Drug Class Review
on
Pharmacologic Treatments for ADHD

Final Report Update 2

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Original Report Date: August 2005
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A literature scan of this topic is done periodically

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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Note: A scan of the medical literature relating to the topic is done periodically (see http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for scanning process description). The Drug Effectiveness Review Project governance group elected to proceed with another update of this report. Please see timeline on the DERP website for details on the date of its release. Prior versions of this report can be accessed at the DERP website.

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INTRODUCTION

According to the most recent NIH Consensus Statement (1998), "attention deficit hyperactivity disorder (ADHD) 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 (MBD) and Hyperkinetic Syndrome, and has continued to evolve over time.[2]

A number of community-based studies have reported ADHD prevalence rates that range from 1.7% to 16%.[3] This is broader than the range of 3 to 5 percent that was estimated by the expert panelists that participated in the NIH Consensus Development Conference on Diagnosis and Treatment of Attention Deficit Hyperactivity Disorder (ADHD) 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 percent.[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 six months, and cause impairment that interferes with functional capacity in at least two performance settings (social, academic, or employment).[4] DSM-IV specifies three 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 percent of cases and into adulthood in 65 percent 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 of 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 co-existing 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. We used the following drug name abbreviations throughout the report: dextroamphetamine=DEX, methylphenidate=MPH, and mixed amphetamine salts=MAS.

Mixed amphetamine salts (MAS): Amphetamines are non-catecholamine sympathomimetic amines with CNS 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 (CNS) 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 MAO-B or phosphodiesterases II-V. While only FDA-approved for narcolepsy treatment, modafinil is also being used to treat ADHD.

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 (DERP). The participating organizations of DERP 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 effects 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 increases the risk of misuse or illicit diversion in patients with no history of misuse or diversion?

        i. stimulants vs. nonstimulants

        ii. immediate release vs. 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 co-morbidities (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 vs. nonstimulants

        ii. immediate release vs. long-acting formulations

        iii. Any included pharmacologic treatment

Inclusion Criteria

Populations
Pediatric, adolescent and adult outpatients with Attention Deficit Disorders
- Attention Deficit Disorder
- Attention Deficit Hyperactivity Disorder

Interventions (immediate release and extended release formulations, where applicable) (Table 1)

Table 1. ADHD drugs and indication

Generic Name	Trade Name*	FDA ADHD Approval	Year Introduced
MAS**	Adderall®*†	Children	1960
	Adderall XR®***	Children, adolescents, and adults	2001
Atomoxetine HCl	Strattera®	Children and adults	2002
Dextroamphetamine sulfate	Dexedrine®*	Children	1976
	Dextrostat®*†	Children	1975
Dexmethylphenidate HCl	Focalin®*†	Children	2001
	Focalin XR®†	Children	2005
Lisdexamfetamine dimesylate	Vyvanse®	Children	2007
Methamphetamine hydrochloride	Desoxyn®†	Children	1943
Methylphenidate HCl	Biphentin®‡	N/A	N/A
	Concerta® (MPH OROS)	Children and adolescents	2000
	Daytrana† (Transdermal patch)	Children	2006
	Metadate CD®† (MPH CD)	Children	2001
	Metadate ER®† (MPH ER)	Children and adults	1999
	Methylin®†	Children and adults	2003
	Ritalin®*	Children and adults	1955
	Ritalin SR® (MPH SR)	Children and adults	1982
	Ritalin LA®† (MPH SODAS)	Children	2002
Modafinil	Provigil®	Adults	1998

*or generic equivalent
** (amphetamine aspartate; amphetamine sulfate; dextroamphetamine saccharate; dextroamphetamine sulfate)
***Notice of Compliance (NOC) suspended in February 2005 by Health Canada in response to case reports of sudden/cardiac death and/or stroke. NOC was reinstated in August 2005 and is again available for prescription in Canada
†Not available in Canada
‡Not available in the United States

Outcomes
- Symptom response (inattention, hyperactivity-impulsivity, aggression, global ratings, etc.)
- Functional capacity (social, academic, and occupational productivity)
- Caregiver satisfaction (parent, teacher)
- Quality of life (child, parent, caregivers, teachers)
- Overall adverse effect reports
- Withdrawals due to adverse effects
- Serious adverse events reported
- Specific adverse events (hepatotoxicity, insomnia, anorexia, effects on growth, abuse potential)
- Misuse/diversion (trading, selling, compliance, overdose, development of substance abuse disorders)
- Time to onset of effectiveness
- Duration of effectiveness

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 (AHRQ), Technical Review #3 (Diagnosis of Attention-Deficit/Hyperactivity Disorder),[8] and Mental Measurements Yearbooks.[9-16] The AHRQ 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 A provides a listing of commonly used scales and tests and associated acronyms.

Study Designs

- Controlled clinical trials and good-quality systematic reviews
- Observational studies with functional or adverse event outcomes

The benefit of the RCT 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, RCT's 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 RCT's 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 RCT's 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.

METHODS

Literature Search

To identify relevant citations, we searched the Cochrane Central Register of Controlled Trials (1st Quarter 2007), Cochrane Database of Systematic Reviews (1st Quarter 1007), MEDLINE (1996 to March Week 3 2007), and PsycINFO (1985 to March Week 4 2007) using terms for included drugs, indications, and study designs (see Appendix B for complete search strategies). We have attempted to identify additional studies through searches of reference lists of included studies and reviews, the FDA web site, as well as searching dossiers submitted by pharmaceutical companies for the current review. All citations were imported into an electronic database (EndNote 9.0).

Study Selection

We assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above. Full-text articles of potentially relevant abstracts were retrieved and a second review for inclusion was conducted by reapplying the inclusion criteria.

Data Abstraction

The following data were abstracted from included trials: study design, setting, 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. In trials with crossover, outcomes for the first intervention were recorded if available. This was because of the potential for differential withdrawal prior to crossover biasing subsequent results and the possibility of either a "carryover effect" (from the first treatment) in studies without a washout period, or "rebound" effect from withdrawal of the first intervention.

Data abstracted from observational studies included design, eligibility criteria duration, interventions, concomitant medication, assessment techniques, age, gender, ethnicity, number of patients screened, eligible, enrolled, withdrawn, or lost to follow-up, number analyzed, and results.

Quality Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria listed in Appendix C. These criteria are based on the U.S. 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 categories 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 C 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 six or more of the seven predefined criteria, fair-quality if they met three to five criteria, and poor-quality if they met two or fewer criteria.

Included systematic reviews were also rated for quality based on pre-defined criteria (see Appendix C), 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 two 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 versus 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.

RESULTS

Overview

Figure 1 details the results of our literature searches. Overall, we identified a total of 3151 citations from searching electronic databases, reviews of reference lists, pharmaceutical manufacturer dossier submissions, and public comment. Of these, 718 were identified in the most recent update. Dossiers were submitted by six pharmaceutical manufacturers for the original review: Shire US (MAS, MAS XL), Eli Lilly (atomoxetine HCl), McNeil (methylphenidate HCl, Concerta®), Novartis (methylphenidate HCl, Ritalin LA®), and Cephalon (modafinil). Shire US (MAS, MAS XL), Eli Lilly (atomoxetine HCl), and McNeil (methylphenidate HCl, Concerta®) submitted additional dossiers for Update #1. Shire US (lisdexamfetamine dimesylate), McNeil (methylphenidate HCl, Concerta®), and Eli Lilly (atomoxetine HCl) submitted dossiers for this most recent update. After applying the eligibility and exclusion criteria to the titles and abstracts, we obtained full-paper copies of 873 publications (290 specific to update #2). After re-applying the criteria for inclusion, we ultimately included 298 publications (108 new in Update #2). A list of excluded studies is reported in Appendix E.

Figure 1. Results of Literature Search
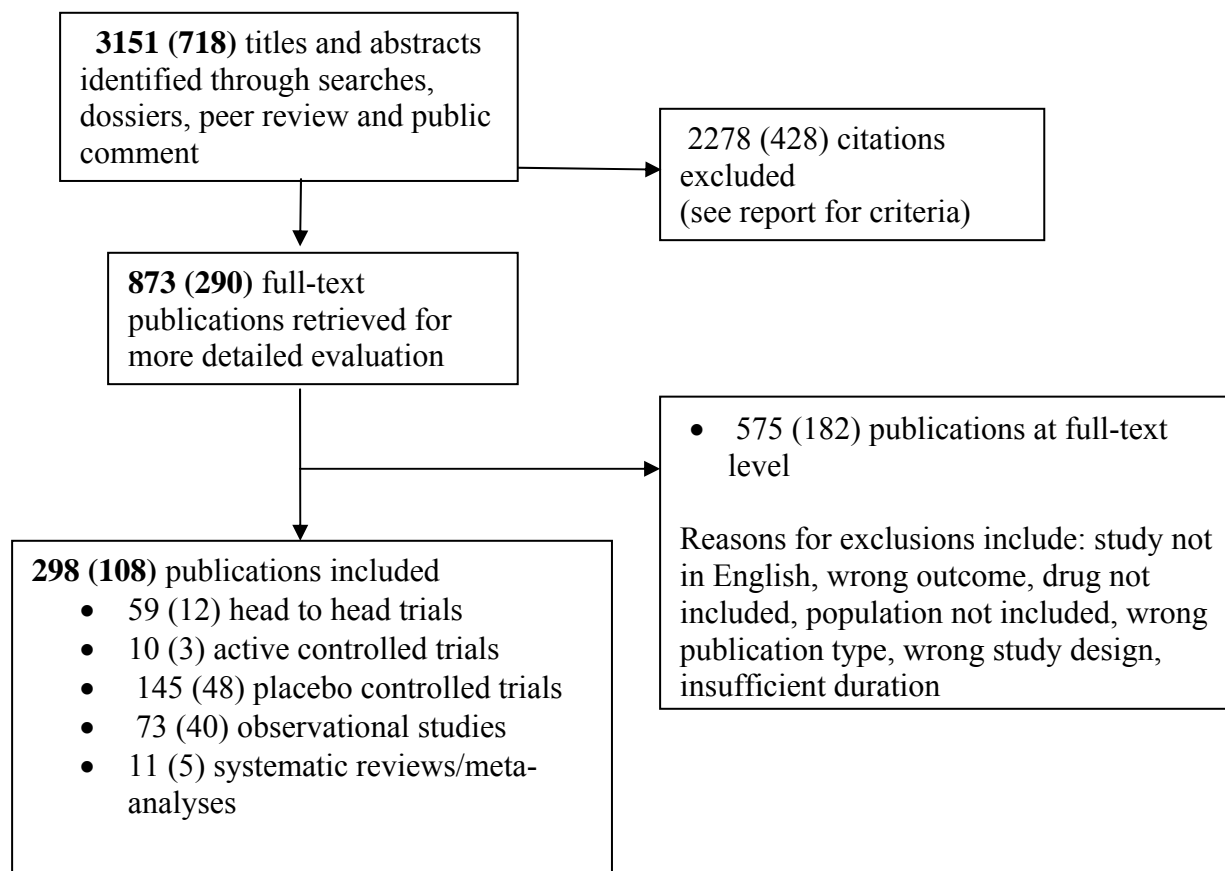
We identified the following numbers of head-to-head comparative trials of pharmacologic treatments for ADHD (Table 2).

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: 11 T: 1	C: 3							
DEX	C: 11 A: 1	--							
DEX-MPH	--	--	--						
Adderall®	C: 5	--	C: 1	--					
Adderall XR®	--	T:1	--	--	C: 1				
Modafinil	--	--	A: 1	--	--				
Atomoxetine	C: 5*	C: 1	--	--	C: 1	--	--		
LisDex	--	--	--	--	C:1	--	--	--	

Abbreviations: C= children, T=adolescents, A=adults
*1 trial vs. 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. We found hundreds of placebo-controlled trials in children. The majority were studies of MPH IR and fewer of various other formulations (OROS, SR and MR). Placebo-controlled trials also studied DEX, Adderall[®], unspecified "psychostimulants," atomoxetine, modafinil, and "amphetamine." Because there are a large number of head-to-head trials, 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 (atomoxetine, dexmethylphenidate, MPH ER, MPH CD, or modafinil). Also for Key Question 1, we included 6 placebo-controlled trials, 3 multimodal trials, and 5 observational studies as the only evidence of remission rates and long-term functional outcomes and response maintenance. One trial of the effects on weight and height of children discontinuing MPH during summers was included (MPH versus no treatment) and is included in Key Question 2. We also included 19 placebo-controlled trials in subgroup populations in Key Question 3. Data abstracted from placebo controlled trials can be found in Evidence Table 5, and relevant quality assessments in Evidence Table 6. For long-term safety, we included 19 observational studies (Evidence Tables 15 and 16).

In adult populations (age 18 and above), we included 20 placebo-controlled trials (Evidence Tables 11 and 12) and one long-term observational study (Evidence Tables 15 and 16) in addition to the head-to-head trials listed in Table 2 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, including one in the U.S.,[5] one in Canada,[23] and one in the U.K.[24] There are some differences in the lists of drugs assessed in these reviews and in our report, the commonalities being MPH IR and SR formulations, DEX, 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 (AAP) Clinical Practice Guideline on treatment of school-aged children with ADHD and the American Academy of Child and Adolescent Psychiatry (AACAP) Practice Parameter for the Assessment and Treatment of Children and Adolescents with ADHD were also reviewed.[25, 26] The AAP guideline considers only stimulant medications, specifically all forms of MPH and DEX. 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 AACAP guideline states that stimulants are first-line, except in situations where substance abuse disorder, comorbid anxiety, or tics are present.[26] The document does 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 to 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] Some of the reasons for these studies not being included in the other reviews are differences in the scope of drugs reviewed, the outcomes included, and study designs included. For example, our review included Adderall® and modafinil, which were not included in the other reviews. Importantly, this current review includes observational studies to assess harms and functional outcomes as well as RCT's with functional outcomes such as academic achievement that were not included in the previous reviews. This review includes comparative evidence on the effect on weight and height, which was not included in the 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.

Overall Summary of the Evidence on Efficacy or Effectiveness, Short-Term Efficacy and Tolerability, and Long-Term Safety of Drugs Used to Treat ADHD

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, and those that did found a significant effect. No head-to-head efficacy trial was good quality. The small numbers of patients in these trials limits 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 is 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 appears 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 vary, but the range in placebo-controlled trials is similar to that found with stimulants. Significant variation in the method of assessment and definition of response are 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.
- MPH was superior to placebo in efficacy in 2 fair-quality placebo-controlled trials that used validated assessment tools; but was also associated with higher rates of adverse events.

Long-term safety
- Evidence from one trial of MPH 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 MPH OROS to be associated with fewer outpatient visits/hospitalization for accidents/injury than MPH IR 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 MPH IR 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
<u>Stimulants</u>
- Immediate Release versus Extended Release formulations:
  - The evidence regarding the comparisons of MPH IR versus MPH OROS (Concerta®) is conflicting, with 2 double-blind trials unable to identify differences, while 2 open-label studies found that MPH OROS (Concerta®) resulted in greater improvements on some but not all assessments.
    - Exploratory pooled analysis of the inattention/overactivity scores of the IOWA Conners' scale indicate MPH OROS may result in greater improvement [weighted mean difference -1.19, 95% CI (-1.78; -0.60)].
  - Limited evidence is available for the comparisons of MPH IR to MPH ER (Medkinet®), MPH SR (Ritalin SR®), or MPH ER (Metadate CD,® Equasym®), with 1 small trial each. Overall, the studies of MPH ER (Medkinet®) and MPH SR (Ritalin SR®) were unable to identify differences compared to MPH IR, while the 3rd study found MPH ER (Metadate CD®, Equasym®) to be noninferior to MPH IR.
  - Database studies using intermediate outcomes report greater persistence with MPH OROS and MPH SODAS compared to MPH IR. Methodologic concerns indicate caution in interpreting this evidence.
- Sustained Release versus Sustained Release formulations:
  - Limited evidence from 2 small crossover studies suggests that MPH XR (Ritalin LA®) was superior to MPH OROS (Concerta®) on some, but not all efficacy

outcomes. However, these results should be interpreted with caution until higher quality evidence is available. We did not find evidence of a difference in adverse events between IR and SR formulations.
  o The COMACS study results suggest that MPH CD was associated with significantly larger effect sizes than MPH OROS in the morning, treatment effects were similar in the afternoon, and MPH OROS was superior in the evening. Methodologic concerns indicate caution in interpreting these findings.
- Dextroamphetamine versus methylphenidate:
  o The body of evidence clearly indicates no difference in efficacy between DEX and MPH IR. Evidence from short-term trials and observational studies suggests that weight loss is greater with DEX than MPH IR.
- Adderall® versus methylphenidate:
  o MAS was superior to MPH IR on a few efficacy outcome measures in two trials, but clear evidence of superiority is lacking. Very limited evidence suggests that twice daily dosing of MAS led to higher rates of loss of appetite and sleep trouble than once daily dosing or MPH IR.
- Dextroamphetamine versus Adderall®:
  o Evidence on the comparison of DEX IR versus SR versus MAS is limited and conflicting, but may suggest that measures made in the morning show DEX IR superior to DEX SR, and afternoon measures show DEX SR superior to MAS. Transient weight loss was greater with MAS and DEX SR than with DEX IR. However, this evidence should be interpreted with caution.
- Lisdexamfetamine versus Adderall XR®:
  o Evidence from CDER medical review and manufacturer-submitted data dossier suggests that mean SKAMP-DS scores were similar in children following one-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.
- Longer-term trials of MPH IR, placebo, or non-medication treatments provide some evidence to assess the ability of MPH IR to maintain effects for longer periods of time. These trials report somewhat mixed results on the ability to maintain short-term improvements in symptoms over 6 to 24 months. While the 14-month MTA found no deterioration over time, 3 other studies found the reverse. One explanation for this finding may be dose. One study found that the higher dose groups did not have deterioration of the gains in symptom control of inattentiveness and hyperactivity, and found an overall dose-response. The mean dose in the MTA study was also higher than in these other trials and used 3 doses per day. A 10-month follow up of patients from the MTA study showed a decrease in the magnitude of effect.

Atomoxetine
- Atomoxetine:
  o Limited evidence suggests that atomoxetine was associated with efficacy outcomes similar to MPH IR in one trial, but was associated with less significant efficacy outcomes than the extended release (XR) form of MAS in another trial. Two additional studies of atomoxetine compared to MPH IR or standard therapies assessed impact on sleep or functional status but were found to be poor quality.

- o Atomoxetine was associated with significantly higher rates of vomiting and somnolence than both MPH IR and MAS XR, while MPH IR caused more 'abnormal thinking' and MAS XR caused more insomnia.

Long-term safety
- Although the observational studies provide some estimate of the prevalence of serious longer-term adverse events with MAS, atomoxetine, DEX, and MPH (IR and SR), few studies directly compared different pharmacologic treatments for ADHD for any one adverse event.
- For outcomes where only uncontrolled evidence is available, it is 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.
- Height change in children:
  - o Evidence on DEX versus MPH is inconsistent. Evidence suggests that MPH IR and MPH OROS adversely impact expected height gain at least during the first 12 months of treatment.
  - o Limited evidence suggests that height changes resulting from atomoxetine are similar to those reported with MPH IR, and are also transient.
- Weight in children:
  - o DEX versus MPH: Results from comparative observational studies suggest that DEX is associated with significantly greater suppression of weight gain than MPH in the first 1-2 years. However, the difference between DEX and MPH appears to resolve by the second year and the difference found in years 1-2 may have been exaggerated by higher relative DEX dosages. Ultimately, these data should be interpreted with caution, due to methodological flaws in the measurement of weight.
  - o The remaining comparative and noncomparative observational studies suggest a small reduction in expected weight gain, especially among those with greater weight at baseline for MPH IR, MPH OROS, and MAS XR for at least the first year of treatment. Effects after 1 year are not clear, but may be less evident.
  - o Limited evidence suggests that weight changes resulting from atomoxetine are similar to those reported with MPH IR, and are also transient.
- There is no comparative evidence on other long-term safety outcomes, including tics, seizures, cardiovascular adverse events, injury frequency, and hepatotoxicity.
- Post-marketing safety concerns: Labeling revisions, changes in market availability:
  - o Adderall XR®: Canadian licensure reinstated in August 2005, following temporary suspension by Health Canada in February 2005 due to reports of sudden death in children.
  - o Atomoxetine: reports of severe hepatotoxicity and risk of suicidality led to additional warnings in product label.

