Drug Class Review

Pharmacologic Treatments for Attention Deficit Hyperactivity Disorder

Final Report
Update 3

October 2009

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The literature on this topic is scanned periodically.

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

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

Drug Effectiveness Review Project
Marian McDonagh, PharmD, Principal Investigator

Oregon Evidence-based Practice Center
Mark Helfand, MD, MPH, Director

Oregon Health & Science University

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

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INTRODUCTION

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

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

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

Historically, drug therapy for ADHD has consisted primarily of stimulant medications. More recently, nonstimulant medication treatment alternatives have been identified. These include atomoxetine, atypical antipsychotics, bupropion, clonidine, and guanfacine. Nonstimulant treatment options *may* offer advantages for individuals (1) seeking medications that have not been identified as having potential for abuse; (2) with concern over the *potential* long-term effects of stimulants on growing children; (3) with a history of nonresponse to or poor tolerance of stimulants; and/or (4) in whom stimulants are contraindicated due to coexisting medical and/or behavioral disorders and/or concomitant medications. Atomoxetine is the only nonstimulant evaluated in this review.

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

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

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

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

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

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

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

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

Purpose and Limitations of Systematic Reviews

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

Systematic reviews emphasize the patient's perspective in the choice of outcome measures used to answer research questions. Studies that measure health outcomes (events or conditions that the patient can feel, such as fractures, functional status, and quality of life) are emphasized over studies of intermediate outcomes (such as change in bone density). Reviews

also emphasize measures that are easily interpreted in a clinical context. Specifically, measures of *absolute risk* or the probability of disease are preferred to measures such as relative risk. The difference in absolute risk between interventions depends on the number of events in both groups, such that the difference (absolute risk reduction) is smaller when there are fewer events. In contrast, the difference in relative risk is fairly constant across groups with different baseline risk for the event, such that the difference (relative risk reduction) is similar across these groups. Relative risk reduction is often more impressive than the absolute risk reduction. Another useful measure is the *number needed to treat* (or harm). The number needed to treat, often referred to as the NNT, is the number of patients who would have to be treated with an intervention for 1 additional patient to benefit (experience a positive outcome or avoid a negative outcome). The absolute risk reduction is used to calculate the number needed to treat.

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

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

Systematic reviews highlight studies that reflect actual clinical *effectiveness* in unselected patients and community practice settings. Effectiveness studies conducted in primary care or office-based settings use less stringent eligibility criteria, more often assess health outcomes, and have longer follow-up periods than most efficacy studies. The results of effectiveness studies are more applicable to the “average” patient than results from the highly selected populations in efficacy studies. Examples of effectiveness outcomes include quality of life, frequency or duration of hospitalizations, social function, and the ability to work. These outcomes are more important to patients, family, and care providers than surrogate or intermediate measures, such as scores based on psychometric scales.

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

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

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

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

Scope and Key Questions

The purpose of this review is to compare the benefits and harms of different pharmacologic treatments for ADHD. The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of

organizations participating in the Drug Effectiveness Review Project. The participating organizations of the Drug Effectiveness Review Project are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. Evidence on Effectiveness and Efficacy
    a. What is the comparative or noncomparative evidence that pharmacologic treatments for attention deficit disorders improve *effectiveness* outcomes?
    b. What is the *comparative* efficacy of different pharmacologic treatments for attention deficit disorders?

2. Tolerability, Serious Adverse Events, Misuse and Diversion
    a. What is the evidence of *comparative* tolerability of different pharmacologic treatments for attention deficit disorders?
    b. What is the evidence of serious adverse events or long-term adverse events associated with use of pharmacologic treatments for attention deficit disorders?
    c. What is the comparative or noncomparative evidence that pharmacologic treatments for attention deficit disorders impact the risk of misuse or illicit diversion in patients with no history of misuse or diversion?
        i. Stimulants compared with nonstimulants
        ii. Immediate release compared with intermediate compared with long-acting formulations
        iii. Any included pharmacologic treatment

3. Evidence in Subgroups of Patients
    a. What is the evidence of benefits and harms of pharmacologic treatments for attention deficit disorders in subgroups of patients based on demographics (age, racial groups, gender), other medications or therapy, or comorbidities (e.g. tics, anxiety, substance use disorders, disruptive behavior disorders)?
    b. What is the comparative or noncomparative evidence of misuse or illicit diversion of pharmacologic treatments for attention deficit disorders in patients with current or past substance use disorder comorbidities?
        i. Stimulants compared with nonstimulants
        ii. Immediate release compared with intermediate compared with long-acting formulations
        iii. Any included pharmacologic treatment

Inclusion Criteria

Populations

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

- Attention deficit disorder
- Attention deficit hyperactivity disorder

Interventions

Included drugs are described in Table 1.

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

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

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

Benefits

Effectiveness outcomes

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

Efficacy outcomes

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

Harms

Tolerability

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

Serious adverse effects

1. Hepatotoxicity
2. Cardiovascular events
3. Growth effects

Misuse/diversion

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

Scales and tests used to measure outcomes

Numerous ADHD-specific and other psychiatric rating scales, as well as neuropsychological testing methods, are used to measure symptoms of ADHD. We limited our analyses to rating scales/tests for which we found published evidence of good reliability and validity. Our primary sources for documentation of the psychometric properties of rating scales included the Agency for Healthcare Research and Quality Technical Review #3 (Diagnosis of Attention-Deficit/Hyperactivity Disorder)[8] and Mental Measurements Yearbooks.[9-16] The Agency for Healthcare Research and Quality Technical Review #3 provides qualitative information on many of the rating scales cited in our report, including "subscales included in each test, comorbid conditions addressed by each checklist, time required to administer, number of items, ages for which norms are available, computer scoring availability, and ordering information, including cost" and reliability and validity. Appendix B provides a listing of commonly used scales and tests and associated acronyms.

Study designs

The benefit of the randomized controlled trial design is the reliably unbiased estimate of treatment effects in a controlled setting by randomizing patients, the best method of producing

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

For this review, the following study designs were included:

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

METHODS

Literature Search

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

Study Selection

Selection of included studies was based on the inclusion criteria created by the Drug Effectiveness Review Project participants. Two reviewers independently assessed titles and abstracts of citations identified through literature searches for inclusion using the criteria below. Full-text articles of potentially relevant citations were retrieved and again were assessed for inclusion by 2 reviewers. Disagreements were resolved by consensus. Results published *only* in abstract form were not included because lack of detail prevented quality assessment.

Data Abstraction

The following data were abstracted by 2 independent reviewers from included trials: study design, setting, and population characteristics (including sex, age, ethnicity, diagnosis); eligibility and exclusion criteria; interventions (dose and duration); comparisons; numbers screened, eligible, enrolled, and lost to follow-up; method of outcome ascertainment; and results for each outcome. We recorded intention-to-treat results when reported. If true intention-to-treat results were not reported, but loss to follow-up was very small, we considered these results to be intention-to-treat results. In cases where only per-protocol results were reported, we calculated intention-to-treat results if the data for these calculations were available.

Validity Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria listed in Appendix D. These criteria are based on the United States Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (U.K.) criteria.[21, 22] We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intention-to-treat analysis. Trials that had a fatal flaw in one or more category were rated "poor-quality"; trials that met all criteria were rated "good-quality"; the remainder were rated "fair-quality." A fatal flaw occurs when there is evidence of bias or confounding in the trial, for example when randomization and concealment of allocation of random order are not reported and baseline characteristics differ significantly between the groups. In this case, randomization has apparently failed and for one reason or another bias has been introduced.

As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair-quality studies are *likely* to be valid, while others are only *probably* valid. A poor-quality trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs. External validity of trials was assessed based on whether the publication adequately described the study population, how similar patients were to the target population in whom the intervention will be applied, and whether the treatment received by the control group was reasonably representative of standard practice. We also recorded the role of the funding source.

Appendix D also shows the criteria we used to rate observational studies. These criteria reflect aspects of the study design that are particularly important for assessing adverse event rates. We rated observational studies as good-quality for adverse event assessment if they adequately met 6 or more of the 7 predefined criteria, fair-quality if they met 3 to 5 criteria, and poor-quality if they met 2 or fewer criteria.

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

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

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

Evidence Synthesis

Effectiveness compared with efficacy

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

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

Data presentation

We constructed evidence tables showing the study characteristics, quality ratings, and results for all included studies. Studies that evaluated one pharmacologic treatment of ADHD against another provided direct evidence of comparative benefits and harms. Outcomes of changes in symptom measured using scales or tools with good validity and reliability are preferred over scales or tools with low validity/reliability or no reports of validity/reliability testing. Where possible, head-to-head data are the primary focus of the synthesis.

In theory, trials that compare these drugs to other interventions or placebos can also provide evidence about effectiveness. This is known as an indirect comparison and can be difficult to interpret for a number of reasons, primarily issues of heterogeneity between trial populations, interventions, and assessment of outcomes. Indirect data are used to support direct comparisons, where they exist, and are also used as the primary comparison where no direct comparisons exist. Such indirect comparisons should be interpreted with caution.

Public comment

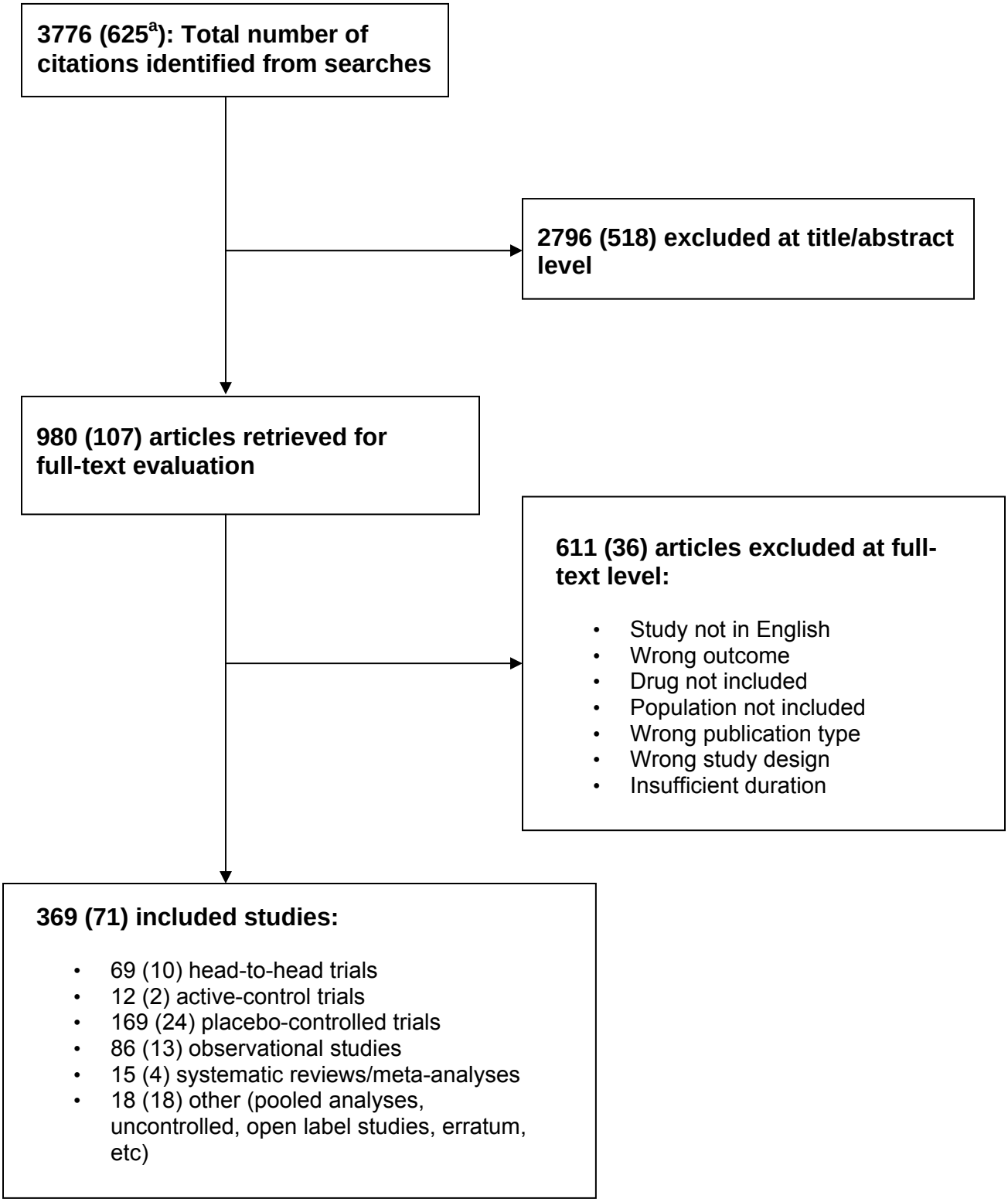
This report was posted to the Drug Effectiveness Review Project website for public comment. We received comments from 3 pharmaceutical companies.

RESULTS

Overview

Figure 1 details the results of our literature searches. Overall, we identified a total of 3776 citations from searching electronic databases, reviews of reference lists, pharmaceutical manufacturer dossier submissions, and public comment. Of these, 625 were identified in the most recent update. Dossiers were submitted by 5 pharmaceutical manufacturers for the original review: Eli Lilly (atomoxetine HCl), McNeil (methylphenidate OROS), Novartis (methylphenidate HCl, Ritalin LA®), Cephalon (modafinil), and Shire US (mixed amphetamine salts, mixed amphetamine salts XR). Additional dossiers were submitted for updates of this report as follows: Update 1, Eli Lilly (atomoxetine HCl) and McNeil (methylphenidate HCl, Concerta®); Update 2, Shire US (lisdexamfetamine dimesylate), McNeil (methylphenidate OROS), and Eli Lilly (atomoxetine HCl); and Update 3, Eli Lilly (atomoxetine HCl), Shire US (lisdexamfetamine dimesylate and transdermal methylphenidate), and McNeil (methylphenidate OROS). A list of excluded studies is reported in Appendix E.

