# Drug Class Review

# Pharmacologic Treatments for Attention Deficit Hyperactivity Disorder

**Final Update 4 Report**

**December 2011**

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.

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The literature on this topic is scanned periodically.

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**The medical literature relating to this topic is scanned periodically. (See http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/methods.cfm for description of scanning process). Prior versions of this report can be accessed at the DERP website.**

**Shading indicates new information for Update 4.**

# 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, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, and reference lists of included studies. We also searched the US Food and Drug Administration Center for Drug Evaluation and Research website for additional unpublished data and requested information from pharmaceutical manufacturers.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 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 formulations of other nonstimulant drugs (clonidine, guanfacine) have no comparative evidence to date. Immediate-release clonidine was similar to immediate-release methylphenidate.

Comparative evidence in adults 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. 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 has 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 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.

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# INTRODUCTION

According to the most recent National Institutes of Health Consensus Statement (1998), "attention deficit hyperactivity disorder is the most commonly diagnosed childhood behavioral disorder."[1] Classification of hyperactivity and defects in attention emerged in the 1960's as Minimal Brain Dysfunction and Hyperkinetic Syndrome, and has continued to evolve over time.[2]

A number of community-based studies have reported attention deficit hyperactivity disorder (ADHD) prevalence rates that range from 1.7% to 16%.[3] This is broader than the range of 3% to 5% that was estimated by the expert panelists that participated in the National Institutes of Health Consensus Development Conference on Diagnosis and Treatment of Attention Deficit Hyperactivity Disorder in 1998.[1] The estimated prevalence cited in the most recent (1997) version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) is 3% to 7%.[4] Differences in prevalence estimates may be due to variation in methods of ascertainment and diagnostic criteria.[5] While no independent diagnostic test exists for ADHD, the DSM-IV provides standardized criteria that can be used as a foundation for clinical diagnosis.[1, 4] According to the DSM-IV, essential features of ADHD include persistent levels of inattention, impulsivity, and/or hyperactivity that exceed usual developmental patterns.[4] In order to qualify for a DSM-IV diagnosis of ADHD, symptoms must date back to before age 7, persist for at least 6 months, and cause impairment that interferes with functional capacity in at least 2 performance settings (social, academic, or employment).[4] The DSM-IV specifies 3 distinct subtypes of ADHD that are characterized by predominantly inattentive, hyperactive-impulsive, or mixed symptoms.[4]

ADHD is diagnosed more frequently in males than in females.[6] Comorbidities such as mood, anxiety, and/or conduct disorders, tics or Tourette syndrome, learning disorders, and mental retardation may be found in up to 65% of individuals with ADHD.[3] With regard to the course of ADHD, symptoms can persist into adolescence in 80% of cases and into adulthood in 65% of cases.[6] Comorbid DSM-IV mood, anxiety, substance use, and/or impulse disorders also commonly occur in combination with ADHD in adults.[7]

Historically, drug therapy for ADHD has consisted primarily of stimulant medications. More recently, nonstimulant medication treatment alternatives have been identified. These include atomoxetine, atypical antipsychotics, bupropion, 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.

## Purpose and Limitations of Systematic Reviews

Systematic reviews, also called evidence reviews, are the foundation of evidence-based practice. A systematic review focuses on the strength and limits of evidence from studies about the effectiveness of a clinical intervention. Systematic reviews begin with a careful formulation of research questions. The goal is to select questions that are important to patients and clinicians, then to examine how well the scientific literature answers those questions. Terms commonly used in systematic reviews, such as statistical terms, are provided in Appendix A and are defined as they apply to reports produced by the Drug Effectiveness Review Project.

Systematic reviews emphasize the patient's perspective in the choice of outcome measures used to answer research questions. Studies that measure health outcomes (events or conditions that the patient can feel, such as fractures, functional status, and quality of life) are emphasized over studies of intermediate outcomes (such as change in bone density). Reviews also emphasize measures that are easily interpreted in a clinical context. Specifically, measures of *absolute risk* or the probability of disease are preferred to measures such as relative risk. The difference in absolute risk between interventions depends on the number of events in both groups, such that the difference (absolute risk reduction) is smaller when there are fewer events. In contrast, the difference in relative risk is fairly constant across groups with different baseline risk for the event, such that the difference (relative risk reduction) is similar across these groups. Relative risk reduction is often more impressive than the absolute risk reduction. Another useful measure is the *number needed to treat* (or harm). The number needed to treat, often referred to as the NNT, is the number of patients who would have to be treated with an intervention for 1 additional patient to benefit (experience a positive outcome or avoid a negative outcome). The absolute risk reduction is used to calculate the number needed to treat.

Systematic reviews weigh the quality of the evidence, allowing a greater contribution from studies that meet high methodological standards that reduce the likelihood of biased results. In general, for questions about the relative benefit of a drug, the results of well-executed, randomized, controlled trials are considered better evidence than results of cohort, case-control, or cross-sectional studies. In turn, these studies provide better evidence than uncontrolled trials and case series. For questions about tolerability and harms, observational study designs may provide important information that is not available from controlled trials. Within the hierarchy of observational studies, cohort designs are preferred when conducted well and for assessing a common outcome. Case-control studies are preferred only when the outcome measure is rare and the study is well conducted.

Systematic reviews pay particular attention to the generalizability of *efficacy studies* performed in controlled or academic settings. Efficacy studies provide the best information about how a drug performs in a controlled setting. These studies attempt to tightly control potential confounding factors and bias; however, for this reason the results of efficacy studies may not be applicable to many, and sometimes to most, patients seen in everyday practice. Most efficacy studies use strict eligibility criteria that may exclude patients based on their age, sex, adherence to treatment, or severity of illness. For many drug classes, including the antipsychotics, unstable or severely impaired patients are often excluded from trials. In addition, efficacy studies frequently exclude patients who have comorbid diseases, meaning diseases other than the one under study. Efficacy studies may also use dosing regimens and follow-up protocols that may be impractical in typical practice settings. And these studies often restrict options that are of value in actual practice, such as combination therapies or switching to other drugs. Efficacy studies also often examine the short-term effects of drugs that in practice are used for much longer periods of time. Finally, efficacy studies tend to assess effects by using objective measures that do not capture all of the benefits and harms of a drug or do not reflect the outcomes that are most important to patients and their families.

Systematic reviews highlight studies that reflect actual clinical *effectiveness* in unselected patients and community practice settings. Effectiveness studies conducted in primary care or office-based settings use less stringent eligibility criteria, more often 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 the highly selected populations in

efficacy studies. Examples of effectiveness outcomes include quality of life, frequency or duration of hospitalizations, social function, and the ability to work. These outcomes are more important to patients, family, and care providers than surrogate or intermediate measures, such as scores based on psychometric scales.

Efficacy and effectiveness studies overlap. For example, a study might use very narrow inclusion criteria like an efficacy study, but, like an effectiveness study, might examine flexible dosing regimens, have a long follow-up period, and measure quality of life and functional outcomes. For this report we sought evidence about outcomes that are important to patients and would normally be considered appropriate for an effectiveness study. However, many of the studies that reported these outcomes were short-term and used strict inclusion criteria to select eligible patients. For these reasons, it was neither possible nor desirable to exclude evidence based on these characteristics. Labeling each study as either an efficacy or an effectiveness study, while convenient, is of limited value; it is more useful to consider whether the patient population, interventions, time frame, and outcomes are relevant to one's practice or to a particular patient.

Studies anywhere on the continuum from efficacy to effectiveness can be useful in comparing the clinical value of different drugs. Effectiveness studies are more applicable to practice, but efficacy studies are a useful scientific standard for determining whether characteristics of different drugs are related to their effects on disease. Systematic reviews thoroughly cover the efficacy data in order to ensure that decision-makers can assess the scope, quality, and relevance of the available data. This thoroughness is not intended to obscure the fact that efficacy data, no matter how much of it there is, may have limited applicability to practice. Clinicians can judge the relevance of the study results to their practice and should note where there are gaps in the available scientific information.

Unfortunately, for many drugs there exist few or no effectiveness studies and many efficacy studies. Yet clinicians must decide on treatment for many patients who would not have been included in controlled trials and for whom the effectiveness and tolerability of the different drugs are uncertain. Systematic reviews indicate whether or not there exists evidence that drugs differ in their effects in various subgroups of patients, but they do not attempt to set a standard for how results of controlled trials should be applied to patients who would not have been eligible for them. With or without an evidence report, these decisions must be informed by clinical judgment.

In the context of development of recommendations for clinical practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of an intervention are based on strong evidence from clinical studies. By themselves, they do not say what to do. Judgment, reasoning, and applying one's values under conditions of uncertainty must also play a role in decision making. Users of an evidence report must also keep in mind that *not proven* does not mean *proven not*; that is, if the evidence supporting an assertion is insufficient, it does not mean the assertion is untrue. The quality of the evidence on effectiveness is a key component, but not the only component, in making decisions about clinical policy. Additional criteria include acceptability to physicians and patients, potential for unrecognized harm, applicability of the evidence to practice, and consideration of equity and justice.

## Scope and Key Questions

The purpose of this review is to compare the benefits and harms of different pharmacologic treatments for ADHD. The Oregon 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. Evidence on Effectiveness and Efficacy
    a. What is the comparative or noncomparative evidence that pharmacologic treatments for attention deficit disorders improve *effectiveness* outcomes?
        i. Comparisons include individual drugs, as well as between stimulants and nonstimulants, and immediate-release compared with intermediate-release compared with long-acting formulations.
        ii. Noncomparative evidence will be considered for drugs with no comparative evidence.
    b. What is the *comparative* efficacy between any included pharmacologic treatment, between stimulants and nonstimulants, and between immediate-release compared with intermediate-release compared with long-acting formulations, for attention deficit disorders?

2. Tolerability, Serious Adverse Events, Misuse, and Diversion
    a. What is the evidence of *comparative* tolerability of different pharmacologic treatments, between stimulants and nonstimulants, and between immediate-release compared with intermediate-release compared with long-acting formulations, for attention deficit disorders?
    b. What is the evidence of serious adverse events or long-term adverse events associated with use of pharmacologic treatments for attention deficit disorders?
    c. What is the comparative or noncomparative evidence that pharmacologic treatments for attention deficit disorders impact the risk of misuse or illicit diversion in patients with no history of misuse or diversion?
        i. Comparisons include individual drugs, as well as between stimulants and nonstimulants, and immediate-release compared with intermediate-release compared with long-acting formulations.
        ii. Noncomparative evidence will be considered for drugs with no comparative evidence.

3. Evidence in Subgroups of Patients
    a. What is the evidence of benefits and harms of pharmacologic treatments, between stimulants and nonstimulants, and between immediate-release compared with intermediate-release compared with long-acting formulations, for attention deficit disorders in subgroups of patients based on demographics (age, racial groups, gender), socioeconomic status, other medications or therapy, or comorbidities (e.g. tics, anxiety, substance use disorders, disruptive behavior disorders)?
    b. What is the comparative or noncomparative evidence of misuse or illicit diversion of pharmacologic treatments for attention deficit disorders in patients with current or past substance use disorder comorbidities?
        i. Comparisons include individual drugs, as well as between stimulants and nonstimulants, and immediate-release compared with intermediate-release compared with long-acting formulations.
        ii. Noncomparative evidence will be considered for drugs with no comparative evidence.

## Inclusion Criteria

### Populations

Pediatric (age <3, <6, and 6-17 years), and adult (age ≥18 years) outpatients with attention deficit disorders

- Attention deficit disorder
- Attention deficit hyperactivity disorder

### Interventions

Included drugs are described in Table 1. Black box warnings for the included interventions are listed in Appendix B.

**Table 1. Attention deficit hyperactivity disorder drugs and indication**

| Active ingredient(s) | Referred to in this report as | Trade name[a] | Forms |
|---|---|---|---|
| Amphetamine mixture (amphetamine aspartate; amphetamine sulfate; dextroamphetamine saccharate; dextroamphetamine sulfate) | Mixed amphetamine salts XR | Adderall XR®[a] | Extended-release oral capsule |
| Atomoxetine hydrochloride | Atomoxetine | Strattera®[b] | Oral capsule |
| Clonidine hydrochloride | Immediate-release clonidine | Catapres®[b] | Oral tablet |
| | Extended-release clonidine | Kapvay™[c] | Extended-release oral tablet |
| Dexmethylphenidate hydrochloride | Immediate-release dexmethylphenidate | Focalin®[b,c] | Oral tablet |

| Active ingredient(s) | Referred to in this report as | Trade name | Forms |
|---|---|---|---|
| | Extended-release dexmethylphenidate | Focalin XR®[c] | Extended-release oral capsule |
| Dextroamphetamine sulfate | Immediate-release dextroamphetamine | Dexedrine®[b] | Oral tablet[d] |
| | Sustained-release dextroamphetamine | Dexedrine Spansule® | Sustained-release oral capsule |
| Guanfacine hydrochloride | Immediate-release guanfacine | Tenex™[b, c] | Oral tablet |
| | Extended-release guanfacine | Intuniv®[c] | Extended-release oral tablet |
| Lisdexamfetamine dimesylate | Lisdexamfetamine | Vyvanse® | Oral capsule |
| Methamphetamine hydrochloride | Methamphetamine | Desoxyn®[b,c] | Oral tablet |
| Methylphenidate | Methylphenidate transdermal | Daytrana®[c] | Extended-release transdermal film |
| Methylphenidate hydrochloride | Methylphenidate osmotic-release oral system | Concerta® | Extended-release oral tablet |
| | Methylphenidate CD | Metadate CD®[c, e] | Extended-release oral capsule |
| | Methylphenidate ER | Metadate ER®[c] | Extended-release oral tablet |
| | Methylphenidate chewable Methylphenidate solution | Methylin®[b,c] | Oral chewable tablet and Oral solution |
| | Immediate-release methylphenidate | Ritalin®[b] | Oral tablet |
| | Methylphenidate long acting | Ritalin LA®[c] | Extended-release oral capsule |
| | Multilayer-release methylphenidate | Biphentin®[d] | Extended-release oral capsule |
| | Methylphenidate sustained-release | Ritalin SR®[b] | Extended-release oral tablet |
| Modafinil | Modafinil | Provigil®[c] | Oral tablet |
| | | Alertec®[d] | Oral tablet |

Abbreviations: ER, extended release; LA, long acting; SR, sustained release; XR, extended release.
[a] The active ingredient for Adderall XR in Canada is amphetamine aspartate monohydrate.
[b] Or generic equivalent.
[c] Not available in Canada.
[d] Not available in the United States.
[e] Metadate CD® is marketed as Equasym XL® in some countries outside the United States and Canada.

## Benefits

### *Effectiveness outcomes*

1. Functional capacity (social, academic, and occupational productivity)
2. Caregiver satisfaction (parent, teacher, other)
3. Quality of life (patient, family members, caregivers, teachers)
4. Time to onset of effectiveness
5. Duration of effectiveness (length of therapy)

### *Efficacy outcomes*

1. Symptom response (inattention, hyperactivity-impulsivity, aggression, global ratings, etc.)

## 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 adverse effects*

1. Hepatotoxicity
2. Cardiovascular events
3. Growth effects

### *Misuse/diversion*

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

## Scales and tests used to measure outcomes

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. Our primary sources for documentation of the psychometric properties of rating scales included the Agency for Healthcare Research and Quality Technical Review #3 (Diagnosis of Attention-Deficit/Hyperactivity Disorder)[8] and Mental Measurements Yearbooks.[9-16] The Agency for Healthcare Research and Quality Technical Review #3 provided qualitative information on many of the rating scales cited in our report, including subscales included in each test, comorbid conditions addressed by each checklist, time required to administer, number of items, ages for which norms are available, computer scoring availability, and ordering information, including cost and reliability and validity. Appendix C provides a listing of commonly used scales and tests and associated acronyms.

### Study designs

The benefit of the randomized controlled trial design is the reliably unbiased estimate of treatment effects in a controlled setting by randomizing patients, the best method of producing comparable groups based on both known and unknown prognostic factors.[17, 18] However, randomized controlled trials can vary in quality and often suffer from limitations in generalizability to the larger patient population. Observational study designs are thought to have greater risk of introducing bias, although they typically represent effects in a broader section of the overall patient population. While it has been shown that some observational studies and randomized controlled trials of the same treatments have similar findings, there are also multiple examples of situations where this has not been true and the question of what type of evidence is best has not been resolved.[19, 20] While randomized controlled trials also provide good evidence on short-term adverse events, observational designs are useful in identifying rare, serious adverse events, which to be identified often require large numbers of patients exposed to a treatment over longer periods of time.

For this review, the following study designs were included:

- Effectiveness: Controlled clinical trials, good-quality systematic reviews, and comparative observational studies (cohort studies including database studies and case-control studies).
- Efficacy and general adverse events: Controlled clinical trials and good-quality systematic reviews.
- Serious adverse events: Controlled clinical trials, good-quality systematic reviews, and comparative observational studies (cohort studies including database studies and case-control studies).
- Misuse/diversion: Controlled clinical trials, good-quality systematic reviews, comparative observational studies (cohort studies including database studies and case-control studies), and noncomparative observational studies (before-after, time-series).
- Subgroups: Controlled clinical trials, good-quality systematic reviews, and comparative observational studies (cohort studies including database studies and case-control studies)

# METHODS

## Literature Search

To identify relevant citations, we searched the Cochrane Central Register of Controlled Trials (2nd Quarter 2011), Cochrane Database of Systematic Reviews (2005 to June 2011), MEDLINE (1996 to June l Week 4 20011), and PsycINFO (1806 to June Week 4 2011) using terms for included drugs, indications, and study designs (see Appendix D for complete search strategies). We have 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®X2, 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 the predefined criteria (see www.ohsu.edu/drugeffectiveness). These criteria are based on the United States Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (U.K.) criteria.[21, 22] We rated the internal validity of each trial 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. Trials that had a fatal flaw in 1 or more category were rated "poor quality"; trials that met all criteria were rated "good quality"; the remainder were rated "fair quality."

As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair-quality studies are *likely* to be valid, while others are only *possibly* valid. A poor-quality trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs. A fatal flaw is reflected by failure to meet combinations of items of the quality assessment checklist. A particular randomized trial might receive 2 different ratings, one for effectiveness and another for adverse events. The criteria used to rate observational studies of adverse events reflect aspects of the study design that are particularly important for assessing adverse event rates. We rated observational studies as good quality for adverse event assessment if they adequately met 6 or more of the 7 predefined criteria, fair quality if they met 3 to 5 criteria, and poor quality if they met 2 or fewer criteria.

Included systematic reviews were also rated for quality based on a clear statement of the questions(s), inclusion criteria, adequacy of search strategy, validity assessment and adequacy of detail provided for included studies, and appropriateness of the methods of synthesis.

Included systematic reviews were also rated for quality. We rated the internal validity based on a clear statement of the 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. Again, these studies were categorized as good when all criteria were met.

## Grading the Strength of Evidence

We graded strength of evidence based on the guidance established for the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality.[23] Developed to grade the overall strength of a body of evidence, this approach incorporates 4 key domains: risk of bias (includes study design and aggregate quality), consistency, directness, and precision of the evidence. It also considers other optional domains that may be relevant for some scenarios, such as a dose-response association, plausible confounding that would decrease the observed effect, strength of association (magnitude of effect), and publication bias.

Table 2 describes the grades of evidence that can be assigned. Grades reflect the strength of the body of evidence to answer key questions on the comparative effectiveness, efficacy, and harms of attention deficit hyperactivity disorder (ADHD) drugs. Grades do not refer to the general efficacy or effectiveness of pharmaceuticals. Two reviewers independently assessed each domain for each outcome and differences were resolved by consensus.

Strength of evidence was graded for each key outcome measure, and was limited to head-to-head comparisons except where a case can be made for assessing the strength of indirect evidence. Outcomes selected for rating the strength of evidence were symptom improvement, response, and withdrawal due to adverse events. Appendix E shows individual assessments for strength of evidence.

### Table 2. Definitions of the grades of overall strength of evidence[23]

| Grade | Definition |
|---|---|
| High | High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect. |
| Moderate | Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate. |
| Low | Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate. |
| Insufficient | Evidence either is unavailable or does not permit estimation of an effect. |

## 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.

An evidence report pays particular attention to the generalizability of *efficacy* studies performed in controlled or academic settings. *Efficacy* studies provide the best information about how a drug performs in a controlled setting, allowing for better control over potential confounding factors and biases. However, the results of efficacy studies are not always applicable to many, or to most, patients seen in everyday practice. This is because most efficacy studies use strict eligibility criteria which may exclude patients based on their age, sex, medication compliance, or severity of illness. For many drug classes severely impaired patients are often excluded from trials. Often, efficacy studies also exclude patients who have "comorbid" diseases, meaning diseases other than the one under study. Efficacy studies may also use dosing regimens and follow-up protocols that may be impractical in other practice settings. They often restrict options, such as combining therapies or switching drugs that are of value in actual practice. They often examine the short-term effects of drugs that, in practice, are used for much longer periods of time. Finally, they tend to use objective measures of effect that do not capture all of the benefits and harms of a drug or do not reflect the outcomes that are most important to patients and their families.

## 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. Studies that evaluated one pharmacologic treatment of ADHD against another provided direct evidence of comparative effectiveness and adverse event rates. Head-to-head evidence is the primary focus. Outcomes of changes in symptoms measured using scales or tools with good validity and reliability are preferred over scales or tools with low validity/reliability or no reports of validity/reliability testing. Direct comparisons were preferred over indirect comparisons; similarly, effectiveness and long-term safety outcomes were preferred to efficacy and short-term tolerability outcomes. In theory, trials that compare these drugs to other interventions or placebos can also provide evidence about effectiveness. This is known as an indirect comparison and can be difficult to interpret for a number of reasons, primarily heterogeneity of trial populations, interventions, and outcomes assessment. Data from indirect comparisons are used to support direct comparisons, where they exist, and are used as the primary comparison where no direct comparisons exist. Indirect comparisons should be interpreted with caution.

Quantitative analyses were conducted using meta-analyses of outcomes reported by a sufficient number of studies that were homogeneous enough that combining their results could be justified. 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 2 content and methodology experts. Their comments were reviewed and, where possible, incorporated into the final document. All 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. Names of peer reviewers for the Drug Effectiveness Review Project are listed at http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/index.cfm/.

### Public Comment

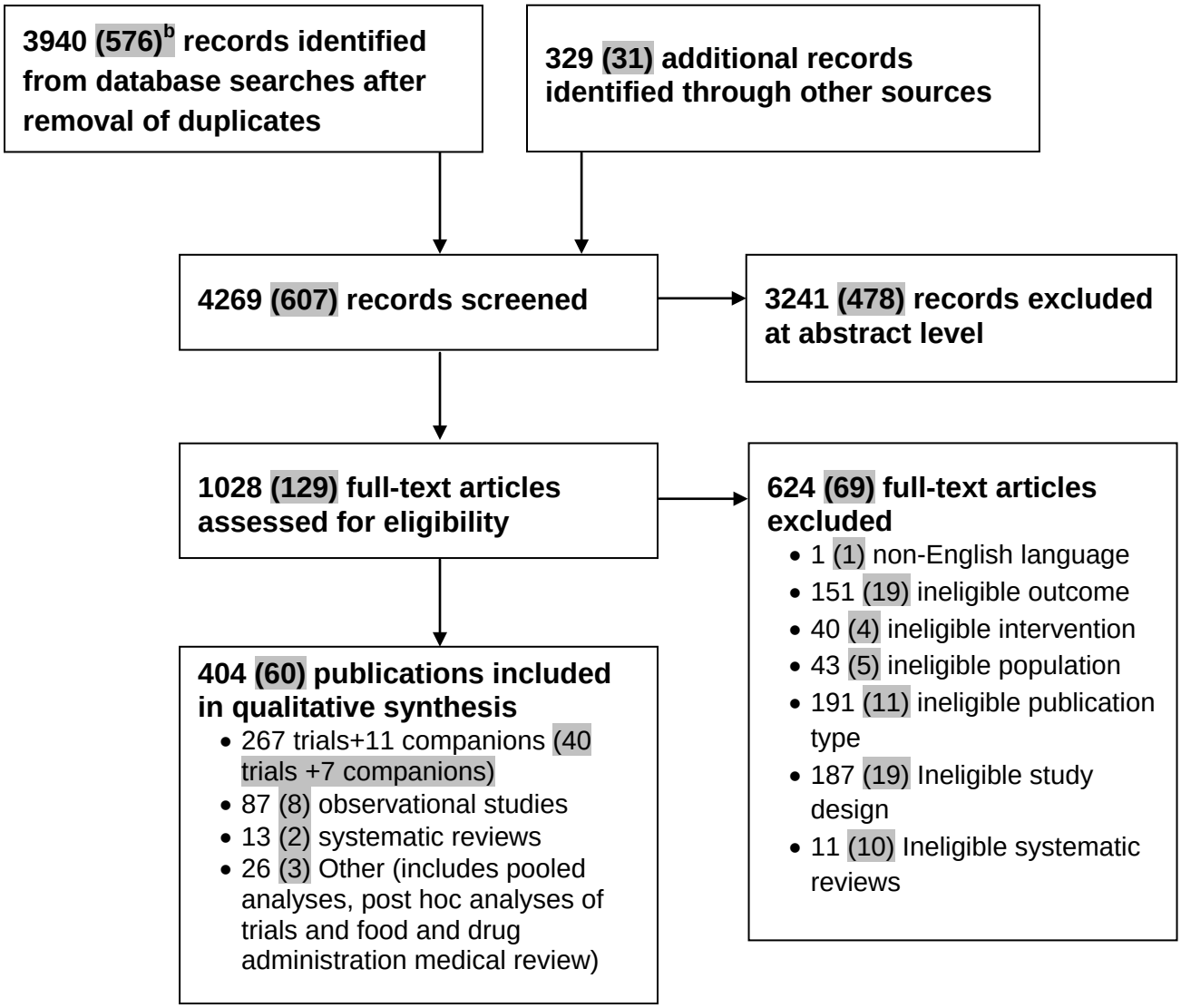
This report was posted to the Drug Effectiveness Review Project website for public comment. We received comments from 6 individuals representing 5 pharmaceutical companies.

## RESULTS

### Overview

Figure 1 details the results of our literature searches. Overall, we identified a total of 4269 citations from searching electronic databases, reviews of reference lists, pharmaceutical manufacturer dossier submissions, peer review, and public comment. Of these, 607 were identified in the most recent update. By applying the eligibility and exclusion criteria to titles and abstracts of all identified citations, we obtained full-text copies of 1028 citations, 129 from Update 4. After re-applying the criteria for inclusion, we ultimately included 404 publications, 60 from Update 4. 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); and Update 4: Shire US, Inc (guanfacine and lisdexamfetamine), UCB, Inc, (methylphenidate CD), Shionogi Inc (clonidine), and Ortho-McNeil Janssen Scientific Affairs, LLC (methylphenidate OROS). A list of excluded studies is reported in Appendix F.

**Figure 1. Results of literature search[a]**




[a] A modified PRISMA diagram was used.[24]
[b] Numbers in parentheses are results of the literature search new to Update 4.

We identified the following numbers of head-to-head comparative trials of pharmacologic treatments for attention deficit hyperactivity disorder (ADHD) (Table 3).

### Table 3. 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 | MAS XR | MODA | ATX | LIS DEX |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **MPH IR** | | | | | | | | | | | | | |
| **MPH ER** | C:15<br>T: 1<br>A:1 (1)[a] | C: 6 (1) | | | | | | | | | | | |
| **MTS** | C:1 (1) | | | | | | | | | | | | |
| **CLON** | C:5 (5) | | | | | | | | | | | | |
| **DEX** | C: 11<br>A: 1 | -- | | | | | | | | | | | |
| **DEX-MPH** | -- | -- | | | -- | | | | | | | | |
| **DEX-MPH ER** | | C:1 (1) | | | | | | | | | | | |
| **GUAN** | | | | | A:1 (1) | | | | | | | | |
| **Adderall®** | C: 5 | -- | | | C: 1 | -- | | | | | | | |
| **Adderall XR®** | -- | T:2 (1) | | | -- | -- | | | C: 1 | | | | |
| **MODA** | C:1 | -- | | | A: 1 | -- | | | -- | | | | |
| **ATX** | C: 6[b] | C: 2 | | | -- | -- | | | C: 1 | -- | -- | | |
| **LIS DEX** | -- | -- | | | A: 1 | -- | | | C: 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.
[a] Parentheses show search results new to Update 4.
[b] One trial compared with standard care.

Data abstracted from head-to-head trials can be found in Evidence Table 1 and the relevant quality assessments in Evidence Table 2. Because there are a large number of head-to-head trials directly comparing the drugs, and indirect comparisons from placebo-controlled trials are less reliable, we have only included placebo-controlled trials of drugs for which we have limited or no head-to-head evidence. Similarly, using a "best evidence" approach, we included observational studies where we had no evidence for important outcomes such as long-term functional outcomes or duration of response. Data abstracted from placebo-controlled trials can be found in Evidence Tables 3, 5, 7, and 11 and relevant quality assessments in Evidence Tables 4, 6, 8, and 12. We included 87 observational studies (Evidence Tables 9 and 10).

In adult populations (age 18 and above), we included 57 placebo-controlled trials (Evidence Tables 11 and 12) and 1 long-term observational study (Evidence Tables 15 and 16) in addition to the head-to-head trials listed in Table 3 above.

### *Previous systematic review findings*

While there are a large number of reviews of pharmacotherapy for symptoms of ADHD, they are generally not comparative, include or exclude drugs that are included or excluded here, and are out of date. These reviews are now outdated and will not be used here.

The American Academy of Pediatrics Clinical Practice 2011 Guideline on treatment of ADHD in children aged 4 years through 18 years and the American Academy of Child and Adolescent Psychiatry Practice Parameter for the Assessment and Treatment of Children and Adolescents with ADHD were also reviewed.[25, 26] The American Academy of Pediatrics recommendations for treatment varied depending on age. In preschool-aged children (4-5 years of age), the American Academy of Pediatrics recommended behavior therapy as first-line treatment and prescription of methylphenidate only if moderate-to-severe disturbance in functioning continued. For elementary school-aged children (6-11 years of age), a combination of behavioral therapy and medications approved by the US Food and Drug Administration was preferred. The guideline stated that the evidence is strongest for stimulant medication, but still did not prefer any one stimulant over another. For atomoxetine, extended-release guanfacine, and extended-release clonidine (in that order), the guideline stated that evidence is sufficient for use, but less strong than for stimulants. Likewise, for adolescents, the American Academy of Pediatrics recommended a combination of behavioral therapy and prescription medications approved by the US Food and Drug Administration, but did not provide any specific guidance on choice of medications. The American Academy of Child and Adolescent Psychiatry guideline stated that stimulants are first-line, except in situations where substance abuse disorder, comorbid anxiety, or tics are present.[26] The document did not differentiate among the stimulants, stating that treatment should be individualized and that the choice is up to the clinician and family. The guideline produced by the National Institute for Health and Clinical Excellence in England was evidence-based, which included evaluation of cost-effectiveness (in the British context, agreed in general with these recommendations).[27]

## Summary of Findings

### *General*

- There were no *trials* of comparative effectiveness of these drugs for treatment of ADHD.
- Good-quality evidence on the use of drugs to affect outcomes relating to global academic performance, consequences of risky behaviors, social achievements, etc. was lacking.
- The evidence for comparative efficacy of drugs for treating ADHD was severely limited by small sample sizes, very short durations, and the lack of studies measuring functional or long-term outcomes. Methods of measuring symptom control varied significantly across studies. The crossover design was frequently used, with few analyzing the effect of order of administration of drugs. Those that did found a significant effect. No head-to-head efficacy trial was good quality. The small numbers of patients in these trials often limited the ability to show a difference between drugs if one exists.
- Limitations to the generalizability of these trials included the following:
    - Characterization of ADHD symptomatology across studies was limited due to use of varied or indeterminate diagnostic processes.
    - Minorities and the most seriously ill patients were underrepresented.
    - The small sample sizes of these trials did not allow for statistical analyses of potential effects of these factors.
- Overall, the rate of response to stimulants appeared to be in the range of 60% to 80%, however the definitions of response rate varied and may not have been comparable. Depending on the definition used, there was lack of clarity on the relationship of response

rate to clinical significance. Response rates of nonstimulants varied, but the range in placebo-controlled trials was similar to that found with stimulants. Significant variation in the method of assessment and definition of response was most likely the reason for the wide variation.

### *Effectiveness*

- Because no trials of effectiveness were found, observational studies were assessed for outcomes of effectiveness.
- The only comparative study found showed that methylphenidate OROS was associated with fewer outpatient visits/hospitalizations for accidents/injury than immediate-release methylphenidate over 12 months. Methodologic concerns over this study suggested caution in interpretation of these findings.
- Results from noncomparative studies suggested:
    - In an uncontrolled study of young adult males who had taken methylphenidate as children (mean age at discontinuation of methylphenidate was 17 years), fewer suicide attempts were associated with higher dosages of methylphenidate. Emancipated living situation and level of relationship commitment was associated with response to methylphenidate. Early response to methylphenidate was negatively associated with high school graduation, however.
    - A follow-up of immediate-release methylphenidate responders reported "improved grades" after 6 to 14 months. Methodological limitations of these studies severely limited the interpretation of these findings.
    - Uncontrolled observational data assessing the effect of duration of treatment with immediate-release methylphenidate found no differences in academic achievement as measured by teachers or the proportion repeating grades, in special education classes, or being tutored. Again, significant methodologic limitations suggested caution in interpreting results.

### *Efficacy and tolerability*

#### Young children (preschool age; 3-5 years)

- Comparative evidence in young children was not found.
- Immediate-release methylphenidate was marginally superior to placebo, depending on the efficacy measure assessed in 2 fair-quality placebo-controlled trials that used validated assessment tools, but was also associated with higher rates of adverse events and a high rate of discontinuation.
- Among young children who had positive response to immediate-release methylphenidate, follow-up after 10 months showed increases in mean dose and maintenance or improvements in efficacy measures.
- Evidence on atomoxetine was insufficient to make conclusions.

#### Children (elementary school age; 6-12 years)

*Stimulants*

- Immediate-release compared with extended-release formulations

  - The evidence regarding immediate-release methylphenidate compared with methylphenidate 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.
    - Exploratory pooled analysis of the inattention/overactivity scores of the IOWA Conners' scale indicated that methylphenidate OROS may result in greater improvement (weighted mean difference –1.19; 95% CI, –1.78 to –0.60).
  - Limited evidence was available for the comparisons of immediate-release methylphenidate to other extended-release formulations. Overall, the studies were unable to identify differences between methylphenidate SR and immediate-release methylphenidate, and methylphenidate CD was found to be noninferior to immediate-release methylphenidate.
  - Database studies using intermediate outcomes reported greater persistence with methylphenidate OROS and methylphenidate SODAS compared with immediate-release methylphenidate. Methodologic concerns indicate caution in interpreting this evidence.
- Sustained-release compared with sustained-release formulations
  - Limited evidence from 2 small crossover studies suggested that methylphenidate LA is 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 associated with significantly larger effect sizes than methylphenidate OROS in the morning, treatment effects were similar in the afternoon, and methylphenidate OROS was superior in the evening. Methodologic concerns indicate caution in interpreting these findings.
    - Methylphenidate OROS had statistically significantly higher rates of insomnia and decreased appetite than methylphenidate CD.
  - Dexmethylphenidate ER resulted in better response from 0 to 2 hours post dose compared with methylphenidate OROS (primary outcome measure). A difference was found up to 6 hours post dose, but methylphenidate OROS resulted in better scores later in the day; from 10 to 12 hours post dose.
  - There was no evidence of a difference in adverse events between immediate-release and sustained-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
  - 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. Very limited evidence suggested that twice daily dosing of immediate-release mixed amphetamine salts led to higher rates of

loss of appetite and sleep trouble than once daily dosing of immediate-release methylphenidate.

- Modafinil compared with methylphenidate
  - Differences were not found between modafinil and immediate-release methylphenidate over 6 weeks.
    - Response rate (>40% reduction in score): Modafinil 73% compared with immediate-release methylphenidate 70% for parents rating.
    - Rates of adverse events were similar between the drugs.
- Dextroamphetamine compared with mixed amphetamine salts
  - Evidence of immediate-release dextroamphetamine compared with dextroamphetamine SR compared with mixed amphetamine salts was limited and conflicting, but may suggest that measures in the morning find immediate-release dextroamphetamine superior to dextroamphetamine SR, and measures in the afternoon find dextroamphetamine SR superior to mixed amphetamine salts. Transient weight loss was greater with mixed amphetamine salts and dextroamphetamine SR than with immediate-release dextroamphetamine. However, this evidence should be interpreted with caution.
- Lisdexamfetamine compared with mixed amphetamine salts XR
  - Evidence from the US Food and Drug Administration medical review and manufacturer-submitted data dossier suggests that mean Swanson, Kotlin, Agler, M-Flynn, and Pelham-Deportment Subscale (SKAMP-DS) scores were similar in children following 1 week of lisdexamfetamine or Adderall XR®. Rates of specific adverse events were not available for the individual treatment groups, but the data dossier did not specify any differences between them.
- Transdermal methylphenidate compared with methylphenidate OROS
  - Methylphenidate transdermal system was found to have similar efficacy to methylphenidate OROS over a 7-week period, based on investigator, teacher, and parent ratings starting 4 hours after administration of dose or application of patch and weekly. Methylphenidate transdermal system was found to have similar efficacy to immediate-release methylphenidate over 12 hours in a simulated classroom setting, starting 30 minutes after dosing.
  - Although rates of adverse events and discontinuations due to adverse events were greater with transdermal methylphenidate than with methylphenidate OROS, differences were not found to be statistically significant. Differences in adverse events were not found between methylphenidate transdermal system and immediate-release methylphenidate.
- Longer-term studies indicated that although the evidence is somewhat mixed, efficacy benefits seen with immediate-release methylphenidate can be maintained over periods of up to 24 months, but that deterioration in benefit is seen with longer follow-up.

### *Nonstimulants*

#### ***Atomoxetine***

- Atomoxetine compared with methylphenidate
  - Evidence from 2 trials suggested that atomoxetine is associated with efficacy outcomes similar to immediate-release methylphenidate.
- Atomoxetine compared with methylphenidate OROS

  - Based on response rates (>40% reduction in ADHD-Rating Scale score), methylphenidate OROS was found superior to atomoxetine with an overall 56% response rate for methylphenidate OROS compared with 45% for atomoxetine (number needed to treat, 9; *P*=0.02).
  - In patients with prior stimulant exposure methylphenidate OROS was found to have a statistically significantly higher rate of response (51%) compared with atomoxetine (37%) (number needed to treat, 8; *P*=0.03). However, in the smaller subgroup without prior stimulant exposure, the 2 drugs were not found to be statistically significantly different in response rates.
- 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.
  - Rates of vomiting ranged from 12% to 13% for atomoxetine, which was approximately 3 times greater than rates for immediate-release methylphenidate or mixed amphetamine salts XR.
  - Rates of somnolence ranged from 6% to 26% for atomoxetine, which was 3 to 4 times greater than rates for longer-acting stimulants (methylphenidate OROS and mixed amphetamine salts XR) and over 7 times greater than rates in trials of immediate-release methylphenidate.
  - Nausea and anorexia were also 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) in this trial may have contributed to this finding.
- 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).

***Immediate-release clonidine***

- Current evidence does 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). Inconsistency in some outcomes suggests caution in interpreting these results.
- 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.

***Extended-release clonidine***

- No evidence directly comparing extended-release clonidine to another ADHD medication was found.
- Placebo-controlled trials focused on children with the combined or hyperactive subtypes of ADHD, finding benefit as an add-on therapy in children with inadequate response to stimulant therapy, and as monotherapy.
- Discontinuation due to adverse events showed a dose-response effect in fixed-dose studies, and was highest in the 0.4 mg daily group. Flexible dosing resulted in similar

rates between placebo and clonidine groups. Somnolence and fatigue were more common in the clonidine groups than placebo, and peaked at 2 weeks.

***Immediate -release guanfacine***

No evidence directly comparing immediate-release guanfacine to another ADHD medication was found. Indirect evidence, based on a single small study with inconsistent findings, was insufficient to make conclusions. Adverse events were inadequately reported.

***Extended-release guanfacine***

- No evidence directly comparing extended-release guanfacine to another ADHD medication was found.
- Placebo-controlled trials indicated superiority of doses 1 to 4 mg daily over placebo in improvement of investigator-assessed symptoms, with a dose-response effect both as monotherapy and as adjunctive therapy with stimulants. Duration of superiority over placebo based on teacher and parent ratings was apparent at 8 hours, but inconsistent across studies and outcomes at 12, 14, and 24 hours.
- Discontinuation due to adverse events showed a dose-response effect in fixed-dose studies, and was highest in the 4 mg daily group. Flexible dosing also resulted in higher rates of discontinuation than placebo. Rates of somnolence, fatigue, and headache were greater in the extended-release guanfacine groups than placebo.

## Adolescents

- Adolescents were studied in a small number of short-term trials that involved immediate-release methylphenidate or methylphenidate OROS (Concerta®). Studies of atomoxetine included adolescents and were discussed above.
- Methylphenidate OROS compared with immediate-release methylphenidate
  - One very small, single blinded study showed methylphenidate OROS superior to immediate-release methylphenidate on some measures of simulated driving skills during tests administered in the late evening or nighttime. No difference was found during other test times.
- Methylphenidate OROS compared with mixed amphetamine salts
  - One small, crossover study found no significant difference between methylphenidate OROS and mixed amphetamine salts in self-reported symptom improvement or subjective ratings of driving performance, although methylphenidate OROS was associated with significantly better overall driving performance relative to mixed amphetamine salts based on testing in a driving simulator.
- Indirect evidence of stimulants
  - Placebo-controlled trials of immediate-release methylphenidate did not provide indirect evidence of comparative efficacy or tolerability due to heterogeneity in outcome reporting.
  - Immediate-release methylphenidate generally was superior to placebo in improving core ADHD symptoms, but was associated with more frequent reports of appetite and sleep disturbances.

  - Lisdexamfetamine was superior to placebo after 4 weeks at 30, 50, and 70 mg daily but with no meaningful differences between doses. Quality of life was not different among groups.

### Adults

- There were no trials of adults with ADHD using clonidine, dexmethylphenidate immediate-release, dextroamphetamine sustained-release, extended-release guanfacine, methamphetamine, methylphenidate chewable tablet or oral solution, or some extended release forms of methylphenidate (Metadate CD®, Ritalin LA®, and Biphentin®).
- In patients with previous good clinical response – good tolerability and satisfaction with immediate-release methylphenidate – there was low-strength evidence of no significant difference in maintenance of response at 6 weeks after switching to methylphenidate OROS compared with remaining on immediate-release methylphenidate. There was insufficient evidence to determine differences between stimulants in any individual adverse events or in proportions of patients with no adverse events.
- There was low-strength evidence of no significant difference between immediate-release guanfacine and immediate-release dextroamphetamine in the mean total symptom score of the DSM-IV ADHD Behavior Checklist for Adults. There was also low-strength evidence of no difference between drugs in number of side effects.
- There was low-strength evidence of no significant differences between immediate-release dextroamphetamine compared with modafinil in response rates (48% for both treatments) or rates of insomnia (38% compared with 19%; NS), muscle tension (24% compared with 19%; NS), and appetite suppression (24% compared with 19%; NS).
- Evidence from placebo-controlled trials was insufficient to support conclusions about the comparative effectiveness and harms in drugs for ADHD in adults. Indirect meta-analysis was not undertaken due to concerns about sparse data for many drugs and heterogeneity in outcome measurement methods and trial duration.
  - Compared with placebo, response rates were significantly greater for atomoxetine, immediate-release dextroamphetamine, dexmethylphenidate ER, lisdexamfetamine, immediate-release methylphenidate, methylphenidate OROS, methylphenidate ER, immediate-release mixed amphetamine salts, and mixed amphetamine salts XR.

## *Long-term safety*

- Although the observational studies provided some estimate of the prevalence of serious longer-term adverse events with mixed amphetamine salts, atomoxetine, immediate-release dextroamphetamine, and methylphenidate (immediate and sustained-release), few studies directly compared different pharmacologic treatments for ADHD for any one adverse event.
- For outcomes where only uncontrolled evidence was available, it was not possible to draw conclusions about comparative long-term safety through indirect comparisons across observational studies due to large differences in study characteristics.
- The *overall* body of evidence was poor quality due to a variety of flaws in design and analysis and should be interpreted with caution.