Abuse/diversion
- Evidence from longitudinal studies with healthy controls, or untreated ADHD controls, is conflicting. Several studies have found no adverse relationship between stimulant

therapy (primarily MPH IR) during childhood or adolescence and later use or abuse of substances, and some studies even find a protective effect. However, other studies have found increased risk of later tobacco use and dependence and cocaine use or dependence. Variations in populations studied, control groups, age at follow-up, extent and type of analysis controlling for potential confounding, and approach to statistical analysis of data may all contribute to these contradictory findings.

- The evidence regarding drug misuse/abuse or diversion relate almost entirely to immediate release stimulants, most often MPH IR. Evidence from a cross-sectional study indicates that MPH OROS is also subject to misuse/abuse or diversion.

Adolescents
Efficacy and tolerability
- Adolescents were studied in a small number of short-term trials that involved MPH IR or MPH OROS (Concerta®). Studies of atomoxetine included adolescents and are discussed above.
- MPH OROS versus MPH IR:
  - A single, very small, *single blinded* study showed MPH OROS superior to MPH IR on some measures of simulated driving skills during tests administered in the late evening or nighttime. No difference was found during other test times.
- MPH OROS versus MAS:
  - One small, crossover study found no significant difference between MPH OROS and MAS in self-reported symptom improvement or subjective ratings of driving performance, although MPH OROS was associated with significantly better overall driving performance relative to MAS based on testing in a driving simulator.
- Indirect evidence: Stimulants:
  - Placebo-controlled trials of MPH IR do not provide indirect evidence of comparative efficacy or tolerability due to heterogeneity in outcome reporting.
  - MPH IR generally was superior to placebo in improving core ADHD symptoms, but was associated with more frequent reports of appetite and sleep disturbances.
- Functional outcomes: Observational studies:
  - Observational studies of MPH IR that report functional outcomes found mixed results. In an uncontrolled study of young adult males who had taken MPH as children (mean age at discontinuation of MPH 17 years), fewer suicide attempts were associated with higher dosages of MPH. Emancipated living situation and level of relationship commitment was associated with response to MPH. Early response to MPH was negatively associated with high school graduation, however.
  - Another uncontrolled follow-up of MPH IR responders reported "improved grades" after 6 – 14 months. Methodological limitations of these studies severely limit the interpretation of these findings.

Long-term safety
- We found no evidence on long-term safety of drugs used to treat ADHD in adolescents.

Adults
Efficacy and tolerability
- Pharmacological treatment of ADHD in adults has not been widely studied.
- There were no trials of adults with ADHD using dexmethylphenidate IR, lis-dexamphetamine, methamphetamine, MPH transdermal patch, MPH chewable tablet, or oral solution, and some extended release forms of MPH (Metadate CD®, Metadate ER®, Ritalin LA®, and Biphentin®).
- Direct comparative evidence was limited to one trial of DEX IR versus modafinil. Equivalent rates of patients (48%) responded to both treatments.
- Indirect comparisons from placebo-controlled trials suggest that atomoxetine, DEX IR, d-MPH ER, MPH IR, MPH SR, MPH OROS, and MAS IR are all effective as short-term treatments for reducing ADHD symptoms, with response rates ranging from 38% to 78%.
  - One poor-quality trial of MAS XR provided inconclusive evidence of benefit for ADHD symptoms and tolerability.
- There is less evidence that any ADHD drugs improve quality of life, other ADHD-related symptoms (depressed mood, anxiety, and cognition), or driving safety in adults.
  - MPH IR showed some benefit in reducing ADHD-associated anxiety symptoms and cognitive deficits and in improving driving safety.
  - Improvements in quality of life were found in one uncontrolled trial for each of atomoxetine and MAS XR.
- Short-term, randomized controlled trials do not provide clear evidence that any one stimulant is more tolerable than another or that nonstimulants offer an advantageous tolerability profile over stimulants.
- We found no studies in adults with ADHD that compared any included ADHD drug to any other or placebo on risk of abuse or illicit diversion outcomes. One study used "preference" as a proxy measure of abuse/diversion and concluded that higher preference of MPH IR over placebo more likely reflected efficacy rather than abuse potential in 10 adults with ADHD.

Subgroups
Demographics
- Race/Ethnicity
  - Only half of studies reported race or ethnicity data. Studies were primarily conducted in White populations.
  - 2 placebo-controlled studies in 100% non-White groups:
  - MPH IR 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-RS-IV mean change score compared to placebo remained statistically significant at the 50mg and 70mg doses, but not the 30mg dose, in a subpopulation of non-Caucasians.
    - Improvements compared to baseline on 90% of measures.
- Gender
  - Limited evidence of difference in efficacy between boys and girls.

- o Lisdexamfetamine: Difference in ADHD-RS-IV mean change score compared to placebo remained statistically significant at the 50mg and 70mg doses, but not the 30mg dose, in a subpopulation of girls, but this analysis may have been under-powered by a small sample size.

ADHD subtypes
- Results from short-term RCT's suggest that atomoxetine, MPH IR, and MPH OROS all have superior efficacy relative to placebo in children with ADHD, regardless of diagnostic subtype.

Commonly occurring comorbidities
- General
  - o Half of studies reported, but none stratified analyses.
  - o Prevalence in studies (AAP estimated prevalence):
    - oppositional defiant disorder: 19-66.7% (35.2)
    - conduct disorder: 9-38.5% (25.7)
    - anxiety: 1.4-42%: (25.8)
    - depression: 0.7-6.6% (18.2).
  - o Adults: Atomoxetine: Tics
    - Placebo-controlled studies of MPH IR do not consistently support a relationship to increased tic severity or frequency. A few measures improved or worsened, but global measures and total scores do not show a difference.
- Mental retardation/developmental delay
  - o In children with mental retardation, evidence indicates that MPH IR is beneficial on most ADHD outcomes compared to placebo.
  - o Adverse events were common, with staring and social withdrawal occurring more often with MPH IR than placebo.
- Learning disability
  - o Very limited evidence that response to MPH IR may be moderated in children with mathematics learning disabilities.
- Pervasive developmental disorders
  - o Very limited evidence is available on the use of atomoxetine or MPH IR in children with autism or epilepsy. However, this evidence suggests that atomoxetine and MPH IR are beneficial on most ADHD outcomes compared to placebo. This evidence should be interpreted with caution.

- Tic disorders
  - o Overall, there was very little evidence across these trials to indicate that MPH IR, DEX IR, or atomoxetine were associated with any tic exacerbation effects. Rather, compared to placebo, MPH IR, DEX IR, and atomoxetine were all consistently associated with improved tic severity and ADHD symptoms.
- Oppositional defiant disorder
  - o Very limited evidence indicates that atomoxetine was associated with significantly greater improvements in ADHD outcomes than placebo.

- Bipolar disorder
  - Very limited evidence indicates that MAS (Adderall[®]) was associated with significantly greater improvements in ADHD outcomes than placebo when added to divalproex in children with co-existing bipolar disorder.
- Psychiatric illness
  - Subgroup analyses of placebo-controlled trials suggested that presence or absence of co-occurring "psychiatric illness" did not alter atomoxetine treatment effects in adults.
- Emotional dysregulation
  - In adults, comorbid ED-influenced patient response to treatment was preset with MPH OROS, but not to atomoxetine. Atomoxetine was superior to placebo on all measures of ADHD symptom improvement regardless of the presence of ED. ADHD symptom improvements were less robust for MPH OROS in patients with comorbid emotional dysregulation.
- Substance abuse
  - Adults: Placebo-controlled trials of MPH IR or SR focused on adults with ADHD and comorbid cocaine dependence, methadone-maintenance, or general alcohol or drug dependence. Overall, these trials do not provide clear support for the use of MPH IR or SR in substance abusers with ADHD.
    - Only cross-sectional data are available to compare MPH OROS and other formulations of MPH. These data are inadequate to make conclusions of a comparative nature.
    - In general, less robust treatment response rates were seen in substance abusers with ADHD compared to non-substance abusers (ranges 34% to 47% vs. 38% to 78%), but the placebo response rates in the substance abuser trials were also substantially greater (ranges 21% to 55% vs. 4% to 16%).
    - Neither MPH IR nor SR had any negative effects on substance use outcomes such as cravings, abstinence duration, proportion of days of substance use, amount of money spent on substances, or number of days until first negative urine sample.
- No conclusions about *comparative* effectiveness or safety based on age, gender, race/ethnicity, or comorbidities can be made from this body of evidence.

Detailed Assessment

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 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 six placebo-controlled trials of MPH IR.[51-58] Of these 6 placebo-controlled trials, 4 were either poor quality and/or lacked a valid assessment tool.[51, 52, 54-56] The remaining 2 studies present a mixed picture, with MPH IR 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 (CPRS-R; learning, conduct, and hyperactivity indices only).[53] 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 CPRS-R 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. MPH 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 (PATS) assessed the efficacy and safety of MPH IR relative to placebo.[57, 58] PATS 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 PATS design[57] 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[58] 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).[57]

The crossover phase of PATS 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 MPH IR doses ranging from 1.25 to 10 mg TID or placebo. The overall composite score of CLAM/SKAMP, based on parent and teacher scores, ranged from 0.91 for high-dose MPH IR to 1.19 for low dose MPH IR and 1.28 for placebo

(higher score reflecting worse symptoms). Effect sizes of treatment relative to placebo during this phase ranged from 0.16 (MPH IR 1.25 mg TID) to 0.72 (MPH IR 7.5 mg TID).

The parallel phase of PATS, in which 114 patients were randomized to either placebo or their optimal dose of MPH IR (as determined in the crossover phase of the trial), found no significant difference in the number of MPH IR patients that met the primary outcome measure of 'excellent response' on the SNAP-IV composite score compared to placebo patients: MPH IR 13/61 (22%) versus placebo 7/53 (13%; p<0.3). An unplanned, post-hoc analysis of composite SNAP scores found that MPH IR patients had a lower mean symptom score than placebo patients after 4 weeks of treatment (MPH IR 1.49 versus placebo 1.79; p<0.02).

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 58-100% of participants across most study populations. The inattentive subtype was generally observed less frequently (prevalence rate range: 9-40%) and the hyperactive subtype was relatively rare (prevalence rate range: 1-8%). 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 U.S. Census Bureau Estimates (White = 80.4%; Black = 12.8%; Asian = 4.2%; and of Hispanic/Latino origin = 14.1%).[59] 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 (19-66.7%), conduct disorder (9-38.5%), anxiety (1.4-42%), and depression (0.7-6.6%). 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 = 35.2 (27.2, 43.8), conduct disorder = 25.7 (12.8, 41.3), anxiety disorder = 25.8 (17.6, 35.3), and depressive disorder = 18.2 (11.1, 26.6).[60] 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 (MPH)

We included 11 trials of MPH IR versus SR formulations.[28, 61-70] 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 (ITT) analysis, lack of information on eligibility criteria, attrition, or post-randomization exclusions (Evidence Table 3).[28, 61, 62, 66] The remaining studies compared MPH IR to 4 extended release formulations of MPH (Concerta[®], Ritalin SR[®], Medikinet[®], or Metadate CD[®]).[63-65, 67-70] In addition, according to

an FDA statistical review (http://www.fda.gov/cder/foi/nda/2000/21-121_Concerta_statr.pdf), MPH OROS (Concerta®) and MPH IR were compared in an additional trial of 64 children that has not yet been published.[71]

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

Table 3. Pharmacokinetic profiles of methylphenidate products*

Drug	Doses per day	Time to peak (hours)	Duration of action (hours)	Delivery system
Short-acting				
MPH IR	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)				
Metadate CD®, Equasym®	1	1st: 1.5 2nd: 4.5	8	Eurand 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

*information obtained from product labels

MPH IR versus MPH OROS (Concerta®)

Four studies have compared MPH IR versus MPH OROS once daily, enrolling a total of 561 children with ADHD (Table 4).[63, 64, 69, 70]

Table 4. Trials of MPH IR versus MPH OROS (Concerta®)

Study details	Mean dose	Mean *change* in IOWA Conners' MPH OROS versus MPH IR	SNAP-IV MPH OROS versus MPH IR
Wolraich, 2001 Double-blind RCT USA N = 282 28 days	MPH IR 29.5 mg/d (TID dosing) Concerta® 34.3 mg/d	**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 Defiant -0.36 vs. -0.32 **Parent SNAP-IV** Inattention -0.91 vs. -0.77 Hyperactivity/Impulsivity -0.91 vs. -0.74 Oppositional Defiant -0.65 vs. -0.41 For all comparisons P = NS
Pelham, 2001 Double-blind Crossover* + Behavioral Treatment USA N = 68 7 days	MPH IR 29 mg/d (TID dosing) Concerta® 35 mg/d	**Teacher Ratings** Inattention/overactivity: 4.96 vs. 4.65 Oppositional/defiant: 2.08 vs. 2.26 P = NS for both comparisons **Parent Ratings** Inattention/overactivity: 4.49 vs. 5.64 P = 0.05; Oppositional/defiant: 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/USA N = 147 8 weeks	MPH IR 33.3 mg/d (usual care; 61% TID, 38% BID) Concerta® 37.8 mg/d	**Teacher Ratings** NA **Parent Ratings** Inattention/overactivity: -3.9 vs. -5.4 p=0.01; Oppositional/defiant: NA	**Parent Ratings** **SNAP-IV Remission†** 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 (CTRS-R-S)	
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	

NA = not applicable –scale not applied
*simulated classroom setting and natural setting data collected; natural setting results reported here
† 0 or 1 on all 18 ADHD items in SNAP-IV.

Two double-blind trials of MPH IR versus MPH OROS did not show overall differences in outcomes,[63, 64] while 2 open-label studies did find a significant difference favoring MPH OROS.[69, 70] 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. Importantly, across the studies, the weighted average daily dose of MPH OROS was 5 mg greater than the MPH IR daily dose. A second issue is the risk of selection bias in that none of the studies report the proportion of patients taking MPH IR or MPH 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 an RCT of 312 children.[64] Similarly, a much smaller crossover trial (68 children) that was 7 days long and included behavioral treatment, found MPH 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.[63]

The study by Steele et. al[70] was open-label, comparing usual care to switching to MPH 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 ODD) of the parent assessed SNAP-IV scale, MPH OROS treatment resulted in more patients being classified as in remission at 8 weeks, with an NNT 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 MPH IR, and it was unblinded, it is potentially biased against MPH IR. The proportion of patients taking MPH IR, MPH 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 MPH OROS; weighted mean difference -1.19 (95% CI (-1.78; -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 MPH OROS superior to MPH IR, assessing the change in Conners' Teacher Rating Scale Revised Short-Form (CTRS-R-S) score by either teacher or parent over 5 time points using a linear mixed model, P value <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 MPH, but again the proportions taking MPH IR versus MPH OROS or other formulations prior to enrollment is 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 MPH (Concerta XL®) from MPH IR of an unknown duration.[72] 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 MPH OROS as included in this review.

The FDA Statistical Review of the NDA for MPH OROS includes criticism of 3 early trials,[63, 64, 73] 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).[71]

MPH IR versus MPH SR (Ritalin SR®)

A small 2-week RCT (34 children) of MPH IR versus MPH SR found mixed results.[65] 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 MPH IR. Parent questionnaires indicated a significant difference favoring MPH SR on the "Conduct Problem" item final score, and the physician scores showed no difference.

MPH IR versus MPH 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 MPH IR BID and MPH ER (Medikinet®) in SKAMP Attention or Deportment subscale scores or in math problems attempted.[67] 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 MPH ER (Medikinet®) is not available in the U.S.

MPH IR versus MPH ER (Metadate CD®, Equasym®)

A 3-week study using over-encapsulation for blinding enrolled 327 children, comparing MPH IR to Equasym® (sold in the U.S. as Metadate CD®). The study analyzed only 87% of patients in the main per-protocol analysis with unclear description of those excluded.[68] 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 MPH IR 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 MPH groups were found similarly superior to placebo at both time points throughout the study.

Other measures of comparative effectiveness of IR versus SR formulations

Clinical trials of extended release versus 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.

Observational database studies reported persistence outcomes for 6-month[74] and 12-month periods,[40, 43, 75] following index prescriptions of short- and long-acting stimulant formulations. Long-acting stimulant formulations (MPH OROS or MPH ER) formulations were associated with better persistence outcomes than shorter-acting formulations (MPH IR or MAS IR) across these studies regardless of measurement methods. 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 (IHCIS) 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 MPH OROS to be associated with greater persistence rates than MPH IR (12% vs. 1%, p<0.0001[40] and 15% vs. 3%, P < 0.0001).[75] The second study also reported persistence using less than a 30-day gap in refills as the definition and found 33% persistent with MPH OROS and 5% with MPH IR.[75] 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 MPH OROS versus MPH IR.

California Medicaid claims files from a 3-year period were examined to identify youth prescribed MPH (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 MPH OROS = 83%, MPH ER = 8.7%, MPH SODAS = 8.3%) than for those taking MPH IR (140.3 vs. 103.4; survival time ratio (STR) 1.37, 95% CI 1.32-1.42). Subgroup analysis results suggest that persistence duration was greatest for MPH OROS (147.2 days, 95% CI 142.6-151.7 days) compared to MPH SODAS (113 days; 95% CI 100.9-125.1 days) or MPH CD (101.1 days, 95% CI 91.2-111.0 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).[74] Prescription refill patterns for children (75.7% male; mean age=9.93 years) with new claims for either MAS IR (n=3,425), MPH IR (n=3,343), or MPH OROS (n=2,781) were evaluated over 6-month assessment periods. Proportion of days of treatment without any 15-day gaps was greater for patients taking MPH OROS than for MPH IR or MAS IR (0.5 vs. 37 vs. 42; p<0.001), as was proportion of patients that continued receiving therapy for 151-180 days (30.23% vs. 13.62% vs. 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 MPH OROS compared to MPH IR or MAS IR (0.76 vs. 0.69 vs. 0.73; p<0.001).

Comparisons of SR formulations
MPH OROS (Concerta[®]) versus MPH 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 MPH OROS 18-54 mg and MPH CD 20-60 mg (both given once daily) depending on time of assessment.[76, 77] 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 MPH IR. Table 5 below illustrates effect sizes which suggest that MPH CD was associated with significantly larger effect sizes than MPH OROS in the morning, treatment effects were similar in the afternoon, and MPH 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 MPH CD and MPH 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

MPH OROS (Concerta®) versus MPH SODAS (Ritalin LA®)

Two small crossover studies have found MPH SODAS superior to MPH OROS. A small 1-week crossover study of MPH SODAS 20mg versus MPH OROS 18mg and 36mg[41] found MPH 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 MPH SODAS superior on one 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 MPH OROS (18 and 36 mg) and MPH 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.[78] Here MPH SODAS 40 mg was found superior to MPH 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 (AUC) analyses, while MPH SODAS 20 mg was not significantly different to either dose of MPH OROS. Here, concerns over the clinical importance of the difference in AUC, 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.