Figure 1. Results of literature search



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

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

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

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

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

Data abstracted from these trials can be found in Evidence Tables 3 and 9 and the relevant quality assessments in Evidence Tables 4 and 10. Because there are a large number of head-to-head trials directly comparing the drugs, and indirect comparisons from placebo-controlled trials are less reliable, we have only included placebo-controlled trials of drugs for which we have limited or no head-to-head evidence. Similarly, using a "best evidence" approach, we included observational studies where we had no evidence for important outcomes such as long-term functional outcomes or duration of response. Data abstracted from placebo-controlled trials can be found in Evidence Tables 5 and 11 and relevant quality assessments in Evidence Tables 6 and 12. For long-term safety, we included 35 observational studies (Evidence Tables 15 and 16).

In adult populations (age 18 and above), we included 44 placebo-controlled trials (Evidence Tables 11 and 12) and 1 long-term observational study (Evidence Tables 15 and 16) in addition to the head-to-head trials listed in Table 1 above.

Previous systematic review findings

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

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

The American Academy of Pediatrics Clinical Practice Guideline on treatment of school-aged children with ADHD and the American Academy of Child and Adolescent Psychiatry Practice Parameter for the Assessment and Treatment of Children and Adolescents with ADHD were also reviewed.[25, 26] The American Academy of Pediatrics guideline considers only stimulant medications, specifically all forms of methylphenidate and immediate-release dextroamphetamine. Stimulant and/or behavior therapy is recommended, the guideline does not prefer one, and states that the Jadad review (cited above) found no difference between these stimulants.[25] The guideline also states, "Individual children, however, may respond to one of the stimulants but not to another." The American Academy of Child and Adolescent Psychiatry guideline states that stimulants are first-line, except in situations where substance abuse disorder, comorbid anxiety, or tics are present.[26] The document did not differentiate among the stimulants, stating that treatment should be individualized and that the choice is up to the clinician and family.

What this review adds

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

Summary of Findings

General

- There are no *trials* of comparative effectiveness of these drugs for treatment of ADHD.
- Good-quality evidence on the use of drugs to affect outcomes relating to global academic performance, consequences of risky behaviors, social achievements, etc. is lacking.
- The evidence for comparative efficacy and adverse events of drugs for treating ADHD is severely limited by small sample sizes, very short durations, and the lack of studies measuring functional or long-term outcomes. Methods of measuring symptom control vary significantly across studies. The crossover design was frequently used, with few analyzing the effect of order of administration of drugs. Those that did found a significant

effect. No head-to-head efficacy trial was good quality. The small numbers of patients in these trials limited the ability to show a difference between drugs if one exists.

- Limitations to the generalizability of these trials include the following:
  - Characterization of ADHD symptomatology across studies was limited due to use of varied or indeterminate diagnostic processes.
  - Minorities and the most seriously ill patients were underrepresented.
  - The small sample sizes of these trials did not allow for statistical analyses of potential effects of these factors.
- Overall, the rate of response to stimulants appeared to be in the range of 60% to 80%, however the definitions of response rate varied and may not be comparable. Depending on the definition used, there is lack of clarity on the relationship of response rate to clinical significance. Response rates of nonstimulants varied, but the range in placebo-controlled trials was similar to that found with stimulants. Significant variation in the method of assessment and definition of response was most likely the reason for the wide variation.

Young children (preschool age; 3-5 years)

Efficacy and tolerability

- No comparative evidence in young children was found.
- Immediate-release methylphenidate was marginally superior to placebo, depending on the efficacy measure assessed in 2 fair-quality placebo-controlled trials that used validated assessment tools; but was also associated with higher rates of adverse events and a high rate of discontinuation.
- Among young children who had positive response to immediate-release methylphenidate, follow-up after 10 months showed increases in mean dose and maintenance or improvements in efficacy measures.

Long-term safety

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

Children (elementary school age; 6-12 years)

Effectiveness

- Because no trials of effectiveness were found, observational studies were assessed for outcomes of effectiveness.
- The only comparative study with relevant outcomes found methylphenidate OROS to be associated with fewer outpatient visits/hospitalizations for accidents/injury than immediate-release methylphenidate over 12 months. Methodologic concerns over this study suggest caution in interpretation of these findings.
- Uncontrolled observational data assessing the effect of duration of treatment with immediate-release methylphenidate found no differences in academic achievement as measured by teachers or the proportion repeating grades, in special education classes, or

being tutored. Again, significant methodologic limitations suggest caution in interpreting these findings.

Efficacy and tolerability

Stimulants

- Immediate release compared with extended release formulations:
  - The evidence regarding immediate-release methylphenidate compared with methylphenidate OROS was conflicting, with 2 double-blind trials unable to identify differences, while 2 open-label studies found that methylphenidate OROS resulted in greater improvements on some but not all assessments.
    - Exploratory pooled analysis of the inattention/overactivity scores of the IOWA Conners' scale indicate methylphenidate OROS may result in greater improvement (weighted mean difference –1.19; 95% CI, –1.78 to –0.60).
  - Limited evidence is available for the comparisons of immediate-release methylphenidate to other extended release formulations. Overall, the studies were unable to identify differences between methylphenidate SR and immediate-release methylphenidate, and methylphenidate CD was found to be noninferior to immediate-release methylphenidate.
  - Database studies using intermediate outcomes reported greater persistence with methylphenidate OROS and methylphenidate SODAS compared with immediate-release methylphenidate. Methodologic concerns indicate caution in interpreting this evidence.
- Sustained-release compared with sustained-release formulations:
  - Limited evidence from 2 small crossover studies suggests that methylphenidate LA is superior to methylphenidate OROS on some, but not all efficacy outcomes. However, these results should be interpreted with caution until higher quality evidence is available.
  - Methylphenidate CD was associated with significantly larger effect sizes than methylphenidate OROS in the morning, treatment effects were similar in the afternoon, and methylphenidate OROS was superior in the evening. Methodologic concerns indicate caution in interpreting these findings.
  - Dexmethylphenidate ER resulted in better response from 2 to 6 hours post-dose compared with methylphenidate OROS, but methylphenidate OROS resulted in better scores later in the day; from 10 to 12 hours post-dose.
  - There is currently no evidence of a difference in adverse events between immediate-release and sustained-release formulations.
- Dextroamphetamine compared with methylphenidate:
  - The body of evidence clearly indicates no difference in efficacy between immediate-release dextroamphetamine and immediate-release methylphenidate. Evidence from short-term trials and observational studies suggests that weight loss is greater with immediate-release dextroamphetamine than immediate-release methylphenidate.
- Mixed amphetamine salts compared with methylphenidate:
  - Immediate-release mixed amphetamine salts was superior to immediate-release methylphenidate on a few efficacy outcome measures in 2 trials, but clear

evidence of superiority is lacking. Very limited evidence suggests that twice daily dosing of immediate-release mixed amphetamine salts led to higher rates of loss of appetite and sleep trouble than once daily dosing of immediate-release methylphenidate.

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

Atomoxetine

- Atomoxetine compared with methylphenidate:
  - Evidence from 2 trials suggests that atomoxetine was associated with efficacy outcomes similar to immediate-release methylphenidate.
- Atomoxetine compared with methylphenidate OROS:
  - Based on response rates (>40% reduction in ADHD-Rating Scale score), methylphenidate OROS was found superior to atomoxetine with an overall 56%

    - In patients with prior stimulant exposure methylphenidate OROS was found to have a statistically significantly higher rate of response (51%) compared with atomoxetine (37%) (number needed to treat, 8; *P*=0.03). However, in the smaller subgroup without prior stimulant exposure, the 2 drugs were not found to be statistically significantly different in response rates.
- Atomoxetine compared with mixed amphetamine salts:
    - Mixed amphetamine salts XR was found superior to atomoxetine on most measures of efficacy in a simulated classroom study.
- Atomoxetine was associated with significantly higher rates of vomiting, somnolence, nausea, and anorexia than stimulants, depending on the specific drug comparison.
    - Rates of vomiting ranged from 12% to 13% for atomoxetine, which was approximately 3 times greater than rates for immediate-release methylphenidate or mixed amphetamine salts XR.
    - Rates of somnolence ranged from 6% to 26% for atomoxetine, which was 3 to 4 times greater than rates for longer-acting stimulants (methylphenidate OROS and mixed amphetamine salts XR) and over 7 times greater than rates in trials of immediate-release methylphenidate.
    - Nausea and anorexia were also greater with atomoxetine compared to immediate-release methylphenidate in 1 trial, however the dose comparison, (atomoxetine at recommended doses, immediate-release methylphenidate at lower end of recommended) in this trial may have contributed to this finding.
- Methylphenidate OROS and mixed amphetamine salts XR caused higher rates of insomnia than atomoxetine in 2 trials (7% atomoxetine, 13% methylphenidate OROS, 28% mixed amphetamine salts XR).

Adolescents

Efficacy and tolerability

- Adolescents were studied in a small number of short-term trials that involved immediate-release methylphenidate or methylphenidate OROS (Concerta®). Studies of atomoxetine included adolescents and are discussed above.
- Methylphenidate OROS compared with immediate-release methylphenidate:
    - One very small, single blinded study showed methylphenidate OROS superior to immediate-release methylphenidate on some measures of simulated driving skills during tests administered in the late evening or nighttime. No difference was found during other test times.
- Methylphenidate OROS compared with mixed amphetamine salts:
    - One small, crossover study found no significant difference between methylphenidate OROS and mixed amphetamine salts in self-reported symptom improvement or subjective ratings of driving performance, although methylphenidate OROS was associated with significantly better overall driving performance relative to mixed amphetamine salts based on testing in a driving simulator.

- Indirect evidence of stimulants:
  - Placebo-controlled trials of immediate-release methylphenidate did not provide indirect evidence of comparative efficacy or tolerability due to heterogeneity in outcome reporting.
  - Immediate-release methylphenidate generally was superior to placebo in improving core ADHD symptoms, but was associated with more frequent reports of appetite and sleep disturbances.
- Functional outcomes of observational studies:
  - Observational studies of immediate-release methylphenidate that reported functional outcomes found mixed results. In an uncontrolled study of young adult males who had taken methylphenidate as children (mean age at discontinuation of methylphenidate was 17 years), fewer suicide attempts were associated with higher dosages of methylphenidate. Emancipated living situation and level of relationship commitment was associated with response to methylphenidate. Early response to methylphenidate was negatively associated with high school graduation, however.
  - Another uncontrolled follow-up of immediate-release methylphenidate responders reported "improved grades" after 6 to 14 months. Methodological limitations of these studies severely limited the interpretation of these findings.

Adults

Efficacy and tolerability

- There were no trials of adults with ADHD using dexmethylphenidate, methamphetamine, methylphenidate transdermal patch, methylphenidate chewable tablet or oral solution, or some extended release forms of methylphenidate (Metadate CD®, Ritalin LA®, and Biphentin®).
- Direct comparative evidence was limited to 1 trial of immediate-release dextroamphetamine compared with modafinil. No differences were found in response rates (48% for both treatments) or rates of insomnia (38% compared with 19%, NS), muscle tension (24% compared with 19%, NS), and appetite suppression (24% compared with 19%, NS). [51]
- Placebo-controlled and uncontrolled trials:
  - Improvement of ADHD symptoms
    - Placebo-controlled trials generally indicated that atomoxetine, immediate-release dextroamphetamine, dexmethylphenidate ER, lisdexamfetamine, immediate-release methylphenidate, methylphenidate SR, methylphenidate OROS, and methylphenidate ER, immediate-release mixed amphetamine salts, and mixed amphetamine salts XR are all effective treatments for reducing ADHD symptoms, with response rates ranging from 34% to 82%.
    - Results from an indirect comparison meta-analysis suggested a relative benefit of clinical response for shorter acting stimulants at 3.26 times greater than for patients taking longer-acting stimulants (95% CI, 2.03 to 5.22) and 2.24 times greater than for patients taking longer-acting forms of bupropion (95% CI, 1.23 to 4.08).

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

Long-term safety

- Although the observational studies provide some estimate of the prevalence of serious longer-term adverse events with mixed amphetamine salts, atomoxetine, immediate-release dextroamphetamine, and methylphenidate (immediate and sustained release), few studies directly compared different pharmacologic treatments for ADHD for any one adverse event.
- For outcomes where only uncontrolled evidence was available, it was not possible to draw conclusions about comparative long-term safety through indirect comparisons across observational studies due to large differences in study characteristics.
- The *overall* body of evidence is poor quality due to a variety of flaws in design and analysis and should be interpreted with caution.
- Sudden cardiac death:
  - Based on a case-control study of 10 years of state vital statistics records and parent surveys, the risk of sudden cardiac death was significantly greater among children who were taking stimulants compared with a control group who were not (odds ratio, 7.4; 95% CI, 1.4 to 74.9). Because exposure was determined by survey (mean of 10 to 13 years after the event), recall bias may be an important limitation in this study.