- Suicide
  - Based on a meta-analysis of placebo-controlled trials, atomoxetine was associated with an increased risk of suicidal behaviors (Mantel-Haenszel Incidence Difference, 0.52; 95% CI, 0.12 to 0.91). Time to onset of suicidal-related behavior was 9 to 32 days. All children experiencing suicidal-related behaviors were boys, ages 7-12, and 33% were African American. African American boys represented 12% of the total population in these studies. Overall rate of suicidal ideation and behavior was 0.44%.
  - In another meta-analysis of data from children and adolescents in open-label studies of atomoxetine with at least 3 years exposure, the overall rate of suicidal ideation, behavior, and suicide attempts was 2%. Time to onset of suicidal-related behavior was 234 days to 5.8 years.
  - Post-hoc analysis of cohort data, with a small number of events, found that the risk for suicide was significantly greater than population norms for older children and adolescents taking methylphenidate or amphetamine (hazard ratio, 161.91; 95% CI, 19.61 to 584.88 for ages 11 to 14, and hazard ratio, 1.84; 95% CI, 0.05 to 10.25 for ages 15 to 20). Results were not adjusted for potential confounding and should be considered preliminary.
- Cardiovascular deaths and events
  - Observational evidence on the risk of cardiovascular death (sudden death or ventricular arrhythmia) associated with ADHD medication use was conflicting. A large retrospective cohort study found no statistically significant increase in risk with methylphenidate, amphetamine, or atomoxetine compared with nonusers, but the point estimate of effect was highest with methylphenidate. Direct statistical comparisons of the drugs were not reported. In contrast, a case-control study of 10 years of state vital statistics records and parent surveys found the risk of sudden cardiac death to be significantly greater among children who were taking "stimulants" compared with a control group who were not (odds ratio, 7.4; 95% CI, 1.4 to 74.9). Because exposure was determined by survey (mean of 10 to 13 years after the event), recall bias may be an important limitation in this study.
  - 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.
  - In adults, the risk of stroke or transient ischemic attack was not significantly different between atomoxetine compared with "stimulant" therapy, but small numbers of cases limited the interpretation of these findings.
- Height change in children
  - Evidence on immediate-release dextroamphetamine compared with methylphenidate was inconsistent. Evidence suggested that immediate-release methylphenidate and methylphenidate OROS adversely impacts expected height gain at least during the first 12 months of treatment.
  - Limited evidence suggested that height changes resulting from atomoxetine were similar to those reported with immediate-release methylphenidate, and were also transient, with the peak of impact on expected height occurring at 18 months, but

the difference resolved by 2 years. Lisdexamfetamine did not result in changes in height over 15 months, based on noncomparative, limited evidence.

- Weight in children
  - Immediate-release dextroamphetamine was associated with significantly greater suppression of weight gain than methylphenidate in the first 1-2 years. The difference appeared to resolve by the second year. Higher relative doses of immediate-release dextroamphetamine may have influenced findings.
  - Noncomparative evidence indicated a small reduction in expected weight gain, especially among those with greater weight at baseline for immediate-release methylphenidate, methylphenidate OROS, mixed amphetamine salts XR, and lisdexamfetamine for at least the first year of treatment.
  - Limited evidence suggested that weight changes resulting from atomoxetine were similar to those reported with immediate-release methylphenidate, and were also transient. Negative impact on weight began after 1 month of treatment, with a peak at 15 months. The difference remained statistically significant up to 3 years of treatment and resolved by 5 years of treatment. Analysis indicated that dose did not impact the change in weight, but those with higher baseline weight had greater losses than those with lower baseline weight.
- Insomnia, decreased appetite, and headaches: Based on a retrospective cohort study with 24 months of exposure:
  - Insomnia
    - Not statistically significantly different among immediate-release methylphenidate, methylphenidate OROS, mixed amphetamine salts, mixed amphetamine salts XR, and atomoxetine, although the crude rate in the mixed amphetamine salts group (22%) was numerically greater than in the other groups (range 4% to 13%).
  - Appetite
    - Decreased appetite was not found to be different among immediate-release methylphenidate, methylphenidate OROS, mixed amphetamine salts, mixed amphetamine salts XR, and atomoxetine. Rates in the immediate-release mixed amphetamine salts, mixed amphetamine salts XR, and methylphenidate OROS groups (range 15% to 22%) were higher than the atomoxetine and immediate-release methylphenidate groups (range 9% to 10%) numerically.
  - Headache
    - 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*

- Abuse or dependence
  - Evidence was based on longitudinal studies of adolescents or adults who had been diagnosed with ADHD as children and compared rates of abuse and dependence in those who were treated with stimulants with those who were not.
  - Nicotine
    - Two studies found no association when analyses controlled for comorbid conduct disorder.
    - Studies that did not control for conduct disorder found stimulant exposure to be protective against regular smoking among teen girls (1 study), and no association with the first cigarette, but those exposed to a stimulant showed a delay in the time (2 years and 1 month) to becoming a regular smoker (1 study).
  - Alcohol
    - No association between alcohol abuse during teen and young adult years and stimulant exposure during childhood was found.
  - Substance abuse
    - Two studies found stimulant use to be protective, but a third study found that controlling for conduct disorder resulted in a nonsignificant finding.
    - Analysis of the National Survey on Drug Use and Health from 2000 and 2001 found that 4.7% were determined to be dependent on or abusing a prescription ADHD stimulant drug, with rates highest among those 12 to 25 years old. Rates of dependence were higher among women, whereas rates of abuse were higher among men.
- Misuse
  - Rates of misuse varied by age group of patients, and were very variable.
  - Misuse of stimulant medication:
    - Children and adolescents (through high school): 5% to 8%
    - College students: 5% to 35%
      - Of those misusing, the reason was for enhancement of academic performance: 26% to 63%.
    - Adults: 29%
      - Misuse of methylphenidate associated with illicit use of cocaine or amphetamines
  - Analysis of the National Survey on Drug Use and Health from 2000, 2001, and 2002 found that the most commonly misused stimulants in this survey were immediate-release methylphenidate and immediate-release dextroamphetamine, with smaller numbers reporting use of other drugs, including mixed amphetamine salts and methylphenidate OROS.
- Diversion
  - Rates of diversion varied by age group of patients and were very variable.
  - Misuse of stimulant medication:
    - Children and adolescents (through high school):
      - 15% to 24% gave them away.
      - 7% to 19% sold them.

        - 4% to 6% had them stolen at some time in the past
    - College students: 23% to 62% were asked to give away or sell their medications.
        - Of these, 26% reported selling or giving medication away.
        - Amphetamine/dextroamphetamine had the highest rate of diversion (70.5%).
        - Methylphenidate and methylphenidate extended-release had similar rates (no formulation specified, 37% compared with 39.1% respectively).
    - Adults: 44% diverted their ADHD medication
        - 97% gave them away, 17% sold them, and 14% did both.
        - Associated with younger age both at the time of the survey and at the time methylphenidate was first prescribed.

### *Subgroups*

#### Demographics

- Race/ethnicity
    - Only half of studies reported race or ethnicity data. Studies were primarily conducted in Caucasian populations.
    - Immediate-release methylphenidate in African American boys
        - 75% of subscale measures showed improvement.
        - This rate was similar to response rates reported in other trials.
        - Linear increases in diastolic blood pressure noted.
    - Lisdexamfetamine
        - Difference in ADHD rating scale IV mean change score compared with placebo remained statistically significant at the 50 mg and 70 mg doses, but not the 30 mg dose, in a subpopulation of non-Caucasians.
    - Atomoxetine
        - Latino population and Caucasian populations had similar improvements in ADHD symptoms over 10 and 11 weeks.
        - Caucasians reported significantly more abdominal and throat pain ($P$=0.006 and $P$=0.037, respectively), whereas Latinos reported significantly more decreased appetite and dizziness ($P$=0.03 and $P$=0.023, respectively).
- Gender
    - Limited evidence from multiple post-hoc subgroup analyses suggested no difference in efficacy between boys and girls with immediate-release methylphenidate.
    - Lisdexamfetamine
        - Difference in ADHD rating scale IV mean change score compared with placebo remained statistically significant at the 50 mg and 70 mg doses, but not the 30 mg dose in a subpopulation of girls. However, this analysis may have been underpowered by a small sample size.

- Atomoxetine
  - A pooled analysis found that at endpoint, atomoxetine resulted in better scores in women on emotional dysregulation (temper + mood lability + emotional overactivity items) on the Wender-Reamer Adults Attention Deficit Disorder Scale than in men. The Sheehan Disability social life subscale demonstrated a significant gender-by-treatment effect ($P$=0.042), with women showing a stronger treatment effect than men, but there was no significant difference on the total score.

### ADHD subtypes

- Results from short-term randomized controlled trials suggested that atomoxetine, immediate-release methylphenidate, modafinil, and methylphenidate OROS all have superior efficacy relative to placebo in children with ADHD, regardless of diagnostic subtype. However, that response or dose-response may differ by diagnostic subtype.
  - Although very preliminary, 2 trials suggested that the greatest symptom improvements may occur at higher dosages of immediate-release methylphenidate or methylphenidate OROS (≥ 30 mg daily) in children diagnosed with ADHD of the combined subtype or attention deficit disorder with hyperactivity, whereas greater symptom improvements may occur at lower dosages (≤ 18 mg daily) in children with ADHD of the inattentive type or attention deficit disorder without hyperactivity. A third small study found no difference in effect based on subtype.
  - In a pooled analysis of data from 3 placebo-controlled trials, modafinil results indicated a statistically significant improvement on the ADHD rating scale IV for both the combined and inattentive subtypes, but no statistically significant difference for the hyperactive-impulsive subtype. However, as this subgroup was very small, this finding may have been due to lack of statistical power rather than a true difference.

### Commonly occurring comorbidities

- Anxiety
  - Differences in the rate of anxiety being reported as an adverse event did not differ statistically significantly in head-to-head studies of immediate-release methylphenidate compared with immediate-release dextroamphetamine, mixed amphetamine salts, methylphenidate SR, methylphenidate OROS, or atomoxetine.
  - Limited evidence suggested that immediate-release methylphenidate is somewhat less effective in reducing ADHD symptoms in children with baseline anxiety symptoms compared with those without these symptoms.
  - Atomoxetine was superior to placebo in improving ADHD and anxiety symptoms in children with anxiety at baseline.
- Learning disability
  - There was very limited evidence that response to immediate-release methylphenidate may be moderated in children with mathematics learning disabilities.

- Tic disorders
  - Overall, there was very little evidence across these trials to indicate that immediate-release methylphenidate, immediate-release dextroamphetamine, or atomoxetine were associated with any tic exacerbation effects. Compared with placebo, immediate-release methylphenidate, immediate-release dextroamphetamine, and atomoxetine were consistently associated with improved tic severity and ADHD symptoms.
  - Immediate-release methylphenidate and immediate-release clonidine both improved ADHD symptom scores and were not found to significantly differ from each other in children with Tourette's disorder.
  - Guanfacine resulted in improvement in tic severity relative to placebo in children with tic disorders (58.8% = Tourette's disorder).
- Oppositional defiant disorder
  - Very limited evidence indicated that immediate-release methylphenidate, mixed amphetamine salts XR, and atomoxetine were associated with greater improvements in ADHD symptoms than placebo.
  - Extended-release guanfacine was superior to placebo in improving both ADHD and oppositional defiant symptoms compared with placebo.
- Bipolar disorder
  - Very limited evidence indicated that immediate-release mixed amphetamine salts and immediate-release methylphenidate were associated with significantly greater improvements in ADHD outcomes than placebo when added to mood stabilizers in children with coexisting bipolar disorder.
  - Immediate-release methylphenidate did not improve ADHD symptoms when added to aripiprazole in children with comorbid ADHD and bipolar disorder.
- Substance abuse
  - Adolescents
    - Methylphenidate SODAS was superior to placebo in reducing ADHD symptoms in teens with substance use disorder. There was no significant treatment effect on drug use.
    - Atomoxetine was not superior to placebo in improving ADHD symptoms in adolescents with substance use disorder and the number of days with abuse was also not affected.
  - Adults
    - Atomoxetine was superior to placebo in improving ADHD symptoms in adults with comorbid alcohol use disorders (n=147).
    - Neither immediate-release methylphenidate nor methylphenidate SR was superior to placebo in improving ADHD symptoms in adults with comorbid cocaine dependence, methadone-maintenance, or general alcohol or drug dependence.

## Key Question 1. What is the comparative efficacy or effectiveness of different pharmacologic treatments for attention deficit disorders?

### *Young children (preschool age; 3-5 years)*

Evidence on the effectiveness of pharmacotherapy for ADHD in young children was seriously lacking (Evidence Tables 1 and 2). We did not find any effectiveness trials or long-term comparative observational studies assessing functional outcomes comparing drugs in young children with ADHD.

The evidence of any short-term benefit of stimulants in this age group came from 6 placebo-controlled trials of immediate-release methylphenidate[28-35] and 1 of atomoxetine.[36] Of these placebo-controlled trials, 5 were either poor quality and/or lacked a valid assessment tool.[28, 29, 31-33] The 1 trial of atomoxetine was rated poor quality because of a high withdrawal rate (33%) and 8% of patients were excluded from the analysis, in addition to unclear methods for blinding outcome assessors, patients, and caregivers.[36]

The remaining 2 studies presented a mixed picture, with immediate-release methylphenidate not clearly superior to placebo but some indication that higher doses may result in better improvement on some symptoms.

One fair-quality trial used an assessment tool with good validity (Children's Psychiatric Rating Scale-Revised; learning, conduct, and hyperactivity indices only).[30] In this study, both the high dose (0.5 mg/kg twice daily) and the low dose (0.3 mg/kg twice daily) resulted in lower scores than placebo at the end of 7 to 10 days of treatment. The high dose resulted in better final scores than the low dose on only the learning component of the Children's Psychiatric Rating Scale-Revised 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 DSM-III criteria were used to diagnose ADHD. ADHD subtypes or ethnicity were not identified in this study. Methylphenidate was associated with higher rates and greater severity of adverse events than placebo, significantly more in the higher dose group. Rates of specific adverse events were not reported.

The Preschool ADHD Treatment Study assessed the efficacy and safety of immediate-release methylphenidate relative to placebo.[34, 35] The Preschool ADHD Treatment Study was a multi-center, multi-phase trial that included a crossover 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 Preschool ADHD Treatment Study design[34] 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[35] 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 SNAP-IV scale ("excellent responder" criteria).[34]

The crossover phase of the Preschool ADHD Treatment Study followed a 10-week parent-training phase and a 1-week, open-label run-in. The parent-training phase served to allow

investigators to remove from the trial those children who were responders to non pharmaceutical intervention, thus only children whose ADHD symptoms were not improved following parent training were randomized to the crossover phase of the trial. Patients received immediate-release methylphenidate doses ranging from 1.25 to 10 mg 3 times daily or placebo. The overall composite score of CLAM/SKAMP, based on parent and teacher scores, ranged from 0.91 for high-dose immediate-release methylphenidate to 1.19 for low dose immediate-release methylphenidate and 1.28 for placebo (higher score reflecting worse symptoms). Effect sizes of treatment relative to placebo during this phase ranged from 0.16 (immediate-release methylphenidate 1.25 mg 3 times daily) to 0.72 (immediate-release methylphenidate 7.5 mg 3 times daily).

The parallel phase of the Preschool ADHD Treatment Study, in which 114 patients were randomized to either placebo or their optimal dose of immediate-release methylphenidate (as determined in the crossover phase of the trial), 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 composite score compared with placebo patients (immediate-release methylphenidate 13/61 [22%] compared with placebo 7/53 [13%; $P<0.3$]). Overall patient withdrawal from this study was high (32%; n=36), with 45% of withdrawals on placebo and 15% on immediate-release methylphenidate. The open-label lead-in phase may have influenced this dropout rate. An unplanned, post-hoc analysis of composite SNAP scores found that immediate-release methylphenidate patients had a lower mean symptom score than placebo patients after 4 weeks of treatment (immediate-release methylphenidate 1.49 compared with placebo 1.79; $P<0.02$).

Additional outcomes were assessed, including the Strengths and Weaknesses of ADHD-Symptoms and Normal Behaviors (SWAN) scale, Social Skills Rating System, the Social Competence Scale, the Parenting Stress Index, the Early Child Inventory (dysthymic disorder and major depressive disorder subscales only), and the Clinical Global Impression-Severity Scale.[37] Of these, only the Early Child Inventory was reported to have reliability and validity testing in preschool aged children. While the study did not necessarily have adequate statistical power to evaluate these outcomes, differences were not found between immediate-release methylphenidate and placebo on 4 of 6 of these measures. Only the Early Child Inventory assessments of mood and the Clinical Global Impression-Severity Scale found methylphenidate OR superior to placebo after 5 weeks. On ratings of major depressive symptoms or dysthymic symptoms, children taking immediate-release methylphenidate had improvements in scores while those taking placebo had deterioration in scores ($P=0.02$ and $P=0.001$, respectively), however these differences were based on only 61 of 114 randomized patients and the difference in final score was approximately 1.5 points. The complete scale was described as having 108 points, but the possible points for these 2 subscales are not reported. The investigator assessment of Clinical Global Impression-Severity Scale also indicated a better final score for those taking immediate-release methylphenidate (mean immediate-release methylphenidate score 3.74 and mean placebo score 4.47 on 0 to 7 scale; $P=0.001$). In view of the high and differential discontinuation rate, the concerning amount of missing data reported, and the unclear implications of the differences found, these secondary analyses should be interpreted with great caution.

Among those who responded well to immediate-release methylphenidate during the open-label run-in phase, 140 enrolled in a 10-month open-label extension phase and only 95 (68%) completed 10 months of follow-up.[38] Discontinuations due to adverse events or

deterioration in response were low (5% each). After 10 months, ADHD rating scales used (SNAP and SWAN) and ratings of parental stress had not changed significantly from enrollment. Dosing had increased from a mean of 14 mg daily to 20 mg daily. Ratings by unblinded clinicians on the Clinicians Global Impression-Severity and Clinicians Global Impression-Improvement scale increased by small absolute, but by statistically significant amounts (0.24 and 0.44 out of 7 possible points; $P=0.02$ and $P<0.001$, respectively). Similarly, unblinded ratings of the Children's Global Assessment Scale and Social Skills Rating Scale improved by 5 points (of 100; $P<0.001$) and 4 points (described as having 70 items, range of scores not described; $P=0.01$).

### *Children (elementary school age; 6-12 years)*

#### Stimulants

##### *Comparison of immediate-release and sustained-release formulations*

***Methylphenidate.*** We included 13 trials of immediate-release methylphenidate compared with methylphenidate SR.[39-49] Of these, 4 were poor quality due to either inadequate or undescribed methods of randomization and allocation concealment, combined with lack of description of an intent to treat analysis, lack of information on eligibility criteria, attrition, or post randomization exclusions (Evidence Table 3).[39, 40, 44, 46] The remaining studies compared immediate-release methylphenidate to 5 extended-release formulations of methylphenidate (Biphentin®, Concerta®, Ritalin SR®, Medikinet®, or Metadate CD®).[41-43, 45, 47-49]

No trials comparing the other extended-release formulations of methylphenidate (Ritalin LA®, Methylin ER®, or Metadate ER®) to immediate-release methylphenidate were found. Table 4, below, presents basic pharmacokinetic information on the methylphenidate products.

***Immediate-release methylphenidate compared with methylphenidate OROS (Concerta®).*** Five studies have compared immediate-release methylphenidate with methylphenidate OROS once daily, enrolling a total of 561 children with ADHD (Table 5).[41, 42, 48-50]

## Table 4. 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<br>2nd: ~4.5 | 10-12 | Multilayer-release system: 40% immediate; 60% delayed |
| Metadate CD®, Equasym® | 1 | 1st: 1.5<br>2nd: 4.5 | 8 | Errand Diffucaps:<br>30% IR & 70% ER beads released from capsule |
| Ritalin LA® | 1 | 1st: 1-3<br>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<br>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.

## Table 5. 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 |
|---|---|---|---|
| Wolraich 2001<br>Double-blind RCT<br>United States<br>N=282<br>28 days | MPH IR 29.5 daily<br>(TID dosing)<br>Concerta® 34.3 daily | *Teacher ratings:*<br>Inattention/overactivity<br>–3.57 vs. –3.76<br>Oppositional/defiance<br>–1.3 vs. –1.6 3<br>*Parent ratings:*<br>Inattention/overactivity<br>–3.73 vs. –4.79<br>Oppositional/defiance<br>–2.36 vs. –3.24<br>*For all comparisons, P*=NS | *Teacher SNAP-IV:*<br>Inattention<br>–0.69 vs. –0.80<br>Hyperactivity/impulsivity<br>–0.64 vs. –0.69<br>Oppositional/defiance<br>–0.36 vs. –0.32<br>*Parent SNAP-IV:*<br>Inattention<br>–0.91 vs. –0.77<br>Hyperactivity/impulsivity<br>–0.91 vs. –0.74<br>Oppositional/defiance<br>–0.65 vs. –0.41<br>*For all comparisons, P*=NS |
| Pelham 2001<br>Double-blind Crossover[a]<br>+ Behavioral Treatment<br>United States<br>N=68<br>7 days | MPH IR 29 mg daily<br>(TID dosing)<br>Concerta® 35 daily | *Teacher ratings:*<br>Inattention/overactivity<br>4.96 vs. 4.65<br>Oppositional/defiance<br>2.08 vs. 2.26<br>*P*=NS for both comparisons<br>*Parent ratings:*<br>Inattention/overactivity<br>4.49 vs. 5.64; *P*=0.05;<br>Oppositional/defiance<br>2.02 vs. 2.46; *P*=NS | Methods indicate SNAP measured, but results not clearly reported separate to other results |
| Swanson 2003<br>Double-blind RCT<br>United States<br>N=64<br>1 week | MPH IR 5-15 mg daily (TID dosing)<br>Concerta® 18-54 mg daily | *Teacher ratings:*<br>*Reported as P = 0.32 between active drug groups.*<br>*Other outcomes compared only to placebo.* | *Not measured.* |
| Steele, 2006<br>Open-label RCT<br>Canada/United States<br>N=147<br>8 weeks | MPH IR 33.3 mg daily<br>(usual care; 61% TID, 38% BID)<br>Concerta® 37.8 mg daily | *Teacher ratings:* NA<br>*Parent ratings:*<br>Inattention/overactivity<br>–3.9 vs. –5.4; *P*=0.01;<br>Oppositional/defiance<br>NA | *Parent ratings:*<br>SNAP-IV Remission[b]<br>16% vs. 44%; P 0.0002; NNT 3.6)<br>Mean Change in SNAP-IV 26 (ADHD + ODD)<br>–17.5 vs. –25.2; *P*=0.004<br>SNAP-IV-18 (ADHD only)<br>–14.3 vs. –19.6; *P*=0.01 |
| | | **Conners' Rating Scale Revised Short-Form** | |
| Gau, 2006<br>Open-label RCT<br>Taiwan<br>N=64<br>28 days | NR | *Teacher ratings:*<br>Inattention –1.90 vs. –1.44<br>Hyperactivity/impulsivity –4.94 vs. –4.00<br>Oppositional –3.03 vs. –1.91<br>*Parent ratings:*<br>Inattention –5.63 vs. –4.19<br>Hyperactivity/impulsivity –7.53 vs. –5.84<br>Oppositional –3.87 vs. –3.41<br>Comparisons of slope (change in score over time) between treatments:<br>*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 US 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.[41, 42, 50] In contrast, the 2 newer, open-label studies did find a significant difference favoring methylphenidate OROS.[48, 49] There is a potential risk of selection bias in that only 1 of the studies[41] 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 approve,[41, 42, 50] 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).[51]

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.[42] 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 based on assessments made by teachers and counselors.[41] An additional study of 64 children was rated poor quality because it lacked adequate reporting on multiple measures to provide meaningful results.[50]

The study by Steele, et al.[49] 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 5). 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 5). 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 here 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.[52] 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.

***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.[43] 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.[47] 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) was reported in the discussion as supporting these results. Additional analysis examined the effects of the drugs in the morning and afternoon, but a direct comparison was made only to the placebo group as both methylphenidate groups were found similarly superior to placebo at both time points throughout the study.

***Immediate-release methylphenidate compared with methylphenidate multilayer-release (Biphentin®).*** Two small, fair-quality, crossover studies compared immediate-release methylphenidate to methylphenidate multilayer-release (Biphentin®, available in Canada, not available in the United States as of September 2011).[53, 54] In the first study, 90 children were randomized to either immediate-release methylphenidate or methylphenidate multilayer-release and had dose titration over 2-3 weeks, with observation by parent, teacher, and investigator over 2 weeks.[54] Discontinuations were similar between groups (86% methylphenidate multilayer-release, 89% immediate-release methylphenidate), and mean daily doses were similar between treatments (0.8 mg/kg daily). Using the Conners' scales, "normal" was defined as a final T-score of <65 on each of the 4 subscales. After 5 weeks of treatment, more children taking immediate-release methylphenidate had achieved a normal score on the ADHD Index compared with those taking methylphenidate multilayer-release (90% compared with 79% on the teacher scale and

81% compared with 77% on the parent scale). The authors reported that the mean ADHD Index T-scale score was statistically significantly better (lower) with immediate-release methylphenidate based on the teacher scale (mean differences, 3.12%; 95% CI, 1.51 to 4.73) but not significant on the parent scale (mean differences, 0.38%; 95% CI, –1.34 to 2.10). No other differences were found between treatment groups.

The second, smaller study (N=18) reported only single-day measurements after 1 week of immediate-release methylphenidate, methylphenidate multilayer-release, or placebo.[53] This study found no statistically significant differences between drug treatments on the Conners' IOWA scale, although baseline scores differed across treatment groups such that these findings should be interpreted with caution; the analyses attempted to control for differences in baseline scores, including assessing for carryover effects. Analyses of time-course responses were not able to identify consistent differences among the drugs compared with placebo.

### *Other measures of comparative effectiveness of immediate-release compared with sustained-release formulations*

Clinical trials of extended-release compared with immediate-release formulations were too short to demonstrate differences in long-term health outcomes. However, the intermediate outcome measure of persistence (the proportion of patients continuing to take or refill prescriptions for a medication after some longer period of time) is thought to be a good proxy for extension of benefits seen in the short-term, or if none were found, evidence of a difference in longer-term, real-life settings. Persistence is an intermediate outcome with unknown validity because direct evidence of a relationship between persistence rates and long-term health outcomes with ADHD drugs is lacking.

In 5 observational studies (6 publications), persistence with treatment with long-acting stimulant formulations (methylphenidate OROS or methylphenidate ER) was significantly longer compared with shorter-acting formulations (immediate-release methylphenidate or immediate-release mixed amphetamine salts) over periods of 6 months and 12 months[55-58] following index prescription. One of these studies examined only adults treated with methylphenidate OROS (median duration of treatment 68 days; 95% CI, 65 to 71) compared with immediate-release methylphenidate (39 days; 95% CI, 33 to 52).[59] The findings of these studies should be interpreted with caution, however, until confirmed by a randomized controlled trial that would serve to rule out potential sources of bias, including between-group baseline differences in unmeasured clinical characteristics, physicians' prescribing preferences, and differences in reasons for discontinuation (e.g., change in insurance benefit and use of promotional samples). We rated these studies fair quality.

Data were derived from the Integrated Health Care Information Services National Managed Care Benchmark Database in 2 studies from the same group of researchers, with overlapping data. Using a definition of persistence as less than a 15-day gap in prescription refills, the studies found methylphenidate OROS to be associated with greater persistence rates than immediate-release methylphenidate (12% compared with 1%, $P<0.0001$[56] and 15% compared with 3%, $P<0.0001$).[57, 58] The second study also reported persistence using less than a 30-day gap in refills as the definition and found 33% persistent with methylphenidate OROS and 5% with immediate-release methylphenidate.[57, 58] There was uncertainty about how well this study population represented patients in actual practice as ethnicity and comorbidity characteristics were not reported and there were age and diagnosis differences between those receiving methylphenidate OROS compared with immediate-release methylphenidate.

California Medicaid claims files from a 3-year period were examined to identify youth prescribed methylphenidate (N=11 537).[55] This study population involved a lower than average proportion of White patients (45.3%) and higher proportions of Hispanic patients (26.1%). Total mean duration (days) of treatment without any 30-day gaps was greater for patients taking extended-release formulations (combined group of methylphenidate OROS = 83%, methylphenidate ER = 8.7%, methylphenidate SODAS = 8.3%) than for those taking immediate-release methylphenidate (140.3 compared with 103.4; survival time ratio, 1.37; 95% CI, 1.32 to 1.42). Subgroup analysis results suggested that persistence duration was greatest for methylphenidate OROS (147.2 days; 95% CI, 142.6 to 151.7 days) compared with methylphenidate SODAS (113 days; 95% CI, 100.9 to 125.1 days) or methylphenidate CD (101.1 days; 95% CI, 91.2 to 111.0 days). Together, extended-release formulations extended persistence duration regardless of ethnicity.

The Texas Medicaid Vendor Drug Program database was used to identify claims for newly started stimulants (2001-2002 school year).[60] Prescription refill patterns for children (75.7% male; mean age 9.93 years) with new claims for either immediate-release mixed amphetamine salts (n=3425), immediate-release methylphenidate (n=3343), or methylphenidate OROS (n=2781) were evaluated over 6-month assessment periods. Proportion of days of treatment without any 15-day gaps was greater for patients taking methylphenidate OROS than for immediate-release methylphenidate or immediate-release mixed amphetamine salts (0.5 compared with 37 compared with 42; $P<0.001$), as was proportion of patients that continued receiving therapy for 151-180 days (30.23% compared with 13.62% compared with 18.89%; $P<0.001$). Within those days of treatment, compliance rates, as measured using the Medication Possession Ratio, were higher in patients taking methylphenidate OROS compared with immediate-release methylphenidate or immediate-release mixed amphetamine salts (0.76 compared with 0.69 compared with 0.73; $P<0.001$).

### *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.[61, 62] 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 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 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[63] found methylphenidate SODAS superior on the attention or 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 similar 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.[64] 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.

***Dexmethylphenidate ER compared with methylphenidate OROS.*** A single, small (N=84) fair-quality crossover study compared 2 doses of dexmethylphenidate ER with 2 doses of methylphenidate OROS or placebo using a simulated classroom assessment.[65] The primary outcome was the mean change in the SKAMP combined score from zero to 2 hours post dose in the dexmethylphenidate ER 20 mg daily group compared with the methylphenidate OROS 36 mg daily group. Children were given the intervention for 7 days prior to the assessment. The mean change in SKAMP combined scores at 2 hours post dose was statistically significantly greater with dexmethylphenidate ER 20 mg daily compared with methylphenidate OROS 36 mg daily (adjusted mean change –11 compared with –6; $P<0.001$). Similar results were found comparing the higher doses (30 mg dexmethylphenidate ER and 54 mg methylphenidate OROS daily) to each other. At other time points, the drugs differed depending on the time of day. For time points up to 6 hours, dexmethylphenidate ER had statistically significantly superior change in SKAMP combined scores comparing either the 2 lower doses or the 2 higher doses to each other ($P$ values ranged from <0.001 to =0.044). Similarly, a statistically significant difference was seen at the first time point, 0.5 hours ($P$=0.044). However, at later time points (10, 11, and 12 hours post dose), methylphenidate OROS had statistically significantly superior 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. In comparison to placebo, dexmethylphenidate ER was superior on SKAMP combined scores starting at 0.5 hours but was not statistically different to placebo at 12 hours. Methylphenidate OROS was superior to placebo starting at 1 hour (not at 0.5 hours) and remained superior through 12 hours.

According to the US Food and Drug Administration Medical Review,[66] data from 2 short-term, randomized, placebo-controlled, double-blind efficacy trials were submitted to the US Food and Drug Administration in the New Drug Application for dexmethylphenidate ER.[67, 68] Both were fair quality. Study 2301 was a 7-week, parallel-group, flexible-dosing trial of 103 children.[67] Study US08 was a 2-week, fixed-dose, crossover trial of 54 children.[68] Dexmethylphenidate ER was significantly superior to placebo for both primary outcomes of

change from baseline to final visit in Conners' ADHD/DSM-IV Scale-Teacher version in Study 2301 (–16.3 compared with –5.7 points; $P<0.001$) and of mean change in SKAMP combined scores from predose to 1-hour post dose in Study US08 (–10.014 compared with 0.078 points, $P<0.001$).

Four small, fair-quality placebo-controlled trials have been conducted with dexmethylphenidate ER.[67-70] A 7-week, parallel-group, flexible-dosing trial of 103 children found dexmethylphenidate ER significantly superior to placebo in change from baseline to final visit in Conners' ADHD/DSM-IV Scale-Teacher version (–16.3 compared with –5.7 points; $P<0.001$).[67] Three crossover studies of dexmethylphenidate ER 20 mg daily evaluated response on the SKAMP scale in a laboratory classroom setting. All found dexmethylphenidate ER superior to placebo on the primary outcome measure of mean change in SKAMP combined score over 1 to 8 or 12 hours post dose. Secondary analyses assessed differences at early time points; 2 studies found a statistically significant difference on mean change in the combined score at 0.5 hours (–2.2 dexmethylphenidate ER compared with 3.5 placebo; $P=0.001$[70] and –0.969 dexmethylphenidate ER compared with 3.336 placebo; $P=0.001$),[70,69] and the third found a difference starting at 1 hour post dose (–10.014 compared with 0.078; $P<0.001$).[68] Lack of adequate variance data prevented pooling of these results. Because these are crossover studies, carryover effects must be taken into account, however results of such analyses were not reported.

No direct comparisons of other extended-release formulations of methylphenidate or other ADHD drugs were found.

***Methylphenidate CD (Metadate CD®) compared with placebo.*** A 3-week trial of Metadate CD® compared with placebo enrolled 314 children out of 507 screened.[71] Twenty-four percent of those excluded at screening were because they responded to placebo during a 1-week washout period. This biases the study population towards the Metadate CD® arm, reducing the applicability of the results. The mean change in the primary outcome measure, the teachers' Clinical Global Impression Scale ratings combined in the morning and afternoon, were significantly lower (better) in the Metadate CD® group. Secondary measures also favored Metadate CD®.

### *Immediate-release formulations: Efficacy outcomes*

***Dextroamphetamine compared with methylphenidate.*** We included 9 fair-quality studies (reported in 11 publications) of immediate-release dextroamphetamine compared with immediate-release methylphenidate.[72-82] Two poor-quality studies and 1 poor-quality subgroup analysis were found.[83-85] All 9 fair-quality studies were randomized, blinded crossover trials. Table 6 summarizes the study characteristics.

## Table 6. Immediate-release dextroamphetamine compared with immediate-release methylphenidate study characteristics

| Study Date | Number Duration | Diagnosis criteria | Final dose[a] | Results |
|---|---|---|---|---|
| Efron 1997 | N=125<br>2 weeks | DSM-IV criteria for ADHD | DEX: 0.15 mg/kg<br>MPH: 0.3 mg/kg | No differences found |
| Efron 1998 | N=102<br>2 weeks | DSM-IV criteria for ADHD | DEX: 0.15 mg/kg<br>MPH: 0.3 mg/kg | No differences found |
| Elia 1990 | N=31<br>3 weeks | DSM-III criteria for attention deficit disorder with hyperactivity | < 30 kg/ > 30 kg:<br>DEX: 40 mg/ 45 mg<br>MPH: 70 mg/ 90 mg | No differences found |
| Elia 1991 | N=48<br>3 weeks | DSM-III criteria for attention deficit disorder with hyperactivity | < 30 kg/ > 30 kg:<br>DEX: 40 mg/ 45 mg<br>MPH: 70 mg/ 90 mg | No differences found |
| Elia 1993 | N=33<br>3 weeks | DSM-III criteria for attention deficit disorder with hyperactivity | < 30 kg/ > 30 kg:<br>DEX: 40/ 45 mg<br>MPH: 70 / 90 mg<br>Placebo | No differences found |
| Sharp 1999 | N=32<br>3 weeks<br>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<br>MPH: 1.28 mg/kg | No differences found |
| Arnold 1978 | N=29<br>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<br>MPH: 30 mg | No differences found |
| Kaufman 1981 | N=12<br>6 weeks | Children diagnosed as "hyperactive", according to a set of predetermined clinical criteria (NR) | DEX: 10-60 mg<br>MPH: 5-30 mg<br>Placebo | No differences found |
| Simpson 1980 | N=12<br>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,[73, 74] which used clear criteria for diagnosis, enrolled children with ADHD in order to test the hypothesis that some adverse events associated with stimulants are actually characteristics of ADHD and would be improved by drug treatment in 1 study,[73] and to test the differences between child and parent assessment of therapy in the other.[74] Neither study provides details on the efficacy results, other than summary statements that there were no differences between the 2 drugs based on children's self-assessment[74] and based on parent and teacher ratings.[73] 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.[81] 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.[81] 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

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

### *Response rates*

Very few studies attempted to make a comparison of the rate of response (defined a priori) between 2 drugs. Table 7 shows the studies that did. Overall, no differences in response rates, as defined below, were found between the comparisons of methylphenidate OROS, immediate-release dextroamphetamine, mixed amphetamine salts or clonidine to immediate-release methylphenidate. Additionally, the majority of these response rates were lower than those reported and quoted from placebo-controlled trials (rates of approximately 75%).

**Table 7. Comparison of response rates to immediate-release methylphenidate**

| | Interventions | Response rate definition | Response rates (%) |
|---|---|---|---|
| **MPH OROS compared with MPH IR** | | | |
| Pelham 2001[a]<br>Crossover<br>N=70 | MPH OROS<br>MPH IR<br>x 1 week | Parent/teacher ratings of Global Effectiveness as “Good” or “Excellent” | Parent: 67.2 vs. 64.7<br>Teacher: 67.2 vs. 57.4 |
| Wolraich 2001[b]<br>Parallel<br>N=192 | MPH OROS<br>MPH IR<br>x 4 weeks | CGI rated as “much” or “very much” improved | 46.2 vs. 47.2 |
| | | Parent/teacher ratings of Global Effectiveness as “Good” or “Excellent” | Parent: 54 vs. 46.5<br>Teacher: 42.9 vs. 46.9 |
| **DEX IR compared with MPH IR** | | | |
| Efron 1998<br>Crossover<br>N=102 | DEX IR<br>MPH IR<br>X 2 weeks | Parental ratings of drug as “very helpful” or “a bit helpful” | 62.4 vs. 73.5 |
| Efron 1997<br>Crossover<br>N=125 | DEX IR<br>MPH IR<br>X 2 weeks | Parental ratings that child improved overall | 68.8 vs. 72.0 |
| Sharp 1999<br>Crossover<br>N=42 | DEX IR<br>MPH IR<br>X 3 weeks | CGI: “very much improved” or “much improved” | 85.0 vs. 83.0 |
| **MAS (Adderall®) compared with MPH IR** | | | |
| Pliszka 2000<br>Parallel<br>N=40 | Adderall®<br>MPH IR<br>x 3 weeks | CGI improvement score of 1 or 2: “very much improved” or “much improved” | 90.0 vs. 65.0; *P*=0.12 |
| **Clonidine compared with MPH IR** | | | |
| van der Meere 1999<br>Parallel<br>N=53 | Clonidine<br>MPH IR<br>x 7 weeks | Clinical responders: behavior improved at home/or at school | 47 vs.53 |

Abbreviations: CGI, Clinical Global Impression Scale; DEX, dextroamphetamine; IR, immediate release; MPH, methylphenidate; OROS, osmotic release oral system.
[a, b] The sample size for Pelham 2001 and Wolraich 2001 were determined based on methylphenidate OROS compared with placebo. It is not clear if these studies were powered to detect a difference between methylphenidate OROS and immediate-release methylphenidate.

### *Immediate-release formulations: Effectiveness outcomes*

We found extremely limited information on effectiveness outcomes from the clinical trials. Therefore, we included observational studies of ≥6 month's duration that reported effectiveness outcomes (Evidence Tables 13 and 14).

***Immediate-release methylphenidate compared with methylphenidate OROS (Concerta®).*** Integrated Health Care Information Services managed care claims data (described above) 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).[56] The study population (N=1,775) was 75% male, 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,[57] 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)[57] and a lower probability of being hospitalized (odds ratio, 0.67; 95% CI, 0.45 to 0.99) over a 12-month period.[58] 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[58] 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.[57] 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.*** In a 4-year follow-up study of 62 children treated with methylphenidate, the effect of duration of treatment on academic performance was assessed.[86] The duration of treatment was divided into <6 months, 6 months to 2 years, 2 to 3 years, 3 to 4 years, and those currently taking stimulants at follow-up. No differences were found between the groups on academic achievement as measured by teachers, the proportion repeating grades, in special education classes, or being tutored. Although the proportion of children repeating grades was lowest in the group continuing to take methylphenidate (8% compared with 46%, 50%, 36%, 31%), this difference was not statistically significant, possibly because of the small numbers of boys per group (n=10 to 14). Due to methodological limitations, this study provides no comparative information.

Adherence rates as proxy measures of duration of effectiveness and caregiver satisfaction were reported for 307 Chinese children with ADHD taking immediate-release methylphenidate that were followed for 6 months of treatment.[87] Parents of 100 children (32.6%) were unsatisfied with their children's adherence to immediate-release methylphenidate and cited the following reasons for missing doses: forgetting to take immediate-release methylphenidate at school (72.9%), the medication having no effect (20%), forgetting to bring immediate-release methylphenidate to school (19.1%), refusing to take immediate-release methylphenidate (12.7%), bitterness (11.4%), side effect (11.4%), and teacher's objection (7.7%). Compared to families with children demonstrating good adherence, poor adherence was associated with increased risk of impairments in maternal psychological status and perceived family support.

***Stimulants.*** In a birth cohort study of 5713 children born in Rochester, Minnesota during the years of 1976 to 1982, 370 children were diagnosed with ADHD. Two hundred ninety-five were treated with a stimulant and 84 were not.[88] Of those exposed to a stimulant, 66% took methylphenidate and 30% took dextroamphetamine (assumed to be immediate-release formulations). Median age of initiation of treatment was 10 years, median duration of treatment was 34 months, and median dose was 21 mg daily methylphenidate or methylphenidate equivalents. In addition to the 84 children diagnosed with ADHD but not receiving a stimulant at any time, the study also identified a control group from the birth cohort. Using a Poisson regression analysis, exposure at any time during follow-up was associated with lower rates of absenteeism ($P$=0.012) and duration of exposure was also significantly associated with lower absenteeism rates ($P$=0.041). Other factors were also found statistically significantly associated with number of days absent: comorbid conditions ($P$=0.006), type of educational interventions ($P$<0.001), and maternal education at birth ($P$=0.005). Reading scores were similar between groups, although among those treated with a stimulant there was a "mild correlation" between the mean dose of stimulant and final reading score recorded (r=0.15; $P$=0.012). Children who were exposed to a stimulant were 1.8 times (95% CI, 1.01 to 3.2) less likely to be retained a grade at any time; based on Kaplan-Meier analysis 66 children were retained a grade level. Dropout rate (based on 69 of 301 cases available for analysis) was significantly associated with maternal education at birth, comorbid conditions, and type of educational intervention, but not stimulant exposure, duration, or dose. While this study had some methodological advantages over other studies, the main limitation was the number of children included, particularly in the nonmedicated group, such that these findings should be interpreted cautiously.

### *Maintenance of short-term symptom response effects*

***Methylphenidate or immediate-release dextroamphetamine compared with placebo or non-drug therapy.*** All of the trials reported above were very short-term trials (range 1 to 9 weeks). Because of this serious limitation, the evidence does not provide information on the long-term benefits of these drugs in treating ADHD. To provide further evidence on duration of effect and longer-term outcomes, placebo- or non-drug therapy controlled trials of ADHD drugs with duration ≥6 months are reported here (Evidence Tables 7 and 8). We found 3 placebo-controlled trials of at least 6 months duration, 1 with immediate-release dextroamphetamine and 2 with immediate-release methylphenidate,[89-91] and 3 trials that randomized children to stimulant medication or nondrug therapy for 12 to 14 months.[92-94] Many of these studied indicated dissipation of medication effects over time, with unmedicated control groups having similar longer-term outcomes, particularly with follow-up of 2 years or greater.

Of these, the largest (N=579) and longest duration of follow-up is the Multimodal Treatment Study of Children with Attention Deficit/Hyperactivity Disorder (MTA). The MTA was a relatively large study funded by the NIMH assessing medication management, behavioral treatments, standard community care, and combined medication management and behavioral treatments over a 14-month period.[92] Following the 14-month trial the groups had follow-up at 2, 3, and 8 years post randomization.[92, 95-97] Medication management could involve any stimulant medication, but started with methylphenidate titration. At study end, 73% of those in 1 of the medication management groups were on methylphenidate and 10% on immediate-release dextroamphetamine, with small numbers of patients taking no medication, pemoline, imipramine, bupropion, or haloperidol, and 6% refusing to be in the medication arm assigned. All participants met DSM-IV criteria for ADHD combined type, had a mean age of 8.5 years,

and 80% were males. The sample population was ethnically diverse, with White (61%), African American (20%), and Hispanic (8%) representation. Comorbidities included anxiety disorder (33.5%), conduct disorder (14.3%), oppositional-defiant disorder (39.9%), affective disorder (3.8%), tic disorder (10.9%), mania/hypomania (2.2%), and other (e.g., bulimia, enuresis) (0.2%). This study was a pragmatic trial in that the treatments were given openly (after blinded titration in the 2 drug treatment arms), and participants could refuse the assigned arm or add or change treatments. In the community care arm, for example, 68% were taking ADHD medications although the mean dose and number of daily doses of methylphenidate was lower in the community care arm than the medication arms. However, the outcome measures were not effectiveness outcomes, so the trial must still be viewed as an efficacy trial.

After 14 months, medication management alone resulted in better scores compared with behavioral therapy for the symptoms of inattention (rated by both parents and teachers) and hyperactive-impulsive symptoms (parent ratings). Medication alone resulted in better scores on all ADHD symptoms than community care, except as measured by a classroom observer. Aggression-oppositional defiant disorder symptoms scores were better with medication alone compared with community care in teacher ratings only. Combined therapy (medication and behavioral therapy) was not different to medication alone on any scale. The effect of medication management was maintained over the 14 month period.