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

Methylphenidate ER (Metadate®) versus placebo

A 3-week trial of Metadate® versus placebo enrolled 314 children out of 507 screened.[79] 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 (CGI) 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 versus Methylphenidate

We included nine fair-quality studies (reported in 11 publications) of DEX versus MPH IR.[35-37, 39, 46-48, 80-83] Two poor-quality studies, and one poor-quality sub-group analysis were found.[29, 84, 85] All nine fair-quality studies were randomized, blinded crossover trials. Table 6 summarizes the study characteristics.

Table 6. Dextroamphetamine IR versus Methylphenidate IR study characteristics

Study	N, Duration	Diagnosis criteria	Final dose*	Results
Efron, 1997	N = 125 2 weeks	DSM-IV criteria for ADHD	DEX: 0.15mg/kg MPH: 0.3 mg/kg	No differences found
Efron, 1998	N = 102 2 weeks	DSM-IV criteria for ADHD	DEX: 0.15mg/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/ 90mg	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/ 90mg	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 six 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"

* All doses divided into morning/noon doses

The two largest studies,[35, 81] 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 one study,[81] 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 two drugs based on children's self-assessment[35] and based on parent and teacher ratings.[81] These 2 studies had similar populations, primarily children with the Mixed subtype (82%), however co-morbidities and ethnicity are not reported.

Of the 7 small studies (n = 12 to 48), only one 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, DEX 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, co-morbidities, 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 MPH OROS, DEX IR, or MAS to MPH IR. 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 MPH IR

	Interventions	Response rate definition	Response rates (% pts)
MPH OROS versus MPH IR			
Pelham, 2001 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 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 versus 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®) vs. 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

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).

MPH IR versus MPH OROS (Concerta®)
        IHCIS managed care claims' data (described above) suggest that MPH OROS was associated with fewer outpatient visits/hospitalization for accidents/injury than MPH IR over a 12-month follow-up period (odds ratio 0.58, 95% CI 0.353 to 0.945).[40] The study population was 75% male, with a mean age of 9.7 years; however no other information regarding ADHD subtypes, comorbidities, or race/ethnicity were provided. The second study of this database found 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 over a 12 month period.[75] The regression also found a reduced probability with MPH OROS compared to MPH IR. However, the study also found that those taking MPH IR were statistically significantly younger (14 years versus 17 years old), had

more total diagnoses, and geographic differences in the proportions of patients taking MPH
OROS versus IR were present.

MPH IR

In a 4-year follow-up study of 62 children treated with MPH, the effect of duration of
treatment on academic performance was assessed.[86] The duration of treatment was divided into
< 6 months, 6 months to 2 years, 2 to 3 years, 3 to 4 years, and those currently taking stimulants
at follow-up. No differences were found between the groups on academic achievement as
measured by teachers, the proportion repeating grades, in special education classes, or being
tutored. Although the proportion of children repeating grades was lowest in the group
continuing to take MPH (8% vs. 46%, 50%, 36%, 31%), this difference was not statistically
significant, possibly because of the small numbers of boys per group (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 MPH IR who were followed for 6
months of treatment.[87] Parents of 100 children (32.6%) were unsatisfied with their children's
adherence to MPH IR and cited the following reasons for missing doses: forgetting to take MPH
IR at school (72.9%), the medication having no effect (20%), forgetting to bring MPH IR to
school (19.1%), refusing to take MPH IR (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.

Maintenance of short-term symptom response effects
MPH or DEX versus 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 DEX IR and 2
with MPH IR,[88-90] and 3 trials that randomized children to stimulant medication or non-drug
therapy for 12 to 14 months.[91-93] Two studies were poor quality due to serious flaws that
represent significant potential for bias. The placebo controlled trial of DEX did not report any
baseline characteristics of the two groups and did not conduct an ITT analysis, while the
numbers and reasons for withdrawal are also not reported.[88] In a trial of MPH IR, cognitive
training or both (n=30) omitted important information about basic information on study design
and outcomes (e.g. randomization, baseline characteristics, blinding, and loss to follow up).[94]

Overall, the MPH IR studies provide a mixed picture of the consistency of efficacy of
MPH over 6 months to 2 years. The only study reporting that the short-term effects were
maintained over the follow-up period was the Multimodal Treatment Study of Children with
Attention Deficit/Hyperactivity Disorder (MTA) study.

The Multimodal Treatment Study of Children with Attention Deficit/Hyperactivity
Disorder (MTA) was a relatively large study (n = 579) funded by the NIMH assessing
medication management, behavioral treatments, standard community care, and combined
medication management and behavioral treatments over a 14-month period.[91] Outcomes are

available for 540 children that were followed an additional 10 months subsequent to trial discontinuation.[44] Medication management could involve any stimulant medication, but started with MPH titration. At study end, 73% of those in one of the medication management groups were on MPH and 10% on DEX, 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%).

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-ODD 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. Important to this review of ADHD medications, the effect of medication management was maintained over the 14 month period. 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 MPH 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 that indicates that with careful monitoring of dose and drug regimen, ADHD stimulant medications can reduce symptoms of ADHD over a 14-month period.

Families were contacted 10 months after the end of the 14-month study (24 months 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 24 months post-randomization, medication alone resulted in better scores on ADHD and ODD 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 improvement magnitude by half from the 14-month to 24-month time points; effect size changes for ADHD symptoms = 0.60 vs. 0.30 and ODD symptoms = 0.39 vs. 0.21.

The other earlier trials reported a dissipation of effect over time (Table 8). Although some of these studies do not report mean doses, of those that do, the doses used in the MTA study were higher.

Table 8. Maintenance of MPH IR short-term effects

Study	Treatments Duration	Sample size mean age (yrs) % male	Results
Kupietz, 1998	MPH IR 0.3, 0.5 or 0.7 mg/kg Placebo x 27 weeks	N=47 9.7 % Male NR	Mean CTRS total ratings worse at Week 27 than Weeks 2 or 14
Lalongo, 1993	MPH IR 0.4 or 0.8 mg/kg Multimodal treatment MPH 0.4 mg/kg + Multimodal Placebo Trial=3 months; 9 months follow-up	N=96 8.27 years 77.4%	Short-term gains deteriorated at 9 months
Firestone, 1986	MPH IR 22 mg Parent training Both x 2 years	N=73 Mean age NR % Male NR	Conners' Hyperactivity Index Scores worsened at 1 (N=52) and 2 (N=30) years

Remission rates: MPH IR

Three studies assessed the effects of withdrawing MPH IR after periods of treatment.[95-97] Two of these were poor quality,[95, 96] but the third study[97] included a group of 21 boys who had been treated with MPH for a mean of 1.75 years and randomized to 3 weeks of placebo or MPH. Using the Conners' Teacher Rating Scale (CTRS), this study found that on the Subscale items of hyperactivity and defiance the scores during the placebo period were significantly worse than during the MPH 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 MPH 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

MAS versus MAS XR (Adderall® versus Adderall XR®)

Fifty-one children were enrolled in a randomized crossover study of MAS XR at 10, 20, and 30mg, MAS IR 10mg, and placebo given once daily for seven days. Study assessments were taken during a single 12-hour day with assessments every 1.5 hours in a simulated classroom setting.[98] The study used a run-in period where children were given MAS XR 20mg 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 30mg dose. However, the 10 and 20mg doses showed more variable benefits early (at 1.5 hours) and late (10.5 and 12 hours). Immediate release MAS IR 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 MAS XR 20 and 30mg once daily to MAS IR 10 mg twice daily.

MAS versus Methylphenidate Immediate Release (MPH-IR)

Three small, fair-quality studies of MAS versus MPH IR were found.[32, 45, 99, 100] One was a parallel group RCT[100] while the other two were randomized cross-over trials.[32, 45, 99] Two additional studies were rated poor quality[42, 101] due to no description of randomization or concealment of randomization code, no ITT analysis, high discontinuation rates or no randomization (clinician selected drug), and no blinding of patients or outcome assessors.

The parallel group RCT enrolled 58 children with ADHD and randomized them to 3 weeks of MAS, MPH IR, or placebo.[100] The mean doses at the end of study were MAS 12.5 mg/day and MPH IR 25.2 mg/day (divided into morning +/- noon doses for both drugs). No differences were found in the mean IOWA CTRS scores (Inattention/Overactivity and Aggression/Defiance subscales) rated by teachers 4 mornings and afternoons a week, but MAS was significantly better on both subscales when morning and afternoon scores were combined. No differences were found in parent ratings. The mean CGI-Improvement score (rated by a blinded psychiatrist) was also significantly lower (better) in the MAS group than the MPH IR group (final score 1.6 vs. 2.35, p<0.05), but the difference in the proportions of responders (90% vs. 65%, respectively) did not reach statistical significance. No differences were found on the Conners Global Index or final weight.

The two crossover studies were conducted in the same manner by the same authors and were conducted in a summer treatment program.[32, 45, 99] These short-term studies (6 – 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 MAS to be superior to MPH IR given once daily, while few or no differences were found when comparing to MPH IR given twice daily, based on counselor and teacher ratings. Ratings of after school behavior indicated that the addition of a third 0.3mg/kg dose of MPH IR or the MAS 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 (10mg twice daily) of MPH IR was not as effective as the higher dose (17.5 mg twice daily) or either dose of MAS (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 two doses of MAS and the higher dose of MPH IR.

MAS versus Dextroamphetamine (DEX)

The evidence is limited to a single poor quality study of dextroamphetamine IR versus dextroamphetamine SR versus MAS versus placebo.[102] No conclusions can be drawn.

Dexmethylphenidate (d-MPH) Immediate Release

Only one of two placebo-controlled studies of d-MPH referred to in the most recent FDA Medical Review (http://www.fda.gov/cder/foi/nda/2001/21-278_Focalin_medr_P1.pdf) has been published.[103] d-MPH was associated with significantly greater mean reductions in Teacher SNAP rating score than placebo (p=0.004) after four weeks in a fair-quality trial of 132 children (88% male; mean age = 9.8 years) with ADHD of mostly the combined type (64%).[103]

A small study of the effects of withdrawing d-MPH after a 6-week titration period was poor quality. No conclusions can be drawn about the comparative efficacy of d-MPH.[95]

Dexmethylphenidate (d-MPH) Extended Release (ER)

According to the Center for Drug Evaluation and Research (CDER) Medical Review,[104] data from two short-term, randomized, placebo-controlled, double-blind efficacy trials were submitted to the FDA in the NDA for d-MPH ER.[105, 106] Both of these trials have been fully published and we are aware of no other controlled trials of d-MPH ER in children. Both were fair-quality. Study 2301 was a 7-week, parallel-group, flexible-dosing trial of 103 children.[105] Study US08 was a 2-week, fixed-dose, crossover trial of 54 children.[106] d-MPH 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 vs. -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 vs. 0.078, p<0.001).

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.[107] 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/day for first 2 weeks and then the dose was increased to 10 mg/day 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 one of two measure 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®)

According to the product label,[108] the efficacy of methylphenidate transdermal system (MTS) was established in two controlled trials in children, only one of which has been fully published.[109] The other, as well as a third trial, is only available as abstracts/posters from conference proceedings.[110, 111]

The fully published trial was a 1-week, randomized, placebo-controlled, crossover trial conducted in a laboratory classroom setting, enrolling 80 children. 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 MTS first had ADHD of the inattentive type (27% vs. 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 MTS was significantly superior to placebo on the SKAMP Deportment and Attention scales and in the number of math problems attempted and number of math problems correct on the Permanent Product Measure of Performance (PERMP).

Lisdexamfetamine dimesylate

We identified two fair-quality, randomized controlled trials of lisdexamfetamine, a 3-way crossover trial that compared 1-week treatment periods of lisdexamfetamine, MAS XR, and placebo in 52 children,[112,297] and a placebo-controlled, 4-week, parallel-group trial of three different dosages of lisdexamfetamine (30mg, 50mg, or 70mg) in 290 children.[113] 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 CDER 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 SKAMP-DS scores across the treatment assessment day,[112, 297] or the change in mean ADHD-RS-IV total score.[113] Scores in all lisdexamfetamine groups were significantly superior to placebo group scores across both trials. There were no significant differences between lisdexamfetamine and MAS 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 MAS XR, regardless of age, gender, race, or baseline illness severity as measured by the CGI. The few exceptions pertained to the 30mg dosage of lisdexamfetamine.[113, 189] Compared to mean changes in ADHD-RS-IV for lisdexamfetamine 30mg versus placebo for the population overall (-21.8 vs. -6.2 points; p<0.0001), treatment effects appeared less robust in the subgroups of girls (-19 vs. -8.1; p=0.0537) and non-Caucasians (-18.5 vs. -10.1; p=0.0754).

Modafinil
        Efficacy findings for modafinil are inconsistent across the five placebo-controlled trials included in this review.[114-118] It appears 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 200-300mg in this study, modafinil was not found to be better than placebo in improving ADHD-RS.
        Among the later trials, there were three 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 361mg to 395mg) or placebo for treatment periods that were 7-9 weeks in duration.[114, 116, 117] Patient mean age was 10 years and 71% were male. Change in the ADHD-RS was identified as the primary outcome in all three 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-RS score change from baseline and also in the proportion of patients that were rated as "much improved" or "very much improved" on the CGI-I.
        In the final and most recent placebo-controlled trial of modafinil, the objective was to compare the efficacy and safety of several different BID and QD dosing regimens.[118] In this trial, 248 children with ADHD were randomized to 4-week treatment periods of either 300mg QD or divided (morning/mid-day) dosages of 200/100mg, 100/200mg, or 200/200mg. The majority of patients were male, with a mean age of 9 years. With regard to mean change from baseline in ADHD-RS, only the groups assigned to 300mg QD or 200/100mg 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 CGI-I.

Atomoxetine

Atomoxetine versus Methylphenidate
        Atomoxetine, the first nonstimulant introduced specifically for ADHD, was compared to MPH IR in 3 RCT's.[119, 120] However, 2 of these studies were really comparisons to placebo, with only few patients enrolled in the MPH arms. Therefore, these are considered placebo-controlled trials, below. The single study comparing atomoxetine and MPH IR found no differences between the drugs based on changes in the ADHD-RS, the CPRS-R hyperactivity item, and the

CGI-S.[119] Concerns over the study quality indicating potential bias suggest caution in interpreting these findings (see Evidence Table 4).

A second study comparing MPH IR and atomoxetine primarily assessed the impact of each drug on sleep, using a crossover design and sleep labs.[121] 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 MPH IR was 42.29 mg/day, and of atomoxetine was 58.27 mg/day. 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 MPH IR 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 versus MPH OROS

The Formal Observation of Concerta® versus Strattera® (FOCUS) trial compared *open-label* methylphenidate OROS and atomoxetine for three weeks in 1,323 children with ADHD.[122] 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 versus MAS XR (Adderall SR®)

The extended release form of MAS (Adderall SR®) 10-30 mg was superior to atomoxetine 0.5-1.2 mg/kg/day on most efficacy outcomes after three weeks in a fair-quality trial of 215 children (mean age = 8.7 years).[123] This trial, also known as StART (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. MAS XR was associated with significantly greater reductions in the mean SKAMP deportment scale scores, which was prespecified as the primary outcome (-0.56 vs. -0.13; p<0.0001). MAS 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 versus Standard Therapy

A British study of atomoxetine compared to 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.[124] The total score of the tool is stated to not have previously been used, but to have been validated by the owner (Riley et al.). 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% vs. 3.1%, previous exposure to stimulants 59.6% vs. 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 versus Placebo

Six placebo-controlled studies of atomoxetine in children and adolescents with ADHD found atomoxetine to be superior based on ADHD-RS as the primary outcome measure and various scales as secondary measures.[120, 125-128] Results of two of the six trials were described as identically-designed and were reported in one publication.[120] The mean change on ADHD-RS 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 $\geq$ 25% reduction in ADHD-RS score) in the atomoxetine group of 59.5% versus 31.3% in the placebo group ($p<0.001$).[128] Remission rates (defined as an endpoint CGI-S score of 1 or 2) were 28.6% and 9.6%, respectively ($p=0.003$). All 5 studies were funded and co-authored by representatives of the manufacturer of atomoxetine, and 4 were part of the NDA submitted to the FDA. 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 co-morbidities also varied across the studies (e.g. 18 to 45% with oppositional defiant disorder). Results of a subgroup analysis from two identically-designed placebo-controlled trials[120] suggested that atomoxetine was associated with significantly greater reductions in ADHD-RS Total Scores than placebo (-17.0 vs. -7.5; $p<0.001$) in 98 of the original 291 children with comorbid ADHD and oppositional defiant disorder (ODD).[129] No sub-group analyses based on ADHD subtypes or other comorbities were reported.

A significantly greater proportion of patients taking once daily dosages of atomoxetine ($\leq$1.8 mg/kg/day) responded to atomoxetine rather than placebo (69% vs. 43.1%; $p=0.003$) in a more recent fair-quality trial (n=153).[130] "Response" was defined as a 20% or greater mean reduction in total scores from the ADHD-RS-IV-Teacher Version. This trial differs from the previous five in that it was designed with a primary measure of response that was based on teacher reports in the school setting rather than on parent ratings.

Atomoxetine was associated with less rapid times to relapse than placebo under double-blind conditions (218 days vs. 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.[128] The primary outcome measure was the number of days to relapse

and relapse was defined as return to 90% of baseline ADHD-RS score and CGI-S score increase of at least 2 points. Similarly, fewer patients on atomoxetine relapsed than on placebo (22% versus 38%, p<0.002).

Atomoxetine: Effectiveness outcomes

A few noncomparative observational studies evaluated duration of effectiveness for atomoxetine.[131, 132] In one study, 229 children who had a $\geq 40\%$ reduction in ADHD-RS 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.[131] 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).[132] 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.

Functional outcomes: MPH IR

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.[86, 133-136] Due to various methodological limitations, these studies do not provide good evidence for long-term effectiveness, even for MPH.

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 MPH for at least 3 years during childhood.[135] 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 MPH group was added. The sizes of the groups also differed, with 64 in the non-treated hyperactive group, 20 in the MPH 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 MPH and untreated groups (Table 9). 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 9. Long-term functional outcomes of MPH from Hechtman, 1984[135]

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
Psychiatric treatment at present	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

The MPH 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.[133] 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 one head-to-head trial of MPH IR and SR (OROS)[137] and in 9 placebo-controlled trials of MPH.[138-147] 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

MPH IR versus MPH OROS (Concerta®)

A single, very small, *single blinded* crossover study of 6 adolescent boys showed MPH (OROS) superior to MPH IR on some simulated measures of driving skills, dependent on the time of day of testing.[137] 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 MPH 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 IR 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 MPH OROS, 2 had been taking MPH IR, 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.

MPH OROS versus MAS XR

A 17-day, small (n=35) crossover study compared the effect of stimulant use on the driving ability of adolescents with ADHD.[148] There was no significant difference between MPH

OROS 72 mg QD and MAS XR 30 mg QD in self-reported symptom improvement among participants (p=0.55) although both interventions appeared to improve symptoms compared to baseline (no further data provided). MPH OROS was associated with significantly better overall driving performance relative to MAS 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 two study drugs.

Indirect comparisons

MAS XR

A 4-week, placebo-controlled study of extended-release MAS (Adderall XR®) using a forced-dose titration schedule (up to 40 mg QD) assessed efficacy in 287 patients using the ADHD-RS-IV and CGI-I scale scores. All doses of extended-release MAS were associated with significant improvement in ADHD-RS-IV scores compared to placebo. Mean change in ADHD-RS-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 MAS (p≤0.005). Based on CGI-I scale scores, the proportion of patients who were improved following treatment with extended-release MAS (range 51.9%-70.7%, dose dependent) was significantly higher than placebo (26.9%; p≤0.01).