  - A smaller study based on 10 years of Florida vital statistics records was not able to find a significant effect of stimulant exposure and death due to circulatory causes, including sudden cardiac death.
- Cardiac adverse events:
  - Emergency department and physician office visits due to cardiac causes occurred significantly more often in the group currently using a stimulant (hazard ratio, 1.20; 95% CI, 1.04 to 1.38) compared with non-users (hazard ratio, 1.21; 95% CI, 1.06 to 1.39). Former use of stimulants was not significantly associated. Using regression analysis, several factors were found to be significantly associated with the increased risk of an emergency department or physician's office visit due to cardiac causes: age ≥ 15 years compared to < 15 years; congenital anomalies; history of circulatory disease; disability; nonblack race; and the use of antidepressants, antipsychotics, and bronchodilators.
- Suicidal behaviors:
  - Based on a meta-analysis of placebo-controlled trials, atomoxetine was associated with an increased risk of suicidal behaviors (Mantel-Haenszel Incidence Difference, 0.52; 95% CI, 0.12 to 0.91). Time to onset of suicidal-related behavior was 9 to 32 days. All children experiencing suicidal-related behaviors were boys, ages 7-12, and 33% were African American. African American boys represented 12% of the total population in these studies. Overall rate of suicidal ideation and behavior was 0.44%.
  - In another meta-analysis of data from children and adolescents in open-label studies of atomoxetine with at least 3 years exposure, the overall rate of suicidal ideation, behavior, and suicide attempts was 2%. Time to onset of suicidal-related behavior was 234 days to 5.8 years.
- Height change in children:
  - Evidence on immediate-release dextroamphetamine compared with methylphenidate is inconsistent. Evidence suggested that immediate-release methylphenidate and methylphenidate OROS adversely impacts expected height gain at least during the first 12 months of treatment.
  - Limited evidence suggests that height changes resulting from atomoxetine were similar to those reported with immediate-release methylphenidate, and were also transient, with the peak of impact on expected height occurring at 18 months, but the difference resolved by 2 years.
- Weight in children:
  - Results from comparative observational studies of immediate-release dextroamphetamine and methylphenidate suggested that immediate-release dextroamphetamine was associated with significantly greater suppression of weight gain than methylphenidate in the first 1-2 years. However, the difference between immediate-release dextroamphetamine and methylphenidate appeared to resolve by the second year and the difference found in years 1 to 2 may have been exaggerated by higher relative immediate-release dextroamphetamine dosages. Ultimately, these data should be interpreted with caution due to methodological flaws in the measurement of weight.
  - The remaining comparative and noncomparative observational studies suggested a small reduction in expected weight gain, especially among those with greater

    - Limited evidence suggests that weight changes resulting from atomoxetine were similar to those reported with immediate-release methylphenidate, and were also transient. Negative impact on weight began after 1 month of treatment, with a peak at 15 months. The difference remained statistically significant up to 3 years of treatment and resolved by 5 years of treatment. Analysis indicated that dose did not impact the change in weight, but those with higher baseline weight had greater losses than those with lower baseline weight.
- Insomnia, decreased appetite, headaches:
    - Based on a retrospective cohort study with 24 months of exposure:
        - Rates of insomnia were not statistically significantly different among immediate-release methylphenidate, methylphenidate OROS, mixed amphetamine salts, mixed amphetamine salts XR, and atomoxetine, although the crude rate in the mixed amphetamine salts group (22%) was numerically greater than in the other groups (range 4% to 13%).
        - Rates of decreased appetite were not found to be different among immediate-release methylphenidate, methylphenidate OROS, mixed amphetamine salts, mixed amphetamine salts XR, and atomoxetine, although the rates in the immediate-release mixed amphetamine salts, mixed amphetamine salts XR, and methylphenidate OROS groups (range 15% to 22%) were also higher than the atomoxetine and immediate-release methylphenidate groups (range 9% to 10%).
        - Atomoxetine had lower rates of headache compared with mixed amphetamine salts XR (0% and 12%; P=0.001), immediate-release mixed amphetamine salts (0% and 11%; P=0.001), or methylphenidate OROS (0% and 10%; P=0.002).
        - Dose was not controlled for in these analyses, and because the data were sparse, a Boneronni correction was used. Thus we suggest caution in interpreting these findings.
- There was no comparative evidence on other long-term safety outcomes, including tics, seizures, cardiovascular adverse events, injury frequency, and hepatotoxicity.

Abuse/diversion

- Abuse or dependence:
    - Evidence was based on longitudinal studies of adolescents or adults who had been diagnosed with ADHD as children and compared rates of abuse and dependence in those who were treated with stimulants with those who were not.
    - Nicotine:
        - Two studies found no association when analyses controlled for comorbid conduct disorder.
        - Studies that did not control for conduct disorder found stimulant exposure to be protective against regular smoking among teen girls (1 study), and no association with the first cigarette, but those exposed to a stimulant

showed a delay in the time (2 years and 1 month) to becoming a regular smoker (1 study).

- Alcohol:
  - No association between alcohol abuse during teen and young adult years and stimulant exposure during childhood was found.
- Substance abuse:
  - Two studies found stimulant use to be protective, but a third study found that controlling for conduct disorder resulted in a nonsignificant finding.
  - Analysis of the National Survey on Drug Use and Health from 2000 and 2001 found that 4.7% were determined to be dependent on or abusing a prescription ADHD stimulant drug, with rates highest among those 12 to 25 years old. Rates of dependence were higher among women, whereas rates of abuse were higher among men.

- Misuse:
  - A systematic review primarily of surveys found that the rate of misuse of methylphenidate or amphetamine was 5% to 8% among children up through high school and 5% to 35% among college students.
  - Among college students, 2 small studies found that rates of misuse of stimulant medications for enhancement of academic performance were 30% to 35%.
  - In a study of 66 adults prescribed methylphenidate, 29% reported inappropriate use during the past month.
    - 84% used it orally, 74% used it nasally, and 11% smoked it.
    - Regression analysis indicated that misuse of methylphenidate was associated with illicit use of cocaine or amphetamines.
  - Analysis of the National Survey on Drug Use and Health from 2000, 2001, and 2002 found:
    - 0.9% in the 12 to 17 year age group had misused an ADHD stimulant (nonmedically) in the past year.
    - 1.3% in the 18 to 25 year old age group had misused an ADHD stimulant (nonmedically) in the past year.
    - 34.7% of respondents had *ever* misused a prescription stimulant intended for use to treat ADHD.
    - The most commonly misused stimulants in this survey were immediate-release methylphenidate and immediate-release dextroamphetamine, with smaller numbers reporting use of other drugs, including mixed amphetamine salts and methylphenidate OROS.
- Diversion
  - Based on small studies or a systematic review of primarily surveys:
    - Among children through high school aged who were prescribed a stimulant:
      - 15% to 24% gave them away.
      - 7% to 19% sold them.
      - 4% to 6% had them stolen at some time in the past.
    - Among college students who were prescribed a stimulant:
      - 23% had been asked to give, to trade, or to sell them.
      - 29% of those surveyed reported selling them.

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

Subgroups

Demographics

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

emotional overactivity items) on the Wender-Reimherr Adults Attention Deficit Disorder Scale than in men. The Sheehan Disability social life subscale demonstrated a significant gender-by-treatment effect (P=0.042), with women showing a stronger treatment effect than men, but there was no significant difference on the total score.

ADHD subtypes

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

Commonly occurring comorbidities

- Learning disability:
    - There was very limited evidence that response to immediate-release methylphenidate may be moderated in children with mathematics learning disabilities.
- Tic disorders:
    - Overall, there was very little evidence across these trials to indicate that immediate-release methylphenidate, immediate-release dextroamphetamine, or atomoxetine were associated with any tic exacerbation effects. Compared with placebo, immediate-release methylphenidate, immediate-release dextroamphetamine, and atomoxetine were consistently associated with improved tic severity and ADHD symptoms.
- Oppositional defiant disorder:
    - Very limited evidence indicated that immediate-release methylphenidate, mixed amphetamine salts XR, and atomoxetine were associated with greater improvements in ADHD symptoms than placebo.
- Bipolar disorder:
    - Very limited evidence indicated that immediate-release mixed amphetamine salts and immediate-release methylphenidate were associated with significantly greater

improvements in ADHD outcomes than placebo when added to mood stabilizers in children with co-existing bipolar disorder.

- Substance abuse:
  - Adolescents:
    - Methylphenidate SODAS was superior to placebo in reducing ADHD symptoms in teens with substance use disorder. There was no significant treatment effect on drug use.
  - Adults:
    - Atomoxetine was superior to placebo in improving ADHD symptoms in adults with comorbid alcohol use disorders (n=147).
    - Neither immediate-release methylphenidate nor methylphenidate SR was superior to placebo in improving ADHD symptoms in adults with comorbid cocaine dependence, methadone-maintenance, or general alcohol or drug dependence.

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

Young children (preschool age; 3-5 years)

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

The evidence of any short-term benefit of stimulants in this age group comes from 6 placebo-controlled trials of immediate-release methylphenidate.[52-59] Of these 6 placebo-controlled trials, 4 were either poor quality and/or lacked a valid assessment tool.[52, 53, 55-57] The remaining 2 studies present a mixed picture, with immediate-release methylphenidate not clearly superior to placebo, but some indication that higher doses may result in better improvement on some symptoms.

One fair-quality trial used an assessment tool with good validity (Children's Psychiatric Rating Scale-Revised; learning, conduct, and hyperactivity indices only).[54] In this study, both the high dose (0.5 mg/kg twice daily) and the low dose (0.3 mg/kg twice daily) resulted in lower scores than placebo at the end of 7 to 10 days of treatment. The high dose resulted in better final scores than the low dose on only the learning component of the Children's Psychiatric Rating Scale-Revised with the low dose resulting in a mean of 8 points (10%) lower, and the high dose a mean of 14 points (18%) lower than the score while on placebo. The clinical importance of these differences is not known, and baseline scores are not reported or accounted for. Based on parental report, medication did not result in better compliance with tasks compared to placebo, although reports of time on task were better with the higher dose (mean 52 seconds longer compared to placebo). The DSM-III criteria were used to diagnose ADHD. ADHD subtypes or ethnicity were not identified in this study. Methylphenidate was associated with higher rates and greater severity of adverse events than placebo, significantly more in the higher dose group. Rates of specific adverse events were not reported.

The Preschool ADHD Treatment Study assessed the efficacy and safety of immediate-release methylphenidate relative to placebo.[58, 59] The Preschool ADHD Treatment Study was a multi-center, multi-phase trial that included a crossover titration phase (5 weeks; N=165), a parallel phase (4 weeks; N=114), and an open-label phase (10 months; N=140). In the publication describing the Preschool ADHD Treatment Study design[58] the primary outcome measure of the crossover phase of the trial is described as a composite of scores from the Swanson, Conners, Milich, and Pelham scale and the Conners, Loney, and Milich Rating (CLAM) scale, while the publication of the results of the trial[59] state that the *a priori* primary outcome measure of the crossover phase is a composite of CLAM and Swanson, Kotlin, Agler, M-Flynn and Pelham (SKAMP) scale scores. The reason for or effect of this discrepancy is not stated. The primary outcome of the parallel phase was a derivative of the SNAP-IV scale ("excellent responder" criteria).[58]

The crossover phase of the Preschool ADHD Treatment Study followed a 10-week parent-training phase and a 1-week, open-label run-in. The parent-training phase served to allow investigators to remove from the trial those children who were responders to non-pharmaceutical intervention, thus only children whose ADHD symptoms were not improved following parent training were randomized to the crossover phase of the trial. Patients received immediate-release methylphenidate doses ranging from 1.25 to 10 mg three times daily or placebo. The overall composite score of CLAM/SKAMP, based on parent and teacher scores, ranged from 0.91 for high-dose immediate-release methylphenidate to 1.19 for low dose immediate-release methylphenidate and 1.28 for placebo (higher score reflecting worse symptoms). Effect sizes of treatment relative to placebo during this phase ranged from 0.16 (immediate-release methylphenidate 1.25 mg three times daily) to 0.72 (immediate-release methylphenidate 7.5 mg three times daily).

The parallel phase of the Preschool ADHD Treatment Study, in which 114 patients were randomized to either placebo or their optimal dose of immediate-release methylphenidate (as determined in the crossover phase of the trial), found no significant difference in the number of immediate-release methylphenidate patients that met the primary outcome measure of 'excellent response' on the SNAP-IV composite score compared to placebo patients (immediate-release methylphenidate 13/61 [22%] compared with placebo 7/53 [13%; $P<0.3$]). Overall patient withdrawal from this study was high (32%; n=36), with 45% of withdrawals on placebo, 15% on immediate-release methylphenidate. The open-label lead-in phase may have influenced this drop out rate. An unplanned, post hoc analysis of composite SNAP scores found that immediate-release methylphenidate patients had a lower mean symptom score than placebo patients after 4 weeks of treatment (immediate-release methylphenidate 1.49 compared with placebo 1.79; $P<0.02$).

Additional outcomes were assessed, including the Strengths and Weaknesses of ADHD-Symptoms and Normal Behaviors (SWAN) scale, Social Skills Rating System, the Social Competence Scale, the Parenting Stress Index, the Early Child Inventory (dysthymic disorder and major depressive disorder subscales only), and the Clinical Global Impression-Severity Scale.[60] Of these, only the Early Child Inventory was reported to have reliability and validity testing in preschool aged children. While the study did not necessarily have adequate statistical power to evaluate these outcomes, differences were not found between immediate-release methylphenidate and placebo on 4 of 6 of these measures. Only the Early Child Inventory assessments of mood and the Clinical Global Impression-Severity Scale found methylphenidate OR superior to placebo after 5 weeks. On ratings of major depressive symptoms or dysthymic

symptoms, children taking immediate-release methylphenidate had improvements in scores while those taking placebo had deterioration in scores (P=0.02 and P=0.001, respectively), however these differences are based on only 61 of 114 randomized patients and the difference in final score was approximately 1.5 points. The complete scale is described as having 108 points, but the possible points for these 2 subscales are not reported. The investigator assessment of Clinical Global Impression-Severity Scale also indicated a better final score for those taking immediate-release methylphenidate (mean immediate-release methylphenidate score 3.74 and mean placebo score 4.47 on 0 to 7 scale; P=0.001). In view of the high and differential discontinuation rate, the concerning amount of missing data reported, and the unclear implications of the differences found, these secondary analyses should be interpreted with great caution.

