Drug Class Review

Pharmacologic Treatments for Attention Deficit Hyperactivity Disorder

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Update 3

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The literature on this topic is scanned periodically.

This report reviews information about the comparative effectiveness and safety of drugs within a pharmaceutical class. The report is neither a usage guideline nor an endorsement or recommendation of any drug, use, or approach. Oregon Health & Science University does not endorse any guideline or recommendation developed by users of this report.

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EVIDENCE TABLES: See separate volume

The medical literature relating to this topic is scanned periodically. (See http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for description of scanning process). Prior versions of this report can be accessed at the DERP website.

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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] 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. Atomoxetine is the only nonstimulant evaluated in this review.

The actions of each of the medications included in this review are briefly described below.

Mixed amphetamine salts: Amphetamines are non-catecholamine sympathomimetic amines with central nervous system stimulant activity. **Dextroamphetamine sulfate** is the dextro isomer of the compound *d,l* -amphetamine sulfate, a sympathomimetic amine of the amphetamine group.

Atomoxetine HCl: The precise mechanism by which atomoxetine produces its therapeutic effects in ADHD is unknown, but is thought to be related to selective inhibition of the pre-

synaptic norepinephrine transporter, as determined in ex vivo uptake and neurotransmitter depletion studies.

Lisdexamfetamine dimesylate: Lisdexamfetamine dimesylate is an inactive prodrug that is converted to dextroamphetamine after absorption through the gastrointestinal tract. The exact mechanism by which dextroamphetamine works to alleviate ADHD symptoms is unknown. However, amphetamines may inhibit the reuptake of norepinephrine and dopamine at the presynaptic neuron, thus increasing their release into the extraneuronal space. In vitro studies with the parent compound, lisdexamfetamine, indicate that it does not bind to sites responsible for the reuptake of norepinephrine and dopamine.

Methamphetamine hydrochloride: Methamphetamine hydrochloride is part of the amphetamine drug class of sympathomimetic amines and possesses central nervous system stimulant activity. The exact mechanism by which methamphetamine works to alleviate ADHD symptoms is unknown.

Methylphenidate HCl: Methylphenidate HCl is a mild central nervous system stimulant. The mode of action in man is not completely understood, but it presumably activates the brain stem arousal system and cortex to produce its stimulant effect. **Dexmethylphenidate HCl** is the more pharmacologically active enantiomer of the *d* - and *l* - enantiomers of methylphenidate and is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

Modafinil: Modafinil is a central nervous system stimulant approved for promoting wakefulness, although the precise mechanism(s) is unknown. Modafinil has wake-promoting actions like sympathomimetic agents including amphetamine and methylphenidate, although the pharmacologic profile is not identical to that of sympathomimetic amines. At pharmacologically relevant concentrations, modafinil does not bind to most potentially relevant receptors for sleep/wake regulation, including those for norepinephrine, serotonin, dopamine, GABA, adenosine, histamine-3, melatonin, or benzodiazepines. Modafinil also does not inhibit the activity of Monoamine Oxidase-B or phosphodiesterases II-V. While only US Food and Drug Administration-approved for narcolepsy treatment, modafinil is also being used to treat ADHD.

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 across 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?
    b. What is the *comparative* efficacy of different pharmacologic treatments for attention deficit disorders?

2. Tolerability, Serious Adverse Events, Misuse and Diversion
    a. What is the evidence of *comparative* tolerability of different pharmacologic treatments 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. Stimulants compared with nonstimulants
        ii. Immediate release compared with intermediate compared with long-acting formulations
        iii. Any included pharmacologic treatment

3. Evidence in Subgroups of Patients
    a. What is the evidence of benefits and harms of pharmacologic treatments for attention deficit disorders in subgroups of patients based on demographics (age, racial groups, gender), 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. Stimulants compared with nonstimulants
        ii. Immediate release compared with intermediate compared with long-acting formulations
        iii. Any included pharmacologic treatment

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.

Table 1. ADHD drugs and indication (immediate-release and extended-release formulations)

Active ingredient(s)	Referred to in this report as	Trade name[a]	Forms
Amphetamine mixture (amphetamine aspartate; amphetamine sulfate; dextroamphetamine saccharate; dextroamphetamine sulfate)	Immediate-release mixed amphetamine salts	Adderall®[a,b]	Oral tablet
	mixed amphetamine salts XR	Adderall XR®	Extended-release oral capsule
Atomoxetine HCl	Atomoxetine	Strattera®	Oral capsule
Dexmethylphenidate hydrochloride	Immediate-release dexmethylphenidate	Focalin®[a,b]	Oral tablet
	Dexmethylphenidate ER	Focalin XR®[b]	Extended-release oral capsule
Dextroamphetamine sulfate	Immediate-release dextroamphetamine	Dexedrine®[a]	Oral tablet
		Dextrostat®[a,d]	Oral tablet
		Liquadd®	Oral solution
	Dextroamphetamine SR	Dexedrine Spansule®	Sustained-release oral capsule
Lisdexamfetamine dimesylate	Lisdexamfetamine	Vyvanse™[d]	Oral capsule
Methamphetamine hydrochloride	Methamphetamine	Desoxyn®[b]	Oral tablet
Methylphenidate hydrochloride	Methylphenidate OROS	Concerta®	Extended-release oral tablet
	Methylphenidate transdermal	Daytrana®[b]	Transdermal patch
	Methylphenidate CD	Metadate CD®[b]	Extended-release oral capsule
	Methylphenidate ER	Metadate ER®[b]	Extended-release oral tablet
		Medikinet®[c]	Extended-release oral tablet
	Methylphenidate chewable Methylphenidate solution	Methylin®[b]	Oral chewable tablet Oral solution
	Immediate-release methylphenidate	Ritalin®[a]	Oral tablet
	Methylphenidate LA	Ritalin LA®[b]	Extended-release oral capsule
	multilayer-release methylphenidate	Biphentin®[c]	Extended-release oral capsule
	Methylphenidate SR	Ritalin SR®	Extended-release oral tablet
Modafinil	Modafinil	Provigil®	Oral tablet
		Alertec®[c]	Oral tablet

[a] Or generic equivalent.
[b] Not available in Canada.
[c] Not available in the United States.
[d] Approved in Canada but not commercially available.

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 provides 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 B 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:

- Assessment of comparative efficacy: Controlled clinical trials or good-quality systematic reviews
- Assessment of comparative effectiveness: Controlled clinical trials, observational studies (cohort or case control studies), or good-quality systematic reviews
- Assessment of comparative harms: Controlled clinical trials, observational studies (cohort or case control studies), or good quality systematic reviews
- Non-comparative harms, including abuse, misuse, and diversion of drugs: Uncontrolled open-label extension, before-after, and time series studies.

METHODS

Literature Search

To identify relevant citations, we searched the Cochrane Central Register of Controlled Trials (1st Quarter 2009), Cochrane Database of Systematic Reviews (1st Quarter 2009), MEDLINE (1996 to April Week 4 2009), and PsycINFO (1806 to April Week 4 2009) using terms for included drugs, indications, and study designs (see Appendix C for complete search strategies). We have attempted to identify additional studies through searches of reference lists of included studies and reviews, the US Food and Drug Administration web site, as well as searching dossiers submitted by pharmaceutical companies for the current review. All citations were imported into an electronic database (EndNote XI).

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 2 reviewers. Disagreements were resolved by consensus. Results published *only* in abstract form were not included because lack of detail prevented quality assessment.

Data Abstraction

The following data were abstracted by 2 independent reviewers from included trials: study design, setting, and population characteristics (including sex, age, ethnicity, diagnosis); eligibility and exclusion criteria; interventions (dose and duration); comparisons; numbers screened, eligible, enrolled, and lost to follow-up; method of outcome ascertainment; and results for each outcome. We recorded intention-to-treat results when reported. If true intention-to-treat results were not reported, but loss to follow-up was very small, we considered these results to be intention-to-treat results. In cases where only per-protocol results were reported, we calculated intention-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 listed in Appendix D. 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 intention-to-treat analysis. Trials that had a fatal flaw in one or more category were rated "poor-quality"; trials that met all criteria were rated "good-quality"; the remainder were rated "fair-quality." A fatal flaw occurs when there is evidence of bias or confounding in the trial, for example when randomization and concealment of allocation of random order are not reported and baseline characteristics differ significantly between the groups. In this case, randomization has apparently failed and for one reason or another bias has been introduced.

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 *probably* 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. External validity of trials was assessed based on whether the publication adequately described the study population, how similar patients were to the target population in whom the intervention will be applied, and whether the treatment received by the control group was reasonably representative of standard practice. We also recorded the role of the funding source.

Appendix D also shows the criteria we used to rate observational studies. These criteria 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 pre-defined criteria (see Appendix D), 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.

Overall quality ratings for the individual study were based on internal and external validity ratings for that trial. A particular randomized trial might receive 2 different ratings: one for effectiveness and another for adverse events. The overall strength of evidence for a particular

key question reflects the quality, consistency, and power of the set of studies relevant to the question.

Evidence Synthesis

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 presentation

We constructed evidence tables showing the study characteristics, quality ratings, and results for all included studies. Studies that evaluated one pharmacologic treatment of ADHD against another provided direct evidence of comparative benefits and harms. Outcomes of changes in symptom 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. Where possible, head-to-head data are the primary focus of the synthesis.

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 issues of heterogeneity between trial populations, interventions, and assessment of outcomes. Indirect data are used to support direct comparisons, where they exist, and are also used as the primary comparison where no direct comparisons exist. Such indirect comparisons should be interpreted with caution.

Public comment

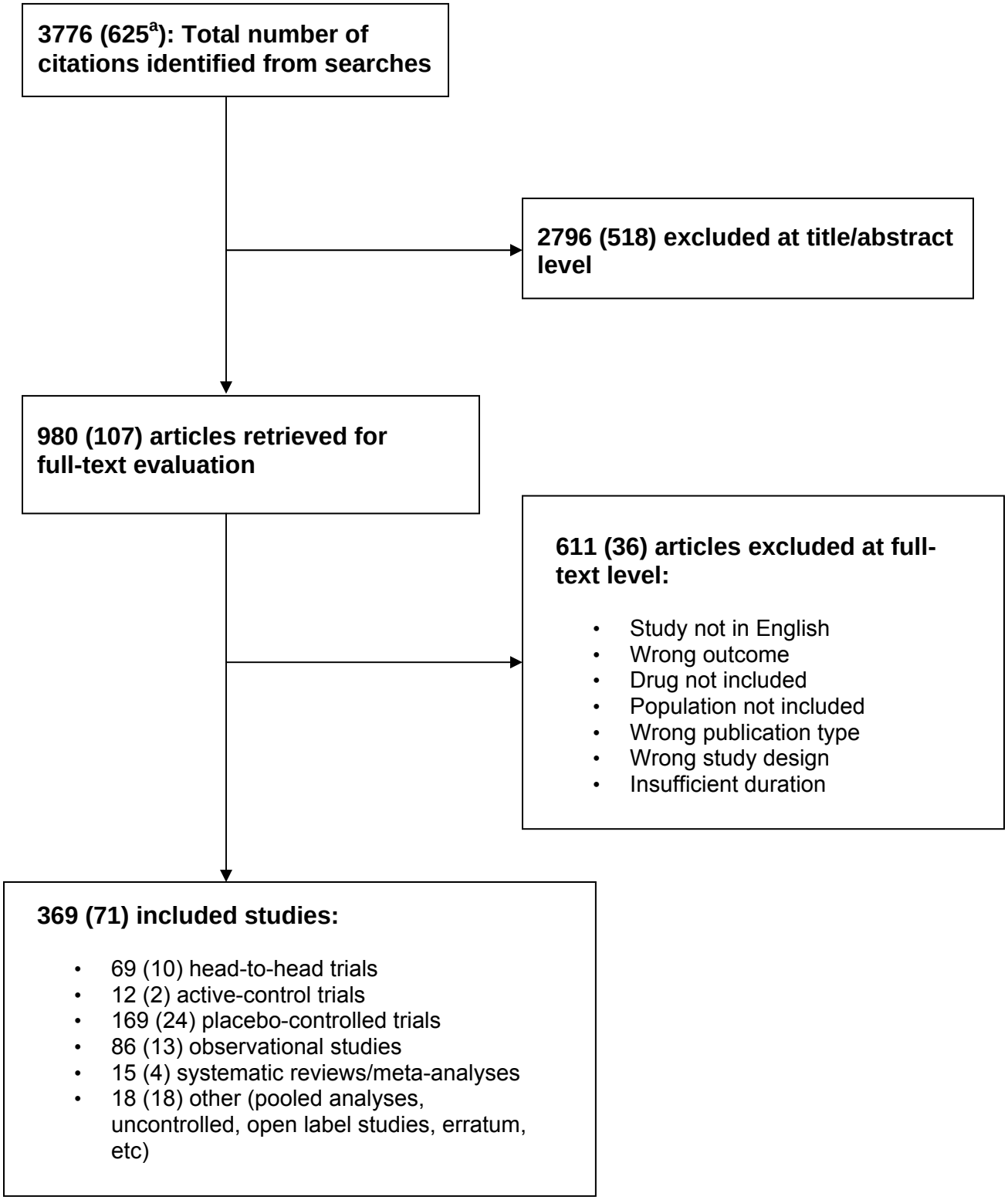
This report was posted to the Drug Effectiveness Review Project website for public comment. We received comments from 3 pharmaceutical companies.

RESULTS

Overview

Figure 1 details the results of our literature searches. Overall, we identified a total of 3776 citations from searching electronic databases, reviews of reference lists, pharmaceutical manufacturer dossier submissions, and public comment. Of these, 625 were identified in the most recent update. 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); and Update 3, Eli Lilly (atomoxetine HCl), Shire US (lisdexamfetamine dimesylate and transdermal methylphenidate), and McNeil (methylphenidate OROS). A list of excluded studies is reported in Appendix E.

Figure 1. Results of literature search



[a] Parentheses show search results new to Update 3.

We identified the following numbers of head-to-head comparative trials of pharmacologic treatments for ADHD (Table 2).

Table 2. Numbers of head-to-head trials of drugs for ADHD

	MPH IR	MPH ER	DEX	DEX-MPH	MAS	MAS XR	Modafinil	Atomoxetine	LisDex
MPH IR									
MPH ER	C:15 (4)[a] T: 1	C: 5 (2)							
DEX	C: 11 A: 1	--							
DEX-MPH	--	--	--						
Adderall®	C: 5	--	C: 1	--					
Adderall XR®	--	T:1	--	--	C: 1				
Modafinil	C:1 (1)	--	A: 1	--	--				
Atomoxetine	C: 6[b] (1)	C: 2 (1)	--	--	C: 1	--	--		
LisDex	--	--	A: 1 (1)	--	C:1	--	--	--	

Abbreviations: A, adults; C, children; T, adolescents.
[a] Parentheses show search results new to Update 3.
[b] One trial compared with standard care.

Data abstracted from these trials can be found in Evidence Tables 3 and 9 and the relevant quality assessments in Evidence Tables 4 and 10. 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 5 and 11 and relevant quality assessments in Evidence Tables 6 and 12. For long-term safety, we included 35 observational studies (Evidence Tables 15 and 16).

In adult populations (age 18 and above), we included 44 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 1 above.

Previous systematic review findings

While there are a large number of reviews of pharmacotherapy for symptoms of ADHD, we found a limited number of good-quality systematic reviews of these drugs for use in children, including 1 in the United States,[5] 1 in Canada,[23] and 1 in the United Kingdom.[24] There were some differences in the lists of drugs assessed in these reviews and in our report, the commonalities being immediate-release methylphenidate and methylphenidate SR, immediate-release dextroamphetamine, atomoxetine, bupropion, and clonidine. The Canadian and British reviews did not include adults. These reviews consistently found a lack of evidence of a difference between the drugs studied in efficacy or adverse events. In some part, the reason for not finding a difference was thought to be due to small sample sizes lacking power to find a

difference, and some studies were given less weight due to poor quality. Differences in adverse events were thought to be minor, although the assessment and reporting of adverse events was criticized. These reviewers also commented on the lack of good-quality studies assessing long-term outcomes, both of effectiveness and serious adverse events. See Appendix F for further description of the findings of these reviews.

The American Academy of Pediatrics Clinical Practice Guideline on treatment of school-aged children with ADHD 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 guideline considers only stimulant medications, specifically all forms of methylphenidate and immediate-release dextroamphetamine. Stimulant and/or behavior therapy is recommended, the guideline does not prefer one, and states that the Jadad review (cited above) found no difference between these stimulants.[25] The guideline also states, "Individual children, however, may respond to one of the stimulants but not to another." The American Academy of Child and Adolescent Psychiatry guideline states 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.

What this review adds

Our review adds to these prior reviews in a number of areas. First and foremost it is a *comparative* review rather than the assessment of effectiveness compared with placebo or no treatment. Secondly, this review is more comprehensive and has recently been updated. Cross-referencing lists of studies included in each review reveals that we have included several studies that the other reviews did not.[27-50] Reasons for these studies not being included in the other reviews include differences in the scope of drugs reviewed, the outcomes included, and study designs included. This review includes Adderall® and modafinil, it includes observational studies to assess harms and functional outcomes as well as randomized controlled trials with functional outcomes such as academic achievement, and it includes comparative evidence of the effect on weight and height – all of which were not included in previous reviews. In addition, special effort has been made to identify the effects of ADHD subtype, diagnostic tool or definition, primary outcomes, comorbidities, and ethnicity.

Summary of Findings

General

- There are 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. is lacking.
- The evidence for comparative efficacy and adverse events of drugs for treating ADHD is 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 vary 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 limited the ability to show a difference between drugs if one exists.

- Limitations to the generalizability of these trials include 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 be comparable. Depending on the definition used, there is 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.

Young children (preschool age; 3-5 years)

Efficacy and tolerability

- No comparative evidence in young children was 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.

Long-term safety

- Evidence from 1 trial of immediate-release methylphenidate showed reduced growth rates based on a mixed-effects regression analysis.

Children (elementary school age; 6-12 years)

Effectiveness

- Because no trials of effectiveness were found, observational studies were assessed for outcomes of effectiveness.
- The only comparative study with relevant outcomes found methylphenidate OROS to be associated with fewer outpatient visits/hospitalizations for accidents/injury than immediate-release methylphenidate over 12 months. Methodologic concerns over this study suggest caution in 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 suggest caution in interpreting these findings.