MPH OROS

One trial compared the efficacy of MPH OROS to placebo in adolescents. Of 220 enrolled subjects, 177 were randomized to a two-week double-blind phase following an open-label titration phase lasting up to 4 weeks.[149] The primary outcome of this trial was change from baseline in ADHD-RS 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-RS scores with MPH OROS compared to placebo (MPH OROS -14.93 versus placebo -9.58; p=0.001). Parent-assessed scores were similar, and also favored MPH 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).

MPH IR

Seven placebo-controlled crossover trials of MPH IR enrolled a total of 171 adolescents.[138-146, 150, 151] Patients were diagnosed primarily using the DSM III-R or DSM-IV criteria. Only one trial clearly described the distributions of the different ADHD subtypes and in this trial there were 87.5% patients with the Combined subtype.[151] MPH IR generally was superior to placebo in improving core ADHD symptoms, but was associated with greater frequency of appetite and sleep problems. MPH mean dosages ranged from 8.8[138] to 75 mg.[143] The trials reported a variety of outcome measures. All but one were consistent in using various forms of the highly valid Conners' rating scales (long and abbreviated forms).[151] However, inconsistency in the way results are reported make estimation of an overall magnitude of effect impossible.

Functional outcomes: MPH IR

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 MPH in an uncontrolled study,[136] 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 MPH as children and teens (mean age at discontinuation of MPH was 17 years) were studied.[134] 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 MPH were fewer suicide attempts positively associated with higher dose of MPH and emancipated living situation and level of relationship commitment were positively associated with response to MPH. Early response to MPH was negatively associated with high school graduation, however.

Adults

Treatment of ADHD in adults has not been widely studied. We found no trials of adults with ADHD using dexmethylphenidate, LIS-dexamphetamine, methamphetamine, MPH transdermal patch, MPH chewable tablet or oral solution, and some extended release forms of MPH (Metadate CD®, Metadate ER®, Ritalin LA®, and Biphentin®).

Only one of three previous, good-quality systematic reviews included studies of adult ADHD.[5] There were few studies of only DEX, MPH IR, and pemoline in adults available at the time of the Jadad review (1999).[5] Jadad et al. criticized these studies for their small sample sizes, short durations ($\leq$ 6 weeks), and for incomplete reporting methods. The review included one study of DEX and MPH[152] and placebo-controlled studies of MPH,[153-155] pemoline,[156] and other drugs not included in our review. Jadad et al. did not draw any conclusions from the study of DEX and MPH because no direct comparisons of these drugs were reported, only changes from baseline.[152] They reported that MPH's efficacy in reducing core ADHD symptoms was inconsistent across placebo-controlled trials and that pemoline was not associated with overall symptom improvement.

Subsequent to the Jadad et al. review, other studies have been published that expand the evidence base for DEX,[157-159] MPH,[160-169] MAS,[170] atomoxetine,[171, 172] and modafinil.[157, 173] These studies are included and reviewed here. The studies were fair quality, with one exception.[169] The most recent study of MPH is poor quality due to serious concerns about the validity of the outcomes in light of unsuccessful randomization (method not described, but uneven distribution of age) and uncertainty about characteristics of the groups analyzed (not an ITT).[169]

Direct comparisons

One head-to-head trial was published subsequent to the Jadad et al. review (Evidence Tables 9 and 10).[157] Identical proportions of adults (n=22) with ADHD responded to modafinil 206.8 mg and DEX IR 21.8 mg (48% vs. 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.[157]

Indirect comparisons

Numerous placebo-controlled trials have been conducted to evaluate whether adults with ADHD benefit from the same treatments that are used in children.[104, 153-156, 159, 161, 162, 164-168, 170-182] The majority of trials were rated fair quality. Three trials were rated poor quality[169, 179, 181] 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.[169, 178] 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 38 years and 64% were male. Among the 27% of trials that reported race, the majority of patients were White. Few studies reported prevalence rates of Inattentive (37-58%), Combined (35-63%), and Hyperactive-Impulsive (0-9%) subtypes.[157, 159] Differing subtype prevalence patterns cannot be ruled out in studies that didn't report this information.[154-156, 160, 163, 168, 170, 171, 175-177] Few trials reported prevalence rates of "any comorbidity" (range=22-78%) and mood/anxiety disorders (range=4.5-68%).[154, 155, 163, 170, 171, 176, 177] One study focused entirely on patients with ADHD and comorbid cocaine dependence.[163] 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[172] and for atomoxetine in patients with comorbidities.[171]

These trials were heterogenous with regard to study duration (2-13 weeks), 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[157, 163, 168, 175] may be characterized by patients with homogenous symptom presentations, whereas studies with less stringent criteria[155, 156, 159, 176, 177] may be more representative of the average patient.

These trials were also heterogenous with regard to their methods of assessing improvement in ADHD symptoms. Treatment response was most commonly measured as a categorical variable and defined as a 30% or greater improvement from baseline on adult ADHD-Rating Scale (ADHD-RS) scores. Other continuous variables used to measure ADHD symptom improvement included change from baseline in rating scale scores and rating scale endpoint scores. Regardless of approach, atomoxetine, DEX, d-MPH ER, MPH IR, MPH SR, MPH OROS, MAS IR, and MAS XR were generally all found to be effective short-term treatments for ADHD symptoms in adults (Table 10). The only exceptions were that the effects of low-dose MPH IR (45 mg/day TID)[183] and 60-90 mg/day of MPH SR BID[184, 185] were notably limited in patients with comorbid substance abuse disorders. Findings from placebo-controlled trials of MPH in adults with ADHD and comorbid substance abuse disorders will be discussed in more detail in Key Question 3.[163, 183-185] It should also be noted that uncertainty remains regarding the efficacy of modafinil in reducing core ADHD symptoms, as the only trial of modafinil we identified focused only on cognitive outcomes.[173]

Table 10. ADHD response rates from placebo-controlled trials

Trial N	Intervention Mean total daily dose	Study duration (weeks)	Response rates
Spencer, 1998 N=22	Tomoxetine BID 76 mg/day	3	≥30% reduction in ADHD-RS:52% vs. 10%; p<0.01
Weiss, 2006 N=98	DEX Max=40mg/day	20	"Much or very much improved" on CGI-ADHD: 64% vs. 16%, p=0.0005**
Schubiner,* 2002 N=48	MPH IR TID Max 90 mg/day	13	Physician efficacy ratings showing moderate improvement (1 or 2 on 7-point scale): 77% vs. 21%; p=0.0039
Spencer, 1995 N=25	MPH IR TID 0.92 mg/kg/day	3	CGI ≤2 and ≥30% reduction in ADHD-RS: 78% vs. 4%; p=<0.0001
Kooij, 2004 N=45	MPH IR QID or five times daily 0.91mg/kg/day	3	≥30% reduction in ADHD-RS: 42% vs. 13%; p=0.011
Carpentier,* 2005 N=25	MPH IR TID Max: 45mg/day	2	≥30% reduction in ADHD-RS: 47% vs. 26%; p=NS
Wender, 1985 N=37	MPH IR BID 43.2mg/day	2	"Moderate-to-marked" rating on Physician's Global Rating Scale: 57% vs. 11%; p=<0.0001
Reimherr, 2007 N=47	MPH OROS Max=90mg/day	4	50% improvement on WRADDS: 49% vs. 15%; p=0.007
Levin, 2006* N=98	MPH SR BID Max=80mg/day	8	≥30% reduction in ADHD-RS: 34% vs. 46%; p=NS
Levin, 2007* N=106	MPH SR BID Max=60mg/day	11	≥30% reduction in ADHD-RS: 47% vs. 55%; p=NS
Spencer, 2001 N=30	MAS BID 53.7mg/day	3	≥30% reduction in ADHD-RS: 70% vs. 7%; P=<0.001

* All patients comorbid for substance abuse disorders
** Calculated using StatsDirect V2.6.2

Indirect comparisons between competing drugs in ADHD symptom improvement outcomes are difficult to interpret across these adult trials due to the heterogeneity in outcome assessment methods. Therefore, we also considered whether any of the various ADHD drugs could be differentiated from the others by any other elements of their respective treatment profiles (Table 11). Other treatment outcomes considered included improvements in ADHD-associated depressive and anxiety symptoms, cognitive deficits, driving performance, and quality of life. Overall, evidence did not provide overwhelming support of the efficacy of these drugs in these areas and evidence regarding the effects of these drugs on quality of life was extremely limited.

MPH IR

A substantially higher number of adults with ADHD (N=542) have been randomized to MPH IR than any other drug in placebo-controlled trials.[153-155, 160-163, 165-169, 175, 177, 178, 183] In considering findings from these trials relative to other trials of competing drugs (Table 11), it appears that MPH IR may be distinguished as more consistently providing an advantage over placebo in reducing ADHD-associated anxiety symptoms and cognitive deficits.[155, 162, 165, 166, 168, 175, 177] Moreover, MPH IR is the only drug that has evidence, albeit limited, of having any advantage over placebo for improving driving safety.[167, 175] Simulator driving performance was assessed in adults with ADHD in two small, single-dose, placebo-controlled trials and results found that MPH IR 10mg significantly improved an Impaired Driving Score (p=0.05),[167] MPH IR 40mg significantly reduced steering variability,[175] and MPH IR 20mg significantly improved

appropriate use of turn signals.[175] Although promising, results from driving 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.

Table 11. Adult ADHD – Other symptom-related outcomes in PCT's

Trial N	Dose (mean) x Duration (wks)	Effective in treating: Depressive symptoms	Anxiety symptoms	Cognition
Atomoxetine				
Spencer, 1998 N=21	76 mg x 3	-	-	Yes
Michelson, 2003*/Faraone, 2003 N=536	94 mg/day x 10	No	No	Mixed (Stroop)
DEX				
Paterson, 1999 N=45	24 mg/day x 6	No	No	-
Weiss, 2006 N=49	40 mg/day x 20	No	No	-
MPH IR				
Bouffard, 2003 N=30	30-45 mg (TID) x 4	No	Yes (HAM-A)	Yes (CPT)
Gualtieri, 1985 N=8	0.3 mg/kg (bid) x 5 days	-	-	Yes (CPT)
Kinsbourne, 2001 N=17	5, 10, or 20 mg/day (QD) x 1 day	-	-	Yes (CPALT)
Tenenbaum, 2002 N=24	45 mg/d (max; QID) x 3	No	Yes (Beck Anxiety)	Yes (CPT)
Wender, 1985 N=37	43 mg x 2	Yes (POMS)	Yes (POMS)	-
Kooij, 2004/Boonstra, 2005 N=45	0.91 mg/kg x 3	No	No	Yes (CPT)
Barkley, 2005 N=52	MPH 10 mg MPH 20 mg	-	-	Mixed (CPT)
MPH SR				
Levin, 2002 N=347	20 mg/day x 4	Yes (POMS)	-	No
Modafinil				
Turner, 2004 N=20	200 mg x single dose	-	-	Mixed (Various)

*2 studies reported together

Atomoxetine

Although we did not find any evidence of the effects of any included ADHD drug on quality of life in any placebo-controlled trials of adult patients, findings from a 6-week trial of atomoxetine that lacked a control group appear somewhat promising.[186] In this trial, 218 adults with ADHD were randomized to double-blind treatment with atomoxetine 80mg, dosed either QD or BID. Based on changes from baseline in SF-36 scores (+4.78 points on Mental Component Summary (MCS) score; p<0.001), the authors concluded that atomoxetine had improved patients' perceived quality of life. The MCS score was noted to be a sum of subscores from the Vitality, Social Function, Role Emotion, and Mental Health domains.

MAS XR

The only other reports of quality of life outcomes we identified was from a 10-week interim analysis of patients taking open MAS XR (10-60mg) as part of the 30-week Quality of life, Effectiveness, Safety, and Tolerability (Q.U.E.S.T) trial.[187] Again, the SF-36 was used to assess quality of life and results suggested significant improvements from baseline on all individual domains except bodily pain.

Key Question 2: Safety

A. 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 MPH IR reported results of adverse event assessments.[53] MPH IR was clearly associated with higher rates of increased sadness, decreased appetite, and sociability impairments than placebo after 7-10 days in 31 preschoolers.

PATS provides some limited evidence on the short-term safety of MPH.[58, 188] Overall, 21/183 (11%) of PATS patients taking MPH 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 MPH use. No other drug-related serious adverse events were reported. Rates of moderate to severe adverse events ranged from 16%-30% in MPH groups and 16%-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.[188]

Parent-rated rates of several specific adverse events were significantly higher with MPH 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 MPH, show that rates of some adverse events significantly decreased ($p \leq 0.03$: irritability, crying, sadness/depression, listless/tired behavior) 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 PATS found that ADHD patients (n=140; mean age 4.4 yrs) enrolled in the study were in general larger than average at baseline, based on CDC growth charts (73.1% for height; 79.7% for weight). Use of MPH (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 MPH: 401 days) were compared to non-completers (n=45; mean duration of exposure to MPH: 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 MPH 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.

<u>Direct evidence</u>
Stimulants
Four of six trials of DEX versus MPH IR reported no differences between the drugs in adverse events.[37, 80-82] However, 2 short-term crossover trials found DEX to cause greater weight loss than MPH IR with mean weight change differences of 0.7 kg to 0.97 kg.[47, 83] One of 3 trials of MAS versus MPH IR found no difference in adverse event rates,[100] but 2 other studies found differences.[45, 99] Limitations in study design and lack of description of analysis methods make results from these 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, [99] and that MAS given twice daily caused the highest rates of these adverse events.[45] All 3 studies of MPH IR versus extended release formulations (MPH OROS, MPH SODAS, and MPH SR) reported no significant differences in the incidence of side effects.[63-65] MAS and DEX SR were found to cause more weight loss than DEX IR during the first week of treatment, but weight gain during the second week was greater with these drugs than with DEX IR.[102] 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 MPH SR (Ritalin LA®) and MPH OROS (Concerta®)[41] or between MPH CD (Metadate CD®) and MPH OROS (Concerta®).[67]

Atomoxetine
Atomoxetine caused significantly more vomiting and somnolence than both MPH IR[119] and Adderall XR®[123] in two trials. Atomoxetine was associated with lower rates of 'abnormal thinking'[119] than MPH IR and lower rates of insomnia than Adderall XR®.[123]

Table 12. Summary of adverse effects reported

Study	Differences found	Study	No differences found
DEX versus MPH IR			
Kauffman, 1981 Crossover; N=12 6 weeks	Significant difference found only on weight change: Mean change in weight (kg): DEX -0.86 vs. MPH +0.11 (Difference 0.97kg, p NR)	Arnold, 1978 Crossover; N=29	P = NS (incidence and weight change)
		Efron1997 Crossover; N=12	P = NS for all (incidence only)
Sharp, 1999 Crossover; N=32	Mean change in body weight (kg) reported to be greater with DEX. Difference 0.7 kg Dextroamphetamine: -1.1; p=0.01 from baseline Methylphenidate: -0.4; p=NS from baseline	Elia,1991 Crossover; N=48	P = NS (incidence and severity)
		Elia, 1993 Crossover; N=33	P = NS (incidence)
Adderall versus MPH IR			
Pelham, 1999a Crossover; N=21	Authors' assessment notes that adding an afternoon dose of either drug resulted in increased reports of loss of appetite or sleep delay. Statistical comparison NR.	Pliszka, 2000 Parallel; N=58	All p=NS (incidence only)
Pelham, 1999b Crossover; N=25	Authors note that differential side effects were seen only for loss of appetite and trouble sleeping with the high (12.5mg/day) dose of Adderall. (p-values NR).		
IR versus SR formulations of MPH			
		Pelham, 2001 Crossover; N=70	P = NS (incidence only)
		Wolraich 2001 Parallel; N=312	P = NS (incidence only)
		Whitehouse 1980 Parallel; N=34	P = NS (incidence only)
Extended release formulations of MPH			
		Lopez, 2003 Crossover; N=36	P = NS (% with at least 1 AE)
		Swanson, 2004 Crossover; n=214	P = NS (Parent ratings of side effects on the Barkley Scale)
Atomoxetine			
Kratochvil, 2002 Parallel; N=228	Atomoxetine vs. MPH IR; p=NS on 24 of 27 AE's reported; Atomoxetine worse: Vomiting: 22 (12%) vs. 0, p=0.017 Somnolence: 20 (10.9%) vs. 0, p=0.029 MPH IR worse: Thinking abnormal: 0 vs. 2 (5%); p=0.031		
Wigal, 2005 Parallel N=203	Atomoxetine vs. Adderall XR[®]; p=NS on 8 of 11 AE's reported Atomoxetine worse: Vomiting: 4.7% vs. 13%; p=0.035 Somnolence: 4.7% vs. 18.5%; p=0.0015 Adderall XR[®] worse: Insomnia: 28% vs. 7.4%; p<0.0001		
Multiple Comparisons			
James, 2001 Crossover; N=35	Based on SERS assessment tool: ANOVA analysis indicates Adderall and DEX SR caused greater decreases in weight than DEX IR, however these groups also had greater recovery of weight during the 2nd week (compared to DEX IR in each case). All other findings p = NS for drug vs. drug comparisons.		

<u>Indirect evidence</u>
Dexmethylphenidate (d-MPH) Extended Release (ER)
        Rates of overall adverse events were comparable for d-MPH ER compared to placebo in both the 2-week (28.3% vs. 22.2%)[106] and 7-week (75.5% vs. 57.4%)[105] trials. The most frequently reported adverse events were typical of stimulant products and were generally comparable between d-MPH 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 d-MPH ER compared to placebo was for decreased appetite in the 7-week trial (30.2% vs. 8.5%; p<0.0068).

Lisdexamfetamine dimesylate
        In the study of lisdexamphetamine and MAS XR, the overall incidence of adverse events were similar.[112, 297] With MAS XR, the most frequent were insomnia (8%) and decreased appetite (6%), while with lisdexamphetamine the most frequent were upper abdominal pain (4%) and decreased appetite (4%). Significant differences were not found in our chi-square analysis.
        In a dose-ranging study, overall adverse event rates were significantly greater (p≤0.05) for patients taking lisdexamfetamine 30mg (71.8%), 50mg (67.6%), or 70mg (83.6%) compared to placebo (47.2%).[113] When compared to placebo, all dosages of lisdexamfetamine were associated with significantly greater rates (p≤0.05) of decreased appetite (39% vs. 4.2%), insomnia (18.8% vs. 2.8%), and irritability (9.6% vs. 0). Weight loss incidence was only greater for patients in the 70mg group compared to placebo (9.2% vs. 1.4%; p≤0.05). Withdrawals due to any of these adverse events only occurred in <1% of patients, however.[189]

Methylphenidate transdermal system (Daytrana®)
        Adverse event rates were similarly low for MTS and placebo (< 4%), and were consistent with the known adverse effects of stimulants. Rates of adverse patch application site effects were not reported, but it was noted that any instances of erythema, irritation, and/or discomfort were mild in severity.

Modafinil
  Overall, modafinil appeared to be well-tolerated. Rates of withdrawal due to adverse events did not exceed 5% for modafinil, and were generally comparable to rates in the placebo groups. An exception was in the trial with the highest mean dosage of modafinil (395mg), where 10% of patients taking modafinil withdrew due to adverse events, compared to 0 in the placebo group (p=0.0058).[114] Insomnia occurred in more patients taking modafinil compared to those taking placebo, pooled RR 5.64 (95% CI 2.97 to 10.71); NNH 5.[114, 116-118] Decreased appetite also occurred in more patients taking modafinil than placebo; pooled RR 5.15 (95% CI 2.41 to 10.99); NNH 9.[114, 116, 117] Although more rare, 2 trials reported rash-related adverse events. Four patients (2%) withdrew due to rash in 1 trial[118] and a patient (0.6%) from a different trial was diagnosed with Stevens-Johnson syndrome.[117]

<u>Growth effects</u>
        A study of withdrawing MPH IR during summer months versus not withdrawing assessed the effect on weight and height.[190] Children with cross-situational, pervasive hyperactive behavior (n = 62) were randomized and followed for a 3 year period. 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. Both groups gained in weight and height over each summer, but during summer 1, the MPH IR ON group gained significantly less (0.9 kg, p=0.005) than the MPH IR OFF group. However, in summer 2 the difference was non-significant (0.6 kg). The effect on height was the reverse of these findings, with no significant difference in summer 1 (0.1 cm), but a significant difference after summer 2 (1.3 cm, p=0.02). The serious limitations of this study, in design and conduct, limit the likelihood that the findings are valid.