Among those who responded well to immediate-release methylphenidate during the open-label run-in phase, 140 enrolled in a 10-month open-label extension phase, and only 95 (68%) completed 10 months of follow-up.[61] Discontinuations due to adverse events or deterioration in response were low (5% each). After 10 months, ADHD rating scales used (SNAP and SWAN) and ratings of parental stress had not changed significantly from enrollment. Dosing had increased from a mean of 14 mg daily to 20 mg daily. Ratings by unblinded clinicians on the Clinicians Global Impression-Severity and Clinicians Global Impression-Improvement scale increased by small absolute, but by statistically significant amounts (0.24 and 0.44 out of 7 possible points; P=0.02 and P<0.001, respectively). Similarly, unblinded ratings of the Children's Global Assessment Scale and Social Skills Rating Scale improved by 5 points (of 100; P<0.001) and 4 points (described as having 70 items, range of scores not described; P=0.01).

Children (elementary school age; 6-12 years)

Generalizability issues

Studies of elementary school age children with ADHD were characterized by under-reporting of baseline subtype classifications, race or ethnicity, co-occurring disorders, and illness severity. This gap in the literature limits the generalizability of the findings to target populations. Only one-quarter of all studies of school-aged children reported ADHD subtype prevalence rates. The mixed subtype was most common, occurring in 58% to 100% of participants across most study populations. The inattentive subtype was generally observed less frequently (prevalence rate range: 9% to 40%) and the hyperactive subtype was relatively rare (prevalence rate range: 1% to 8%). Only one-half of all studies of elementary school-aged children reported race or ethnicity among the baseline characteristics. The racial/ethnic make-up of the majority of these study populations was consistent with the current United States Census Bureau Estimates (White = 80.4%; Black = 12.8%; Asian = 4.2%; and of Hispanic/Latino origin = 14.1%).[62] However, the prevalence of ADHD among ethnic groups may not correlate with these data.

Just over half of studies reported prevalence rates of co-occurring disorders, including oppositional defiant disorder (19% to 66.7%), conduct disorder (9% to 38.5%), anxiety (1.4% to 42%), and depression (0.7% to 6.6%). With the exception of depression, the ranges of comorbidities reported in these trials encompass the American Academy of Pediatrics estimates on prevalence of common comorbidities: Oppositional defiant disorder, 35%; conduct disorder, 26%; anxiety disorder, 26%; and depressive disorder, 18%.[63] Illness severity was not presented as a baseline characteristic in most studies, and comparisons across studies based on scales used

to assess symptoms are hampered by variation in scale choice and method of reporting. Diagnostic processes also varied across studies. Seventy-two percent of studies used either the DSM III, DSM III-R, or DSM IV criteria to diagnose ADHD, however many used additional criteria and the clinical comparability of patients enrolled is not clear.

Stimulants

Comparison of immediate-release and sustained-release formulations

Methylphenidate. We included 13 trials of immediate-release methylphenidate compared with methylphenidate SR.[28, 64-73] Of these, 4 were poor quality due to either inadequate or undescribed methods of randomization and allocation concealment, combined with lack of description of an intention to treat analysis, lack of information on eligibility criteria, attrition, or post-randomization exclusions (Evidence Table 3).[28, 64, 65, 69] The remaining studies compared immediate-release methylphenidate to 5 extended-release formulations of methylphenidate (Biphentin®, Concerta®, Ritalin SR®, Medikinet®, or Metadate CD®).[66-68, 70-73] In addition, according to a US Food and Drug Administration statistical review (http://www.fda.gov/cder/foi/nda/2000/21-121_Concerta_statr.pdf), methylphenidate OROS (Concerta®) and immediate-release methylphenidate were compared in an additional trial of 64 children that has not yet been published.[74]

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

Table 3. Pharmacokinetic profiles of methylphenidate products[a]

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

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

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

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

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

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

In the 2 earlier, double-blind trials, in which the primary comparison of interest was specified as methylphenidate OROS compared with placebo, methylphenidate OROS and immediate-release methylphenidate did not differ significantly on the majority of direct comparisons.[66, 67] In contrast, the 2 newer, open-label studies did find a significant difference favoring methylphenidate OROS.[72, 73] While all of the studies suffer from design or conduct challenges and none were rated good quality, the 2 newer studies present more concerns of bias than the earlier studies. There is also a potential risk of selection bias in that only one of the studies[66] reported the proportion of patients taking immediate-release methylphenidate or methylphenidate OROS prior to enrollment.

In the largest, highest quality study, there were no significant differences between the formulations on the primary outcome measure (IOWA Conners' scale) or on 11 secondary measures in a randomized controlled trial of 312 children.[67] Similarly, a much smaller crossover trial (68 children) that was 7 days long and included behavioral treatment, found methylphenidate OROS to have lower scores on the Abbreviated Conners' Parents scale (total), and on the inattention/overactivity item (out of 16 items), however no differences were found based on assessments made by teachers and counselors.[66]

The study by Steele et. al[73] was open-label, comparing usual care to switching to methylphenidate OROS. Based on a definition of remission as a score of 0 or 1 (none or just a little) on the 18 items relating to ADHD symptoms only (excluding the items pertaining to oppositional defiant disorder) of the parent assessed SNAP-IV scale, methylphenidate OROS treatment resulted in more patients being classified as in remission at 8 weeks, with a number needed to treat near 4 (see Table 4). Similar results were found using other measures of parental assessment. This study does not include teacher ratings. Because the study was open to patients currently receiving treatment, including immediate-release methylphenidate, and it was unblinded, it is potentially biased against immediate-release methylphenidate. The proportion of patients taking immediate-release methylphenidate, methylphenidate OROS, or who were not taking drug therapy prior to study enrollment is not reported.

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

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

In contrast, findings from a retrospective study of 92 children from a "real-life clinical situation" in the UK suggest that 32% ($P<0.001$) were considered treatment failures when switched to an extended release form of methylphenidate (Concerta XL®) from immediate-release methylphenidate of an unknown duration.[75] The validity and generalizability of these findings are unclear, however, as the study was retrospective in nature, physicians' use of personal case load to identify patients may have introduced a selection bias, treatment failure was not precisely defined, and it is unclear whether the UK formulation is comparable to methylphenidate OROS as included in this review.

The US Food and Drug Administration Statistical Review of the New Drug Application for methylphenidate OROS includes criticism of 3 early trials,[66, 67, 76] indicating that an assumption of equivalence should not be made based on these studies alone. (http://www.fda.gov/cder/foi/nda/2000/21-121_Concerta_statr.pdf - page 32).[74]

Immediate-release methylphenidate compared with methylphenidate SR (Ritalin SR®). A small 2-week randomized controlled trial (34 children) of immediate-release methylphenidate compared with methylphenidate SR found mixed results.[68] The outcome measures included questionnaires (not validated) completed by a physician, a teacher, and a parent. The teacher questionnaires indicated significant differences in final total score and the "Conduct Problem" scores favoring immediate-release methylphenidate. Parent questionnaires indicated a significant difference favoring methylphenidate SR on the "Conduct Problem" item final score, and the physician scores showed no difference.

Immediate-release methylphenidate compared with methylphenidate ER (Metadate CD®, Equasym®). A 3-week study using over-encapsulation for blinding enrolled 327 children, comparing immediate-release methylphenidate to Equasym® (sold in the United States as Metadate CD®). The study analyzed only 87% of patients in the main per-protocol analysis with unclear description of those excluded.[71] The study included a non-inferiority analysis, assuming a difference of ≤ 1.5 points on the I/O score of the Conners' IOWA teachers rating scale to indicate equivalence (non-inferiority). At weeks 1, 2, and 3 immediate-release methylphenidate was found equivalent to Equasym®. Intention to treat analysis as well as subgroup analyses (country, dose, ADHD subtype) were reported in the discussion as supporting these results. Additional analysis examined the effects of the drugs in the morning and afternoon, but a direct comparison was made only to the placebo group as both methylphenidate groups were found similarly superior to placebo at both time points throughout the study.

Immediate-release methylphenidate compared with methylphenidate multilayer-release (Biphentin®). Two small, fair-quality, crossover studies compared immediate-release methylphenidate to methylphenidate multilayer-release (Biphentin®, available in Canada, not available in the United States as of June 2009).[77, 78] In the first study, 90 children were randomized to either immediate-release methylphenidate or methylphenidate multilayer-release and had dose titration over 2-3 weeks, with observation by parent, teacher, and investigator over 2 weeks.[78] Discontinuations were similar between groups (86% methylphenidate multilayer-release, 89% immediate-release methylphenidate), and mean daily doses were similar between treatments (0.8 mg/kg daily). Using the Conners' scales, "normal" was defined as a final T-score of <65 on each of the 4 subscales. After 5 weeks of treatment, more children taking immediate-release methylphenidate had achieved a normal score on the ADHD Index compared to those taking methylphenidate multilayer-release (90% compared to 79% on the teacher scale and 81%

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

The second, smaller study (N=18) reported only single-day measurements after 1 week of immediate-release methylphenidate, methylphenidate multilayer-release, or placebo.[77] This study found no statistically significant differences between drug treatments on the Conners' IOWA scale, although baseline scores differed across treatment groups such that these findings should be interpreted with caution; the analyses attempted to control for differences in baseline scores, including assessing for carryover effects. Analyses of time-course responses were not able to identify consistent differences among the drugs compared with placebo.

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

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

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

In five observational studies (6 publications) persistence with treatment with long-acting stimulant formulations (methylphenidate OROS or methylphenidate ER) was significantly longer compared with shorter-acting formulations (immediate-release methylphenidate or immediate-release mixed amphetamine salts) over periods of 6-month79 and 12-months [40, 43, 80, 81] following index prescription. One of these studies examined only adults treated with methylphenidate OROS (median duration of treatment 68 days; 95% CI, 65 to 71) compared with immediate-release methylphenidate (39 days; 95% CI, 33 to 52).[82] The findings of these studies should be interpreted with caution, however, until confirmed by a randomized controlled trial that would serve to rule out potential sources of bias, including between-group baseline differences in unmeasured clinical characteristics, physicians' prescribing preferences, and differences in reasons for discontinuation (e.g., change in insurance benefit, use of promotional samples). We rated these studies fair quality.

Data were derived from the Integrated Health Care Information Services National Managed Care Benchmark Database in 2 studies from the same group of researchers, with overlapping data. Using a definition of persistence as less than a 15-day gap in prescription

refills, the studies found methylphenidate OROS to be associated with greater persistence rates than immediate-release methylphenidate (12% compared with 1%, $P<0.0001$[40] and 15% compared with 3%, $P<0.0001$).[80, 81] The second study also reported persistence using less than a 30-day gap in refills as the definition and found 33% persistent with methylphenidate OROS and 5% with immediate-release methylphenidate.[80, 81] There is uncertainty about how well this study population represents patients in actual practice as ethnicity and comorbidity characteristics are not reported, and there are age and diagnosis differences between those receiving methylphenidate OROS compared with immediate-release methylphenidate.

California Medicaid claims files from a 3-year period were examined to identify youth prescribed methylphenidate (N=11 537).[43] This study population involved a lower than average proportion of White patients (45.3%) and higher proportions of Hispanic patients (26.1%). Total mean duration (days) of treatment without any 30-day gaps was greater for patients taking ER formulations (combined group of methylphenidate OROS = 83%, methylphenidate ER = 8.7%, methylphenidate SODAS = 8.3%) than for those taking immediate-release methylphenidate (140.3 compared with 103.4; survival time ratio, 1.37; 95% CI, 1.32 to 1.42). Subgroup analysis results suggest that persistence duration was greatest for methylphenidate OROS (147.2 days; 95% CI, 142.6 to 151.7 days) compared to methylphenidate SODAS (113 days; 95% CI, 100.9 to 125.1 days) or methylphenidate CD (101.1 days; 95% CI, 91.2 to 111.0 days). Together, ER formulations extended persistence duration regardless of ethnicity.

The Texas Medicaid Vendor Drug Program database was used to identify claims for newly started stimulants (2001-2002 school year).[79] Prescription refill patterns for children (75.7% male; mean age 9.93 years) with new claims for either immediate-release mixed amphetamine salts (n=3425), immediate-release methylphenidate (n=3343), or methylphenidate OROS (n=2781) were evaluated over 6-month assessment periods. Proportion of days of treatment without any 15-day gaps was greater for patients taking methylphenidate OROS than for immediate-release methylphenidate or immediate-release mixed amphetamine salts (0.5 compared with 37 compared with 42; $P<0.001$), as was proportion of patients that continued receiving therapy for 151-180 days (30.23% compared with 13.62% compared with 18.89%; $P<0.001$). Within those days of treatment, compliance rates, as measured using the Medication Possession Ratio (MPR), were higher in patients taking methylphenidate OROS compared to immediate-release methylphenidate or immediate-release mixed amphetamine salts (0.76 compared with 0.69 compared with 0.73; $P<0.001$).

Comparisons of SR formulations

Methylphenidate OROS (Concerta®) compared with methylphenidate CD (Metadate CD®).

Results from the fair-quality COMACS crossover study of 184 children suggest that relative improvements in SKAMP deportment and attention scale scores differed for the comparison of methylphenidate OROS 18-54 mg and methylphenidate CD 20-60 mg (both given once daily) depending on time of assessment.[83, 84] This study examined the pharmacodynamic differences of these products resulting from differences in pharmacokinetic profiles. The children were mostly male (73.8%), with a mean age of 9.6 years and they were randomized to low, medium, or high dosage treatment group sequences based on their previous dosages of immediate-release methylphenidate. Table 5 below illustrates effect sizes which suggest that methylphenidate CD was associated with significantly larger effect sizes than methylphenidate OROS in the morning, treatment effects were similar in the afternoon, and methylphenidate OROS was superior in the evening. This study presents several problems, however, in that the SKAMP scale has been

criticized for lack of sensitivity to change in symptoms, and that ANOVA analysis found the interaction of site x treatment x sequence (the order to randomization within patients) was found to be statistically significant. This finding resulted in the authors conducting additional analyses, however the effect of sequence was not included in these subsequent analyses. Therefore, these findings should be interpreted with caution.