Efficacy and tolerability

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 indicate methylphenidate OROS may result in greater improvement (weighted mean difference –1.19; 95% CI, –1.78 to –0.60).
  - Limited evidence is 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 suggests 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.
  - Dexmethylphenidate ER resulted in better response from 2 to 6 hours post-dose compared with methylphenidate OROS, but methylphenidate OROS resulted in better scores later in the day; from 10 to 12 hours post-dose.
  - There is currently no evidence of a difference in adverse events between immediate-release and sustained-release formulations.
- Dextroamphetamine compared with methylphenidate:
  - The body of evidence clearly indicates no difference in efficacy between immediate-release dextroamphetamine and immediate-release methylphenidate. Evidence from short-term trials and observational studies suggests that weight loss is greater with immediate-release dextroamphetamine than immediate-release methylphenidate.
- Mixed amphetamine salts compared with methylphenidate:
  - Immediate-release mixed amphetamine salts was superior to immediate-release methylphenidate on a few efficacy outcome measures in 2 trials, but clear

evidence of superiority is lacking. Very limited evidence suggests 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 is 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 Center for Drug Evaluation and Research 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®. Adverse event data 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. Assessments were made either weekly or starting 4 hours after administration of dose or application of patch.
  - Although rates of adverse events and discontinuations due to adverse events were greater with transdermal methylphenidate, differences were not found to be statistically significant.
- Longer-term studies indicate 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.

Atomoxetine

- Atomoxetine compared with methylphenidate:
  - Evidence from 2 trials suggests that atomoxetine was 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%

    - 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 to 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).

Adolescents

Efficacy and tolerability

- 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 are 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.
- Functional outcomes of observational studies:
  - Observational studies of immediate-release methylphenidate that reported functional outcomes found mixed results. 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.
  - Another uncontrolled 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.

Adults

Efficacy and tolerability

- There were no trials of adults with ADHD using dexmethylphenidate, methamphetamine, methylphenidate transdermal patch, methylphenidate chewable tablet or oral solution, or some extended release forms of methylphenidate (Metadate CD®, Ritalin LA®, and Biphentin®).
- Direct comparative evidence was limited to 1 trial of immediate-release dextroamphetamine compared with modafinil. No differences were found 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). [51]
- Placebo-controlled and uncontrolled trials:
  - Improvement of ADHD symptoms
    - Placebo-controlled trials generally indicated that atomoxetine, immediate-release dextroamphetamine, dexmethylphenidate ER, lisdexamfetamine, immediate-release methylphenidate, methylphenidate SR, methylphenidate OROS, and methylphenidate ER, immediate-release mixed amphetamine salts, and mixed amphetamine salts XR are all effective treatments for reducing ADHD symptoms, with response rates ranging from 34% to 82%.
    - Results from an indirect comparison meta-analysis suggested a relative benefit of clinical response for shorter acting stimulants at 3.26 times greater than for patients taking longer-acting stimulants (95% CI, 2.03 to 5.22) and 2.24 times greater than for patients taking longer-acting forms of bupropion (95% CI, 1.23 to 4.08).

- Other efficacy outcomes
  - Atomoxetine: Generally not significantly better than placebo in improving quality of life and driving performance outcomes in placebo-controlled trials.
  - Immediate-release methylphenidate: Several trials of immediate-release methylphenidate have demonstrated an advantage over placebo in reducing anxiety and improving cognition and driving performance outcomes. No differences in sleep improvements were found between immediate-release methylphenidate and placebo on 5 of 6 assessments in 1 trial.
  - Mixed amphetamine salts XR: Greater improvements in overall simulated driving performance were found for mixed amphetamine salts XR than for placebo both at 7-hours and 12-hours post-dose in 1 trial of 19 young adults.
  - Methylphenidate OROS: Superior to placebo in improving some, but not all parenting skill measures in a 2-week trial of 23 mothers.
- Tolerability
  - Compared to placebo, rates of appetite disturbance and sleep disturbance were generally greater for atomoxetine, immediate-release dextroamphetamine, dexmethylphenidate ER, lisdexamfetamine, methylphenidate ER, immediate-release methylphenidate, methylphenidate SR, methylphenidate OROS, immediate-release mixed amphetamine salts, and mixed amphetamine salts XR.
  - Results of our 2008 indirect comparison meta-analysis suggested no significant differences between different drug types (appetite loss: Chi Sq = 0.78; P=0.68; sleep disturbance: Chi Sq = 2.62; P=0.45).

Long-term safety

- Although the observational studies provide 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 is poor quality due to a variety of flaws in design and analysis and should be interpreted with caution.
- Sudden cardiac death:
  - Based on a case-control study of 10 years of state vital statistics records and parent surveys, the risk of sudden cardiac death was 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.

  - A smaller study based on 10 years of Florida vital statistics records was not able to find a significant effect of stimulant exposure and death due to circulatory causes, including sudden cardiac death.
- Cardiac adverse events:
  - Emergency department and physician office visits due to cardiac causes occurred significantly more often in the group currently using a stimulant (hazard ratio, 1.20; 95% CI, 1.04 to 1.38) compared with non-users (hazard ratio, 1.21; 95% CI, 1.06 to 1.39). Former use of stimulants was not significantly associated. Using regression analysis, several factors were found to be significantly associated with the increased risk of an emergency department or physician's office visit due to cardiac causes: age ≥ 15 years compared to < 15 years; congenital anomalies; history of circulatory disease; disability; nonblack race; and the use of antidepressants, antipsychotics, and bronchodilators.
- Suicidal behaviors:
  - 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.
- Height change in children:
  - Evidence on immediate-release dextroamphetamine compared with methylphenidate is 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 suggests 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.
- Weight in children:
  - Results from comparative observational studies of immediate-release dextroamphetamine and methylphenidate suggested that immediate-release dextroamphetamine was associated with significantly greater suppression of weight gain than methylphenidate in the first 1-2 years. However, the difference between immediate-release dextroamphetamine and methylphenidate appeared to resolve by the second year and the difference found in years 1 to 2 may have been exaggerated by higher relative immediate-release dextroamphetamine dosages. Ultimately, these data should be interpreted with caution due to methodological flaws in the measurement of weight.
  - The remaining comparative and noncomparative observational studies suggested a small reduction in expected weight gain, especially among those with greater

  - Limited evidence suggests 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, headaches:
  - Based on a retrospective cohort study with 24 months of exposure:
    - Rates of insomnia were 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%).
    - Rates of decreased appetite were not found to be different among immediate-release methylphenidate, methylphenidate OROS, mixed amphetamine salts, mixed amphetamine salts XR, and atomoxetine, 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 Boneronni correction was used. Thus we suggest caution in interpreting these findings.
- There was no comparative evidence on other long-term safety outcomes, including tics, seizures, cardiovascular adverse events, injury frequency, and hepatotoxicity.

Abuse/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:
    - A systematic review primarily of surveys 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 rates of misuse of stimulant medications for enhancement of academic performance were 30% to 35%.
    - In a study of 66 adults prescribed methylphenidate, 29% reported inappropriate use during the past month.
        - 84% used it orally, 74% used it nasally, and 11% smoked it.
        - Regression analysis indicated that misuse of methylphenidate was associated with illicit use of cocaine or amphetamines.
    - Analysis of the National Survey on Drug Use and Health from 2000, 2001, and 2002 found:
        - 0.9% in the 12 to 17 year age group had misused an ADHD stimulant (nonmedically) in the past year.
        - 1.3% in the 18 to 25 year old age group had misused an ADHD stimulant (nonmedically) in the past year.
        - 34.7% of respondents had *ever* misused a prescription stimulant intended for use to treat ADHD.
        - 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
    - Based on small studies or a systematic review of primarily surveys:
        - Among children through high school aged who were prescribed a stimulant:
            - 15% to 24% gave them away.
            - 7% to 19% sold them.
            - 4% to 6% had them stolen at some time in the past.
        - Among college students who were prescribed a stimulant:
            - 23% had been asked to give, to trade, or to sell them.
            - 29% of those surveyed reported selling them.

        - In a longitudinal follow-up study of adults, 11% reported having sold their ADHD medications in the last 4 years.
        - Among adults who were prescribed a stimulant:
            - 44% reported diverting their medication to someone else, with 97% giving it away, 17% selling it, and 14% doing both.
            - 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.
    - The evidence regarding drug misuse/abuse or diversion related almost entirely to immediate release stimulants, most often immediate-release methylphenidate. Evidence from a cross-sectional study indicated that methylphenidate OROS is also subject to misuse/abuse or diversion.

Subgroups

Demographics

- Race/ethnicity:
    - Only half of studies reported race or ethnicity data. Studies were primarily conducted in white populations.
    - Immediate-release methylphenidate in African American boys:
        - 75% of subscale measures showed improvement.
        - This rate is 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 to 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 suggested no difference in efficacy between boys and girls with immediate-release methylphenidate.
    - Lisdexamfetamine:
        - Difference in ADHD rating scale IV mean change score compared to 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-Reimherr 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 differs 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.
    - 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

- 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.
- 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.
- 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 co-existing 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.
  - 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 is 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 comes from 6 placebo-controlled trials of immediate-release methylphenidate.[52-59] Of these 6 placebo-controlled trials, 4 were either poor quality and/or lacked a valid assessment tool.[52, 53, 55-57] The remaining 2 studies present 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).[54] 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 to placebo, although reports of time on task were better with the higher dose (mean 52 seconds longer compared to 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.[58, 59] 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[58] 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[59] 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).[58]

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 three 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 three times daily) to 0.72 (immediate-release methylphenidate 7.5 mg three 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 to 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, 15% on immediate-release methylphenidate. The open-label lead-in phase may have influenced this drop out 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.[60] 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 are based on only 61 of 114 randomized patients and the difference in final score was approximately 1.5 points. The complete scale is 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.[61] 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)

Generalizability issues

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. This gap in the literature limits the generalizability of the findings to target populations. 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%).[62] However, the prevalence of ADHD among ethnic groups may not correlate with these data.

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%.[63] 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.

Stimulants

Comparison of immediate-release and sustained-release formulations

Methylphenidate. We included 13 trials of immediate-release methylphenidate compared with methylphenidate SR.[28, 64-73] 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 intention to treat analysis, lack of information on eligibility criteria, attrition, or post-randomization exclusions (Evidence Table 3).[28, 64, 65, 69] The remaining studies compared immediate-release methylphenidate to 5 extended-release formulations of methylphenidate (Biphentin®, Concerta®, Ritalin SR®, Medikinet®, or Metadate CD®**)**.[66-68, 70-73] In addition, according to a US Food and Drug Administration statistical review (http://www.fda.gov/cder/foi/nda/2000/21-121_Concerta_statr.pdf), methylphenidate OROS (Concerta®) and immediate-release methylphenidate were compared in an additional trial of 64 children that has not yet been published.[74]

No trials comparing the other extended release formulations of methylphenidate (Ritalin LA®, Methylin ER®, or Metadate ER®) to immediate-release methylphenidate were found. Table 3, below, presents basic pharmacokinetic information on the methylphenidate products.

Table 3. Pharmacokinetic profiles of methylphenidate products[a]

Drug	Doses per day	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
Long-acting (biphasic pharmacokinetic profiles)				
Biphentin®[b]	1	1st: 1.7-2.6 2nd: ~4.5	10-12	Multilayer-release system: 40% immediate; 60% delayed
Metadate CD®, Equasym®	1	1st: 1.5 2nd: 4.5	8	Errand Diffucaps: 30% IR & 70% ER beads released from capsule
Ritalin LA®	1	1st: 1-3 2nd: 4-5	8-10	Spheroidal Oral Drug Absorption System (SODA): 50% IR; 50% delayed-release beads released from capsule
Concerta®	1	1st: 1-2 2nd: 6-8	12	Osmotic Release Oral System (OROS): 22% IR tablet coating; 78% released from tablet utilizing osmotic pressure

[a] Information obtained from product labels.
[b] Not available in the United States.

Immediate-release methylphenidate compared with methylphenidate OROS (Concerta®). Four studies have compared immediate-release methylphenidate compared with methylphenidate OROS once daily, enrolling a total of 561 children with ADHD (Table 4).[66, 67, 72, 73]

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

Study details	Mean dose	Mean *change* in IOWA Conners' MPH OROS vs. MPH IR	SNAP-IV MPH OROS vs. MPH IR
Wolraich 2001 Double-blind RCT United States N=282 28 days	MPH IR 29.5 daily (TID dosing) Concerta® 34.3 daily	*Teacher ratings:* Inattention/overactivity –3.57 vs. –3.76 Oppositional/defiance –1.3 vs. –1.6 3 *Parent ratings:* Inattention/overactivity –3.73 vs. –4.79 Oppositional/defiance –2.36 vs. –3.24 *For all comparisons, P*=NS	*Teacher SNAP-IV:* Inattention –0.69 vs. –0.80 Hyperactivity/impulsivity –0.64 vs. –0.69 Oppositional/defiance –0.36 vs. –0.32 *Parent SNAP-IV:* Inattention –0.91 vs. –0.77 Hyperactivity/impulsivity –0.91 vs. –0.74 Oppositional/defiance –0.65 vs. –0.41 *For all comparisons, P*=NS
Pelham 2001 Double-blind Crossover[a] + Behavioral Treatment United States N=68 7 days	MPH IR 29 mg daily (TID dosing) Concerta® 35 daily	*Teacher ratings:* Inattention/overactivity 4.96 vs. 4.65 Oppositional/defiance 2.08 vs. 2.26 *P*=NS for both comparisons *Parent ratings:* Inattention/overactivity 4.49 vs. 5.64; *P*=0.05; Oppositional/defiance 2.02 vs. 2.46; *P*=NS	Methods indicate SNAP measured, but results not clearly reported separate to other results
Steele, 2006 Open-label RCT Canada/United States N=147 8 weeks	MPH IR 33.3 mg daily (usual care; 61% TID, 38% BID) Concerta® 37.8 mg daily	*Teacher ratings:* NA *Parent ratings:* Inattention/overactivity –3.9 vs. –5.4; *P*=0.01; Oppositional/defiance NA	*Parent ratings:* SNAP-IV Remission[b] 16% vs. 44%; P 0.0002; NNT 3.6) Mean Change in SNAP-IV 26 (ADHD + ODD) –17.5 vs. –25.2; *P*=0.004 SNAP-IV-18 (ADHD only) –14.3 vs. –19.6; *P*=0.01
		Conners' Rating Scale Revised Short-Form	
Gau, 2006 Open-label RCT Taiwan N=64 28 days	NR	*Teacher ratings:* Inattention –1.90 vs. –1.44 Hyperactivity/impulsivity –4.94 vs. –4.00 Oppositional –3.03 vs. –1.91 *Parent ratings:* Inattention –5.63 vs. –4.19 Hyperactivity/impulsivity –7.53 vs. –5.84 Oppositional –3.87 vs. –3.41 Comparisons of slope (change in score over time) between treatments: *P*<0.0001 for all comparisons	

Abbreviations: ADHD, attention deficit hyperactivity disorder; BID, twice daily; NA, not applicable – scale not applied; NNT, number needed to treat; ODD, oppositional defiant disorder; RCT, randomized controlled trial; TID, three 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 2 earlier, double-blind trials, 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.[66, 67] In contrast, the 2 newer, open-label studies did find a significant difference favoring methylphenidate OROS.[72, 73] While all of the studies suffer from design or conduct challenges and none were rated good quality, the 2 newer studies present more concerns of bias than the earlier studies. There is also a potential risk of selection bias in that only one of the studies[66] reported the proportion of patients taking immediate-release methylphenidate or methylphenidate OROS prior to enrollment.

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.[67] 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.[66]

The study by Steele et. al[73] was open-label, comparing usual care to switching to methylphenidate OROS. Based on a definition of remission as a score of 0 or 1 (none or just a little) on the 18 items relating to ADHD symptoms only (excluding the items pertaining to oppositional defiant disorder) of the parent assessed SNAP-IV scale, methylphenidate OROS treatment resulted in more patients being classified as in remission at 8 weeks, with a number needed to treat near 4 (see Table 4). Similar results were found using other measures of parental assessment. This study does 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 is not reported.

We undertook an exploratory analysis, pooling the parent ratings of inattention/overactivity subscale items of the IOWA Conners' scale from these 3 studies, as it was the only item reported across all 3 (see Table 4). While the Wolraich and Pelham studies did not find significant differences in the mean change on this item, the pooled analysis with the Steele study does result in a statistically significant finding, favoring methylphenidate OROS; weighted mean difference –1.19; 95% CI, –1.78 to –0.60. However, we do 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 are 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 has 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 UK suggest 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.[75] The validity and generalizability of these findings are 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 is unclear whether the UK formulation is comparable to methylphenidate OROS as included in this review.

The US Food and Drug Administration Statistical Review of the New Drug Application for methylphenidate OROS includes criticism of 3 early trials,[66, 67, 76] 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).[74]

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.[68] 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 favoring 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.[71] 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®. Intention to treat analysis as well as subgroup analyses (country, dose, ADHD subtype) were 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 June 2009).[77, 78] 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.[78] 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 to those taking methylphenidate multilayer-release (90% compared to 79% on the teacher scale and 81%

compared to 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.[77] 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.

Immediate-release methylphenidate compared with methylphenidate ER (Medikinet®). Results from a fair-quality, 2.5-week crossover trial of 79 pediatric patients did not suggest any differences between flexible dosages (≤1 mg/kg) of immediate-release methylphenidate twice daily and methylphenidate ER (Medikinet®) in SKAMP Attention or Deportment subscale scores or in math problems attempted.[70] Effect sizes were relatively similar regardless of time of day (9:30 a.m. through 4:45 p.m.). This study was conducted in outpatient clinics in Germany and the formulation of methylphenidate ER (Medikinet®) is not available in the United States.

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 five 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-month79 and 12-months [40, 43, 80, 81] 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).[82] 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, 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%, $P<0.0001$[40] and 15% compared with 3%, $P<0.0001$).[80, 81] 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.[80, 81] There is uncertainty about how well this study population represents patients in actual practice as ethnicity and comorbidity characteristics are not reported, and there are 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).[43] 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 ER 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 suggest that persistence duration was greatest for methylphenidate OROS (147.2 days; 95% CI, 142.6 to 151.7 days) compared to 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, ER 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).[79] 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 (MPR), were higher in patients taking methylphenidate OROS compared to immediate-release methylphenidate or immediate-release mixed amphetamine salts (0.76 compared with 0.69 compared with 0.73; $P<0.001$).

Comparisons of SR formulations

Methylphenidate OROS (Concerta®) compared with methylphenidate CD (Metadate CD®). Results from the fair-quality COMACS crossover study of 184 children suggest 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.[83, 84] This study examined the pharmacodynamic differences of these products resulting from differences in pharmacokinetic profiles. The children were mostly male (73.8%), with a mean age of 9.6 years and they were randomized to low, medium, or high dosage treatment group sequences based on their previous dosages of immediate-release methylphenidate. Table 5 below illustrates effect sizes which suggest that 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. This study presents 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.