Families were contacted 10 months after the end of the 14-month study (2 years post randomization) to assess longer-term persistence of treatment effects.[95] A total of 540 (93%) of the originally randomized 579 participated and 10 months after study end, 72% in the medication management alone group, 70% in the combined therapy group, 38% in the behavioral therapy group, and 62% in the community care group were taking medication for ADHD. At 2 years, medication alone still resulted in better scores on ADHD and oppositional defiant disorder symptoms than behavioral therapy and community care. Despite this, analyses of combined outcomes from the medication management alone and combined therapy groups compared with those of the behavioral therapy and community care groups suggest a reduction in the magnitude of benefit by half from the 14-month to 24-month time points; effect size changes for ADHD symptoms were 0.60 compared with 0.30 and oppositional defiant disorder symptoms were 0.39 compared with 0.21. At 3 years of follow-up, 485 children participated (84%) and the proportions taking medication had changed. There was a decrease from 91% to 71% in the medication only/combined therapy group, an increase from 14% to 45% in the behavioral therapy group; and about constant (60% to 62%) in the community care group.[96] Along with these changes, the difference between groups in outcome measures was no longer statistically significant although all groups had improved compared with baseline scores on all measures. Further analyses indicated a benefit of regular medication use during the 14 month and 24 month periods, but not at 36 months. At 6 and 8 years, follow-up was possible in 78% and 75%, respectively.[96] Regular medication use was reported in 42% at 6 years and in 31% at 8 years, with no significant differences among the groups. Among children taking a stimulant at 3 and 8 years follow-up, mean dose had increased from a mean of 31 mg daily to 43 mg daily. Small numbers of children were taking a nonstimulant. Again, no differences were found between groups in efficacy measures. This follow-up included questions about other outcomes, including police contacts and arrests; academic performance on reading and math tests; grade point average; use of school services; and grade retention, but no differences among groups were found.

The other smaller trials of immediate-release methylphenidate, compared with placebo[89-91] or other non-drug interventions,[92-94] reported a dissipation of effect at earlier time points, 9 months to 2 years. Although some of these studies do not report mean doses, of those that do, the doses used in the MTA study were higher. Two studies were poor quality due to serious flaws that represent significant potential for bias, primarily due to no details on the subject's characteristics at baseline and no details on those who discontinued the study.[89, 98]

### *Remission rates: Immediate-release methylphenidate*

Three studies assessed the effects of withdrawing immediate-release methylphenidate after periods of treatment.[99-101] Two of these were poor quality,[99, 100] but the third study[101] included a group of 21 boys who had been treated with methylphenidate for a mean of 1.75 years and randomized to 3 weeks of placebo or methylphenidate. Using the Conners' Teacher Rating Scale, this study found that on the Subscale items of hyperactivity and defiance the scores during the placebo period were significantly worse than during the methylphenidate period. No baseline assessments were presented, and the analyses are based on scores at week 3 of each condition only so there is no information about the effectiveness of their pre-existing methylphenidate regimen at baseline. In addition, the effect of order of drug/placebo was not analyzed in this crossover study, so the results must be interpreted with caution.

## Other stimulants

***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 amphetamine salts XR at 10, 20, and 30 mg, immediate-release mixed amphetamine salts 10 mg, and placebo given once daily for 7 days. Study assessments were taken during a single 12-hour day with assessments every 1.5 hours in a simulated classroom setting.[102] The study used a run-in period where children were given mixed amphetamine salts XR 20 mg after which 4% (2 of 51) dropped out after this session; the reasons were reported as withdrawal of consent. Based on the SKAMP scale deportment and attention variables and a math test (PERMP), the extended-release formulation had statistically 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. Considering these results, a more informative comparison would have been mixed amphetamine salts XR 20 and 30 mg once daily to immediate-release mixed amphetamine salts 10 mg twice daily.

***Mixed amphetamine salts compared with immediate-release methylphenidate.*** Three small, fair-quality studies of mixed amphetamine salts compared with immediate-release methylphenidate were found.[103-106] One was a parallel group randomized controlled trial[106] while the other 2 were randomized crossover trials.[103-105] Two additional studies were rated poor quality[107, 108] 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.[106] 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 mixed amphetamine salts was 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 or final weight.

The 2 crossover studies were conducted in the same manner by the same authors and were conducted in a summer treatment program.[103-105] 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.

***Mixed amphetamine salts compared with immediate-release dextroamphetamine.*** The evidence was limited to a single poor-quality study of immediate-release dextroamphetamine compared with dextroamphetamine SR compared with mixed amphetamine salts compared with placebo.[109] No conclusions can be drawn.

***Immediate-release dexmethylphenidate.*** Only 1 of 2 placebo-controlled studies of immediate-release dexmethylphenidate referred to in the most recent US Food and Drug Administration Medical Review (http://www.fda.gov/cder/foi/nda/2001/21-278_Focalin_medr_P1.pdf) has been published.[110] Immediate-release dexmethylphenidate was associated with significantly greater mean reductions in Teacher SNAP rating score than placebo ($P=0.004$) after 4 weeks in a fair-quality trial of 132 children (88% male; mean age, 9.8 years) with ADHD of mostly the combined type (64%).[110]

A small study of the effects of withdrawing immediate-release dexmethylphenidate after a 6-week titration period was poor quality. No conclusions can be drawn about the comparative efficacy of immediate-release dexmethylphenidate.[99]

***Methamphetamine.*** The only evidence we identified for methamphetamine was in the form of a dissertation report published in 1973 and is characterized by measures of cognitive impulsivity,

planning, new learning, IQ, and social behavior.[111] In this trial, 32 boys with hyperkinesis were randomized to 4 week treatment periods of either methamphetamine or placebo. Methamphetamine was started at 5 mg daily for first 2 weeks and then the dose was increased to 10 mg daily for the following 2 weeks. The main findings were that methamphetamine was superior to placebo in improving scores on measures of impulsivity, social behavior, and on 1 of 2 measures of new learning. There were no between-group differences on measures of general intelligence. It did not appear that adverse effects were assessed in this trial.

***Methylphenidate transdermal system (Daytrana®).*** In 2 head-to-head studies of transdermal methylphenidate compared directly to other stimulants, neither found a statistically significant difference in efficacy overall. 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.[112] 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-Rating Scale (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, and the proportion of children whose improvement in score would be considered a response was not reported. Although no difference was found between transdermal 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.

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.[113] 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.

Two placebo-controlled trials of transdermal methylphenidate have also been published.[114, 115] Two of these studies had serious flaws and were rated poor quality (e.g. unclear methods for randomization, allocation concealment and/or blinding, high withdrawal rates) and do not add to the studies above. [115, 116] In study designed to assess varying wear-times, 117 children were assigned to placebo or transdermal methylphenidate worn for shorter periods (4 or 6 hours), with 5 weeks of dose-optimization but with a practice day in the classroom plus 3 separate laboratory classroom days with assessments every 2 hours up to 10 hours after patch application.[114] The SKAMP deportment scale scores (no change from baseline) were the primary outcome, and the analysis reported primarily the comparison of the transdermal methylphenidate groups with placebo averaged over the time the patches were actually worn (4 and 6 hours). During this time, the mean score with placebo was 11.5 compared with 5.7 and 5.9 with the 4- and 6-hour transdermal methylphenidate groups, respectively ($P<0.001$). The difference between placebo and either transdermal methylphenidate group was seen at the first time point (2 hours post application) and reductions in scores began 2 hours after transdermal methylphenidate removal. At 4 hours after removal the scores were similar to baseline.

***Lisdexamfetamine dimesylate***. We identified 2 fair-quality, randomized controlled trials of lisdexamfetamine, a 3-way crossover trial that compared 1-week treatment periods of lisdexamfetamine, mixed amphetamine salts XR, and placebo in 52 children,[117,297] and a placebo-controlled, 4-week, parallel-group trial of 3 different dosages of lisdexamfetamine (30 mg, 50 mg, or 70 mg) in 290 children.[118] Both trial populations are notable for reflecting more racial diversity than in other randomized controlled trials, and results of subgroup analyses based on race were reported in the Center for Drug Evaluation and Research Medical Review (see Key Question 3 below for further discussion). In these trials, only 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.

Primary efficacy analyses were performed using the average of Swanson, Kotlin, Agler, M-Flynn and Pelham - Deportment Subscale (SKAMP-DS) scores across the treatment assessment day,[117, 297] or the change in mean ADHD rating scale IV total score.[118] There were no significant differences between lisdexamfetamine and mixed amphetamine salts XR in LS-mean SKAMP-DS scores. Results of subgroup analyses generally suggested that lisdexamfetamine was superior in efficacy compared with placebo and 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.

Two trials have examined the benefits of lisdexamfetamine at various time points after morning dosing.[119, 120] A post-hoc analysis of the effects of lisdexamfetamine compared with placebo during the 8 to 10 AM, noon to 2 PM, and 4 to 6 PM times indicated placebo to be superior in the percent change on the Conners' scale parent ratings (total and ADHD index at all 3 time periods).[119] Similarly, a placebo-controlled trial of 117 children evaluated single-day measures in a simulated classroom setting, finding that lisdexamfetamine was superior to placebo on improvement in SKAMP-DS and attention subscale scores at every time point, beginning at 1.5 hours post dose up to 13 hours post dose. [120]

***Modafinil.*** 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).[121] Using the ADHD parent and teacher rating scale, significant differences were seen compared with baseline, 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.

In 6 fair-quality placebo-controlled trials,[122-127] modafinil was superior to placebo in all but 1 very small (N = 24) study, using 200-300 mg of modafinil daily.[124] In a somewhat larger study (N=46) of 200-300 mg daily dose of modafinil, ADHD-RS-IV scores were significantly improved compared with placebo after 6 weeks.[122]

Three trials used very similar designs, involved very similar patient populations, and higher doses of modafinil than in the other 2 studies. In these trials, a total of 638 children with ADHD were randomized to either modafinil (mean dosage range 361 mg to 395 mg) or placebo for treatment periods that were 7-9 weeks in duration.[123, 125, 126] Change in the ADHD rating scale was identified as the primary outcome in all 3 trials. In these trials, using a higher dosage level

than in the earlier trial, modafinil was found to be consistently superior to placebo on ADHD rating scale score change from baseline and also in the proportion of patients that were rated as "much improved" or "very much improved" on the Clinical Global Impression-Improvement Scale.

In a placebo-controlled trial of modafinil whose objective was to compare the efficacy and safety of several different once and twice daily dosing regimens, 248 children with ADHD were randomized to 4-week treatment periods of either 300 mg once daily or divided (morning/mid-day) dosages of 200/100 mg, 100/200 mg, or 200/200 mg.[127] With regard to mean change from baseline in ADHD rating scale, only the groups assigned to 300 mg once daily or 200/100 mg divided dosages had significantly greater score reductions than those in the placebo group. However, none of the groups were superior to placebo for the proportions of patients rated as "much improved" or "very much improved" on the Clinical Global Impression-Improvement Scale.

## Nonstimulants

### *Atomoxetine*

***Atomoxetine compared with methylphenidate.*** While 4 studies have included both atomoxetine and immediate-release methylphenidate, only 2 made relevant comparisons for assessing comparative efficacy.[128, 129] 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%).[129] 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.[128] Concerns over the study quality indicating potential bias suggest caution in interpreting these findings (see Evidence Table 4).

A second study comparing immediate-release methylphenidate and atomoxetine primarily assessed the impact of each drug on sleep, using a crossover design and sleep labs.[130] This small study (N=75) evaluated sleep onset (latency) using actigraphy, a device worn on the wrist to measure activity over 7 weeks. The mean dose of immediate-release methylphenidate was 42.29 mg daily, and of atomoxetine was 58.27 mg daily. Only 50 of 85 patients (59%) randomized were included in the analysis, mostly due to inadequacy of actinography data, a number that does not reach the stated 60 needed to adequately power this analysis. Additionally, 21% of those screened (22 of 107) were excluded for a variety of reasons relating largely to not complying with a pre-specified "light-out" time consistently. The primary outcome was the comparison of the mean *change* in sleep-onset latency from baseline to endpoint. At baseline, 43.5% were not taking stimulants. Both groups experienced an increase in time to fall asleep, but the immediate-release methylphenidate group had a significantly longer increase (39.24 minutes) compared with atomoxetine (12.06 minutes). A similar decrease in overall sleep time was also seen. Differences were not found between the drugs in ratings of ADHD symptoms. Results of planned ANOVA analysis of sequence were not reported, so the impact of order of randomization cannot be assessed here but may be important. The study involved funding, data

analysis, and authorship by the maker of atomoxetine. Because of the above concerns, we have rated this study poor quality.

***Atomoxetine compared with methylphenidate OROS.*** In a 6-week fair-quality noninferiority trial, atomoxetine was not found noninferior to methylphenidate OROS.[131] Using response (40% or more reduction of the 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). In this subgroup, atomoxetine was not found different than placebo. 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 but no data are reported. Also, atomoxetine was administered in a divided dose rather than given once daily.

The Formal Observation of Concerta® compared with Strattera® (FOCUS) trial compared open-label methylphenidate OROS and atomoxetine for 3 weeks in 1323 children with ADHD.[132] The main findings from the FOCUS trial are summarized in Evidence Table 3, but will not be discussed here due to concerns about study quality. 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 4).

***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).[133] 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 standard therapy.*** A British study of atomoxetine compared with standard treatment assessed the child's function and health status using the final score on the Child Health and Illness Profile – Child Edition as the primary outcome measure.[134] The total score of the tool was stated to not have previously been used, but to have been validated by the owner (Riley and colleagues). This research was cited only as "submitted for publication," and a

recent search did not uncover such a publication, so it is considered an unvalidated tool here. A total of 201 patients were randomized to 10 weeks of treatment with either atomoxetine or whatever treatment (including no treatment) prescribed by the investigator or the treating physician. This was an open-label study, with parent making the assessments. This study is poor quality, with no description of randomization and allocation concealment procedures, and some imbalances between the groups at baseline (Inattentive ADHD subtype 11.5% compared with 3.1%, previous exposure to stimulants 59.6% compared with 70% in atomoxetine and control groups, respectively). Additional concerns were that the higher discontinuation rate in the atomoxetine group was not taken into account by the modified intent to treat analysis described (it appears only 75% of atomoxetine group is included in the analysis, compared with 94% of control group), the standard treatment group was described as having their treatment determined by unblinded investigators, and the primary author being an employee of the manufacturer of atomoxetine.

***Atomoxetine compared with placebo.*** Six placebo-controlled studies of atomoxetine in children and adolescents with ADHD found atomoxetine to be superior based on ADHD rating scale as the primary outcome measure and various scales as secondary measures.[135-140] Results of 2 of the 6 trials were described as identically-designed and were reported in 1 publication.[137] The mean change on ADHD rating scale in these 6 to 9 week studies ranged from –12.8 to –16.7 with atomoxetine compared with –5.0 to –7.0 for placebo. A study of once daily dosing reported response rates (defined as ≥25% reduction in ADHD rating scale score) in the atomoxetine group of 59.5% compared with 31.3% in the placebo group ($P<0.001$).[139] Remission rates (defined as an endpoint Clinical Global Impression-Severity Scale score of 1 or 2) were 28.6% and 9.6%, respectively ($P=0.003$). All studies were funded and coauthored by representatives of the manufacturer of atomoxetine. All used the DSM-IV criteria, however the proportions of ADHD subtypes varied, for example 52% to 79% of enrolled children had the Mixed subtype. More concerning is the variation in the proportions of children with each subtype per assigned group. Proportions of children with comorbidities also varied across the studies (e.g. 18% to 45% with oppositional defiant disorder). Results of a subgroup analysis from 2 identically-designed placebo-controlled trials[137] suggested that atomoxetine was associated with significantly greater reductions in ADHD rating scale total scores than placebo (–17.0 compared with –7.5; $P<0.001$) in 98 of the original 291 children with comorbid ADHD and oppositional defiant disorder.[141] No subgroup analyzed based on ADHD subtypes or other comorbidities were reported. Based on what appeared to be post-hoc analysis of secondary outcome measures of 1 of these trials,[140] no statistically significant difference between atomoxetine and placebo was seen in academic performance (based on the Academic Performance Rating Scale) or quality of life (based on the Children's Health Questionnaire psychological summary score) after 7 weeks.[142]

In a good-quality systematic review, these 6 trials and 3 additional trials with placebo and active arms were combined in a meta-analysis that indicated atomoxetine was superior to placebo in improving ADHD rating scale total score (standardized mean difference, –0.638; 95% CI, –0.76 to –0.516), as well as subscale scores on inattentive symptoms, hyperactivity/impulsive symptoms, and the Conners' scales with teacher and parent ratings.[143] Meta-regression identified study duration and number of study sites, male sex, ADHD hyperactive/impulsive subtype, oppositional defiant disorder, baseline ADHD rating scale total score, inattention score, and hyperactivity/impulsivity score to be negatively associated with response. After adjusting for these confounders, atomoxetine remained superior over placebo. Six adverse events were found

to occur significantly more often with atomoxetine (numbers needed to harm; *P* value): decrease in appetite (8; $P<0.05$), somnolence (19; $P<0.05$), abdominal pain (22; $P=0.02$), vomiting (30; $P=0.02$), dyspepsia (49; $P<0.01$), dizziness (53; $P=0.01$), fatigue (62; $P=0.01$), infection (72; $P=0.02$), and pruritus (120; $P=0.04$). Risk of adverse events was found to be negatively associated with mean age, ADHD inattentive subtype, baseline ADHD rating scale score, and hyperactivity/impulsivity score. Meta-regression identified high ADHD rating scale total and hyperactivity/impulsivity scores at baseline to be significantly associated with adverse events ($P<0.01$).

Based on the 6 placebo-controlled trials above, with data apparently provided by the manufacturer, meta-analysis was performed to assess differences in response between younger (ages 6-7) and older (ages 8-12) children. Atomoxetine was found statistically significantly superior to placebo on the ADHD–RS and Conners' scales, in both age groups, although the difference between atomoxetine and placebo was smaller in the older age group compared with the smaller age group.[144] This study also found that abdominal pain, decreased appetite, vomiting, and somnolence occurred significantly more often with atomoxetine than placebo in younger children, and decreased appetite, somnolence, irritability, and fatigue among older children. There was a significant treatment by age effect in abdominal pain ($P=0.04$), vomiting ($P=0.053$), pyrexia ($P=0.058$), and cough ($P=0.007$). Statistically significant but small increases in pulse were seen in both younger and older children, and older children experienced increases in both systolic and diastolic blood pressure. In these short-term studies, statistically significant weight decrease was seen in both age groups (–0.5 and –0.6 kg).

Atomoxetine was associated with less rapid times to relapse than placebo under double-blind conditions (218 days compared with 146 days; $P<0.001$) in a randomized subgroup of 416 children (out of 603) that were classified as "responders" following an initial 12-week, open-label period of treatment with atomoxetine.[139] The primary outcome measure was the number of days to relapse and relapse was defined as return to 90% of baseline ADHD rating scale score and Clinical Global Impression-Severity Scale score increase of at least 2 points. Similarly, fewer patients on atomoxetine relapsed than on placebo (22% compared with 38%; $P<0.002$). As a continuation of that study, subjects initially randomized to atomoxetine were rerandomized to an additional 6 months of either atomoxetine (n=81) or placebo (n=82), with mean time to relapse being 160 days for atomoxetine and 130.8 for placebo, $P<0.008$. Relapse rates were 2.5% for atomoxetine and 2% for placebo and the relative risk for relapse during placebo treatment was 5.6 (95% CI, 1.2 to 25.6).[145]

***Atomoxetine: Effectiveness outcomes.*** A few noncomparative observational studies evaluated duration of effectiveness for atomoxetine.[146, 147] In 1 study, 229 children who had a ≥40% reduction in ADHD rating scale total score after a 7- to 9-week trial of atomoxetine (51% of original sample) were randomly assigned to continue treatment for 8 months at the same or lower dosages.[146] In the other study, stability of treatment response over time was examined in 312 children who had completed 24 months of open treatment with atomoxetine (34% of original sample).[147] Both studies were consistent in finding that improvements in ADHD symptoms and in aspects of health-related quality of life were maintained during longer-term treatment periods, even with reduced dosages of atomoxetine. Although encouraging, findings from these studies must be interpreted with caution, mainly due to the extremely high attrition rates.

In a pooled analysis of data from 714 children who received atomoxetine for at least 3 years in open-label studies, 1.7% of children and 2% of adolescents discontinued due to adverse events indicating high rates of persistence in both age groups.[148]

### *Clonidine*

***Immediate-release clonidine compared with methylphenidate.*** Four parallel group randomized controlled trials of immediate-release clonidine compared with immediate-release methylphenidate were found.[149-152] 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.[150, 152] 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 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.[151] 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 8). 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.

**Table 8. Summary of differences in results of ADHD/Tourette's disorder study**

| | Immediate-release clonidine vs. placebo | Immediate-release methylphenidate vs. placebo |
|---|---|---|
| ***ADHD symptoms*** | | |
| **IOWA Total score** | No Difference | Drug Found Significantly Better |
| **IOWA OD** | No Difference | No Difference |
| **Classroom Observation: On Task** | No Difference | Drug Found Significantly Better |
| **Conners' CPT Attentiveness** | No Difference | No Difference |
| **Conners' CPT Risk Taking** | No Difference | No Difference |
| ***Tourette' s symptoms*** | | |
| **YGTSS Motor** | Drug Found Significantly Better | No Difference |
| **YGTSS Vocal** | Drug Found Significantly Better | No Difference |
| **GTRS Teacher** | No Difference | No Difference |

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.[149] 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 9 below. Using the 2x 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 the 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, but it may be that clonidine has a lesser effect.

**Table 9. 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

***Clonidine compared with placebo.*** Two placebo-controlled trials were not helpful in examining the comparative effectiveness of immediate-release clonidine. A small randomized placebo-controlled crossover trial was rated poor quality.[153, 154] The other[155] did not report clear eligibility criteria but it appears that the children had to have a diagnosis of ADHD and Tourette's disorder based on DSM-IIIR. Outcomes were assessed using primarily Child Behavior Checklists for parents and teachers, and linear analogue scales of parent assessments of hyperactivity and tics, as compared with any time in the past. Based on the linear analogue assessments, clonidine was not significantly different to placebo. The assessment of tics, based on 4 scales, did not show a difference between placebo and clonidine. Multiple subgroup analyses of the checklists resulted in clonidine being superior to placebo on some subscale items. A poor quality systematic review

included 11 studies of varying design. These studies did not meet inclusion criteria for this review, and were inappropriately pooled regardless of their varying study designs. [156]

***Clonidine ER compared with placebo.*** Two studies of extended-release clonidine have been published to date, with additional completed studies not published to date according to ClinicalTrials.gov.[157, 158] The trials enrolled children with the hyperactive or combined subtype of ADHD with less than adequate response (ADHD-RS-IV scale score $\geq$ 26 out of 54) to a stable dose of stimulant, and used the ADHD-RS-IV scale assessed by investigators as the primary outcome measure. Parent measurements on the Conners' Parent Rating Scale and the Parent Global Assessment were secondary outcomes.

In a fair-quality trial of 198 children randomized to flexible dose clonidine ER (0.1 to 0.4 mg daily) or placebo in addition to their stimulant, after 5 weeks children on clonidine ER had more improvement in their ADHD-RS-IV scores than those on placebo (–15.7 compared with –11.5; $P$=0.009), although the absolute difference was very small.[158] Parent assessments found the group with clonidine XR to have better improvement in the Conners' Parent Rating scale (–40.2 and –27.1; $P$=0.017) and better final Global Assessment scores (2.7 and 3.4; $P$=0.001) compared with the placebo group. Subgroup analysis by specific stimulants failed to show statistical significant benefits, most likely due to inadequate sample sizes (Type II error).

In a fair-quality fixed-dose trial of 236 children, monotherapy clonidine ER 0.2 or 0.4 mg, given in 2 divided doses, resulted in greater improvement in ADHD-RS-IV scores at 5 weeks compared with placebo (–15.6, –16.5, and –7.5 respectively; $P$<0.0001 for each compared with placebo) with little difference between doses.[157] Week by week analysis indicated that the difference between drug (ether dose) and placebo started at week 2. Parent assessment using the Conners' rating scale and the Parent Global Assessment also indicated a significant difference between changes in score at either dose compared with placebo, but actual scores were not reported.

### *Guanfacine*

***Immediate-release guanfacine compared with placebo.*** A small study of 24 children with ADHD, all of the mixed type, and a tic disorder studied the effects of immediate-release guanfacine compared with placebo for 8 weeks.[159] Slightly more than half of enrolled children had Tourette's disorder (58.8%), and 35% had chronic motor tic disorder. Teachers and investigators rated immediate-release guanfacine superior to placebo, while parent ratings did not. Teacher ratings resulted in a 37% decrease on the ADHD Rating Scale at 8 weeks, compared with an 8% drop with placebo group ($P$<0.001) while parent ratings showed a 27% improvement with immediate-release guanfacine and 21% with placebo.

***Guanfacine XR compared with placebo.*** Four fair-quality placebo-controlled trials 8-9 weeks in duration of 1341 children have been published with guanfacine XR. Two were monotherapy dose-ranging studies of 1 to 4 mg daily, included in the initial US Food and Drug Administration documents reviewed, [160-162] and another monotherapy study included only children aged 6-12 years with comorbid oppositional symptoms using a flexible dose of 1 to 4 mg daily.[163] The fourth study assessing guanfacine XR as adjunctive therapy to stimulants was subsequently submitted to the US Food and Drug Administration.[164] Baseline mean ADHD-RS-IV scores (test results in score ranging from 0 to 54) were 37, 40, 37, and 42, respectively.

In the dose-ranging studies, the placebo-adjusted change from baseline to endpoint in the ADHD-RS-IV score (primary outcome) was statistically significantly greater than placebo for all doses, although the absolute difference in score was not large (least squares mean difference –5.41 to –9.99). In both studies the largest difference in score change was with the 4 mg daily dose (–9.99 and –7.88).[160-162] For 2, 3, and 4 mg daily doses the difference compared with placebo was statistically significant starting at week 2. Revised Conners' Parent and Conners' Teacher Rating Scales also showed guanfacine XR superior to placebo in mean change from baseline to endpoint scores. Assessment of the duration of effect using these measures throughout the day showed all doses to have effect through 8 hours, but variable effects by dose and study at 12, 14, and 24 hours. Post-hoc analysis of weight-based dosing and outcome indicated a greater response with 0.09- 0.12 mg/kg and 0.13-0.17 mg/kg compared with lower doses, but differentiating between these dosing ranges is not possible from these data.

A study of 217 children aged 6-12 years with comorbid ADHD and oppositional symptoms using flexible dosing (1-4 mg daily) over 8 weeks found that the mean least squares mean change on the ADHD-RS-IV scale was –23.8 in the drug group and –11.5 in the placebo group ($P<0.001$ from a baseline of 42 in both groups).[163] The subscale scores on the CPRS-RS-L oppositional defiant subscale also improved more with guanfacine XR (–10.9 compared with –6.8; $P<0.001$) and the change in the 2 scores was found to be highly correlated (r=0.74). Slightly more patients were taking 3 mg daily, and only a few took 1 mg daily.

As adjunctive therapy to stimulant therapy with suboptimal response (ADHD-RS-IV $\geq$ 24 and CGI-S $\geq$ 3 after at least 4 weeks treatment), guanfacine XR (given at night or in the morning) was found superior to placebo on the ADHD-RS-IV scale, least squares mean difference in Total score of –4.5 ($P=0.02$) for morning dosing and –5.3 ($P=0.001$) for evening dosing compared with placebo.[164] Following dose-optimization, a mean dose of 0.09 mg/kg was reached in both drug groups (median doses were 3 mg daily in the evening group and 3 mg daily in the morning group). As a secondary outcome measure, response (defined as reduction of ADHD-RS-IV Total score of $\geq$ 25% from baseline), the evening dosing of guanfacine XR was superior to placebo (83.1% vs. 69.7%; $P=0.007$), while the morning dosing was not statistically different to placebo ($P=0.062$). Multiple subgroup and secondary analyses were conducted but are not presented here because they are comparisons to placebo.

### Functional outcomes: Immediate-release methylphenidate

We found extremely limited information on functional capacity outcomes from the clinical trials. Therefore, we included observational studies of $\geq$6 month's duration that reported outcomes reflecting functional capacity, for example academic achievement in terms of progression through grades, suicide attempts, police contacts, etc. We found 2 studies that reported these outcomes among adult patients who had been treated as children.[86, 165-168] Due to various methodological limitations, these studies do not provide good evidence for long-term effectiveness, even for methylphenidate.

In a cross-sectional follow-up study of young men diagnosed with "persistent hyperactivity" at ages 6 to 12 years, those who had not received medication were compared with a group that had received methylphenidate for at least 3 years during childhood.[167] The groups were initially seen in different time-periods, separated by 5 to 15 years. Because the groups were from different periods, a third group of normal children who were contemporaneous to the methylphenidate group was added. The sizes of the groups also differed, with 64 in the non-treated hyperactive group, 20 in the methylphenidate treated group, and 20 in the normal

controls, and data were not available for all subjects on all questions. Mean follow-up of the hyperactive groups was 10 to 12 years. No information on baseline characteristics from childhood was given. No consistent differences in functional outcomes were found between the methylphenidate and untreated groups (Table 10). Considering the potential confounding of differences in the years the children were treated, and the very small numbers of subjects per group per variable, these results should be interpreted with caution.

**Table 10. Long-term functional outcomes of methylphenidate from Hechtman, 1984[167]**

| Variable | Favors | MPH group | Nontreated | *P* value |
|---|---|---|---|---|
| Age at follow-up | NA | 22 years | 20 years | <0.01 |
| Living with girlfriend/wife (n) | MPH | 8 | 5 | <0.01 |
| Duration last job held | Nontreated | 21 weeks | 70 weeks | <0.001 |
| Aggression | Untreated | | | <0.06 |
| Current psychiatric treatment (n) | MPH | 1 | 22 | <0.02 |
| Age starting alcohol use | Nontreated | 14.8 years | 16.2 years | <0.03 |
| Duration of alcohol use | Nontreated | 25 months | 10.8 months | <0.05 |
| Abuse/addiction to alcohol (n) | MPH | 13 | 26 | <0.05 |
| Age at first cocaine use | MPH | 20 years | 18.9 years | <0.02 |
| Age stopping cocaine use | Nontreated | 22 years | 18.9 years | <0.001 |

Abbreviations: MPH, Methylphenidate; NA, not applicable.

The methylphenidate group in this study was previously reported after 5 years of follow-up (as adolescents), with comparison groups of boys treated with chlorpromazine or untreated boys.[165] This study reported academic performance, with no differences found between the groups.

### *Adolescents (ages 13 to 17)*

Evidence on the effectiveness of pharmacotherapy for ADHD in adolescents was very limited (Evidence Tables 1 and 2). We did not find any effectiveness trials or long-term observational studies (assessing functional or safety outcomes) in adolescents with ADHD. Adolescents were studied in 1 head-to-head trial of immediate-release methylphenidate and methylphenidate SR (OROS)[169] and in 9 placebo-controlled trials of methylphenidate.[170-179] Mixed-age populations including adolescents were studied in efficacy trials of atomoxetine, however data were not stratified by school age and adolescents so are considered in the school-age children section (above).

#### Direct comparisons

***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.[169] 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.[180] 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.

### Indirect comparisons

***Mixed amphetamine salts XR.*** A 4-week, placebo-controlled study of extended-release mixed amphetamine salts (Adderall XR®) using a forced-dose titration schedule (up to 40 mg once daily) assessed efficacy in 287 patients using the ADHD rating scale IV and Clinical Global Impression-Improvement Scale scores. All doses of extended-release mixed amphetamine salts were associated with significant improvement in ADHD rating scale IV scores compared with placebo. Mean change in ADHD rating scale IV score from baseline was –17.8 for active treatment (all doses) and –9.4 for placebo ($P<0.001$ for all doses except 10 mg dose, for which $P<0.005$) with significant score improvement for all doses of extended-release mixed amphetamine salts ($P\leq0.005$). Based on Clinical Global Impression-Improvement Scale scores, the proportion of patients who were improved following treatment with extended-release mixed amphetamine salts (range 51.9% to 70.7%, dose dependent) was significantly higher than placebo (mean difference, 26.9%; $P\leq0.01$).

***Methylphenidate OROS.*** One trial compared the efficacy of methylphenidate OROS to placebo in adolescents. Of 220 enrolled subjects, 177 were randomized to a 2-week double-blind phase following an open-label titration phase lasting up to 4 weeks.[181] The primary outcome of this trial was change from baseline in ADHD rating scale score, although the Conner-Wells Adolescent Self-report of Symptoms Scale and the Child Conflict Index were also used to assess efficacy. There was a significantly higher mean change in investigator-assessed ADHD rating scale scores

with methylphenidate OROS compared with placebo (–14.93 compared with –9.58; *P*=0.001). Parent-assessed scores were similar, and also favored methylphenidate OROS over placebo (*P*=0.008), as did Conner-Wells Adolescent Self-Report of Symptoms Scale scores (*P*=0.001) and Child Conflict Index scores (*P*=0.005).

***Immediate-release methylphenidate.*** Seven placebo-controlled crossover trials of immediate-release methylphenidate enrolled a total of 171 adolescents.[170-178, 182, 183] Patients were diagnosed primarily using the DSM III-R or DSM-IV criteria. Only 1 trial clearly described the distributions of the different ADHD subtypes and in this trial there were 87.5% of patients with the Combined subtype.[183] Immediate-release methylphenidate generally was superior to placebo in improving core ADHD symptoms, but was associated with greater frequency of appetite and sleep problems. Methylphenidate mean dosages ranged from 8.8[170] to 75 mg.[175] The trials reported a variety of outcome measures. All but 1 were consistent in using various forms of the highly valid Conners' rating scales (long and abbreviated forms).[183] However, inconsistency in the way results are reported make estimation of an overall magnitude of effect impossible.

***Lisdexamfetamine.*** In a large study of 314 adolescents, lisdexamfetamine was superior to placebo after 4 weeks based on the ADHD-RS-IV scale at 30, 50, and 70 mg daily but with no meaningful differences between doses (mean change –18.5, –21.1, –20.7l, respectively, compared with –12.8; *P*=0.0056).[184] Quality of life was not different among groups based on the Youth QOL- Research Version scale.

***Atomoxetine.*** In a pooled analysis of data on 601 children aged 12 to 16 from 6 placebo-controlled trials (short term) and 7 open-label extension studies (up to 2 years in duration) of atomoxetine were analyzed.[185] Data out to 24 months treatment was available for 217 adolescents (36%). Overall, the combined analysis showed an improvement of 20 .2 points (*P*<0.001 compared with baseline) on the ADHD rating scale. Improvements reached their peak at 6 months, and improvements were maintained out to 24 months. The mean dose also peaked at 6 months (1.47 mg/kg/day). These data reflect highly selected patients, with those tolerating atomoxetine out to 2 years only.

## Functional outcomes: Immediate-release methylphenidate

We found extremely limited information on functional capacity outcomes from the clinical trials. Therefore, we included observational studies of ≥6 month's duration that reported outcomes that reflect functional capacity, for example academic achievement in terms of progression through grades, suicide attempts, police contacts, etc. We found only 2 studies reporting outcomes in adolescents. In an uncontrolled study, a simple follow-up of 16 of 27 (59%) adolescents who had responded to methylphenidate in an uncontrolled study,[168] after 6 to 14 months of follow-up the authors simply report that 15 of the 16 had "improved grades".

In a study using interviews and data from patient charts, 97 young adult males who had taken methylphenidate as children and teens (mean age at discontinuation of methylphenidate was 17 years) were studied.[166] There was no comparison group in this descriptive study. The authors conducted a hierarchical analysis to assess the effect of various factors. Significant findings relating to use of methylphenidate were fewer suicide attempts positively associated with higher dose of methylphenidate, and emancipated living situation and level of relationship

commitment were positively associated with response to methylphenidate. Early response to methylphenidate was negatively associated with high school graduation, however.

### *Adults*

#### Direct evidence

*Methylphenidate OROS compared with immediate-release methylphenidate*
In a fair-quality, single-blind trial of 53 adults, there was no significant difference in maintenance of response (much or very much improved on the Clinical Global Impression Scale-I) 6 weeks after switching from stable treatment with immediate-release methylphenidate administered 3 times daily to methylphenidate OROS compared with remaining on immediate-release methylphenidate 3 times daily (63% compared with 58%; *P*=0.8).[186] The similarity in efficacy was maintained in spite of the significantly greater average number of missed doses over the 6-week study with the immediate-release formulation of methylphenidate 3 times daily (7.3 compared with 3.3; *P*=0.02). Mean dosage was not reported, but was not to exceed 1.3 mg/kg/day or 144 mg/day total. Results of this trial are primarily applicable to patients who have been receiving a stable dose of immediate-release methylphenidate for at least 4 weeks and who have achieved a good clinical response, have good tolerability, and are satisfied with their treatment experience.

*Immediate-release guanfacine compared with immediate-release dextroamphetamine*
In a very small, 2-week, fair-quality, crossover trial of 17 adults, there was no significant difference between immediate-release guanfacine and immediate-release dextroamphetamine in the DSM-IV ADHD Behavior Checklist for Adults mean total symptom score at endpoint.(23.3 points compared with 24.2 points).[187] The average dose was 1.10 mg for immediate-release guanfacine and 10.2 mg for immediate-release dextroamphetamine. However, these results should be interpreted with caution as these drugs were administered only once daily in the morning and the small sample size may have lacked adequate statistical power to detect a significant difference. Baseline total symptom scores were not reported, preventing calculation of mean change, and response rate was also not reported.

*Modafinil compared with immediate-release dextroamphetamine*
In a fair-quality, crossover trial of 22 adults, identical proportions responded to 2 weeks of treatment with modafinil 206.8 mg and immediate-release dextroamphetamine 21.8 mg (48% compared with 48%; *P*=NS).[188] Response was defined as a 30% or greater mean improvement in ADHD Rating Scale total scores. Patients in this trial were mostly male (59%) and had a mean age of 40.8 years.[188]

#### Indirect evidence

*Atomoxetine*
We included 10 placebo-controlled trials of atomoxetine (N=2493).[189-197] Two trials focused on subgroups of patients with either marijuana dependency[197] or comorbid social anxiety[196] and will be discussed under Key Question 3. All of the remaining trials were rated fair quality and ranged in duration from 3 weeks to 6 months. Mean age ranged from 34 years to 41 years and proportions of male patients ranged from 44% to 64%.

***Response.*** Response rate was only reported in 3 trials[192, 193, 195] and was significantly greater for atomoxetine in 2 of them.[192, 195] The 2 trials that found significantly greater response rates for atomoxetine differed in duration and definition of response. In the shorter-term trial, 21 adults (48% male, mean age of 34 years) were randomized to tomoxetine 40 mg twice daily or placebo for 3 weeks of treatment and response was defined as at least a 30% reduction in the ADHD Rating Scale score.[192] Response rate was 52% for tomoxetine and 10% for placebo ($P<0.01$).[192] The longer-term trial randomized 510 adults (48% male, mean age of 41 years) to 24 weeks of treatment with atomoxetine, at a mean dose of 90.3 mg given once daily, or placebo and response was measured using the Conners' Adult ADHD Rating Scale, Self-Report Screening Version .[195] Response rates were significantly greater with atomoxetine, both when defined as at least a 25% decrease from baseline (68% compared with 42%, $P<0.001$) and when defined as at least a 40% decrease from baseline (47% compared with 28%, $P<0.001$).

The trial that did not find a significant difference in response between atomoxetine 40-80 mg (mean dosage not reported) and placebo had the smallest sample size (N=16) and was comprised of somewhat younger patients (mean age of 22.4 years), more of which who were male (87%).[193] Response was defined as at least a 30% reduction in the ADHD Rating Scale score and no significant difference was found between atomoxetine and placebo (40% compared with 25%, $P$=not significant).

***Other ADHD symptom outcomes.*** In the other trials,[189-191] ADHD symptoms were measured based on mean change from baseline on either the Conners' Adult ADHD Rating Scale, Self-Report Screening Version or the ADHD-RS. Improvements in self-ratings were significantly greater for atomoxetine in all 4 trials. Improvements based on investigator or other ratings were significantly for atomoxetine in 3 of 4 trials.[190, 191]

***Quality of life.*** We identified 1 placebo-controlled trial that examined the effects of atomoxetine on quality of life in adults.[189] A 6-month trial of atomoxetine compared with placebo (N=410; mean age, 36.5; 60% male; 82% Caucasian), dose flexible from 40 mg to 100 mg daily based on tolerability, found no difference in change from baseline between treatment groups in relationships, psychological health, productivity, and work productivity.

***Driving performance.*** The majority of evidence from 3 placebo-controlled trials found that atomoxetine was not significantly superior to placebo in improving driving outcomes. One large trial and 2 smaller trials assessed simulator driving performance among subjects taking atomoxetine compared with placebo. A 24-week trial of 410 subjects (mean age 36.5; 60% male) of atomoxetine (dose flexible from 40 mg to 100 mg daily based on tolerability) compared with placebo[189] found no differences in self report of the Driving Behavior Survey between treatment groups. Driving behavior was rated as significantly more improved for the atomoxetine group compared with the placebo group in a subsample of 252 of 410 patients for which observer ratings were available (mean improvement 6.1 compared with 2.0; $P=0.01$). A smaller, 3-week trial of twenty subjects (mean age 36; 44% male) comparing atomoxetine (titrated up to 1.2 mg/kg for 3 weeks) to placebo[190] reported mixed results. Self-ratings, but not other-ratings (such as friends or spouse) or examiner-ratings, were significantly greater for atomoxetine on the Safe Driving Behavior Scale and on simulator driving performance. Finally, a small 3-week trial of young adults (ages 19-25) found that atomoxetine (titrated up to 80 mg daily) was not statistically different than placebo in mean total driving score.[193]

### *Immediate-release dextroamphetamine*

The percentage of participants rated as treatment responders was significantly greater for immediate-release dextroamphetamine in both of 2 fair-quality trials.[198, 199] The first trial randomized 51 adults (53% male, mean age of 35.5 years) to 6 weeks of immediate-release dextroamphetamine (mean dose 23.8 mg) or placebo. The percentage of patients in the immediate-release dextroamphetamine group who were much improved or very much improved on the Global Improvement Scale was 58% ($P<0.001$) whereas in the placebo group, 90% of patients were rated as unchanged or minimally worse and no patients were very much improved.[199] In the second trial, 98 adults (64% male, mean age of 37.5 years) were randomly assigned to psychotherapy plus a maximum dosage of immediate-release dextroamphetamine 20 mg twice daily (average dosage not reported), paroxetine, both or placebo for 20 weeks. Response was defined as much or very much improved on the Clinical Global Impressions-Improvement Scale for ADHD and rates were 64% for immediate-release dextroamphetamine and 16% for placebo (*P* not reported).[198]

### *Extended-release dexmethylphenidate*

We included 1 fair-quality trial of extended-release dexmethylphenidate.[200] Compared with placebo (34%), after 5 weeks, treatment response was significantly greater for extended-release dexmethylphenidate 20 mg (58%, $P=0.017$) and 40 mg (61%, $P=0.007$), but not with the 30 mg dosage (54%, $P=0.054$).[200] This trial randomized 221 adults (57% male, mean age of 38.7 years) and treatment response was defined as a 30% or greater improvement on the DSM-IV ADHD-RS Total Score. The comparison between extended-release dexmethylphenidate and placebo was not influenced by gender, age or ADHD subtype. There was no significant difference between any dose of extended-release dexmethylphenidate and placebo in quality of life as measured by the patient-rated Quality of Life Enjoyment and Satisfaction Questionnaire.

### *Lisdexamfetamine*

We included 1 fair-quality trial[201] and 1 poor-quality trial of lisdexamfetamine.[202, 203] The more recent trial of lisdexamfetamine used a crossover design and was rated poor quality due to a failure to meet a *combination* of criteria which may be related in indicating the presence of bias, including incomplete outcome data, as well as the inadequate reporting of the allocation concealment method and comparability of baseline patient characteristics based on order of randomization.[202] In the fair-quality trial, post-hoc analysis found that, compared with placebo (34%), treatment response at endpoint (≥ 30% reduction in ADHD-RS Total Score, estimated from Figure 3) was significantly greater for lisdexamfetamine 30 mg (60%; $P<0.001$), 50 mg (64%, $P<0.0001$), and 70 mg (65%; $P<0.0001$).[201] This trial randomized 420 adults for 4 weeks of treatment. The mean age was 35.1 years, 54% were men, and 82% were White.

### *Mixed amphetamine salts immediate-release*

We included 1 fair-quality, crossover trial that compared 3 weeks of treatment with mixed amphetamine salts immediate-release 54 mg to placebo in 30 adults (50% male, mean age of 38 years).[204] Compared to placebo, significantly more patients taking mixed amphetamine salts immediate-release achieved clinical improvement, both when defined as more than a 30% reduction on the ADHD Rating Scale (70% compared with 7%, $P<0.001$) and when defined as much or very much improved on the Clinical Global Improvement Scale (67% compared with 4%, $P<0.001$).

### *Mixed amphetamine salts extended-release*

We included 2 fair-quality trials of mixed amphetamine salts extended-release.[193, 205] Compared with placebo, the proportion of adults with at least a 30% reduction in the ADHD Rating Scale total score was significantly greater with mixed amphetamine salts extended-release in 1 of 2 trials.[193] The first trial randomized 255 adults to 4 weeks of mixed amphetamine salts extended-release 20 mg, 40 mg, 60 mg, or placebo.[205] Mean age ranged from 39 years to 40 years and proportion of males ranged from 48% to 68%. Proportion of responders was only analyzed for the subgroup of completers (72%) and reported as "substantially higher" for mixed amphetamine salts extended-release 20 mg (74%), 40 mg (80%) and 60 mg (82%) compared with placebo (61%), but the *P* values were not reported.