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

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

Abbreviations: CON, Concerta; MCD, Metadate CD.

Methylphenidate OROS (Concerta®) compared with methylphenidate SODAS (Ritalin LA®). Two small crossover studies have found methylphenidate SODAS superior to methylphenidate OROS. A small 1-week crossover study of methylphenidate SODAS 20 mg compared with methylphenidate OROS 18 mg and 36 mg[41] found methylphenidate SODAS superior on the attention or deportment subscores of the SKAMP scale depending on the time-point and dose comparison. Secondary outcome assessment also found methylphenidate SODAS superior on 1 measure (proportion correct on math test). These limited differences are mitigated by concerns over the assessment tool (SKAMP) sensitivity, use of a simulated classroom, involvement of study sponsor in authorship, and differences in groups at baseline. A similar second crossover study of methylphenidate OROS (18 and 36 mg) and methylphenidate SODAS (20 and 40 mg) also assessed children in a simulated classroom setting after a single dose of the study medication using the SKAMP scale.[85] Here methylphenidate SODAS 40 mg was found superior to methylphenidate OROS 36 mg at all time points (0-4, 0-8, and 0-12 hours) based on the SKAMP attention subscale score area under the curve analyses, while methylphenidate SODAS 20 mg was not significantly different to either dose of methylphenidate OROS. Here, concerns over the clinical importance of the difference in area under the curve, involvement of study sponsor in authorship, and the impact of sequence of randomized treatment (analysis of treatment sequence was stated to be planned but results not reported) are present.

Dexmethylphenidate ER compared with methylphenidate OROS. A single, small (N=84) fair-quality crossover study compared 2 doses of dexmethylphenidate ER with 2 doses of methylphenidate OROS or placebo using a simulated classroom assessment.[86] The primary outcome was the mean change in the SKAMP combined score at 2 hours post-dose in the dexmethylphenidate ER 20 mg daily group compared to the methylphenidate OROS 36 mg daily group. Children were given the intervention for 7 days prior to the assessment. The mean change in SKAMP combined scores at 2 hours post-dose was statistically significantly greater with

dexmethylphenidate ER 20 mg daily compared with methylphenidate OROS 36 mg daily (adjusted mean change –11 compared with –6; $P<0.001$). Similar results were found comparing the higher doses (30 mg dexmethylphenidate ER and 54 mg methylphenidate OROS daily) to each other. At other time points, the drugs differed depending on the time of day. For time points up to 6 hours, dexmethylphenidate ER had statistically significantly superior change in SKAMP combined scores comparing either the 2 lower doses or the 2 higher doses to each other (*P* values ranged from <0.001 to =0.044). However, at later time points (10, 11, and 12 hours post-dose), methylphenidate OROS had statistically significantly superior change in SKAMP combined scores (*P* values ranged from <0.001 to <0.05). At hours 7, 8, and 9 there was no statistically significant difference between the drugs at either dose levels and analysis by Area Under the Curve from 0-6 and 6-12 hours was unable to identify statistically significant differences between the drugs. Analysis of attention and deportment subscale scores showed similar results. Assessments of math scores and problems attempted showed dexmethylphenidate ER superior up to 4 hours post-dose and methylphenidate OROS superior at 11 and 12 hours post-dose. In comparison to placebo, dexmethylphenidate ER was superior on SKAMP combined scores starting at 0.5 hours but was not statistically different to placebo at 12 hours. Methylphenidate OROS was superior to placebo starting at 1 hour (not at 0.5 hours) and remained superior through 12 hours.

According to the Center for Drug Evaluation and Research Medical Review,[87] data from 2 short-term, randomized, placebo-controlled, double-blind efficacy trials were submitted to the US Food and Drug Administration in the New Drug Application for dexmethylphenidate ER.[88, 89] Both were fair-quality. Study 2301 was a 7-week, parallel-group, flexible-dosing trial of 103 children.[88] Study US08 was a 2-week, fixed-dose, crossover trial of 54 children.[89] Dexmethylphenidate ER was significantly superior to placebo for both primary outcomes of change from baseline to final visit in Conners' ADHD/DSM-IV Scale-Teacher version in Study 2301 (–16.3 compared with –5.7 points; $P<0.001$) and of mean change in SKAMP-Combined scores from predose to 1-hour post-dose in Study US08 (–10.014 compared with 0.078 points, $P<0.001$).

Four small, fair-quality placebo-controlled trials have been conducted with dexmethylphenidate ER.[88-91] A 7-week, parallel-group, flexible-dosing trial of 103 children found dexmethylphenidate ER significantly superior to placebo in change from baseline to final visit in Conners' ADHD/DSM-IV Scale-Teacher version (–16.3 compared with –5.7 points; $P<0.001$).[88] Three crossover studies of dexmethylphenidate ER 20 mg daily evaluated response on the SKAMP scale in a laboratory classroom setting. All found dexmethylphenidate ER superior to placebo on the primary outcome measure of mean change in SKAMP combined score over 1 to 8 or 12 hours post-dose. Secondary analyses assessed differences at early time points; 2 studies found a statistically significant difference on mean change in the combined score at 0.5 hours (–2.2 dexmethylphenidate ER compared with 3.5 placebo; $P=0.001$[91] and –0.969 dexmethylphenidate ER compared with 3.336 placebo; $P=0.001$),[91,90] and the third found a difference starting at 1 hour post-dose (–10.014 compared with 0.078; $P<0.001$).[89] Lack of adequate variance data prevent pooling of these results. Because these are crossover studies, carryover effects must be taken into account, however results of such analyses were not reported.

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

Methylphenidate ER (Metadate®) compared with placebo. A 3-week trial of Metadate® compared with placebo enrolled 314 children out of 507 screened.[92] Twenty-four percent of those excluded at screening were because they responded to placebo during a 1-week washout period. This biases the study population towards the Metadate® arm, reducing the applicability of the results. The mean change in the primary outcome measure, the teachers' Clinical Global Impression Scale ratings combined in the morning and afternoon, were significantly lower (better) in the Metadate® group. Secondary measures also favored Metadate®.

Immediate release formulations: Efficacy outcomes

Dextroamphetamine compared with methylphenidate. We included 9 fair-quality studies (reported in 11 publications) of immediate-release dextroamphetamine compared with immediate-release methylphenidate.[35-37, 39, 46-48, 93-96] Two poor-quality studies and 1 poor-quality sub-group analysis were found.[29, 97, 98] All 9 fair-quality studies were randomized, blinded crossover trials. Table 6 summarizes the study characteristics.

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

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

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

The 2 largest studies,[35, 94] which used clear criteria for diagnosis, enrolled children with ADHD in order to test the hypothesis that some adverse events associated with stimulants are actually characteristics of ADHD and would be improved by drug treatment in 1 study,[94] and to test the differences between child and parent assessment of therapy in the other.[35] Neither study provides details on the efficacy results, other than summary statements that there were no differences between the 2 drugs based on children's self-assessment[35] and based on parent and teacher ratings.[94] These 2 studies had similar populations, primarily children with the Mixed subtype (82%), however comorbidities and ethnicity are not reported.

Of the 7 small studies (N=12 to 48), only 1 found a difference between the drugs.[48] This study assessed attention to task and deviant behavior in the usual classroom settings using a modified version of the Werry-Quay Direct Observational System.[48] The text of the paper reports that in a post hoc analysis, immediate-release dextroamphetamine was the most effective drug *in instances where a positive effect was seen.* Because this study did not use a standardized tool for diagnosis, and ADHD subtypes, comorbidities, or ethnicity are not reported, it must be assumed that significant heterogeneity in the population may have lead to the discordant results.

Response rates

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

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

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

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

Immediate-release formulations: Effectiveness outcomes

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

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

Integrated Health Care Information Services managed care claims data (described above) suggest that methylphenidate OROS was associated with fewer outpatient visits/hospitalization for accidents/injury than immediate-release methylphenidate over a 12-month follow-up period (odds ratio, 0.58; 95% CI, 0.353 to 0.945).[40] The study population (N=1,775) was 75% male, with a mean age of 9.7 years; however no other information regarding ADHD subtypes, comorbidities, or race/ethnicity were provided. In a second study, reported in two publications,[80] that also used data from the Integrated Health Care Information Services database to derive a larger sample (N=5,939) of somewhat older children (mean age of 15 years) who were also mostly male (77%), findings also suggest that methylphenidate OROS was associated with a lower probability of an emergency room visit (odds ratio, 0.79; 95% CI, 0.60 to 0.95)[80] and a lower probability of being hospitalized (odds ratio, 0.67; 95% CI, 0.45 to 0.99) over a 12-month

period.[81] This study also found that age, prior number of diagnoses, and drug or alcohol abuse were statistically significantly associated with the probability of being hospitalized [81] and that geographic region, total number of diagnoses, presence of drug or alcohol abuse, or accident or injury were statistically significantly associated with the probability of an emergency room visit and the number of visits.[80] However, the study also found that those taking immediate-release methylphenidate were statistically significantly younger (14 years compared with 17 years old), had more total diagnoses, and geographic differences in the proportions of patients taking methylphenidate OROS compared with immediate-release methylphenidate were present.

Immediate-release methylphenidate. In a 4-year follow-up study of 62 children treated with methylphenidate, the effect of duration of treatment on academic performance was assessed.[99] The duration of treatment was divided into <6 months, 6 months to 2 years, 2 to 3 years, 3 to 4 years, and those currently taking stimulants at follow-up. No differences were found between the groups on academic achievement as measured by teachers, the proportion repeating grades, in special education classes, or being tutored. Although the proportion of children repeating grades was lowest in the group continuing to take methylphenidate (8% compared with 46%, 50%, 36%, 31%), this difference was not statistically significant, possibly because of the small numbers of boys per group (n=10 to 14). Due to methodological limitations, this study provides no comparative information.

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

Stimulants. In a birth cohort study of 5713 children born in Rochester, Minnesota during the years of 1976 to 1982, 370 children were diagnosed with ADHD; 295 were treated with a stimulant and 84 were not.[101] Of those exposed to a stimulant, 66% took methylphenidate and 30% took dextroamphetamine (assumed to be immediate-release formulations). Median age of initiation of treatment was 10 years, median duration of treatment was 34 months, and median dose was 21 mg daily methylphenidate or methylphenidate equivalents. In addition to the 84 children diagnosed with ADHD but not receiving a stimulant at any time, the study also identified a control group from the birth cohort. Using a Poisson regression analysis, exposure at any time during follow-up was associated with lower rates of absenteeism (P=0.012) and duration of exposure was also significantly associated with lower absenteeism rates (P=0.041). Other factors were also found statistically significantly associated with number of days absent: Comorbid conditions (P=0.006), type of educational interventions (P<0.001), and maternal education at birth (P=0.005). Reading scores were similar between groups, although among those treated with a stimulant there was a "mild correlation" between the mean dose of stimulant and final reading score recorded (r=0.15; P=0.012). Children who were exposed to a stimulant were 1.8 times (95% CI, 1.01 to 3.2) less likely to be retained a grade at any time; based on

Kaplan-Meier analysis 66 children were retained a grade level. Drop-out rate (based on 69 of 301 cases available for analysis) was significantly associated with maternal education at birth, comorbid conditions, and type of educational intervention, but not stimulant exposure, duration, or dose. While this study has some methodological advantages over other studies, the main limitation is the number of children included, particularly in the non-medicated group, such that these findings should be interpreted cautiously.

Maintenance of short-term symptom response effects

Methylphenidate or immediate-release dextroamphetamine compared with placebo or non-drug therapy. All of the trials reported above are very short-term trials (range 1 to 9 weeks). Because of this serious limitation, the evidence does not provide information on the long-term benefits of these drugs in treating ADHD. To provide further evidence on duration of effect and longer-term outcomes, placebo- or non-drug therapy controlled trials of ADHD drugs with duration ≥6 months are reported here (Evidence Tables 7 and 8). We found 3 placebo-controlled trials of at least 6 months duration, 1 with immediate-release dextroamphetamine and 2 with immediate-release methylphenidate,[102-104] and 3 trials that randomized children to stimulant medication or non-drug therapy for 12 to 14 months.[105-107] Many of these studied indicated dissipation of medication effects over time, with unmedicated control groups having similar longer-term outcomes, particularly with follow-up of 2 years or greater.

Of these, the largest (N=579) and longest duration of follow-up is the Multimodal Treatment Study of Children with Attention Deficit/Hyperactivity Disorder (MTA). The MTA was a relatively large study funded by the NIMH assessing medication management, behavioral treatments, standard community care, and combined medication management and behavioral treatments over a 14-month period.[105] Following the 14-month trial the groups had follow-up at 2, 3, and 8 years post-randomization.[44, 105, 108, 109] Medication management could involve any stimulant medication, but started with methylphenidate titration. At study end, 73% of those in one of the medication management groups were on methylphenidate and 10% on immediate-release dextroamphetamine, with small numbers of patients taking no medication, pemoline, imipramine, bupropion, or haloperidol, and 6% refusing to be in the medication arm assigned. All participants met DSM-IV criteria for ADHD combined type, had a mean age of 8.5 years, and 80% were males. The sample population was ethnically diverse, with White (61%), African American (20%), and Hispanic (8%) representation. Comorbidities included anxiety disorder (33.5%), conduct disorder (14.3%), oppositional-defiant disorder (39.9%), affective disorder (3.8%), tic disorder (10.9%), mania/hypomania (2.2%), and other (e.g., bulimia, enuresis) (0.2%). This study was a pragmatic trial in that the treatments were given openly (after blinded titration in the 2 drug treatment arms), and participants could refuse the assigned arm or add or change treatments. In the community care arm, for example, 68% were taking ADHD medications although the mean dose and number of doses per day of methylphenidate was lower in the community care arm than the medication arms. However, the outcome measures were not effectiveness outcomes, so the trial must still be viewed as an efficacy trial.