Table 5. Effect sizes for methylphenidate CD and methylphenidate OROS by time of day (COMACS study)

	9:00 am	10:30 am	12:00 pm	2:30 pm	4:00 pm	7:30 pm
SKAMP Deportment						
MCD	0.82	0.89	0.80	0.76	0.54	0.06
CON	0.52	0.50	0.50	0.66	0.51	0.25
SKAMP Attention						
MCD	0.70	0.72	0.66	0.65	0.50	0.00
CON	0.41	0.48	0.42	0.64	0.53	0.20

Abbreviations: CON, Concerta; MCD, Metadate CD.

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[41] 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 are 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.[85] 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) are 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.[86] The primary outcome was the mean change in the SKAMP combined score at 2 hours post-dose in the dexmethylphenidate ER 20 mg daily group compared to 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). 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 Center for Drug Evaluation and Research Medical Review,[87] 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.[88, 89] Both were fair-quality. Study 2301 was a 7-week, parallel-group, flexible-dosing trial of 103 children.[88] Study US08 was a 2-week, fixed-dose, crossover trial of 54 children.[89] 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.[88-91] 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; $P<0.001$).[88] 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; $P=0.001$[91] and –0.969 dexmethylphenidate ER compared with 3.336 placebo; $P=0.001$),[91,90] and the third found a difference starting at 1 hour post-dose (–10.014 compared with 0.078; $P<0.001$).[89] Lack of adequate variance data prevent 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 ER (Metadate®) compared with placebo. A 3-week trial of Metadate® compared with placebo enrolled 314 children out of 507 screened.[92] 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® 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® group. Secondary measures also favored Metadate®.

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.[35-37, 39, 46-48, 93-96] Two poor-quality studies and 1 poor-quality sub-group analysis were found.[29, 97, 98] 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 2 weeks	DSM-IV criteria for ADHD	DEX: 0.15 mg/kg MPH: 0.3 mg/kg	No differences found
Efron 1998	N=102 2 weeks	DSM-IV criteria for ADHD	DEX: 0.15 mg/kg MPH: 0.3 mg/kg	No differences found
Elia 1990	N=31 3 weeks	DSM-III criteria for attention deficit disorder with hyperactivity	< 30 kg/ > 30 kg: DEX: 40 mg/ 45 mg MPH: 70 mg/ 90 mg	No differences found
Elia 1991	N=48 3 weeks	DSM-III criteria for attention deficit disorder with hyperactivity	< 30 kg/ > 30 kg: DEX: 40 mg/ 45 mg MPH: 70 mg/ 90 mg	No differences found
Elia 1993	N=33 3 weeks	DSM-III criteria for attention deficit disorder with hyperactivity	< 30 kg/ > 30 kg: DEX: 40/ 45 mg MPH: 70 / 90 mg Placebo	No differences found
Sharp 1999	N=32 3 weeks 100% girls	ADHD symptoms present in at least 2 settings; Conners' Hyperactivity factor scores at least 2 SD greater than age and sex norms	DEX: 0.64 mg/kg MPH: 1.28 mg/kg	No differences found
Arnold 1978	N=29 3 weeks	Diagnosis of Minimal Brain Dysfunction; total score of 24 or more on the first 6 items of the David's Hyperkinetic Rating Scale	DEX: 15 mg MPH: 30 mg	No differences found
Kaufman 1981	N=12 6 weeks	Children diagnosed as "hyperactive", according to a set of predetermined clinical criteria (NR)	DEX: 10-60 mg MPH: 5-30 mg Placebo	No differences found
Simpson 1980	N=12 8 weeks	Hyperactivity that had been long term; complaints of hyperactivity by parents and teachers; at least average intellectual abilities as measured by the WISC-R	NR	Post-hoc analysis: DEX "the most effective drug, where a positive effect was seen"

Abbreviations: ADHD, attention deficit hyperactivity disorder; NR, not reported.
[a] All doses divided into morning/noon doses.

The 2 largest studies,[35, 94] 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,[94] and to test the differences between child and parent assessment of therapy in the other.[35] 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[35] and based on parent and teacher ratings.[94] These 2 studies had similar populations, primarily children with the Mixed subtype (82%), however comorbidities and ethnicity are not reported.

Of the 7 small studies (N=12 to 48), only 1 found a difference between the drugs.[48] 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.[48] The text of the paper reports 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 are 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, or mixed amphetamine salts to immediate-release methylphenidate. Additionally, the majority of these response rates are 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] Crossover N=70	MPH OROS MPH IR x 1 week	Parent/teacher ratings of Global Effectiveness as "Good" or "Excellent"	Parent: 67.2 vs. 64.7 Teacher: 67.2 vs. 57.4
Wolraich 2001[b] Parallel N=192	MPH OROS MPH IR 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 Teacher: 42.9 vs. 46.9
DEX IR compared with MPH IR			
Efron 1998 Crossover N=102	DEX IR MPH IR X 2 weeks	Parental ratings of drug as "very helpful" or "a bit helpful"	62.4 vs. 73.5
Efron 1997 Crossover N=125	DEX IR MPH IR X 2 weeks	Parental ratings that child improved overall	68.8 vs. 72.0
Sharp 1999 Crossover N=42	DEX IR MPH IR X 3 weeks	CGI: "very much improved" or "much improved"	85.0 vs. 83.0
MAS (Adderall®) compared with MPH IR			
Pliszka 2000 Parallel N=40	Adderall® MPH IR x 3 weeks	CGI improvement score of 1 or 2: "very much improved" or "much improved"	90.0 vs. 65.0; *P*=0.12

Abbreviations: CGI, Clinical Global Impression Scale.
[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).[40] 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 two publications,[80] 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)[80] and a lower probability of being hospitalized (odds ratio, 0.67; 95% CI, 0.45 to 0.99) over a 12-month

period.[81] 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 [81] 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.[80] 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.[99] 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.[100] 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; 295 were treated with a stimulant and 84 were not.[101] 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. Drop-out 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 has some methodological advantages over other studies, the main limitation is the number of children included, particularly in the non-medicated 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 are 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,[102-104] and 3 trials that randomized children to stimulant medication or non-drug therapy for 12 to 14 months.[105-107] 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.[105] Following the 14-month trial the groups had follow-up at 2, 3, and 8 years post-randomization.[44, 105, 108, 109] Medication management could involve any stimulant medication, but started with methylphenidate titration. At study end, 73% of those in one 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 doses per day 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 to 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 to 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.[44] 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 to 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.[108] Along with these changes, the difference between groups in outcome measures was no longer statistically significant although all groups had improved compared to 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.[108] 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 non-stimulant. 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 to placebo[102-104] or other non-drug interventions,[105-107] 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.[102,110]

Remission rates: Immediate-release methylphenidate

Three studies assessed the effects of withdrawing immediate-release methylphenidate after periods of treatment.[111-113] Two of these were poor quality,[111, 112] but the third study[113] 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.[114] 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 are 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 to 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.[32, 45, 115, 116] One was a parallel group randomized controlled trial[116] while the other 2 were randomized cross-over trials.[32, 45, 115] Two additional studies were rated poor quality[42, 117] due to no description of randomization or concealment of randomization code, no intention 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.[116] 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.[32, 45, 115] 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 indicate 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 is limited to a single poor quality study of immediate-release dextroamphetamine compared with dextroamphetamine SR compared with mixed amphetamine salts compared with placebo.[118] 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.[119] 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%).[119]

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.[111]

Methamphetamine. The only evidence we identified for methamphetamine is 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.[120] 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 a fair quality trial (N=270), transdermal methylphenidate was not found to be significantly different to methylphenidate OROS after a 7-week period. Dose on either treatment was titrated in a double blind fashion over 5 weeks.[121] Children applied the patch (placebo or active) and took the capsule (placebo or active) at 7 am each day. The primary outcome measure was the investigator's assessment of the total score on the ADHD-Rating Scale, completed once a week, although multiple other scales were used as secondary outcome measures. No difference was found between drugs in the mean change from baseline (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 (measured twice weekly) or parents (measured at 11 am and 3 pm) 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.

Two placebo-controlled trials of transdermal methylphenidate have been published.[122, 123] A 1-week, randomized, placebo-controlled, crossover trial conducted in a laboratory classroom setting (N=80), examined transdermal methylphenidate compared placebo patch worn for 9 hours, after a 5 week dose-optimization period. Compared to the group randomized to the treatment sequence which started with placebo, we noted that a significantly greater proportion of patients randomized to receive transdermal methylphenidate first had ADHD of the inattentive type (27% compared with 5%; P=0.01). As no period or sequence effects were found for scores on the primary outcome of SKAMP Deportment, however, this baseline difference was unlikely to have seriously biased the results. Findings from a mixed linear model ANOVA showed that transdermal methylphenidate was significantly superior to placebo on the SKAMP Deportment and Attention scales at timepoints starting at 2 hours up to 12 hours post-dose, and in the number of math problems attempted and number of math problems correct on the Permanent Product Measure of Performance (PERMP). In a somewhat similar study, 117 children were assigned to placebo or transdermal methylphenidate worn for shorter periods (4 or 6 hours), again 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.[122] 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,[124,297] 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.[125] 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,[124, 297] or the change in mean ADHD rating scale IV total score.[125] Scores in all lisdexamfetamine groups were significantly superior to placebo group scores across both trials.

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 to 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. The few exceptions pertained to the 30 mg dosage of lisdexamfetamine.[125, 189] Compared to mean changes in ADHD rating scale IV for lisdexamfetamine 30 mg compared with placebo for the population overall (–21.8 compared with –6.2 points; $P<0.0001$), treatment effects appeared less robust in the subgroups of girls (–19 compared with –8.1; $P=0.0537$) and non-Caucasians (–18.5 compared with –10.1; $P=0.0754$). 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).[126] The difference between placebo and lisdexamfetamine showed a small declined over time. For example, the difference between placebo and drug at 10 am was 47%, at 2 pm was 47.6%, and at 6 pm was 43.9%. We have also identified another placebo-controlled trial of lisdexamfetamine that was listed as completed on clinicaltrials.gov (Study NTC00500149). This study enrolled 129 children, with a primary outcome of onset of efficacy and secondary outcome of duration of efficacy (up to 13 hours), but a published version is not yet available.

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 per day of immediate-release methylphenidate (based on a weight cut-off of 30 kg).[127] Using the ADHD parent and teacher rating scale, significant differences were seen compared to 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.

Efficacy findings for modafinil were inconsistent across 5 placebo-controlled trials.[128-132] It appeared that dosing regimen may play an important role in the efficacy of this product. The first study randomized involved 24 patients who were followed for mean durations of 5 or 6 weeks (placebo and modafinil, respectively). The mean age of patients was 8 years and 58% were male. In this study, less than 1/3 had oppositional defiant disorder or conduct disorder (27% combined), and the ADHD subtype was primarily Mixed (73%). Two children (8%) in the modafinil group were excluded from the analysis because they did not have post-randomization assessments. When dosed at 200-300 mg in this study, modafinil was not found to be better than placebo in improving ADHD rating scale.

Among the later trials, there were 3 that used very similar designs and involved very similar patient populations. 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.[128, 130, 131] Patient mean age was 10 years and 71% were male. 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 the final and most recent placebo-controlled trial of modafinil, the objective was to compare the efficacy and safety of several different once and twice daily dosing regimens.[132] In this trial, 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. The majority of patients were male, with a mean age of 9 years. 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.

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.[133, 134] 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%).[134] 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.[133] 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.[135] 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 is 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 to 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.[136] 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 to 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.[137] 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).[138] This trial, also known as Strattera®/Adderall XR® Randomized Trial, was conducted in a simulated classroom setting which involved 12 hours of observation per day. 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.[139] The total score of the tool is 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 intention to treat analysis described (it appears only 75% of atomoxetine group is included in the analysis, compared to 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.[140-145] Results of 2 of the 6 trials were described as identically-designed and were reported in 1 publication.[142] The mean change on ADHD rating scale in these 6 to 9 week studies ranged from –12.8 to –16.7 with atomoxetine compared to –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 ($P<0.001$).[144] 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 co-authored 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[142] 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.[146] No subgroup analyses based on ADHD subtypes or other comorbities were reported. Based on what appears to be post hoc analysis of secondary outcome measures of 1 of these trials,[145] 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.[147]

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.[148] Meta-regression identified study duration and number of study sites, male sex, ADHD hyperactive/impusive 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.[149] 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.[144] 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).[150]

Atomoxetine: Effectiveness outcomes. A few noncomparative observational studies evaluated duration of effectiveness for atomoxetine.[151, 152] 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.[151] 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).[152] 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.[153]

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 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.[99, 154-157] 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 to a group that had received methylphenidate for at least 3 years during childhood.[156] 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 is given. No consistent differences in functional outcomes were found between the methylphenidate and untreated groups (Table 8). 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 8. Long-term functional outcomes of methylphenidate from Hechtman, 1984[156]

Variable	Favors	MPH group	Non-treated	*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	Non-treated	21 weeks	70 weeks	<0.001
Aggression	Untreated			<0.06
Current psychiatric treatment (n)	MPH	1	22	<0.02
Age starting alcohol use	Non-treated	14.8 years	16.2 years	<0.03
Duration of alcohol use	Non-treated	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	Non-treated	22 years	18.9 years	<0.001

Abbreviations: 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.[154]

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 is 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)[158] and in 9 placebo-controlled trials of methylphenidate.[159-168] Mixed age populations including adolescents were studied in efficacy trials of atomoxetine, however data are not stratified by school age and adolescents and 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.[158] 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 are 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.[169] 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 to 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 to 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.[170] 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.[159-167, 171, 172] 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.[172] 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[159] to 75 mg.[164] 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).[172] However, inconsistency in the way results are reported make estimation of an overall magnitude of effect impossible.

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.[173] 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 to 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,[157] 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.[155] There is 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

For evaluation of ADHD treatment in adults, we included 1 head-to-head trial and 40 placebo-controlled trials. We found no trials of adults with ADHD using dexmethylphenidate, methamphetamine, methylphenidate transdermal, methylphenidate chewable tablet or oral solution, and some extended release forms of methylphenidate (Metadate CD®, Ritalin LA®, and Biphentin®).

Direct comparisons

Only 1 head-to-head trial has been published to date focusing on symptoms of adult ADHD (Evidence Tables 9 and 10).[51] Identical proportions of adults (n=22) with ADHD responded to modafinil 206.8 mg and immediate-release dextroamphetamine 21.8 mg (48% compared with 48%; *P*=NS). 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.[51 51]

Placebo-controlled trials

Characteristics

Numerous placebo-controlled trials have been conducted to evaluate the effects of treatment on adults with ADHD.[87, 174-212] Among these, only 3 trials of immediate-release methylphenidate[192, 213, 214] were previously evaluated in a prior good-quality systematic review conducted by Jadad and colleagues with McMaster Evidence-based Practice Center in 1999 for the Agency for Healthcare Research and Quality.[5] Results from the review by Jadad and colleagues will not be discussed here, however, because it includes so few of the overall number of trials now available.

The majority of trials were rated fair quality. Three trials were rated poor quality[179, 199, 207, 215] due to inadequately described randomization and allocation concealment methods, between-groups differences at baseline, and exclusion of up to 28% of patients from outcome analyses.[199, 204] Findings from the poor quality trials can be found in Evidence Tables 11 and 12, but no details will be summarized here.

Overall, patients were characterized by a mean age of 34.5 years and 55% were male. Of the small number of trials that reported race, the majority of patients were White. Few studies reported prevalence rates of Inattentive (8% to 58%), Combined (35% to 97%), and Hyperactive-Impulsive (0% to 9%) subtypes.[51, 175, 177, 183, 193, 195, 197, 206, 216] Differing subtype prevalence patterns cannot be ruled out in studies that didn't report this information.[178, 180, 181, 186, 188, 198, 200, 201, 206, 210, 213, 214, 217] Few trials reported prevalence rates of "any comorbidity" (range, 22% to

78%) and mood/anxiety disorders (range, 4.5% to 68%).[180, 188, 193, 198, 200, 201, 213, 214] One study focused entirely on patients with ADHD and comorbid cocaine dependence.[198] Few studies examined the roles of ADHD subtypes or comorbidities in accounting for drug effects. Those that did reported a lack of adequate statistical power to detect differences and found similar response rates for atomoxetine in patients with inattentive and combined subtypes[194] and for atomoxetine in patients with comorbidities.[201]

These trials were heterogenous with regard to study duration (2-24weeks), medication dosage levels, and in ADHD diagnosis methods. Studies differed in ADHD diagnosis methods with regard to usages of diagnostic criteria (Utah criteria, DSM-III-R, or DSM-IV), requirement of second reporter corroboration (i.e., family member), and symptom severity thresholds (e.g., various measurement scale cut-off scores). Studies with more rigorous diagnostic methods[51, 178, 181, 198] may be characterized by patients with homogenous symptom presentations, whereas studies with less stringent criteria[180, 188, 195, 210, 214] may be more representative of the average patient. These trials were also heterogenous with regard to their methods of assessing improvement in ADHD symptoms.

ADHD symptom assessment

ADHD symptom improvement was assessed using a variety of rating scales, including measurement of change from baseline and endpoint scores based on the numbers of patients who achieved various definitions of clinically meaningful treatment response (such as 30% or greater improvement from baseline on the adult ADHD-Rating Scale). Regardless of approach, atomoxetine, immediate-release dextroamphetamine, dexmethylphenidate ER, lisdexamfetamine, immediate-release methylphenidate, methylphenidate SR, methylphenidate OROS, methylphenidate ER, immediate-release mixed amphetamine salts, and mixed amphetamine salts XR were generally all found to be effective short-term treatments for ADHD symptoms in adults, with anywhere from 34% to 82% of patients in the drug groups and from 4% to 61% of patients in the placebo groups met criteria for achievement of a clinically meaningful response (Table 9). Some exceptions were that the effects of low-dose immediate-release methylphenidate (45 mg three times daily)[182] and 60-90 mg of methylphenidate SR twice daily[190, 191] were notably limited in patients with comorbid substance abuse disorders. Findings from placebo-controlled trials of methylphenidate in adults with ADHD and comorbid substance abuse disorders will be discussed in more detail in Key Question 3.[182, 190, 191, 198] It should also be noted that uncertainty remains regarding the efficacy of modafinil in reducing core ADHD symptoms, as the single trial of modafinil we identified focused only on cognitive outcomes.[205, 218]

Table 9. Ranges of response rates from placebo-controlled trials in adults with ADHD

ADHD drug	Number of trials	Drug group rates	Placebo group rates
Atomoxetine	3	40% to 52%	10% to 25%
Shorter-acting stimulants			
Immediate-release dextroamphetamine	1	64%	16%
Immediate-release methylphenidate	6	42% to 78%	4% to 26%
Immediate-release mixed amphetamine salts	1	70%	7%
Longer-acting stimulants			
Lisdexamfetamine	1	60% to 70%	35%
Dexmethylphenidate SR	1	58% to 61%	34%
Methylphenidate SR[a]	2	34% to 47%	46% to 55%
Methylphenidate OROS	5	37% to 77%	15% to 48%
Methylphenidate ER	1	61%	42%
Mixed amphetamine salts XR	2	74% to 82%	13% to 61%

Abbreviations: ADHD, attention deficit hyperactivity disorder.
[a] Trials in patients with comorbid substance abuse.