Adolescents

Placebo-controlled trials of MPH IR[138-147, 150, 191] provide limited evidence of short-term stimulant tolerability in adolescents. MPH IR was associated with significant appetite and sleep disturbances across some, but not all placebo-controlled trials.[140, 141, 144, 147] Additionally, adolescents taking MPH IR frequently reported increases in dulled affect, social withdrawal, irritability, and stomachache in two placebo-controlled trials.[143, 147]

Trials of other stimulants provide no long-term evidence on safety. One 17-day study comparing MPH OROS and MAS reports a single adverse event – urinary difficulty – in a patient receiving MPH OROS.[148] Another multi-phase, placebo-controlled study of MPH OROS reported no serious adverse events during the two-week double-blind phase, although one 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 MPH OROS and for placebo and the only withdrawal due to adverse events was reported in a placebo patient.[149] Results from a four-week trial found that when compared to placebo, MAS XR was associated with higher rates of anorexia/decreased appetite (35.6% versus 1.9% for placebo), insomnia (12.0% versus 3.7%), abdominal pain (10.7% versus 1.9%), and weight loss (9.4% versus 0%.). Five patients taking MAS 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

There is considerable interest in alternative, nonstimulant treatments for ADHD to address the needs of individuals intolerant of adverse effects that are often associated with stimulants (e.g., insomnia, appetite suppression). Therefore, this review particularly addresses the important question of how atomoxetine and stimulant treatments compare in adverse effects.

In summary, randomized controlled trials do not provide evidence that any one stimulant is more tolerable than another or that atomoxetine is more tolerable than stimulants. Trials were short-term in duration and heterogenous for types of adverse events measured. Adverse events were inadequately defined and ascertainment methods were unclear.

Direct comparisons of stimulants versus nonstimulants

Modafinil and DEX IR were associated with similar rates of insomnia (38% vs. 19%, NS), muscle tension (24% vs. 19%, NS) and appetite suppression (24% vs. 19%, NS) in the only included head-to-head trial.[157] There were no withdrawals due to adverse effects.

Indirect comparisons

Adverse event reporting was limited in placebo-controlled trials of adults with ADHD (Table 13).[104, 163, 170, 172, 177, 180, 182-185] Indirect comparisons between competing drugs in tolerability and adverse event rates are difficult to interpret across these adult trials due to incomplete reporting and heterogeneity in adverse event definitions, as evidence by variation in placebo group rates. We noted that atomoxetine was the only drug to be associated with significantly higher rates of adverse event-related withdrawals relative to placebo, however this may be due to shorter follow-up durations and the smaller sample sizes used in the stimulant trials.

Table 13. Specific adverse events in placebo-controlled trials of adults

Trial	Treatment (mean) x Duration (wks)	Insomnia	Appetite loss	Withdrawal due to AEs
Stimulants				
Spencer, 2001 N=27	MAS 53.7 mg x 3	37 vs. 14.8% (NS)	29.6 vs. 11.1% (p=0.03)	NR
Weiss, 2006 N=49	DEX Max=40mg/day x 20	NR	NR	13% vs. 8%, (NS)
Unpublished study 2302	d-MPH ER 20, 30, or 40mg x 5	17% vs. 13% vs. 18% vs. 11% (NS)	19% vs. 17% vs. 18% vs. 11% (NS)	10% vs. 13% vs. 9% vs. 7% (NS)
Schubiner, 2002 N=48	MPH IR 90 mg x 3	63% vs. 33%; p<0.05	50% vs. 25% (NS)	0 vs. 4.2% (NS)
Kooij, 2004 N=45	MPH IR 0.91 mg/kg x 3	33% vs. 22% (NS)	22% vs. 4%; p=0.039	None
Carpentier, 2005 N=25	MPH IR TID Max: 45 mg/day x 2	NR	NR	0 vs. 4% (NS)
Levin, 2006 N=98	MPH SR Max=90 mg/day BID x 8	NR	NR	6% vs. 3% (NS)
Levin, 2007 N=106	MPH SR Max=60 mg/day BID x 11	9% vs. 2% (NS)	NR	2% vs. 2% (NS)
Reimherr, 2007 N=47	MPH OROS Max=90 mg/day x 4	19% vs. 6%; p=0.05	11% vs. 0; p=0.025	NR
Atomoxetine				
Michelson, 2003* N=536	Atomoxetine bid 94.4 mg x 10	20.8 vs. 8.7% (p<0.001)	11.5 vs. 3.4% (p<0.001)	8.5% vs. 3.4%; p=0.03

*pooled results from 2 trials

B. 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.[166, 192-210] Eight studies used cohort designs to compare groups taking MPH to DEX,[197, 198, 205, 207] MPH to MAS,[210] and unmedicated hyperactives.[195, 205, 206] Twelve non-comparative studies involved patients exposed to MPH IR,[166, 193, 194, 200, 201, 203, 209] MPH SR (OROS),[202] atomoxetine,[192, 197, 208] or Adderall®,[204] making comparisons before and after treatment or to growth charts. We are aware of an ongoing open-label, one-year safety study of lisdexamfetamine (Study 302).[189] Interim findings for the first 272 enrolled patients were reported at the Annual Meeting of the American Academy of Child and Adolescent Psychiatry in October 2006,[211] and were described in the data dossier provided by Shire US for this update,[212] but not enough detail about study methodology is yet available for quality assessment and inclusion in this review.

All but two studies were 1 to 5 years in duration.[166, 193] All but one study involved elementary school-aged children.[204] The exception was one before-after study of MAS in adults with ADHD.[204]

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 MPH IR compared to an unexposed control group, finding no difference.[213]

No study was rated good quality. All but one 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 MPH and DEX due to our concerns about how possible additional biases may have affected the results.[207] 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.

Height and weight effects

A frequently cited nonsystematic review concluded that effects on weight and height associated with MPH IR vary across short-term clinical trials and long-term observational studies and are mostly transient.[214] We reached similar conclusions based on our analysis of a larger number of primarily long-term observational studies that compared MPH IR to DEX IR,[198, 199, 205] imipramine,[195] or unmedicated hyperactive control groups.[201, 205, 206] Height and weight changes associated with MPH IR[194, 196, 200, 202, 203] and OROS were also observed in long-term noncomparative studies.[202] A noncomparative study of MAS (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.[215]

Comparative studies

Height. These studies do not answer the question of whether any one stimulant suppresses growth in height any more than any other, nor do they clearly support a relationship between MPH and suppression of height.

The only comparative evidence comes from two studies of DEX and MPH,[198, 205] and one of MPH and MAS.[210] Results are mixed across the MPH versus DEX studies (Table 14). Both

reported changes in height percentiles using the outdated Iowa City norms. DEX and MPH were both associated with similar height *increases* at final follow-up (mean 6 years) in one study,[198] and DEX was associated with significantly greater height *decreases* than MPH after at least two years in the other.[205] It is impossible to establish whether heterogeneity in group characteristics across studies may possibly contribute to the contradictory findings, as one of the studies did not report mean age, dosage, or duration.[205]

The study of MPH (any formulation) versus MAS (any formulation) did not find statistically significant differences in the z-score for height change over 3 years of continuous treatment.[210] MAS appeared to have a small negative impact at year 1, but this difference was not statistically significant. The authors found that the adjusted cumulative dose showed a statistically significant negative relationship to height (both drugs combined) (r = -0.26, P = 0.001), but when 3 outlier values were removed from the regression the findings were no longer statistically significant.

Weight. Results from three comparative studies suggest that DEX is associated with significantly greater suppression of weight gain than MPH, at least in the first 1 to 2 years (Table 14).[198, 199, 205] DEX was associated with a significantly lower mean weight gain (kg) than MPH after nine months in one study,[199] significantly greater declines in weight percentiles after the first of 5 years another study,[198] and at end of treatment ($\geq$ 2 years) in yet another.[205] In the 5-year, partly retrospective and partly prospective study that involved 84 children (mean age at initiation of drug therapy=9 years and 82% male), however, differences in decreased weight percentiles between DEX and MPH 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).[198]

The 9-month study also reported subgroup analyses.[199] The first suggests that comparison of mean weight gain between DEX and MPH may have been confounded by dosage disparities. Apparently, the difference between DEX and MPH resolved when four patients taking lower-dose MPH (20 mg/day) were removed from the analysis (0.13 vs. 0.12 kg per month). Weight gain in children who continued medication over the summer versus those who discontinued medication during the summer was also reported. In patients taking DEX, medication continuation was associated with significantly lower mean weight gain than in children who discontinued medication (0.14 vs. 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 MPH.

A study of MPH compared to MAS (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 MAS and z-score (P = 0.029), indicating a greater impact on weight over time.[210] Overall, the children in the study were heavier than average, such that the mean final weights were not below average for age.

MPH was associated with decreases in weight percentiles similar to imipramine after one year[195] and absolute weight changes that were similar to those in unmedicated healthy controls in another 2-year study.[201] Results were mixed across two studies that compared children taking MPH to unmedicated hyperactives, however.[195, 206] In one study, MPH was associated with significantly greater declines in weight percentiles than in the unmedicated children after one year.[195] The differences between the MPH 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 MPH group and the unmedicated group demonstrated similar absolute weight gain (kg) after 364 days.[206]

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

Study	Interventions (mean dose) x duration Sample size	Age Gender Population	Height	Weight
Gross, 1976	DEX 16.5 mg, n=12 6.8 yrs 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 yrs follow-up MAS, n = 66 2.4 yrs 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

Noncomparative studies

Multiple noncomparative study findings provide inconclusive evidence regarding MPH IR effects on children's height and weight. A pooled analysis of data from open-label extensions of 13 trials of atomoxetine assessed the effect on height and weight.[192]

Height. In summary, studies of children taking MPH IR at various doses for 1-4 years showed inconsistent suppression of growth in height as compared to children taking imipramine,[195] those who were unmedicated,[195, 201, 206] and those in noncomparative studies that reported varied analyses including differences between expected and actual growth,[194] change in percentile,[196] percent of expected growth,[200] and proportion of patients with decreased growth rates.[203]

A study of children previously enrolled in a study of MPH IR were followed for 5 years, and a negative relationship between stimulant (any) dose and z-scores for height was found.[209] Further analysis indicated that the impact on height occurred after the dose reached >/= 2.5 mg/kg MPH 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 MPH 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 MPH OROS 40 mg/day for 12 months.[216] 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.

Based on the PATS trial, preschool-aged children treated with MPH IR were found to be taller at baseline than age-based norms (+2.04 cm).[217] Children who remained on MPH had reduced growth, a mean of 1.38 cm/year.

Weight.

MPH IR. Noncomparative studies[194, 196, 200, 203] provide mixed evidence about the association between MPH IR 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 MPH (max dose 20 mg) over 16 months.[203] The other 34 boys gained weight. The next study, published in 1979, involved 72 boys (age range 6-12) with hyperactivity that were taking MPH for up to two years.[200] A significant growth weight deficit (30%, p<0.05) was associated with MPH 24.2 mg/day (0.47 mg/kg) in the 72 boys who completed the first year. The growth weight deficit associated with MPH 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 MPH (39.9 to 41.3 mg) and followed children with hyperactivity over the longest observation period (4 years).[196] MPH was associated with significant declines in weight percentiles in all four years of the study (Years 1: -9.7 vs. 2: -15.9 vs. 3: -18.6 vs. 4: -20.8; p<0.001 for all). The final study, published in 1999, found an insignificant difference (0.72 kg) between expected versus actual weight gain in 29 patients who took MPH 34.5 mg for two years.[194]

In a study following children taking stimulants for 5 years, described above, stimulant dose >/= 2.5 mg/kg MPH equivalent was found to be negatively associated with weight gain (p<0.001).[209] 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 to be 1.41 kg at 1.5 mg/kg/day, 2.17 kg at 2 mg/kg/day, and 2.89 kg at 2.5 mg/kg/day 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.

Based on data from the PATS study, preschool-aged children were heavier than age-based norms by 1.78 kg.[217] After a year of treatment, those who stayed on MPH IR experienced less weight gain than those who did not complete by 1.32 kg/year.

MPH 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 lbs) less than expected for age.[216]

MAS XR. Twenty-seven of 568 (4.7%) children withdrew due to weight loss in a 24-month before-after study of MAS XR.[215, 218] Eligibility for this study was restricted to patients that completed either of two 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 MAS XR-treated adolescents (mean age 14 yrs; 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.[219] The mean weight decreased by 2.4 kg (5.2 lbs), with approximately 9.2 lb weight loss being the mean among MAS 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-75th percentile (1.5 kg), while those below the 25th percentile gained 0.5 kg (mean).

Atomoxetine. Based on 412 patients (children and adolescents) who had received atomoxetine for at least 2 years and had at least one post-baseline height and weight measurement, atomoxetine resulted in a mean decrease in expected weight of 0.87 kg, and decrease in expected height of 0.44 cm.[192] 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. Height changes appeared to occur over a longer period of time, but also regressed toward the mean by 2 years. Results from another before-after study of 10 boys (mean age NR) suggested that tomoxetine (same as atomoxetine) was associated with a weight loss of 1.15 kg after 10 weeks.[208]

Tics

Four studies and 1 meta-analysis reported tic-related outcomes.[194, 202, 204, 216, 220,221] One of these is a long-term placebo-controlled trial[220] of MPH IR. Table 15 summarizes the characteristics and outcomes from these studies. Although the 1-year study started out with similar numbers assigned to placebo and MPH, by the study end 72 were on MPH and only 18 on placebo. Development of new tics or worsening of pre-existing tics was not different between the two 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.[221] This same publication also reported on 2 open-label studies of MPH OROS, 1 of which was already included here,[202] the other is a report on a 9-month community-use study in children, adolescents, and adults, for which no reference is given (see table 15).

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

Table 15. Tic-related outcomes in observational studies

Study	Intervention Sample size Duration	Population	Tics
Children			
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/day 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/day 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/day N=24 1 year	ADHD	Motor tics: 1 (4%)

Seizures

The study that compared MPH (< 20 mg/day, 20.56 mg/day, and > 20 mg/day) to imipramine 65.4 mg/day and an untreated group (discussed earlier) also assessed seizures as an adverse event.[195] None of the 70 males with hyperactivity experienced a seizure over the one-year study period.

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 MPH prescriptions as a proxy for diagnosis using data in a Triplicate Prescription Program.[193] Injury frequencies in children prescribed MPH at least once between 1/1/1990 and 12/31/1996 (n=16,806) were compared to those in children not taking MPH (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 MPH than for those not taking MPH (OR 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 MPH. Since MPH was used simply as a proxy for behavioral disorders, the relationship between the drug and the increase in injuries is not necessarily clear.

Suicide

One before-after study followed 8 adult males (mean age of 27.2 years) that continued on open MPH for three to six months subsequent to participation in short-term clinical trials.[166] One participant (12.5%) attempted to commit suicide by consuming a month's supply of MPH.

In September 2005, FDA issued a public health advisory and a directive to update the product label with a black boxed warning regarding a potential association of atomoxetine and risk of suicidality in children and adolescents (http://www.fda.gov/bbs/topics/news/2005/new01237.html). This came after an FDA review of results from an unpublished meta-analysis of 12 placebo-controlled trials of children in which atomoxetine was associated with significantly higher risk of suicidal ideation than placebo: 0.37% (5/1357) vs. 0% (0/851); Maentel-Haenzel Incidence Difference 0.46, 95% CI 0.09, 0.83; p=0.016. Suicide attempts were slightly higher with atomoxetine; 0.07% (1/1357) vs. 0% (0/851).[222]

Cardiovascular adverse events

MPH OROS. An open-extension of a trial of MPH OROS reported small changes in blood pressure (3.3 mmHg systolic and 1.5 mmHg diastolic) and heart rate (3.9 bpm) over a one year study period.[223] 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.[216]

MAS XR. Four open-label extension studies of MAS XR, one each in children,[224, 225] adolescents,[226] and adults examined the cardiovascular effects over periods of 6 to 24 months.[227] 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 ECG measure were found in children in the short-term trial, 2% (11/568) had DBP > 90 mmHg, and 9% (50/568) had a SBP > 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 MAS XR for a period of up to 15 weeks.[225] The absolute numbers of patients with cardiovascular adverse events are not clearly reported. It is reported that 0.2% (7/2968) discontinued MAS 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 MAS XR.

Thirteen of 79 adolescent patients (16%) experienced adverse events during a 4-week study of MAS XR versus placebo that included cardiovascular symptoms such as syncope, tachycardia, and ECG abnormality.[226] 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.[227] Statistically significant, but not considered clinically meaningful, increases in SBP and DBP were seen at various points throughout the study (mean increase SBP 2.3 mmHg, DBP 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[197] and in adults.[228] 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.[197] The timing of ECG 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.[197] 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.[228]

     Post-marketing Surveillance Evidence. An analysis conducted by the Office of Drug Safety (ODS) in April 2004 evaluated reports of sudden death or serious cardiovascular events associated with use of amphetamine and methylphenidate products at usual dosages (http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4202B1_05_FDA-Tab05.pdf) received by the FDA Adverse Event Reporting System (AERS). ODS recently updated this analysis 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 16.

Table 16. Cardiovascular risk of ADHD drugs

	Amphetamine products		Methylphenidate products		Atomoxetine	
January 1, 1999 through December 31, 2003						
	Cases	**Per Million Rx's**	**Cases**	**Per Million Rx's**		
Children						
Sudden Death	12	0.36	7	0.16		
Serious CV Events	18	0.53	8	0.18		
Adults						
Sudden Death	5	0.53	1	0.07		
Serious CV 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

     The more recent findings were presented in meetings on February 9, 2006 for the Drug Safety and Risk Management Advisory Committee (DSaRM) and on March 22, 2006 for the Pediatric Advisory Committee. In both meetings there was consensus that it is not yet possible to determine causality, impact of pre-existing heart disease, and magnitude of risk due to limitations in the reliability of spontaneous report data. Reports indicate that the DSaRM called for adding a black box warning to ADHD drug product labels. The Pediatric Advisory

Committee agreed there was a need to supplement the labels with information about potential cardiovascular risks, but concluded that the available evidence does not yet warrant the seriousness level of a black box warning.