After 14 months, medication management alone resulted in better scores compared to behavioral therapy for the symptoms of inattention (rated by both parents and teachers) and hyperactive-impulsive symptoms (parent ratings). Medication alone resulted in better scores on all ADHD symptoms than community care, except as measured by a classroom observer. Aggression-oppositional defiant disorder symptoms scores were better with medication alone compared to community care in teacher ratings only. Combined therapy (medication and

behavioral therapy) was not different to medication alone on any scale. The effect of medication management was maintained over the 14 month period.

Families were contacted 10 months after the end of the 14-month study (2 years post-randomization) to assess longer-term persistence of treatment effects.[44] A total of 540 (93%) of the originally randomized 579 participated and 10 months after study end, 72% in the medication management alone group, 70% in the combined therapy group, 38% in the behavioral therapy group, and 62% in the community care group were taking medication for ADHD. At 2 years, medication alone still resulted in better scores on ADHD and oppositional defiant disorder symptoms than behavioral therapy and community care. Despite this, analyses of combined outcomes from the medication management alone and combined therapy groups compared to those of the behavioral therapy and community care groups suggest a reduction in the magnitude of benefit by half from the 14-month to 24-month time points; effect size changes for ADHD symptoms were 0.60 compared with 0.30 and oppositional defiant disorder symptoms were 0.39 compared with 0.21. At 3 years of follow-up, 485 children participated (84%) and the proportions taking medication had changed. There was a decrease from 91% to 71% in the medication only/combined therapy group, an increase from 14% to 45% in the behavioral therapy group; and about constant (60% to 62%) in the community care group.[108] Along with these changes, the difference between groups in outcome measures was no longer statistically significant although all groups had improved compared to baseline scores on all measures. Further analyses indicated a benefit of regular medication use during the 14 month and 24 month periods, but not at 36 months. At 6 and 8 years, follow-up was possible in 78% and 75%, respectively.[108] Regular medication use was reported in 42% at 6 years and in 31% at 8 years, with no significant differences among the groups. Among children taking a stimulant at 3 and 8 years follow-up, mean dose had increased from a mean of 31 mg daily to 43 mg daily. Small numbers of children were taking a non-stimulant. Again, no differences were found between groups in efficacy measures. This follow-up included questions about other outcomes, including police contacts and arrests; academic performance on reading and math tests; grade point average; use of school services; and grade retention, but no differences among groups were found.

The other smaller trials of immediate-release methylphenidate, compared to placebo[102-104] or other non-drug interventions,[105-107] reported a dissipation of effect at earlier time points, 9 months to 2 years. Although some of these studies do not report mean doses, of those that do, the doses used in the MTA study were higher. Two studies were poor quality due to serious flaws that represent significant potential for bias, primarily due to no details on the subject's characteristics at baseline and no details on those who discontinued the study.[102,110]

Remission rates: Immediate-release methylphenidate

Three studies assessed the effects of withdrawing immediate-release methylphenidate after periods of treatment.[111-113] Two of these were poor quality,[111, 112] but the third study[113] included a group of 21 boys who had been treated with methylphenidate for a mean of 1.75 years and randomized to 3 weeks of placebo or methylphenidate. Using the Conners' Teacher Rating Scale, this study found that on the Subscale items of hyperactivity and defiance the scores during the placebo period were significantly worse than during the methylphenidate period. No baseline assessments were presented, and the analyses are based on scores at week 3 of each condition only so there is no information about the effectiveness of their pre-existing methylphenidate

regimen at baseline. In addition, the effect of order of drug/placebo was not analyzed in this crossover study, so the results must be interpreted with caution.

Other stimulants

Mixed amphetamine salts compared with mixed amphetamine salts XR (Adderall® compared with Adderall XR®). Fifty-one children were enrolled in a randomized crossover study of mixed amphetamine salts XR at 10, 20, and 30 mg, immediate-release mixed amphetamine salts 10 mg, and placebo given once daily for 7 days. Study assessments were taken during a single 12-hour day with assessments every 1.5 hours in a simulated classroom setting.[114] The study used a run-in period where children were given mixed amphetamine salts XR 20 mg after which 4% (2 of 51) dropped out after this session; the reasons are reported as withdrawal of consent. Based on the SKAMP scale deportment and attention variables and a math test (PERMP), the extended release formulation had statistically significantly better scores compared to placebo on all time points for the 30 mg dose. However, the 10 and 20 mg doses showed more variable benefits early (at 1.5 hours) and late (10.5 and 12 hours). Immediate-release mixed amphetamine salts showed a benefit over placebo early in the day, and more variable results as the day progressed. Direct comparisons were not undertaken. Considering these results, a more informative comparison would have been mixed amphetamine salts XR 20 and 30 mg once daily to immediate-release mixed amphetamine salts 10 mg twice daily.

Mixed amphetamine salts compared with immediate-release methylphenidate. Three small, fair-quality studies of mixed amphetamine salts compared with immediate-release methylphenidate were found.[32, 45, 115, 116] One was a parallel group randomized controlled trial[116] while the other 2 were randomized cross-over trials.[32, 45, 115] Two additional studies were rated poor quality[42, 117] due to no description of randomization or concealment of randomization code, no intention to treat analysis, high discontinuation rates or no randomization (clinician selected drug), and no blinding of patients or outcome assessors.

The parallel group randomized controlled trial enrolled 58 children with ADHD and randomized them to 3 weeks of mixed amphetamine salts, immediate-release methylphenidate, or placebo.[116] The mean doses at the end of study were mixed amphetamine salts 12.5 mg daily and immediate-release methylphenidate 25.2 mg daily (divided into morning +/- noon doses for both drugs). No differences were found in the mean IOWA Conners' Teacher Rating Scale scores (Inattention/Overactivity and Aggression/Defiance subscales) rated by teachers 4 mornings and afternoons a week, but mixed amphetamine salts was significantly better on both subscales when morning and afternoon scores were combined. No differences were found in parent ratings. The mean Clinical Global Impression-Improvement Scale score (rated by a blinded psychiatrist) was also significantly lower (better) in the mixed amphetamine salts group than the immediate-release methylphenidate group (final score 1.6 compared with 2.35; $P<0.05$), but the difference in the proportions of responders (90% compared with 65%, respectively) did not reach statistical significance. No differences were found on the Conners Global Index or final weight.

The 2 crossover studies were conducted in the same manner by the same authors and were conducted in a summer treatment program.[32, 45, 115] These short-term studies (6 to 8 weeks) enrolled 21 and 25 children with a higher prevalence of comorbid oppositional defiant disorder (67% and 52%) than the general population of children with ADHD. The first study found mixed amphetamine salts to be superior to immediate-release methylphenidate given once daily, while

few or no differences were found when comparing to immediate-release methylphenidate given twice daily, based on counselor and teacher ratings. Ratings of after school behavior indicated that the addition of a third 0.3 mg/kg dose of immediate-release methylphenidate or the mixed amphetamine salts 0.3 mg/kg once daily dose lead to the best results based on combinations of parent ratings and child task completion. The results of the second study indicate that on a few measures the low dose (10 mg twice daily) of immediate-release methylphenidate was not as effective as the higher dose (17.5 mg twice daily) or either dose of mixed amphetamine salts (7.5 or 12.5 mg twice daily). Measures where this difference was seen were interruption, conduct problems, negative verbalizations, the daily report card score, and counselor ratings of oppositional defiant scores. No difference in response was seen between the 2 doses of mixed amphetamine salts and the higher dose of immediate-release methylphenidate.

Mixed amphetamine salts compared with immediate-release dextroamphetamine. The evidence is limited to a single poor quality study of immediate-release dextroamphetamine compared with dextroamphetamine SR compared with mixed amphetamine salts compared with placebo.[118] No conclusions can be drawn.

Immediate-release dexmethylphenidate. Only 1 of 2 placebo-controlled studies of immediate-release dexmethylphenidate referred to in the most recent US Food and Drug Administration Medical Review (http://www.fda.gov/cder/foi/nda/2001/21-278_Focalin_medr_P1.pdf) has been published.[119] Immediate-release dexmethylphenidate was associated with significantly greater mean reductions in Teacher SNAP rating score than placebo (P=0.004) after 4 weeks in a fair-quality trial of 132 children (88% male; mean age, 9.8 years) with ADHD of mostly the combined type (64%).[119]

A small study of the effects of withdrawing immediate-release dexmethylphenidate after a 6-week titration period was poor quality. No conclusions can be drawn about the comparative efficacy of immediate-release dexmethylphenidate.[111]

Methamphetamine. The only evidence we identified for methamphetamine is in the form of a dissertation report published in 1973 and is characterized by measures of cognitive impulsivity, planning, new learning, IQ, and social behavior.[120] In this trial, 32 boys with hyperkinesis were randomized to 4 week treatment periods of either methamphetamine or placebo. Methamphetamine was started at 5 mg daily for first 2 weeks and then the dose was increased to 10 mg daily for the following 2 weeks. The main findings were that methamphetamine was superior to placebo in improving scores on measures of impulsivity, social behavior, and on 1 of 2 measures of new learning. There were no between-group differences on measures of general intelligence. It did not appear that adverse effects were assessed in this trial.

Methylphenidate transdermal system (Daytrana®). In a fair quality trial (N=270), transdermal methylphenidate was not found to be significantly different to methylphenidate OROS after a 7-week period. Dose on either treatment was titrated in a double blind fashion over 5 weeks.[121] Children applied the patch (placebo or active) and took the capsule (placebo or active) at 7 am each day. The primary outcome measure was the investigator's assessment of the total score on the ADHD-Rating Scale, completed once a week, although multiple other scales were used as secondary outcome measures. No difference was found between drugs in the mean change from baseline (difference in least squares mean change –2.6; 95% CI, –6.7 to 1.5). Similarly,

differences were not found between drugs in ratings by teachers (measured twice weekly) or parents (measured at 11 am and 3 pm) using the Conners' scale. Measurements before 11 am were not taken, and the proportion of children whose improvement in score would be considered a response was not reported. Although no difference was found between transdermal methylphenidate and methylphenidate OROS, the study may not have been powered to detect such a difference, as the sample size was determined based on transdermal methylphenidate compared with placebo.

Two placebo-controlled trials of transdermal methylphenidate have been published.[122, 123] A 1-week, randomized, placebo-controlled, crossover trial conducted in a laboratory classroom setting (N=80), examined transdermal methylphenidate compared placebo patch worn for 9 hours, after a 5 week dose-optimization period. Compared to the group randomized to the treatment sequence which started with placebo, we noted that a significantly greater proportion of patients randomized to receive transdermal methylphenidate first had ADHD of the inattentive type (27% compared with 5%; P=0.01). As no period or sequence effects were found for scores on the primary outcome of SKAMP Deportment, however, this baseline difference was unlikely to have seriously biased the results. Findings from a mixed linear model ANOVA showed that transdermal methylphenidate was significantly superior to placebo on the SKAMP Deportment and Attention scales at timepoints starting at 2 hours up to 12 hours post-dose, and in the number of math problems attempted and number of math problems correct on the Permanent Product Measure of Performance (PERMP). In a somewhat similar study, 117 children were assigned to placebo or transdermal methylphenidate worn for shorter periods (4 or 6 hours), again with 5 weeks of dose-optimization but with a practice day in the classroom plus 3 separate laboratory classroom days with assessments every 2 hours up to 10 hours after patch application.[122] The SKAMP deportment scale scores (no change from baseline) were the primary outcome, and the analysis reported primarily the comparison of the transdermal methylphenidate groups with placebo averaged over the time the patches were actually worn (4 and 6 hours). During this time, the mean score with placebo was 11.5 compared with 5.7 and 5.9 with the 4- and 6-hour transdermal methylphenidate groups, respectively (P<0.001). The difference between placebo and either transdermal methylphenidate group was seen at the first time point (2 hours post-application) and reductions in scores began 2 hours after transdermal methylphenidate removal. At 4 hours after removal the scores were similar to baseline.

Lisdexamfetamine dimesylate. We identified 2 fair-quality, randomized controlled trials of lisdexamfetamine, a 3-way crossover trial that compared 1-week treatment periods of lisdexamfetamine, mixed amphetamine salts XR, and placebo in 52 children,[124,297] and a placebo-controlled, 4-week, parallel-group trial of 3 different dosages of lisdexamfetamine (30 mg, 50 mg, or 70 mg) in 290 children.[125] Both trial populations are notable for reflecting more racial diversity than in other randomized controlled trials, and results of subgroup analyses based on race were reported in the Center for Drug Evaluation and Research Medical Review (see Key Question 3 below for further discussion). In these trials, only 54% of patients were White, 24% were African American, 16% were Hispanic, 1% were Asian, 1% were Native Hawaiian/Pacific Islander, and 4% were Other.

Primary efficacy analyses were performed using the average of Swanson, Kotlin, Agler, M-Flynn and Pelham - Deportment Subscale (SKAMP-DS) scores across the treatment assessment day,[124, 297] or the change in mean ADHD rating scale IV total score.[125] Scores in all lisdexamfetamine groups were significantly superior to placebo group scores across both trials.