Additionally, in 2008, we pooled response rate data from 22 placebo-controlled trials available at that time and generated a combined relative risk and 95% confidence interval (Table 10), which we used to conduct an adjusted indirect meta-analysis to evaluate the differences between drug types.[219] Based on indirect comparison meta-analysis, relative benefit of clinical response for shorter-acting stimulants was 3.26 times greater than for patients taking longer-acting stimulants (95% CI, 2.03 to 5.22) and 2.24 times greater than for patients taking longer-acting forms of bupropion (95% CI, 1.23 to 4.08).

Table 10. Pooled relative risks for ADHD drugs compared with placebo

Drug type	Number of trials	N	Relative risk	95% CI
Shorter-acting stimulants (MPH IR)	8	424	4.32	(3.03 to 6.16)
Longer-acting stimulants (MPH OROS, MAS XR, d-MPH-ER, MPH SR)	6	839	1.35	(1.00 to 1.84)

Additional outcomes

In addition to assessment of improvement in ADHD symptoms, a limited number of placebo-controlled trials also assessed the effects of some of the drugs on quality of life, driving performance, sleep quality, anxiety, and parenting skills.

Atomoxetine. Atomoxetine was generally not significantly better than placebo in improving quality of life and driving performance outcomes in placebo-controlled trials.

Atomoxetine: Quality of life. We identified 1 placebo-controlled and 1 uncontrolled trial that examined the effects of atomoxetine on quality of life in adults.[175, 220] 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,[175] found no difference in change from baseline between treatment groups in relationships, psychological health, productivity, and work productivity. The study reported a significant decrease in mean change from baseline to endpoint for the atomoxetine group (–11.5) compared to the placebo group (–9.9; P=0.027) in the Conners' Adult Attention Deficit/Hyperactivity Disorder Rating Scale (CAARS), but found no differences between the treatment groups in the ADHD Inattention and Hyperactivity-impulsivity sub-scales or the Adult Self-Report Scale (ASRS).

Findings from a 6-week trial of atomoxetine that lacked a control group appeared somewhat promising.[220] In this trial, 218 adults with ADHD were randomized to double-blind treatment with atomoxetine 80 mg, dosed either once daily or twice daily. Based on changes from baseline in SF-36 scores (+4.78 points on the Mental Component Summary score; P<0.001), the authors concluded that atomoxetine had improved patients' perceived quality of life.[220 220] The Mental Component Summary score was noted to be a sum of subscores from the Vitality, Social Function, Role Emotion, and Mental Health domains.

Atomoxetine: 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[175] found no differences in self report of the Driving Behavior Survey (DBS) 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[177] 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.[186]

Immediate-release methylphenidate. In three of four small trials, immediate-release methylphenidate was superior to placebo in reducing anxiety as measured using the Hamilton Anxiety Scale,[181] the Beck Anxiety Scale,[203] and the tension-anxiety subscale of the Profile of Mood States scale.[214] Whereas, in the fourth trial (N=45), 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.[188] A 3-week trial[216] 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; $P<0.01$).

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.[178, 184, 206] 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.[206] In order to test the primary outcome measure, a camara was mounted on the roof of the test vehicle to measure the amount of weaving of the car (standard deviation of lateral position-SDLP). 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.[206] Two additional studies have examined simulator driving performance trials. Results found that immediate-release methylphenidate 10 mg significantly improved an Impaired Driving Score ($P=0.05$),[184] immediate-release methylphenidate 40 mg significantly reduced steering variability,[178] and immediate-release methylphenidate 20 mg significantly improved appropriate use of turn signals.[178] 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.

Mixed amphetamine salts XR: Quality of life. The only evidence we found of the effects of mixed amphetamine salts XR on quality-of-life outcomes comes from a 10-week interim analysis of patients taking open mixed amphetamine salts XR (10-60 mg) as part of the 30-week Quality of life, Effectiveness, Safety, and Tolerability (QUEST) trial.[221] The SF-36 was used to assess quality of life and results suggested significant improvements from baseline on all individual domains except bodily pain.

Mixed amphetamine salts XR: Driving performance. We identified a small, 3-week, placebo-controlled, crossover trial that measured the effects of mixed amphetamine salts XR on simulated driving performance in 19 young adults (mean age of 22 years, 89% male). mixed amphetamine salts XR was given based on a forced-dose titration schedule of 20 mg in the first week, 40 mg in the second week, and 50 mg in the third week. 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 XR 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; $P=0.005$).[186]

Methylphenidate OROS: Parenting. We included 1 trial that focused on ADHD mothers who had children with ADHD. This study assessed the effects of ADHD symptoms on parenting in a 2-week study and involved 23 mothers (mean age 40; ADHD sub-types: combined, 56.5%;

inattentive, 34.8%; hyperactive/impulse, 8.7%).[183] Parenting skills were measured using the 42-item, validated Alabama Parenting Questionnaire (APQ) based on mother self-report and collateral reports from individuals who lived with or were close to the mothers. 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.

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 placebo-controlled trial of immediate-release methylphenidate reported results of adverse event assessments.[54] Immediate-release methylphenidate was clearly associated with higher rates of increased sadness, decreased appetite, and sociability impairments than placebo after 7-10 days in 31 preschoolers.

The Preschool ADHD Treatment Study provides some limited evidence on the short-term safety of methylphenidate.[59, 222] Overall, 21/183 (11%) of Preschool ADHD Treatment Study patients taking methylphenidate withdrew due to adverse events, although there is 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.[222]

Parent-rated rates of several specific adverse events were significantly higher with methylphenidate use compared to 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 to 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.[37, 93-95] 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.[47, 96] One of 3 trials of mixed amphetamine salts compared with immediate-release methylphenidate found no difference in adverse event rates,[116] but 2 other studies found differences.[45, 115] Limitations in study design and lack of description of analysis methods make 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,[115] and that mixed amphetamine salts given twice daily caused the highest rates of these adverse events.[45] 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.[127]

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.[66-68] 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.[118] 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®)[41] or between methylphenidate CD (Metadate CD®) and methylphenidate OROS (Concerta®).[70] No differences in adverse events were found between multilayer-release methylphenidate (Biphentin®) and immediate-release methylphenidate in 2 studies.[77, 78]

A trial of transdermal methylphenidate compared with methylphenidate OROS reported higher percentages of adverse events and discontinuations due to adverse events, but these differences were not found to be statistically significant in post hoc analyses.[121]

Atomoxetine. Atomoxetine consistently caused more vomiting and somnolence than the stimulant comparators in 4 trials and all differences were statistically significant.[133,134, 136, 138] 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.[138] Rates of somnolence ranged from 6% to 26% with atomoxetine, which was 3 to 4 times greater than rates with methylphenidate OROS[136, 138] and mixed amphetamine salts XR [138] and over 7 times greater than rates with immediate-release methylphenidate.[133,134] 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).[133,136] Rates of nausea and anorexia were greater with atomoxetine compared to 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.[134]

Indirect evidence

Dexmethylphenidate ER. Rates of overall adverse events were comparable for dexmethylphenidate ER compared to placebo in the short-term trials, with rates of 16% to 28% with dexmethylphenidate ER compared to 16 to 22% with placebo in the 1-2 week trials.[89-91] The 7-week trial reported much higher, but similar, rates in both groups; 75.5% dexmethylphenidate ER compared with 57.4% placebo.[88] 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 to placebo was for decreased appetite in the 7-week trial (30.2% compared with 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.[124] With mixed amphetamine salts XR, the most frequent were insomnia (8%) and decreased appetite (6%), while with lisdexamfetamine 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 ($P\leq0.05$) for patients taking lisdexamfetamine 30 mg (71.8%), 50 mg (67.6%), or 70 mg (83.6%) compared to placebo (47.2%).[125] When compared to placebo, all dosages of lisdexamfetamine were associated with significantly greater rates ($P\leq0.05$) 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 to placebo (9.2% compared with 1.4%; $P\leq0.05$). Withdrawals due to any of these adverse events only occurred in <1% of patients, however.[223]

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.[224] 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 to

placebo). Similarly, total sleep time was shorter with either immediate-release methylphenidate dose compared to placebo (means of 51 and 60 minutes less with low and high doses compared to placebo). Other sleep outcomes (wake after sleep onset, sleep efficiency, activity, and time of lights out) did not differ between groups.

Adolescents

Placebo-controlled trials of immediate-release methylphenidate[159-168, 171, 225] provide 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.[161, 162, 165, 168] Additionally, adolescents taking immediate-release methylphenidate frequently reported increases in dulled affect, social withdrawal, irritability, and stomachache in 2 placebo-controlled trials.[164, 168]

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.[169] 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.[170] Results from a 4-week trial found that when compared to 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.

Adults

Direct comparisons

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) in the only included head-to-head trial.[51] There were no withdrawals due to adverse effects.

Placebo-controlled trials

Adverse event reporting among adults with ADHD is limited in placebo-controlled trials. In our 2008 meta-analysis, we pooled data from 13 placebo-controlled trials of atomoxetine, shorter-acting stimulants, and longer-acting stimulants and generated combined rates of duration-adjusted treatment discontinuations, appetite loss, and sleep disturbance for each drug group.[219] Pooled rates of duration-adjusted treatment discontinuations were 30% for atomoxetine, 30% for shorter-acting stimulants, and 26% for longer-acting stimulants, which were similar or slightly lower than pooled rates from the placebo groups. However, pooled rates of appetite loss and sleep disturbance were significantly greater for all drug groups compared with placebo (Table 11). However, results of our indirect comparison meta-analysis suggested no significant

differences between different drug types (appetite loss: Chi Sq = 0.78; *P*=0.68; sleep disturbance: Chi Sq = 2.62; *P*=0.45).

Table 11. Pooled analysis of ADHD drugs compared with placebo on rates of appetite loss and sleep disturbance[219]

	Appetite loss			Sleep disturbance		
	% with event		Relative risk (95% CI)	% with event		Relative risk (95% CI)
ADHD drug	Drug	Placebo		Drug	Placebo	
Atomoxetine	11%	3%	3.37 (1.63 to 6.93)	12%	3%	3.33 (1.68 to 6.61)
Shorter-acting stimulants	29%	10%	2.75 (1.61 to 4.71)	34%	20%	1.81 (1.26 to 2.61)
Longer-acting stimulants	21%	4%	5.85 (1.64 to 20.91)	17%	8%	2.19 (1.42 to 3.39)

Abbreviations: ADHD, attention deficit hyperactivity disorder.

Rates of adverse events for atomoxetine[175, 177, 186] and longer-acting stimulants[176, 186, 193, 197] were also generally greater than placebo in trials published subsequent to our 2008 meta-analysis, with 1 exception. In 1 short-term trial (3 weeks), atomoxetine had a lower prevalence of sleep disturbance than placebo.[186]

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.[185, 226-251] The studies were 1 to 5 years in duration. All but 1 study involved elementary school-aged children.[245] The exception was 1 before-after study of mixed amphetamine salts in adults with ADHD.[245]

Growth (height and weight) was commonly reported in these studies. Other long-term safety outcomes were assessed, including tics, seizures, cardiovascular adverse events, injuries, and attempted suicide. One study reported on tooth maturation in children taking immediate-release methylphenidate compared to an unexposed control group, finding no difference.[252]

No study was rated good quality. All but 1 was rated fair quality due to biased patient selection processes and/or biased or unspecified outcome ascertainment methods. 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.[248] 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.

Suicide

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.[226] Based on 12 short-term clinical trials in children with ADHD or enuresis, 1357 children taking atomoxetine were compared to 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 to 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 one 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).[226] A subsequent black box warning is included in Appendix G.

A higher rate was found in an analysis of children taking atomoxetine for at least 3 years.[153] 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 is no control group for this analysis, and because much of these data come from extension studies where some level of selection bias exists, these findings must be viewed as suggestive only.

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.[185] One participant (12.5%) attempted to commit suicide by consuming a month's supply of methylphenidate.

Cardiovascular deaths

Stimulants. 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.[253] A control group was selected from children who died from motor vehicle traffic accidents. The cases and controls were matched on a 1:1 basis, with 564 resulting 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 to 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 was raised as a potential limitation of 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 to the motor vehicle death group (10 years).

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.[232] Of these, 32 807 had used a stimulant (either currently or formerly) and 22 576 had never used a stimulant medication. Those who had used a stimulant at any time were more likely to be male, white, non-Hispanic, and to have used other psychoactive drugs. 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 to 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. Using regression analysis, several factors were found to be significantly associated with the increased risk of an emergency department or physician's office visit due to cardiac causes: age ≥15 years compared to <15 years; congenital anomalies; history of circulatory disease; disability; nonblack race; and the use of antidepressants, antipsychotics, and bronchodilators.

An analysis conducted by the Office of Drug Safety in April 2004 evaluated reports of sudden death or serious cardiovascular events associated with use of amphetamine and methylphenidate products at usual dosages received by the US Food and Drug Administration Adverse Event Reporting System, and updated this report in 2006 to include a broader reporting period and which also included atomoxetine (http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4210b_06_01_Gelperin.pdf). The results of these 2 analyses are summarized below in Table 12.

Table 12. Cardiovascular risks of ADHD drugs

	Amphetamine products		Methylphenidate products		Atomoxetine	
January 1, 1999 through December 31, 2003						
	Cases	**Per million prescriptions**	**Cases**	**Per million prescriptions**		
Children						
Sudden death	12	0.36	7	0.16		
Serious cardiovascular events	18	0.53	8	0.18		
Adults						
Sudden death	5	0.53	1	0.07		
Serious cardiovascular events	17	1.79	11	0.74		
January 1992 through February 2005						
	Cases	**Per 100,000 patient-years**	**Cases**	**Per 100,000 patient-years**	**Cases**	**Per 100,000 patient-years**
Children						
Sudden death	13	0.3	11	0.2	3	0.50
Adults						
Sudden death	6	0.3	2	0.1	4	2.8

Blood pressure, pulse, electrocardiographic changes

Lisdexamfetamine. A small, open-label, uncontrolled 11-month study of lisdexamfetamine (30, 50, or 70 mg daily) in 272 six- to twelve-year-olds did not find any cases of "clinically relevant" changes in blood pressure or electrocardiographic parameters.[254]

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.[255] 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.[256]

In a seven-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 mm Hg 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).[176]

Mixed amphetamine salts XR. Four open-label extension studies of mixed amphetamine salts XR, 1 each in children,[257, 258] adolescents,[259] and adults examined the cardiovascular effects over periods of 6 to 24 months.[260] 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 to 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 to 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.[258] The absolute numbers of patients with cardiovascular adverse events are not clearly reported. It is 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.[259] 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.[260] 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[238] and in adults.[261] One report involved 169 children and adolescents that continued on open or blinded atomoxetine (max dose of 2 mg/kg divided into twice daily) for at least 1 year following 3 short-term, placebo-controlled trials.[238] The timing of electrocardiogram measurements is not stated, but is presented by increasing dose. Linear regression suggests that there is no evidence of an increase in QTc with increasing dosage of atomoxetine.[238] An interim analysis of an open-label extension study in adults reports no "clinically relevant changes in QTc" after a mean of 97 months of follow-up.[261]

Height and weight 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.[227] Their 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.[262] 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,[239, 240, 246] or unmedicated hyperactive control groups.[242, 246, 247] Height and weight changes associated with immediate-release methylphenidate[235, 237, 241, 243, 244] and OROS were also observed in long-term noncomparative studies.[243] 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.[263] 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. [230, 233]

Table 13. 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 6.8 years follow-up MPH 34 mg, n=60 5.8 years follow-up	Mean age=9 82% male Children/adolescents with hyperkinetic syndrome or minimal brain dysfunction	Change in percentile: +10.9, *P*<0.01 vs. +12.8, *P*<0.001	Change in percentile: +16.0, *P*<0.02 vs. +11.4, *P*<0.001
Safer 1972	DEX 11.7 mg, n=3 11.8 mg, n=8 MPH 37.5 mg, n=4 24.0 mg, n=5 9 months follow-up	Mean age=9.8 Gender NR	NR	Weight gain (kg): 0.23 vs. 0.12, t=1.8, *P*<0.05 Weight gain (excluding patients taking low-dose MPH, n=16) (kg): 0.13 vs. 0.12, t=0.137, NS ON vs. OFF Weight gain (kg) over a 3-month summer period: MPH= 0.29 vs. 0.41, t=0.526, *P*=NS; DEX= 0.14 vs. 0.47, t=2.523, *P*<0.01
Safer 1973	DEX, n=29 MPH, n=20 Unmedicated controls, n=14 ≥ 2 years follow-up Mean dosages NR	Mean age NR 89.8% male in children on medication; 100% male in unmedicated control group 100% White	Change in percentile: DEX: –13.45 MPH > 20 mg: –9.40 All MPH: –5.20 MPH ≤ 20 mg: –1.00 Controls: +1.29 DEX > MPH all-dose, low-dose and control groups DEX=MPH high-dose group MPH high-dose > controls MPH all-dose and low-dose=controls	DEX; MPH: high-dose (> 20 mg), all, low-dose (≤ 20 mg); controls Percentile changes in: Weight: –20.38; –10.0, –6.35, –2.7, +6.79 DEX > all MPH dosage groups and controls; MPH high-dose and all doses > controls; MPH low-dose=controls
Pliszka 2006	MPH, n=113 2.7 years follow-up MAS, n=66 2.4 years follow-up Mean dose NR	Mean age 9 81% male	Change in z-score: MPH 0.1 MAS 0.1	Change in z-score: MPH 0 MAS 0.3

Abbreviations: NR, not reported.

Height

Comparative studies. The only comparative evidence comes from 2 studies of immediate-release dextroamphetamine and methylphenidate,[239, 246] and 1 of methylphenidate and mixed amphetamine salts.[251] Results are 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,[239] and immediate-release dextroamphetamine was associated with significantly greater height *decreases* than methylphenidate after at least 2 years in the other.[246] 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.[246] 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.[251] 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 to children who were unmedicated,[264,236, 242, 247] and those in noncomparative studies that reported varied analyses including differences between expected and actual growth,[235] change in percentile,[237] percent of expected growth,[241] and proportion of patients with decreased growth rates.[244]

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.[250] 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 to 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.[256] 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, $P=0.02$).[264] 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).[265] Children who remained on methylphenidate had reduced growth, a mean of 1.38 cm/year.