The second trial used a crossover design to compare 3 weeks each of mixed amphetamine salts extended-release 50 mg to placebo in 19 young adults (mean age of 22 years, 89% male).[193] It was primarily designed to assess simulated driving changes, but also reported that there was a significantly greater proportion of responders with mixed amphetamine salts extended-release compared with placebo (80% compared with 13%; $P=0.0004$). Improvement in driving ability was measured based on lowering of the numerical overall Driving Safety Score, which reflects the mean of z-scores from each of 8 simulator-derived variables including total citations, total collisions, time to collision, driving out-of-lane incidents, percentage of time above excessive speed threshold, number of times overcornering, number of times tailgating, and response to crash-likely events. Greater improvements in overall simulated driving performances were found for mixed amphetamine salts extended release than for placebo both at 7-hours post dose (–0.31 compared with +0.33; $P=0.013$) and at 12-hours post dose (–0.29 compared with +0.31; $P=0.005$).[193]

### *Immediate-release methylphenidate*

We included 17 placebo-controlled trials of immediate-release methylphenidate (N=593).[206-222] We rated 1 trial poor quality[216] and the rest were rated fair quality. The majority of trials enrolled small samples of adults (N<50), used crossover designs, and were very short-term (≤ 3 weeks). The longest trial involved 12 weeks of treatment, but focused only on a subgroup of men who were cocaine dependent.[215] Overall, in trials of methylphenidate immediate-release, mean age ranged from 22 years to 42 years and the proportion of males ranged from 40% to 100%. Along with the trial of cocaine dependent men, another trial focused only on a subgroup of patients with substance abuse disorders[208] and results from both trials will be discussed in Key Question 3. Additionally, results of placebo-controlled trials relating to effects on pre-existing anxiety will be discussed in Key Question 3 as comorbidity.

***Response.*** Only 3 fair-quality trials of average adults with ADHD reported response (N=98)[212, 213, 217] and rates were significantly greater for immediate-release methylphenidate compared with placebo in 2 of them.[212, 217] In all 3 trials, mean dosages were right around 0.9 mg/kg. In the first trial of 23 adults (43% male), response was defined as at least a 30% reduction in the ADHD Rating Scale plus a Clinical Global Impression score of 2 or less (much or very much improved) and 3-week rates were 78% for immediate-release methylphenidate and 4% for placebo ($P<0.0001$).[217] In the second trial of 30 adults, with a higher proportion of males (73%), response was defined as a Clinical Global Impression score of 2 or less, but 7-week rates were not significantly difference for immediate-release methylphenidate and placebo (50% compared with 27%).[213] Finally, in the third trial of 45 adults, response was defined as at least a 30%

reduction in the ADHD Rating Scale and 3-week rates were 42% for immediate-release methylphenidate and 13% for placebo ($P$=0.011).[212]

***Driving.*** Immediate-release methylphenidate was also 1 of 3 drugs with data available regarding driving behavior. Driving performance was assessed in 3 small single-dose, placebo-controlled trials.[206, 209, 220] A recent placebo-controlled crossover study of 18 ADHD patients (mean age 38, male 61%) performed on a primary highway during normal traffic assessed a single mean dose of 14.7 mg methylphenidate.[220] In order to test the primary outcome measure, a camera was mounted on the roof of the test vehicle to measure the amount of weaving of the car (standard deviation of lateral position). Drivers were instructed to drive with a steady lateral position while maintaining a constant speed of 95 km/hr (60 mph). The study found that amount of weaving was significantly less with immediate-release methylphenidate (18.8 cm) compared with placebo (21.1 cm; $P$=0.004). Self-reports on various measures of driving quality and driving style were also superior for methylphenidate relative to placebo. However, the study also found that mean lateral position, standard deviation of speed (km/h), and mean speed were not significantly different between the 2 groups.[220] Two additional studies have examined simulator driving performance trials. Results found that immediate-release methylphenidate 10 mg significantly improved an Impaired Driving Score ($P$=0.05),[209] immediate-release methylphenidate 40 mg significantly reduced steering variability,[206] and immediate-release methylphenidate 20 mg significantly improved appropriate use of turn signals.[206] Although promising, results from driving methylphenidate performance trials should be considered preliminary and would be strengthened by further confirmation based on assessment of effects in patients driving their own vehicles in every-day traffic settings, across multiple occasions.

### *Methylphenidate extended-release*

We included 1 fair-quality trial that compared 24 weeks of treatment with methylphenidate extended-release 41.3 mg to placebo in 363 adults (50% male, mean age of 34 years).[223] Compared with placebo, when defined as 30% reduction of psychopathology by the Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS), significantly more patients taking methylphenidate extended-release achieved treatment response (61% compared with 41%, $P$=0.001). The difference between methylphenidate extended-release and placebo in treatment response was not statistically significant when defined as much or very much on the Clinical Global Impression scale (55% compared with 37%; $P$ not reported).

### *Methylphenidate OROS*

We included 7 placebo-controlled trials of methylphenidate OROS, which randomized a total of 1316 adults.[224-230] One trial was rated good quality,[229] 1 was rated poor quality,[224] and the rest were rated fair quality. Treatment duration ranged from 2 weeks to 11 weeks. Dosage regimen was flexible in all but 1 trial, with mean levels ranging from 68 mg to 84 mg. In the remaining trial, adults were randomized to fixed dosages of 18 mg, 36 mg, or 72 mg.[226] Mean age ranged from 31 years to 40 years. One trial only enrolled mother-child dyads in which both were diagnosed with ADHD.[225] Otherwise, the proportion of males ranged from 54% to 66%.

Response rates were reported in all 6 fair-to-good quality trials (Table 11). Regardless of the heterogenous definitions, response rates were generally significantly greater in the methylphenidate OROS groups compared with the placebo groups.

## Table 11. Response rates in placebo-controlled trials of methylphenidate OROS

| Author<br>Year<br>Sample size | Weeks | Response rates |
|---|---|---|
| Chronis-Tuscano<br>2008[225]<br>N=23 | 2 | CAARS-S-SV: T-scores below 65: 67% vs.26%; *P*=NR |
| Reimherr<br>2007[228]<br>N=47 | 4 | ≥ 50% WRAADDS improvement: 49% vs.15%; *P*=0.007 |
| Medori<br>2008[226]<br>N=401 | 5 | ≥ 50% WRAADDS improvement: 18 mg=22% vs. 36 mg=25% vs.75 mg=31%, vs. placebo=14%; *P*<0.01 |
| Biederman<br>2010[230]<br>N=223 | 6 | ≥ 30% improvement on AISRS AND CGI-I score of 1 or 2: 62% vs.37%; *P*<0.001 |
| Adler<br>2009[227]<br>N=226 | 7 | ≥ 30% improvement on AISRS AND CGI-I score of 1 or 2: 37% vs.21%; *P*<0.009 |
| Winhusen<br>2010[229]<br>N=255 | 11 | ≥ 30% improvement on ADHD-RS Total AND ≥ 1 point reduction in CGI-S: 71% vs.44%; *P*<0.001 |

Abbreviations: AISRS, ADHD Investigator Symptom Report Scale; ADHD-RS, ADHD Ratings Scale; CAARS-S:SV, Conners' Adult ADHD Rating Scale, Self-Report Screening Version; CGI-I, Clinical Global Impression-Improvement; CGI-S, Clinical Global Impression-Severity; NR, not reported; WRAADDS, Wender-Reimherr Adult Attention Deficit Disorder Scale.

In the trial that focused on ADHD mothers who had children with ADHD, parenting skills were also measured using the 42-item, validated Alabama Parenting Questionnaire based on mother self-report and collateral reports from individuals who lived with or were close to the mothers.[225] During Phase 1, all mothers were titrated on methylphenidate OROS over 5 weeks for identification of a maximally effective dose. During Phase 2, mothers were then randomized to 2 weeks of treatment with their maximally effective dose of methylphenidate OROS (mean dose 83.7 mg daily) or placebo. Compared with placebo, maximally effective doses of methylphenidate OROS were superior in decreasing the frequency with which mothers used corporal punishment methods and inconsistent discipline. Significant differences were not found between methylphenidate OROS and placebo in effects on involvement, positive parenting, or poor monitoring/supervision behaviors.

Additionally, in 1 of the trials, adults judged to be responders after the first 6 weeks were eligible for a double-blind, 24-week maintenance phase to assess relapse rates.[230] Among the 96 adults who entered the maintenance phase (42% of original group), there was no significant differences between methylphenidate OROS and placebo in the relapse rate, defined as a deterioration of at least 2 points on the Clinical Global Impression-Improvement Scale or decline of the ADHD Investigator Symptom Rating Scale to below a 15% improvement (18% compared with 18%).

### *Methylphenidate sustained-release*

We included 4 fair-quality trials of methylphenidate sustained-release.[231-234] Three of the trials focused on subgroups of adults who were methadone-maintained,[233] cocaine-dependent,[231] or amphetamine abusers,[234]and results from these will be discussed in Key Question 3.

The remaining trial compared 4 weeks of treatment with methylphenidate sustained-release 20 mg to nicotine, nicotine plus methylphenidate sustained-release, or placebo in 40 stimulant-naïve, nonsmoking adults (62.5% male, mean age of 37 years).[232] This trial did not report the proportions of adults who achieved a predefined level of clinical response. ADHD symptoms were assessed based on mean scores on the Clinical Global Impressions severity score and the group administered sustained-release methylphenidate alone did not demonstrate significantly greater improvement than those administered placebo. In fact, severity of ADHD symptoms was rated as somewhat higher in the group taking sustained-release methylphenidate alone.

### *Methylphenidate transdermal system*

We found one 4-week, randomized controlled crossover trial that evaluated the effect of methylphenidate transdermal system in 67 adults.[235] However, we rated this trial as poor quality due to an unacceptable level of attrition (22%) and inadequate reporting of methods of randomization and allocation concealment, comparability of baseline patient characteristics based on order of randomization, and numbers analyzed.

### *Modafinil*

The effects of modafinil on core ADHD symptoms in adults remain unknown. We only found 1 crossover trial that compared a single 200 mg dose of modafinil to placebo in 20 adults with ADHD.[236] However, this trial focused on cognitive outcomes and did not evaluate the efficacy of modafinil in treating ADHD symptoms.

## Key Question 2. Safety

### Key Question 2a. What is the comparative tolerability and safety of different pharmacologic treatments for attention deficit disorders?

#### *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.[30] 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.

The Preschool ADHD Treatment Study provides some limited evidence on the short-term safety of methylphenidate.[35, 237] Overall, 21/183 (11%) of Preschool ADHD Treatment Study patients taking methylphenidate withdrew due to adverse events, although there was no data on

withdrawals among placebo patients during the phases of the trial that included placebo arms. One serious adverse event, a suspected seizure, was potentially linked to methylphenidate use. No other drug-related serious adverse events were reported. Rates of moderate to severe adverse events ranged from 16% to 30% in methylphenidate groups and 16% to 21% in placebo groups. While numerous severe adverse events are listed in the Wigal publication, only overall rates are provided with no stratification according to intervention, nor is there any indication which adverse events were potentially associated with use of the active intervention.[237]

Parent-rated rates of several specific adverse events were significantly higher with methylphenidate use compared with placebo during the crossover titration phase of the study. These include 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 ($P \leq 0.01$). Data from the 10-month open-label phase of the study, in which all patients who had previously improved with active treatment received methylphenidate, showed that 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).

### Growth effects

An analysis of growth data from the Preschool ADHD Treatment Study found that ADHD patients (N=140; mean age 4.4 years) enrolled in the study were in general larger than average at baseline, based on Centers for Disease Control growth charts (73.1% for height; 79.7% for weight). Use of methylphenidate (mean 337 days) was associated with a reduction in growth rate based on a mixed-effect regression analysis, with a mean loss of –6.35 percentiles in height and –14.42 percentiles in weight. When completers (n=95; mean duration of exposure to methylphenidate, 401 days) were compared with non-completers (n=45; mean duration of exposure to methylphenidate, 202 days) the trend toward reduced growth rate remained. For height, completers had a mean loss of –7.53 percentiles, while non-completers had a mean loss of –3.84 percentiles, while for weight, completers had a mean loss of –13.18 percentiles and non completers had a loss of –17.19 percentile points. Subgroup analysis found that sex, initial height, and initial methylphenidate dose did not moderate the growth reductions. However, initial weight at screening was a significant predictor of greater weight loss during time on trial ($F_{1,137}$=7.89; $P$<0.06).

## *Short-term trial evidence in children (elementary school age; 6-12 years)*

Adverse events were reported in 17 head-to-head trials. The results are summarized in Table 12 below, full reporting of adverse event data can be found in Evidence Table 3.

### Direct evidence

#### *Stimulants*

Four of 6 trials of immediate-release dextroamphetamine compared with immediate-release methylphenidate reported no differences between the drugs in adverse events.[72, 73, 76, 77] 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.[79, 80] One of 3 trials of mixed amphetamine salts compared with immediate-release

methylphenidate found no difference in adverse event rates,[106] but 2 other studies found differences.[103, 104] 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,[103] and that mixed amphetamine salts given twice daily caused the highest rates of these adverse events.[104] 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.[121]

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.[41-43] 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.[109] 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®).[63] No differences in adverse events were found between multilayer-release methylphenidate (Biphentin®) and immediate-release methylphenidate in 2 studies.[53, 54]

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.[238]

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 analyses.[112] 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. [113]

### *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.[128,129, 131, 133] Rates of vomiting were 12% to 13% for atomoxetine, approximately 3 times greater than rates for immediate-release methylphenidate[133,134] or amphetamine salts XR.[129, 131, 133] Rates of somnolence ranged from 6% to 26% with atomoxetine, which was 3 to 4 times greater than rates with methylphenidate OROS[131, 133] and mixed amphetamine salts XR [129, 131, 133] and over 7 times greater than rates with immediate-release methylphenidate.[128,129] 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).[128,129, 131, 133] 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.[129]

***Immediate-release clonidine compare with methylphenidate.*** Two trials have compared clonidine to methylphenidate and reported adverse events.[151, 239] 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).[239] 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, the clonidine group gained 2 kg, while the immediate-release methylphenidate group gained 0.3 kg. 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.[151] 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.

## Indirect evidence

### *Dexmethylphenidate ER*

Rates of overall adverse events were comparable for dexmethylphenidate ER and placebo in the short-term trials, with rates of 16% to 28% with dexmethylphenidate ER compared with 16% to 22% with placebo in the 1-2 week trials.[68-70] The 7-week trial reported much higher, but similar, rates in both groups; 75.5% dexmethylphenidate ER compared with 57.4% placebo.[67] The most frequently reported adverse events were typical of stimulant products and were generally comparable between dexmethylphenidate ER and placebo. These included decreased appetite, anorexia, upper abdominal pain, fatigue, insomnia, headache, and nausea. The only occasion for which rates of a specific adverse event were statistically significantly higher in patients taking dexmethylphenidate ER compared with placebo was for decreased appetite in the 7-week trial (30.2% vs. 8.5%; *P*<0.0068).

### *Lisdexamfetamine dimesylate*

In the study of lisdexamfetamine and mixed amphetamine salts XR, the overall incidence of adverse events were similar.[117] With lisdexamfetamine, the most frequent were insomnia (8%) and decreased appetite (6%), while with mixed amphetamine salts XR the most frequent were upper abdominal pain (4%) and decreased appetite (4%). Significant differences were not found in our chi-square analysis.

In a dose-ranging study, overall adverse event rates were significantly greater (*P*≤0.05) for patients taking lisdexamfetamine 30 mg (71.8%), 50 mg (67.6%), or 70 mg (83.6%) compared with placebo (47.2%).[118] When compared with placebo, all dosages of lisdexamfetamine were associated with significantly greater rates (*P*≤0.05) of decreased appetite (39% compared with 4.2%), insomnia (18.8% compared with 2.8%), and irritability (9.6% compared with 0). Weight loss incidence was only greater for patients in the 70 mg group

compared with placebo (19.2% compared with 1.4%; $P \leq 0.05$). Withdrawals due to any of these adverse events only occurred in <1% of patients, however.[240]

### *Immediate-release methylphenidate*

In a small study (N=21) of children ages 6 to 12 with ADHD, sleep diaries were assessed over 7 days after receiving placebo, immediate-release methylphenidate 15 to 30 mg daily, or immediate-release methylphenidate 30 to 45 mg daily (divided into 3 daily doses) in a crossover study.[241] Based on an analysis of contrasts, there was no difference between the 2 dose levels, but medication periods caused statistically significant increased sleep onset latency (means of 41 and 44 minutes longer; $P<0.001$ for both compared with placebo). Similarly, total sleep time was shorter with either immediate-release methylphenidate dose compared with placebo (means of 51 and 60 minutes less with low and high doses compared with placebo). Other sleep outcomes (wake after sleep onset, sleep efficiency, activity, and time of lights out) did not differ between groups.

### *Clonidine ER*

Compared with placebo, overall rates of adverse events reported were similar between clonidine ER and placebo. Rate of discontinuation due to adverse event was greater in the fixed-dose study, with 19% in the 0.4 mg daily group, 7% in the 0.2 mg daily group, and 1% in the placebo group,[157] but similar among groups in the flexible dose study (3% placebo compared with 1% clonidine ER).[158] Across the 2 studies, somnolence and fatigue were the most common adverse events in the clonidine groups, and there was some evidence that the rate of adverse events peaked at 2 weeks in the clonidine groups.

### *Guanfacine XR*

Adverse events were reported more frequently with guanfacine XR, in a dose-dependent manner, in 2 of 3 studies compared with placebo.[160, 161, 163] The rate of adverse events in drug groups ranged from 74% with fixed dosing (1 to 4 mg daily) to 88.4% with 3 mg daily fixed dose. Discontinuations due to adverse events were also more frequent in a dose-dependent manner with extended-release guanfacine. The rates for 2, 3, and 4 mg daily were: 3%, 9%, and 14% in 1 study[161] and 10%, 15%, and 23% in the other [160] compared with 8% and 1% with placebo respectively. Flexible dosing resulted in a 10% discontinuation rate due to adverse events. The most common individual adverse events reported in the guanfacine XR groups were somnolence, fatigue, and headache.

## *Adolescents*

Placebo-controlled trials of immediate-release methylphenidate[170-179, 182, 242] provided limited evidence of short-term stimulant tolerability in adolescents. Immediate-release methylphenidate was associated with significant appetite and sleep disturbances across some, but not all placebo-controlled trials.[172, 173, 176, 179] Additionally, adolescents taking immediate-release methylphenidate frequently reported increases in dulled affect, social withdrawal, irritability, and stomachache in 2 placebo-controlled trials.[175, 179]

Trials of other stimulants provide no long-term evidence on safety. One 17-day study comparing methylphenidate OROS and mixed amphetamine salts reported a single adverse event – urinary difficulty – in a patient receiving methylphenidate OROS.[180] Another multi-phase,

placebo-controlled study of methylphenidate OROS reported no serious adverse events during the 2-week double-blind phase, although 1 serious adverse event (suicidal ideation) was reported during a run-in, open-label dose titration phase. Other adverse events commonly reported during the open-label dose titration phase were headache (25% of patients), decreased appetite (21%), insomnia (15%), and abdominal pain (9%). However, adverse event rates during the double-blind phase were similar for methylphenidate OROS and for placebo and the only withdrawal due to adverse events was reported in a placebo patient.[181] Results from a 4-week trial found that when compared with placebo, mixed amphetamine salts XR was associated with higher rates of anorexia/decreased appetite (35.6% compared with 1.9%), insomnia (12.0% compared with 3.7%), abdominal pain (10.7% compared with 1.9%), and weight loss (9.4% compared with 0%). Five patients taking mixed amphetamine salts XR withdrew from the study due to adverse events. No placebo patients discontinued due to adverse events and no serious adverse events were reported in either group.

In adolescents, lisdexamfetamine resulted in a higher rate of overall adverse events compared with placebo, with the highest rate associated with 70 mg daily (30 mg = 65%, 50 mg = 69%, 70 mg = 72%, and placebo = 58%).[184] Decreased appetite was the most frequent adverse event reported, at 34% for all lisdexamfetamine doses, compared with 2.6% with placebo. Insomnia was reported by 11% with lisdexamfetamine and 4% with placebo, with the highest rate again being in the 70 mg daily group (14%). Weight decrease was reported in a clearly dose-dependent manner (30 mg = 4%, 50 mg = 9%, 70 mg = 15%, and placebo = 0).

### *Adults*

#### Direct evidence

##### *Methylphenidate OROS compared with immediate-release methylphenidate*

Among 41 adults with good tolerability on immediate-release methylphenidate, the proportion with no adverse events dropped by 7% after switching to methylphenidate OROS. In contrast, the proportion with no adverse events increased by 25% among 12 adults who continued with immediate-release methylphenidate. The statistical significance of this difference is unclear, however, as analysis of the change was not presented and the study was limited by a small sample size and the presence of a between-groups imbalance at baseline in the proportion who started out with no adverse effects.[186]

##### *Immediate-release guanfacine compared with immediate-release dextroamphetamine*

The number of adverse events reported was similar in 17 adults after 2 weeks of once daily treatment with either immediate-release guanfacine 1.10 mg or immediate-release dextroamphetamine 10.2 mg (1.00 compared with 0.70, *P* not reported).[187] Muscle tension was the most common side effect with immediate-release dextroamphetamine (29%). Fatigue was the most common side effect with immediate-release guanfacine (23%). Withdrawals due to adverse events were not reported.

##### *Modafinil compared with immediate-release dextroamphetamine*

Modafinil and immediate-release dextroamphetamine were associated with similar rates of insomnia (38% compared with 19%, *P*=NS), muscle tension (24% compared with 19%; *P*=NS) and appetite suppression (24% compared with 19%, *P*=NS).[188] There were no withdrawals due to adverse events.

## Indirect evidence

### *Atomoxetine*

Adverse events were reported in all 8 placebo-controlled trials of atomoxetine of general samples of adults with ADHD (Table 12).[189-195] Withdrawals due to adverse events increased over time and were generally greater for atomoxetine than for placebo. Appetite disturbance was consistently significantly more common with atomoxetine than for placebo; whereas, the difference between atomoxetine and placebo was more variable with regard to insomnia.

**Table 12. Adverse events in placebo-controlled trials of atomoxetine**

| Author Year Sample size | Treatment regimen | Withdrawals due to adverse events | Appetite disturbance | Insomnia |
|---|---|---|---|---|
| Spencer 1998[192] N=22 | 76 mg x 3 weeks | 4% vs.0, *P*=NR | "Occurred significantly more often"; data NR | "Did not occur significantly more often"; data NR |
| Barkley 2007[190] N=18 | 1.2 mg/kg x 4 weeks | NR | NR | NR |
| Kay 2009[193] N=16 | 40-80 mg x 3 weeks | 0% vs.12%, *P*=NR | Anorexia: 13% vs.0, *P*=NR | 0 vs.6%, *P*=NR |
| Michelson 2003 #1[191] N=280 | 60-120 mg x 10 weeks | 8% vs.4%; *P*=NS | 12% vs.3%; *P*<0.001[a] | 21% vs.9%; *P*<0.001[a] |
| Michelson 2003 #2[191] N=256 | 60-120 mg x 10 weeks | 9% vs.2%; *P*=0.03 | | |
| Adler 2008[189] N=410 | 40-80 mg x 24 weeks | 14% vs.2%; *P*<0.001 | Significantly more; data NR | Significantly more; data NR |
| Adler 2009[194] N=510 | 84.5 mg QD x 24 weeks | 17% vs.6%; *P*<0.001 | 14% vs.3%; *P*<0.001 | 10% vs.9%; *P*=0.876 |
| Young 2011 N=501[195] | 90.3 mg QD x 24 weeks | 38% vs.22%; *P*=NR | 20% vs.4%; *P*<0.001 | 13% vs.6%; *P*=0.006 |

Abbreviations: NR, not reported; NS, not significant; QD, once daily.
[a] Data available only as pooled rates from both trials.

### *Immediate-release dextroamphetamine*

Some reporting of adverse events was available in both of 2 fair-quality trials.[198, 199] Between-group statistical comparisons were not reported in the 6-week trial of 51 adults, but rates were generally higher for immediate-release dextroamphetamine 23.8 mg than for placebo in withdrawals due to adverse events (4% compared with 0) and sleep disturbance (39% compared with 5%). In the second trial of 98 adults, after 20 weeks there was no significant difference between immediate-release dextroamphetamine 20 mg twice daily or placebo in withdrawals due to adverse events (13% compared with 8%), but rates of individual adverse events were not reported.[198]

### *Extended-release dexmethylphenidate*

We included 1 fair-quality, placebo-controlled trial of 5 weeks of treatment with extended-release dexmethylphenidate (N=221).[200] There was no significant difference between extended-release dexmethylphenidate and placebo in withdrawals due to adverse events (11% compared with 8%), decreased appetite (18% compared with 11%), or insomnia (16% compared with 11%).

### *Lisdexamfetamine*

We included 1 fair-quality trial[201] and 1 poor-quality trial of lisdexamfetamine.[202] In the fair-quality trial, rates of various common adverse events were reported for lisdexamfetamine and placebo, but statistical analysis of between-groups differences was not reported. For lisdexamfetamine 30 mg, 50 mg, 70 mg, and placebo, respectively, rates of withdrawals due to adverse events were 3%, 7%, 7%, and 2% and rates of decreased appetite were 29%, 28%, 23%, and 2%. Using data from this trial, analysis of numerous aspects of the impact lisdexamfetamine had on sleep quality was presented in a subsequent publication. It was unclear whether all the sleep analyses were prespecified. Although statistical analysis of between-group differences was not reported, the rates of treatment-emergent insomnia were numerically greater for all 3 doses of lisdexamfetamine compared with placebo and a dose-response may have been in effect (19% for 30 mg, 17% for 50 mg, and 21% for 70 mg compared with 5% for placebo).[243]

### *Mixed amphetamine salts immediate-release*

We included 1 fair-quality, crossover trial that compared 3 weeks of treatment with mixed amphetamine salts immediate-release 54 mg to placebo in 30 adults (50% male, mean age of 38 years).[204] Compared to placebo, there was a significantly greater proportion of patients taking mixed amphetamine salts immediate-release with a loss of appetite (30% compared with 11%; $P=0.03$), but not with insomnia (37% compared with 15%). Withdrawals due to adverse events were not reported.

### *Mixed amphetamine salts extended-release*

Both of 2 fair-quality included trials of mixed amphetamine salts extended-release reported rates of various common adverse events, but results of a statistical comparison to placebo were not reported.[193, 205] In the first 4-week trial (N=255), for mixed amphetamine salts extended-release 20 mg, 40 mg, 60 mg, and placebo, respectively, rates of adverse event withdrawals were 14%, 9%, 13%, and 2%; rates of anorexia were 20%, 42%, 38%, and 3%; and rates of insomnia were 21%, 30%, 26%, and 13%.[205] In the second 3-week trial of 19 young adults, for mixed amphetamine salts extended-release 50 mg and placebo, respectively, rates of adverse event withdrawals were 11% and 10%, rates of anorexia were 50% and 0%, and rates of insomnia were 19% and 0%.[193]

### *Immediate-release methylphenidate*

Adverse event report was extremely limited in trials of immediate-release methylphenidate. Withdrawals due to adverse events were only reported in 2 trials and rates for immediate-release methylphenidate and placebo, respectively, were 9% and 2% after 3 weeks (N=23; *P* not reported)[217] and 25% and 9% after 7 weeks (N=30, *P* not reported).[213] In the 2 trials that reported sleep difficulties, there were no significant differences between immediate-release methylphenidate and placebo at 2 weeks (mild trouble sleeping, 22% compared with 17%;

moderate trouble sleeping, 4% compared with 8%; severe trouble sleeping, 0% compared with 4%)[207] or at 3 weeks (sleeping problems, 33% compared with 22%).[212] In those same 2 trials, regarding appetite loss, the difference between immediate-release methylphenidate and placebo was not significant at 2 weeks (23% compared with 5%; N=38) but was significant at 3 weeks (22% compared with 4%; *P*=0.039; N=45).

A 3-week trial[244] examined sleep quality among 33 adults (97% combined ADHD subtype) with a mean age of 38 years. No differences were found in 5 of 6 assessments, although the immediate-release methylphenidate group experienced fewer nocturnal awakenings (0.82 compared with 0.99; *P*<0.01).

### *Methylphenidate extended-release*

We included 1 fair-quality trial that compared 24 weeks of treatment with methylphenidate extended-release 41.3 mg to placebo in 363 adults (50% male, mean age of 34 years).[223] Withdrawals due to adverse events (13% compared with 8%), decreased appetite (38% compared with 13%), and difficulties falling asleep (25% compared with 18%) were described as "more frequent" with methylphenidate extended-release compared with placebo, but *P* values were not provided.

### *Methylphenidate OROS*

Adverse events were reported in all 6 fair-to good-quality included placebo-controlled trials of methylphenidate OROS (Table 13).[225-230] However, statistical comparison of methylphenidate OROS and placebo was only undertaken in 3 trials.[228-230] In those trials, rates of decreased appetite were consistently significantly greater for methylphenidate OROS compared with placebo. Otherwise, for adverse event withdrawals and insomnia, differences between methylphenidate OROS and placebo did not consistently reach statistical significance.

**Table 13. Adverse events in placebo-controlled trials of methylphenidate OROS**

| Author Year | Weeks | Mean dose | Adverse event withdrawals | Decreased appetite | Insomnia |
|---|---|---|---|---|---|
| Reimherr 2007[228] N=47 | 4 | 18-90 mg daily (mean NR) | NR | 12% vs.0%; *P*=0.025 | 21% vs.7%; *P*=0.05 |
| Medori 2008[226] N=401 | 5 | 18 mg, 36 mg, 72 mg or placebo | 1% vs.4% vs.8% vs.1%; *P*=NR | 10% vs.22% vs. 34% vs.7%; *P*=NR | 12% vs.12% vs.17% vs.7%; *P*=NR |
| Chronis-Tuscano 2008[225] N=23 | 2 | 83.7 mg | 11% vs.0; *P*=NR | NR | NR |
| Adler 2009[227] N=226 | 7 | 67.7 mg | 14% vs.5%; *P*=NR | 25% vs.6%; *P*=NR | 9% vs.5%, *P*=NR |
| Biederman 2010[230] N=223 | 6 | 78.4 mg | 11% vs.3%; *P*=0.01 | 24% vs.5%; *P*<0.05 | 11% vs.4%, *P*<0.05 |
| Winhusen 2010[229] N=255 | 11 | 72 mg | 5% vs.2%; *P*=NS | 18% vs.5%; *P*=0.00 | 17% vs.13%, *P*=NS |

Abbreviations: NR, not reported; NS, not significant.

### *Sustained-release methylphenidate*

We included 4 fair-quality trials of sustained-release methylphenidate.[231-234] Three of the trials focused on subgroups of adults who were methadone-maintained[233] cocaine-dependent[231] or amphetamine abusers[234] and results from these will be discussed in Key Question 3.

The remaining trial did not report an analysis of adverse events.[232]

### *Methylphenidate transdermal system*

No data was available regarding the adverse event profile of methylphenidate transdermal system, as the single included placebo-controlled trial was rated poor quality.[235]

### *Modafinil*

No data was available regarding the adverse event profile of modafinil in adults with ADHD, as analysis of harms was not reported in the single included placebo-controlled trial.[236]

## Key Question 2b. What is the evidence of serious adverse effects associated with use of pharmacologic treatments for attention deficit disorders?

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

We included observational studies for analysis of long-term safety parameters.[210, 245-275] The studies were 1 to 5 years in duration. All but 2 involved elementary school-aged children.

#### Suicide

### *Atomoxetine*

Two analyses indicate an increased risk of suicidal ideation and behaviors with use of atomoxetine in the short term, and a third analysis indicates a potential for this risk to be increased with longer duration of therapy.

Using data on file from all clinical trials of atomoxetine in children, the manufacturer conducted an independent meta-analysis of suicidal-related behavior in response to requests from the US Food and Drug Administration and other organizations.[245] Based on 12 short-term clinical trials in children with ADHD or enuresis, 1357 children taking atomoxetine were compared with 851 taking placebo (6 to 18 week trials), finding an increased risk of suicidal ideation (n=5) or suicidal behaviors (n=1) in those taking atomoxetine; 0.44% overall. No suicidal-behavior events occurred in the placebo groups, such that the risk difference between the groups was statistically significant (Mantel-Haenszel Incidence Difference, 0.52; 95% CI, 0.12 to 0.91) indicating an increased risk with atomoxetine compared with placebo. Time to onset of suicidal-related behavior was 9 to 32 days. All children experiencing suicidal-related behaviors were boys, ages 7-12, and 2 of 6 (33%) were African American – whereas the proportion of African American children in these studies was 12%. Two of 6 had comorbid psychiatric disorders. Analysis of data from 2 trials comparing atomoxetine to methylphenidate found 1 case of suicidal ideation in each group (atomoxetine or methylphenidate), with no significant difference. Prior to this analysis, a US Food and Drug Administration analysis of the same data also found an increased risk, but identified 1 case as a suicide attempt and identified 1 fewer case of suicidal behavior overall. Atomoxetine was associated with significantly higher risk of suicidal ideation than placebo: 0.37% (5/1357) compared with 0% (0/851); Maentel-Haenzel Incidence Difference 0.46; 95% CI, 0.09 to 0.83; $P$=0.016. Suicide attempts were slightly higher

with atomoxetine; 0.07% (1/1357) compared with 0% (0/851).[245] A subsequent black box warning is included in Appendix B.

A higher rate was found in an analysis of children taking atomoxetine for at least 3 years.[148] Based on data from 2 extension studies and 3 open label studies, 2% (14 of 714) experienced suicide-related outcomes (11 suicidal ideation, 2 suicide attempts, and 1 suicidal behavior). These events occurred as early as 234 days and as late as 5.8 years of treatment, with only case 1 occurring before 2 years of treatment. Because there was no control group for this analysis, and because much of these data came from extension studies where some level of selection bias exists, these findings must be viewed as suggestive only.

### *Other drugs*

A single before-after study followed 8 adult males (mean age of 27.2 years) that continued on open methylphenidate for 3 to 6 months subsequent to participation in short-term clinical trials.[210] One participant (12.5%) attempted to commit suicide by consuming a month's supply of methylphenidate.

A retrospective cohort study based on the GPRD database in the United Kingdom (N=5351) found an increased risk of suicide among children and teens taking methylphenidate or amphetamine in comparison with population normative data.[273] The standardized mortality ratios were for children age 11 to 14, 161.91 (95% CI, 19.61 to 584.88) and for children age 15 to 20, 1.84 (95% CI, 0.05 to 10.25). This finding was based on a post-hoc analysis, a very small number of events, was not able to adjust for potential confounding, and should be interpreted with caution.

## Cardiovascular deaths and events

Three retrospective cohort studies evaluated cardiovascular cardiac death (e.g. sudden death) and cardiovascular events in children exposed, or not exposed, to ADHD medications,[251, 273-275] and 1 retrospective cohort study evaluated cardiovascular events in adults exposed to ADHD medications.[271]

The largest study evaluating cardiac death in children included 241 417 incident (new) users of ADHD medications (specifically, amphetamines, methylphenidate, and atomoxetine) and evaluated only validated cases of sudden death or ventricular arrhythmia.[274] Estimates for risk of sudden death or ventricular arrhythmia associated with methylphenidate current use compared with never use was elevated but not statistically significant, with a wide confidence interval (hazard ratio, 2.36; 95% CI, 0.29 to 23.69). Risk with use of any of the 3 types of medication was lower but also not found to be statistically significantly elevated (hazard ratio, 1.60; 95% CI, 0.19 to 13.60). Unfortunately, this study did not make direct comparisons among the different drugs, but the crude incidence rates per 10 000 person years was higher in methylphenidate users (hazard ratio, 0.16; 95% CI, 0.00 to 0.89) than either amphetamines or atomoxetine (both hazard ratios, 0.00; 95% CIs, 0.00 to 0.79 and 0.00 to 5.8, respectively). 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). In a much smaller study based on the GPRD database in the United Kingdom, 5321 patients (age 2 to 21 years) who had received at least 1

prescription for methylphenidate, dexamphetamine, or atomoxetine, 7 deaths occurred and none were deemed to be caused by "sudden death".[273]

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.[251, 275] 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.

In a good-quality case-control study, children (ages 7 to 19) who had died from "sudden unexplained death" during the years of 1985 to 1996 were identified from state vital statistics from each of the 50 United States.[276] A control group was selected from children who died from motor vehicle traffic accidents, with 1:1 matching resulting in 564 in each group. The exposure was defined as stimulant use immediately prior to death, based on survey of parents. Ten (1.8%) of those with sudden death were reported to have been taking immediate-release methylphenidate at the time of their death, compared with 2 (0.4%) in the motor vehicle death group, resulting in an odds ratio of 7.4 (95% CI, 1.4 to 74.9). Sensitivity analyses altering the way exposure was identified or removing children also taking a tricyclic antidepressant did not meaningfully alter the results. Recall bias is the greatest risk in this study, as the time since the child's death to the survey of the parent was longer in the sudden death group (13 years) compared with the motor vehicle death group (10 years).

In a 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).[271] Overall the numbers of cases were small, limiting the ability to determine statistically significant differences if they were to exist.

### Blood pressure, pulse, electrocardiographic changes

***Lisdexamfetamine.*** Three trials of lisdexamfetamine 30, 50, or 70 mg daily compared with placebo reported various intermediate outcome measures of cardiovascular function. Small increases in blood pressure and heart rate were seen in all 3 studies, with none being deemed clinically important. A small, open-label, uncontrolled 11-month study of lisdexamfetamine in 272 children did not find any cases of "clinically relevant" changes in blood pressure or electrocardiographic parameters.[277] A 4-week, placebo-controlled trial of 314 adolescents reported increases in heart rate of 2 to 3 beats per minute with lisdexamfetamine (1 beat per minute increase with placebo).[184] Change in blood pressure was negligible. Two patients, both taking 70 mg daily doses of lisdexamfetamine, discontinued drug after 1 week due to increased QTc intervals. Additionally, a 4-week randomized, placebo-controlled trial of 30 mg, 50 mg, and

70 mg of lisdexamfetamine in 420 adults (54% male, mean age was 35.1 years) reported cardiovascular adverse events.[278] Although statistical analysis of between-group differences was not reported, for lisdexamfetamine 30 mg, 50 mg, 70 mg, and placebo, respectively, rates for blood pressure increase were 1%, 3%, 4% and 0%, for increased heart rate were 1%, 3%, 3%, and 0%, for palpitations were 2%, 1%, 3%, and 0%, and for tachycardia were 1%, 3%, 0%, and 0%.[278]

***Methylphenidate OROS.*** An open-extension of a trial of methylphenidate OROS reported small changes in blood pressure (3.3 mmHg systolic and 1.5 mmHg diastolic) and heart rate (3.9 bpm) over a 1 year study period.[279] During this time, 33% discontinued treatment, but only 1 withdrew due to systolic blood pressure >130 mmHg. ANOVA analyses showed no relationship to dose or age and no tolerance development over time was found, but those children with the lowest blood pressure at baseline had the greatest increases. The final report from this 2-year study found no additional withdrawals due to cardiovascular adverse events.[280]

In a 7-week study of 226 adults (56% male, mean age of 39 years), similar proportions of participants in the methylphenidate OROS and placebo groups, respectively, had systolic blood pressure greater than 140 mmHg at any post baseline visit (8% compared with 6%), but greater proportions of participant in the methylphenidate OROS group had diastolic blood pressure greater than 90 mm Hg (10% compared with 3%; *P* not reported) and a pulse rate of greater than 100 bpm (7% compared with 2%; *P* not reported).[227]

***Mixed amphetamine salts XR.*** Four open-label extension studies of mixed amphetamine salts XR, 1 each in children,[281, 282] adolescents,[283] and adults examined the cardiovascular effects over periods of 6 to 24 months.[284] In each of these studies the subjects were populations of patients who were highly selected and were described as being healthy other than the diagnosis of ADHD. The studies in children and adolescents also included a short-term placebo-controlled phase. While no statistically significant differences compared with placebo in any electrocardiogram measure were found in children in the short-term trial, 2% (11/568) had diastolic blood pressure >90 mmHg, and 9% (50/568) had a systolic blood pressure >130 mmHg at some point during follow-up. Overall, 0.7% (4/586) withdrew from the study due to a cardiovascular adverse event; 1 due to tachycardia (max 121 bpm compared with 108 bpm at baseline), 2 due to chest pain (both had sinus bradycardia at baseline), and 1 due to elevated blood pressure (130/90 mmHg that resolved to 115/80mmHg after 1 month without drug). In a shorter duration open-label study, 2968 children were given mixed amphetamine salts XR for a period of up to 15 weeks.[282] The absolute numbers of patients with cardiovascular adverse events were not clearly reported. It was reported that 0.2% (7/2968) discontinued mixed amphetamine salts XR due to cardiovascular adverse events. Nine patients had treatment emergent cardiovascular adverse events that were moderate or serious in intensity, 5 of which were deemed probably related to mixed amphetamine salts XR.

Thirteen of 79 adolescent patients (16%) experienced adverse events during a 4-week study of mixed amphetamine salts XR compared with placebo that included cardiovascular symptoms such as syncope, tachycardia, and electrocardiogram abnormality.[283] Of these, 2 were withdrawn from study drug, 1 with palpitations and 1 with severe migraine and syncope. During 6-month follow-up there were no serious cardiovascular adverse events reported, although 4% (6/138) reported adverse events with cardiovascular symptoms, however none withdrew due to these adverse events. In a 2-year extension study in adults with ADHD, two-thirds discontinued

the study prior to completing 2 years, 22% because of adverse events.[284] Statistically significant, but not considered clinically meaningful, increases in systolic blood pressure and diastolic blood pressure were seen at various points throughout the study (mean increase in systolic blood pressure, 2.3 mmHg; diastolic blood pressure, 1.3 mmHg at endpoint). While a statistically significant increase in QTcB (7.2 msec; $P<0.001$) was found, no patient had a QTcB >480 msec. Three percent withdrew due to cardiovascular events (2 due to palpitations or tachycardia – extent not reported, and 5 due to hypertension).

***Atomoxetine.*** Open-label extension studies of atomoxetine have reported on cardiovascular adverse events in children or teens[257] and in adults.[285] One report involved 169 children and adolescents that continued on open or blinded atomoxetine (maximum dose of 2 mg/kg divided into twice daily) for at least 1 year following 3 short-term, placebo-controlled trials.[257] The timing of electrocardiogram measurements was not stated, but was presented by increasing dose. Linear regression suggested that there was no evidence of an increase in QTc with increasing dosage of atomoxetine.[257] An interim analysis of an open-label extension study in adults reported no "clinically relevant changes in QTc" after a mean of 97 months of follow-up.[285]

## 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.[246] 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.[286] 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,[258, 259, 265] or unmedicated hyperactive control groups.[261, 265, 266] Height and weight changes associated with immediate-release methylphenidate[254, 256, 260, 262, 263] and OROS were also observed in long-term noncomparative studies.[262] A noncomparative study of mixed amphetamine salts (Adderall XR®) found a low overall rate of withdrawal due to weight loss (4.8%), however weight loss was the most common reason for withdrawal from this 24-month extension of placebo-controlled trials.[287] Multiple noncomparative study findings provide inconclusive evidence regarding immediate-release methylphenidate effects on children's height and weight. Analysis of 2- and 5-year data from open-label extensions of 13 trials of atomoxetine assessed the effect on height and weight.[249, 252]

We did not analyze results from a poor-quality, comparative study of growth rebound in methylphenidate and immediate-release dextroamphetamine due to our concerns about how possible additional biases may have affected the results.[267] We cannot rule out the possibility of between-groups differences in baseline characteristics because no information/analysis was provided. We also cannot rule out the possibility that the results were confounded by time and other relevant factors. An additional study related to growth reported on tooth maturation in

children taking immediate-release methylphenidate compared with an unexposed control group, finding no difference (Table 14).[288]

## Table 14. Direct comparisons of long-term height and weight outcomes

| Study | Interventions (mean dose) Duration Sample size | Age Gender Population | Height | Weight |
|---|---|---|---|---|
| Gross 1976 | DEX 16.5 mg, n=12<br>6.8 years follow-up<br>MPH 34 mg, n=60<br>5.8 years follow-up | Mean age=9<br>82% male<br>Children/adolescents with hyperkinetic syndrome or minimal brain dysfunction | Change in percentile:<br>+10.9, *P*<0.01 vs.<br>+12.8, *P*<0.001 | Change in percentile:<br>+16.0, *P*<0.02 vs.<br>+11.4, *P*<0.001 |
| Safer 1972 | DEX<br>11.7 mg, n=3<br>11.8 mg, n=8<br>MPH<br>37.5 mg, n=4<br>24.0 mg, n=5<br>9 months follow-up | Mean age=9.8<br>Gender NR | NR | Weight gain (kg): 0.23 vs. 0.12, t=1.8, *P*<0.05<br>Weight gain (excluding patients taking low-dose MPH, n=16) (kg): 0.13 vs. 0.12, t=0.137, NS<br>ON vs. OFF<br>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 | DEX, n=29<br>MPH, n=20<br>Unmedicated controls, n=14<br>≥ 2 years follow-up<br>Mean dosages NR | Mean age NR<br>89.8% male in children on medication; 100% male in unmedicated control group<br>100% White | Change in percentile:<br>DEX: –13.45<br>MPH > 20 mg: –9.40<br>All MPH: –5.20<br>MPH ≤ 20 mg: –1.00<br>Controls: +1.29<br>DEX > MPH all-dose, low-dose and control groups<br>DEX=MPH high-dose group<br>MPH high-dose > controls<br>MPH all-dose and low-dose=controls | DEX; MPH: high-dose (> 20 mg), all, low-dose (≤ 20 mg); controls<br>Percentile changes in:<br>Weight: –20.38; –10.0, –6.35, –2.7, +6.79<br>DEX > all MPH dosage groups and controls; MPH high-dose and all doses > controls; MPH low-dose=controls |
| Pliszka 2006 | MPH, n=113<br>2.7 years follow-up<br>MAS, n=66<br>2.4 years follow-up<br>Mean dose NR | Mean age 9<br>81% male | Change in z-score:<br>MPH 0.1<br>MAS 0.1 | Change in z-score:<br>MPH 0<br>MAS 0.3 |

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

### *Height*

***Comparative studies.*** The only comparative evidence came from 2 studies of immediate-release dextroamphetamine and methylphenidate[258, 265] and 1 of methylphenidate and mixed amphetamine salts.[270] Results were mixed across the methylphenidate compared with immediate-release dextroamphetamine studies (Table 14). 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[258] and immediate-release dextroamphetamine was associated with significantly greater height *decreases* than methylphenidate after at least 2 years in the other.[265] 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.[265] The 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.[270] 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.