There were no significant differences between lisdexamfetamine and mixed amphetamine salts XR in LS-mean SKAMP-DS scores. Results of subgroup analyses generally suggested that lisdexamfetamine was superior in efficacy compared to placebo, and similar in efficacy to mixed amphetamine salts XR, regardless of age, gender, race, or baseline illness severity as measured by the Clinical Global Impression Scale. The few exceptions pertained to the 30 mg dosage of lisdexamfetamine.[125, 189] Compared to mean changes in ADHD rating scale IV for lisdexamfetamine 30 mg compared with placebo for the population overall (–21.8 compared with –6.2 points; $P<0.0001$), treatment effects appeared less robust in the subgroups of girls (–19 compared with –8.1; $P=0.0537$) and non-Caucasians (–18.5 compared with –10.1; $P=0.0754$). A post hoc analysis of the effects of lisdexamfetamine compared with placebo during the 8 to 10 am, noon to 2 pm, and 4 to 6 pm times indicated placebo to be superior in the percent change on the Conners' scale parent ratings (total and ADHD index at all 3 time periods).[126] The difference between placebo and lisdexamfetamine showed a small declined over time. For example, the difference between placebo and drug at 10 am was 47%, at 2 pm was 47.6%, and at 6 pm was 43.9%. We have also identified another placebo-controlled trial of lisdexamfetamine that was listed as completed on clinicaltrials.gov (Study NTC00500149). This study enrolled 129 children, with a primary outcome of onset of efficacy and secondary outcome of duration of efficacy (up to 13 hours), but a published version is not yet available.

Modafinil. In a fair-quality randomized controlled trial of 60 children and teens, modafinil was found to be similar to immediate-release methylphenidate after 3 and 6 weeks of treatment with 200 to 300 mg of modafinil or 20 to 30 mg per day of immediate-release methylphenidate (based on a weight cut-off of 30 kg).[127] Using the ADHD parent and teacher rating scale, significant differences were seen compared to baseline, but not between groups ($P=0.74$ for parents; $P=0.60$ for teachers). Similarly, no statistically significant differences were seen in the proportion of responders (>40% reduction in score; 73% compared with 70% for parents rating of modafinil and immediate-release methylphenidate, respectively; 73% in both groups based on teachers ratings). Although the study was well-conducted, details about children at baseline were too limited to guide generalization of the results.

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

Among the later trials, there were 3 that used very similar designs and involved very similar patient populations. In these trials, a total of 638 children with ADHD were randomized to either modafinil (mean dosage range 361 mg to 395 mg) or placebo for treatment periods that were 7-9 weeks in duration.[128, 130, 131] Patient mean age was 10 years and 71% were male. Change in the ADHD rating scale was identified as the primary outcome in all 3 trials. In these trials, using a higher dosage level than in the earlier trial, modafinil was found to be consistently superior to placebo on ADHD rating scale score change from baseline and also in the proportion

of patients that were rated as "much improved" or "very much improved" on the Clinical Global Impression-Improvement Scale.

In the final and most recent placebo-controlled trial of modafinil, the objective was to compare the efficacy and safety of several different once and twice daily dosing regimens.[132] In this trial, 248 children with ADHD were randomized to 4-week treatment periods of either 300 mg once daily or divided (morning/mid-day) dosages of 200/100 mg, 100/200 mg, or 200/200 mg. The majority of patients were male, with a mean age of 9 years. With regard to mean change from baseline in ADHD rating scale, only the groups assigned to 300 mg once daily or 200/100 mg divided dosages had significantly greater score reductions than those in the placebo group. However, none of the groups were superior to placebo for the proportions of patients rated as "much improved" or "very much improved" on the Clinical Global Impression-Improvement Scale.

Atomoxetine

Atomoxetine compared with methylphenidate. While 4 studies have included both atomoxetine and immediate-release methylphenidate, only 2 made relevant comparisons for assessing comparative efficacy.[133, 134] In a fair-quality, 8-week, noninferiority trial (N=330), atomoxetine was found noninferior to immediate-release methylphenidate based on ADHD rating scale response rates (>40% reduction in score; atomoxetine, 77%; immediate-release methylphenidate, 82%; P=0.4, assuming a margin [delta] of 18%).[134] The mean final doses of drug were somewhat imbalanced, with 44 mg daily of atomoxetine and 18 mg daily for immediate-release methylphenidate. Differences were not found between groups using other measures or through logistic regression controlling for multiple factors. Another study comparing atomoxetine and immediate-release methylphenidate found no differences between the drugs based on changes in the ADHD rating scale, the Conners' Parent Rating Scale Revised hyperactivity item, and the Clinical Global Impression-Severity Scale.[133] Concerns over the study quality indicating potential bias suggest caution in interpreting these findings (see Evidence Table 4).

A second study comparing immediate-release methylphenidate and atomoxetine primarily assessed the impact of each drug on sleep, using a crossover design and sleep labs.[135] This small study (N=75) evaluated sleep onset (latency) using actigraphy, a device worn on the wrist to measure activity over 7 weeks. The mean dose of immediate-release methylphenidate was 42.29 mg daily, and of atomoxetine was 58.27 mg daily. Only 50 of 85 patients (59%) randomized were included in the analysis, mostly due to inadequacy of actinography data, a number that does not reach the stated 60 needed to adequately power this analysis. Additionally, 21% of those screened (22 of 107) were excluded for a variety of reasons relating largely to not complying with a pre-specified "light-out" time consistently. The primary outcome is the comparison of the mean *change* in sleep-onset latency from baseline to endpoint. At baseline, 43.5% were not taking stimulants. Both groups experienced an increase in time to fall asleep, but the immediate-release methylphenidate group had a significantly longer increase (39.24 minutes) compared to atomoxetine (12.06 minutes). A similar decrease in overall sleep time was also seen. Differences were not found between the drugs in ratings of ADHD symptoms. Results of planned ANOVA analysis of sequence were not reported, so the impact of order of randomization cannot be assessed here but may be important. The study involved funding, data analysis, and authorship by the maker of atomoxetine. Because of the above concerns, we have rated this study poor quality.

Atomoxetine compared with methylphenidate OROS. In a 6-week fair quality noninferiority trial, atomoxetine was not found noninferior to methylphenidate OROS.[136] Using response (40% or more reduction of the ADHD–RS) as the primary outcome, and a margin of 15%, methylphenidate OROS was found superior to atomoxetine with an overall 56% response rate with methylphenidate OROS compared with 45% with atomoxetine (number needed to treat, 9; *P*=0.02). Analysis of the subgroup with prior stimulant exposure (n=310) found again a statistically significantly higher rate of response with methylphenidate OROS (51%) compared to atomoxetine (37%) (number needed to treat, 8; *P*=0.03). In this subgroup, atomoxetine was not found different than placebo. However, in the smaller subgroup without prior stimulant exposure, (n=191) the 2 drugs were not found to be statistically significantly different in response rates (57% atomoxetine compared with 64% methylphenidate OROS). Secondary outcome measures, such as the mean change in ADHD rating scale total and subscale scores, resulted in similar findings. This study used over-encapsulation of methylphenidate OROS. The authors reported that dissolution studies indicated no alteration in drug release but no data are reported. Also, atomoxetine was administered in a divided dose rather than given once daily.

The Formal Observation of Concerta® compared with Strattera® (FOCUS) trial compared open-label methylphenidate OROS and atomoxetine for 3 weeks in 1323 children with ADHD.[137] Main findings from the FOCUS trial are summarized in Evidence Table 3, but will not be discussed here due to concerns about study quality. The FOCUS trial was rated poor quality based on a combination of flaws including undescribed methods of randomization and allocation concealment, significant between-groups baseline differences in ADHD severity, and lack of information about attrition and number of patients included in analyses (Evidence Table 4).

Atomoxetine compared with mixed amphetamine salts XR (Adderall SR®). The extended release form of mixed amphetamine salts (Adderall SR®) 10-30 mg was superior to atomoxetine 0.5-1.2 mg/kg daily on most efficacy outcomes after 3 weeks in a fair-quality trial of 215 children (mean age, 8.7 years).[138] This trial, also known as Strattera®/Adderall XR® Randomized Trial, was conducted in a simulated classroom setting which involved 12 hours of observation per day. Participants were mostly male (71.9%) who were diagnosed with ADHD of either the hyperactive/impulsive or combined subtypes. Mixed amphetamine salts XR was associated with significantly greater reductions in the mean SKAMP deportment scale scores, which was prespecified as the primary outcome (–0.56 compared with –0.13; *P*<0.0001). Mixed amphetamine salts XR was also associated with superior outcomes on multiple secondary outcome measures including mean change in SKAMP Attention scale scores, proportions of SKAMP scale "responders" (≥ 25% improvement on deportment and/or attention scales), and numbers of math problems attempted and/or completed correctly.

Atomoxetine compared with standard therapy. A British study of atomoxetine compared with standard treatment assessed the child's function and health status using the final score on the Child Health and Illness Profile – Child Edition as the primary outcome measure.[139] The total score of the tool is stated to not have previously been used, but to have been validated by the owner (Riley and colleagues). This research was cited only as "submitted for publication," and a recent search did not uncover such a publication, so it is considered an unvalidated tool here. A total of 201 patients were randomized to 10 weeks of treatment with either atomoxetine or whatever treatment (including no treatment) prescribed by the investigator or the treating

physician. This was an open-label study, with parent making the assessments. This study is poor quality, with no description of randomization and allocation concealment procedures, and some imbalances between the groups at baseline (Inattentive ADHD subtype 11.5% compared with 3.1%, previous exposure to stimulants 59.6% compared with 70% in atomoxetine and control groups, respectively). Additional concerns were that the higher discontinuation rate in the atomoxetine group was not taken into account by the modified intention to treat analysis described (it appears only 75% of atomoxetine group is included in the analysis, compared to 94% of control group), the standard treatment group was described as having their treatment determined by unblinded investigators, and the primary author being an employee of the manufacturer of atomoxetine.

Atomoxetine compared with placebo. Six placebo-controlled studies of atomoxetine in children and adolescents with ADHD found atomoxetine to be superior based on ADHD rating scale as the primary outcome measure and various scales as secondary measures.[140-145] Results of 2 of the 6 trials were described as identically-designed and were reported in 1 publication.[142] The mean change on ADHD rating scale in these 6 to 9 week studies ranged from –12.8 to –16.7 with atomoxetine compared to –5.0 to –7.0 for placebo. A study of once daily dosing reported response rates (defined as ≥25% reduction in ADHD rating scale score) in the atomoxetine group of 59.5% compared with 31.3% in the placebo group ($P<0.001$).[144] Remission rates (defined as an endpoint Clinical Global Impression-Severity Scale score of 1 or 2) were 28.6% and 9.6%, respectively ($P=0.003$). All studies were funded and co-authored by representatives of the manufacturer of atomoxetine. All used the DSM IV criteria, however the proportions of ADHD subtypes varied, for example 52% to 79% of enrolled children had the Mixed subtype. More concerning is the variation in the proportions of children with each subtype per assigned group. Proportions of children with comorbidities also varied across the studies (e.g. 18% to 45% with oppositional defiant disorder). Results of a subgroup analysis from 2 identically-designed placebo-controlled trials[142] suggested that atomoxetine was associated with significantly greater reductions in ADHD rating scale total scores than placebo (–17.0 compared with –7.5; $P<0.001$) in 98 of the original 291 children with comorbid ADHD and oppositional defiant disorder.[146] No subgroup analyses based on ADHD subtypes or other comorbities were reported. Based on what appears to be post hoc analysis of secondary outcome measures of 1 of these trials,[145] no statistically significant difference between atomoxetine and placebo was seen in academic performance (based on the Academic Performance Rating Scale) or quality of life (based on the Children's Health Questionnaire psychological summary score) after 7 weeks.[147]

In a good-quality systematic review, these 6 trials and 3 additional trials with placebo and active arms were combined in a meta-analysis that indicated atomoxetine was superior to placebo in improving ADHD rating scale total score (standardized mean difference, –0.638; 95% CI, –0.76 to –0.516), as well as subscale scores on inattentive symptoms, hyperactivity/impulsive symptoms, and the Conners' scales with teacher and parent ratings.[148] Meta-regression identified study duration and number of study sites, male sex, ADHD hyperactive/impusive subtype, oppositional defiant disorder, baseline ADHD rating scale total score, inattention score, and hyperactivity/impulsivity score to be negatively associated with response. After adjusting for these confounders, atomoxetine remained superior over placebo. Six adverse events were found to occur significantly more often with atomoxetine (numbers needed to harm; *P* value): decrease in appetite (8; $P<0.05$), somnolence (19; $P<0.05$), abdominal pain (22; $P=0.02$), vomiting (30; $P=0$ .02), dyspepsia (49; $P<0.01$), dizziness (53; $P=0.01$), fatigue (62; $P=0.01$), infection (72;

P=0.02), and pruritus (120; *P*=0.04). Risk of adverse events was found to be negatively associated with mean age, ADHD inattentive subtype, baseline ADHD rating scale score, and hyperactivity/impulsivity score. Meta-regression identified high ADHD rating scale total and hyperactivity/impulsivity scores at baseline to be significantly associated with adverse events (*P*<0.01).

Based on the 6 placebo-controlled trials above, with data apparently provided by the manufacturer, meta-analysis was performed to assess differences in response between younger (ages 6-7) and older (ages 8-12) children. Atomoxetine was found statistically significantly superior to placebo on the ADHD–RS and Conners' scales, in both age groups, although the difference between atomoxetine and placebo was smaller in the older age group compared with the smaller age group.[149] This study also found that abdominal pain, decreased appetite, vomiting, and somnolence occurred significantly more often with atomoxetine than placebo in younger children, and decreased appetite, somnolence, irritability, and fatigue among older children. There was a significant treatment by age effect in abdominal pain (*P*=0.04), vomiting (*P*=0.053), pyrexia (*P*=0.058), and cough (*P*=0.007). Statistically significant but small increases in pulse were seen in both younger and older children, and older children experienced increases in both systolic and diastolic blood pressure. In these short-term studies, statistically significant weight decrease was seen in both age groups (–0.5 and –0.6 kg).