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.[233] 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.[230] 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 suggest 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).[239, 240, 246] Immediate-release dextroamphetamine was associated with a significantly lower mean weight gain (kg) than methylphenidate after 9 months in 1 study,[240] significantly greater declines in weight percentiles after the first of 5 years another study,[239] and at end of treatment (≥ 2 years) in yet another.[246] 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).[239]

The 9-month study also reported subgroup analyses.[240] 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 to 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.[251] 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[235, 237, 241, 244] 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.[244] 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.[241] 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 to 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).[237] 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.[235]

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 ($P<0.001$).[250] 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 to 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).[264] 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.[236, 247] In 1 study, methylphenidate was associated with significantly greater declines in weight percentiles than in the unmedicated children after 1 year.[236] 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.[247]

Based on data from the Preschool ADHD Treatment Study study, preschool-aged children were heavier than age-based norms by 1.78 kg.[265] 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.[256]

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.[263, 266] 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) reports that 25% (34/138) experienced weight loss as an adverse event over 6 months, 2 of whom discontinued drug for this reason.[215] 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 75th percentile for weight lost more weight (mean 4.2 kg) compared to those in the 25th to 75th percentile (1.5 kg), while those below the 25th percentile gained 0.5 kg (mean).

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.[233] 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.[230] 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.[229] 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 to 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 Boneronni correction was used, thus we suggest caution in interpreting these findings.

Tics

Five studies and 1 meta-analysis reported tic-related outcomes.[229, 235, 243, 245, 256, 267, 268] One of these is a long-term placebo-controlled trial[267] of immediate-release methylphenidate. Table 14 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 the groups.[268] This same publication also reported on 2 open-label studies of methylphenidate OROS, 1 of which was already included here,[243] 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 14).

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 14. Tic-related outcomes in observational studies

Study	Intervention Sample size Duration	Population	Tics
Children			
Miller-Horn 2008	MPH IR, MPH OROS, MAS IR, MAS XR N=150 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 N=72 1 year	ADHD with no prior treatment for tics or ADHD	New onset tics: 19.6% MPH IR vs. 16.7% placebo (NS) Exacerbation of pre-existing tics: 33% both groups (NS)
Gadow 1999	MPH IR 34.5 mg daily N=29 2 years	ADHD and chronic tics or Tourette's	Tic frequency and severity significantly higher at baseline No significant differences across placebo and 12, 18, 24 month follow-up periods
Wilens 2003, 2005	MPH OROS 41 mg daily N=407 1 year	ADHD	New onset tics: 23 (6.4%) at interim analysis; 24 (7%) at final analysis
Palumbo 2004	MPH OROS N=1088 9 months (unpublished)	ADHD	0.18% new onset tics 1.2% overall 0.6% withdrawal due to tics
Palumbo 2004	Meta-analysis of 3 RCTs of MPH OROS, MPH IR, placebo 1-4 weeks	ADHD	MPH OROS, 4%; MPH IR, 2.3%; placebo, 3.7%; *P*=0.5249
Adults			
Horrigan 2000	Adderall 10 mg daily N=24 1 year	ADHD	Motor tics: 1 (4%)

Abbreviations: ADHD, attention deficit hyperactivity disorder; NS, not significant; RTC, randomized controlled trial.

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.[231]

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.[234] Injury frequencies in children prescribed methylphenidate at least once between January 1, 1990 and December 31, 1996 (n=16 806) were compared to 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").[269]

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.[228] 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.[270]

Direct evidence

We found only 1 poor-quality study attempting to compare methylphenidate OROS to other formulations of methylphenidate.[271] This 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 2000 (the year of its US Food and Drug Administration approval) to 2002 or 2003. The authors found that methylphenidate OROS had a lower risk of emergency room visits (Drug Abuse Warning Network), reports to the Adverse Event Warning System, and theft or losses reported to the Drug Enforcement Administration compared to methylphenidate in general (combined data for any other formulation). The study is based on groups of cross-sectional data, each of which has 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.

Indirect evidence

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

This is a much-discussed topic in the literature,[272-280] 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 to 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 one study as conclusive.

We found a total of 12 fully published studies,[155, 281-294] 3 of which has follow-up publications with additional analysis.[281-286, 289] 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.[295-301] Several of these made comparisons to groups of children without ADHD.[282, 284-286, 288, 289, 302, 303] Because these comparisons are less relevant than those comparing adolescents and adults with ADHD as children who did and did not received stimulants, these are not considered

further. There are 7 studies that made relevant comparisons.[155, 281, 290-292, 294, 302] Below is a summary of the findings of these studies (Table 15). These are 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 to 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,[290, 292, 294, 302] 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).[294] 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.[292] Two other studies, in males, however found no associations after controlling for confounding factors including conduct disorder.[290, 302]

Four studies found no associations between alcohol abuse during teen and young adult years and stimulant exposure during childhood.[155, 281, 290, 291] Earlier examinations of data from 1 longitudinal follow-up study had indicated a protective effect at 5 years of follow-up,[282] but this association was no longer seen with 10 years of follow-up.[290]

In examining substance abuse, 2 studies found stimulant use to be protective,[291, 294] but a third study found that controlling for conduct disorder resulted in a nonsignificant finding.[290]

Table 15. Relationship between stimulant treatment for ADHD and later substance abuse and dependence

Study	Nicotine
Huss 2008 N=215 Children with ADHD Mean age at follow-up: 21.75 years 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 N=114 Females with ADHD Mean age at follow-up: 16.2 years Mean years to follow-up: 5 years	Stimulant use found protective; hazard ratio, 0.28; 95% CI, 0.14 to 0.60
Biederman 2008 N=112 Males with ADHD Mean age at follow-up: 22 years 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 N=164 Boys with disruptive behavior disorders Mean age at follow-up: 13-15 years 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 N=42 Hyperactive children Follow-up age 13-14 years 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 N=212 Children with ADHD Follow-up >5 years	Stimulants found protective; alcohol abuse or dependence OR 0.16 (confidence intervals not given)
Biederman 2008 N=112 Males with ADHD Mean age at follow-up: 22 years 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 N=121 Children with hyperactivity 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 N=91 Mean age stimulant group: 21.6	Stimulant exposed 23% vs. non-exposed 38%; *P*=NS

Mean age control group: 30.8 Mean years to follow-up: NR	
Study	**Substance abuse**
Wilens 2008 N=114 Females with ADHD Mean age at follow-up: 16.2 years Mean years to follow-up: 5 years	Substance use disorder (hazard ratio, 0.27; 95% CI, 0.13 to 0.60)
Biederman 2008 N=112 Males with ADHD Mean age at follow-up: 22 years 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 N=91 Mean age stimulant group: 21.6 Mean age control group: 30.8 Mean years to follow-up: NR	Adults with ADHD seeking stimulant treatment; those with history of stimulant exposure as children compared to 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

In a fair- to poor-quality systematic review, 21 studies of misuse or diversion of methylphenidate or amphetamine reported from 1995 to 2006 were included.[304] The review did not adequately describe inclusion criteria and did not include a quality assessment of studies. 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. 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.[305] We review this study in more detail below.

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, 23% had been asked to give, to trade, or to sell their ADHD medications, and in another study 29% of those surveyed had reported selling them. In a longitudinal follow-up study of adults, 11% reported having sold their ADHD medications in the last 4 years. These studies did not report specific products or formulations of stimulants.

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.[305] 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 to older participants, and among Whites compared to 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. This study indicates a serious problem with dependence and abuse of ADHD stimulant drugs, but does not provide insight into the course of development of abuse or dependence, or the medical history of those found to be abusing or dependent on stimulants.

Two studies not included in the systematic review are also relevant.[306, 307] Similar to the studies included, 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.[306] Regression analysis indicated that misuse of methylphenidate was associated with illicit use of cocaine or amphetamines. Forty-four percent reported diverting their medication to someone else, with 97% giving it away, 17% selling it, and 14% doing both. 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.

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.[307] 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.

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.[308, 309] 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.[310] 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.[310] 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).[159, 225] Immediate-release methylphenidate had a positive effect on 75% of efficacy measures. This response rate is 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 suggests 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).[43] 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.[311] 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.

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[223] In the 1-week, crossover study (#201), average Swanson, Kotlin, Agler, M-Flynn and Pelham - Deportment Subscale (SKAMP-DS) 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 to 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.[312] This study reported statistically significantly greater improvements on the ADHD-Rating Scale-IV scale with atomoxetine compared to 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 sub-group 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 to Caucasians in children age 6 to < 18 years with ADHD.[313] 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 make up only a small proportion of the total children enrolled in ADHD trials, which reflects the differential in the rates of ADHD diagnoses among the sexes.

Direct comparisons

Subgroup analyses based on gender were performed based on data from 2 double-blind, randomized controlled trials of lisdexamfetamine[223] 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 to 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 post hoc subgroup analysis of the START study, comparing mixed amphetamine salts XR and atomoxetine, examined the effects in the 57 girls enrolled.[314] 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 to 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.[315]

Indirect comparisons

We found 3 studies examining differences in response to stimulants (primarily immediate-release methylphenidate) between boys and girls.[47, 316, 317] Two found no differences between boys and girls,[47, 317] 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.[316] 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.[318] 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.[319] The study found that when compared to 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.

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.[79] 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.

A sub-group analysis of adults with ADHD[175] 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 to 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 4 small, short-term placebo-controlled trials of immediate-release methylphenidate,[320, 321] methylphenidate OROS,[322] and modafinil.[323] 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. One trial each of immediate-release methylphenidate (N=40)[320] and methylphenidate OROS (N=47)[322] examined the potential relationship between stimulant dose and ADHD subtype. Although very preliminary, there were findings in both trials suggesting 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.

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, arithmetic performance, and inattention were improved in both subtypes.[321]

In a second trial of immediate-release methylphenidate (N=30), conclusions about dose-response relationship were based entirely on clinical judgment.[320] At the end of this trial, the

supervising psychologist and pediatrician were asked to judge which was the best dose for each child, based on consideration as to 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 without hyperactivity were recommended for no treatment or the lowest dose of immediate-release methylphenidate (10 mg daily), whereas children with attention deficit disorder with hyperactivity were considerably more likely to receive a recommendation for the moderate or high doses (20-30 mg daily).

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.[322] 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.[323] 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%.[63] 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).[324] 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.[146, 325-328] Meta-analyses of data from 2 earlier[146] and 3 more recent[327] 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 post hoc analyses of data from single placebo-controlled trials.[325, 326] Collectively, these studies consistently found that the presence of oppositional defiant disorder does not impact the effectiveness of atomoxetine in treating children with ADHD. One analysis, pooling data from placebo-controlled trials found children with ADHD and oppositional defiant disorder taking atomoxetine demonstrated similar or greater improvements than placebo on all quality-of-life-related subscales of the Child Health Questionnaire except 'parental impact-emotional', 'parental impact-time', and 'self-esteem'.[327] Evidence to date is not conclusive that there is a benefit in oppositional defiant disorder symptoms with atomoxetine.[328]

In a post hoc analysis of a placebo-controlled trial, findings suggest that response to treatment of ADHD in children with comorbid oppositional defiant disorder (N=113) may be related to dose.[325] 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.

Immediate-release methylphenidate. A placebo-controlled trial of 3 different doses (0.1 mg/kg, 0.3 mg/kg, and 0.5 mg/kg) of immediate-release methylphenidate given twice daily studied 31 children ages 6-12 years with oppositional defiant disorder and both comorbid chronic multiple tic disorder and ADHD.[329] The study found that according to teacher ratings, all 3 doses of immediate-release methylphenidate were superior to placebo ($P<0.0001$ for both Abbreviated Conners' factor 1 scale and IOWA Inattention-Overactivity subscale) in reducing ADHD symptoms. For mother ratings (Abbreviated Conners' Rating Scale factor 1 and Mothers' Objective Method for Subgrouping hyperactivity subscale), only the difference between placebo compared to the 0.5 mg/kg dose was significant ($P=0.03$; $P=0.0006$). Teacher ratings indicated large treatment effects for placebo compared to the 0.5 mg/kg dose (effect size>1.0), but the effect size for the mother ratings were moderate (effect size=0.61 to 0.63).

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.[330] 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 to 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.

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.[331] 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 to 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, 6 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 1 placebo-controlled trial reported it as a symptom of ADHD. 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 were found, although for some comparisons numerical differences were apparent.[68, 72, 73, 114, 116, 133, 332] For example, compared to 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 to Adderall® (10% compared with 5%) or methylphenidate OROS (31.3% compared with 18.7% in 1 study, 12% compared with 13% in another). 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.[54, 130, 131, 140, 142, 333-338] Reports of anxiety were similar between placebo and atomoxetine in 2 studies[140, 142] and placebo and modafinil in 2 others.[130, 131] 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. The 2 trials that assessed anxiety symptoms as part of ADHD did not find a difference between

immediate-release methylphenidate and methylphenidate SR in children with minimal brain dysfunction[68] or between immediate-release methylphenidate and placebo in children with ADHD and mental retardation.[337]

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.[339] In the intention 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. Ten percent dropped out during a 2-week placebo run-in phase, and another 16% dropped out during the 10-week treatment phase. The last observation carried forward method was used to include patients who discontinued the study early in the analysis. With a high drop-out rate, we recommend caution in interpreting these findings.

Adults

For adults, we found 1 publication that 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 to placebo.[340] The main finding of these subanalyses was that compared to adults with "pure" ADHD (no comorbidities), adults with ADHD and post-traumatic stress disorder had greater improvements on atomoxetine compared to 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 [194] and are discussed under Key Question 1.

Additionally, numerous placebo-controlled trials examined whether treatment with ADHD drugs improves comorbid anxiety symptoms.[178, 181, 185, 187-189, 194, 203, 205, 208, 214] However, only immediate-release methylphenidate was consistently associated with improvements in anxiety symptoms in adults with ADHD.[181, 203, 210] 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.[179, 196]

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; $P<0.001$).[341] No statistically significant differences in depression scale scores or rates of treatment emergent mania were found.

For adults, the only evidence regarding the effects of depressive disorders on response to medication comes from the 1 publication that reported findings from exploratory, post hoc analyses using pooled data from 2 placebo-controlled trials of atomoxetine discussed above in the section on anxiety.[340] Here, the main relevant findings were that compared to 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.

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).[342] 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.

A 4-week placebo-controlled, cross-over study of methylphenidate twice a day (5 mg, 10 mg, or 15 mg compared with best dose week) added to mood stabilizers including 20 euthymic youths (ages 5-17) found that best dose week was superior to placebo in improving ADHD symptoms (ADHD rating scale IV) ($P<0.02$; effect size= 0.90).[343] 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.

Psychiatric comorbidities

One placebo-controlled trial of atomoxetine[201] 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.[201] This trial does not provide evidence of comparative efficacy among subgroups of patients with comorbidities.

Tic disorders including Tourette's Disorder

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.[49, 98, 344-350] Immediate-release dextroamphetamine and atomoxetine treatments for ADHD have also been studied in children with tic disorders.[98, 347, 349, 351]

The majority of these trials were of short duration and involved very small numbers of children.[98, 344-346, 348] 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.[344, 346] 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.[98] Otherwise, compared to 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 to 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.[235]

Substance use disorder

Adolescents

We identified 1 trial of methylphenidate-SODAS focusing on the subpopulation of substance use disorder.[352] This 6-week, single-blind, placebo-controlled crossover study assessed the efficacy of escalated doses of methylphenidate SODAS on ADHD symptoms in 16 adolescents with ADHD and comorbid substance use disorder (marijuana N=16 and cocaine N=7). Medication dose was titrated to 1.2 mg/kg per day. The trial 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 $\leq$0.001). There was no significant treatment effect on drug use (number of marijuana cigarettes per day; urine tests for either cannabis or cocaine).

Adults

Placebo-controlled trials of atomoxetine, immediate-release methylphenidate, and methylphenidate SR have evaluated treatment of ADHD in adults with comorbid substance abuse. Atomoxetine treatment has been assessed in a 12-week placebo-controlled trial of 147 adults with ADHD and comorbid alcohol use disorders.[353] 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.

Two trials each of immediate-release methylphenidate[182, 198] and methylphenidate SR[190, 191] 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,[182]while the others focused on either patients with cocaine dependence[191, 198] or methadone-maintained patients.[190] 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),[190, 191, 198] immediate-release methylphenidate or methylphenidate SR also did not appear to offer much of a benefit in the reduction of these patients' ADHD symptoms.[182, 190, 191, 198] In all but 1

of these trials, not only were there less robust treatment response rates in substance abusers with ADHD compared to 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%).[182, 190, 191] 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.[354] 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[182, 198] and methylphenidate SR[190, 191] 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,[182] while the others focused on either patients with cocaine dependence[191, 198] or methadone-maintained patients.[190] 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.[190, 191, 198] 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).[190, 191]

Limitations of this Review

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 short-comings 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.

SUMMARY

Key Questions are summarized in Table 16, below.

Table 16. Summary of the evidence

	Comparison: Overall strength of the evidence	Conclusion
Key Question 1. Benefits		
General		
Effectiveness	No trials found: Poor	No conclusions about comparative effectiveness of different pharmacotherapies for ADHD can be made.
Young children		
Efficacy	Overall: Poor	
	MPH IR	The evidence on efficacy of MPH IR in the short term is mixed.
Children		
Efficacy	Overall: Fair (individual ratings below)	
Stimulants		
IR vs. SR formulations	MPH IR vs. MPH SR: Fair	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 are conflicting; a difference was not found in double-blind studies while open-label studies indicate greater improvement with MPH OROS on some measures.
SR vs. SR formulations	MPH SR vs. MPH SR formulations: Poor	Limited evidence from 2 small crossover studies suggests that MPH LA was superior to MPH OROS on some, but not all efficacy outcomes. Limited evidence suggests that MPH CD was superior to MPH OROS on outcomes

	Comparison: Overall strength of the evidence	Conclusion
		in the morning; they had similar effects in the afternoon; and MPH OROS was superior in the evening. 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: Good	The body of evidence clearly indicates no difference in efficacy between DEX and MPH IR.
	MAS IR vs. MPH IR: Fair	MASIR was superior to MPH IR on a few efficacy outcome measures in 2 trials, but clear evidence of superiority is lacking.
	DEX IR vs. DEX ER vs. MAS: Poor	Evidence on the comparison of DEX IR vs. 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: Fair	Based on 1 trial, modafinil was similar to MPH IR in efficacy
	Dexmethylphenidate: NA	Only placebo-controlled evidence was found.
Transdermal MPH	MTS vs. MPH OROS	Based on 1 trial, MTS and MPH OROS had similar efficacy
Lisdexamfetamine	Fair	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	Poor	
	Atomoxetine vs. MPH IR	Limited evidence suggests a lack of a difference in efficacy compared to MPH IR.
	Atomoxetine vs. MAS XR	Limited evidence suggests that MAS XR is superior to atomoxetine on most efficacy measures.
	Atomoxetine vs. MPH OROS	MPH OROS was superior to atomoxetine in response rates
Adolescents		
Efficacy	Poor	
	MPH OROS vs. MAS IR	Effectiveness outcomes: NR Short-term improvements in core ADHD symptoms: No differences. Other: MPH OROS > MAS IR on overall simulator driving performance.
	MPH IR vs. MPH OROS	Functional capacity: NR Short-term improvements of core ADHD symptoms: NR. Driving performance: MPH OROS > MPH IR in evening and at night.
	Placebo-controlled studies of MPH IR	Functional capacity: NR Short-term improvements of core ADHD symptoms: MPH IR generally efficacious.
Adults		
Efficacy	Fair	
Direct comparisons	DEX IR vs. modafinil	Limited evidence suggests a lack of a difference in efficacy between DEX IR and modafinil.