Hepatotoxicity

Atomoxetine. Two case reports (via the FDA MedWatch system) of hepatotoxicity in patients taking atomoxetine (one adult, one 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 two 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 two years of postmarketing experience. In one patient, liver injury, manifested by elevated hepatic enzymes [up to 40 X upper limit of normal (ULN) and jaundice (bilirubin up to 12 X ULN)], 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 (e.g., pruritus, dark urine, jaundice, right upper quadrant tenderness, or unexplained "flu-like" symptoms)."[229]

C. Evidence on the risk of 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 one 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.[230]

Direct evidence

We found only 1 poor quality study attempting to compare MPH OROS to other formulations of MPH.[231] This study used combinations of data from the Drug Abuse Warning Network (DAWN), DEA claims of theft or losses, and the FDA Adverse Event Warning System (AERS) to evaluate the risk of abuse or diversion with MPH OROS for 2000 (the year of its FDA approval) to 2002 or 2003. The authors find that MPH OROS has a lower risk of emergency room visits (DAWN), reports to the AERS, and theft or losses reported to the DEA compared to MPH 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 DAWN data do not

report product specific information, but the authors report small numbers of cases from DAWN where MPH 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,[232-240] but a clear conclusion has not yet been reached. The evidence is largely limited to longitudinal studies with healthy control groups assessing the relationship of treatment with a stimulant during childhood and later substance use in adolescence or adulthood. None of these studies is comparative in terms of the specific stimulant drugs used during treatment, with most reporting MPH IR 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 suffer 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. 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 (e.g. 'ever use' versus substance use disorder), and exposure to substances during childhood (e.g. 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 7 fully published studies,[134, 241-249] 3 of which have follow-up publications with additional analysis.[241-246, 249] Additional studies are cited by others, many of which are only published as abstracts, do not address stimulant use, or were not available to us.[250-256]

Below is a summary of the findings of these studies (Table 17). Four studies reporting follow-up during adolescence reported no association between substance abuse/dependence,[244, 248, 249, 257] and 2 found that the presence of conduct disorder was independently associated with substance use.[244, 257] Biederman in fact reported a reduction in the odds of any substance use disorder or alcohol abuse or dependence, and no impact on marijuana, hallucinogen, cocaine, or tobacco use. One of these studies did find an increased risk of tobacco use among those who had used stimulants to treat ADHD in childhood,[257] but the others did not. These studies had heterogeneous methods, including the definition of substance use.

Three studies reported on findings at early adulthood.[134, 245, 248] These studies report more conflicting results. The studies by Paternite and Fischer find that stimulant use was protective; Fischer found that stimulant use for ≥ 1 year resulted in lower rates of cocaine or hallucinogen abuse, and Paternite found that higher doses of MPH were associated with lower rates of alcohol abuse. Fischer found that conduct disorder was a significant variable increasing the risk of

abuse, and Paternite found that higher scores of aggression on ADHD scales was significantly related to substance abuse. In contrast, Lambert found significantly increased odds of tobacco, cocaine, and cocaine/amphetamine dependence among those who had used stimulants for ≥ 1 year (no impact on amphetamine alone, alcohol, or marijuana). While factors such as severity of ADHD and age of first cigarette were also associated with these outcomes, conduct disorder was not.

Table 17. Relationship of stimulant treatment for ADHD and later substance abuse and dependence

Study Details	Results of Longitudinal Studies
Follow-up During Adolescence	
Biederman, 1997, 2003, 2005 Children with ADHD and controls N = 212 f/u ≥ 15 yrs	Logistic regression controlling for age at f/u, socioeconomic status, conduct disorder, and parent substance use disorder resulted in significantly increased risk of any SUD (OR 6.3) or alcohol abuse or dependence (OR 5.8) among those with untreated ADHD compared to controls without ADHD. The model showed that those treated for ADHD had reduced risk of any SUD (OR 0.15) or alcohol abuse or dependence (OR 0.16) compared to those with ADHD and not treated. All other comparisons were NS (e.g. marijuana, hallucinogens, cocaine, tobacco). The comparison of ADHD treated to controls was not reported. Unclear if treatment was continued or stopped at time of study.
Burke, 2001 Boys with disruptive behavior disorders; N = 164 f/u = age 13-15 yrs	Childhood ADHD was predictive of tobacco use (OR 2.2; p< 0.05), but not other drugs of abuse. ADHD during adolescence was associated with both tobacco use (OR 2.3; P = 0.008) and alcohol use (OR 2.2; P = 0.02). All of these relationships became non-significant when conduct disorder comorbidity was controlled for. Bivariate analysis indicated stimulant use was significantly associated with tobacco use in adolescence (OR 2.19; P = 0.061), where a P-value of 0.1 was significant, but this variable was ultimately dropped from the final logistic regression model.
Chilcoat, 1999 Low and Normal Birth Weight children; N = 717 f/u = age 11	Had used drugs at least once: 28.8% ADHD vs. 16.6% No ADHD Relative Odds 1.7 (95% CI 1.1-2.7). Drug Use by Treated/Not Treated for ADHD: 31% vs. 28.2% (NS). Analysis controlling for severity of ADHD also showed no significant difference between treated/not treated groups.
Blouin, 1978 Hyperactive children N = 30 f/u age 13 yrs	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%.
Follow-up During Young Adulthood	
Peternite, 1999 Children treated with MPH IR for hyperactivity N = 121 f/u = 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. With age at diagnosis and childhood inattentive/ overactivity sores constant, higher scores on aggression were significantly correlated with later drug abuse disorder diagnosis (p<0.05).
Lambert, 1998, 2005 Children with ADHD; N = 399 f/u = early adulthood	Compared to those who had not used stimulants, stimulant use was associated with higher rates of tobacco dependence (P< 0.01) and cocaine dependence (P <0.01). Among those who had used substances by age 26, stimulant use was associated with higher rates of daily smoking of tobacco (P<0.001), and having used amphetamine > 20 times (P<0.05) compared to those who had not used stimulants. Multivariate analysis of substance use by age 26 resulted in statistically significant odds ratios for stimulant use of 1 yr or more (compared to less than 1 year) for tobacco (OR 1.9), cocaine (OR 2.3), and cocaine and/or amphetamine (OR 1.9) dependence (95% CI's not reported). No significant relationship was found for amphetamine alone. Other factors found significant in the model were severe ADHD, male gender, and first cigarette by age 11 or 13 for tobacco dependence, severe ADHD, first cigarette by age 13, and being in the older age group for cocaine, and severe ADHD and first cigarette by age 13 for cocaine and/or amphetamine dependence. In this model, conduct problems were *not* found to be significantly associated with any of the substances. Alcohol and marijuana use were not associated with stimulant use in any analysis.

Follow-up During Adolescence and Young Adulthood	
Fischer, 2003 Children with ADHD; N = 127 at 12-20 yrs; 147 at 19-25 yrs	74% had been treated with various stimulants in childhood, 5% still taking stimulants as young adults. **Teen f/u compared to Untreated controls:** Illicit stimulant use as teens: 6% treated, 10% untreated (NS). No difference found comparing treatment for > vs. < 1 year at teen f/u. **Young Adult f/u compared to Untreated controls:** No differences found in categorical (yes/no) or frequency variables after controlling for baseline symptoms. Conduct disorder significantly associated with cocaine abuse (OR 2.27, P<0.001). Those treated for < 1 year in childhood were more likely than those treated for > 1 year to have cocaine abuse (6% vs. 0%) and hallucinogen abuse (9% vs. 2%, p = 0.05). Stimulant use during high school ages was not significantly correlated with any substance use outcome. Conduct disorder again was the primary mitigating factor in the relationship between ADHD stimulant use and later cocaine abuse.

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.[258, 259] The logic behind this is that choice of one 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 MPH IR was chosen significantly more often than placebo (50% vs. 32.5%; p<0.001), but that perceived effectiveness ratings for patients who reliably chose MPH were also significantly greater than non-MPH choosers (4.8 vs. 3.2 points; p=0.04). Based on these findings, authors concluded that the higher MPH 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 MPH IR, the findings are not conclusive because the effectiveness data either showed no effect of MPH 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.

Diversion

We found a single study of the misuse or diversion of prescription stimulants.[260] This study used data collected as part of the National Survey on Drug Use and Health from 2000, 2001, and 2002. This study found that 34.7% had ever misused a prescription stimulant intended for use to treat ADHD. The most commonly misused stimulants in this survey were methylphenidate and dexamphetamine, with smaller numbers reporting use of other drugs, including MAS and MPH 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.

A study of the Texas Poison Control Network revealed that 8.5% (322 of 3789) of calls about human exposures to methylphenidate during 1998-2004 were cases of abuse.[261] The database did not record the formulation of MPH involved, although they report that the number of calls regarding MPH had reduced during 1998-2000, then increased during 2001-2004.

A questionnaire-based survey reported small numbers of teenagers who reported having taken higher than prescribed doses, purposefully mixing ADHD drugs with other substances, having lost a bottle of ADHD medications, etc.[262] Multiple ADHD medications had been used by the survey respondents, and these results do not provide insight into comparative risk for future substance abuse among users of ADHD drugs.

Key Question 3: Subgroups

A. Are there subgroups of patients based on demographics (age, racial groups, gender, and ethnicity), other medications, or co-morbidities 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 one poor-quality trial reported results of a subgroup analysis of Black children with ADHD.[263] 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 1,323 children that participated in the overall trial) found treatment outcomes to be similar to those for the overall study population.[263] 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).

MPH IR

MPH IR 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).[138, 191] MPH IR had a positive effect on 75% of efficacy measures. This response rate is similar to that seen in other placebo-controlled trials of MPH IR. MPH IR 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 MPH ER formulations (OROS and SODAS) than for those taking MPH IR regardless of ethnicity (White, Black, Hispanic).[43] This same data indicates that mean treatment durations overall (MPH OROS, SODAS, and IR) were significantly shorter for Black children (survival time ratio (STR) 0.77; 95% CI 0.73-0.80), Hispanic children (STR 0.81; 95% CI 0.78-0.84), and other ethnicities (STR 0.81; 95% CI 0.75-0.87) than for White children.

MPH OROS

A four-week, noncomparative trial evaluated the efficacy and tolerability of MPH OROS in 119 Korean children with ADHD.[264] 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 CGI-S. 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 MPH OROS' treatment effects in Korean children compare to those in children of different ethnic descent.

Lisdexamfetamine

Subgroup analyses of ethnic origin (Caucasian vs. Non-Caucasian) were performed using data from two double-blind, randomized controlled trials of lisdexamfetamine and results were reported in the CDER Medical Review.[189] In the one-week, crossover study (#201), average SKAMP-DS scores for lisdexamfetamine were similar to MAS XR and superior to placebo, regardless of ethnic origin. In the 4-week, parallel-group study (#301), mean changes in ADHD-RS-IV for lisdexamfetamine 30mg versus placebo appeared less robust for the subgroup of non-Caucasians (-18.5 vs. -10.1; p=0.0754) compared to the population overall (-21.8 vs. -6.2 points; p<0.0001). Treatment effects for the lisdexamfetamine 50mg and 70mg dosage groups also appeared less robust in non-Caucasians, but mean changes in the ADHD-RS-IV scores remained statistically significantly greater than placebo.

Atomoxetine

A placebo-controlled study of atomoxetine was undertaken in Taiwanese children with ADHD.[265] This study reported statistically significantly greater improvements on the ADHD-RS-IV scale with atomoxetine compared to placebo (-17.15 vs. -9.31; P <0.01). The mean change in score is slightly greater than those seen in trials of atomoxetine conducted in the US (-12.8 to -16.7 with atomoxetine compared to -5.0 to -7.0 for placebo). The most frequently reported adverse event was decreased appetite (36% vs. 17%; P = 0.002), followed by somnolence (22% vs. 9%, NS), and nausea (17% vs. 0; P <0.01).

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.

<u>Direct Comparisons</u>

Subgroup analyses based on gender were performed based on data from two double-blind, randomized controlled trials of lisdexamfetamine.[189] The average SKAMP-DS scores for lisdexamfetamine were similar to MAS XR and superior to placebo regardless of gender in the one-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-RS-IV lost statistical significance only in the 30mg treatment group (-19 vs. -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 MAS XR and atomoxetine, examined the effects in the 57 girls enrolled.[266] Similar to the overall study analysis, MAS 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.

<u>Indirect Comparisons</u>

We found 3 studies examining differences in response to stimulants (primarily MPH IR) between boys and girls.[47, 267, 268] Two found no differences between boys and girls,[47, 268] 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.[267] All three studies suffer from design and conduct flaws, including important differences between the groups at baseline and not accounted for in the analysis, comparison to historical controls, etc.

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.[269] These placebo-controlled trials are reported in full above. 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 versus girls.

Extremely limited adverse event data was provided in these studies, and no comparison between boys and girls can be made on these measures.

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 MPH IR, MAS IR, or MPH OROS.[74] 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.

ADHD subtypes

The potentially moderating effects of ADHD subtypes (inattentive, hyperactive/impulsive, or combined) in children have been examined in short-term placebo-controlled trials of atomoxetine,[128] MPH IR,[270, 271] and MPH OROS.[272] Results from all trials suggest that these drugs have superior efficacy relative to placebo in children with ADHD, regardless of diagnostic subtype.

One trial each of MPH IR (n=40)[270] and MPH OROS (n=47)[272] also 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 MPH IR or OROS (≥ 30mg/day) in children diagnosed with ADHD of the combined subtype or ADD with hyperactivity, whereas greater symptom improvements may occur at lower dosages (≤ 18 mg/day) in children with ADHD of the inattentive type or ADD without hyperactivity.

In the trial of MPH IR, conclusions about the dose-response relationship were based entirely on clinical judgment.[270] 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 MPH IR (10 mg/day), whereas children with ADD+hyperactivity were considerably more likely to receive a recommendation for the moderate or high doses (20-30 mg/day).

In the trial of MPH OROS, analyses were based on linear and higher-order dose-response curves.[272] In this trial, significant relationships between ADHD subtype and MPH OROS were detected for some, but not all, efficacy outcomes. When parent-ratings of the Inattention and Hyperactivity subscales from the ADHD-RS-IV were considered, it was noted that children with the combined type of ADHD had the greatest decreases in symptoms between the 36mg and 54mg dosages of MPH OROS, whereas children with the inattentive type of ADHD had the greatest decreases in symptoms between placebo and the 18mg dosages of MPH OROS. We recommend using caution when interpreting this finding, however, as differences in appearance between placebo and MPH 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 CGI scale-related ratings were considered.

Co-morbidity

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 35.2% (27.2, 43.8), conduct disorder 25.7% (12.8, 41.3), anxiety disorder 25.8% (17.6, 35.3), and depressive disorder 18.2% (11.1, 26.6).[60] The American Academy of Child and Adolescent Psychiatry estimate somewhat higher proportions; 54-84% with comorbid oppositional defiant disorder, 0-33% with depressive disorders, up to 33% with an anxiety disorder, and 25-35% with learning disabilities.[26] The co-morbidities considered here are oppositional defiant disorder, conduct disorder, learning disabilities, anxiety

disorders, depression, bipolar disorders, and tic disorders (see methods section for discussion of selection).

Oppositional Defiant Disorder (ODD)

The impact of comorbid oppositional defiant disorder on treatment of ADHD in children has been most widely studied for atomoxetine.[129, 273-275] Meta-analyses of data from two earlier[129] and three more recent[275] placebo-controlled trials of atomoxetine were respectively designed to evaluate the efficacy and adverse effects of atomoxetine in children with ADHD and comorbid ODD. Additionally, findings are available from post-hoc analyses of data from single placebo-controlled trials evaluating this same issue.[273, 274] Collectively, these studies consistently found that the presence of ODD does not impact the effectiveness of atomoxetine in treating children with ADHD.

In the meta-analyses that pooled outcomes from different subsets of children with coexisting ADHD and ODD, atomoxetine was consistently associated with significantly greater reductions in ADHD-RS Total Scores across two earlier (-17.0 vs. –7.5; $p<0.001$; n=98)[129] and three more recent placebo-controlled trials (-15.8 vs. -4.2; $p<0.001$; n=99).[275] Additionally, in the most recent meta-analysis (2007), children with ADHD and ODD taking atomoxetine demonstrated similar or greater improvements than placebo on all quality-of-life-related subscales of the Child Health Questionnaire (CHQ) except 'parental impact-emotional', 'parental impact-time', and 'self-esteem'.[275]

A few additional aspects of atomoxetine treatment in children with ADHD and ODD were evaluated in the post-hoc analyses of single placebo-controlled trials.[273, 274] In the first of these, main findings suggest that response to treatment of ADHD in children with comorbid ODD (n=113) may be related to dose.[273] In this post-hoc analysis, improvements in ADHD symptoms and QOL measures after 8 weeks were significantly greater for atomoxetine than placebo for the group of children with ODD taking 1.8 mg/kg, but not for the 1.2 mg/kg or 0.5 mg/kg groups.

The second post-hoc study involved data from a longer-term, 9-month, placebo-controlled trial.[274] The objective was to evaluate whether the presence of ODD influenced the risk of relapse during atomoxetine treatment, but the design seemed a little unusual.[274] In the primary trial, following 10 weeks of open atomoxetine treatment, 416 children with ADHD deemed "responders" were randomized to continue on double-blind atomoxetine or placebo.[128] The primary trial analyses focused on *between-treatment group* comparisons and the main result was that staying on atomoxetine significantly reduced the risk of relapse when compared to switching to placebo (RR 0.59; 95% CI 0.43, 0.80). Subsequently, findings from post-hoc, *within-groups* analyses suggested that risk of relapse in ADHD symptoms were not significantly altered in the presence of comorbid ODD either in children taking atomoxetine (RR 0.67; 95% CI 0.42, 1.06) or in children taking placebo (RR 1.27; 95% CI 0.81, 1.99). However, no subgroup analyses based on presence of ODD were reported for the comparisons between atomoxetine and placebo. Based on this indirect evidence, the authors were careful not to directly conclude that staying on atomoxetine was superior to switching to placebo, regardless of comorbid ODD. However, it seemed this was implied by a statement in the Discussion section that, "The finding is placed within the context of atomoxetine affording an overall protective effect against relapse in the sample compared to placebo."

The efficacy and adverse effects of MAS XR 10-40mg (Adderall® XR) has also been studied in 235 children with ADHD and ODD.[276] This was a 4-week, parallel-design, randomized, placebo-controlled trial that focused on ODD as the primary diagnosis, with only 79.2% of the original 308 children having comorbid ADHD. In the ODD+ADHD subgroup ITT population, improvements in ADHD symptoms were significantly greater for MAS XR compared to placebo on the parent- and teacher-rated ADHD subscale of the SNAP-IV for the 10mg, 30mg, and 40mg groups and on the clinician-rated CGI-I for ADHD for the 20mg, 30mg, and 40mg groups. Adverse event outcomes were not reported separately for the ODD+ADHD subgroup, but were typically higher for MAS XR compared to placebo for anorexia/decreased appetite, insomnia, headache, abdominal pain, and weight loss.

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. Although between-groups baseline characteristics were reportedly comparable at baseline for all 308 patients (mean age=10.6 years; 79.2% male), it is unclear if baseline characteristics were similar among the subgroup of 235 children with ODD and ADHD.

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 one study that examined whether children with and without learning disabilities benefit from MPH IR to the same extent when treated for ADHD.[277] This study was based on outcome data from 95 children with ADHD (85% male, mean age=9.2 years) who participated in a two-week, placebo-controlled, crossover trial of MPH IR BID 0.5 mg/kg. ADHD-related symptoms before and after MPH IR were primarily assessed based on the Restricted Academic Situation Scale (RASS), the Continuous Performance Task (CPT), 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 (CCR) scores (0=nonresponder, 1=mild response, 2=moderate response, 3=large response) to reflect overall degree of ADHD symptom control while taking MPH IR. Children with CCR scores of 0-1 were categorized as "nonresponders" and children with CCR scores of 2-3 were categorized as "responders." When compared to children without learning disabilities, the number of "responders" to MPH IR were significantly fewer in children with learning disabilities overall (75% vs. 55%; p=0.034) and when the disability was specific to mathematics (72% vs. 50%; p=0.034), but not when the disability was specific to reading (68% vs. 59%; p=NS).

