulations of methylphenidate. *J Am Acad Child Adolesc Psychiatry.* Jun 2007;46(6):701-710.
131. Mikami AY, Cox DJ, Davis MT, Wilson HK, Merkel RL, Burket R. Sex differences in effectiveness of extended-release stimulant medication among adolescents with attention-deficit/hyperactivity disorder. *J Clin Psychol Med Settings.* Sep 2009;16(3):233-242.
132. Efron D, Jarman F, Barker M. Methylphenidate versus dexamphetamine in children with attention deficit hyperactivity disorder: A double-blind, crossover trial. *Pediatrics.* 1997c;100(6):1025.

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.

133. Population Division USCB. *Table 4: Annual Estimates of the Population by Race Alone and Hispanic or Latino Origin for the United States and States.* Population Division, U.S. Census Bureau; July 1, 2004 (SC-EST2004-04) 2004.
134. American Academy of Pediatrics. Committee on Quality Improvement and Subcommittee on Attention-Deficit/Hyperactivity Disorder Clinical Practice Guideline: Diagnosis and Evaluation of the Child With Attention-Deficit/Hyperactivity Disorder. *Pediatrics.* 2000;May 2000(105):1158-1170.

Property of the Drug Effectiveness Review Project. For use by Idaho only.
Copyright Drug Effectiveness Review Project. All rights reserved.