	Comparison: Overall strength of the evidence	Conclusion
Indirect comparisons	Atomoxetine, DEX IR, d-MPH XR, lisdexamfetamine, MPH ER, MPH IR, MPH SR, MPH OROS, MAS IR, MAS XR: Fair	ADHD symptom improvement: • All were found to be effective short-term treatments for reducing ADHD symptoms in placebo-controlled trials • Pooled analysis suggest a relative benefit of clinical response for shorter acting stimulants at 3.26 times greater than for patients taking longer-acting stimulants (95% CI, 2.03 to 5.22) Other efficacy outcomes: • Atomoxetine: Not consistently significantly superior to placebo in improving quality of life and driving performance outcomes • MPH IR: Consistently superior to placebo in improving cognition and driving performance outcomes; not significantly superior to placebo on 5 of 6 sleep outcomes in 1 trial • MAS XR: Superior to placebo in improving overall simulated driving performance outcomes in 1 trial • MPH OROS: Superior to placebo in improvements on some parenting skill measures in 1 trial
	Dexmethylphenidate IR, methamphetamine, MPH transdermal patch, MPH chewable tablet or oral solution, and some extended release forms of MPH (Metadate CD, Ritalin LA®, and Biphentin®): Poor	No evidence.
Key Question 2. Safety		
2b. Short-term trial evidence		
Young children	1 placebo-controlled trial of MPH: Poor	Indirect comparisons cannot be made; MPH associated with higher rates of adverse events than placebo.
Children	Poor	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.
	DEX vs. MPH IR	Limited evidence from short-term trials suggests that weight loss is greater with DEX than MPH IR.
	MAS vs. MPH IR	Very limited evidence suggests 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.

	Comparison: Overall strength of the evidence	Conclusion
	Comparisons to atomoxetine	Rates of vomiting ranged from 12% to 13% for atomoxetine, which was approximately 3 times greater than rates for MPH IR or MAS XR. Rates of somnolence ranged from 6% to 26% for atomoxetine, which was 3 to 4 times greater than rates for longer-acting stimulants (MPH OROS and MPH XR) and over 7 times greater than rates in trials of MPH IR. Nausea and anorexia were greater with atomoxetine compared to MPH IR in 1 trial. MPH OROS and MAS XR caused higher rates of insomnia (7% atomoxetine, 13% MPH OROS, 28% MAS XR) than atomoxetine in 2 trials.
	Lisdexamfetamine	No differences in adverse event rates between lisdexamfetamine vs. MAS XR.
Adolescents	Poor	Very few studies reported methods for assessing adverse events a priori.
	Placebo-controlled studies of MPH IR	No indirect comparisons possible. Placebo-controlled trials only involved assessment of MPH IR.
Adults	Poor	Very few studies reported methods for assessing adverse events a priori. Rates of appetite disturbance and sleep disturbance were generally greater for atomoxetine, DEX IR, d-MPH-ER, lisdexamfetamine, MPH ER, MPH IR, MPH SR, MPH OROS, MAS IR, and MAS XR. Our adjusted indirect meta-analysis found that shorter-acting stimulants, longer-acting stimulants, and atomoxetine groups had significantly higher risk of appetite loss and sleep disturbance relative to placebo, but indirect comparisons suggest no significant difference between drug types.
Stimulants	Adderall and MPH IR	Indirect comparisons from placebo-controlled trials suggest both are associated with higher rates of insomnia, appetite loss and withdrawal due to adverse events than placebo.
	DEX IR and MPH SR	Indirect comparisons cannot be made.
Atomoxetine	Atomoxetine	Very limited indirect comparative evidence across few placebo-controlled trials suggests that atomoxetine is associated with rates of insomnia, appetite loss and withdrawals due to adverse events similar to stimulants.
2b. Long-term safety: Observational studies		
Mixed populations, primarily children	Fair	
	Sudden cardiac death	Increased risk associated with current stimulant use (odds ratio 7.4; 95% CI, 1.4 to 74.9) based on case control study. Smaller study found no association. Recall bias may be an issue.

	Comparison: Overall strength of the evidence	Conclusion
	Cardiac events	Emergency room and physician office visits for cardiac causes significantly more frequent among those taking stimulants compared with those not (hazard ratio, 1.20; 95% CI, 1.04 to 1.38 compared with hazard ratio, 1.21; 95% CI, 1.06 to 1.30).
	Suicidal behavior	Increased risk with atomoxetine compared to 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 to 1.7% in another meta-analysis of longer-term duration.
	Height	• DEX vs. MPH IR: Mixed findings; DEX=MPH in 6-year height increases in 1 study, DEX>MPH in 2-year height decreases in the other • MPH IR vs. unmedicated controls: No significant differences in 2 studies. • MPH IR in uncontrolled studies: Inconsistent effects across 4 studies • Atomoxetine: Uncontrolled studies suggest that height changes are similar to those reported with MPH IR, and are also transient
	Weight	• DEX vs. MPH: Three studies consistently suggest that DEX>MPH in weight gain suppression in the first 1-2 years. The longest-term (5 years) of these studies also reported that DEX=MPH in exceeding weight gain expectations at final follow-up. These findings are weakened by methodological flaws, however • MPH IR in other comparative (imipramine and unmedicated hyperactives or healthy controls) and noncomparative studies: Evidence does not support an indisputable relationship between MPH and weight gain suppression • MPH OROS and tomoxetine (atomoxetine): Evidence from noncomparative studies (1 each) doesn't suggest weight gain suppression effects • Atomoxetine: Uncontrolled studies suggest that weight changes are similar to those reported with MPH IR, and are also transient
	Tics, seizures, cardiovascular adverse events, injuries, and suicidal behavior	No comparative evidence.
2c. Abuse/diversion		

	Comparison: Overall strength of the evidence	Conclusion
Teens and young adults	Poor	Stimulant use during childhood 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. Evidence on misuse and diversion reports wide ranges of prevalence with no comparative data.
Key Question 3. Subgroups		
Children	Fair	
	ADHD subtypes or severity	Atomoxetine, MPH IR, MPH OROS all have superior efficacy relative to placebo in children with ADHD, regardless of diagnostic subtype but response may be better in those with combined or inattentive subtype.
	Race/ethnicity	Most trials conducted in primarily White populations. Ethnicity/race only reported in one half of studies. No analyses based on race. Very limited evidence suggests 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.
	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 indicates atomoxetine may have better response on emotional regulation items in women than men.
	Common comorbidities	Rates on commonly occurring comorbidities reported in only one half of trials. No study analyzed data stratified by these conditions. Rates of prevalence of these among study participants were generally similar to prevalence rates reported by American Academy of Pediatrics for the overall ADHD population.
	Tic disorders	No consistent evidence that atomoxetine, DEX IR or MPH IR increased tic severity or frequency compared to placebo. All of these studies of MPH IR showed a benefit of MPH IR on ADHD outcome measures compared to placebo.
	Oppositional defiant disorder	Very limited evidence suggests that atomoxetine is beneficial on most ADHD outcomes compared to placebo.
	Bipolar disorder	Very limited evidence suggests that MAS IR or MPH IR have benefit on most ADHD outcomes compared to placebo.

Abbreviations: ADHD, attention deficit hyperactivity disorder; d-MPH, dexmethylphenidate; DEX, dextroamphetamine; ER, extended release; IR, immediate release; MAS, mixed amphetamine salts; MPH, methylphenidate.

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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 was hypothetically repeated on a collection of 100 random samples of studies, the resulting 100 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.

Intention 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 intention 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 intention-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 cross-over 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. 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 scales 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 C. Search strategy: Update 3

Searches on Medline, PsycINFO, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Database of Abstracts of Reviews of Effects were repeated in April of 2009 and gave additional citations that were reviewed and incorporated when they met eligibility criteria.

Database: Ovid MEDLINE(R) <1950 to November Week 3 2008>
Search Strategy:
---
1 exp Amphetamine/ or "amphetamine$".mp. (26520)
2 adderall.mp. (108)
3 atomoxetine.mp. (490)
4 strattera.mp. (34)
5 dexmethylphenidate.mp. (31)
6 focalin.mp. (11)
7 dextroamphetamine.mp. or exp Dextroamphetamine/ (6245)
8 dexedrine.mp. (73)
9 dextrostat.mp. (0)
10 methylphenidate.mp. or exp Methylphenidate/ (4918)
11 concerta.mp. (55)
12 metadate.mp. (18)
13 methylin.mp. (4)
14 Ritalin.mp. (429)
15 biphentin.mp. (1)
16 modafinil.mp. (657)
17 provigil.mp. (22)
18 Alertec.mp. (0)
19 methamphetamine.mp. or exp methamphetamine/ (6502)
20 desoxyn.mp. (7)
21 lisdexamfetamine.mp. (22)
22 vivanse.mp. (0)
23 daytrana.mp. (1)
24 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 (35343)
25 Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (13388)
26 Attention deficit disorder.mp. (13668)
27 attention deficit$.mp. (16337)
28 adhd.mp. (7078)
29 27 or 25 or 28 or 26 (16554)
30 24 and 29 (3054)
31 (200703$ or 200704$ or 200705$ or 200706$ or 200707$ or 200708$ 200709$ or 20071$ or 2008$ or 2009$).ed. (1208352)
32 30 and 31 (554)
33 limit 32 to (english language and humans) (447)

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") (270)
35 observational stud$.mp. or exp Cohort Studies/ or cohort$.mp. or exp Retrospective Studies/ or retrospective$.mp. (1052665)
36 35 and 33 (62)
37 34 or 36 (300)
38 from 37 keep 1-300 (300)

Database: Ovid MEDLINE(R) <1996 to January Week 2 2009>
Search Strategy:
---
1 exp Amphetamine/ or "amphetamine$".mp. (9058)
2 adderall.mp. (104)
3 atomoxetine.mp. (450)
4 strattera.mp. (32)
5 dexmethylphenidate.mp. (32)
6 focalin.mp. (11)
7 dextroamphetamine.mp. or exp Dextroamphetamine/ (1177)
8 dexedrine.mp. (21)
9 dextrostat.mp. (0)
10 methylphenidate.mp. or exp Methylphenidate/ (2441)
11 concerta.mp. (52)
12 metadate.mp. (17)
13 methylin.mp. (1)
14 Ritalin.mp. (243)
15 biphentin.mp. (1)
16 modafinil.mp. (596)
17 provigil.mp. (23)
18 Alertec.mp. (0)
19 methamphetamine.mp. or exp methamphetamine/ (3610)
20 desoxyn.mp. (0)
21 lisdexamfetamine.mp. (22)
22 vivanse.mp. (0)
23 daytrana.mp. (1)
24 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 (13968)
25 Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (8973)
26 Attention deficit disorder.mp. (9127)
27 attention deficit$.mp. (11441)
28 adhd.mp. (6272)
29 27 or 25 or 28 or 26 (11641)
30 Central Nervous system Stimulants.mp. or exp Central Nervous System Stimulants/ (24689)
31 30 or 24 (29700)
32 31 and 29 (2764)
33 diversion.mp. (5359)

34 exp Substance-Related Disorders/ (71560)
35 ((drug$ or substance$ or stimula$) adj3 (abus$ or addict$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (29751)
36 (misuse$ or misusing).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (5922)
37 exp Behavior, Addictive/ (2277)
38 (addict$ adj3 behav$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (2970)
39 (drug$ adj3 seek$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (990)
40 38 or 35 or 33 or 39 or 34 or 36 or 37 (91385)
41 32 and 40 (327)
42 illegal$.mp. (2966)
43 unlawful$.mp. (154)
44 illicit$.mp. (4199)
45 criminal$.mp. (7010)
46 42 or 45 or 43 or 44 (13777)
47 32 and 46 (34)
48 41 or 47 (332)
49 limit 48 to (english language and humans) (282)
50 (200703$ or 200704$ or 200705$ or 200706$ or 200707$ or 200708$ or 200709$ or 20071$ or 2008$ or 2009$).ed. (1271234)
51 50 and 49 (92)
52 limit 51 to (clinical trial, all or clinical trial or comparative study or controlled clinical trial or evaluation studies or meta analysis or multicenter study or randomized controlled trial or "review") (51)
53 observational stud$.mp. or exp Cohort Studies/ or cohort$.mp. or exp Retrospective Studies/ or retrospective$.mp. (665615)
54 53 and 51 (15)
55 52 or 54 (59)
56 from 55 keep 1-59 (59)

Database: PsycINFO <1806 to December Week 4 2008>
Search Strategy:
---
1 exp Amphetamine/ or "amphetamine$".mp. (10362)
2 adderall.mp. (70)
3 atomoxetine.mp. (239)
4 strattera.mp. (18)
5 dexmethylphenidate.mp. (17)
6 focalin.mp. (10)
7 dextroamphetamine.mp. or exp Dextroamphetamine/ (2295)
8 dexedrine.mp. (77)
9 dextrostat.mp. (0)
10 methylphenidate.mp. or exp Methylphenidate/ (2726)
11 concerta.mp. (29)
12 metadate.mp. (6)
13 methylin.mp. (2)

14 Ritalin.mp. (398)
15 biphentin.mp. (0)
16 modafinil.mp. (332)
17 provigil.mp. (11)
18 Alertec.mp. (0)
19 methamphetamine.mp. or exp methamphetamine/ (1996)
20 desoxyn.mp. (2)
21 lisdexamfetamine.mp. (4)
22 vivanse.mp. (0)
23 daytrana.mp. (2)
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 (13662)
25 Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (7459)
26 Attention deficit disorder.mp. (12357)
27 attention deficit$.mp. (15316)
28 adhd.mp. (10299)
29 27 or 25 or 28 or 26 (15800)
30 24 and 29 (1879)
31 limit 30 to yr="2007 - 2009" (313)
32 limit 31 to (human and english language) (258)
33 from 32 keep 1-258 (258)

Database: PsycINFO <1806 to December Week 4 2008>
Search Strategy:
---
1 exp Amphetamine/ or "amphetamine$".mp. (10362)
2 adderall.mp. (70)
3 atomoxetine.mp. (239)
4 strattera.mp. (18)
5 dexmethylphenidate.mp. (17)
6 focalin.mp. (10)
7 dextroamphetamine.mp. or exp Dextroamphetamine/ (2295)
8 dexedrine.mp. (77)
9 dextrostat.mp. (0)
10 methylphenidate.mp. or exp Methylphenidate/ (2726)
11 concerta.mp. (29)
12 metadate.mp. (6)
13 methylin.mp. (2)
14 Ritalin.mp. (398)
15 biphentin.mp. (0)
16 modafinil.mp. (332)
17 provigil.mp. (11)
18 Alertec.mp. (0)
19 methamphetamine.mp. or exp methamphetamine/ (1996)
20 desoxyn.mp. (2)
21 lisdexamfetamine.mp. (4)

22 vivanse.mp. (0)
23 daytrana.mp. (2)
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 (13662)
25 Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (7459)
26 Attention deficit disorder.mp. (12357)
27 attention deficit$.mp. (15316)
28 adhd.mp. (10299)
29 27 or 25 or 28 or 26 (15800)
30 Central Nervous system Stimulants.mp. or exp Central Nervous System Stimulants/ (59)
31 30 or 24 (13701)
32 31 and 29 (1885)
33 diversion.mp. (1176)
34 substance abuse.mp. or exp Substance-Related Disorders/ (18864)
35 misuse.mp. (4506)
36 addictive behavior.mp. or exp Behavior, Addictive/ (631)
37 35 or 33 or 34 or 36 (24640)
38 32 and 37 (58)
39 limit 38 to yr="2007 - 2009" (17)
40 from 39 keep 1-17 (17)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2008>
Search Strategy:
---
1 exp Amphetamine/ or "amphetamine$".mp. (1008)
2 adderall.mp. (44)
3 atomoxetine.mp. (100)
4 strattera.mp. (6)
5 dexmethylphenidate.mp. (12)
6 focalin.mp. (7)
7 dextroamphetamine.mp. or exp Dextroamphetamine/ (470)
8 dexedrine.mp. (15)
9 dextrostat.mp. (0)
10 methylphenidate.mp. or exp Methylphenidate/ (1098)
11 concerta.mp. (27)
12 metadate.mp. (6)
13 methylin.mp. (0)
14 Ritalin.mp. (97)
15 biphentin.mp. (1)
16 modafinil.mp. (200)
17 provigil.mp. (3)
18 Alertec.mp. (0)
19 methamphetamine.mp. or exp methamphetamine/ (213)
20 desoxyn.mp. (0)
21 lisdexamfetamine.mp. (4)
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 (2412)
25 Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (995)
26 Attention deficit disorder.mp. (1104)
27 attention deficit$.mp. (1322)
28 adhd.mp. (830)
29 27 or 25 or 28 or 26 (1454)
30 24 and 29 (848)
31 limit 30 to yr="2007 - 2008" (98)
32 from 31 keep 1-98 (98)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2008>
Search Strategy:
---
1 exp Amphetamine/ or "amphetamine$".mp. (1008)
2 adderall.mp. (44)
3 atomoxetine.mp. (100)
4 strattera.mp. (6)
5 dexmethylphenidate.mp. (12)
6 focalin.mp. (7)
7 dextroamphetamine.mp. or exp Dextroamphetamine/ (470)
8 dexedrine.mp. (15)
9 dextrostat.mp. (0)
10 methylphenidate.mp. or exp Methylphenidate/ (1098)
11 concerta.mp. (27)
12 metadate.mp. (6)
13 methylin.mp. (0)
14 Ritalin.mp. (97)
15 biphentin.mp. (1)
16 modafinil.mp. (200)
17 provigil.mp. (3)
18 Alertec.mp. (0)
19 methamphetamine.mp. or exp methamphetamine/ (213)
20 desoxyn.mp. (0)
21 lisdexamfetamine.mp. (4)
22 vivanse.mp. (0)
23 daytrana.mp. (0)
24 11 or 21 or 7 or 17 or 2 or 22 or 1 or 18 or 23 or 16 or 13 or 6 or 3 or 9 or 12 or 20 or 14 or 15 or 8 or 4 or 19 or 10 or 5 (2412)
25 Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (995)
26 Attention deficit disorder.mp. (1104)
27 attention deficit$.mp. (1322)
28 adhd.mp. (830)
29 27 or 25 or 28 or 26 (1454)