***Noncomparative studies: Immediate-release methylphenidate.*** In summary, studies of children taking immediate-release methylphenidate at various doses for 1-4 years showed inconsistent suppression of growth in height as compared with children who were unmedicated,[289,255, 261, 266] and those in noncomparative studies that reported varied analyses including differences between expected and actual growth,[254] change in percentile,[256] percent of expected growth,[260] and proportion of patients with decreased growth rates.[263]

A study of children previously enrolled in a study of immediate-release methylphenidate were followed for 5 years, and a negative relationship between stimulant (any) dose and z-scores for height was found.[269] Further analysis indicated that the impact on height occurred after the dose reached ≥2.5 mg/kg methylphenidate equivalent and a duration of treatment of ≥4 years. Extrapolation from the regression model indicates that a 13 year-old-boy receiving 2.5 mg/kg methylphenidate for >4 years would have 1.9 cm less increase in height compared with norms. This study is based on small numbers of patients (N=91 at baseline, N=68 at year 5) and many patients did not have height and weight data available for all years.

A before-after study followed 407 children with ADHD taking methylphenidate OROS 40 mg daily for 12 months.[280] Absolute height increased by a mean of 10.2 cm at 21 months. Analysis of z-scores for height change indicates the final height to be a mean of 0.23 cm less than expected.

A 3-year randomized controlled trial (N=62) of withdrawing immediate-release methylphenidate during summer months compared with not withdrawing found no significant difference in height after summer 1 (0.1 cm), but a significant difference after summer 2 (1.3 cm, $P=0.02$).[289] Serious limitations of this study, in design and conduct, limit the likelihood that the findings are valid. Overall, 42% of those randomized withdrew, with data available for 58 children at the end of summer 1 (ON n=32, OFF n=26) and 34 at the end of summer 2 (ON n=20, OFF n=14). Weight and height were collected by unblinded secretaries, but not for the purposes of this study.

Based on the Preschool ADHD Treatment Study trial, preschool-aged children treated with immediate-release methylphenidate were found to be taller at baseline than age-based norms (+2.04 cm).[290] Children who remained on methylphenidate had reduced growth, a mean of 1.38 cm/year.

***Noncomparative studies: Lisdexamfetamine.*** Based on children (ages 6 to 13) enrolled in open-label extension studies, height was not affected over 15 months of treatment.[291] Two hundred eighty children were enrolled and had baseline measurements, but only 45% of children had measurements at 12 to 15 months. The mean height of the children at baseline was in the 55th percentile and was in the 54th percentile at 12 to 15 months follow-up.

***Noncomparative studies: Atomoxetine.*** Based on 412 patients (children and adolescents) who had received atomoxetine for at least 2 years and had at least 1 post baseline height measurement, atomoxetine resulted in a mean decrease in expected height of 0.44 cm.[252] Height changes appeared to regress toward the mean by 2 years. In an extension of this study, 1312 children (ages 6-17 at study entry) were followed under open-label conditions.[249] Of those enrolled in the study, 16% discontinued due to lack of efficacy and 5% due to adverse events. Based on the data from the small subset (N=53) that had reached 5 years of follow-up and had height data, analysis indicated that there was a negative impact on expected height up to 18 months of treatment. At baseline, the children's mean height percentile was 55.7, and at 18 months it was 49.0; $P<0.001$. However, the difference at 2 years was no longer statistically significant, and by 5 years patients were at the 59th percentile. The largest decrease in height percentile occurred in the group in the 3rd quartile (50th to 75th percentile), but this analysis was based on very few patients.

### *Weight*

***Comparative studies: Immediate-release methylphenidate and immediate-release dextroamphetamine.*** Results from 3 comparative studies suggested that immediate-release dextroamphetamine is associated with significantly greater suppression of weight gain than methylphenidate, at least in the first 1 to 2 years (Table 14).[258, 259, 265] Immediate-release dextroamphetamine was associated with a significantly lower mean weight gain (kg) than methylphenidate after 9 months in 1 study,[259] significantly greater declines in weight percentiles after the first of 5 years another study,[258] and at end of treatment (≥ 2 years) in yet another.[265] 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).[258]

The 9-month study also reported subgroup analyses.[259] 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.

***Comparative studies: 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.[270] Overall, the children in the study were heavier than average, such that the mean final weights were not below average for age.

***Noncomparative studies: Immediate-release methylphenidate.*** Noncomparative studies[254, 256, 260, 263] provide mixed evidence about the association between immediate-release methylphenidate and suppression of weight gain in school-aged children. In the earliest study (1977), only 2 of 36 boys with minimal brain dysfunction (5.5%) lost weight while taking methylphenidate (maximum dose 20 mg) over 16 months.[263] The other 34 boys gained weight. The next study, published in 1979, involved 72 boys (age range 6-12) with hyperactivity that were taking methylphenidate for up to 2 years.[260] A significant growth weight deficit (30%; $P$<0.05) was associated with methylphenidate 24.2 mg daily (0.47 mg/kg) in the 72 boys who completed the first year. The growth weight deficit associated with methylphenidate 0.59 mg/kg of 10% was insignificant for the 48 boys who completed the second year of treatment. Results of a subgroup analysis suggest that the deficit in weight gain was only significant in patients that continue to use medication over the summer months compared with those who did not. The third study, published in 1983, involved relatively higher mean dosages of methylphenidate (39.9 to 41.3 mg) and followed children with hyperactivity over the longest observation period (4 years).[256] Methylphenidate was associated with significant declines in weight percentiles in all 4 years of the study (Year 1 [–9.7] compared with Year 2 [–15.9] compared with Year 3 [–18.6] compared with Year 4 [–20.8]; $P$<0.001 for all). The final study, published in 1999, found an insignificant difference (0.72 kg) between expected compared with actual weight gain in 29 patients who took methylphenidate 34.5 mg for 2 years.[254]

In a study following children taking stimulants for 5 years, described above, stimulant dose ≥2.5 mg/kg methylphenidate equivalent was found to be negatively associated with weight gain ($P$<0.001).[269] Comparing the models for height and weight, the authors find that the impact of increased dose is greater on weight than height. Using the change in z-score based on dose, the estimated difference in weight gain in a 10 year old boy using a stimulant for more than 1 year was found to be 1.41 kg at 1.5 mg/kg daily, 2.17 kg at 2 mg/kg daily, and 2.89 kg at 2.5 mg/kg daily compared with age-based norms. Again, these results are based on small numbers of children and could be subject to change in a larger sample were used.

A 3-year randomized controlled trial (N=62) of withdrawing immediate-release methylphenidate during summer months compared with not withdrawing found that after summer 1, the immediate-release methylphenidate ON group gained significantly less (0.9 kg, $P$=0.005) than the immediate-release methylphenidate OFF group. However, in summer 2 the difference was non-significant (0.6 kg).[289] Serious limitations of this study, in design and conduct, limited the likelihood that the findings were valid. Overall, 42% of those randomized withdrew, with data available for 58 children at the end of summer 1 (ON, n=32; OFF, n=26); and 34 at the end of summer 2 (ON, n=20; OFF, n=14). Weight and height were collected by unblinded secretaries, but not for the purposes of this study.

Results were mixed across 2 studies that compared children taking methylphenidate to unmedicated hyperactive children, however.[255, 266] In 1 study, methylphenidate was associated

with significantly greater declines in weight percentiles than in the unmedicated children after 1 year.[255] The differences between the methylphenidate groups and the unmedicated group increased numerically along with the dosages (<20 mg, –6.88; 20.56 mg, –8.81; >20 mg, –15.40; all $P<0.005$). In the other study, the methylphenidate group and the unmedicated group demonstrated similar absolute weight gain (kg) after 364 days.[266]

Based on data from the Preschool ADHD Treatment Study, preschool-aged children were heavier than age-based norms by 1.78 kg.[290] After a year of treatment, those who stayed on immediate-release methylphenidate experienced less weight gain than those who did not complete by 1.32 kg/year.

***Noncomparative studies: Methylphenidate OROS.*** In the before-after study of 407 children (above), absolute weight increased a mean of 6.0 kg during 21 months, with the baseline weight being slightly above expected and the final weight being slightly below expected for age. The final weight was 1.23 kg (2.64 pounds) less than expected for age.[280]

***Noncomparative studies: Mixed amphetamine salts XR.*** Twenty-seven of 568 (4.7%) children withdrew due to weight loss in a 24-month before-after study of mixed amphetamine salts XR.[287, 292] Eligibility for this study was restricted to patients that completed either of 2 placebo-controlled trials without any clinically relevant adverse events or withdrew for any other reasons. Overall, the children had a mean weight deficit at endpoint (change in age-adjusted weight quartile, –15.15). The deficit was greatest among those in the highest quartiles at baseline, and among those who were stimulant naïve. Weight change was greatest during the first year, with change in the second year not statistically significant. A second open-label study of mixed amphetamine salts XR-treated adolescents (mean age 14 years; N=138) reported that 25% (34/138) experienced weight loss as an adverse event over 6 months, 2 of whom discontinued drug for this reason.[293] The mean weight decreased by 2.4 kg (5.2 lbs), with approximately 9.2 lb weight loss being the mean among mixed amphetamine salts XR-naïve patients. The study also found that those in the 75$^{th}$ percentile for weight lost more weight (mean 4.2 kg) compared with those in the 25$^{th}$ to 75$^{th}$ percentile (1.5 kg), while those below the 25$^{th}$ percentile gained 0.5 kg (mean).

***Noncomparative studies: Lisdexamfetamine.*** Based on children (ages 6 to 13) enrolled in open-label extension studies, weight (and Basal Metabolic Index) was negatively affected over 15 months of treatment.[291] Two hundred eighty children were enrolled and had baseline measurements, but only 45% of children had measurements at 12 to 15 months. The mean weight of the children at baseline was in the 65$^{th}$ percentile and was in the 47$^{th}$ percentile at 12 to 15 months follow-up. The mean weight increase from baseline to last observation carried forward was –0.2 kg, while population norms were reported to be +3.5 kg over this time. The analysis found that the change in weight was significantly correlated to baseline weight; the greater the baseline weight the greater the negative impact on weight gain. Similar results were found for basal metabolic index.

***Noncomparative studies: Atomoxetine.*** Based on 412 patients (children and adolescents) who had received atomoxetine for at least 2 years and had at least 1 post baseline weight measurement, atomoxetine resulted in a mean decrease in expected weight of 0.87 kg.[252] Analysis of change over time indicated that weight changes were greatest in the early months of

treatment, with some regression toward the mean percentile at 2 years. In an extension of this study, 1312 children (ages 6-17 at study entry) were followed under open-label conditions.[249] Of those enrolling in the study, 16% discontinued due to lack of efficacy and 5% due to adverse events. Based on the data from the small subset (N=62) that had reached 5 years of follow-up and had weight data, analysis indicated that there was a negative impact on weight up to 18 months of treatment. At baseline, the children's mean weight percentile was 68. After only 1 month the mean weight percentile had dropped to 66 ($P<0.001$), and by 15 months it was 58 ($P<0.001$). This change was statistically significant up to 3 years of treatment, when the percentile had risen to 65. At 5 years, the mean percentile was 71. Analysis indicated that the modal dose did not impact the change in weight. At 5 years, those children with who were in the 4th quartile (75th to 100th percentile) at baseline had lost weight (–8 percentiles; $P<0.048$), while those in the lower quartiles had gained weight. Those in the 1st quartile gained the most, followed by those in the 2nd and then the 3rd quartile. However, this analysis is based on very few patients.

### 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 database.[248] 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 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

Five observational studies and 2 meta-analyses reported tic-related outcomes.[248, 254, 262, 264, 280, 294-296] One of these was a long-term placebo-controlled trial[294] of immediate-release methylphenidate. Table 15 summarizes the characteristics and outcomes from these studies. Although the 1-year study started out with similar numbers assigned to placebo and methylphenidate, by the study end 72 were on methylphenidate and only 18 on placebo. Development of new tics or worsening of pre-existing tics was not different between the 2 groups. The studies do not provide any information about how different pharmacologic treatments for ADHD compare in safety with regard to 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.[295] This same publication also reported on 2 open-label studies of methylphenidate OROS, 1 of which was already included here,[262] the other is a report on a 9-month community-use study in children, adolescents, and adults, for which no reference is given (see table 15). A second meta-analysis included 9 trials involving dextroamphetamine, methylphenidate "derivatives", clonidine, guanfacine, and atomoxetine among other drugs not included in this

review.[296] This analysis found that methylphenidate "derivatives" (primarily immediate-release methylphenidate) did not increase tic severity, but improved ADHD symptoms, compared with placebo. Clonidine and guanfacine combined improved tic severity (Table 15) compared with placebo.

The rate of treatment emergent tics varied widely across the studies. Because these studies lack comparative elements and vary in design, higher quality evidence is needed to establish the risk of developing treatment emergent tics with ADHD medications.

### Table 15. Tic-related outcomes in observational studies

| Study | Intervention<br>Sample size<br>Duration | Population | Tics |
|---|---|---|---|
| **Children** | | | |
| Miller-Horn 2008 | MPH IR, MPH OROS, MAS IR, MAS XR<br>N=150<br>2 years | ADHD | MAS XR, 0%; MAS IR, 6%; MPH OROS, 3%; atomoxetine, 3%; MPH IR, 9%; NS by one-way ANOVA analysis |
| Law 1999 | MPH IR 0.5 mg/kg twice daily vs. placebo<br>N=72<br>1 year | ADHD with no prior treatment for tics or ADHD | New onset tics: 19.6% MPH IR vs. 16.7% placebo (NS)<br>Exacerbation of pre-existing tics: 33% both groups (NS) |
| Gadow 1999 | MPH IR 34.5 mg daily<br>N=29<br>2 years | ADHD and chronic tics or Tourette's | Tic frequency and severity significantly higher at baseline<br>No significant differences across placebo and 12, 18, 24 month follow-up periods |
| Wilens 2003, 2005 | MPH OROS 41 mg daily<br>N=407<br>1 year | ADHD | New onset tics: 23 (6.4%) at interim analysis;<br>24 (7%) at final analysis |
| Palumbo 2004 | MPH OROS<br>N=1088<br>9 months (unpublished) | ADHD | 0.18% new onset tics<br>1.2% overall<br>0.6% withdrawal due to tics |
| Bloch 2009 | Meta-analysis of 9 trials | ADHD | Effect size for change in tic severity:<br>Methylphenidate 0.28 (95% CI -0.03 to 0.58; 4 trials)<br>Clonidine/guanfacine 0.74 (95% CI 0.44 to 1.04; 3 trials)<br>Atomoxetine 0.32 (95% CI 0.09 to 0.56) |
| Palumbo 2004 | Meta-analysis of 3 RCTs of MPH OROS, MPH IR, placebo<br>1-4 weeks | ADHD | MPH OROS, 4%; MPH IR, 2.3%; placebo, 3.7%; *P*=0.5249 |
| **Adults** | | | |
| Horrigan 2000 | Adderall 10 mg daily<br>N=24<br>1 year | ADHD | Motor tics: 1 (4%) |

Abbreviations: ADHD, attention deficit hyperactivity disorder; IR, immediate release; MAS, mixed amphetamine salts; MPH, methylphenidate; NS, not significant; OROS, osmotic release oral system; RTC, randomized controlled trial; XR, extended release.

## Seizures

In an analysis of post marketing data and clinical trials data, the manufacturer of atomoxetine found that the rate of seizure was 01.% to 0.2%, with no statistically significant difference in rate between atomoxetine, methylphenidate, and placebo, although the comparative data were

limited.[250] 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 was statically significant.[272] The confidence intervals are quite wide and unfortunately, the study did not make direct statistical comparisons of the drugs and drawing conclusions from these findings was not possible.

### Injuries

A retrospective database study analyzed an association between childhood behavioral disorders and common childhood injuries by using the British Columbia Linked Health Data Set to identify injuries. Children with behavioral disorders were identified using methylphenidate prescriptions as a proxy for diagnosis using data in a Triplicate Prescription Program.[253] Injury frequencies in children prescribed methylphenidate at least once between January 1, 1990 and December 31, 1996 (n=16 806) were compared with those in children not taking methylphenidate (n=1,010,067). Children were 51.4% male and less than 19 years in age. Mean duration of exposure was not identified. Odds of any injury (fractures, open wounds, poisoning/toxic effect, intracranial, concussion, and burns) were significantly higher in children taking methylphenidate than for those not taking methylphenidate (odds ratio, 1.67; 95% CI, 1.54 to 1.81), even after adjusting for baseline age, sex, socioeconomic status, and region. This study design clearly suffers from lack of sensitivity to diagnosis, in that an unknown number of children with behavioral disorders are included in the group not taking methylphenidate. Since methylphenidate was used simply as a proxy for behavioral disorders, the relationship between the drug and the increase in injuries is not necessarily clear.

### *Hepatotoxicity*

***Atomoxetine.*** Two case reports (via the US Food and Drug Administration MedWatch system) of hepatotoxicity in patients taking atomoxetine (1 adult, 1 child) have resulted in the addition of a warning in the product labeling: "Postmarketing reports indicate that Strattera® can cause severe liver injury in rare cases. Although no evidence of liver injury was detected in clinical trials of about 6000 patients, there have been 2 reported cases of markedly elevated hepatic enzymes and bilirubin, in the absence of other obvious explanatory factors, out of more than 2 million patients during the first 2 years of postmarketing experience. In 1 patient, liver injury, manifested by elevated hepatic enzymes (up to 40 times the upper limit of normal) and jaundice (bilirubin up to 12 times the upper limit of normal), recurred upon re-challenge and was followed by recovery upon drug discontinuation, providing evidence that Strattera® caused the liver injury. Such reactions may occur several months after therapy is started, but laboratory abnormalities may continue to worsen for several weeks after drug is stopped. Because of probable under reporting, it is impossible to provide an accurate estimate of the true incidence of these events. The patients described above recovered from their liver injury and did not require a liver transplant. However, in a small percentage of patients, severe drug-related liver injury may progress to acute liver failure resulting in death or the need for a liver transplant. Strattera® should be discontinued in patients with jaundice or laboratory evidence of liver injury, and should not be restarted. Laboratory testing to determine liver enzyme levels should be done upon the first symptom or sign of liver dysfunction (pruritus, dark urine, jaundice, right upper quadrant tenderness, or unexplained "flu-like" symptoms").[297]

### *Raynaud's Syndrome*

A small (N=64) case-control study found a statistically significant association between current or past stimulant (methylphenidate or immediate-release dextroamphetamine) use and Raynaud's Syndrome in children, mean age 16 years with a chi square of 5.00; $P$=0.01.[247] This study was not high quality, with only limited description of the cases and controls selected, particularly potentially confounding factors, and only chart review determination of exposure to stimulant medications. However, these findings suggest that further research is needed.

## Key Question 2c. 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.[298]

### *Direct evidence*

Two poor-quality studies compared rates of misuse and abuse of drugs used to treat ADHD.[299, 300] 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.

### *Indirect evidence*

#### Association between treatment of ADHD with drug therapy in childhood and later development of substance abuse

This was a much-discussed topic in the literature,[301-309] but a clear conclusion has not yet been reached. The evidence is largely limited to longitudinal studies assessing the relationship of treatment with a stimulant during childhood and later substance use in adolescence or adulthood. None of these studies were comparative in terms of the specific stimulant drugs used during treatment, with most reporting immediate-release methylphenidate as the most commonly used drug. We did not find any evidence assessing the impact of nonstimulant drugs or extended-release stimulants on later substance use/abuse in patients with ADHD. In general these studies suffered from methodologic flaws that hinder clear conclusions from being drawn. Some depend

on data that appear to have been collected for other purposes, or at least not for the specific purpose of assessing future substance abuse, and definition or methods of determination of substance abuse is not consistent across studies. There is general agreement that the rate of substance use in adolescence or adulthood is higher among those diagnosed with ADHD in childhood, compared with healthy controls, and that age of diagnosis (younger ages), severity of symptoms, and presence of conduct disorder increase the likelihood of later substance use. However, the impact of drug treatment during childhood on later substance use is not clear, and in fact there is distinctly conflicting evidence. The major concern raised regarding these studies is the lack of controlling for potential confounding, particularly severity of ADHD, age at follow-up (assessment during adolescence not allowing enough time for exposure to illicit substances), the definition of substance use (for example "ever use" compared with substance use disorder), and exposure to substances during childhood (for example cigarette smoking by parents or other relatives). We have rated all of these studies as fair quality and suggest caution in interpreting the results of any 1 study as conclusive.

We found a total of 12 fully published studies,[166, 310-323] 3 of which had follow-up publications with additional analysis.[310-315, 318] Additional studies were cited by others, many of which are only published as abstracts, do not address stimulant use, or were not available to us.[324-330] Several of these made comparisons to groups of children without ADHD.[311, 313-315, 317, 318, 331, 332] Because these comparisons were less relevant than those comparing adolescents and adults with ADHD as children who did and did not received stimulants, these were not considered further. There were 7 studies that made relevant comparisons.[166, 310, 319-321, 323, 331] Below is a summary of the findings of these studies (Table 16). These were generally small studies, with limited ability to control for all important confounding factors. Importantly, differences among the groups at baseline that may have lead to 1 group receiving a stimulant and the other not well identified particularly in the older studies where these data may not have been recorded. Therefore, the findings should be interpreted as suggestive and require further research to confirm. Overall, the studies of stimulant use in childhood and later abuse or dependence on nicotine, alcohol, or illicit drugs compared with children with ADHD but not exposed to stimulants did not indicate an increased risk. Some indicate a protective effect, but it appears that conduct disorder may be an important modifying factor.

Rates of nicotine abuse and dependence were assessed in 4 studies,[319, 321, 323, 331] with 1 finding stimulant use in girls protective against nicotine abuse (regular smoking) as adolescents (hazard ratio, 0.28; 95% CI, 0.14 to 0.60).[323] Another found no association with the rate of or timing of the first cigarette, but did find that stimulant exposure delayed the time to regular smoking by 2 years and 1 month.[321] Two other studies, in males, however found no associations after controlling for confounding factors including conduct disorder.[319, 331]

Four studies found no associations between alcohol abuse during teen and young adult years and stimulant exposure during childhood.[166, 310, 319, 320] Earlier examinations of data from 1 longitudinal follow-up study had indicated a protective effect at 5 years of follow-up,[311] but this association was no longer seen with 10 years of follow-up.[319]

In examining substance abuse, 2 studies found stimulant use to be protective,[320, 323] but a third study found that controlling for conduct disorder resulted in a nonsignificant finding.[319]

## Table 16. Relationship between stimulant treatment for ADHD and later substance abuse and dependence

| Study | Nicotine |
|---|---|
| Huss 2008<br>N=215<br>Children with ADHD<br>Mean age at follow-up: 21.75 years<br>Mean years to follow-up: 12.6 years | No difference in rate or age of first cigarette, or rate of nicotine abuse or nicotine dependence. Time to nicotine abuse significantly greater in stimulant group, by 2 years, 1 month (*P*=0.049) |
| Wilens 2008<br>N=114<br>Females with ADHD<br>Mean age at follow-up: 16.2 years<br>Mean years to follow-up: 5 years | Stimulant use found protective; hazard ratio, 0.28; 95% CI, 0.14 to 0.60 |
| Biederman 2008<br>N=112<br>Males with ADHD<br>Mean age at follow-up: 22 years<br>Mean years to follow-up: 10 years | Controlling for conduct disorder; nicotine dependence hazard ratio, 1.1; 95% CI, 0.6 to 2.1 |
| Burke 2001<br>N=164<br>Boys with disruptive behavior disorders<br>Mean age at follow-up: 13-15 years<br>Mean years to follow-up: NR | Regression did not find stimulant use to significantly associated with tobacco use in adolescence (odds ratio, 2.19; *P*=0.061) |
| **Study** | **Alcohol** |
| Blouin 1978<br>N=42<br>Hyperactive children<br>Follow-up age 13-14 years<br>Mean years to follow-up: 5 years | 39.3% of those MPH IR group had used alcohol once or twice vs. 21.4% of untreated group. Current users: MPH IR group 46. 4% vs. untreated 26.4%. |
| Biederman 1997 and 2003<br>N=212<br>Children with ADHD<br>Follow-up >5 years | Stimulants found protective; alcohol abuse or dependence OR 0.16 (confidence intervals not given) |
| Biederman 2008<br>N=112<br>Males with ADHD<br>Mean age at follow-up: 22 years<br>Mean years to follow-up: 10 years | Controlling for conduct disorder: Alcohol abuse hazard ratio, 1.1; 95% CI, 0.6 to 2.1; dependence hazard ratio, 1.0; 95% CI, 0.5 to 2.4. Duration of alcohol abuse was longer in those who had received stimulant treatment. |
| Paternite 1999<br>N=121<br>Children with hyperactivity<br>follow-up = age 21-23 | Holding age at diagnosis and childhood symptoms constant, no statistically significant correlations with alcoholism, although authors indicate a trend towards higher dose of MPH may be related to lower rates of alcoholism |

| | |
|---|---|
| Goksoyr 2008<br>N=91<br>Mean age stimulant group: 21.6<br>Mean age control group: 30.8<br>Mean years to follow-up: NR | Stimulant exposed 23% vs. non-exposed 38%; *P*=NS |
| **Study** | **Substance abuse** |
| Wilens 2008<br>N=114<br>Females with ADHD<br>Mean age at follow-up: 16.2 years<br>Mean years to follow-up: 5 years | Substance use disorder (hazard ratio, 0.27; 95% CI, 0.13 to 0.60) |
| Biederman 2008<br>N=112<br>Males with ADHD<br>Mean age at follow-up: 22 years<br>Mean years to follow-up: 10 years | Controlling for conduct disorder: Abuse hazard ratio, 1.6; 95% CI, 0.8 to 3.2; dependence hazard ratio, 1.0; 95% CI, 0.4 to 2.6. Age at initiation of stimulant, or duration of stimulant not significantly associated with substance use disorders. Previous reports from this group had found stimulant use protective. |
| Goksoyr 2008<br>N=91<br>Mean age stimulant group: 21.6<br>Mean age control group: 30.8<br>Mean years to follow-up: NR | Adults with ADHD seeking stimulant treatment; those with history of stimulant exposure as children compared with those without such history. Stimulant exposed 23% vs. non-exposed 49%; *P*<0.05 |

Abbreviations: ADHD, attention deficit hyperactivity disorder; NR, not reported; NS, not significant.

### *Misuse and diversion of ADHD medications*

We found a fair- to poor-quality systematic review, and 4 other studies not included in the systematic review relevant to this question.[333-337] In the systematic review, 21 studies of misuse or diversion of methylphenidate or amphetamine reported from 1995 to 2006 were included.[333] The majority of studies were surveys or questionnaires, involving 113 145 participants, with 12 studies including college students and smaller numbers including children from elementary, middle, and high schools or mixed populations.

***Misuse.*** Using data collected as part of the National Survey on Drug Use and Health from 2000, 2001, and 2002, 34.7% of respondents had ever misused a prescription stimulant intended for use to treat ADHD.[338] As noted in the systematic review (above), no psychiatric diagnosis information is available from the survey, so it is not known what proportion of respondents had ADHD. The most commonly misused stimulants in this survey were methylphenidate and dexamphetamine, with smaller numbers reporting use of other drugs, including mixed amphetamine salts and methylphenidate OROS. Similarly, 30% had misused an ADHD stimulant in the past year, with significantly higher rates among those aged 12- 25 years compared with older participants, and among Whites compared with other races. Using combined data from 2000 and 2001 (due to low numbers in each survey), 4.7% were determined to be dependent or abusing a prescription ADHD stimulant drug, with rates highest again among those 12 -25 years old. Rates of dependence were higher among women, whereas rates of abuse were higher among men.

The review found that the rate of misuse of methylphenidate or amphetamine was 5% to 8% among children up through high school and 5% to 35% among college students. Among college students, 2 small studies found that higher rates of misuse (30% to 35%) were for

enhancement of academic performance. The review reported on the findings of a study of data from of the National Survey on Drug Use and Health from 2000, 2001, and 2002 and indicated that of all respondents, 0.9% in the 12- to 17-year-old age group and 1.3% in the 18- to 25-year-old age group had misused an ADHD stimulant (nonmedically) in the past year.[338] Two additional studies of college student misuse of ADHD medications were found. A study using a web-based survey tool to study students at Duke University and the University of North Carolina on various aspects of drug and alcohol misuse included questions on ADHD medication misuse.[336] While 115 students reported having a drug prescribed to treat their ADHD, and responded to questions about misuse, the survey did not identify what the drugs being taken were. Similar to the studies discussed above, 31% reported misusing the drug (e.g. taking more frequently than prescribed), and 26% to 63% of these misuses were for reasons related to improving academic performance.

A small study of 66 adults prescribed methylphenidate found that 29% reported inappropriate use during the past month, with 84% using it orally, 74% using it nasally, and 11% smoking it.[334] Regression analysis indicated that misuse of methylphenidate was associated with illicit use of cocaine or amphetamines. This was a very small study, however, and such regression analyses should be interpreted with caution. A study of the Texas Poison Control Network revealed that 8.5% (322 of 3789) of calls about human exposures to methylphenidate during 1998 to 2004 were cases of abuse.[335] The database did not record the formulation of methylphenidate involved, although they report that the number of calls regarding methylphenidate had reduced during 1998 to 2000, then increased during 2001 to 2004.

***Diversion.*** In looking at the evidence on diversion of these stimulants, the systematic review found that among children up through high school aged, 15% to 24% gave them away, 7% to 19% sold them, and 4% to 6% had them stolen at some time in the past. Among college students, 3 studies reported rates of diversion with widely varying rates reported. The lowest rate found in the systematic review, 23% to 29% had been asked to give, to trade, or to sell their ADHD medications to another student.[333] A web-based survey tool used to study students at Duke University and the University of North Carolina on various aspects of drug and alcohol misuse included questions on ADHD medication diversion, and rates of diversion among 115 students who had a drug prescribed to treat their ADHD were found to be higher. Fifty-six percent had been asked to sell their ADHD medications and 26% reported either giving or selling their medications to another student.[336] 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.[337] This group of students had the highest rate of diverting ADHD medication at 61.7%. The highest rate of 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). Data on sharing compared with selling medications were not stratified by type. In a small study of 66 adults prescribed methylphenidate, 44% reported diverting their medication to someone else, with 97% giving it away, 17% selling it, and 14% doing both.[334] Regression analyses indicated that diversion was associated with younger age both at the time of the survey and at the time methylphenidate was first prescribed. This was a very small study, however, and such regression analyses should be interpreted with caution.

### *Reinforcing effects of ADHD medications*

We found 2 very small studies (1 in 5 children with ADHD, 1 in 10 adults with ADHD) that used a choice procedure as a proxy measurement of abuse potential.[339, 340] The logic behind this is that choice of 1 treatment over another may be reflective of the reinforcing effects of a drug, which is often considered to be predictive of abuse potential. The trials involved short-term administration of blinded drug (sampling days) and then allowing them to choose their preferred condition on other days (choice days). In the adult study, ADHD symptom improvement was self-assessed using a 5-point scale (1="not effective" and 5="extremely effective"). The main findings were that Immediate-release methylphenidate was chosen significantly more often than placebo (50% compared with 32.5%; $P<0.001$), but that perceived effectiveness ratings for patients who reliably chose methylphenidate were also significantly greater than non-methylphenidate choosers (4.8 compared with 3.2 points; $P=0.04$). Based on these findings, authors concluded that the higher methylphenidate preference demonstrated by these patients was more reflective of therapeutic efficacy rather than abuse potential.

In the study of children, effectiveness was measured in a variety of ways, none of which were standard ADHD rating scales. While the study found a higher rate of preference with immediate-release methylphenidate, the findings are not conclusive because the effectiveness data either showed no effect of methylphenidate or what was called an idiosyncratic response (no pattern identifiable). In addition, for both of these studies we feel that because the order of condition was not randomized and the sample sizes were so small, the studies should be considered exploratory only.

## Key Question 3. Subgroups

### Key Question 3a. Are there subgroups of patients based on demographics (age, racial groups, gender, and ethnicity), other medications, or comorbidities for which one pharmacologic treatment is more effective or associated with fewer adverse events?

ADHD subtypes, comorbidities, and race or ethnicity were not recorded in most randomized controlled trials and observational studies. For example, only one-quarter of all studies of school-aged children reported ADHD subtype prevalence rates. Importantly, of those that did record demographic information, only 1 poor-quality trial reported results of a subgroup analysis of Black children with ADHD.[341] While the data available from the studies that do report this information can be useful in determining the generalizability of results, the lack of attention to assessing the impact of these factors means there is almost no evidence on potential differences in response or adverse events.

### *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 1323 children that participated in the overall trial) found treatment outcomes to be similar to those for the overall study population.[341] Main findings from the subgroup analysis are summarized in Evidence Table 3, 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 4).

***Immediate-release methylphenidate.*** Immediate-release methylphenidate 0.15, 0.30, and 0.50 mg/kg was studied in a placebo-controlled, crossover trial (2 weeks in each arm) of 11 Black male adolescents (mean age=13.6 years).[170, 242] Immediate-release methylphenidate had a positive effect on 75% of efficacy measures. This response rate was similar to that seen in other placebo-controlled trials of immediate-release methylphenidate. Immediate-release methylphenidate was associated with significant linear elevations diastolic blood pressure among these patients.

An analysis of California Medicaid claims data suggested that mean persistence (days of treatment without any 30-day gaps) was longer for children taking methylphenidate ER formulations (OROS and SODAS) than for those taking immediate-release methylphenidate regardless of ethnicity (White, Black, Hispanic).[55] This same data indicates that mean treatment durations overall (methylphenidate OROS, SODAS, and immediate release) were significantly shorter for Black children (survival time ratio, 0.77; 95% CI, 0.73 to 0.80), Hispanic children (survival time ratio, 0.81; 95% CI, 0.78 to 0.84), and other ethnicities (survival time ratio, 0.81; 95% CI, 0.75 to 0.87) than for White children.

***Methylphenidate OROS.*** A 4-week, noncomparative trial evaluated the efficacy and tolerability of methylphenidate OROS in 119 Korean children with ADHD.[342] Significant improvements were seen in the children's scores on both the parent and teacher versions of the IOWA Conners' Rating Scale, as well as on the investigator-rated Clinical Global Impression-Severity Scale. Only 2 (1.7%) patients withdrew due to adverse events of decreased appetite and insomnia. However, these findings do not provide reliable information about how methylphenidate OROS treatment effects in Korean children compare to those in children of different ethnic descent.

Additionally, a subgroup analysis from a 4-week, placebo-controlled trial of 255 adult smokers with ADHD found a significantly greater reduction of ADHD Rating Scale scores with methylphenidate OROS 72 mg in subgroups of White and non-White patients.[343]

***Lisdexamfetamine.*** Subgroup analyses of ethnic origin (Caucasian compared with Non-Caucasian) were performed using data from 2 double-blind, randomized controlled trials of lisdexamfetamine and results were reported in the Center for Drug Evaluation and Research Medical Review[240] In the 1-week, crossover study (#201), average Swanson, Kotlin, Agler, M-Flynn and Pelham - Deportment Subscale scores for lisdexamfetamine were similar to mixed amphetamine salts XR and superior to placebo, regardless of ethnic origin. In the 4-week, parallel-group study (#301), mean changes in ADHD rating scale IV for lisdexamfetamine 30 mg compared with placebo appeared less robust for the subgroup of non-Caucasians (–18.5

compared with –10.1; $P$=0.0754) compared with the population overall (–21.8 compared with –6.2 points; $P$<0.0001). Treatment effects for the lisdexamfetamine 50 mg and 70 mg dosage groups also appeared less robust in non-Caucasians, but mean changes in the ADHD rating scale IV scores remained statistically significantly greater than placebo.

***Atomoxetine.*** A placebo-controlled study of atomoxetine was undertaken in Taiwanese children with ADHD.[344] This study reported statistically significantly greater improvements on the ADHD-Rating Scale-IV scale with atomoxetine compared with placebo (–17.15 compared with –9.31; $P$<0.01). The mean change in score is slightly greater than those seen in trials of atomoxetine conducted in the United States (–12.8 to –16.7 with atomoxetine compared with –5.0 to –7.0 for placebo). The most frequently reported adverse event was decreased appetite (36% compared with 17%; $P$=0.002), followed by somnolence (22% compared with 9%, NS), and nausea (17% compared with 0; $P$<0.01).

A subgroup analysis of 1198 participants from 2 multi-center, open-label trials of atomoxetine with follow-up periods of 10 and 11 weeks was performed to assess response to atomoxetine among Latinos compared with Caucasians in children age 6 to < 18 years with ADHD.[345] There were 5 significant differences between the 2 groups at baseline (mean age, ADHD subtype, previous substance use, percent of slow metabolizers, and ADHD rating scale IV-PI total mean score). The study reported significant and similar improvements in ADHD (ADHD rating scale IV-PI) with an improved score of 54% for the Latino population (N=107) and an improved score of 52% for the Caucasian population (–22.10 compared with –19.55; $P$=0.47). The only significant between-group difference was a greater decrease in the ADHD rating scale IV-PI hyperactive/impulsive subscale during the last 4 weeks of treatment for Latinos (effect size=0.35). Latinos, however, had higher baseline scores than Caucasians. The incidence of treatment-emergent adverse events was comparable among the 2 groups with the following exceptions: Caucasians reported significantly more abdominal and throat pain ($P$=0.006; $P$=0.037, respectively), whereas Latinos reported significantly more decreased appetite and dizziness ($P$=0.03; $P$=0.023, respectively).

### *Gender*

Girls typically made up only a small proportion of the total children enrolled in ADHD trials, which reflected the differential in the rates of ADHD diagnoses among the sexes.

#### Direct comparisons

Based on post-hoc subgroup analyses, differences in ADHD symptom response between boys and girls were not found in 5 trials of various drugs. Subgroup analyses based on gender were performed based on data from 2 double-blind, randomized controlled trials of lisdexamfetamine.[240] The average SKAMP-DS scores for lisdexamfetamine were similar to mixed amphetamine salts XR and superior to placebo regardless of gender in the 1-week, crossover study (#201). In the 4-week, parallel-group trial, treatment effects appeared less robust in subgroups of girls for all dosage groups of lisdexamfetamine compared with placebo, but changes in ADHD rating scale IV lost statistical significance only in the 30 mg treatment group (–19 compared with –8.1; $P$=0.0537). Results from the subgroups of girls in study #301 must be interpreted with caution, however, due to the small sample sizes (N=88).

A subgroup analysis of the START study, comparing mixed amphetamine salts XR and atomoxetine, examined the effects in the 57 girls enrolled.[346] Similar to the overall study analysis, mixed amphetamine salts XR was found to have greater improvements in symptoms based on the SKAMP deportment and attention subscale scores compared with atomoxetine. In the original analysis, 71.9% of the children enrolled were boys. 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.[347] 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.[348] This study was small, and may have not had adequate statistical power (Type II error).

### Indirect comparisons

We found 3 studies examining differences in response to stimulants (primarily immediate-release methylphenidate) between boys and girls.[80, 349, 350] Two found no differences between boys and girls,[80, 350] while the third found that during the task period, boys were significantly more compliant and mothers gave fewer commands and more praise comments than in the girls group.[349] All 3 studies suffer from design and conduct flaws, including important differences between the groups at baseline and not accounted for in the analysis, and comparison to historical controls.

Data from girls enrolled in 2 separate placebo-controlled trials of atomoxetine with identical protocols were analyzed post-hoc to assess the effects in this subgroup of children.[351] This analysis of 52 girls reported similar efficacy to that reported for the whole trial group (atomoxetine superior to placebo on most measures) but did not make a comparison of the effects in boys compared with girls.

A pooled analysis of two 10-week, placebo-controlled trials (N=536; 35% female, 65% male) of atomoxetine in adults examined gender differences.[352] The study found that when compared with baseline, a statistically significant change favoring atomoxetine was observed among both genders on the multiple ADHD rating scales ($P<0.05$). This study conducted multiple exploratory analyses of differences in gender based on treatment effects. At endpoint, atomoxetine resulted in better scores in women on emotional dysregulation (temper + mood lability + emotional overactivity) items on the Wender-Reimherr Adults Attention Deficit Disorder Scale compared with men. The Sheehan Disability social life subscale demonstrated a significant gender-by-treatment effect ($P=0.042$), with women showing a stronger treatment effect than men, but there was no significant difference on the total score. No other analyses showed a gender difference. Considering the post-hoc, exploratory nature of these analyses and the smaller number of women than men in these studies, these findings are preliminary.

Post-hoc analyses of data from the COMACS study, combining methylphenidate OROS and methylphenidate CD adverse event data compared with placebo, found that sex was not a predictor of appetite/sleep disturbance adverse events.[238] A small (N = 35; 19 males and 16 females), fair-quality, crossover study of methylphenidate OROS and extended-release mixed amphetamine salts in adolescents reported analyses of the differences in effects based on sex and drug assigned.[348] Multiple ANOVA analyses were conducted on parent and student assessed

Connors scale, a modified Connors scale for use by adolescents using a hand-held computer, and simulated driving scores comparing medication to either placebo or standard care (minimal or no medication). While this study had limitations, the analyses did not show a correlation between sex and effect with medication.

### *Age*

Subanalyses of persistence and compliance outcomes based on age were conducted using data from a Texas Medicaid Vendor Drug Program database on children taking immediate-release methylphenidate, immediate-release mixed amphetamine salts, or methylphenidate OROS.[60] More details of this database review are discussed under Key Question 1. Findings suggest that patients aged 5-9 years (0.43) had significantly higher rates of persistence than children aged 10-14 years (0.41) and children aged 15-18 (0.41). There were also higher rates of compliance (Medication Possession Ratio) in children aged 5-9 years (0.73) and aged 10-14 years (0.73) than in children aged 15-18 (0.67). This, however, doesn't provide any information about how persistence and compliance rates compared between the long-acting and shorter-acting stimulants within each age group.

Post-hoc analyses of data from the COMACS study, combining methylphenidate OROS and methylphenidate CD adverse event data compared with placebo, found that age was not a predictor of appetite/sleep disturbance adverse events.[238]

Based on data from the manufacturer, a meta-analysis of 5 atomoxetine studies (N=794) compared the results in children (ages 6 to 12) and adolescents (ages 13 to 15) on the ADHD-IV rating scale and on the Child Health and Illness Profile, Child edition (CHIP-CE; a measure of quality of life).[353] At baseline, more children had the combined type ADHD than did adolescents, and the total ADHD-RS score was higher in children (by 3 points, $P$=0.002). The authors concluded that atomoxetine resulted in greater improvements in the risk avoidance and threats to achievement domains of the CHIP-CE compared to children, based analyses of all 5 studies (3 placebo-controlled trials and 1 open-label vs. standard of care, and 1 uncontrolled study). We do not believe that combining such diverse studies in a meta-analytic way adheres to the highest standards for meta-analysis. Results from only the 3 placebo-controlled trials do not seem to support the conclusions.

A subgroup analysis of adults with ADHD[189] showed that age demonstrated a trend towards interacting with treatment ($P$=0.057) and that younger patients (ages 18-30) showed more functional improvement when compared with placebo (mean change 19.4 compared with 10.4; $P$=0.010) than older age groups who did not differ by treatment.

### *ADHD subtypes*

The potentially moderating effects of ADHD subtypes (inattentive, hyperactive/impulsive, or combined) in children have been examined in 5 small, short-term placebo-controlled trials of immediate-release methylphenidate,[354-356] methylphenidate OROS,[357] and modafinil.[358] Results from all trials suggest that these drugs have superior efficacy relative to placebo in children with ADHD, but that response or dose-response differs by diagnostic subtype.

***Immediate-release methylphenidate.*** In a small study (N=41), children were stratified into 2 subtypes, combined or inattentive. After 6 weeks of treatment, immediate-release

methylphenidate had a significant effect on parent and teacher ratings of inattention and hyperactivity in both ADHD subtypes. Ratings of hyperactivity and aggression were improved in more the group with combined subtype, while task-incompatible behavior, performance, and inattention were improved in both subtypes.[356] In a second small (N=25) crossover study of immediate-release methylphenidate and placebo, assessing these same subtypes found no difference in response on the ADHD-RS-IV scale. Assessments were made after 1 week.[354]

In a trial of immediate-release methylphenidate (N=30), the supervising psychologist and pediatrician were asked to judge which was the best dose for each child, based on which dose led to improvements on the majority of measures with the least degree of side effects. An evaluation of their judgments revealed that considerably more children with hyperactivity were likely to receive a recommendation for the moderate or high doses (20-30 mg daily), compared with the combined subtype who were more likely to be recommended a lower dose or no drug treatment.[355]

***Methylphenidate OROS.*** In another small trial (N=47) analyses based on linear and higher-order dose-response curves were used to evaluate the impact of dose on response in subtypes with methylphenidate OROS.[357] In this trial, significant relationships between ADHD subtype and methylphenidate OROS were detected for some, but not all, efficacy outcomes. When parent-ratings of the Inattention and Hyperactivity subscales from the ADHD rating scale IV were considered, it was noted that children with the combined type of ADHD had the greatest decreases in symptoms between the 36 mg and 54 mg dosages of methylphenidate OROS, whereas children with the inattentive type of ADHD had the greatest decreases in symptoms between placebo and the 18 mg dosages of methylphenidate OROS. We recommend using caution when interpreting this finding, however, as differences in appearance between placebo and methylphenidate OROS capsules may have increased parents' awareness of medication condition and could have affected efficacy ratings. Also, a similar pattern in subtype differences based on dosage was not observed when Clinical Global Impression Scale-related ratings were considered.