Anxiety disorders

Children. Overall, 6 head-to-head trials and 10 PCT's reported symptoms of anxiety or nervousness as an adverse event and 1 head-to-head comparison and 1 PCT reported it as a symptom of ADHD. In the head-to-head comparisons (MPH IR vs. DEX, MAS, MPH SR, MPH

OROS, or atomoxetine), no statistically significant differences were found, although for some comparisons numerical differences were apparent.[65, 69, 70, 98, 100, 119, 278] For example, compared to MPH IR, rates were higher with atomoxetine (15.8% vs. 10% nervousness) and DEX (68% vs. 61%), but lower compared to Adderall® (10% vs. 5%) or MPH OROS (31.3% vs. 18.7% in one study, 12% vs. 13% in another). Placebo-controlled trial evidence is conflicting; some studies show higher rates of anxiety or nervousness with MPH, indicating a dose-dependent effect, while others show no increase over placebo rates.[53, 116, 117, 120, 125, 279-284] Reports of anxiety were similar between placebo and atomoxetine in 2 studies,[120, 125] and modafinil in 2 others.[116, 117] Because most of these studies are reporting 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 MPH IR and MPH SR in children with minimal brain dysfunction[65] or between MPH IR and placebo in children with ADHD and mental retardation.[283]

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.[285] In the intention to treat analysis, atomoxetine was superior to placebo in both improvements on ADHD symptoms and anxiety symptoms (-4.5 versus -2.4 points on the Pediatric Anxiety Rating Scale; P <0.010). This study had a high drop-out rate, 25% overall. 10% dropped out during a 2-week placebo run-in phase, and another 16% dropped out during the 10-week treatment phase. 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 one 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.[286] The main finding of these subanalyses was that compared to adults with "pure" ADHD (no comorbidities), adults with ADHD and Post-Traumatic Stress Disorder (PTSD) 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 [172] and are discussed under Key Question 1.

Additionally, numerous placebo-controlled trials examined whether treatment with ADHD drugs improves comorbid anxiety symptoms.[155, 162, 164-166, 168, 172, 173, 175, 177, 182] However, only MPH IR was consistently associated with improvements in anxiety symptoms in adults with ADHD.[156, 162, 168] Finally, in terms of adverse effects, only MPH OROS has been associated with significantly greater adverse anxiety effects in adults than placebo across two trials.[179, 180]

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-RS-IV -13.3 AMT, -5.1 placebo; P <0.001).[287] 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 one publication that reported findings from exploratory, post-hoc analyses using pooled data from two placebo-controlled trials of atomoxetine discussed above in the section on anxiety.[286] 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 NOS, consistently had greater improvements on atomoxetine compared to placebo across multiple rating scale scores. As noted previously, however, methodological weaknesses limit interpretation of these findings.

Bipolar Disorder

When added to divalproex, MAS (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).[288] 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.

"Psychiatric co-morbidities"

One placebo-controlled trial of atomoxetine[171] 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.[171] 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 MPH IR have examined these issues.[49, 85, 289-294] DEX IR and atomoxetine treatments for ADHD have also been studied in children with tic disorders.[85, 292, 294]

The majority of these trials were only 2-3 weeks in duration and involved very small numbers of children.[85, 289-291, 293] Children participating in these trials were mostly male (≥ 85%), with a mean age of 10.5 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 (YGTSS).

Overall, there was very little evidence across these trials to indicate that MPH IR, DEX IR, or atomoxetine were associated with any tic exacerbation effects. Paradoxically, in one 2-week trial of 34 children, only the lowest dose of MPH IR (0.1 mg/kg/day) was associated with any tic worsening, characterized by an increase in motor tics only in the classroom setting.[289, 291] In another 3-week trial of 12 children, only the higher dosages of MPH IR (0.67 mg/kg/day or 1.20 mg/kg/day) were associated with tic exacerbations.[85] Otherwise, compared to placebo, MPH IR, DEX IR, and atomoxetine were all consistently associated with improved tic severity in

these trials. Furthermore, children also showed greater improvements in ADHD symptoms with MPH IR, DEX IR, and atomoxetine compared to placebo. Observational evidence of the impact of MPH IR 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 MPH IR treatment follow-up periods.[194]

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?

Adolescents

A retrospective chart review of 450 teens treated at a substance abuse center in Canada from 1993-1999 examined the prevalence of abuse of MPH or DEX.[295] Twenty-three percent had ever used, and 6% were currently using MPH or DEX, most often reported to be used as crushed tablets taken intranasally. Further assessment of covariates indicated that higher rates of abuse of MPH/DEX 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 to 24% of non abusers (not statistically significant). An assessment of correlation of abuse of MPH/DEX 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 MPH IR[163, 183] and MPH SR[184, 185] focused only on patients with ADHD and comorbid substance abuse disorders. One trial of MPH IR involved a broader population of patients with any alcohol or drug dependence,[296] while the others focused on either patients with cocaine dependence[163, 185] or methadone-maintained patients.[184] None reported results of direct assessment of misuse or illicit diversion outcomes. As a potential proxy measure of abuse/diversion, three trials reported medication compliance.[163, 184, 185] Patient self-reported compliance rates were similar in treatment and placebo groups across all three trials (88.5% to 95%). Additionally, no differences were found between MPH and placebo in the proportions of riboflavin positive fluorescence (range 0.77 to 0.84).[184, 185]

The primary objectives of these trials were to investigate (1) whether use of MPH IR or 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 MPH IR or SR use may have on the course of the substance abuse disorder. Overall, although use of MPH IR or 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),[163, 184, 185] MPH IR or SR also did not appear to offer much of a benefit in the reduction of these patients' ADHD symptoms.[163, 183-185] In all but one of these trials, not only were there less robust treatment response rates in substance abusers with ADHD compared to non-substance abusers (34% - 47% vs. 38% - 78%), but the placebo response rates in the substance abuser trials were also substantially greater (ranges 21% to 55% vs. 4% to 16%).[183-185] Trial authors noted

several possible factors that may have led to these abnormally negative findings, including that MPH 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.

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 co-morbid conditions are not well addressed by the studies. In large part, the failure to address either subtypes or co-morbidities 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.

OVERALL SUMMARY

Key Questions are summarized in Table 18, below.

Table 18. Overall table summary

Key Question 1: Benefits	Quality of Evidence	Conclusion
General		
Effectiveness	Poor, no trials found	No conclusions about comparative effectiveness of different pharmacotherapies for ADHD can be made.
Young children		
Efficacy	Overall: Poor	
	MPH IR	MPH IR was superior to placebo on CPRS-R efficacy outcomes.
Children		
Efficacy	Overall: Fair (individual ratings below)	
Stimulants		
IR vs. SR formulations	MPH IR vs. MPH SR (fair)	Studies of MPH IR versus 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 XR (Ritalin LA®) was superior to MPH OROS (Concerta®) on some, but not all efficacy outcomes. However, these results should be interpreted with caution until higher quality evidence is available. Limited evidence suggests that Metadate CD® was superior to Concerta® on outcomes in the morning; they had similar effects in the afternoon; and Concerta® was superior in the evening.
IR vs. IR	DEX vs. MPH IR (good)	The body of evidence clearly indicates no difference in efficacy between DEX and MPH IR.
	MAS vs. MPH IR (fair)	MAS was superior to MPH IR on a few efficacy outcome measures in two trials, but clear evidence of superiority is lacking.
	DEX IR vs. DEX ER vs. MAS (poor)	Evidence on the comparison of DEX IR versus SR versus 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 (poor)	Very limited evidence from placebo-controlled trials suggests modafinil is superior to placebo on most efficacy measures.
	Dexmethylphenidate (NA)	Only incomplete evidence was found.
Lisdexamfetamine	Fair	Lisdexamfetamine was comparable to MAS XR on average SKAMP-DS scores and superior to placebo on same, as well as on ADHD-RS-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 SR is superior to atomoxetine on most efficacy measures.
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.
Indirect comparisons	Atomoxetine, DEX IR, d-MPH XR, MPH IR, MPH SR, MPH OROS, MAS IR: Fair	All were found to be effective short-term treatments for reducing ADHD symptoms in placebo-controlled trials. MPH IR showed some benefit in reducing ADHD-associated anxiety symptoms and cognitive deficits and in improving driving safety. Atomoxetine showed some benefit in improving quality of life in an uncontrolled trial.
	MAS XR: Poor	One placebo-controlled trial rated poor quality. Preliminary evidence from open trial of MAS XR suggests benefits in quality of life.
	Dexmethylphenidate IR, lisdexamfetamine, methamphetamine, MPH transdermal patch, MPH chewable tablet or oral solution, and some extended release forms of MPH (Metadate CD®, Metadate ER®, Ritalin LA®, and Biphentin®): Poor	No evidence.

Key Question 2: Safety	Quality of Evidence	Conclusion
A. Short-term Trial Evidence		
Young children	Poor – 1 placebo-controlled trial of MPH	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.
	Comparisons to atomoxetine	Atomoxetine caused more vomiting and somnolence than MPH IR and MAS XR. MPH IR caused more 'abnormal thinking'. MAS XR caused more insomnia.
	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.
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.

B. Long-Term Safety – Observational Studies		
Mixed populations, primarily children	Fair	
	Height	• DEX vs. MPH IR: Mixed findings. DEX=MPH in 6-year height increases in one study; DEX>MPH in 2-year height decreases in the other. • MPH IR vs. unmedicated controls: No significant differences in two studies. • MPH IR in uncontrolled studies: Inconsistent effects across four 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 (one 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 attempted suicide	No comparative evidence.
	Drugs with warnings or removal from market	Adderall XR®: reports of sudden death in children - withdrawn from market in Canada, not US. Atomoxetine: reports of hepatotoxicity led to additional warnings in product label.
C. Abuse/diversion		
Children		
Adults	Poor	Higher preference of MPH IR over placebo more likely reflected efficacy rather than abuse potential in 10 adults with ADHD.
Key Question 3: Subgroups	**Quality of Evidence**	**Conclusion**
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
	Race / Ethnicity	Most trials conducted in primarily White populations. Ethnicity/race only reported in 1/2 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.
	Age	Evidence in adolescents is very limited. The mean age of children in the trials is 8 to 10 years.
	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.
	Common Co-morbidities	Rates on commonly occurring comorbidities reported in only ½ 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 AAP 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.
	Mental Retardation	MPH IR is beneficial on most ADHD outcomes compared to placebo. Adverse events include staring and social withdrawal. Adverse events include drowsiness and blood pressure lowering.
	Autism	Very limited evidence suggests that atomoxetine and MPH IR are beneficial on most ADHD outcomes compared to placebo.
	Epilepsy	Very limited evidence suggests that MPH IR is beneficial on most ADHD outcomes 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 (Adderall®) is benefit on most ADHD outcomes compared to placebo.
Adults	Poor	
Demographics	Age, gender, race	No conclusions about comparative efficacy or safety in demographic subgroups of adults can be made.
Comorbidities	Emotional dysregulation	Atomoxetine was superior to placebo on all measures of ADHD symptom improvement regardless of the presence of ED. ADHD symptom improvements were less robust for MPH OROS in patients with comorbid emotional dysregulation.
	Substance abuse disorders	No trials reported results of direct assessment of misuse or illicit diversion outcomes. Evidence did not clearly support the use of MPH IR or SR in substance abusers with ADHD.

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Appendix A. 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 U.S. 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]

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. [7]

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. [8]

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 .30 to .71 (median=.60). [9, 10]

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. [11]

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. [12] 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. [13]

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. [14]

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.[15]

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=.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.[16]

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.[17]

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 seven (extremely severe). But unfortunately, we can't find any information about the reliability and validity of the scale.[18]

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.[19-23]

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 seven-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.[24] 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.

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 .87 in the hyperactive factor that demonstrated the ASQ-T's ability to identify children's hyperactive behaviors.[25] 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.[25]

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.[26]

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.[27]

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).[19]

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).[25]

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.[19] 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). [25]

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.[28]

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.[29]

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".[30]

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".[31]

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.[32]

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. [33]

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).[34]

"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.[35]

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.[36]

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.[37] The differential validity of IO and A factors had been tested as well.[38]

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.[39]

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.[40]

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 seven 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 seven 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.[41] 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.[42]

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.[43]

Physician's Global Rating Scale is a seven-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.[44]

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. [44]

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.[45-47]

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 six 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.[48, 49]

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. [45, 50]

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. [51, 52]

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. [53]

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. [54]

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 eight 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.[55, 56]

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.[27]

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. [57] 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.[58] SKAMP comprises of two subscales (deportment [SKAMPDS] and attention [SKAMP-AS]).[42]

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.[59]

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).[60]

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 [61]. The test-retest reliability was proved with Cronbach alpha ranged from .69 to .90. The validity was demonstrates as well with factor analysis.[62, 63]

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.[64]

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 [65] 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.[66]

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. [40]

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Appendix B. Search strategies

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2005>
Search Strategy:
----
1   Methylphenidate.mp.
2   concerta.mp.
3   metadate.mp.
4   methylin.mp.
5   ritalin.mp.
6   dexmethylphenidate.mp.
7   focalin.mp.
8   pemoline.mp.
9   cylert.mp.
10   amphetamine$.mp.
11   adderall.mp. (21)
12   dextroamphetamine.mp.
13   Dexedrine.mp.
14   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
15   Atomoxetine.mp.
16   Strattera.mp.
17   wellbutrin.mp.
18   bupropion.mp.
19   modafinil.mp.
20   provigil.mp.
21   clonidine.mp.
22   catapres.mp.
23   guanfacine.mp.
24   tenex.mp.
25   aripiprazole.mp.
26   clozapine.mp.
27   clozaril.mp.
28   olanzapine.mp.
29   zyprexa.mp.
30   quetiapine.mp.
31   seroquel.mp.
32   risperidone.mp.
33   risperdal.mp.
34   ziprasidone.mp.
35   geodon.mp.
36   15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
or 31 or 32 or 33 or 34 or 35
37   Attention Deficit Disorder with Hyperactivity/
38   attention deficit disorder/
39   attention deficit.mp.
40   adhd.mp.

41   37 or 38 or 39 or 40
42   14 or 36
43   41 and 42
44   from 43 keep 1-524

Database: Ovid MEDLINE(R) <1966 to October Week 1 2005>
Search Strategy:
----
1   Methylphenidate.mp.
2   concerta.mp.
3   metadate.mp.
4   methylin.mp.
5   ritalin.mp.
6   dexmethylphenidate.mp.
7   focalin.mp.
8   pemoline.mp.
9   cylert.mp.
10   amphetamine$.mp.
11   adderall.mp.
12   dextroamphetamine.mp.
13   Dexedrine.mp.
14   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
15   Atomoxetine.mp.
16   Strattera.mp.
17   wellbutrin.mp.
18   bupropion.mp.
19   modafinil.mp.
20   provigil.mp.
21   clonidine.mp.
22   catapres.mp.
23   guanfacine.mp.
24   tenex.mp.
25   aripiprazole.mp.
26   clozapine.mp.
27   clozaril.mp.
28   olanzapine.mp.
29   zyprexa.mp.
30   quetiapine.mp.
31   seroquel.mp.
32   risperidone.mp.
33   risperdal.mp.
34   ziprasidone.mp.
35   geodon.mp.

36   15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
or 31 or 32 or 33 or 34 or 35
37   Attention Deficit Disorder with Hyperactivity/
38   attention deficit.mp.
39   adhd.mp.
40   37 or 38 or 39
41   14 or 36
42   40 and 41
43   limit 42 to (controlled clinical trial or meta analysis or randomized controlled trial) (429)
44   (systemat$ adj5 review$).mp.
45   Randomized Controlled Trials/
46   cohort$.mp.
47   44 or 45 or 46
48   42 and 47
49   43 or 48
50   adverse effect$.mp. or ae.fs.
51   poisoning.mp. or po.fs.
52   toxicity.mp. or to.fs.
53   50 or 51 or 52
54   41 and 53
55   limit 54 to (controlled clinical trial or meta analysis or randomized controlled trial)
56   47 and 54
57   55 or 56
58   49 or 57
59   limit 58 to human
60   limit 59 to english language
61   limit 59 to abstracts
62   60 or 61
63   from 62 keep 1-1630

- -

Database: PsycINFO <1974 to September Week 4 2005>
Search Strategy:
----
1   Methylphenidate.mp.
2   concerta.mp.
3   metadate.mp.
4   methylin.mp.
5   ritalin.mp.
6   dexmethylphenidate.mp.
7   focalin.mp.
8   pemoline.mp.
9   cylert.mp.
10   amphetamine$.mp.
11   adderall.mp.
12   dextroamphetamine.mp.

13   Dexedrine.mp.
14   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
15   Atomoxetine.mp.
16   Strattera.mp.
17   wellbutrin.mp.
18   bupropion.mp.
19   modafinil.mp.
20   provigil.mp.
21   clonidine.mp.
22   catapres.mp.
23   guanfacine.mp.
24   tenex.mp.
25   aripiprazole.mp.
26   clozapine.mp.
27   clozaril.mp.
28   olanzapine.mp.
29   zyprexa.mp.
30   quetiapine.mp.
31   seroquel.mp.
32   risperidone.mp.
33   risperdal.mp.
34   ziprasidone.mp.
35   geodon.mp.
36   15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
or 31 or 32 or 33 or 34 or 35
37   Attention Deficit Disorder with Hyperactivity/
38   attention deficit.mp.
39   adhd.mp.
40   37 or 38 or 39
41   14 or 36
42   40 and 41
43   ((systemat$ adj5 review$) or meta-analysis).mp.
44   (random$ or double blind$ or placebo$).mp.
45   controlled clinical trial$.mp.
46   cohort$.mp.
47   43 or 44 or 46
48   42 and 47
49   exp "Side Effects (Drug)"/ or exp Drug Interactions/ or adverse effect$.mp.
50   36 and 47 and 49
51   48 or 50
52   limit 51 to english language
53   51 not 52
54   limit 53 to abstracts
55   52 or 54
56   from 55 keep 1-740

Embase

(((('methylphenidate'/exp OR 'concerta'/exp OR metadata OR methylin OR 'ritalin'/exp OR 'dexmethylphenidate'/exp OR 'focalin'/exp OR 'pemoline'/exp OR 'cylert'/exp OR amphetamine$ OR 'adderall'/exp OR 'dextroamphetamine'/exp OR 'dexedrine'/exp AND [embase]/lim) OR ('atomoxetine'/exp OR 'strattera'/exp OR 'wellbutrin'/exp OR 'bupropion'/exp OR 'modafinil'/exp OR 'provigil'/exp OR 'clonidine'/exp OR 'catapres'/exp OR 'guanfacine'/exp OR 'tenex'/exp OR 'aripiprazole'/exp OR 'clozapine'/exp OR 'clozaril'/exp OR 'olanzapine'/exp OR 'zyprexa'/exp OR 'quetiapine'/exp OR 'seroquel'/exp OR 'risperidone'/exp OR 'risperdal'/exp OR 'ziprasidone'/exp OR 'geodon'/exp AND [embase]/lim))
AND
('attention deficit disorder'/exp OR adhd OR 'attention deficit'/exp AND [embase]/lim))
AND
([meta analysis]/lim OR [randomized controlled trial]/lim)
AND
[embase]/lim

Update# 2 Search Strategies

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <1st Quarter 2007>
Search Strategy:
----
1   exp Amphetamine/ or "amphetamine$".mp. (943)
2   adderall.mp. (40)
3   atomoxetine.mp. (55)
4   strattera.mp. (4)
5   dexmethylphenidate.mp. (5)
6   focalin.mp. (4)
7   dextroamphetamine.mp. or exp Dextroamphetamine/ (443)
8   dexedrine.mp. (14)
9   dextrostat.mp. (0)
10   methylphenidate.mp. or exp Methylphenidate/ (949)
11   concerta.mp. (21)
12   metadate.mp. (6)
13   methylin.mp. (0)
14   ritalin.mp. (87)
15   modafinil.mp. (152)
16   provigil.mp. (3)
17   1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (1986)
18   Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (826)
19   Attention Deficit Disorder.mp. (919)
20   attention deficit$.mp. (1077)
21   adhd.mp. (647)
22   18 or 19 or 20 or 21 (1190)
23   17 and 22 (710)
24   limit 23 to yr="2005 - 2006" (99)
25   from 24 keep 1-99 (99)