30 Central Nervous system Stimulants.mp. or exp Central Nervous System Stimulants/ (3531)
31 30 or 24 (4471)
32 31 and 29 (866)
33 diversion.mp. (183)
34 substance abuse.mp. or exp Substance-Related Disorders/ (6492)
35 misuse.mp. (222)
36 addictive behavior.mp. or exp Behavior, Addictive/ (168)
37 35 or 33 or 34 or 36 (6872)
38 32 and 37 (25)
39 limit 38 to yr="2007 - 2008" (5)
40 from 39 keep 1-5 (5)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <4th Quarter 2008>
Search Strategy:
---
1 exp Amphetamine/ or "amphetamine$".mp. (57)
2 adderall.mp. (0)
3 atomoxetine.mp. (5)
4 strattera.mp. (0)
5 dexmethylphenidate.mp. (1)
6 focalin.mp. (0)
7 dextroamphetamine.mp. or exp Dextroamphetamine/ (16)
8 dexedrine.mp. (5)
9 dextrostat.mp. (0)
10 methylphenidate.mp. or exp Methylphenidate/ (32)
11 concerta.mp. (1)
12 metadate.mp. (0)
13 methylin.mp. (0)
14 Ritalin.mp. (3)
15 biphentin.mp. (0)
16 modafinil.mp. (13)
17 provigil.mp. (3)
18 Alertec.mp. (0)
19 methamphetamine.mp. or exp methamphetamine/ (15)
20 desoxyn.mp. (0)
21 lisdexamfetamine.mp. (0)
22 vivanse.mp. (0)
23 daytrana.mp. (0)
24 11 or 21 or 7 or 17 or 2 or 22 or 1 or 18 or 23 or 16 or 13 or 6 or 3 or 9 or 12 or 20 or 14 or 15 or 8 or 4 or 19 or 10 or 5 (82)
25 Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (7)
26 Attention deficit disorder.mp. (12)
27 attention deficit$.mp. (41)
28 adhd.mp. (24)
29 27 or 25 or 28 or 26 (45)
30 24 and 29 (18)

31 from 30 keep 1-18 (18)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <4th Quarter 2008>
Search Strategy:
---
1 exp Amphetamine/ or "amphetamine$".mp. (57)
2 adderall.mp. (0)
3 atomoxetine.mp. (5)
4 strattera.mp. (0)
5 dexmethylphenidate.mp. (1)
6 focalin.mp. (0)
7 dextroamphetamine.mp. or exp Dextroamphetamine/ (16)
8 dexedrine.mp. (5)
9 dextrostat.mp. (0)
10 methylphenidate.mp. or exp Methylphenidate/ (32)
11 concerta.mp. (1)
12 metadate.mp. (0)
13 methylin.mp. (0)
14 Ritalin.mp. (3)
15 biphentin.mp. (0)
16 modafinil.mp. (13)
17 provigil.mp. (3)
18 Alertec.mp. (0)
19 methamphetamine.mp. or exp methamphetamine/ (15)
20 desoxyn.mp. (0)
21 lisdexamfetamine.mp. (0)
22 vivanse.mp. (0)
23 daytrana.mp. (0)
24 11 or 21 or 7 or 17 or 2 or 22 or 1 or 18 or 23 or 16 or 13 or 6 or 3 or 9 or 12 or 20 or 14 or 15 or 8 or 4 or 19 or 10 or 5 (82)
25 Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (7)
26 Attention deficit disorder.mp. (12)
27 attention deficit$.mp. (41)
28 adhd.mp. (24)
29 27 or 25 or 28 or 26 (45)
30 Central Nervous system Stimulants.mp. or exp Central Nervous System Stimulants/ (17)
31 30 or 24 (90)
32 31 and 29 (18)
33 diversion.mp. (39)
34 substance abuse.mp. or exp Substance-Related Disorders/ (150)
35 misuse.mp. (129)
36 addictive behavior.mp. or exp Behavior, Addictive/ (1)
37 35 or 33 or 34 or 36 (266)
38 32 and 37 (8)
39 from 38 keep 1-8 (8)

Database: EBM Reviews - Database of Abstracts of Reviews of Effects <4th Quarter 2008>
Search Strategy:
---
1 exp Amphetamine/ or "amphetamine$".mp. (11)
2 adderall.mp. (2)
3 atomoxetine.mp. (5)
4 strattera.mp. (0)
5 dexmethylphenidate.mp. (1)
6 focalin.mp. (0)
7 dextroamphetamine.mp. or exp Dextroamphetamine/ (8)
8 dexedrine.mp. (0)
9 dextrostat.mp. (0)
10 methylphenidate.mp. or exp Methylphenidate/ (27)
11 concerta.mp. (0)
12 metadate.mp. (0)
13 methylin.mp. (0)
14 Ritalin.mp. (2)
15 biphentin.mp. (0)
16 modafinil.mp. (1)
17 provigil.mp. (0)
18 Alertec.mp. (0)
19 methamphetamine.mp. or exp methamphetamine/ (1)
20 desoxyn.mp. (0)
21 lisdexamfetamine.mp. (0)
22 vivanse.mp. (0)
23 daytrana.mp. (0)
24 11 or 21 or 7 or 17 or 2 or 22 or 1 or 18 or 23 or 16 or 13 or 6 or 3 or 9 or 12 or 20 or 14 or 15 or 8 or 4 or 19 or 10 or 5 (32)
25 Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (36)
26 Attention deficit disorder.mp. (38)
27 attention deficit$.mp. (47)
28 adhd.mp. (24)
29 27 or 25 or 28 or 26 (48)
30 24 and 29 (23)
31 from 30 keep 1-23 (23)

Appendix D. Methods used to assess quality of studies

Study quality was objectively assessed using predetermined criteria for internal validity, which were based on a combination of the United States Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination[1, 2] criteria.

All included studies, regardless of design, were assessed for quality and assigned a rating of "good," "fair," or "poor". Studies that have a fatal flaw were rated poor quality. A fatal flaw was the failure to meet combinations of criteria that may be related to indicate the presence of bias. An example would be inadequate procedures for allocation concealment combined with important differences between groups in prognostic factors at baseline and following randomization. Studies that meet all criteria were rated good quality; the remainder were rated fair quality. As the fair-quality category was broad, studies with this rating varied in their strengths and weaknesses: The results of some fair-quality studies were *likely* to be valid, while others were only *possibly* valid. A poor-quality trial was not valid; the results were at least as likely to reflect flaws in the study design as a true difference between the compared drugs.

Criteria for assessing applicability (external validity) are also listed, although they were not used to determine study quality.

Systematic Reviews

1. Does the systematic review report a clear review question and clearly state inclusion and exclusion criteria for primary studies?

A good-quality review focuses on a well-defined question or set of questions, which ideally refer to the inclusion/exclusion criteria by which decisions are made about whether to include or exclude primary studies. These criteria would relate to the four components of study design, indications (patient populations), interventions (drugs), and outcomes of interest. A good-quality review also includes details about the process of decision-making, that is, how many reviewers were involved, whether the studies were examined independently, and how disagreements between reviewers were resolved.

2. Is there evidence of a substantial effort to find all relevant research?

If details of electronic database searches and other identification strategies are given, the answer to this question usually is yes. Ideally, search terms, date restrictions, and language restrictions are presented. In addition, descriptions of hand-searches, attempts to identify unpublished material, and any contact with authors, industry, or research institutes should be provided. The appropriateness of the database(s) searched by the authors should also be considered. For example, if only MEDLINE is searched for a systematic review about health education, then it is unlikely that all relevant studies will be located.

3. Is the validity of included studies adequately assessed?

If the review systematically assesses the quality of primary studies, it should include an explanation of the basis for determining quality (for example, method of randomization, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis) and the process by which assessment is carried out (that is, how many reviewers are involved, whether the assessment is independent, and how discrepancies between reviewers are resolved). Authors

may have used either a published checklist or scale or one that they designed specifically for their review.

4. Is sufficient detail of the individual studies presented?

The review should show that the included studies are suitable to answer the question posed and that a judgment on the appropriateness of the authors' conclusions can be made. It is usually considered sufficient if a paper includes a table giving information on the design and results of individual studies or includes a narrative description of the studies. If relevant, the tables or text should include information on study design, sample size for each study group, patient characteristics, interventions, settings, outcome measures, follow-up, drop-out rate (withdrawals), effectiveness results, and adverse events.

5. Are the primary studies summarized appropriately?

The authors should attempt to synthesize the results from individual studies. In all cases, there should be a narrative summary of results, which may or may not be accompanied by a quantitative summary (meta-analysis).

For reviews that use a meta-analysis, heterogeneity between studies should be assessed using statistical techniques. If heterogeneity is present, the possible reasons (including chance) should be investigated. In addition, the individual evaluations should be weighted in some way (for example, according to sample size or according to inverse of the variance) so that studies that are thought to provide the most reliable data have greater impact on the summary statistic.

Controlled Trials

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?
    - Adequate approaches to sequence generation:
        - Computer-generated random numbers
        - Random numbers tables
    - Inferior approaches to sequence generation:
        - Use of alternation, case record number, birth date, or day of week
    - Not reported

2. Was the treatment allocation concealed?
    - Adequate approaches to concealment of randomization:
        - Centralized or pharmacy-controlled randomization
        - Serially-numbered identical containers
        - On-site computer based system with a randomization sequence that is not readable until allocation
    - Inferior approaches to concealment of randomization:
        - Use of alternation, case record number, birth date, or day of week
        - Open random numbers lists
        - Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)

Not reported

3. Were the groups similar at baseline in terms of prognostic factors?

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to treatment allocation?

6. Was the care provider blinded?

7. Was the patient kept unaware of the treatment received?

8. Did the article include an intention-to-treat analysis or provide the data needed to calculate it (that is, number assigned to each group, number of subjects who finished in each group, and their results)?

9. Did the study maintain comparable groups?

10. Did the article report attrition, crossovers, adherence, and contamination?

11. Is there important differential loss to follow-up or overall high loss to follow-up? (Study should give number for each group.)

Nonrandomized studies

Assessment of Internal Validity

1. Was the selection of patients for inclusion unbiased? (Was any group of patients systematically excluded?)

2. Was there important differential loss to follow-up or overall high loss to follow-up? (Numbers should be given for each group.)

3. Were the events investigated specified and defined?

4. Was there a clear description of the techniques used to identify the events?

5. Was there unbiased and accurate ascertainment of events (that is, by independent ascertainers using a validated ascertainment technique)?

6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?

7. Was the duration of follow-up reasonable for investigated events?

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1. Center for Reviews and Dissemination, University of York, 2001. Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews. *CRD ReportNumber 4(2nd edition)..*

2. Harris RP, Helfand M, Woolf SH. Current methods of the US Preventive Services Task Force: a review of the process. . *American Journal of Preventive Medicine.* 2001;20(3 Suppl):21-35.

Appendix E. Excluded trials

Exclusion codes

2=Outcome not included
3=Intervention not included
4=Population not included
5=Publication type not included
6=Study design not included

Excluded studies	Exclusion code
Head-to-head trials	
Aarskog D, Fevang FO, Klove H, Stoa KF, Thorsen T. The effect of the stimulant drugs, dextroamphetamine and methylphenidate, on secretion of growth hormone in hyperactive children. Journal of Pediatrics. 1977;90(1):136-139.	6
Borcherding BG, Keysor CS, Cooper TB, Rapoport JL. Differential effects of methylphenidate and dextroamphetamine on the motor activity level of hyperactive children. Neuropsychopharmacology. 1989;2(4):255-263.	2
Dewan MJ, Anand VS. Evaluating the tolerability of the newer antidepressants. Journal of Nervous & Mental Disease. Feb 1999;187(2):96-101.	2
Efron D, Jarman F, Barker M. Methylphenidate versus dexamphetamine in children with attention deficit hyperactivity disorder: A double-blind, crossover trial. Pediatrics. 1997c;100(6):1025.	5
Efron D, Jarman FC, and Barker MJ. Methylphenidate vs dexamphetamine in children with attention deficit hyperactivity disorder: a double-blind cross-over trial. Journal of Paediatrics & Child Health. 1997b;33(4).	5
Faraone SV, Wigal SB, Hodgkins P. Forecasting three-month outcomes in a laboratory school comparison of mixed amphetamine salts extended release (Adderall XR) and atomoxetine (Strattera) in school-aged children With ADHD. Journal of Attention Disorders. Jul 2007;11(1):74-82.	6
Findling RL, Short EJ, Manos MJ. Developmental aspects of psychostimulant treatment in children and adolescents with attention-deficit/hyperactivity disorder. Journal of the American Academy of Child & Adolescent Psychiatry. 2001a;40(12):1441-1447.	3
Gross MD. Imipramine in the treatment of minimal brain dysfunction in children. Psychosomatics. 1973;14(5):283-285.	3
Jasinski D, Krishnan S. A double-blind, randomized, placebo- and active-controlled, 6-period crossover study to evaluate the likability, safety, and abuse potential of lisdexamfetamine dimesylate (LDX) in adult stimulant abusers. Paper presented at: The 2006 U.S. Psychiatric & Mental Health Congress; November 18, 2006, 2006; New Orleans, LA.	4

Excluded studies	Exclusion code
Jasinski D, Krishnan S. Abuse liability of intravenous lisdexamfetamine (LDX; NRP104). Paper presented at: 58th Institute on Psychiatric Services; October 6, 2006, 2006; New York, NY.	4
Kollins SH, Shapiro SK, Newland MC, Abramowitz A. Discriminative and participant-rated effects of methylphenidate in children diagnosed with attention deficit hyperactivity disorder (ADHD). Experimental & Clinical Psychopharmacology. 1998;6(4):375-389.	2
Mick E, Spencer T, Surman C, Hammerness P, Doyle R, Biederman J. Randomized single blind substitution study of OROS Methylphenidate (Concerta) in adults recieving immediate release methylphenidate. Paper presented at: The 160th Annual Meeting of the American Psychiatric Association, 2007; San Diego, CA.	5
Parasrampuria D, Schoedel KA, Schuller Rea. Do Formulation Differences Alter Abuse Liability of Methylphenidate? A Placebo controlled, Randomized, Double blind, Crossover Study in Recreational Drug Users. Journal of Clinical Psychopharmacology. 2007;27(5):459-467.	4
Parasrampuria D, Shoedel K, Schuller R, al. e. Abuse Potential of OROS Methylphenidate Versus Immediate-Release Methylphenidate and Placebo. Paper presented at: The 2005 American Academy of Child and Adolescent Psychiatry/Canadian Academy of Child and Adolescent Psychiatry Joint Annual Meeting; October 20, 2005, 2005; Toronto, Ontario, Canada.	5
Pelham WE, Hoffman MT, and Lock T. Evaluation of once-a-day OROS methylphenidate HCI (MPH) extended release tablets vs MPH tid in children with ADHD in a laboratory setting. Pediatric Research. 2000;47(4):31A.	5
Short EJ, Manos MJ, Findling RL, Schubel EA. A prospective study of stimulant response in preschool children: insights from ROC analyses. Journal of the American Academy of Child & Adolescent Psychiatry. 2004;43(3):251-259.	3
Spencer TJ, Biederman J, Ciccone P, Daughterty DD, Fisch AJ. A PET study examining pharmacokinetics and dopamine transporter receptor occupancy of two long acting formulations of methylphenidate in adults. Paper presented at: The 160th Annual Meeting of the American Psychiatric Association 2007; San Diego, CA.	4
Swanson JM, Wigal SB, Wigal T, et al. A comparison of once-daily extended-release methylphenidate formulations in children with attention-deficit/hyperactivity disorder in the laboratory school (the Comacs Study). Pediatrics. 2004;113(3 Pt 1):e206-216.	6
Wilson HK, Cox DJ, Merkel RL, Moore M, Coghill D. Effect of extended release stimulant-based medications on neuropsychological functioning among adolescents with Attention-Deficit/Hyperactivity Disorder. Archives of Clinical Neuropsychology. Dec 2006;21(8):797-807.	2
Winsberg BG, Press M, Bialer I, Kupietz S. Dextroamphetamine and methylphenidate in the treatment of hyperactive-aggressive children. Pediatrics. 1974;53(2):236-241.	6

Excluded studies	Exclusion code
Wolraich ML. Efficacy and safety of OROS(r) methylphenidate HCl (mph) extended-release tablets (CONCERTA(tm)), conventional MPH, and placebo in children with ADHD. International Journal of Neuropsychopharmacology. 2000;3(Supplement 1):S329.	5
Active-control trials	
Ajibola O, Clement PW. Differential effects of methylphenidate and self-reinforcement on attention-deficit hyperactivity disorder. Behavior Modification. 1995;19(2):211-233.	6
Aman MG, Kern RA, McGhee DE, Arnold LE. Fenfluramine and methylphenidate in children with mental retardation and ADHD: clinical and side effects. Journal of the American Academy of Child & Adolescent Psychiatry. 1993;32(4):851-859.	4
Aman MG, Kern RA, McGhee DE, Arnold LE. Fenfluramine and methylphenidate in children with mental retardation and attention deficit hyperactivity disorder: laboratory effects. Journal of Autism & Developmental Disorders. 1993;23(3):491-506.	4
Aman MG, Kern RA, Osborne P, Tumuluru R, Rojahn J, del Medico V. Fenfluramine and methylphenidate in children with mental retardation and borderline IQ: clinical effects. American Journal of Mental Retardation. 1997;101(5):521-534.	4
Aman MG, Marks RE, Turbott SH, Wilsher CP, Merry SN. Clinical effects of methylphenidate and thioridazine in intellectually subaverage children. Journal of the American Academy of Child & Adolescent Psychiatry. 1991;30(2):246-256.	4
Aman MG, Marks RE, Turbott SH, Wilsher CP, Merry SN. Methylphenidate and thioridazine in the treatment of intellectually subaverage children: effects on cognitive-motor performance. Journal of the American Academy of Child & Adolescent Psychiatry. 1991;30(5):816-824.	4
Arnold LE, Abikoff HB, Cantwell DP, et al. National Institute of Mental Health Collaborative Multimodal Treatment Study of Children with ADHD (the MTA). Design challenges and choices. Archives of General Psychiatry. 1997;54(9):865-870.	6
Arnold LE, Huestis RD, Smeltzer DJ, Scheib J, Wemmer D, Colner G. Levoamphetamine vs dextroamphetamine in minimal brain dysfunction. Replication, time response, and differential effect by diagnostic group and family rating. Archives of General Psychiatry. 1976;33(3):292-301.	4
Arnold LE, Wender PH, McCloskey K, Snyder SH. Levoamphetamine and dextroamphetamine: comparative efficacy in the hyperkinetic syndrome. Archives of General Psychiatry. 1972;27(6):816-822.	5
Brown RT, Borden KA, Wynne ME, Spunt AL, Clingerman SR. Compliance with pharmacological and cognitive treatments for attention deficit disorder. Journal of the American Academy of Child & Adolescent Psychiatry. 1987;26(4):521-526.	2
Brown RT, Borden KA, Wynne ME, Spunt AL, Clingerman SR. Patterns of compliance in a treatment program for children with attention deficit disorder. Journal of Compliance in Health Care. 1988;3(1):23-39.	2