***Modafinil.*** In a pooled analysis of data from 3 placebo-controlled trials, 638 children age 6 to 17 years, 30% with inattentive subtype, 27% with combined subtype, and only 4% with hyperactive-impulsive subtype, were stratified.[358] Results indicated a statistically significant improvement on the ADHD rating scale IV for both the combined and inattentive subtypes, but no statistically significant difference for the hyperactive-impulsive subtype. However, as this subgroup was very small, this finding may have been due to lack of statistical power rather than a true difference.

### *Comorbidity*

Rates of commonly occurring comorbidities were only reported in around half of all studies. 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%.[359] The American Academy of Child and Adolescent Psychiatry estimate somewhat higher proportions; 54% to 84% with comorbid oppositional defiant disorder,

0% to 33% with depressive disorders, up to 33% with an anxiety disorder, and 25% to 35% with learning disabilities.[26]

The comorbidities considered here are oppositional defiant disorder, conduct disorder, learning disabilities, anxiety disorders, depression, bipolar disorders, and tic disorders, and substance use (see methods section for discussion of selection).

In a small study (N=90), immediate-release methylphenidate 10 to 30 mg daily was given for 15 days, with outcome assessment for adverse events evaluated using the Barkley Stimulants Side Effects Rating Scale (BSSERS).[360] Post-hoc analyses indicated that gender, age, dose, and baseline severity of ADHD symptoms were not associated with an increase in the BSSERS, but presence of a comorbidity was significantly associated with an increase (61% "not affected" and 85% "affected"; $P<0.05$). However, analysis of individual comorbidities did not result in significant differences. The small size and post-hoc nature of this analysis indicates a need for further research to confirm and expand these findings.

### *Oppositional Defiant Disorder*

***Atomoxetine.*** The impact of comorbid oppositional defiant disorder on treatment of ADHD in children has been most widely studied for atomoxetine.[141, 361-366] Meta-analyses of data from 2 earlier[141] and 3 more recent[365] placebo-controlled trials of atomoxetine were respectively designed to evaluate the efficacy and adverse effects of atomoxetine in children with ADHD and comorbid oppositional defiant disorder. Additionally, findings are available from 3 individual placebo-controlled trials.[361-364] Collectively, these studies consistently found that the presence of oppositional defiant disorder does not impact the effectiveness of atomoxetine in treating children with ADHD. The effects on symptoms of oppositional defiant disorder were less consistent in that not all studies found atomoxetine to be superior to placebo.

In a post-hoc analysis of a placebo-controlled trial, findings suggested that response to treatment of ADHD in children with comorbid oppositional defiant disorder (N=113) may be related to dose.[363] Improvements in ADHD symptoms and quality of life measures after 8 weeks were significantly greater for atomoxetine than placebo for the group of children with oppositional defiant disorder taking 1.8 mg/kg, but not for the 1.2 mg/kg or 0.5 mg/kg groups.

***Guanfacine XR***
A study of 217 children with comorbid ADHD and oppositional symptoms using flexible dosing (1-4 mg daily) over 8 weeks found that the mean least squares mean change on the ADHD-RS-IV scale was –23.8 in the drug group and –11.5 in the placebo group ($P<0.001$ from a baseline of 42 in both groups).[163] The subscale scores on the CPRS-RS-L oppositional defiant subscale also improved more with guanfacine XR (–10.9 compared with –6.8; $P<0.001$) and the change in the 2 scores was found to be highly correlated (r=0.74). Slightly more patients were taking 3 mg daily doses, and only few were taking 1 mg daily.

***Immediate-release methylphenidate.*** Two placebo-controlled trials of immediate-release methylphenidate given twice daily studied children with oppositional defiant disorder and ADHD.[367, 368] In both studies, immediate-release methylphenidate was effective in reducing ADHD symptoms relative to placebo. In the larger study (N=267), the presence of oppositional defiant disorder as a comorbidity did not affect the response to immediate-release methylphenidate 0.5 mg/kg compared with those without this comorbidity.[368] In the smaller

study (N=31), 3 doses were studied and only the 0.5 mg/kg dose was consistently found effective in the presence of oppositional defiant disorder as a comorbidity.[367]

***Mixed amphetamine salts XR.*** The efficacy and adverse effects of mixed amphetamine salts XR 10-40 mg has also been studied in 235 children with ADHD and oppositional defiant disorder.[369] This 4-week placebo-controlled trial focused on oppositional defiant disorder as the primary diagnosis, with only 79.2% of the original 308 children having comorbid ADHD. In the oppositional defiant disorder plus ADHD subgroup population, improvements in ADHD symptoms were significantly greater for mixed amphetamine salts XR compared with placebo on the parent- and teacher-ratings on the ADHD subscale of the SNAP-IV. Although these findings are encouraging, there are some limitations to consider. Mean change from baseline on the ADHD subscale of the SNAP-IV was included as a secondary outcome measure and it is unclear if the analysis was adequately powered to measure between-group differences.

***Methylphenidate OROS and methylphenidate CD***

Post-hoc analyses of data from the COMACS study, combining methylphenidate OROS and methylphenidate CD adverse event data compared with placebo, found that comorbidity with oppositional defiant disorder was not a predictor of appetite/sleep disturbance adverse events.[238]

### *Conduct Disorder*

We found no evidence of the impact of conduct disorder on the benefits or harms of any ADHD drug.

### *Learning Disabilities*

We identified 1 study that examined whether children with and without learning disabilities benefit from immediate-release methylphenidate to the same extent when treated for ADHD.[370] This study was based on outcome data from 95 children with ADHD (85% male; mean age, 9.2 years) who participated in a 2-week, placebo-controlled, crossover trial of immediate-release methylphenidate twice daily 0.5 mg/kg. ADHD-related symptoms before and after immediate-release methylphenidate were primarily assessed based on the Restricted Academic Situation Scale, the Continuous Performance Test, and personal impressions of parents, teachers, clinicians and researchers. Data from the placebo-control phase were not reported. Ultimately, children were assigned consensus clinical response scores (0=nonresponder, 1=mild response, 2=moderate response, 3=large response) to reflect overall degree of ADHD symptom control while taking immediate-release methylphenidate. Children with consensus clinical response scores of 0-1 were categorized as “nonresponders” and children with consensus clinical response scores of 2-3 were categorized as “responders.” When compared with children without learning disabilities, the number of “responders” to immediate-release methylphenidate were significantly fewer in children with learning disabilities overall (75% compared with 55%; $P$=0.034) and when the disability was specific to mathematics (72% compared with 50%; $P$=0.034), but not when the disability was specific to reading (68% compared with 59%; $P$=NS).

## *Anxiety Disorders*

### *Children*

Overall, 7 head-to-head trials and 10 placebo-controlled trials reported symptoms of anxiety or nervousness as an adverse event and 1 head-to-head comparison and 3 placebo-controlled trials reported it as a symptom of ADHD or comorbidity.

In the head-to-head comparisons (immediate-release methylphenidate compared with immediate-release dextroamphetamine, mixed amphetamine salts, methylphenidate SR, methylphenidate OROS, or atomoxetine), no statistically significant differences in the rate of reporting anxiety as an adverse event were found, although for some comparisons numerical differences were apparent.[43, 48, 49, 102, 106, 128, 371] 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 Adderall® (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[43] or between immediate-release methylphenidate and placebo in children with ADHD and mental retardation.[372]

Placebo-controlled trial evidence was conflicting; some studies showed higher rates of anxiety or nervousness with methylphenidate, indicating a dose-dependent effect, while others showed no increase over placebo rates.[30, 125, 126, 135, 137, 372-377] Reports of anxiety were similar between placebo and atomoxetine in 2 studies[135, 137] and placebo and modafinil in 2 others.[125, 126] Because most of these studies reported these as spontaneously reported adverse events, we do not believe that the quality of the data warrants a conclusion.

A placebo-controlled trial examining the impact of comorbidities on ADHD response to immediate-release methylphenidate found that the small subgroup of children with symptoms of anxiety at baseline (N=28) had statistically significantly lower response rate, based on a clinical consensus of response compared with those who did not have anxiety at baseline (N=239; 50% compared with 71.9%; $P$=0.02).[368] A second study of children with ADHD, tic disorders, and anxiety was rated poor quality due to inadequate reporting on multiple methods including blinding, comparison of patient characteristics at baseline between exposure groups, attrition, and handling of missing data.[367]

A 12-week fair-quality placebo-controlled study of atomoxetine in children with both ADHD and anxiety disorder diagnoses examined the affect on both ADHD and anxiety symptoms.[378] In the intent to treat analysis, atomoxetine was superior to placebo in both improvements on ADHD symptoms and anxiety symptoms (–4.5 compared with –2.4 points on the Pediatric Anxiety Rating Scale; $P$<0.010). This study had a high drop-out rate; 25% overall; 10% dropped out during a 2-week placebo run-in phase, and another 16% dropped out during the 10-week treatment phase. With a high drop-out rate, we recommend caution in interpreting these findings.

### *Adults*

The effect of atomoxetine on ADHD and comorbid anxiety has been evaluated in 2 trials.[196, 379] One trial prospectively enrolled only adults with ADHD and comorbid social anxiety disorder (N=442).[196] After 14 weeks, there was a significantly greater improvement with atomoxetine 82.9 mg than placebo on the primary efficacy measure of mean change on the Conners' Adult

ADHD Rating Scale, Self-Report Screening Version (–8.7 points compared with –5.6 points; $P<0.001$). Response rates were not reported.

The second publication reported findings from exploratory, post-hoc analyses of the effects of *lifetime*, but not current, diagnoses of DSM-IV comorbidity on response to atomoxetine compared with placebo.[379] The main finding of these subanalyses was that compared with adults with "pure" ADHD (no comorbidities), adults with ADHD and post-traumatic stress disorder had greater improvements on atomoxetine compared with placebo when based on Investigator ratings, but not when based on patient self-report measures. While these findings provide rationale for design of future prospective research, they must be viewed in light of their limitations. These were post-hoc analyses of subgroups of unknown size and it was unclear as to whether they involved comparisons of atomoxetine and placebo groups that were well-matched on important baseline characteristics or whether there was any adjustment for potential confounders. Results from the primary analyses of these data were reported in an earlier, separate publication [191] and are discussed under Key Question 1.

Additionally, numerous placebo-controlled trials examined whether treatment with ADHD drugs improves comorbid anxiety symptoms.[181,191, 198, 206, 207, 210-212, 218, 221, 232, 236] However, only immediate-release methylphenidate was generally consistently associated with improvements in anxiety symptoms in adults with ADHD.[207, 218, 380] The only exception was that in a trial of 45 adults, similar numbers of participants with immediate-release methylphenidate compared with placebo (7% compared with 4%), had anxiety as defined as a Hamilton Anxiety Scale score above 21 points.[206, 207, 210-212, 218, 221] Finally, in terms of adverse effects, only methylphenidate OROS has been associated with significantly greater adverse anxiety effects in adults than placebo across 2 trials.[224, 228]

### *Depression*

In adolescents with DSM-IV diagnoses of ADHD and major depression, 9 weeks of atomoxetine treatment resulted in significantly greater improvement in ADHD symptoms (change in ADHD rating scale IV was –13.3; atomoxetine, –5.1; placebo; $P<0.001$).[381] No statistically significant differences in depression scale scores or rates of treatment emergent mania were found.

For adults, there is very limited evidence regarding treatment of ADHD with comorbid depression. One publication reported findings from exploratory, post-hoc analyses using pooled data from 2 placebo-controlled trials of atomoxetine discussed above in the section on anxiety.[379] Here, the main relevant findings were that compared with adults with "pure" ADHD (no comorbidities), adults with ADHD and major depression, but not adults with ADHD and depression not otherwise specified, consistently had greater improvements on atomoxetine compared with placebo across multiple rating scale scores. As noted previously, however, methodological weaknesses limit interpretation of these findings. Additionally, results of an exploratory, post-hoc analysis of 36 adults with ADHD and depression[382] was reported based on data from a fair-quality, 4-week, randomized, placebo-controlled trial of lisdexamfetamine 30 mg, 50 mg, and 70 mg in 420 adults (54% men, mean age of 35.1 years).[201] The significant improvement in ADHD-RS scores with lisdexamfetamine was observed both in patients with and without a history of depression.

### *Bipolar Disorder*

When added to divalproex, mixed amphetamine salts (Adderall®) was associated with significantly greater improvements in ADHD symptoms than placebo after 4 weeks, but had no effect on bipolar disorder symptoms in 30 pediatric patients with comorbid ADHD and bipolar disorder (mean age 9.8 years).[383] This fair-quality study included 30 children who achieved a significant response to 8 weeks of open-label divalproex out of 40 enrolled in the run-in phase.

Two very small studies of immediate-release methylphenidate report conflicting results. A 4-week placebo-controlled, crossover study of methylphenidate twice a day (5 mg, 10 mg, or 15 mg compared with best dose week) added to mood stabilizers in 20 euthymic youths (ages 5-17) found that methylphenidate at the "best dose" was superior to placebo in improving ADHD symptoms (ADHD rating scale IV, $P<0.02$; effect size= 0.90).[384] However, no single dose level of methylphenidate was found to be superior to placebo in the study population. No suicidal behaviors were observed or reported. A second small (N=16) 2-week placebo-controlled, crossover study of immediate-release methylphenidate (0.3 to 0.7 mg/kg daily) added to aripiprazole in children with ADHD and comorbid bipolar disorder found no benefit from the addition of immediate-release methylphenidate on either ADHD (using the SNAP-IV scale and mixed-effects model analysis; $P=0.97$) or bipolar symptoms (using the Young Mania Rating Scale and mixed effects model analysis; $P=0.34$).[385] This study was very small, and may have lacked statistical power (Type II error).

### *Psychiatric Comorbidities*

One placebo-controlled trial of atomoxetine[192] in adults reported results of subgroup analyses stratified by comorbidities. Atomoxetine treatment effects were not altered by the presence or absence of "psychiatric comorbidity" in a 3-week trial of 22 adults.[192] This trial did not provide evidence of comparative efficacy among subgroups of patients with comorbidities.

### *Tic Disorders Including Tourette's Disorder*

#### Direct evidence

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.[151] 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 is 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 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.

### Indirect evidence

There is concern that stimulant drugs may be contraindicated in ADHD patients with comorbid tic disorders due to possible tic exacerbation. There has also been uncertainty about whether stimulants treat ADHD symptoms as well in children with ADHD and established tic disorders as they do in children with primary ADHD. Several placebo-controlled trials of primarily immediate-release methylphenidate have examined these issues.[85, 151, 386-392] Immediate-release dextroamphetamine and atomoxetine treatments for ADHD have also been studied in children with tic disorders.[85, 389, 391, 393]

The majority of these trials were of short duration and involved very small numbers of children.[85, 386-388, 390, 394] Children participating in these trials were mostly male (≥ 85%), with a range in age of 8.3 years to 11.2 years. Motor and verbal tic frequency and severity were assessed in classroom, lunchroom, and playground settings using a variety of different rating scales. The most common tic rating scale used was the Yale Global Tic Severity Scale.

Overall, there was very little evidence across these trials to indicate that immediate-release methylphenidate, immediate-release dextroamphetamine, or atomoxetine were associated with any tic exacerbation effects. Paradoxically, in one 2-week trial of 34 children, only the lowest dose of immediate-release methylphenidate (0.1 mg/kg daily) was associated with any tic worsening, characterized by an increase in motor tics only in the classroom setting.[386, 388] In another 3-week trial of 12 children, only the higher dosages of immediate-release methylphenidate (0.67 mg/kg daily or 1.20 mg/kg daily) were associated with tic exacerbations.[85] Otherwise, compared with placebo, immediate-release methylphenidate, immediate-release dextroamphetamine, and atomoxetine were all consistently associated with improved tic severity in these trials. Furthermore, children also showed greater improvements in ADHD symptoms with immediate-release methylphenidate, immediate-release dextroamphetamine, and atomoxetine compared with placebo. Observational evidence of the impact of immediate-release methylphenidate treatment indicates that the baseline frequency and severity of motor and vocal tics was significantly higher than during the placebo phase of the study, and no differences were found among the placebo and 12, 18, and 24 month immediate-release methylphenidate treatment follow-up periods.[395]

#### *Nonstimulants: Guanfacine*

In a small study of 24 children with ADHD, all of the mixed type *and* a tic disorder, studied the effects of guanfacine compared with placebo for 8 weeks.[159] Slightly more than half of enrolled children had Tourette's disorder (58.8%), and 35% had chronic motor tic disorder. In this study, the mean Yale Global Tic Severity Scale scores improved in children taking guanfacine (–4.5 out of 100 point scale) compared with placebo (no change).

### Substance use disorder

#### *Adolescents*

Two placebo-controlled trials, 1 of methylphenidate-SODAS and 1 of atomoxetine focused on the subpopulation of substance use disorder with differing results.[396, 397] The small (N=16) 6-week, single-blind, placebo-controlled crossover study of methylphenidate SODAS in

adolescents with ADHD and comorbid substance use disorder (marijuana N=16 and cocaine N=7) found that methylphenidate SODAS was superior to placebo in reducing ADHD symptoms and improving global functioning for all main outcome measures (SNAP-IV and Clinical Global Impression Scale scores; *P* values for all measures were ≤0.001).[396] There was no significant treatment effect on drug use (number of marijuana cigarettes daily; urine tests for either cannabis or cocaine).

A 12-week, double-blind, parallel group placebo-controlled trial of atomoxetine (N=70) in adolescents with at least 1 non-nicotine substance-use disorder found that atomoxetine was not statically different to placebo in improving ADHD symptoms or substance use (self-report DSM IV ADHD checklist mean change –18.19 with atomoxetine and –19.02 with placebo, *P*=0.29).[397] Number of days using non nicotine substances was also not statistically significantly different, although numerically was lower in the atomoxetine group (–5.28 compared with –2.24 days, *P*=0.11). Importantly, in this study both groups received non drug treatments that may have had significant impact on the results.

### *Adults*

Placebo-controlled trials of atomoxetine, immediate-release methylphenidate, and methylphenidate SR have evaluated treatment of ADHD in adults with comorbid substance abuse.

***Atomoxetine.*** Atomoxetine treatment has been assessed in a 12-week placebo-controlled trial of 147 adults with ADHD and comorbid alcohol use disorders.[398] In this trial, reductions in ADHD symptoms, as measured by reductions in the Total Score on the ADHD Investigator Symptom Rating Scale (AISRS), were significantly greater for atomoxetine (–13.6 points; *P*=0.007) compared with placebo (–8.3 points).

The atomoxetine group also made significant improvement relative to placebo on the Clinical Global Impression-ADHD-S (*P*=0.048) and Clinical Global Impression-ADHD-I (*P*=0.006) scales. There were no significant differences in time to relapse between the 2 treatments (*P*=0.93), nor other drinking-related measures.

Another trial of atomoxetine in marijuana-dependent adults with ADHD was rated poor quality primarily due to an unacceptable level of attrition (65%), inadequate reporting of randomization methods, and the resulting baseline comparability of all randomized patients.[197]

***Lisdexamfetamine.*** Results of an exploratory, post-hoc analysis of 17 adults with ADHD and substance use disorder[382] was reported based on data from a fair-quality, 4-week, randomized, placebo-controlled trial of lisdexamphetamine 30 mg, 50 mg, and 70 mg in 420 adults (54% men, mean age of 35.1 years).[201] The significant improvement in ADHD-RS scores with lisdexamfetamine was observed both in patients with and without a history of substance use disorder.

***Immediate-release and sustained-release methylphenidate.*** Two trials of immediate-release methylphenidate[208, 215] and 3 trials of methylphenidate SR[231, 233, 234] focused only on patients with ADHD and comorbid substance abuse disorders. One trial of immediate-release methylphenidate involved a broader population of patients with any alcohol or drug dependence,[208] while the others focused on either patients with cocaine dependence,[215, 231] methadone-maintained patients,[233] or amphetamine abuse.[234] The primary objectives of these trials were to investigate

(1) whether use of immediate-release methylphenidate or methylphenidate SR in adult substance abusers with ADHD reduces ADHD symptoms to a similar extent as in non-substance abusers and with ADHD, and (2) what kind of impact immediate-release methylphenidate or methylphenidate SR use may have on the course of the substance abuse disorder. Overall, although use of immediate-release methylphenidate or methylphenidate SR in adult substance abusers with ADHD did not appear to negatively influence the course of the substance abuse disorder recovery process (cravings, abstinence duration, proportion of days of substance use, amount of money spent on substances, or number of days until first negative urine sample),[215, 231, 233] immediate-release methylphenidate or methylphenidate SR also did not appear to offer much of a benefit in the reduction of these patients' ADHD symptoms.[208, 215, 231, 233, 234] Among the trials that reported response rates, in all but 1 of these trials, not only were there less robust treatment response rates in substance abusers with ADHD compared with non-substance abusers (34% to 47% compared with 38% to 78%), but the placebo response rates in the substance abuser trials were also substantially greater (ranges 21% to 55% compared with 4% to 16%).[208, 231, 233] Trial authors noted several possible factors that may have led to these abnormally negative findings, including that methylphenidate treatment-resistance may be characteristic of substance abusers in general and/or that patients in substance abuse treatment may be more eager to please research staff and have a tendency to over-endorse improvements in any areas of functioning.

### Key Question 3b. What is the comparative or noncomparative evidence of misuse or illicit diversion of pharmacologic treatments for attention deficit disorders in patients with current or past substance use disorder comorbidities?

#### *Adolescents*

A retrospective chart review of 450 teens treated at a substance abuse center in Canada from 1993 to 1999 examined the prevalence of abuse of methylphenidate or immediate-release dextroamphetamine.[399] Twenty-three percent had ever used, and 6% were currently using methylphenidate or immediate-release dextroamphetamine, most often reported to be used as crushed tablets taken intranasally. Further assessment of covariates indicated that higher rates of abuse of methylphenidate or immediate-release dextroamphetamine were associated with the teen being out of school or having an eating disorder ($P<0.01$), but not with a diagnosis of ADHD; 36% of abusers had a diagnosis of ADHD compared with 24% of non abusers (not statistically significant). An assessment of correlation of abuse of methylphenidate or immediate-release dextroamphetamine with abuse of other substances did not reveal any statistically significant results. The authors note that this population had a higher psychiatric comorbidity rate than the general adolescent population, which may have affected the results.

#### *Adults*

Two trials each of immediate-release methylphenidate[208, 215] and methylphenidate SR[231, 233] focused only on patients with ADHD and comorbid substance abuse disorders. One trial of immediate-release methylphenidate involved a broader population of patients with any alcohol or drug dependence,[208] while the others focused on either patients with cocaine dependence[215, 231] or methadone-maintained patients.[233] None reported results of direct assessment of misuse or illicit diversion outcomes. As a potential proxy measure of abuse/diversion, 3 trials reported

medication compliance.[215, 231, 233] Patient self-reported compliance rates were similar in treatment and placebo groups across all 3 trials (88.5% to 95%). Additionally, no differences were found between methylphenidate and placebo in the proportions of riboflavin positive fluorescence (range 0.77 to 0.84).[231, 233]

# SUMMARY

## Limitations of this Review

The results of this review are summarized in Table 17, 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 or poorly 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 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%).[400] 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%.[359] 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 14) 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.

## Studies Pending Review

Two potentially relevant studies (one retrospective cohort study of cardiovascular harms in patients with ADHD and 1 systematic review of interventions for pre-school age children with ADHD) were published after our inclusion dates and have not been incorporated here.[401, 402]

## Table 17. Summary of the evidence

| | 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: Low | The evidence on efficacy of MPH IR compared with placebo in the short term was inconsistent. |
| | Atomoxetine: Insufficient | One placebo-controlled trial. |

| | Comparison:<br>Overall strength of the evidence | Conclusion |
|---|---|---|
| ***Children: Efficacy*** | | |
| Stimulants | | |
| IR vs. SR formulations | MPH IR vs. MPH SR: Moderate | 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. |
| SR vs. SR formulations | MPH SR vs. MPH SR formulations: Low | Limited evidence from 2 small crossover studies suggested that MPH LA was superior to MPH OROS on some, but not all efficacy outcomes.<br>Limited evidence suggested that MPH CD was superior to MPH OROS on outcomes in the morning; they had similar effects in the afternoon; and MPH OROS was superior in the evening.<br>d-MPH ER was superior to MPH OROS at 2 to 6 hours post dose and MPH OROS was superior at 10 to 12 hours in 1 trial. |
| IR vs. IR | DEX IR vs. MPH IR: High | The body of evidence clearly indicated no difference in efficacy between DEX and MPH IR. |
| | MAS IR vs. MPH IR: Moderate | 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: Moderate | 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: Moderate<br>MTS vs. MPH IR: Low | Based on 1 trial each, MTS had similar efficacy compared with MPH OROS or MPH IR. |
| Lisdexamfetamine | Moderate | Lisdexamfetamine was comparable to MAS XR on average SKAMP-DS scores and superior to placebo on same, as well as on ADHD rating scale IV mean changes. |
| 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 is superior to atomoxetine on most efficacy measures. |
| | Atomoxetine vs. MPH OROS: Moderate | MPH OROS was superior to atomoxetine in response rates. |
| 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. Placebo-controlled trials indicated modest benefit as add-on or monotherapy. |
| Guanfacine | Guanfacine IR: Low | No head-to-head evidence. Indirect evidence was insufficient to make conclusions. |
| | Guanfacine XR: Insufficient | No head-to-head evidence. Placebo-controlled trials indicated modest benefit up to 8 hours post dose. |
| ***Adolescents: Efficacy*** | | |
| | MPH OROS vs. MAS IR: Moderate | Effectiveness outcomes: NR<br>Short-term improvements in core ADHD symptoms: No |

| | Comparison:<br>Overall strength of the evidence | Conclusion |
|---|---|---|
| | | differences.<br>Other: MPH OROS > MAS IR on overall simulator driving performance. |
| | MPH IR vs. MPH OROS: Moderate | Functional capacity: NR<br>Short-term improvements of core ADHD symptoms: NR.<br>Driving performance: MPH OROS > MPH IR in evening and at night. |
| | Placebo-controlled studies of MPH IR and Lisdexamfetamine: Insufficient | Functional capacity: NR<br>Short-term improvements of core ADHD symptoms. |
| ***Adults: Efficacy*** | | |
| | Switch to MPH OROS vs. continuing on MPH IR: Low | No significant difference in maintenance of response at 6 weeks. |
| | IR guanfacine vs. DEX IR: Low | No significant difference in mean total symptom score of the DSM-IV ADHD Behavior Checklist for Adults. |
| | Modafinil vs. DEX IR: Low | No significant difference in response rates. |
| | Placebo-controlled evidence of atomoxetine, DEX IR, d-MPH XR, lisdexamfetamine, MPH ER, MPH IR, MPH OROS, MAS IR, MAS XR: Insufficient | Compared with placebo, response rates were significantly greater for all.<br>*Other efficacy outcomes:*<br>Atomoxetine: Not consistently significantly superior to placebo in improving quality of life and driving performance outcomes.<br>MPH IR: Consistently superior to placebo in improving driving performance outcomes; not significantly superior to placebo on 5 of 6 sleep outcomes in 1 trial.<br>MAS XR: Superior to placebo in improving overall simulated driving performance outcomes in 1 trial.<br>MPH OROS: Superior to placebo in improvements on some parenting skill measures in 1 trial. |
| | Methylphenidate transdermal system: Insufficient | No conclusions could be drawn based on the single included poor-quality, placebo-controlled trial. |
| **Key Question 2. Safety** | | |
| **2b. Short-term trial evidence** | | Very few studies reported methods for assessing adverse events a priori. |
| ***Young children*** | | |
| | 1 placebo-controlled trial of MPH: Insufficient | Indirect comparisons cannot be made; MPH associated with higher rates of adverse events than placebo. |
| ***Children*** | | |
| | Moderate | Very few studies reported methods for assessing adverse events a priori. |
| | MPH IR vs. MPH SR | There is no evidence of a difference in adverse events between IR and SR formulations. |
| | MPH SR vs. MPH SR formulations | No differences in adverse events were found, 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 | Very limited evidence suggested 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 was greater with MAS and DEX SR than with DEX IR. |
| | Lisdexamfetamine | No differences in adverse event rates between lisdexamfetamine vs. MAS XR. |

| | Comparison:<br>Overall strength of the evidence | Conclusion |
|---|---|---|
| | Atomoxetine vs. MPH IR, MPH OROS, MAS XR | Vomiting: atomoxetine rates 12% to 13%, approximately 3 times greater than rates for MPH IR or MAS XR.<br>Somnolence: atomoxetine rates 6% to 26%, which was 3 to 4 times greater than MPH OROS and MPH XR; 7 times greater than MPH IR.<br>Nausea and anorexia: greater with atomoxetine than MPH IR in 1 trial.<br>Insomnia: 13% MPH OROS, 28% MAS XR vs. 7% atomoxetine. |
| | Clonidine IR vs. MPH IR: Moderate | Sedation: 42% with clonidine, 14% MPH IR.<br>28% reported as moderate to severe, may improve over time. |
| | Clonidine ER: Insufficient | No head-to-head evidence. In placebo-controlled trials somnolence and fatigue were the most common adverse events with clonidine ER and peaked at 2 weeks. Dose-response in withdrawal due to adverse events, flexible dosing improved discontinuation rate. |
| | Guanfacine XR: Insufficient | No head-to-head evidence. Placebo-controlled trials indicated somnolence, fatigue, and headache most common adverse events with guanfacine XR, dose-response in withdrawals due to adverse events; flexible dosing did not resolve the difference compared with placebo. |
| ***Adults*** | | |
| | Switch to MPH OROS vs. continuing on MPH IR: Insufficient | Difference in proportions of patients with no adverse events was unclear due to serious methodological limitations of the trial. |
| | IR guanfacine vs. DEX IR: Low | No significant difference in number of adverse events. Withdrawals due to adverse events were not reported. |
| | Modafinil vs. DEX IR: Low | No withdrawals due to adverse events. No significant differences in insomnia or appetite suppression. |
| | Placebo-controlled evidence on atomoxetine, DEX IR, d-MPH XR, lisdexamfetamine, MPH ER, MPH IR, MPH OROS, MAS IR, MAS XR: Insufficient | Indirect meta-analysis of harms was not undertaken due to concerns about sparse data and heterogeneity in outcome measurement methods and trial duration. Conclusions about comparisons to placebo were also limited by a scarcity of statistical analyses. |
| | Methylphenidate transdermal system: Insufficient | No conclusions could be drawn based on the single included poor-quality, placebo-controlled trial. |
| **2b. Long-term safety: Observational studies** | | |
| ***Mixed populations, primarily children*** | | |
| | Suicidal behavior/suicide: Low | Increased risk with atomoxetine compared with placebo (risk difference, 0.52; 95% CI, 0.12 to 0.91) based on meta-analysis. Time to onset of behavior 9 to 32 days. Overall rate of suicidal behavior and ideation was 0.44% in this study compared with 1.7% in another meta-analysis of longer-term duration. |
| | Sudden cardiac death: Low | Evidence was inconsistent. Stimulant medications, particularly MPH IR, may have increased risk compared with nonuse, but comparative evidence was insufficient to make conclusions. |

| | Comparison:<br>Overall strength of the evidence | Conclusion |
|---|---|---|
| | Cardiac events: Low | Emergency room visits for cardiac causes were not found statistically significantly different between current users of methylphenidate products and amphetamine products. Former use of these products also resulted in a nonsignificant finding.<br>In adults, risk of stroke or TIA not found different between 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.<br>Limited evidence suggested that height changes resulting from atomoxetine were similar to those reported with MPH IR and were also transient, with peak impact at 18 months, but the difference resolved by 2 years. |
| | 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.<br>Noncomparative evidence indicated a small reduction in expected weight gain, especially among those with greater weight at baseline for MPH IR, MPH OROS, and MAS XR for at least the first year of treatment.<br>Limited evidence suggested that weight changes resulting from atomoxetine were similar to those reported with MPH IR, and were also transient, but longer lasting - resolving by 5 years of treatment. |
| | Tics, seizures, cardiovascular adverse events, injuries, and suicidal behavior | No comparative evidence. |
| **2c. Abuse/misuse/diversion** | | |
| Abuse | Low | Stimulant use during childhood was not associated with alcohol abuse later. May be protective against or delay nicotine dependence, but comorbid conduct disorder may be a significant confounder. Stimulant use may protect against later substance abuse, but again comorbid conduct disorder may be a confounder.<br>Evidence on misuse and diversion reported wide ranges of prevalence with no comparative data. |
| Misuse | Low | Children and adolescents: 5% to 8%<br>College students: 5% to 35% (26% to 63% for enhancement of academic performance)<br>Adults: 29%<br>Misuse of methylphenidate associated with illicit use of cocaine or amphetamines |

| | Comparison:<br>Overall strength of the evidence | Conclusion |
|---|---|---|
| Diversion | Low | Children and adolescents:<br>15% to 24% gave them away<br>7% to 19% sold them<br>4% to 6% had them stolen<br>College students: 26% reported selling or giving medication away. Of these:<br>70.5% Amphetamine/dextroamphetamine<br>37% Methylphenidate<br>39.1% methylphenidate OROS<br>Adults:<br>44% reported diversion<br>97% gave it away<br>17% sold it<br>14% both<br>Diversion is associated with younger age both at the time of the survey and at the time methylphenidate was first prescribed. |
| **Key Question 3. Subgroups** | | |
| ***Children*** | Low | |
| | ADHD subtypes or severity | Atomoxetine, MPH IR, and MPH OROS had superior efficacy relative to placebo in children with ADHD, regardless of diagnostic subtype. There was inconsistency in evidence that response may be better in those with combined or inattentive subtype. |
| | Race/ethnicity | Children: Most trials were conducted in primarily White populations. Ethnicity/race was only reported in one-half of studies. No analyses based on race. Very limited evidence suggested MPH IR in African American boys results in response rates similar to other populations studied. Evidence from subgroup analysis of a placebo-controlled trial suggested that effects of lisdexamfetamine may be less robust in non-Caucasian children.<br>Adults: Significantly greater reduction of ADHD Rating Scale scores with methylphenidate OROS vs. placebo subgroups of white and non-white patients |
| | Gender | Subgroup analyses based on gender were limited. Evidence from subgroup analysis of a placebo-controlled trial suggested that lisdexamfetamine may be less efficacious in girls. Exploratory analysis indicated atomoxetine may have better response on emotional regulation items in women than men. |
| ***Common comorbidities*** | Low | Head-to-head trials provided no evidence in subgroups of interest. |

| | Comparison: Overall strength of the evidence | Conclusion |
|---|---|---|
| | Anxiety | 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.<br>Limited evidence suggested that MPH IR is somewhat less effective in reducing ADHD symptoms in children with baseline anxiety symptoms compared with those without these symptoms.<br>Atomoxetine was superior to placebo in improving ADHD and anxiety symptoms in children with anxiety at baseline.<br>Adults: In adults with ADHD and comorbid social anxiety disorder, there was significantly greater improvement in ADHD and anxiety symptoms for atomoxetine vs. placebo. MPH IR was generally significantly more effective than placebo in improving ADHD and anxiety symptoms in patients with ADHD but no diagnosis of anxiety disorder. |
| | Tic disorders | No consistent evidence that atomoxetine, DEX IR, or MPH IR increased tic severity or frequency compared with placebo.<br>MPH IR showed a benefit on ADHD symptoms compared with placebo.<br>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.<br>Guanfacine resulted in improvement in tic severity relative to placebo in children with tic disorders (58.8% = Tourette's disorder). |
| | Oppositional defiant disorder | Very limited evidence suggested that atomoxetine is beneficial on most ADHD outcomes compared with placebo.<br>Guanfacine XR was superior to placebo in improving both ADHD and oppositional defiant symptoms compared with placebo. |
| | Bipolar disorder | Very limited evidence suggested that MAS IR or MPH IR have benefit on most ADHD outcomes compared with placebo.<br>MPH IR did not improve ADHD symptoms when added to aripiprazole in children with comorbid ADHD and bipolar disorder. |
| | Substance abuse/substance use disorder | Adolescents:<br>MPH SODAS was superior to placebo in reducing ADHD symptoms in teens with SUD. No significant treatment effect on drug use.<br>Atomoxetine was not superior to placebo in improving ADHD symptoms in teens with SUD; number of days with abuse also was not affected.<br>Adults:<br>Substance use disorder: Atomoxetine and lisdexamfetamine both had limited evidence of significantly improving ADHD symptoms vs. placebo in adults, whereas no significant benefits were found with IR MPH and SR MPH vs. placebo. |

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 formulations of other nonstimulant drugs (clonidine, guanfacine) have 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 has 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 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.

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# Appendix A. Glossary

This glossary defines terms as they are used in reports produced by the Drug Effectiveness Review Project. Some definitions may vary slightly from other published definitions.

*Absolute risk:* The probability or chance that a person will have a medical event. Absolute risk is expressed as a percentage. It is the ratio of the number of people who have a medical event divided by all of the people who could have the event because of their medical condition.

*Add-on therapy*: An additional treatment used in conjunction with the primary or initial treatment.

*Adherence:* Following the course of treatment proscribed by a study protocol.

*Adverse drug reaction*: An adverse effect specifically associated with a drug.

*Adverse event:* A harmful or undesirable outcome that occurs during or after the use of a drug or intervention but is not necessarily caused by it.

*Adverse effect:* An **adverse event** for which the causal relation between the intervention and the event is at least a reasonable possibility.

*Active-control trial:* A trial comparing a drug in a particular class or group with a drug outside of that class or group.

*Allocation concealment:* The process by which the person determining randomization is blinded to a study participant's group allocation.

*Applicability:* see *External Validity*

*Before-after study:* A type nonrandomized study where data are collected before and after patients receive an intervention. Before-after studies can have a single arm or can include a control group.

*Bias:* A systematic error or deviation in results or inferences from the truth. Several types of bias can appear in published trials, including selection bias, performance bias, detection bias, and reporting bias.

*Bioequivalence*: Drug products that contain the same compound in the same amount that meet current official standards, that, when administered to the same person in the same dosage regimen result in equivalent concentrations of drug in blood and tissue.

*Black box warning:* A type of warning that appears on the package insert for prescription drugs that may cause serious adverse effects. It is so named for the black border that usually surrounds the text of the warning. A black box warning means that medical studies indicate that the drug carries a significant risk of serious or even life-threatening adverse effects. The US Food and Drug Administration (FDA) can require a pharmaceutical company to place a black box warning on the labeling of a prescription drug, or in literature describing it. It is the strongest warning that the FDA requires.

*Blinding:* A way of making sure that the people involved in a research study — participants, clinicians, or researchers —do not know which participants are assigned to each study group. Blinding usually is used in research studies that compare two or more types of treatment for an illness. Blinding is used to make sure that knowing the type of treatment does not affect a participant's response to the treatment, a health care provider's behavior, or assessment of the treatment effects.

*Case series:* A study reporting observations on a series of patients receiving the same intervention with no control group.

*Case study:* A study reporting observations on a single patient.

*Case-control study:* A study that compares people with a specific disease or outcome of interest (cases) to people from the same population without that disease or outcome (controls).

*Clinical diversity:* Differences between studies in key characteristics of the participants, interventions or outcome measures.

*Clinically significant:* A result that is large enough to affect a patient's disease state in a manner that is noticeable to the patient and/or a caregiver.

*Cohort study:* An observational study in which a defined group of people (the cohort) is followed over time and compared with a group of people who were exposed or not exposed to a particular intervention or other factor of interest. A prospective cohort study assembles participants and follows them into the future. A retrospective cohort study identifies subjects from past records and follows them from the time of those records to the present.

*Combination Therapy*: The use of two or more therapies and especially drugs to treat a disease or condition.

*Confidence interval:* The range of values calculated from the data such that there is a level of confidence, or certainty, that it contains the true value. The 95% confidence interval is generally used in Drug Effectiveness Review Project reports. If the report were hypothetically repeated on a collection of 100 random samples of studies, the resulting 95% confidence intervals would include the true population value 95% of the time.

*Confounder:* A factor that is associated with both an intervention and an outcome of interest.

*Controlled clinical trial:* A clinical trial that includes a control group but no or inadequate methods of randomization.

*Control group:* In a research study, the group of people who do not receive the treatment being tested. The control group might receive a placebo, a different treatment for the disease, or no treatment at all.

*Convenience sample:* A group of individuals being studied because they are conveniently accessible in some way. Convenience samples may or may not be representative of a population that would normally be receiving an intervention.

*Crossover trial:* A type of clinical trial comparing two or more interventions in which the participants, upon completion of the course of one treatment, are switched to another.

*Direct analysis:* The practice of using data from head-to-head trials to draw conclusions about the comparative effectiveness of drugs within a class or group. Results of direct analysis are the preferred source of data in Drug Effectiveness Review Project reports.

*Dosage form:* The physical form of a dose of medication, such as a capsule, injection, or liquid. The route of administration is dependent on the dosage form of a given drug. Various dosage forms may exist for the same compound, since different medical conditions may warrant different routes of administration.

*Dose-response relationship:* The relationship between the quantity of treatment given and its effect on outcome. In meta-analysis, dose-response relationships can be investigated using meta-regression.

*Double-blind:* The process of preventing those involved in a trial from knowing to which comparison group a particular participant belongs. While double-blind is a frequently used term

in trials, its meaning can vary to include blinding of patients, caregivers, investigators, or other study staff.

*Double-dummy:* The use of two placebos in a trial that match the active interventions when they vary in appearance or method of administrations (for example, when an oral agent is compared with an injectable agent).

*Effectiveness:* The extent to which a specific intervention *used under ordinary circumstances* does what it is intended to do.

*Effectiveness outcomes:* Outcomes that are generally important to patients and caregivers, such as quality of life, responder rates, number and length of hospitalizations, and ability to work. Data on effectiveness outcomes usually comes from longer-term studies of a "real-world" population.

*Effect size/estimate of effect:* The amount of change in a condition or symptom because of a treatment (compared to not receiving the treatment). It is commonly expressed as a risk ratio (relative risk), odds ratio, or difference in risk.

*Efficacy:* The extent to which an intervention produces a beneficial result *under ideal conditions* in a selected and controlled population.

*Equivalence level*: The amount which an outcome from two treatments can differ but still be considered equivalent, as in an equivalence trial, or the amount which an outcome from treatment A can be worse than that of treatment B but still be considered noninferior, as in a noninferiority trial.

*Equivalence trial:* A trial designed to determine whether the response to two or more treatments differs by an amount that is clinically unimportant. This lack of clinical importance is usually demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence level of clinically acceptable differences.

*Exclusion criteria:* The criteria, or standards, set out before a study or review. Exclusion criteria are used to determine whether a person should participate in a research study or whether an individual study should be excluded in a systematic review. Exclusion criteria may include age, previous treatments, and other medical conditions. Criteria help identify suitable participants.

*External validity*: The extent to which results provide a correct basis for generalizations to other circumstances. For instance, a meta-analysis of trials of elderly patients may not be generalizable to children. (Also called generalizability or applicability.)

*Fixed-effect model*: A model that calculates a pooled estimate using the assumption that all observed variation between studies is due to by chance. Studies are assumed to be measuring the same overall effect. An alternative model is the random-effects model.

*Fixed-dose combination product*: A formulation of two or more active ingredients combined in a single dosage form available in certain fixed doses.

*Forest plot:* A graphical representation of the individual results of each study included in a meta-analysis and the combined result of the meta-analysis. The plot allows viewers to see the heterogeneity among the results of the studies. The results of individual studies are shown as squares centered on each study's point estimate. A horizontal line runs through each square to show each study's confidence interval—usually, but not always, a 95% confidence interval. The overall estimate from the meta-analysis and its confidence interval are represented as a diamond. The center of the diamond is at the pooled point estimate, and its horizontal tips show the confidence interval.

*Funnel plot:* A graphical display of some measure of study precision plotted against effect size that can be used to investigate whether there is a link between study size and treatment effect.

*Generalizability:* See *External Validity.*

*Half- life:* The time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50%.

Harms: See *Adverse Event*

*Hazard ratio:* The increased risk with which one group is likely to experience an outcome of interest. It is similar to a risk ratio. For example, if the hazard ratio for death for a treatment is 0.5, then treated patients are likely to die at half the rate of untreated patients.

*Head-to-head trial:* A trial that directly compares one drug in a particular class or group with another in the same class or group.

*Health outcome:* The result of a particular health care practice or intervention, including the ability to function and feelings of well-being. For individuals with chronic conditions – where cure is not always possible – results include health-related quality of life as well as mortality.

*Heterogeneity:* The variation in, or diversity of, participants, interventions, and measurement of outcomes across a set of studies.

$I^2$: A measure of statistical heterogeneity of the estimates of effect from studies. Values range from 0% to 100%. Large values of $I^2$ suggest heterogeneity. $I^2$ is the proportion of total variability across studies that is due to heterogeneity and not chance. It is calculated as (Q-(n-1))/Q, where n is the number of studies.

*Incidence:* The number of new occurrences of something in a population over a particular period of time, e.g. the number of cases of a disease in a country over one year.

*Indication:* A term describing a valid reason to use a certain test, medication, procedure, or surgery. In the United States, indications for medications are strictly regulated by the Food and Drug Administration, which includes them in the package insert under the phrase "Indications and Usage".