- -

Database: EBM Reviews - Cochrane Database of Systematic Reviews <1st Quarter 2007>
Search Strategy:
----
1   exp Amphetamine/ or "amphetamine$".mp. (39)
2   adderall.mp. (0)
3   atomoxetine.mp. (2)
4   strattera.mp. (0)
5   dexmethylphenidate.mp. (0)
6   focalin.mp. (0)
7   dextroamphetamine.mp. or exp Dextroamphetamine/ (12)
8   dexedrine.mp. (0)
9   dextrostat.mp. (0)
10   methylphenidate.mp. or exp Methylphenidate/ (21)

11   concerta.mp. (0)
12   metadate.mp. (0)
13   methylin.mp. (0)
14   ritalin.mp. (1)
15   modafinil.mp. (5)
16   provigil.mp. (2)
17   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 (57)
18   Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with
Hyperactivity/ (2)
19   Attention Deficit Disorder.mp. (7)
20   attention deficit$.mp. (30)
21   adhd.mp. (15)
22   18 or 19 or 20 or 21 (32)
23   17 and 22 (11)
24   from 23 keep 1-11 (11)

Database: Ovid MEDLINE(R) <1996 to March Week 3 2007>
Search Strategy:
----
1   exp Amphetamine/ or "amphetamine$".mp. (7430)
2   adderall.mp. (82)
3   atomoxetine.mp. (287)
4   strattera.mp. (24)
5   dexmethylphenidate.mp. (20)
6   focalin.mp. (9)
7   dextroamphetamine.mp. or exp Dextroamphetamine/ (981)
8   dexedrine.mp. (20)
9   dextrostat.mp. (0)
10   methylphenidate.mp. or exp Methylphenidate/ (1876)
11   concerta.mp. (40)
12   metadate.mp. (15)
13   methylin.mp. (1)
14   ritalin.mp. (202)
15   modafinil.mp. (423)
16   provigil.mp. (17)
17   1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (9500)
18   Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with
Hyperactivity/ (6817)
19   Attention Deficit Disorder.mp. (6936)
20   attention deficit$.mp. (8651)
21   adhd.mp. (4597)
22   18 or 19 or 20 or 21 (8795)
23   17 and 22 (1594)
24   (20051$ or 2006$ or 2007$).ed. (933372)

25   23 and 24 (405)
26   limit 25 to (humans and english language) (337)
27   limit 26 to (humans and english language and (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")) (213)
28   from 27 keep 1-213 (213)

- -

Database: PsycINFO <1985 to March Week 4 2007>
Search Strategy:
----
1   exp Amphetamine/ or "amphetamine$".mp. (6021)
2   adderall.mp. (61)
3   atomoxetine.mp. (145)
4   strattera.mp. (13)
5   dexmethylphenidate.mp. (11)
6   focalin.mp. (10)
7   dextroamphetamine.mp. or exp Dextroamphetamine/ (936)
8   dexedrine.mp. (26)
9   dextrostat.mp. (0)
10   methylphenidate.mp. or exp Methylphenidate/ (1788)
11   concerta.mp. (23)
12   metadate.mp. (4)
13   methylin.mp. (1)
14   ritalin.mp. (236)
15   modafinil.mp. (230)
16   provigil.mp. (7)
17   1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (7912)
18   Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (5136)
19   Attention Deficit Disorder.mp. (9813)
20   attention deficit$.mp. (12197)
21   adhd.mp. (8242)
22   18 or 19 or 20 or 21 (12539)
23   17 and 22 (1434)
24   limit 23 to (human and english language and yr="2005 - 2007") (293)
25   limit 24 to (human and english language and english and human and yr="2005 - 2007") (293)
26   from 25 keep 1-293 (293)

Appendix C. Quality assessment methods for drug class reviews for the Drug Effectiveness Review Project

Study quality is objectively assessed using predetermined criteria for internal validity, based on the combination of the US Preventive Services Task Force and the NNS Center for Reviews and Dissemination (Anonymous 2001; Harris, Helfand et al. 2001) criteria.

All studies regardless of design, that are included are assessed for quality, and assigned a rating of "good", "fair" or "poor". Studies that have a fatal flow are rated poor quality. A fatal flow is reflected in failing to meet combinations of criteria which may be related in indicating the presence of bias. An example would be failure or inadequate procedures for randomization and/or allocation concealment combined with important differences in prognostic factors at baseline. Studies which meet all criteria are rated good quality and the remainder is rated fair quality. As the "fair" quality category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair quality studies are likely to be valid, while others are only 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.

Systematic Reviews:

1. Is there a clear review question and inclusion/exclusion criteria reported relating to the primary studies?

A good quality review should focus on a well-defined question or set of questions, which ideally will refer to the inclusion/exclusion criteria by which decisions are made on whether to include or exclude primary studies. The criteria should relate to the four components of study design, indications (patient populations), interventions (drugs), and outcomes of interest. In addition, details should be reported relating to the process of decision-making, i.e., 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 search for all relevant research?

This is usually the case if details of electronic database searches and other identification strategies are given. Ideally, details of the search terms used, date and language restrictions should be presented. In addition, descriptions of hand-searching, attempts to identify unpublished material, and any contact with authors, industry, and research institutes should be provided. The appropriateness of the database(s) searched by the authors should also be considered, e.g. if MEDLINE is searched for a review looking at health education, then it is unlikely that all relevant studies will have been located.

3. Is the validity of included studies adequately assessed?

A systematic assessment of the quality of primary studies should include an explanation of the criteria used (e.g., method of randomization, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis). Authors may use either a published checklist or scale, or one that they have designed specifically for their review. Again, the process relating to the assessment should be explained (i.e. how many reviewers involved,

whether the assessment was independent, and how discrepancies between reviewers were resolved).

4. Is sufficient detail of the individual studies presented?

The review should demonstrate that the studies included are suitable to answer the question posed and that a judgement on the appropriateness of the authors' conclusions can be made. If a paper includes a table giving information on the design and results of the individual studies, or includes a narrative description of the studies within the text, this criterion is usually fulfilled. If relevant, the tables or text should include information on study design, sample size in each study group, patient characteristics, description of 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 (e.g., according to sample size, or inverse of the variance) so that studies that are considered to provide the most reliable data have greater impact on the summary statistic.

Controlled Trials:

<u>Assessment of Internal Validity</u>

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 numbers, birth dates or week days
      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
            Other approaches sequence to clinicians and patients
      Inferior approaches to concealment of randomization:
            Use of alternation, case record numbers, birth dates or week days

> 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 the 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 (i.e., 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 followup or overall high loss to followup? (Give numbers in each group)

Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom the intervention would be applied?

2. How many patients were recruited?

3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

4. What was the funding source and role of funder in the study?

5. Did the control group receive the standard of care?

6. What was the length of followup? (Give numbers at each stage of attrition.)

Non-randomized studies
Assessment of Internal Validity

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

2. Is there important differential loss to followup or overall high loss to followup? (Give numbers in 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 non-biased and accurate ascertainment of events (independent ascertainers; validation of ascertainment technique)?

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

7. Did the duration of followup correlate to reasonable timing for investigated events? (Does it meet the stated threshold?)

Assessment of External Validity

1. Was the description of the population adequate?

2. How similar is the population to the population to whom the intervention would be applied?

3. How many patients were recruited?

4. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

5. What was the funding source and role of funder in the study?

References:
Anonymous (2001). Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews CRD Report Number 4 (2nd edition). York, UK, NHS Centre for Reviews and Dissemination.

Harris, R. P., M. Helfand, et al. (2001). "Current methods of the third U.S. Preventive Services Task Force." American Journal of Preventive Medicine **20**(3S): 21-35.

Appendix D. Excluded Studies - Update 2

1.   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.   Epstein JN, Conners CK, Hervey AS, et al. Assessing medication effects in the MTA study using neuropsychological outcomes.[see comment]. *Journal of Child Psychology & Psychiatry & Allied Disciplines.* May 2006;47(5):446-456.

3.   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.

4.   McGough JJ, McBurnett K, Bukstein O, et al. Once-daily OROS methylphenidate is safe and well tolerated in adolescents with attention-deficit/hyperactivity disorder. *Journal of Child & Adolescent Psychopharmacology.* Jun 2006;16(3):351-356.

5.   Hoare P, Remschmidt H, Medori R, et al. 12-month efficacy and safety of OROS MPH in children and adolescents with attention-deficit/hyperactivity disorder switched from MPH. *European Child & Adolescent Psychiatry.* Sep 2005;14(6):305-309.

6.   Fallu A, Richard C, Prinzo R, Binder C. Does OROS-methylphenidate improve core symptoms and deficits in executive function? Results of an open-label trial in adults with attention deficit hyperactivity disorder. *Current Medical Research & Opinion.* Dec 2006;22(12):2557-2566.

7.   Collins SL, Levin FR, Foltin RW, Kleber HD, Evans SM. Response to cocaine, alone and in combination with methylphenidate, in cocaine abusers with ADHD. *Drug & Alcohol Dependence.* Apr 28 2006;82(2):158-167.

8.   Barbaresi WJ, Katusic SK, Colligan RC, Weaver AL, Leibson CL, Jacobsen SJ. Long-term stimulant medication treatment of attention-deficit/hyperactivity disorder: results from a population-based study. *Journal of Developmental & Behavioral Pediatrics.* Feb 2006;27(1):1-10.

9.   Ambrosini PJ, Sallee FR, Lopez FA, Shi L, Michaels MA, Group LCS. A community assessment, open-label study of the safety, tolerability, and effectiveness of mixed amphetamine salts extended release in school-age children with ADHD. *Current Medical Research & Opinion.* Feb 2006;22(2):427-440.

10.   Adler L, Dietrich A, Reimherr FW, et al. Safety and tolerability of once versus twice daily atomoxetine in adults with ADHD. *Annals of Clinical Psychiatry.* Apr-Jun 2006;18(2):107-113.

11.   Hazel-Fernandez LA, Klorman R, Wallace JM, Cook S. Methylphenidate improves aspects of executive function in African American children with ADHD. *Journal of Attention Disorders.* May 2006;9(4):582-589.

12.   Grizenko N, Kovacina B, Amor LB, Schwartz G, Ter-Stepanian M, Joober R. Relationship between response to methylphenidate treatment in children with ADHD and psychopathology in their families. *Journal of the American Academy of Child & Adolescent Psychiatry.* Jan 2006;45(1):47-53.

13.   Aharonovich E, Garawi F, Bisaga A, et al. Concurrent Cannabis Use During Treatment for Comorbid ADHD and Cocaine Dependence: Effects on Outcome. *American Journal*

of Drug and Alcohol Abuse. 2006;32(4):629-635.

14.   Santosh P, Baird G, Pityaratstian N, Tavare E, Gringras P. Impact of comorbid autism spectrum disorders on stimulant response in children with attention deficit hyperactivity disorder: A retrospective and prospective effectiveness study. *Child: Care, Health and Development.* Sep 2006;32(5):575-583.

15.   Gimpel GA, Collett BR, Veeder MA, et al. Effects of stimulant medication on cognitive performance of children with ADHD. *Clinical Pediatrics.* Jun 2005;44(5):405-411.

16.   Samuels JA, Franco K, Wan F, Sorof JM. Effect of stimulants on 24-h ambulatory blood pressure in children with ADHD: a double-blind, randomized, cross-over trial. *Pediatric Nephrology.* Jan 2006;21(1):92-95.

17.   Jain U, Hechtman L, Weiss M, et al. Efficacy of a novel biphasic controlled-release methylphenidate formula in adults with attention-deficit/hyperactivity disorder: results of a double-blind, placebo-controlled crossover study. *Journal of Clinical Psychiatry.* Feb 2007;68(2):268-277.

18.   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.

19.   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.

20.   Troost PW, Steenhuis M-P, Tuynman-Qua HG, et al. Atomoxetine for Attention-Deficit/Hyperactivity Disorder Symptoms in Children with Pervasive Developmental Disorders: A Pilot Study. *Journal of Child and Adolescent Psychopharmacology.* Oct 2006;16(5):611-619.

21.   Posey DJ, Wiegand RE, Wilkerson J, Maynard M, Stigler KA, McDougle CJ. Open-Label Atomoxetine for Attention-Deficit/Hyperactivity Disorder Symptoms Associated with High-Functioning Pervasive Developmental Disorders. *Journal of Child and Adolescent Psychopharmacology.* Oct 2006;16(5):599-610.

22.   Gonzalez-Heydrich J, Whitney J, Hsin O, al e. Efficacy of OROS MPH for Treatment of ADHD Plus Epilepsy. *The 53rd Annual Meeting of the American Academy of Child and Adolescent Psychiatry.* October 25, 2006.

23.   Flapper BC, Houwen S, Schoemaker MM. Fine motor skills and effects of methylphenidate in children with attention-deficit-hyperactivity disorder and developmental coordination disorder. *Developmental Medicine & Child Neurology.* Mar 2006;48(3):165-169.

24.   Connor DF, Spencer TJ. Short-Term Cardiovascular Effects of Mixed Amphetamine Salts Extended Release in Children and Adolescents With Oppositional Defiant Disorder. *Cns Spectrums.* Oct 2005;10(10,Suppl15):31-38.

25.   Mannuzza S, Klein RG, Moulton JL, 3rd. Does stimulant treatment place children at risk for adult substance abuse? A controlled, prospective follow-up study. *Journal of Child & Adolescent Psychopharmacology.* 2003;13(3):273-282.

26.   Mick E, Spencer T, Surman C, Hammerness P, Doyle R, Biederman J. Randomized single blind substitution study of OROS Methylphenidate (Concerta) in adults receiving immediate release methylphenidate. Paper presented at: The 160th Annual Meeting of the

American Psychiatric Association, 2007; San Diego, CA.

27.   Zhang HF, Kemner JE, Starr HL, al. e. OROS MPH Treatment Effects Between Girls and
       Boys with ADHD. *58th Institute on Psychiatric Services.* October 5-8, 2006.

28.   Tamayo JM, Pumariega A, Durell TM, Williams DW. Efficacy and safety of atomoxetine
       in Latino versus Caucasian pediatric outpatients with ADHD: A combined analysis of 2
       acute open label studies. *The 53rd Annual Meeting of the American Academy of Child
       and Adolescent Psychiatry.* 2006.

29.   Sumner C, Wietecha L, Williams DW, et al. Atomoxetine for children and adolescents
       with ADHD and reading disorders. Paper presented at: The 53rd Annual Meeting of the
       American Academy of Child and Adolescent Psychiatry, 2006; San Diego, CA.

30.   Kooij JJ, Medori R, Buitelaar R, Ramos-Quiroga JA, Emma L, Casas M. Open-Label
       extension trial of the safety and tolerability of OROS methylphenidate in adults with
       ADHD-the long acting methylphenidate in adult ADHD (LAMDA) trial. Paper presented
       at: The 160th Annual Meeting of the American Psychiatric Association, 2007; San Diego,
       CA.

31.   Ciccone P, Starr H, Coleman JJ, Mrazik T, DuPont R, Bensinger PB. OROS MPH: A
       Methylphenidate formulation with a low potential for abuse. Paper presented at: 160th
       Annual Meeting of the American Psychiatric Association, 2007; San Diego, CA.

32.   Wilens TE, Spencer TJ, Biederman J, Weisler RH, Read SC, Partiot A. Mixed
       Amphetamine Salts XR: Cardiovascular Safety in Adolescents With ADHD. *158th
       Annual Meeting of the American Psychiatric Association.* 2005.

33.   Wilens TE, Adler LA, Weiss MD, et al. Atomoxetine treatment of adults with ADHD and
       comorbid alcohol abuse. Paper presented at: The 160th Annual Meeting of the American
       Psychiatric Association, 2007; San Diego, CA.

34.   Swanson JM, Boellner S, Rugino T, Sangal RB, Wigal SB. Pediatric formulation of
       modafinil effective in children and adolescents with ADHD. *158th Annual Meeting of the
       American Psychiatric Association.* 2005.

35.   Sutton V, Kelsey D, Lewis D, Schuh K, Sumner C, Quintana H. Morning-Dosed
       VERSUS Evening-Dosed Atomoxetine for Treating ADHD in Children. *158th Annual
       Meeting of the American Psychiatric Association.* 2005.

36.   Parasrampuria D, Schoedel K, Schuller R, et al. A double blind placebo controlled
       randomized crossover study to assess the pharmacokinetics and pharmacodynamics of
       abuse potential for OROS methylphenidate versus immediate release methylphenidate.
       Paper presented at: The 160th Annual Meeting of the American Psychiatric Association,
       2007; San Diego, CA.

37.   Medori R, Kooij JJ, Ramos-Quiroga JA, Buitelaar J, Lee E, Casas M. Efficacy and safety
       of OROS methylphenidate in Adults with ADHD-the long acting methylphenidate in
       adult ADHD (LMDA) trial. Paper presented at: The 160th Annual Meeting of the
       American Psychiatric Association, 2007; San Diego, CA.

38.   Kelsey DK, Sutton V, Lewis D, Schuh K, Sumner C, Quintana H. Morning-VERSUS
       Evening-Dosed Atomoxetine: Effects on Core ADHD Symptoms. *158th Annual Meeting
       of the American Psychiatric Association.* 2005.

39.   Greenhill LL, Wigal SB, Kratochvil C, Boellner S. ADHD symptoms and behavior
       improved with modafinil pediatric formulation. *158th Annual Meeting of the American
       Psychiatric Association.* 2005.

40.   Biederman J, Wilens TE, Lopez FA. Modafinil pediatric formulation has early and

sustained effect in ADHD. *158th Annual Meeting of the American Psychiatric Association.* 2005.

41.   Biederman J, Mick E, Surman C, et al. Impact of psychiatric comorbidity and concomitant use of antidepressants on the efficacy of OROS MPH in adults with ADHD. Paper presented at: The 160th Annual Meeting of the American Psychiatric Association, 2007; San Diego, CA.

42.   Bangs ME, Hazell P, Danckaerts M, Williams DW, Moore JR, Levine AR. Atomoxetine for the treatment of attention-deficit/hyperactivity disorder. Paper presented at: The 159th Annual Meeting of the American Psychiatric Association, 2006; Toronto, Canada.

43.   Zhang HF, Cooper KM. Gender Differences in Inattention and Hyperactivity Improvement With Stimulant Treatment in Adolescents with ADHD. *18th Annual U.S. Psychiatric & Mental Health Congress.* November 8, 2005.

44.   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.

45.   Swanson J, Gupta S, Lam A, et al. Development of a new once-a-day formulation of methylphenidate for the treatment of attention-deficit/hyperactivity disorder: proof-of-concept and proof-of-product studies. *Archives of General Psychiatry.* 2003;60(2):204-211.

46.   Gehricke J-G, Whalen CK, Jamner LD, Wigal TL, Steinhoff K. The reinforcing effects of nicotine and stimulant medication in the everyday lives of adult smokers with ADHD: A preliminary examination. *Nicotine & Tobacco Research.* Feb 2006;8(1):37-47.

47.   Boellner SW, Earl CQ, Arora S. Modafinil in children and adolescents with attention-deficit/hyperactivity disorder: a preliminary 8-week, open-label study. *Current Medical Research & Opinion.* Dec 2006;22(12):2457-2465.

Appendix E. 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 MPH, DEX and pemoline. Additionally, the Jadad review (1999) summarized findings from longer-term, placebo-controlled trials of DEX and MPH 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 MPH, 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, TCAs and SSRIs	*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. *Longer-term therapy* (mean duration=20 weeks): Placebo-

Review	Characteristics	Main findings

	Total # of included trials (total # patients not reported):
	  Drug vs drug=22
	  Long-term therapy=14
	  Treatment of ADHD in adults=12
		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: RCTs 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

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