Excluded studies	Exclusion code
Brown RT, Wynne ME, Borden KA, Clingerman SR, Geniesse R, Spunt AL. Methylphenidate and cognitive therapy in children with attention deficit disorder: a double-blind trial. Journal of Developmental & Behavioral Pediatrics. 1986;7(3):163-174.	2
Butter HJ, Lapierre Y, Firestone P, Blank A. A comparative study of the efficacy of ACTH4-9 analog, methylphenidate, and placebo on attention deficit disorder with hyperkinesis. Journal of Clinical Psychopharmacology. 1983;3(4):226-230.	3
Butter HJ, Lapierre Y, Firestone P, Blank A. Efficacy of ACTH 4-9 analog, methylphenidate, and placebo on attention deficit disorder with hyperkinesis. Progress in Neuro Psychopharmacology & Biological Psychiatry. 1984;8(4-6):661-664.	3
Chase SN, Clement PW. Effects of self-reinforcement and stimulants on academic performance in children with Attention Deficit Disorder. Journal of Clinical Child Psychology. Win 1985;14(4):323-333.	6
Daviss WB, Patel NC, Robb AS, et al. Clonidine for attention-deficit/hyperactivity disorder: II. ECG changes and adverse events analysis. Journal of the American Academy of Child & Adolescent Psychiatry. Feb 2008;47(2):189-198.	3
Donnelly M, Rapoport JL, Potter WZ, Oliver J, Keysor CS, Murphy DL. Fenfluramine and dextroamphetamine treatment of childhood hyperactivity. Clinical and biochemical findings. Archives of General Psychiatry. 1989;46(3):205-212.	3
Dorrego MF, Canevaro L, Kuzis G, Sabe L, Starkstein SE. A randomized, double-blind, crossover study of methylphenidate and lithium in adults with attention-deficit/hyperactivity disorder: preliminary findings. Journal of Neuropsychiatry & Clinical Neurosciences. 2002;14(3):289-295.	3
Epstein JN, Conners CK, Hervey AS, et al. Assessing medication effects in the MTA study using neuropsychological outcomes. Journal of Child Psychology & Psychiatry & Allied Disciplines. May 2006;47(5):446-456.	2
Ercan ES, Varan A, Deniz U. Effects of combined treatment on Turkish children diagnosed with attention-deficit/hyperactivity disorder: a preliminary report. Journal of Child & Adolescent Psychopharmacology. Apr 2005;15(2):203-219.	6
Filho AGC, Bodanese R, Silva TL, Alvares JP, Aman M, Rohde LA. Comparison of Risperidone and Methylphenidate for Reducing ADHD Symptoms in Children and Adolescents With Moderate Mental Retardation. Journal of the American Academy of Child & Adolescent Psychiatry. Aug 2005;44(8):748-755.	6
Garfinkel BD, Webster CD, Sloman L. Individual responses to methylphenidate and caffeine in children with minimal brain dysfunction. CMAJ: Canadian Medical Association Journal. 1975;113(8):729-732.	4
Garfinkel BD, Webster CD, Sloman L. Methylphenidate and caffeine in the treatment of children with minimal brain dysfunction. American Journal of Psychiatry. 1975;132(7):723-728.	4

Excluded studies	Exclusion code
Garfinkel BD, Webster CD, Sloman L. Responses to methylphenidate and varied doses of caffeine in children with attention deficit disorder. Canadian Journal of Psychiatry Revue Canadienne de Psychiatrie. 1981;26(6):395-401.	3
Garfinkel BD, Wender PH, Sloman L, O'Neill I. Tricyclic antidepressant and methylphenidate treatment of attention deficit disorder in children. J Am Acad Child Psychiatr. 1983;22(4):343-348.	6
Greenberg LM, Deem MA, McMahon S. Effects of dextroamphetamine, chlorpromazine, and hydroxyzine on behavior and performance in hyperactive children. American Journal of Psychiatry. 1972;129(5):532-539.	6
Gulley V, Northup J, Hupp S, Spera S, LeVelle J, Ridgway A. Sequential evaluation of behavioral treatments and methylphenidate dosage for children with attention deficit hyperactivity disorder. Journal of Applied Behavior Analysis. 2003;36(3):375-378.	6
Jensen P. Longer term effects of stimulant treatments for Attention-Deficit/Hyperactivity Disorder. Journal of Attention Disorders. 2002;6(Suppl 1):S45-56.	5
Klein RG, Abikoff H. Behavior therapy and methylphenidate in the treatment of children with ADHD. Journal of Attention Disorders. Jul 1997;2(2):89-114.	3
Kolko DJ, Bukstein OG, Barron J. Methylphenidate and behavior modification in children with ADHD and comorbid ODD or CD: main and incremental effects across settings. Journal of the American Academy of Child & Adolescent Psychiatry. 1999;38(5):578-586.	3
Mohammadi MR, Kashani L, Akhondzadeh S, Izadian ES, Ohadinia S. Efficacy of theophylline compared to methylphenidate for the treatment of attention-deficit hyperactivity disorder in children and adolescents: A pilot double-blind randomized trial. Journal of Clinical Pharmacy and Therapeutics. 2004;29(2):139-144.	6
Nemzer ED, Arnold LE, Votolato NA, McConnell H. Amino acid supplementation as therapy for attention deficit disorder. Journal of the American Academy of Child Psychiatry. 1986;25(4):509-513.	6
Overtoom CC, Verbaten MN, Kemner C, et al. Effects of methylphenidate, desipramine, and L-dopa on attention and inhibition in children with Attention Deficit Hyperactivity Disorder. Behavioural Brain Research. 2003;145(1-2):7-15.	2
Pataki CS, Carlson GA, Kelly KL, Rapport MD, Biancaniello TM. Side effects of methylphenidate and desipramine alone and in combination in children. Journal of the American Academy of Child & Adolescent Psychiatry. 1993;32(5):1065-1072.	6
Potashkin BD, Beckles N. Relative efficacy of ritalin and biofeedback treatments in the management of hyperactivity. Biofeedback & Self Regulation. 1990;15(4):305-315.	2
Schmidt MH, Mocks P, Lay B, et al. Does oligoantigenic diet influence hyperactive/conduct-disordered children--a controlled trial. European Child & Adolescent Psychiatry. 1997;6(2):88-95.	6

Excluded studies	Exclusion code
Solanto MV, Wender EH, Bartell SS. Effects of methylphenidate and behavioral contingencies on sustained attention in attention-deficit hyperactivity disorder: a test of the reward dysfunction hypothesis. Journal of Child & Adolescent Psychopharmacology. 1997;7(2):123-136.	6
Vitiello B, Severe JB, Greenhill LL, et al. Methylphenidate dosage for children with ADHD over time under controlled conditions: lessons from the MTA. Journal of the American Academy of Child & Adolescent Psychiatry. 2001;40(2):188-196.	6
Wells KC, Chi TC, Hinshaw SP, et al. Treatment-related changes in objectively measured parenting behaviors in the multimodal treatment study of children with attention-deficit/hyperactivity disorder. Journal of Consulting & Clinical Psychology. Aug 2006;74(4):649-657.	2

There were > 200 placebo-controlled trials excluded that were not listed here, many are trials of immediate-release methylphenidate which are reviewed elsewhere[1] and others that do not contribute to this comparative review as direct evidence was available.

Reference:

1. Jadad AR, Boyle M, Cunningham C, Kim M, Schachar R. Treatment of attention-deficit/hyperactivity disorder. *Evidence Report: Technology Assessment (Summary).* 1999(11):i-viii, 1-341.

Appendix F. Previous systematic reviews

Previous systematic reviews of this evidence are numerous.[1-20] We included only four systematic reviews that we rated good quality.[14, 16, 20, 21] The table below summarizes the characteristics and main findings of these four reviews. We rated the other reviews fair-poor quality primarily because they did not use standard methods of study appraisal. Also, many were not comprehensive in searching multiple databases and were nonspecific with regard to eligibility criteria and literature search strategies.

Inclusion criteria (study design, publication date, population characteristics, and interventions) and methods of analysis varied across the good-quality reviews. Despite this, main findings were generally consistent in suggesting that there are no clear differences in short-term efficacy and tolerability between methylphenidate, immediate-release dextroamphetamine, and pemoline. Additionally, the Jadad review (1999) summarized findings from longer-term, placebo-controlled trials of immediate-release dextroamphetamine and methylphenidate that suggest these stimulants are associated with general improvement that persists over time.[20] The Jadad review also summarized findings from placebo-controlled trials of methylphenidate, antidepressants, pemoline, nicotine, and phenylalanine in adults which suggested that the short-term efficacy of these treatments remained in question at that time.

Our review encompasses studies from all three good-quality reviews, as well as any published since 2001 and those that met our broader scope of interventions.

Summary of good-quality systematic reviews

Review	Characteristics	Main findings
King 2004 (Centre for Reviews and Dissemination, Centre for Health Economics, University of York)	Study design: RCTs for efficacy/adverse events; systematic reviews for adverse events Publication date: MPH=1999 and onward; DEX=1997 and onward; atomoxetine=1981 and onward Population: Children and adolescents (≤ 18 years of age) diagnosed with ADHD (including hyperkinetic disorder Interventions: MPH, DEX, atomoxetine Total # of included studies: 65	In general, inadequate reporting of study methodology limited reliability of results. There was little evidence of consistent differences in short-term efficacy between MPH IR and ER, MPH IR and DEX IR, or MPH IR and atomoxetine. Adequate data regarding potential short-term adverse effects of MPH IR, MPH ER, DEX IR and atomoxetine is lacking.
Schachter 2001 (EPC at University of Ottawa)	Study design: Placebo-controlled RCTs Publication date: 1981 or later Population: ADD with or without hyperactivity; median age=8.7 years Intervention: short-acting MPH Total # of included trials: 62 (2897 patients)	Short-acting MPH demonstrated consistent short-term efficacy in reducing most ADD-related symptoms. Significant short-term harms reported by parents/patients included decreased appetite, insomnia, stomach ache, drowsiness and dizziness.
Jadad 1999 (EPC at McMaster University)	Study design: RCTs Publication date: 1966 or later Population: ADHD in humans Interventions: DEX, MPH, pemoline, clonidine, bupropion,	*Drug vs. drug:* There were few, if any differences in short-term efficacy between MPH, DEX and pemoline. Results of MPH and TCAs comparisons were conflicting. Body of drug vs. drug evidence did not include any studies of clonidine, bupropion or SSRIs.

Review	Characteristics	Main findings
	TCAs and SSRIs Total # of included trials (total # patients not reported): Drug vs. drug=22 Long-term therapy=14 Treatment of ADHD in adults=12	*Longer-term therapy* (mean duration=20 weeks): Placebo-controlled trials of DEX or MPH in primarily school-age children suggest trends in general improvement over time regardless of treatment *ADHD in adults*: Short-term efficacy of MPH inconsistent across placebo-controlled trials *Adverse effects:* Short-term trials of stimulants most frequently examined sleep disorders/disturbances, headaches, motor tics, decreased appetite/anorexia, abdominal pain and irritability and no differences were reported. Nausea, fatigue and tiredness were also commonly examined and rates were similar for stimulants and antidepressants. Long-term safety data is inadequate to make any conclusions.
Klassen 1998 Klassen 1999 (CCOHTA)	Study design: Randomized controlled trials Publication date: 1981 or later Population: Children 0-18 years with diagnosis of ADD, ADDH or ADHD Intervention: DEX, MPH or pemoline for ≥ 1 week in duration Total # of included trials: 26 (999 patients)	No clear differences in short-term efficacy were found between MPH, DEX and pemoline. Safety: not reported

References for Appendix F

1. Biederman J, Faraone SV, Monuteaux MC, Grossbard JR. How informative are parent reports of attention-deficit/hyperactivity disorder symptoms for assessing outcome in clinical trials of long-acting treatments? A pooled analysis of parents' and teachers' reports. *Pediatrics.* 2004;113(6 I):1667-1671.

2. Connor DF. Preschool attention deficit hyperactivity disorder: a review of prevalence, diagnosis, neurobiology, and stimulant treatment. *Journal of Developmental & Behavioral Pediatrics.* 2002;23(1 Suppl):S1-9.

3. Connor DF, Glatt SJ, Lopez ID, Jackson D, Melloni Jr. RH. Psychopharmacology and Aggression. I: A Meta-Analysis of Stimulant Effects on Overt/Covert Aggression-Related Behaviors in ADHD. *Journal of the American Academy of Child and Adolescent Psychiatry.* 2002;41(3):253-261.

4. Faraone SV, Biederman J. Efficacy of Adderall for Attention-Deficit/Hyperactivity Disorder: a meta-analysis. *Journal of Attention Disorders.* 2002;6(2):69-75.

5. Faraone SV, Biederman J, Roe C. Comparative efficacy of Adderall and methylphenidate in attention-deficit/hyperactivity disorder: a meta-analysis. *Journal of Clinical Psychopharmacology.* 2002;22(5):468-473.

6. Faraone SV, Wilens T. Does stimulant treatment lead to substance use disorders? *Journal of Clinical Psychiatry.* 2003;64(SUPPL. 11):9-13.

7. Faraone SV, Spencer T, Aleardi M, Pagano C, Biederman J. Meta-Analysis of the Efficacy of Methylphenidate for Treating Adult Attention-Deficit/Hyperactivity Disorder. *Journal of Clinical Psychopharmacology.* 2004;24(1):24-29.

8. Findling RL. Use of quetiapine in children and adolescents. *Journal of Clinical Psychiatry.* 2002;63(Suppl13):27-31.

9. Findling RL, Kusumakar V, Daneman D, Moshang T, De Smedt G, Binder C. Prolactin Levels during Long-Term Risperidone Treatment in Children and Adolescents. *Journal of Clinical Psychiatry.* 2003;64(11):1362-1369.

10. Gerardin P, Cohen D, Mazet P, Flament MF. Drug treatment of conduct disorder in young people. *European Neuropsychopharmacology.* 2002;12(5):361-370.

11. Gilmore A, Milne R. Methylphenidate in children with hyperactivity: review and cost-utility analysis. *Pharmacoepidemiology & Drug Safety.* 2001;10(2):85-94.

12. Greenhill LL, Halperin JM, Abikoff H. Stimulant medications. *Journal of the American Academy of Child and Adolescent Psychiatry.* 1999;38(5):503-512.

13. Jin C, Schachar R. Methylphenidate treatment of attention-deficit/hyperactivity disorder secondary to traumatic brain injury: a critical appraisal of treatment studies. *Cns Spectrums.* 2004;9(3):217-226.

14. Klassen A, Miller A, Raina P, Lee SK, Olsen L. Attention-deficit hyperactivity disorder in children and youth: A quantitative systematic review of the efficacy of different management strategies. *Canadian Journal of Psychiatry.* 1999;44(10):1007-1016.

15. Schachar R, Tannock R. Childhood hyperactivity and psychostimulants: A review of extended treatment studies. *Journal of Child & Adolescent Psychopharmacology.* Sum 1993;3(2):81-97.

16. Schachter HM, Pham B, King J, Langford S, Moher D. How efficacious and safe is short-acting methylphenidate for the treatment of attention-deficit disorder in children and adolescents? A meta-analysis. *CMAJ Canadian Medical Association Journal.* 2001;165(11):1475-1488.

17. Wilens TE, Biederman J, Spencer TJ, Prince J. Pharmacotherapy of adult attention deficit/hyperactivity disorder: a review. *Journal of Clinical Psychopharmacology.* 1995;15(4):270-279.

18. Wilens TE, Faraone SV, Biederman J, Gunawardene S. Does stimulant therapy of attention-deficit/hyperactivity disorder beget later substance abuse? A meta-analytic review of the literature. *Pediatrics.* 2003;111(1):179-185.

19. Connor DF, Fletcher KE, Swanson JM. A meta-analysis of clonidine for symptoms of attention-deficit hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry.* 1999;38(12):1551-1559.

20. Jadad AR, Boyle M, Cunningham C, Kim M, Schachar R. Treatment of attention-deficit/hyperactivity disorder. *Evidence Report: Technology Assessment (Summary).* 1999(11):i-viii, 1-341.

21. King S, Griffin S, Hodges Z, et al. Methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder in children. http://www.nice.org.uk/pdf/ADHD_assessment_report.pdf

Appendix G. Black box warnings of ADHD drugs approved by the US Food and Drug Administration

Trade name	Active ingredient(s)	Boxed warnings
Adderall®	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. Misuse of amphetamine may cause sudden death and serious cardiovascular events.
Dexedrine®, Dexedrine Spansule®	Dextroamphetamine sulfate	
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. 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. Misuse of amphetamine may cause sudden death and serious cardiovascular events.
Vyvanse®	Lisdexamfetamine dimesylate	
Concerta®	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.
Daytrana®	Methylphenidate hydrochloride	
Focalin® and Focalin® XR	Dexmethylphenidate hydrochloride	
Metadate® CD	Methylphenidate hydrochloride	
Ritalin®, Ritalin® SR, Ritalin® LA	Methylphenidate 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.

Trade name	Active ingredient(s)	Boxed warnings
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.
Metadate® ER	Methylphenidate hydrochloride	
Strattera®	Atomoxetine HCL	WARNING: SUICIDAL IDEATION IN CHILDREN AND ADOLESCENTS 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. 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.