*Indirect analysis:* The practice of using data from trials comparing one drug in a particular class or group with another drug outside of that class or group or with placebo and attempting to draw conclusions about the comparative effectiveness of drugs within a class or group based on that data. For example, direct comparisons between drugs A and B and between drugs B and C can be used to make an indirect comparison between drugs A and C.

*Intent to treat:* The use of data from a randomized controlled trial in which data from all randomized patients are accounted for in the final results. Trials often incorrectly report results as being based on intent to treat despite the fact that some patients are excluded from the analysis.

*Internal validity:* The extent to which the design and conduct of a study are likely to have prevented bias. Generally, the higher the interval validity, the better the quality of the study publication.

*Inter-rater reliability:* The degree of stability exhibited when a measurement is repeated under identical conditions by different raters.

*Intermediate outcome:* An outcome not of direct practical importance but believed to reflect outcomes that are important. For example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and myocardial infarction (hear attack).

*Logistic regression:* A form of regression analysis that models an individual's odds of disease or some other outcome as a function of a risk factor or intervention.

*Masking*: See *Blinding*

*Mean difference:* A method used to combine measures on continuous scales (such as weight) where the mean, standard deviation, and sample size are known for each group.

*Meta-analysis:* The use of statistical techniques in a systematic review to integrate the results of included studies. Although the terms are sometimes used interchangeably, meta-analysis is not synonymous with systematic review. However, systematic reviews often include meta-analyses.

*Meta-regression:* A technique used to explore the relationship between study characteristics (for example, baseline risk, concealment of allocation, timing of the intervention) and study results (the magnitude of effect observed in each study) in a systematic review.

*Mixed treatment comparison meta analysis:* A meta-analytic technique that simultaneously compares multiple treatments (typical 3 or more) using both direct and indirect evidence. The multiple treatments form a network of treatment comparisons. Also called multiple treatment comparisons, network analysis, or umbrella reviews.

*Monotherapy:* the use of a single drug to treat a particular disorder or disease.

*Multivariate analysis:* Measuring the impact of more than one variable at a time while analyzing a set of data.

*N-of-1 trial:* A randomized trial in an individual to determine the optimum treatment for that individual.

*Noninferiority trial:* A trial designed to determine whether the effect of a new treatment is not worse than a standard treatment by more than a prespecified amount. A one-sided version of an equivalence trial.

*Nonrandomized study:* Any study estimating the effectiveness (harm or benefit) of an intervention that does not use randomization to allocate patients to comparison groups. There are many types of nonrandomized studies, including cohort studies, case-control studies, and before-after studies.

*Null hypothesis:* The statistical hypothesis that one variable (for example, treatment to which a participant was allocated) has no association with another variable or set of variables.

*Number needed to harm:* The number of people who would need to be treated over a specific period of time before one bad outcome of the treatment will occur. The number needed to harm (NNH) for a treatment can be known only if clinical trials of the treatment have been performed.

*Number needed to treat:* An estimate of how many persons need to receive a treatment before one person would experience a beneficial outcome.

*Observational study:* A type of nonrandomized study in which the investigators do not seek to intervene, instead simply observing the course of events.

*Odds ratio:* The ratio of the odds of an event in one group to the odds of an event in another group. An odds ratio of 1.0 indicates no difference between comparison groups. For undesirable outcomes an odds ratio that is <1.0 indicates that the intervention was effective in reducing the risk of that outcome.

*Off-label use:* When a drug or device is prescribed outside its specific FDA-approved indication, to treat a condition or disease for which it is not specifically licensed.

*Outcome:* The result of care and treatment and/ or rehabilitation. In other words, the change in health, functional ability, symptoms or situation of a person, which can be used to measure the

effectiveness of care/treatment/rehabilitation. Researchers should decide what outcomes to measure before a study begins; outcomes are then assessed at the end of the study.

*Outcome measure:* Is the way in which an outcome is evaluated---the device (scale) used for measuring. With this definition YMRS is an outcome measure, and a patient's outcome after treatment might be a 12-point improvement on that scale.

*One-tailed test (one-sided test):* A hypothesis test in which the values that reject the null hypothesis are located entirely in one tail of the probability distribution. For example, testing whether one treatment is better than another (rather than testing whether one treatment is either better or worse than another).

*Open-label trial:* A clinical trial in which the investigator and participant are aware which intervention is being used for which participant (that is, not blinded). Random allocation may or may not be used in open-label trials.

*Per protocol:* The subset of participants from a randomized controlled trial who complied with the protocol sufficiently to ensure that their data would be likely to exhibit the effect of treatment. Per protocol analyses are sometimes misidentified in published trials as intent-to-treat analyses.

*Pharmacokinetics:* the characteristic interactions of a drug and the body in terms of its absorption, distribution, metabolism, and excretion.

*Placebo:* An inactive substance commonly called a "sugar pill." In a clinical trial, a placebo is designed to look like the drug being tested and is used as a control. It does not contain anything that could harm a person. It is not necessarily true that a placebo has no effect on the person taking it.

*Placebo-controlled trial:* A study in which the effect of a drug is compared with the effect of a placebo (an inactive substance designed to resemble the drug). In placebo-controlled clinical trials, participants receive either the drug being studied or a placebo. The results of the drug and placebo groups are then compared to see if the drug is more effective in treating the condition than the placebo is.

*Point estimate:* The results (e.g. mean, weighted difference, odds ratio, relative risk or risk difference) obtained in a sample (a study or a meta-analysis) which are used as the best estimate of what is true for the relevant population from which the sample is taken. A confidence interval is a measure of the uncertainty (due to the play of chance) associated with that estimate.

*Pooling:* The practice of combing data from several studies to draw conclusions about treatment effects.

*Power:* The probability that a trial will detect statistically significant differences among intervention effects. Studies with small sample sizes can frequently be underpowered to detect difference.

*Precision:* The likelihood of random errors in the results of a study, meta-analysis, or measurement. The greater the precision, the less the random error. Confidence intervals around the estimate of effect are one way of expressing precision, with a narrower confidence interval meaning more precision.

*Prospective study:* A study in which participants are identified according to current risk status or exposure and followed forward through time to observe outcome.

*Prevalence:* How often or how frequently a disease or condition occurs in a group of people. Prevalence is calculated by dividing the number of people who have the disease or condition by the total number of people in the group.

*Probability:* The likelihood (or chance) that an event will occur. In a clinical research study, it is the number of times a condition or event occurs in a study group divided by the number of people being studied.

*Publication bias:* A bias caused by only a subset of the relevant data being available. The publication of research can depend on the nature and direction of the study results. Studies in which an intervention is not found to be effective are sometimes not published. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. In addition, a published report might present a biased set of results (for example, only outcomes or subgroups for which a statistically significant difference was found).

*P value:* The probability (ranging from zero to one) that the results observed in a study could have occurred by chance if the null hypothesis was true. A *P* value of ≤0.05 is often used as a threshold to indicate statistical significance.

*Q-statistic:* A measure of statistical heterogeneity of the estimates of effect from studies. Large values of Q suggest heterogeneity. It is calculated as the weighted sum of the squared difference of each estimate from the mean estimate.

*Random-effects model:* A statistical model in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis. When there is heterogeneity among the results of the included studies beyond chance, random-effects models will give wider confidence intervals than fixed-effect models.

*Randomization:* The process by which study participants are allocated to treatment groups in a trial. Adequate (that is, unbiased) methods of randomization include computer generated schedules and random-numbers tables.

*Randomized controlled trial:* A trial in which two or more interventions are compared through random allocation of participants.

*Regression analysis:* A statistical modeling technique used to estimate or predict the influence of one or more independent variables on a dependent variable, for example, the effect of age, sex, or confounding disease on the effectiveness of an intervention.

*Relative risk:* The ratio of risks in two groups; same as a risk ratio.

*Retrospective study:* A study in which the outcomes have occurred prior to study entry.

*Risk:* A way of expressing the chance that something will happen. It is a measure of the association between exposure to something and what happens (the outcome). Risk is the same as probability, but it usually is used to describe the probability of an adverse event. It is the rate of events (such as breast cancer) in the total population of people who could have the event (such as women of a certain age).

*Risk difference:* The difference in size of risk between two groups.

*Risk Factor:* A characteristic of a person that affects that person's chance of having a disease. A risk factor may be an inherent trait, such as gender or genetic make-up, or a factor under the person's control, such as using tobacco. A risk factor does not usually cause the disease. It changes a person's chance (or risk) of getting the disease.

*Risk ratio:* The ratio of risks in two groups. In intervention studies, it is the ratio of the risk in the intervention group to the risk in the control group. A risk ratio of 1 indicates no difference between comparison groups. For undesirable outcomes, a risk ratio that is <1 indicates that the intervention was effective in reducing the risk of that outcome.

*Run-in period*: Run in period: A period before randomization when participants are monitored but receive no treatment (or they sometimes all receive one of the study treatments, possibly in a blind fashion). The data from this stage of a trial are only occasionally of value but can serve a valuable role in screening out ineligible or non-compliant participants, in ensuring that participants are in a stable condition, and in providing baseline observations. A run-in period is sometimes called a washout period if treatments that participants were using before entering the trial are discontinued.

*Safety:* Substantive evidence of an absence of harm. This term (or the term ‘‘safe’’) should not be used when evidence on harms is simply absent or is insufficient.

*Sample size:* The number of people included in a study. In research reports, sample size is usually expressed as "n." In general, studies with larger sample sizes have a broader range of participants. This increases the chance that the study's findings apply to the general population. Larger sample sizes also increase the chance that rare events (such as adverse effects of drugs) will be detected.

*Sensitivity analysis*: An analysis used to determine how sensitive the results of a study or systematic review are to changes in how it was done. Sensitivity analyses are used to assess how robust the results are to uncertain decisions or assumptions about the data and the methods that were used.

*Side effect:* Any unintended effect of an intervention. Side effects are most commonly associated with pharmaceutical products, in which case they are related to the pharmacological properties of the drug at doses normally used for therapeutic purposes in humans.

*Standard deviation (SD):* A measure of the spread or dispersion of a set of observations, calculated as the average difference from the mean value in the sample.

*Standard error (SE):* A measure of the variation in the sample statistic over all possible samples of the same size. The standard error decreases as the sample size increases.

*Standard treatment:* The treatment or procedure that is most commonly used to treat a disease or condition. In clinical trials, new or experimental treatments sometimes are compared to standard treatments to measure whether the new treatment is better.

*Statistically significant:* A result that is unlikely to have happened by chance.

*Study:* A research process in which information is recorded for a group of people. The information is known as data. The data are used to answer questions about a health care problem.

*Study population:* The group of people participating in a clinical research study. The study population often includes people with a particular problem or disease. It may also include people who have no known diseases.

*Subgroup analysis:* An analysis in which an intervention is evaluated in a defined subset of the participants in a trial, such as all females or adults older than 65 years.

*Superiority trial:* A trial designed to test whether one intervention is superior to another.

*Surrogate outcome:* Outcome measures that are not of direct practical importance but are believed to reflect outcomes that are important; for example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and heart attacks. Surrogate endpoints are often physiological or biochemical markers that can be relatively quickly and easily measured, and that are taken as being predictive of important clinical outcomes. They are often used when observation of clinical outcomes requires long follow-up.

*Survival analysis:* Analysis of data that correspond to the time from a well-defined time origin until the occurrence of some particular event or end-point; same as time-to-event analysis.

*Systematic review:* A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research and to collect and analyze data from the studies that are included in the review.

*Tolerability:* For therapeutic drugs, it refers a drug's lack of "nuisance side effects," side effects that are thought to have no long-term effect but that are unpleasant enough to the patient that adherence to the medication regimen is affected.

The extent to which a drug's adverse effects impact the patient's ability or willingness to continue taking the drug as prescribed. These adverse effects are often referred to as nuisance side effects, because they are generally considered to not have long-term effects but can seriously impact compliance and adherence to a medication regimen.

*Treatment regimen*: The magnitude of effect of a treatment versus no treatment or placebo; similar to "effect size". Can be calculated in terms of relative risk (or risk ratio), odds ratio, or risk difference.

*Two-tailed test (two-sided test):* A hypothesis test in which the values that reject the null hypothesis are located in both tails of the probability distribution. For example, testing whether one treatment is different than another (rather than testing whether one treatment is either better than another).

*Type I error:* A conclusion that there is evidence that a treatment works, when it actually does not work (false-positive).

*Type II error:* A conclusion that there is no evidence that a treatment works, when it actually does work (false-negative).

*Validity:* The degree to which a result (of a measurement or study) is likely to be true and free of bias (systematic errors).

*Variable:* A measurable attribute that varies over time or between individuals. Variables can be

- *Discrete*: taking values from a finite set of possible values (e.g. race or ethnicity)
- *Ordinal*: taking values from a finite set of possible values where the values indicate rank (e.g. 5-point Likert scale)
- *Continuous:* taking values on a continuum (e.g. hemoglobin A1c values).

*Washout period*: [In a crossover trial] The stage after the first treatment is withdrawn, but before the second treatment is started. The washout period aims to allow time for any active effects of the first treatment to wear off before the new one gets started.

# Appendix B. Boxed warnings of ADHD drugs

| Trade name | Active ingredient(s) | Boxed warnings |
|---|---|---|
| Adderall XR® | Amphetamine mixture (amphetamine aspartate; amphetamine sulphate; dextroamphetamine saccharate; dextroamphetamine sulfate) | Amphetamines have a high potential for abuse. Administration of amphetamines for prolonged periods of time may lead to drug dependence and must be avoided. Particular attention should be paid to the possibility of subjects obtaining amphetamines for nontherapeutic use or distribution to others and the drugs should be prescribed or dispensed sparingly.<br>Misuse of amphetamine may cause sudden death and serious cardiovascular events. |
| Dexedrine®, Dexedrine Spansule® | Dextroamphetamine sulfate | |
| Vyvanse® | Lisdexamfetamine dimesylate | |
| Concerta®, Daytrana®, Metadate® CD, Ritalin®, Ritalin® SR, Ritalin® LA | Methylphenidate hydrochloride | Drug dependence: These drugs should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic, abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up. |
| Focalin® and Focalin® XR | Dexmethylphenidate hydrochloride | |
| Desoxyn® | Methamphetamine hydrochloride | Methamphetamine has a high potential for abuse. It should be tried only in weight reduction programs for patients in whom alternative therapy has been ineffective. Administration of methamphetamine for prolonged periods of time in obesity may lead to drug dependence and must be avoided. Particular attention should be paid to the possibility of subjects obtaining methamphetamine for non-therapeutic use or distribution to others, and the drugs should be prescribed or dispensed sparingly. Misuse of methamphetamine may cause sudden death and may lead to serious cardiovascular events. |
| Methylin® | Methylphenidate hydrochloride | Drug abuse and dependence: Methylin® should be given cautiously to emotionally unstable patients, such as those with a history of drug dependence or alcoholism, because such patients may increase dosage on their own initiative. Chronically abusive use can lead to marked tolerance and psychic dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during drug withdrawal, since severe depression as well as the effects of chronic overactivity can be unmasked. Long-term follow-up may be required because of the patient's basic personality disturbances. |

| Trade name | Active ingredient(s) | Boxed warnings |
|---|---|---|
| Strattera® | Atomoxetine Hydrochloride | WARNING: SUICIDAL IDEATION IN CHILDREN AND ADOLESCENTS<br>Strattera® (atomoxetine) increased the risk of suicidal ideation in short-term studies in children or adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD). Anyone considering the use of Strattera® in a child or adolescent must balance this risk with the clinical need. Co-morbidities occurring with ADHD may be associated with an increase in the risk of suicidal ideation and/or behavior. Patients who are started on therapy should be monitored closely for suicidality (suicidal thinking and behavior), clinical worsening, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Strattera® is approved for ADHD in pediatric and adult patients. Strattera® is not approved for major depressive disorder.<br>Pooled analyses of short-term (6 to 18 weeks) placebo-controlled trials of Strattera® in children and adolescents (a total of 12 trials involving over 2200 patients, including 11 trials in ADHD and 1 trial in enuresis) have revealed a greater risk of suicidal ideation early during treatment in those receiving Strattera® compared to placebo. The average risk of suicidal ideation in patients receiving Strattera® was 0.4% (5/1357 patients), compared to none in placebo-treated patients (851 patients). No suicides occurred in these trials. |

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# Appendix C. Scales used to assess efficacy and adverse events

The following narrative briefly describes the most commonly used assessment scales and summarizes methods of scoring and validation.

*Aberrant Behavior Checklist (ABC)* is a symptom checklist for assessing problem behaviors of children and adults with mental retardation at home, in residential facilities, ICFs/MR, and work training centers. It is also useful for classifying problem behaviors of children and adolescents with mental retardation in educational settings, residential and community-based facilities, and developmental centers. The ABC asks for degree of retardation, the person's medical status, and current medication condition. Then 58 specific symptoms are rated and an extensive manual gives comprehensive descriptions for each assessed behavior. The checklist can be completed by parents, special educators, psychologists, direct caregivers, nurses, and others with knowledge of the person being assessed.

Extensive psychometric assessment of the ABC has indicated that its subscales have high internal consistency, adequate reliability, and established validity. Average subscale scores are available for both United States and overseas residential facilities and for children and adults living in the community.[1]

*ADHD Behavior Checklist/ADHD Rating Scale* evaluates inattentive and hyperactive-impulsive symptoms, is based on DSM criteria for diagnosing ADHD. DSM-III uses a 14-item checklist while DSM-IV updated it to an 18-item checklist with two nine-item subscales. Items are rated for severity from zero to three according to how often the symptoms are present (0=never/rarely, 1=sometimes, 2=often, and 3=very often). The maximum scores are 42 points and 54 points for DSM-III and DSM-IV respectively. The test-retest reliability was demonstrated. The intraclass correlation coefficient was .90s ($P<0.001$). The content validity and construct validity were proved as well. The checklist has established validity, reliability, and age-matched cut-off values [2, 3]

*ADHDRS- IV or ADHD rating scale IV:* an 18-item scale based on a semistructured interview with the patient's parent by the investigator to assess symptom severity. Each item, corresponding to one of the 18 DSM-IV diagnostic criteria, is rated on a 4-point scale (0 =never or rarely; 1 = sometimes; 2 =often; 3 = very often). This scale has been shown to be a reliable and valid instrument of ADHD symptom severity.[4]

*The ADHDRS-IV-PI* is an 18-item scale assessing ADHD symptoms over the past week based on clinician interviews with patients and parents. Items correspond to symptoms in the DSM-IV diagnosis of ADHD and are scored from 0 to 3 (0 = rarely or never, 3 = very often). The total score is the sum of all of the item scores.[5]

*ADD-H Comprehensive Teacher Rating Scale (ACTeRS)* contains both parent and teacher forms. Both versions are used to assess attention, hyperactivity, social skills, and oppositional behavior in children and adolescents ages 6-14. Each form contains 24 items and takes 5-10 minutes to complete, and measures 4 areas of behaviors. This scale can be used for screening or to measure response to treatments.[6]

*The ADHD Investigator Symptom Rating Scale (AISRS)* is an 18-item scale that helps assess the impact and severity of ADHD among adults. It is clinician-administered scale that assesses each of the 18 individual criteria symptoms of ADHD in DSM-IV on a scale from 0 to 3 (0 =not present; 3= severe). The total score ranges from a minimum of 0 to a maximum of 54.

*The Adult Self-Report Scale (ASRS)* is a checklist of 18 questions about symptoms that are based on the diagnostic criteria of DSM-IV (Diagnostic and Statistical Manual –IV). The scales are rated on a range from 0 to 4 with o being never and 4 being very often. Higher scores on this scale indicate greater symptom severity. This scale has been shown to be valid for assessing ADHD symptom severity.[7]

*The Alabama Parenting Questionnaire (APQ)* is used to assess the five areas of parenting practices that are commonly associated with conduct disorders. The APQ has four components and contains formats for parent and child to respond to questions about "typical" parenting practices used in the home and rate them on a Likert-type scale with 1(Never) to 5 (Always). The APQ also includes a phone interview where the informant is requested to estimate the frequency of parenting behavior over the past 3 days. This questionnaire has been shown to be valid and reliable in assessing parental practices.[8]

*Barkley's Attention Deficit Hyperactivity Disorder Checklist and Scale* is a self-report rating system that measures the occurrence of symptoms. The range of the scale is 0=never or rarely, 1=sometimes, 2=often, and 3=very often. The checklist is used as a measurement to define symptoms of the disorder. No reliability or validity information available. [9]

*Barkley's Stimulants Side Effects Rating Scale* is a 17-item questionnaire that evaluates the severity and the frequency of common side affects in individuals taking stimulant medications. It can be completed by a parent, teachers or child. The side effects scale ranges from 0 (absent) to 9 (severe).[10]

*Barratt Impulsiveness Scale (BIS-10)* is a 34-item scale that covers three types of impulsiveness: motor, cognitive, and non-planning. It consists of a four-point scale ranging ("rarely/never", "occasionally", "often", and "almost always/always"). These three factors are considered reliable under a study with an alpha coefficient range from 0.89 to 0.92. No validity information available.[11]

*Beck Anxiety Inventory (BAI)* quickly assesses the severity of patient anxiety. It was specifically designed to reduce the overlap between depression and anxiety scales by measuring anxiety symptoms shared minimally with those of depression. Both physiological and cognitive components of anxiety are addressed in the 21 items describing subjective, somatic, or panic-related symptoms. In the assessment, the respondent is asked to rate how much he or she has been bothered by each symptom over the past week on a 4-point scale ranging from 0 to 3, and takes about 5 to 10 minutes to complete. The scale obtained high internal consistency and item-total correlations ranging from 0.30 to 0.71 (median=0.60).[12, 13]

*Brown ADD scale* is a 40-item self report scale for assessing the executive function aspects associated with ADHD. The scale has been proved with good internal consistency and good test-

retest reliability. The total score ranges from 0 to 120: patients with score >55 = highly probable ADHD; score 40-54 = 'probable' ADHD; score <40 = 'possible' ADHD.[14]

*Child Behavior Checklist (CBCL)* originally had three axes, the parent report form, teacher report form, and self-report form for children over 11 years of age.[15] But it had been added to have two more axes, which are cognitive assessment and physical assessment from observations and interviews. It was demonstrated to have high reliability and validity through various studies.[16]

*Child Autism Rating Scale or Childhood Autism Rating Scale (CARS)* is a 15 item behavioral rating scale developed to identify children ages 2 years and older with autism, and to distinguish them from developmentally handicapped children without the autism syndrome. It provides quantifiable ratings based on direct behavior observation. The CARS is especially effective in discriminating between autistic children and those children who are considered trainable mentally retarded; it distinguishes children with autism in the mild to moderate range from children with autism in the moderate to severe range. It can also be used to evaluate adolescents or adults who have never received a diagnosis of autism. The CARS includes items drawn from five of the most widely used systems for diagnosing autism. Each item covers a distinct characteristic, ability, or behavior.[17]

*Children's Depression Rating Scale-Revised (CDRS-R)* is a clinician rated instrument that covers 17 symptom areas of depression and used to diagnose depression and can be repeated to measure response to treatments. CDRS-R total scores range from 17 to 113 and Fourteen of the 17 items are rated on a scale from 1 to 7, with an item score of 3 suggestive of mild, 4 or 5 moderate, and 6 or 7 severe symptoms. The other 3 items are rated on a scale from 1 to 5. Both children and their parents provide input into the first 14 items of the scale. A child's nonverbal behavior is rated by the observer for items 15 through 17. A CDRS-R ≥ 40 suggests the presence of depressive disorder. CDRS-R was administered to determine the convergent validity of BDI.[18]

*Children's Global Assessment Scale (CGAS)* is an adaptation of the Global Assessment Scale (GAS). This scale is designed to measure the lowest level of functioning during a specific time period for children aged 4 to 16. Children are rated on a scale of 1 (needs constant supervision) to 100 (superior functioning) with anchor points in between. Scores above 70 indicate normal function. The CGAS has demonstrated discriminate validity ($P$=0.001) in detecting the level of impairment between inpatients and outpatients. The CGAS has also demonstrated concurrent validity with the Conners' ten-item Abbreviated Parent Checklist; the correlation was –0.25 (P > .05, df=17) when used in outpatients.[19]

*Child Health and Illness Profile – Child Edition (CHIP-CE*) is a self-report health status instrument for children 6 to 11 years old that is designed to assess the health and well-being of children. It includes 5 domains: Satisfaction (with self and health), Comfort (emotional and physical symptoms and limitations), Resilience (positive activities that promote health), Risk Avoidance (risky behaviors that influence future health), and Achievement (of social expectations in school and with peers). The internal consistency and test-retest reliability of the domains are good to excellent, with a definite age gradient such that younger children's responses are less reliable although still acceptable. Validity is supported through criterion and construct validity tests and structural analyses. Standard scores (mean, 50; standard deviation, 10) were established. The survey takes about 30 minutes.[20]

*Children's Psychiatric Rating Scale (CPRS)* is a comprehensive, 63-item scale that aims to assess a broad spectrum of psychopathology for children up to age 15. Therefore, items on the CPRS will have varying degrees of relevance when used in a specific diagnostic group. Each item is rated from one (not present) to 7 (extremely severe). But unfortunately, we can't find any information about the reliability and validity of the scale.[21]

*Clinical Global Impression Scale (CGI)* is used in both children and adults and consists of three global scales for rating mental illness. The first two items (severity of illness and global improvement) are rated on a 7-point scale (1 = very much improved, 7 = very much worse). The third item (efficacy index) uses a matrix to rate the effectiveness of therapy in relation to adverse reactions.[27] The CGI includes Global Severity (from 1 to 7; 1 = *not ill*, 3 = *mildly ill*, 5 = *markedly ill*, and 7 = *extremely ill*) and Global Improvement (1 = *very much improved* and 7 = *very much worse*) scales.

*Clinical Global Impression - Improvement Scale (CGI-I)* is a 7-point scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of the intervention. Patients are rated as: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; or 7, very much worse.

*Clinical Global Impression - Severity Scale (CGI-S)* is a 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis. Considering total clinical experience, a patient is assessed on severity of mental illness at the time of rating 1, normal, not at all ill; 2, borderline mentally ill; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; or 7, extremely ill.

*CGI-ADHD-S* is a single-item rating of the clinician's assessment of the global severity of ADHD symptoms in relation to the clinician's total experience with other ADHD patients. Severity was rated on a 7-point scale (1 =normal, not at all ill; 7 = among the most extremely ill).[4]

*Conners' Abbreviated Questionnaires (ASQ-P)* is an abbreviated version of the CPRS. It contains 10 items only, and is known as the Hyperactivity Index. The inter co-relation of ASQ–P and CPRS-R was high as 0.87 in the hyperactive factor that demonstrated the ASQ-T's ability to identify children's hyperactive behaviors.[28] Parents rate their child's symptoms from zero to three (0=not at all present, 1=just a little present, 2=pretty much present, 3=very much present), which yields a range of possible total scores between 0 and 30.

*Conners' Abbreviated Questionnaires (ASQ-T)* is an abbreviated version of the CTRS. It contains 10 items only, and is known as the Hyperactivity Index. The intercorrelation of ASQ –T and CTRS-R was high from .79-.90 that demonstrated the ASQ-T's ability to identify children's problem behaviors.[28]

*Conners' Adult ADHD Rating Scale (CAARS)* was used to assess adult symptomatology. The scale consists of 66-items that are rated using a 4-point Likert scale (ranging from "0" for "not at all true" to "3" for "very much true"). Four factors emerge from this 66-item scale: Inattention/Cognitive Problems, Hyperactivity/Restlessness, Impulsivity/Emotional Lability, and Problems with Self-Concept. An ADHD index score comprised of 12 CAARS items can also be derived that is highly related to ADHD diagnosis. Sensitivity and specificity of the ADHD Index score are 71% and 75% respectively (Conners et al., 1999). The reliability and validity of the CAARS factors are satisfactory; internal reliability of the factor scales ranged between .86 and .92; test-retest reliabilities ranged between .88 and .91.[29]

*Conners, Loney and Milich Rating (CLAM) Scale* is a 13-item questionnaire that measures classroom ADHD symptoms and yields the IOWA Conners' Scale, with divergently valid factors of inattention/overactivity and aggression/defiance. It has been shown to be sensitive to medication effects in the analog classroom and in the natural environments of home and school.[30]

*Conners' Parent Rating Scale (CPRS)* is a 93-item parent rating scale to evaluate children's psychiatric symptoms. It is the original version of the CPRS. Parents rate their child's symptoms from one to four (1=not at all present, 2=just a little present, 3=pretty much present, 4=very much present).[22] A newer version of this scale is now available (CPRS-R).[31]

*The 48-item Conners' Parent Rating Scale – Revised (CPRS-R)* is a revised version of the 93-item Conners' Parent Rating Scale and includes norms down to age three. Parents rate their child's symptoms from zero to three (0=not at all present, 1=just a little present, 2=pretty much present, 3=very much present).[28]

*Conners' Teacher Rating Scale (CTRS)* is a 39-item teacher rating scale teachers use to evaluate children's symptoms and behaviors before and after medication. The four-points scale (1-not at all, 2-just a little, 3-quite a bit, and 4-very much) was rated. Factor analysis was used to prove the stability of the scale. It is highly sensitive to drug effectiveness.[22] Teachers rate their child's symptoms from zero to three (0=not at all present, 1=just a little present, 2=pretty much present, 3=very much present), which yields a range of possible total scores between 0 and 30.

*The 28-item Conners' Teacher Rating Scale – Revised (CTRS-R)* is a revised version of the 48-item Conners' Teacher Rating Scale and includes norms down to age three. Teachers rate their child's symptoms from zero to three (0=not at all present, 1=just a little present, 2=pretty much present, 3=very much present). [28]

*Conners' Teacher Rating Scale Revised Short-Form (CTRS-R-S) & Conners' Parent Rating Scale Revised Short-Form (CPRS-R-S)* each contains four subscales that are approximately one-third to one-half the length of their longer counterparts: 27 items comprise the CPRS-RS and 28 items comprise the CTRS-RS. Parents and teachers are asked to consider the child's behavior during the past month and rate their occurrence on a 4 point scale (not at all true, just a little true, pretty much true or very much true.[32]

*The Consensus Clinical Response (CCR)* measures the overall improvement of the patient for each week of a trial. It is scored on a 4-point scale ranging from 0 (nonresponder) to 3 (moderate response). The CCR combines and assesses multiple factors that can possibly affect and be relevant to the patient's improvement.

*Continuous Paired-Associate Learning Test (CPALT)* is a paired-associate learning task that uses consonant pairs as stimulus terms (S) and digits (0-9) as response terms (R). At each session, the computer randomly generates the pairing of stimulus and response, and the sequence in which the pairs are presented. The subject is instructed to memorize the digit (R) associated with each pair of consonants (S). The task begins with the presentation of an S-R pair for study for 8 seconds, followed by a test sequence in which only the stimulus term is presented. The subject is allowed 5 seconds to key in the corresponding response term. If the response is correct, the S-R pair is presented again simultaneously with a "YES". Then a new S-R pair is presented for study and added to the S-R pool. This sequence continues until an error is made. If the response was incorrect or not forthcoming in the allotted time, the correct answer is displayed. The earliest presented pair is then dropped from the active S-R string and the subject is immediately tested on the remaining pairs. If two errors are made, the two earliest presented pairs are dropped, and so forth. Although the presentations are uninterrupted, this test format permits the subdivision of the total block of trials into a set of comparable epochs for subsequent scoring. The test continues for 30 minutes. It is arbitrarily subdivided into 10 epochs, each of which lasts 3 minutes.[33]

*Continuous Performance Test (CPT)* is a monitoring task in which subjects are given a series of visual or auditory stimuli and are asked to press a button when certain infrequent target stimuli appear. There is no standardized version. There is usually a "low-level" version and a more sophisticated version where the stimulus may or may not be a target depending on what precedes it in the series.[22-26]

*Copeland Symptom Checklist for Adult Attention Deficit Disorder*, an 8-category, 63-item checklist with each item rated on a severity scale from 0 (symptoms not present) through 4 (very much present). It contains the information about cognitive, emotional and social symptoms. Its validity and reliability have been established, but we were unsuccessful in retrieving the original source, "Copeland Symptom Checklist for Adult Attention Deficit Disorders".[34]

*Diagnostic Interview Schedule for Children (DISC-IV)* was developed by the National Institute of Mental Health and is a highly structured psychiatric diagnostic interview designed to assess DSM-IV psychiatric disorders and symptoms in children and adolescents aged 6 to 17 years. The DISC was designed to be given by lay interviewers for epidemiological research. It has a parent and a child version, both of which ask about the child's psychiatric symptoms. The majority of DISC questions have been worded so that they can be answered "yes," "no," and "somewhat" or "sometimes".[35]

*Driver behavior survey (DBS)* is a 26-item scale in children and adults with attention deficit hyperactivity disorder (ADHD). Questions are rated on a scale of 1 to 4 with a possible maximum score of 104. The items assess the driving and safety behaviors of the driver with scores ranging from 1 = not at all or rarely and 4= very often. The questionnaire can be completed by the patient or by an individual that is familiar with the patient's driving. Lower

scores on the DBS indicates less safe driving behaviors. The survey has been shown to be valid in assessing driver behaviors.[36]

*DuPaul ADHD Rating Scale IV* consists of 18 items adapted from the symptom list for ADHD delineated in the DSM-IV. Factor analytic studies have indicated that the nine-item Inattention factor and the nine-item Hyperactivity-Impulsivity factor of this measure closely correspond to the two-dimensional structure in the DSM-IV. Estimates of internal consistency, test--retest reliability, and concurrent validity strongly support the psychometric integrity of this measure.[37]

*Global Assessment Scale (GAS)* is a single rating scale for assessing the overall functioning of a patient. The scale values range from 1 to 100, with 1 being the hypothetical sickest person and 100 being the hypothetical healthiest person. There are ten equal intervals ranging from 1-10, 11-20, 21-30 and so on up until 91-100; if a patient falls in the upper two intervals, it is considered "positive mental health." A patient is rated based on observing his behavior during the preceding week and comparing it to the current time period, and adjustments are made to base on specific characteristics defined in each interval. The GAS is found to have good reliability based on five studies with an intraclass correlation coefficient range of 0.61 to 0.95 and an associated standard error of measurement range of 5.0 to 8.0 units. Strong concurrent validity was proved as well. [38]

*Hamilton Anxiety Scale (HAMA or HAM-A)* is a rating scale developed to quantify the severity of anxiety symptomatology, often used in psychotropic drug evaluation. It consists of 14 items, each defined by a series of symptoms. Each item is rated on a 5-point scale, ranging from 0 (not present) to 4 (severe).[39]

*"How I Feel" Questionnaire*, a 28-item scale, is an adaptation of the van Kammen-Murphy Mood Scale, which has been proved to be sensitive to the effects of amphetamine. It uses 4-point scale: 0= "not at all"; 1="a little"; 2="some"; 3="a lot". No reliability or validity information is available.[40]

*Impaired Driving Score (IDS)* is used to compare the various aspects of driving poorly, and the score represents an accumulative effect size across the multiple driving variables: summed SDs of steering, driving off the road, veering across the midline, inappropriate braking while on the open road, missed stopped signals, collisions, exceeding speed limit, SD of speed, time at stop sign deciding when to turn left, and time to complete left turns. A higher IDS reflects poorer driving skill, with more driving across midline and off road, more speeding, higher SD of speed, less time spent at stop signs and executing left turns, and more crashes. An IDS of 0 represents average driving, an IDS less than 0 represents better than average driving (e.g., an IDS of -1 represents driving performance 1 SD better than average), and an IDS greater than 0 represents worse than average driving.[41]

*Inattention/Overactivity With Aggression Conners' Teacher Rating Scale (IOWA CTRS)* is revised from the 39-item Conners' Teacher scale. 10 items were devised to determine Inattention-Overactivity (IO) and aggression (A) behaviors. Teachers rate their child's symptoms from zero to three (0=not at all, 1=just a little, 2=pretty much, 3=very much). Coefficient alpha was tested as .89 for the IO scale and .86 for the A scale. They only tested the sensitivity and specificity scores of the IO scale, and the scores depend on the screen score being rated. Therefore, it recommended the use of an IO scale for at least 11 points for research purpose, and

7 points for clinical purpose.[42] The differential validity of IO and A factors had been tested as well.[43]

*Life Participation Scale for ADHD-Revised (LPS-ADHD-R)* is a 24- item, parent-rated scale assessing changes in adaptive functioning related to ADHD treatment.[5]

*Mental Component Summary (MCS)* provides the clinician with information on the patient's HRQL summarized in just two values, thereby reducing the number of statistical analyses needed and offering easier interpretation of the data. The MCS have been demonstrated to have good discriminant validity for identifying differences between clinically meaningful groups.[44]

*Montgomery Asberg Depression Rating Scale (MADRS):* The MADRS was originally a subscale of Comprehensive Psychopathological Rating Scale, developed by Montgomery and Asberg in 1979. This scale measures the effect of treatment on depression severity, and as such requires a baseline assessment (before treatment) with subsequent assessments during course of treatment. The MADRS measures the severity of a number of symptoms on a scale from 0-6 (Table 2), including mood and sadness, tension, sleep, appetite, energy, concentration, suicidal ideation and restlessness.[45]

*Multidimensional Anxiety Scale for Children (MASC)* is a 39-item self-report scale assessing physical symptoms, social anxiety, harm avoidance, and separation anxiety using an anchored ordinal scale from 0 (never true) to 3 (often true) that shows excellent internal and test-retest reliability (score range 0-117).[5]

*Pediatric Anxiety Rating Scale (PARS)* assesses frequency, severity, and associated impairment of separation anxiety, social phobia, and generalized anxiety symptoms based on clinician interviews with patients and parents. Items were derived from DSM-IV criteria for anxiety disorders. A checklist is used to assess symptoms experienced during the preceding 7 days. The clinician then integrates child and parent reports to rate each symptom on 7 dimensions using a 6-point scale (0 = none, 1Y5 = minimal to extreme). The PARS total score (ranging from 0 to 25) is the sum of scores on five of the 7 dimensions.[5]

*Permanent Product Measure of Performance (PERMP)* is an age-adjusted collection of math problems that measures a child's ability to pay attention and stay on task as demonstrated by an increase in the number of attempted and successfully completed problems.[46] It is a validated 10-min math test developed to evaluate response to stimulant medication. Con taining 400 age-appropriate math problems, the test is scored to obtain an objective measure of academic performance by grading the number of attempted (PERMP-A) and completed problems. Subjects are given different levels of the math test based on their ability, as determined by a math pretest completed during the practice visit. Different versions of the math tests for a given level are used across the multiple classroom sessions so that subjects did not repeat the same test more than once during the classroom day. PERMP has been shown to be sensitive to dosage and time effects of stimulant medications.[47]

*Personality Inventory for Children-Revised (PIC-R):* This empirically derived 280-item true/false instrument (caregiver report) assesses psychosocial adjustment in preschool through adolescent youths. Twelve scales measure three development dimensions (achievement, development,

intelligence) and nine adjustment dimensions (anxiety, depression, delinquency, family relations, hyperactivity, psychosis, social skills, somatic concern, and withdrawal). The scales are interpreted through actuarial guidelines derived for T-score ranges that vary by scale.[48]

*Physician's Global Rating Scale* is a 7-point rating of the overall functioning of a patient. The physician rates the patient improvement on a scale from –3 to +3. The number measures the change seen in the patient (–3=marked worsening, –2=moderate worsening, –1=slight worsening, 0=no change, +1=mild improvement, +2=moderate improvement, +3=marked improvement). No validity or reliability information is available.[49]

*Physician's Target Symptom Scale* is a four-point rating scale, ranging from 0 to 3 (0=not at all, 1=mild, 2=moderate, 3=marked). It measures specific symptoms of attention deficit disorder: conduct disorder (CD), disorganization, depression, temper, short attention span, and hyperactivity. No validity or reliability information is available. [49]

*Preschool Behavior Questionnaire (PBQ)* represents a modification to the Children's Behavior Questionnaire (Rutter, 1967). Developed as a screening instrument for use by mental health professionals, the PBQ identifies preschoolers who indicate symptoms of emotional problems. This instrument can also be used as a pre- and post test measure of children to show changes in behavior over time. During the 34-month period since its publication in late 1974, the scale has been used to a considerable extent in the screening of young children. Those who have used the scale evaluate it highly. However, the variations in the application of the scale provide clear indications that additional normative data are needed, as well as additional research in the area of the relationship between behavior rating scales and behavior observation techniques.[50-52]

*Profile of Mood States (POMS)* is a self-report measure of mood states that can be used to monitor transient or fluctuating affective states in therapeutic and research environments. The items on the scale were derived from a list of 100 different adjective scales using repeated factor analysis. There are three versions: the POMS Standard which includes 65 items, the POMS Brief which includes 30 items, and the POMS Bipolar version (POMS-Bi) which includes 72 items. Respondents rate a series of mood states (such as "Untroubled" or "Sorry for things done") based on how well each item describes the respondent's mood during one of three time frames (i.e., during the past week, including today; right now; other). Normative data are based on the "during the past week, including today" time frame. The POMS Standard form takes approximately 10 minutes to complete, and the respondent rates each item on a 5-point scale ranging from "Not at all" to "Extremely". The POMS Brief form, which is ideal for use with patients for whom ordinary tasks can be difficult and time-consuming, uses the same scale as the POMS Standard form, but contains only 30 items. It takes only 5 minutes to complete. Both the POMS Standard and POMS Brief assessments measure 6 identified mood factors: tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment. They are designed for people ages 18 and older. Numerous studies have shown it to be a valid and strong measure of mood states. Internal consistency for all items was 0.90 or above, test-retest reliability ranged between 0.65 for Vigor and 0.74 for Depression.[53, 54]

*The Restricted Academic Situation Scale (RASS)* is a tool that measures and assesses 5 specific behaviors (off-task, playing with objects, out of seat, vocalizing and fidgeting) of a child as the

child performs specific academic tasks, within a clinical setting, that are appropriate for the child's current grade. This scale assesses a child's sustained attention while performing academic work with potential distractions present and lacking adult supervision. The score for this scale is the total number of recorded behavioral events of the child during the task in the 15 minute period. This scale has been validated for determining children with ADHD according to behavioral conduct.[55]

*Revised Behavioral Problem Checklist (RBPC)* is used to rate problem behaviors observed in adolescents and young children. The RBPC has been used for a variety of purposes: to screen for behavior disorders in children; as an aid in clinical diagnosis; to measure behavior change associated with psychological and pharmacological interventions; as part of a battery to classify juvenile offenders; and to select subjects for research on behavior disorders in children and adolescents. The RBPC yields factorially 6 independent subscales: CD, AP, AW, SA, PB and ME. Alpha reliabilities for the 6 scales from 6 different samples have ranged from .70 (for ME) to .95 (for CD). Teacher ratings over a 2 month interval on a sample of 149 public school children in grades 1 to 6 produced reliabilities ranging from .83 (for AP) to .49 (for SA). Although the values for SA and PB were attenuated for very limited variances for these subscales, 85% and 94% of the sample received exactly the same score at both times for SA and PB respectively. [50, 56]

*Safe Driving Behavior Rating Scale* contains 26 items that assess the participant's driving behavior and skills in a number of areas including braking properly at intersections, driving within the speed limit, keeping the radio at reasonably low volume, using mirrors properly, staying a safe distance from other vehicles, and so forth. Each item is rated on a 1 to 4 Likert-type scale (corresponding to *not at all, sometimes, often,* and *very often,* respectively). Higher scores reflect better driving behavior and use of sound driving habits. This scale has been validated.[57]

*SCL-90 Rating Scale* is a self-report clinical rating scale. It uses a 90-item checklist that covers nine symptom constructs, and three global indices of pathology. It consists of a five-point scale that measures the amount of distress a patient has felt to identify symptomatic behavior of psychiatric outpatients: 0=not at all, 1=a little bit, 2=moderately, 3=quite a bit, 4=extremely. There is evidence of strong convergent validity when compared to MMPI. No reliability information is available.[58, 59]

*Selective Reminding Test (SRT)*: The SRT as developed by Buschke, measures verbal learning and memory during a multiple-trial list-learning task. Participants are read a list of 12 common words and are immediately asked to recall as many of these words as possible. Participants are given a minute for recall, which is immediately followed by the next trial. Each subsequent learning trial involves the selective presentation of only those items that were not recalled on the immediately preceding trial. After the selective presentation (or "reminding") of the missed words, the subject is asked to recall as many words as possible from the whole list. There are 12 trials in all. There are multiple forms of the word list. The SRT is included as a measure of immediate recall and learning and allows for a fine-grained analysis of encoding, storage and retrieval mechanisms.[60]

*Sheehan Disability Scale (SDS)*, a three-item instrument for assessing psychiatric impairment in occupational, social and family functioning, each rated from 0 to 10 (0-3: mild impairment; 4-6: moderate impairment; 7-10: severe impairment). Internal consistency reliability was demonstrated with the coefficient alpha was 0.89 for three-item scale. Reliability of each item ranged from 0.67 for work impairment to 0.77 for family impairment and 0.81 for social impairment. The construct validity was proved as well.[61]

*SF-36 Health Survey* is a 36-item instrument for measuring health status and outcomes from the patient's point of view. Designed for use in surveys of general and specific populations, health policy evaluations, and clinical practice and research, the survey can be self administered by people 14 years of age or older, or administered by trained interviewers either in person or by telephone. The SF-36® measures the following 8 health concepts, which are relevant across age, disease and treatment groups: limitations in physical activities because of health problems; limitations in usual role activities because of physical health problems; bodily pain; general health perceptions; vitality (energy and fatigue); limitations in social activities because of physical or emotional problems; limitations in usual role activities because of emotional problems; and mental health (psychological distress and well-being). The survey's standardized scoring system yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. Accordingly, the SF-36 has proven useful in surveys of general and specific populations, comparing the relative burden of diseases, and in differentiating the health benefits produced by a wide range of different treatments.[62, 63]

*The Social Skills Rating System (SSRS)* is a self-report instrument with each item having fixed choices for the rater to select. The SSRS comes in many different versions because it depends on who the rater is and the age and grade of the child being rated. There are different forms for teachers, parents and children. The number of items for the scales range between 34 to 55 and they are all rated on a 3-point Likert scale.[64]

*The Strengths and Weaknesses of ADHD symptoms and Normal behavior scale (SWAN)* consist of 18 items and is derived from the DSM-IV-TR. The scale measures attention problems and positive attention skills. It uses a 7-point scale to rate behavior with the following options: –3=far below average, –2=below average, –1=slightly below average, 0=average, 1=slightly above average, 2=above average and 3=far above average. Scores are averaged to range from –3 to 3 with negative scores indicating better attention behaviors.

*Swanson, Conners, Milich and Pelham Scale* is a 13-item questionnaire that measures the ability to function in the classroom, follow instructions, complete tasks, and perform accurately. Its two variables, attention and deportment, are sensitive to stimulant medication time-response effects in multiple cycle assessments.[30]

*Swanson, Kotlin, Agler, M-Flynn and Pelham (SKAMP) scale* is a 15-item scale. Ten items describe typical behaviors in a classroom setting and other five items were used for recording specific behavior. [65] Items are rated on a 7-point impairment scale (none, slight, mild, moderate, severe, very severe, and maximal). The reliabilities were from .70 to .78 for the SKAMP

Attention ratings, and were from .63 to .73 for the SKAMP Deportment ratings. The concurrent validity was established by calculating correlations with Conners and the IOWA Conners' Rating scale.[66] SKAMP comprises of two subscales (deportment [SKAMPDS] and attention [SKAMP-AS]).[47]

*Swanson, Nolan, and Pelham-IV Questionnaire (SNAP-IV Rating Scale)* was the first of many scales to present DSM criteria in a rating scale format and has been updated with each DSM revision. It has been widely used in research. The shortened and most frequently used version of the SNAP-IV includes core DSM-IV-derived ADHD subscales along with summary questions in each domain. An extended version adds symptom criteria for comorbid DSM-IV disorders, making it more like the CRS-R. The SNAP-IV and scoring information are conveniently provided free at www.ADHD.net. Its free availability has made the SNAP-IV popular in clinical practice and an alternative to the CRS-R. The SNAP-IV is sensitive to treatment effects and is frequently used for monitoring treatment. The full version has 90 items and takes 20-30 minutes to complete; the shorter ADHD + ODD version has 31 items for and takes 5-10 minutes to complete. The scale has 4 ratings, from "not at all" to "very much." It was developed by Swanson, Nolan, and Pelham.[67]

*Targeted Adult Attention Deficit Disorder Scale (TAADDS)* is a semi-structured interview that consists of the seven target symptoms that are the defining attributes of the Utah Criteria: attention, hyperactivity, temper, mood instability, over-reactivity, disorganization and impulsivity. The instrument assesses core ADHD symptoms, as well as other associated symptoms such as anger and mood lability. Anchor points range from "0" (none) to "4" (very much).[68]

*Wender Utah Rating Scale (WURS)* is a 61-item scale for adults to evaluate childhood behavior. It has been demonstrated to be sensitive in identifying childhood attention deficit hyperactivity disorder. It is rated on the five-point scale: 'not at all or slightly', 'mildly', 'moderately', 'quite a bit', and 'very much'. A subset of 25 of the items successfully identified 86% of patients diagnosed with ADHD and 99% of the normal, control individuals [69]. The test-retest reliability was proved with Cronbach alpha ranged from .69 to .90. The validity was demonstrates as well with factor analysis.[70, 71]

*Wechsler Intelligence Scale for Children, 3rd edition (WISC-III)* is an instrument assessing the intellectual ability of children aged 6 to16 years. It consists of different measures to estimates individual's intellectual abilities. Each subtest is derived from four factors, verbal comprehension, perceptual organization, freedom from distractibility and processing speed. The reliability coefficients of the subscales are from .69-.96. Besides, it has been demonstrated in construct validity and internal validity.[72] This scale supersedes the WISC-R scale.

*Werry-Quay Direct Observational System* assesses behaviors including out-of-seat; physical contact or disturbing others; audible noise; ninety-degree turn, seated; inappropriate vocalizations; other deviant behaviors; and daydreaming. Retrieval of reliability and validity findings [73] are pending and will be addressed in the updated report.

*Wender-Reimherr Adult Attention Deficit Disorder Scale (WRADDS)* is intended to measure the severity of the target symptoms of adults with ADHD using the Utah Criteria, which Wender developed. It measures symptoms in 7 categories: attention difficulties, hyperactivity/restlessness, temper, affective lability, emotional overreactivity, disorganization, and impulsivity. The scale rates individual items from 0 to 2 (0 = not present, 1 = mild, 2 = clearly present) and summarizes each of the 7 categories on a 0-to-4 scale (0 = none, 1 = mild, 2 = moderate, 3 = quite a bit, 4 = very much). The WRAADS may be particularly useful in assessing the mood lability symptoms of ADHD.[74]

*Yale Global Tic Severity Scale (YGTSS)* is a clinical instrument designed to be used by experienced clinicians for the assessment of TIC severity in children, adolescents, and adults. Clinicians rate the severity of motor and phonic Tics of the patient with respect to 5 dimensions: number, frequency, intensity, complexity and interference. A 6-point scale was developed for each area, which contains descriptive statements and examples. A higher YGTSS score indicates severe symptoms. This scale has been shown to be reliable and valid for the assessment of Tic severity. [75] The YGTSS supersedes the Tourette's Syndrome Global Scales (TSGS).

*Young Mania Rating Scale (YMRS)* This scale is used to assess disease severity in patients already diagnosed with mania. This 11-item scale is intended to be administered by a trained clinician who assigns a severity rating for each item based on a personal interview. [45]

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# Appendix D. Search strategies Update 4

*Searches were repeated in July 2011 to identify additional citations.*

Database: Ovid MEDLINE(R) without Revisions <1996 to January Week 4 2011>
Search Strategy:
---

1 exp Amphetamine/ or "amphetamine$".mp. (10584)
2 adderall.mp. (113)
3 atomoxetine.mp. (645)
4 strattera.mp. (38)
5 dexmethylphenidate.mp. (43)
6 focalin.mp. (15)
7 dextroamphetamine.mp. or exp Dextroamphetamine/ (1340)
8 dexedrine.mp. (21)
9 dextrostat.mp. (0)
10 methylphenidate.mp. or exp Methylphenidate/ (3023)
11 concerta.mp. (67)
12 metadate.mp. (20)
13 methylin.mp. (1)
14 Ritalin.mp. (272)
15 biphentin.mp. (1)
16 modafinil.mp. (816)
17 provigil.mp. (29)
18 Alertec.mp. (0)
19 methamphetamine.mp. or exp methamphetamine/ (4493)
20 desoxyn.mp. (0)
21 lisdexamfetamine.mp. (52)
22 vivanse.mp. (0)
23 daytrana.mp. (4)
24 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 (16739)
25 Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (11409)
26 Attention deficit disorder.mp. (11586)
27 attention deficit$.mp. (14584)
28 adhd.mp. (8178)
29 25 or 26 or 27 or 28 (14858)
30 24 and 29 (2712)
31 (2009$ or 2010$ or 2011$).ed. (1459797)
32 30 and 31 (590)
33 limit 32 to (english language and humans) (435)
34 limit 33 to (clinical trial, all or clinical trial or comparative study or controlled clinical trial or evaluation studies or meta analysis or multicenter study or randomized controlled trial or "review") (248)
35 observational stud$.mp. or exp Cohort Studies/ or cohort$.mp. or exp Retrospective Studies/ or retrospective$.mp. (823043)

36 33 and 35 (67)
37 34 or 36 (284)

Database: Ovid MEDLINE(R) without Revisions <1996 to January Week 4 2011>
Search Strategy:
---
1 exp Amphetamine/ or "amphetamine$".mp. (10584)
2 adderall.mp. (113)
3 atomoxetine.mp. (645)
4 strattera.mp. (38)
5 dexmethylphenidate.mp. (43)
6 focalin.mp. (15)
7 dextroamphetamine.mp. or exp Dextroamphetamine/ (1340)
8 dexedrine.mp. (21)
9 dextrostat.mp. (0)
10 methylphenidate.mp. or exp Methylphenidate/ (3023)
11 concerta.mp. (67)
12 metadate.mp. (20)
13 methylin.mp. (1)
14 Ritalin.mp. (272)
15 biphentin.mp. (1)
16 modafinil.mp. (816)
17 provigil.mp. (29)
18 Alertec.mp. (0)
19 methamphetamine.mp. or exp methamphetamine/ (4493)
20 desoxyn.mp. (0)
21 lisdexamfetamine.mp. (52)
22 vivanse.mp. (0)
23 daytrana.mp. (4)
24 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 (16739)
25 Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (11409)
26 Attention deficit disorder.mp. (11586)
27 attention deficit$.mp. (14584)
28 adhd.mp. (8178)
29 25 or 26 or 27 or 28 (14858)
30 Central Nervous system Stimulants.mp. or exp Central Nervous System Stimulants/ (38845)
31 24 or 30 (44848)
32 29 and 31 (3446)
33 diversion.mp. (6404)
34 exp Substance-Related Disorders/ (135546)
35 ((drug$ or substance$ or stimula$) adj3 (abus$ or addict$)).mp. (35433)
36 (misuse$ or misusing).mp. (7077)
37 exp Behavior, Addictive/ (3156)
38 (addict$ adj3 behav$).mp. (4053)
39 (drug$ adj3 seek$).mp. (1272)

40 33 or 34 or 35 or 36 or 37 or 38 or 39 (159162)
41 32 and 40 (469)
42 illegal$.mp. (3656)
43 unlawful$.mp. (181)
44 illicit$.mp. (5269)
45 criminal$.mp. (8535)
46 42 or 43 or 44 or 45 (16948)
47 32 and 46 (40)
48 41 or 47 (474)
49 limit 48 to (english language and humans) (397)
50 (2009$ or 2010$ or 2011$).ed. (1459797)
51 49 and 50 (83)
52 limit 51 to (clinical trial, all or clinical trial or comparative study or controlled clinical trial or evaluation studies or meta analysis or multicenter study or randomized controlled trial or "review") (41)
53 observational stud$.mp. or exp Cohort Studies/ or cohort$.mp. or exp Retrospective Studies/ or retrospective$.mp. (823043)
54 51 and 53 (12)
55 52 or 54 (48)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2010>
Search Strategy:
---
1 exp Amphetamine/ or "amphetamine$".mp. (1106)
2 adderall.mp. (45)
3 atomoxetine.mp. (146)
4 strattera.mp. (7)
5 dexmethylphenidate.mp. (17)
6 focalin.mp. (8)
7 dextroamphetamine.mp. or exp Dextroamphetamine/ (512)
8 dexedrine.mp. (15)
9 dextrostat.mp. (0)
10 methylphenidate.mp. or exp Methylphenidate/ (1203)
11 concerta.mp. (31)
12 metadate.mp. (6)
13 methylin.mp. (0)
14 Ritalin.mp. (104)
15 biphentin.mp. (1)
16 modafinil.mp. (277)
17 provigil.mp. (7)
18 Alertec.mp. (0)
19 methamphetamine.mp. or exp methamphetamine/ (250)
20 desoxyn.mp. (0)
21 lisdexamfetamine.mp. (13)
22 vivanse.mp. (0)
23 daytrana.mp. (0)
24 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 (2731)

25 Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (1154)
26 Attention deficit disorder.mp. (1274)
27 attention deficit$.mp. (1548)
28 adhd.mp. (1008)
29 25 or 26 or 27 or 28 (1707)
30 24 and 29 (960)
31 limit 30 to yr="2009 -Current" (74)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2010>
Search Strategy:
---
1 exp Amphetamine/ or "amphetamine$".mp. (1106)
2 adderall.mp. (45)
3 atomoxetine.mp. (146)
4 strattera.mp. (7)
5 dexmethylphenidate.mp. (17)
6 focalin.mp. (8)
7 dextroamphetamine.mp. or exp Dextroamphetamine/ (512)
8 dexedrine.mp. (15)
9 dextrostat.mp. (0)
10 methylphenidate.mp. or exp Methylphenidate/ (1203)
11 concerta.mp. (31)
12 metadate.mp. (6)
13 methylin.mp. (0)
14 Ritalin.mp. (104)
15 biphentin.mp. (1)
16 modafinil.mp. (277)
17 provigil.mp. (7)
18 Alertec.mp. (0)
19 methamphetamine.mp. or exp methamphetamine/ (250)
20 desoxyn.mp. (0)
21 lisdexamfetamine.mp. (13)
22 vivanse.mp. (0)
23 daytrana.mp. (0)
24 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 (2731)
25 Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (1154)
26 Attention deficit disorder.mp. (1274)
27 attention deficit$.mp. (1548)
28 adhd.mp. (1008)
29 25 or 26 or 27 or 28 (1707)
30 Central Nervous system Stimulants.mp. or exp Central Nervous System Stimulants/ (3771)
31 24 or 30 (4855)
32 29 and 31 (988)
33 diversion.mp. (209)

34 substance abuse.mp. or exp Substance-Related Disorders/ (7400)
35 misuse.mp. (258)
36 addictive behavior.mp. or exp Behavior, Addictive/ (215)
37 35 or 33 or 34 or 36 (7836)
38 32 and 37 (30)
39 limit 38 to yr="2009 -Current" (3)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to January 2011>
Search Strategy:
---
1 exp Amphetamine/ or "amphetamine$".mp. (67)
2 adderall.mp. (2)
3 atomoxetine.mp. (13)
4 strattera.mp. (0)
5 dexmethylphenidate.mp. (4)
6 focalin.mp. (4)
7 dextroamphetamine.mp. or exp Dextroamphetamine/ (21)
8 dexedrine.mp. (6)
9 dextrostat.mp. (1)
10 methylphenidate.mp. or exp Methylphenidate/ (47)
11 concerta.mp. (4)
12 metadate.mp. (0)
13 methylin.mp. (1)
14 Ritalin.mp. (8)
15 biphentin.mp. (0)
16 modafinil.mp. (21)
17 provigil.mp. (3)
18 Alertec.mp. (0)
19 methamphetamine.mp. or exp methamphetamine/ (17)
20 desoxyn.mp. (0)
21 lisdexamfetamine.mp. (1)
22 vivanse.mp. (0)
23 daytrana.mp. (1)
24 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 (113)
25 Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (12)
26 Attention deficit disorder.mp. (21)
27 attention deficit$.mp. (64)
28 adhd.mp. (35)
29 25 or 26 or 27 or 28 (69)
30 24 and 29 (30)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to January 2011>
Search Strategy:
---
1 exp Amphetamine/ or "amphetamine$".mp. (67)

2 adderall.mp. (2)
3 atomoxetine.mp. (13)
4 strattera.mp. (0)
5 dexmethylphenidate.mp. (4)
6 focalin.mp. (4)
7 dextroamphetamine.mp. or exp Dextroamphetamine/ (21)
8 dexedrine.mp. (6)
9 dextrostat.mp. (1)
10 methylphenidate.mp. or exp Methylphenidate/ (47)
11 concerta.mp. (4)
12 metadate.mp. (0)
13 methylin.mp. (1)
14 Ritalin.mp. (8)
15 biphentin.mp. (0)
16 modafinil.mp. (21)
17 provigil.mp. (3)
18 Alertec.mp. (0)
19 methamphetamine.mp. or exp methamphetamine/ (17)
20 desoxyn.mp. (0)
21 lisdexamfetamine.mp. (1)
22 vivanse.mp. (0)
23 daytrana.mp. (1)
24 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 (113)
25 Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (12)
26 Attention deficit disorder.mp. (21)
27 attention deficit$.mp. (64)
28 adhd.mp. (35)
29 25 or 26 or 27 or 28 (69)
30 Central Nervous system Stimulants.mp. or exp Central Nervous System Stimulants/ (23)
31 24 or 30 (123)
32 29 and 31 (31)
33 diversion.mp. (43)
34 substance abuse.mp. or exp Substance-Related Disorders/ (187)
35 misuse.mp. (163)
36 addictive behavior.mp. or exp Behavior, Addictive/ (4)
37 35 or 33 or 34 or 36 (331)
38 32 and 37 (13)

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Database: PsycINFO <1806 to February Week 1 2011>
Search Strategy:
---
1 exp Amphetamine/ or "amphetamine$".mp. (11712)
2 adderall.mp. (83)
3 atomoxetine.mp. (383)
4 strattera.mp. (20)

5 dexmethylphenidate.mp. (24)
6 focalin.mp. (9)
7 dextroamphetamine.mp. or exp Dextroamphetamine/ (2339)
8 dexedrine.mp. (79)
9 dextrostat.mp. (0)
10 methylphenidate.mp. or exp Methylphenidate/ (3183)
11 concerta.mp. (44)
12 metadate.mp. (9)
13 methylin.mp. (2)
14 Ritalin.mp. (436)
15 biphentin.mp. (1)
16 modafinil.mp. (467)
17 provigil.mp. (14)
18 Alertec.mp. (0)
19 methamphetamine.mp. or exp methamphetamine/ (2691)
20 desoxyn.mp. (2)
21 lisdexamfetamine.mp. (26)
22 vivanse.mp. (0)
23 daytrana.mp. (3)
24 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 (15744)
25 Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (9910)
26 Attention deficit disorder.mp. (14839)
27 attention deficit$.mp. (18558)
28 adhd.mp. (13031)
29 25 or 26 or 27 or 28 (19274)
30 24 and 29 (2355)
31 limit 30 to yr="2009 - 2011" (397)
32 limit 31 to (human and english language) (294)

Database: PsycINFO <1806 to February Week 1 2011>
Search Strategy:
---
1 exp Amphetamine/ or "amphetamine$".mp. (11712)
2 adderall.mp. (83)
3 atomoxetine.mp. (383)
4 strattera.mp. (20)
5 dexmethylphenidate.mp. (24)
6 focalin.mp. (9)
7 dextroamphetamine.mp. or exp Dextroamphetamine/ (2339)
8 dexedrine.mp. (79)
9 dextrostat.mp. (0)
10 methylphenidate.mp. or exp Methylphenidate/ (3183)
11 concerta.mp. (44)
12 metadate.mp. (9)
13 methylin.mp. (2)

14 Ritalin.mp. (436)
15 biphentin.mp. (1)
16 modafinil.mp. (467)
17 provigil.mp. (14)
18 Alertec.mp. (0)
19 methamphetamine.mp. or exp methamphetamine/ (2691)
20 desoxyn.mp. (2)
21 lisdexamfetamine.mp. (26)
22 vivanse.mp. (0)
23 daytrana.mp. (3)
24 11 or 21 or 7 or 17 or 2 or 22 or 1 or 18 or 23 or 16 or 13 or 6 or 3 or 9 or 12 or 20 or 14 or 15 or 8 or 4 or 19 or 10 or 5 (15744)
25 Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (9910)
26 Attention deficit disorder.mp. (14839)
27 attention deficit$.mp. (18558)
28 adhd.mp. (13031)
29 27 or 25 or 28 or 26 (19274)
30 Central Nervous system Stimulants.mp. or exp Central Nervous System Stimulants/ (63)
31 30 or 24 (15784)
32 31 and 29 (2361)
33 diversion.mp. (1461)
34 substance abuse.mp. or exp Substance-Related Disorders/ (22039)
35 misuse.mp. (5470)
36 addictive behavior.mp. or exp Behavior, Addictive/ (768)
37 35 or 33 or 34 or 36 (29035)
38 32 and 37 (84)
39 limit 38 to yr="2009 - 2011" (19)
40 limit 39 to (human and english language) (14)

Database: EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2011>
Search Strategy:
---
1 exp Amphetamine/ or "amphetamine$".mp. (15)
2 adderall.mp. (3)
3 atomoxetine.mp. (11)
4 strattera.mp. (0)
5 dexmethylphenidate.mp. (2)
6 focalin.mp. (0)
7 dextroamphetamine.mp. or exp Dextroamphetamine/ (14)
8 dexedrine.mp. (0)
9 dextrostat.mp. (0)
10 methylphenidate.mp. or exp Methylphenidate/ (41)
11 concerta.mp. (0)
12 metadate.mp. (0)
13 methylin.mp. (0)
14 Ritalin.mp. (2)

15 biphentin.mp. (0)
16 modafinil.mp. (4)
17 provigil.mp. (0)
18 Alertec.mp. (0)
19 methamphetamine.mp. or exp methamphetamine/ (2)
20 desoxyn.mp. (0)
21 lisdexamfetamine.mp. (0)
22 vivanse.mp. (0)
23 daytrana.mp. (0)
24 11 or 21 or 7 or 17 or 2 or 22 or 1 or 18 or 23 or 16 or 13 or 6 or 3 or 9 or 12 or 20 or 14 or 15 or 8 or 4 or 19 or 10 or 5 (49)
25 Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (49)
26 Attention deficit disorder.mp. (51)
27 attention deficit$.mp. (78)
28 adhd.mp. (44)
29 27 or 25 or 28 or 26 (79)
30 24 and 29 (34)

Database: EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2011>
Search Strategy:
---
1 exp Amphetamine/ or "amphetamine$".mp. (15)
2 adderall.mp. (3)
3 atomoxetine.mp. (11)
4 strattera.mp. (0)
5 dexmethylphenidate.mp. (2)
6 focalin.mp. (0)
7 dextroamphetamine.mp. or exp Dextroamphetamine/ (14)
8 dexedrine.mp. (0)
9 dextrostat.mp. (0)
10 methylphenidate.mp. or exp Methylphenidate/ (41)
11 concerta.mp. (0)
12 metadate.mp. (0)
13 methylin.mp. (0)
14 Ritalin.mp. (2)
15 biphentin.mp. (0)
16 modafinil.mp. (4)
17 provigil.mp. (0)
18 Alertec.mp. (0)
19 methamphetamine.mp. or exp methamphetamine/ (2)
20 desoxyn.mp. (0)
21 lisdexamfetamine.mp. (0)
22 vivanse.mp. (0)
23 daytrana.mp. (0)
24 11 or 21 or 7 or 17 or 2 or 22 or 1 or 18 or 23 or 16 or 13 or 6 or 3 or 9 or 12 or 20 or 14 or 15 or 8 or 4 or 19 or 10 or 5 (49)

25 Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (49)
26 Attention deficit disorder.mp. (51)
27 attention deficit$.mp. (78)
28 adhd.mp. (44)
29 27 or 25 or 28 or 26 (79)
30 Central Nervous system Stimulants.mp. or exp Central Nervous System Stimulants/ (28)
31 30 or 24 (60)
32 31 and 29 (38)
33 diversion.mp. (22)
34 substance abuse.mp. or exp Substance-Related Disorders/ (116)
35 misuse.mp. (33)
36 addictive behavior.mp. or exp Behavior, Addictive/ (0)
37 35 or 33 or 34 or 36 (161)
38 32 and 37 (2)

Database: Ovid MEDLINE(R) without Revisions <1996 to February Week 1 2011>
Search Strategy:
---
1 Guanfacine.mp. (229)
2 Tenex.mp. (3)
3 Intuniv.mp. (4)
4 Clonidine.mp. (4849)
5 Catapres.mp. (5)
6 Kapvay.mp. (0)
7 Nexiclon.mp. (0)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (4980)
9 Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (11432)
10 Attention deficit disorder.mp. (11609)
11 attention deficit$.mp. (14613)
12 adhd.mp. (8191)
13 9 or 10 or 11 or 12 (14889)
14 8 and 13 (205)
15 (200405$ or 200406$ or 200407$ or 200408$ or 200409$ or 20041$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$).ed. (4431682)
16 14 and 15 (109)
17 limit 16 to (english language and humans) (95)
18 limit 17 to (clinical trial, all or clinical trial or comparative study or controlled clinical trial or evaluation studies or meta analysis or multicenter study or randomized controlled trial or "review") (59)
19 observational stud$.mp. or exp Cohort Studies/ or cohort$.mp. or exp Retrospective Studies/ or retrospective$.mp. (825408)
20 17 and 19 (12)
21 18 or 20 (63)

Database: Ovid MEDLINE(R) without Revisions <1996 to March Week 1 2011>
Search Strategy:

---
1 Guanfacine.mp. (229)
2 Tenex.mp. (3)
3 Intuniv.mp. (4)
4 Clonidine.mp. (4905)
5 Catapres.mp. (5)
6 Kapvay.mp. (0)
7 Nexiclon.mp. (0)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (5036)
9 Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (11573)
10 Attention deficit disorder.mp. (11753)
11 attention deficit$.mp. (14794)
12 adhd.mp. (8297)
13 9 or 10 or 11 or 12 (15074)
14 8 and 13 (206)
15 diversion.mp. (6509)
16 exp Substance-Related Disorders/ (137658)
17 ((drug$ or substance$ or stimula$) adj3 (abus$ or addict$)).mp. (35977)
18 (misuse$ or misusing).mp. (7183)
19 exp Behavior, Addictive/ (3206)
20 (addict$ adj3 behav$).mp. (4120)
21 (drug$ adj3 seek$).mp. (1300)
22 15 or 16 or 17 or 18 or 19 or 20 or 21 (161663)
23 14 and 22 (24)
24 illegal$.mp. (3716)
25 unlawful$.mp. (183)
26 illicit$.mp. (5340)
27 criminal$.mp. (8663)
28 24 or 25 or 26 or 27 (17201)
29 14 and 28 (1)
30 23 or 29 (24)
31 limit 30 to (english language and humans) (24)
32 (200405$ or 200406$ or 200407$ or 200408$ or 200409$ or 20041$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$).ed. (4508311)
33 31 and 32 (12)
34 limit 33 to (clinical trial, all or clinical trial or comparative study or controlled clinical trial or evaluation studies or meta analysis or multicenter study or randomized controlled trial or "review") (7)
35 observational stud$.mp. or exp Cohort Studies/ or cohort$.mp. or exp Retrospective Studies/ or retrospective$.mp. (837641)
36 33 and 35 (2)
37 34 or 36 (8)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <1st Quarter 2011>
Search Strategy:
---
1 Guanfacine.mp. (116)

2 Tenex.mp. (0)
3 Intuniv.mp. (0)
4 Clonidine.mp. (2355)
5 Catapres.mp. (18)
6 Kapvay.mp. (0)
7 Nexiclon.mp. (0)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (2432)
9 Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (1180)
10 Attention deficit disorder.mp. (1302)
11 attention deficit$.mp. (1585)
12 adhd.mp. (1038)
13 9 or 10 or 11 or 12 (1750)
14 8 and 13 (39)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <1st Quarter 2011>
Search Strategy:
---
1 Guanfacine.mp. (116)
2 Tenex.mp. (0)
3 Intuniv.mp. (0)
4 Clonidine.mp. (2355)
5 Catapres.mp. (18)
6 Kapvay.mp. (0)
7 Nexiclon.mp. (0)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (2432)
9 Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (1180)
10 Attention deficit disorder.mp. (1302)
11 attention deficit$.mp. (1585)
12 adhd.mp. (1038)
13 9 or 10 or 11 or 12 (1750)
14 Central Nervous system Stimulants.mp. or exp Central Nervous System Stimulants/ (3816)
15 8 or 14 (6216)
16 13 and 15 (734)
17 diversion.mp. (211)
18 exp Substance-Related Disorders/ (6996)
19 ((drug$ or substance$ or stimula$) adj3 (abus$ or addict$)).mp. (2636)
20 (misuse$ or misusing).mp. (284)
21 exp Behavior, Addictive/ (205)
22 (addict$ adj3 behav$).mp. (275)
23 (drug$ adj3 seek$).mp. (62)
24 17 or 18 or 19 or 20 or 21 or 22 or 23 (8687)
25 16 and 24 (33)
26 illegal$.mp. (75)
27 unlawful$.mp. (0)
28 illicit$.mp. (329)

29 criminal$.mp. (295)
30 26 or 27 or 28 or 29 (671)
31 16 and 30 (2)
32 25 or 31 (33)
33 limit 32 to yr="2004 -Current" (21)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to January 2011>
Search Strategy:
---
1 Guanfacine.mp. (10)
2 Tenex.mp. (1)
3 Intuniv.mp. (0)
4 Clonidine.mp. (81)
5 Catapres.mp. (5)
6 Kapvay.mp. (0)
7 Nexiclon.mp. (0)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (81)
9 Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (12)
10 Attention deficit disorder.mp. (21)
11 attention deficit$.mp. (64)
12 adhd.mp. (35)
13 9 or 10 or 11 or 12 (69)
14 8 and 13 (7)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to January 2011>
Search Strategy:
---
1 Guanfacine.mp. (10)
2 Tenex.mp. (1)
3 Intuniv.mp. (0)
4 Clonidine.mp. (81)
5 Catapres.mp. (5)
6 Kapvay.mp. (0)
7 Nexiclon.mp. (0)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (81)
9 Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (12)
10 Attention deficit disorder.mp. (21)
11 attention deficit$.mp. (64)
12 adhd.mp. (35)
13 9 or 10 or 11 or 12 (69)
14 Central Nervous system Stimulants.mp. or exp Central Nervous System Stimulants/ (23)
15 8 or 14 (104)
16 13 and 15 (14)
17 diversion.mp. (43)
18 [exp Substance-Related Disorders/] (0)

19 ((drug$ or substance$ or stimula$) adj3 (abus$ or addict$)).mp. (293)
20 (misuse$ or misusing).mp. (173)
21 [exp Behavior, Addictive/] (0)
22 (addict$ adj3 behav$).mp. (24)
23 (drug$ adj3 seek$).mp. (19)
24 17 or 18 or 19 or 20 or 21 or 22 or 23 (446)
25 16 and 24 (7)
26 illegal$.mp. (43)
27 unlawful$.mp. (3)
28 illicit$.mp. (74)
29 criminal$.mp. (92)
30 26 or 27 or 28 or 29 (160)
31 16 and 30 (2)
32 25 or 31 (7)

Database: PsycINFO <1806 to February Week 3 2011>
Search Strategy:
---
1 Guanfacine.mp. (164)
2 Tenex.mp. (2)
3 Intuniv.mp. (2)
4 Clonidine.mp. (1903)
5 Catapres.mp. (8)
6 Kapvay.mp. (0)
7 Nexiclon.mp. (0)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (2007)
9 Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (9953)
10 Attention deficit disorder.mp. (14883)
11 attention deficit$.mp. (18608)
12 adhd.mp. (13077)
13 9 or 10 or 11 or 12 (19328)
14 8 and 13 (185)
15 limit 14 to yr="2004 -Current" (81)
16 limit 15 to (human and english language) (71)

Database: PsycINFO <1806 to February Week 3 2011>
Search Strategy:
---
1 Guanfacine.mp. (164)
2 Tenex.mp. (2)
3 Intuniv.mp. (2)
4 Clonidine.mp. (1903)
5 Catapres.mp. (8)
6 Kapvay.mp. (0)
7 Nexiclon.mp. (0)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (2007)

9 Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (9953)
10 Attention deficit disorder.mp. (14883)
11 attention deficit$.mp. (18608)
12 adhd.mp. (13077)
13 9 or 10 or 11 or 12 (19328)
14 Central Nervous system Stimulants.mp. or exp Central Nervous System Stimulants/ (64)
15 8 or 14 (2070)
16 13 and 15 (195)
17 diversion.mp. (1466)
18 substance abuse.mp. or exp Substance-Related Disorders/ (22095)
19 misuse.mp. (5492)
20 addictive behavior.mp. or exp Behavior, Addictive/ (770)
21 17 or 18 or 19 or 20 (29117)
22 16 and 21 (5)
23 limit 22 to yr="2004 -Current" (3)
24 limit 23 to (human and english language) (2)

Database: EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2011>
Search Strategy:
---
1 Guanfacine.mp. (4)
2 Tenex.mp. (0)
3 Intuniv.mp. (0)
4 Clonidine.mp. (56)
5 Catapres.mp. (0)
6 Kapvay.mp. (0)
7 Nexiclon.mp. (0)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (58)
9 Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (49)
10 Attention deficit disorder.mp. (51)
11 attention deficit$.mp. (78)
12 adhd.mp. (44)
13 9 or 10 or 11 or 12 (79)
14 8 and 13 (6)

Database: EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2011>
Search Strategy:
---
1 Guanfacine.mp. (4)
2 Tenex.mp. (0)
3 Intuniv.mp. (0)
4 Clonidine.mp. (56)
5 Catapres.mp. (0)
6 Kapvay.mp. (0)
7 Nexiclon.mp. (0)

8 1 or 2 or 3 or 4 or 5 or 6 or 7 (58)
9 Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (49)
10 Attention deficit disorder.mp. (51)
11 attention deficit$.mp. (78)
12 adhd.mp. (44)
13 9 or 10 or 11 or 12 (79)
14 Central Nervous system Stimulants.mp. or exp Central Nervous System Stimulants/ (28)
15 8 or 14 (83)
16 13 and 15 (22)
17 diversion.mp. (22)
18 [exp Substance-Related Disorders/] (0)
19 ((drug$ or substance$ or stimula$) adj3 (abus$ or addict$)).mp. (165)
20 (misuse$ or misusing).mp. (35)
21 [exp Behavior, Addictive/] (0)
22 (addict$ adj3 behav$).mp. (12)
23 (drug$ adj3 seek$).mp. (0)
24 17 or 18 or 19 or 20 or 21 or 22 or 23 (210)
25 16 and 24 (3)
26 illegal$.mp. (8)
27 unlawful$.mp. (0)
28 illicit$.mp. (24)
29 criminal$.mp. (31)
30 26 or 27 or 28 or 29 (57)
31 16 and 30 (0)
32 25 or 31 (3)

# Appendix E. Strength of evidence

## Table 1: Methylphenidate OROS compared with immediate-release methylphenidate

| Domains pertaining to strength of evidence | | | | | Magnitude of effect | Strength of evidence |
|---|---|---|---|---|---|---|
| **Number of Studies; Number of Subjects** | **Risk of Bias (Design/ Quality)** | **Consistency** | **Directness** | **Precision** | **Summary Effect Size (95% Confidence Interval)** | **High, Moderate, Low, Insufficient** |
| **Response** | | | | | | |
| No data | NA | NA | NA | NA | NA | Insufficient |
| **Maintenance of response (much or very much improved on the Clinical Global Impression Scale)** | | | | | | |
| 1; N=53 | Medium (RCT/Fair) | NA | Direct | Imprecise | 63% vs 58%, *P*=0.8 | Low |
| **Withdrawals due to adverse events** | | | | | | |
| No data | NA | NA | NA | NA | NA | Insufficient |
| **Decreased appetite** | | | | | | |
| 1; N=53 | Medium (RCT/Fair) | NA | Direct | Imprecise | 27% vs 11%, *P* not reported | Insufficient |
| **Sleep disturbance** | | | | | | |
| No data | NA | NA | NA | NA | NA | Insufficient |

Abbreviations: NA, not applicable; RCT, randomized controlled trial.

## Table 2: Immediate-release guanfacine compared with immediate-release dextroamphetamine

| Domains pertaining to strength of evidence | | | | | Magnitude of effect | Strength of evidence |
|---|---|---|---|---|---|---|
| **Number of Studies; Number of Subjects** | **Risk of Bias (Design/ Quality)** | **Consistency** | **Directness** | **Precision** | **Summary Effect Size (95% Confidence Interval)** | **High, Moderate, Low, Insufficient** |
| **Response** | | | | | | |
| No data | NA | NA | NA | NA | NA | Insufficient |
| **ADHD Symptoms: mean total symptom score of the DSM-IV ADHD Behavior Checklist for Adults** | | | | | | |
| 1, N=17 | Medium (RCT/Fair) | NA | Direct | Imprecise | 23.3 points vs. 24.2 points | Low |
| **Withdrawals due to adverse events** | | | | | | |
| No data | NA | NA | NA | NA | NA | Insufficient |
| **Decreased appetite** | | | | | | |
| No data | NA | NA | NA | NA | NA | Insufficient |
| **Sleep disturbance** | | | | | | |
| No data | NA | NA | NA | NA | NA | Insufficient |

Abbreviations: NA, not applicable; RCT, randomized controlled trial.

## Table 3: Modafinil compared with immediate-release dextroamphetamine

| Domains pertaining to strength of evidence | | | | | Magnitude of effect | Strength of evidence |
|---|---|---|---|---|---|---|
| **Number of Studies; Number of Subjects** | **Risk of Bias (Design/ Quality)** | **Consistency** | **Directness** | **Precision** | **Summary Effect Size (95% Confidence Interval)** | **High, Moderate, Low, Insufficient** |
| **Response:** 30% or greater mean improvement in ADHD Rating Scale total scores | | | | | | |
| 1; N=22 | Medium (RCT/Fair) | NA | Direct | Imprecise | 48% vs 48% | Low |
| **Withdrawals due to adverse events** | | | | | | |
| 1; N=22 | Medium (RCT/Fair) | NA | Direct | Imprecise | 0 vs 0 | Low |
| **Decreased appetite** | | | | | | |
| 1; N=22 | Medium (RCT/Fair) | NA | Direct | Imprecise | 24% vs 19%, *P*=NS | Low |
| **Sleep disturbance** | | | | | | |
| 1; N=22 | Medium (RCT/Fair) | NA | Direct | Imprecise | 38% vs 19%, *P*=NS | Low |

Abbreviations: NA, not applicable; NS, not significant; RCT, randomized controlled trial.

# Appendix F. Excluded trials Update 4

The following full-text publications were considered for inclusion but failed to meet the criteria for this report. See previous versions of the report on the Drug Effectiveness Review Project website for studies excluded previously.

Exclusion codes: 2=ineligible outcome, 3=ineligible intervention, 4=ineligible population, 5=ineligible publication type, 6=ineligible study design

| Excluded trials | Exclusion code |
|---|---|
| *Head-to-head trial* | |
| Jasinski D, Krishnan S. Human pharmacology of intravenous lisdexamfetamine dimesylate: Abuse liability in adult stimulant abusers. Journal of Psychopharmacology. Jun 2009;23(4):410-418. | 4 |
| Schulz E, Fleischhaker C, Hennighausen K, et al. A double-blind, randomized, placebo/active controlled crossover evaluation of the efficacy and safety of Ritalin LA in children with attention-deficit/hyperactivity disorder in a laboratory classroom setting. Journal of Child & Adolescent Psychopharmacology. Oct 2010;20(5):377-385. | 3 |
| Yildiz O, Sismanlar SG, Memik NC, Karakaya I, Agaoglu B. Atomoxetine and methylphenidate treatment in children with ADHD: The efficacy, tolerability and effects on executive functions. Child psychiatry and human development. Jun 2011;42(3):257-269. | 2 |
| *Active-control trial* | |
| Nair V, Mahadevan S. Randomised controlled study-efficacy of clonidine versus carbamazepine in children with ADHD. J Trop Pediatr. Apr 2009;55(2):116-121. | 6 |
| *Placebo controlled trials* | |
| Abikoff H, Nissley-Tsiopinis J, Gallagher R, et al. Effects of MPH-OROS on the organizational, time management, and planning behaviors of children with ADHD. Journal of the American Academy of Child & Adolescent Psychiatry. Feb 2009;48(2):166-175. | 2 |
| Adler L, Wilens T, Zhang S, et al. Retrospective safety analysis of atomoxetine in adult ADHD patients with or without comorbid alcohol abuse and dependence. American Journal on Addictions. Sep-Oct 2009;18(5):393-401. | 6 |
| Adler LA, Weisler RH, Goodman DW, Hamdani M, Niebler GE. Short-term effects of lisdexamfetamine dimesylate on cardiovascular parameters in a 4-week clinical trial in adults with attention-deficit/hyperactivity disorder. Journal of Clinical Psychiatry. Dec 2009;70(12):1652-1661. | 2 |
| Agarwal V, Sitholey P, Kumar S, Prasad M. Double-blind, placebo-controlled trial of clonidine in hyperactive children with mental retardation. Mental Retardation. 2001;39(4):259-267. | 4 |
| Block SL, Kelsey D, Coury D, et al. Once-daily atomoxetine for treating pediatric attention-deficit/hyperactivity disorder: comparison of morning and evening dosing. Clinical Pediatrics. Sep 2009;48(7):723-733. | 6 |
| Brown TE, Holdnack J, Saylor K, et al. Effect of atomoxetine on executive function impairments in with ADHD. Journal of Attention Disorders. Feb 2011;15(2):130-138. | 2 |
| Childress AC, Spencer T, Lopez F, et al. Efficacy and safety of dexmethylphenidate extended-release capsules administered once daily to children with attention-deficit/hyperactivity disorder. Journal of Child & Adolescent Psychopharmacology. Aug 2009;19(4):351-361. | 6 |
| Escobar R, Montoya A, Polavieja P, et al. Evaluation of patients' and parents' quality of life in a randomized placebo-controlled atomoxetine study in attention-deficit/hyperactivity disorder. Journal of Child & Adolescent Psychopharmacology. Jun 2009;19(3):253-263. | 6 |
| Gonzalez-Heydrich J, Whitney J, Waber D, et al. Adaptive phase I study of OROS methylphenidate treatment of attention deficit hyperactivity disorder with epilepsy. Epilepsy Behav. Jul 2010;18(3):229-237. | 4 |

| Excluded trials | Exclusion code |
|---|---|
| Grizenko N, Paci M, Joober R. Is the inattentive subtype of ADHD different from the combined/hyperactive subtype? Journal of Attention Disorders. May 2010;13(6):649-657. | 6 |
| Handen BL, Sahl R, Hardan AY. Guanfacine in children with autism and/or intellectual disabilities. Journal of Developmental & Behavioral Pediatrics. Aug 2008;29(4):303-308. | 4 |
| Ironside S, Davidson F, Corkum P. Circadian motor activity affected by stimulant medication in children with attention-deficit/hyperactivity disorder. Journal of Sleep Research. Dec 2010;19(4):546-551. | 2 |
| Kent JD, Blader JC, Koplewicz HS, Abikoff H, Foley CA. Effects of late-afternoon methylphenidate administration on behavior and sleep in attention-deficit hyperactivity disorder.[comment]. Pediatrics. 1995;96(2 Pt 1):320-325. | 4 |
| Lyon GJ, Samar SM, Conelea C, et al. Testing tic suppression: comparing the effects of dexmethylphenidate to no medication in children and adolescents with attention-deficit/hyperactivity disorder and Tourette's disorder. Journal of Child & Adolescent Psychopharmacology. Aug 2010;20(4):283-289. | 6 |
| Manos M, Frazier TW, Landgraf JM, Weiss M, Hodgkins P. HRQL and medication satisfaction in children with ADHD treated with the methylphenidate transdermal system. Current Medical Research & Opinion. Dec 2009;25(12):3001-3010. | 2 |
| Martenyi F, Zavadenko NN, Jarkova NB, et al. Atomoxetine in children and adolescents with attention-deficit/hyperactivity disorder: a 6-week, randomized, placebo-controlled, double-blind trial in Russia. European Child & Adolescent Psychiatry. Jan 2010;19(1):57-66. | 6 |
| Mayes SD, Crites DL, Bixler EO, Humphrey FJ, 2nd, Mattison RE. Methylphenidate and ADHD: influence of age, IQ and neurodevelopmental status. Developmental Medicine & Child Neurology. 1994;36(12):1099-1107. | 6 |
| Montoya A, Hervas A, Cardo E, et al. Evaluation of atomoxetine for first-line treatment of newly diagnosed, treatment-naive children and adolescents with attention deficit/hyperactivity disorder. Current Medical Research & Opinion. Nov 2009;25(11):2745-2754. | 6 |
| Murray D, Childress A, Giblin J, Williamson D, Armstrong R, Starr H. Effects of OROS methylphenidate on Academic, Behavioral, and Cognitive tasks in Children 9 to 12 years of age with attention-deficit/hyperactivity disorder. Clinical Pediatrics. 2011;50(4):308-320. | 2 |
| Rosler M, Retz W, Fischer R, et al. Twenty-four-week treatment with extended release methylphenidate improves emotional symptoms in adult ADHD. World Journal of Biological Psychiatry. Aug 2010;11(5):709-718. | 2 |
| Svanborg P, Thernlund G, Gustafsson PA, Hagglof B, Poole L, Kadesjo B. Efficacy and safety of atomoxetine as add-on to psychoeducation in the treatment of attention deficit/hyperactivity disorder: a randomized, double-blind, placebo-controlled study in stimulant-naive Swedish children and adolescents. European Child & Adolescent Psychiatry. Apr 2009;18(4):240-249. | 6 |
| Svanborg P, Thernlund G, Gustafsson PA, Hagglof B, Schacht A, Kadesjo B. Atomoxetine improves patient and family coping in attention deficit/hyperactivity disorder: a randomized, double-blind, placebo-controlled study in Swedish children and adolescents. European Child & Adolescent Psychiatry. Dec 2009;18(12):725-735. | 6 |
| Wigal SB, Wigal T, Schuck S, et al. Academic, behavioral, and cognitive effects of OROSReg. methylphenidate on older children with attention-deficit/hyperactivity disorder. Journal of Child and Adolescent Psychopharmacology. Apr 2011;21(2):121-131. | 6 |
| Wigal T, Brams M, Gasior M, et al. Randomized, double-blind, placebo-controlled, crossover study of the efficacy and safety of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder: novel findings using a simulated adult workplace environment design. Behavioral & Brain Functions [Electronic Resource]: BBF. 2010;6:34. | 2 |