Atomoxetine was associated with less rapid times to relapse than placebo under double-blind conditions (218 days compared with 146 days; *P*<0.001) in a randomized subgroup of 416 children (out of 603) that were classified as "responders" following an initial 12-week, open-label period of treatment with atomoxetine.[144] The primary outcome measure was the number of days to relapse and relapse was defined as return to 90% of baseline ADHD rating scale score and Clinical Global Impression-Severity Scale score increase of at least 2 points. Similarly, fewer patients on atomoxetine relapsed than on placebo (22% compared with 38%; *P*<0.002). As a continuation of that study, subjects initially randomized to atomoxetine were rerandomized to an additional 6 months of either atomoxetine (n=81) or placebo (n=82), with mean time to relapse being 160 days for atomoxetine and 130.8 for placebo, *P*<0.008. Relapse rates were 2.5% for atomoxetine and 2% for placebo and the relative risk for relapse during placebo treatment was 5.6 (95% CI, 1.2 to 25.6).[150]

Atomoxetine: Effectiveness outcomes. A few noncomparative observational studies evaluated duration of effectiveness for atomoxetine.[151, 152] In 1 study, 229 children who had a ≥40% reduction in ADHD rating scale total score after a 7- to 9-week trial of atomoxetine (51% of original sample) were randomly assigned to continue treatment for 8 months at the same or lower dosages.[151] In the other study, stability of treatment response over time was examined in 312 children who had completed 24 months of open treatment with atomoxetine (34% of original sample).[152] Both studies were consistent in finding that improvements in ADHD symptoms and in aspects of health-related quality of life were maintained during longer-term treatment periods, even with reduced dosages of atomoxetine. Although encouraging, findings from these studies must be interpreted with caution, mainly due to the extremely high attrition rates.

In a pooled analysis of data from 714 children who received atomoxetine for at least 3 years in open-label studies, 1.7% of children and 2% of adolescents discontinued due to adverse events indicating high rates of persistence in both age groups.[153]

Functional outcomes: Immediate-release methylphenidate

We found extremely limited information on functional capacity outcomes from the clinical trials. Therefore, we included observational studies of ≥6 month's duration that reported outcomes reflecting functional capacity, for example academic achievement in terms of progression through grades, suicide attempts, police contacts, etc. We found 2 studies that reported these outcomes among adult patients who had been treated as children.[99, 154-157] Due to various methodological limitations, these studies do not provide good evidence for long-term effectiveness, even for methylphenidate.

In a cross-sectional follow-up study of young men diagnosed with 'persistent hyperactivity' at ages 6 to 12 years, those who had not received medication were compared to a group that had received methylphenidate for at least 3 years during childhood.[156] The groups were initially seen in different time-periods, separated by 5 to 15 years. Because the groups were from different periods, a third group of normal children who were contemporaneous to the methylphenidate group was added. The sizes of the groups also differed, with 64 in the non-treated hyperactive group, 20 in the methylphenidate treated group, and 20 in the normal controls, and data were not available for all subjects on all questions. Mean follow-up of the hyperactive groups was 10 to 12 years. No information on baseline characteristics from childhood is given. No consistent differences in functional outcomes were found between the methylphenidate and untreated groups (Table 8). Considering the potential confounding of differences in the years the children were treated, and the very small numbers of subjects per group per variable, these results should be interpreted with caution.

Table 8. Long-term functional outcomes of methylphenidate from Hechtman, 1984[156]

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

Abbreviations: NA, not applicable.

The methylphenidate group in this study was previously reported after 5 years of follow-up (as adolescents), with comparison groups of boys treated with chlorpromazine or untreated boys.[154]

This study reported academic performance, with no differences found between the groups.

Adolescents (ages 13 to 17)

Evidence on the effectiveness of pharmacotherapy for ADHD in adolescents is very limited (Evidence Tables 1 and 2). We did not find any effectiveness trials or long-term observational studies (assessing functional or safety outcomes) in adolescents with ADHD. Adolescents were studied in 1 head-to-head trial of immediate-release methylphenidate and methylphenidate SR (OROS)[158] and in 9 placebo-controlled trials of methylphenidate.[159-168] Mixed age populations including adolescents were studied in efficacy trials of atomoxetine, however data are not stratified by school age and adolescents and so are considered in the school-age children section (above).

Direct comparisons

Immediate-release methylphenidate compared with methylphenidate OROS (Concerta®). A single, very small, *single blinded* crossover study of 6 adolescent boys showed methylphenidate OROS superior to immediate-release methylphenidate on some simulated measures of driving skills, dependent on the time of day of testing.[158] ADHD was confirmed using the DePaul ADHD Rating Scale IV (parents completed), the Diagnostic Interview Schedule for Children (DISC-IV), and the Standardized Interview for Adult ADHD. Four of the 6 had inattentive type ADHD. After 7 days of dosing, the teens performed significantly better while taking methylphenidate OROS on 3 of 9 measures (inappropriate braking, missed stop signals, and speed control) at each testing time (2 pm, 5 pm, 8 pm, and 11 pm). Because only F- and P-values are reported, it is not possible to interpret the magnitude of differences found. An analysis of a combined score of 7 (of 9) measures at each of the 4 time points indicated that there were no differences between the formulations at the 2 pm and 5 pm test times, but the scores were significantly lower with the immediate-release formulation at the 8 pm and 11 pm times ($P<0.01$). Self-evaluations of risky driving behavior did not show any differences between the formulations. Adverse events were not measured. Since 2 teens were previously on methylphenidate OROS, 2 had been taking immediate-release methylphenidate, and the only person blinded was an observer in the driving simulator, it would be important to know the effect of prior medication and order of randomization. These were not assessed.

Methylphenidate OROS compared with mixed amphetamine salts XR. A 17-day, small (N=35) crossover study compared the effect of stimulant use on the driving ability of adolescents with ADHD.[169] There was no significant difference between methylphenidate OROS 72 mg once daily and mixed amphetamine salts XR 30 mg once daily in self-reported symptom improvement among participants ($P=0.55$) although both interventions appeared to improve symptoms compared to baseline (no further data provided). methylphenidate OROS was associated with significantly better overall driving performance relative to mixed amphetamine salts based on testing in a driving simulator ($P=0.03$). However, subjective ratings of driving performance by participants failed to detect a difference between the 2 study drugs.

Indirect comparisons

Mixed amphetamine salts XR. A 4-week, placebo-controlled study of extended-release mixed amphetamine salts (Adderall XR®) using a forced-dose titration schedule (up to 40 mg once daily) assessed efficacy in 287 patients using the ADHD rating scale IV and Clinical Global Impression-Improvement Scale scores. All doses of extended-release mixed amphetamine salts

were associated with significant improvement in ADHD rating scale IV scores compared to placebo. Mean change in ADHD rating scale IV score from baseline was –17.8 for active treatment (all doses) and –9.4 for placebo ($P<0.001$ for all doses except 10 mg dose, for which $P<0.005$) with significant score improvement for all doses of extended-release mixed amphetamine salts ($P\leq0.005$). Based on Clinical Global Impression-Improvement Scale scores, the proportion of patients who were improved following treatment with extended-release mixed amphetamine salts (range 51.9% to 70.7%, dose dependent) was significantly higher than placebo (mean difference, 26.9%; $P\leq0.01$).

Methylphenidate OROS. One trial compared the efficacy of methylphenidate OROS to placebo in adolescents. Of 220 enrolled subjects, 177 were randomized to a 2-week double-blind phase following an open-label titration phase lasting up to 4 weeks.[170] The primary outcome of this trial was change from baseline in ADHD rating scale score, although the Conner-Wells Adolescent Self-report of Symptoms Scale and the Child Conflict Index were also used to assess efficacy. There was a significantly higher mean change in investigator-assessed ADHD rating scale scores with methylphenidate OROS compared with placebo (–14.93 compared with –9.58; $P=0.001$). Parent-assessed scores were similar, and also favored methylphenidate OROS over placebo ($P=0.008$), as did Conner-Wells Adolescent Self-Report of Symptoms Scale scores ($P=0.001$) and Child Conflict Index scores ($P=0.005$).

Immediate-release methylphenidate. Seven placebo-controlled crossover trials of immediate-release methylphenidate enrolled a total of 171 adolescents.[159-167, 171, 172] Patients were diagnosed primarily using the DSM III-R or DSM-IV criteria. Only 1 trial clearly described the distributions of the different ADHD subtypes and in this trial there were 87.5% of patients with the Combined subtype.[172] Immediate-release methylphenidate generally was superior to placebo in improving core ADHD symptoms, but was associated with greater frequency of appetite and sleep problems. Methylphenidate mean dosages ranged from 8.8[159] to 75 mg.[164] The trials reported a variety of outcome measures. All but 1 were consistent in using various forms of the highly valid Conners' rating scales (long and abbreviated forms).[172] However, inconsistency in the way results are reported make estimation of an overall magnitude of effect impossible.

Atomoxetine. In a pooled analysis of data on 601 children aged 12 to 16 from 6 placebo-controlled trials (short-term) and 7 open-label extension studies (up to 2 years in duration) of atomoxetine were analyzed.[173] Data out to 24 months treatment was available for 217 adolescents (36%). Overall, the combined analysis showed an improvement of 20 .2 points ($P<0.001$ compared to baseline) on the ADHD rating scale. Improvements reached their peak at 6 months, and improvements were maintained out to 24 months. The mean dose also peaked at 6 months (1.47 mg/kg/day). These data reflect highly selected patients, with those tolerating atomoxetine out to 2 years only.

Functional outcomes: Immediate-release methylphenidate

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

responded to methylphenidate in an uncontrolled study,[157] after 6 to 14 months of follow-up the authors simply report that 15 of the 16 had "improved grades".

In a study using interviews and data from patient charts, 97 young adult males who had taken methylphenidate as children and teens (mean age at discontinuation of methylphenidate was 17 years) were studied.[155] There is no comparison group in this descriptive study. The authors conducted a hierarchical analysis to assess the effect of various factors. Significant findings relating to use of methylphenidate were fewer suicide attempts positively associated with higher dose of methylphenidate and emancipated living situation and level of relationship commitment were positively associated with response to methylphenidate. Early response to methylphenidate was negatively associated with high school graduation, however.

Adults

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

Direct comparisons

Only 1 head-to-head trial has been published to date focusing on symptoms of adult ADHD (Evidence Tables 9 and 10).[51] Identical proportions of adults (n=22) with ADHD responded to modafinil 206.8 mg and immediate-release dextroamphetamine 21.8 mg (48% compared with 48%; *P*=NS). Response was defined as a 30% or greater mean improvement in ADHD Rating Scale total scores. Patients in this trial were mostly male (59%) and had a mean age of 40.8 years.[51 51]

Placebo-controlled trials

Characteristics

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

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

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

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

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

ADHD symptom assessment

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

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

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

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

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

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

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

Additional outcomes

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

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

Atomoxetine: Quality of life. We identified 1 placebo-controlled and 1 uncontrolled trial that examined the effects of atomoxetine on quality of life in adults.[175, 220] A 6-month trial of atomoxetine compared with placebo (N=410; mean age, 36.5; 60% male; 82% Caucasian), dose flexible from 40 mg to 100 mg daily based on tolerability,[175] found no difference in change from baseline between treatment groups in relationships, psychological health, productivity, and work productivity. The study reported a significant decrease in mean change from baseline to endpoint for the atomoxetine group (–11.5) compared to the placebo group (–9.9; P=0.027) in the Conners' Adult Attention Deficit/Hyperactivity Disorder Rating Scale (CAARS), but found no differences between the treatment groups in the ADHD Inattention and Hyperactivity-impulsivity sub-scales or the Adult Self-Report Scale (ASRS).

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

Atomoxetine: Driving performance. The majority of evidence from 3 placebo-controlled trials found that atomoxetine was not significantly superior to placebo in improving driving outcomes. One large trial and 2 smaller trials assessed simulator driving performance among subjects taking atomoxetine compared with placebo. A 24-week trial of 410 subjects (mean age 36.5; 60% male) of atomoxetine (dose flexible from 40 mg to 100 mg daily based on tolerability) compared with placebo[175] found no differences in self report of the Driving Behavior Survey (DBS) between treatment groups. Driving behavior was rated as significantly more improved for the atomoxetine group compared with the placebo group in a subsample of 252 of 410 patients for which observer ratings were available (mean improvement 6.1 compared with 2.0; P=0.01). A smaller, 3-week trial of twenty subjects (mean age 36; 44% male) comparing atomoxetine (titrated up to 1.2 mg/kg for 3 weeks) to placebo[177] reported mixed results. Self-ratings, but not other-ratings (such as friends or spouse) or examiner-ratings, were significantly greater for atomoxetine on the Safe Driving Behavior Scale and on simulator driving performance. Finally, a small 3-week trial of young adults (ages 19-25) found that atomoxetine (titrated up to 80 mg daily) was not statistically different than placebo in mean total driving score.[186]

Immediate-release methylphenidate. In three of four small trials, immediate-release methylphenidate was superior to placebo in reducing anxiety as measured using the Hamilton Anxiety Scale,[181] the Beck Anxiety Scale,[203] and the tension-anxiety subscale of the Profile of Mood States scale.[214] Whereas, in the fourth trial (N=45), similar numbers of participants with immediate-release methylphenidate compared with placebo (7% compared with 4%), had anxiety as defined as a Hamilton Anxiety Scale score above 21 points.[188] A 3-week trial[216] examined sleep quality among 33 adults (97% combined ADHD subtype) with a mean age of 38 years. No differences were found in 5 of 6 assessments, although the immediate-release

methylphenidate group experienced fewer nocturnal awakenings (0.82 compared with 0.99; $P<0.01$).

Immediate-release methylphenidate was also 1 of 3 drugs with data available regarding driving behavior. Driving performance was assessed in 3 small single-dose, placebo-controlled trials.[178, 184, 206] A recent placebo-controlled crossover study of 18 ADHD patients (mean age 38, male 61%) performed on a primary highway during normal traffic assessed a single mean dose of 14.7 mg methylphenidate.[206] In order to test the primary outcome measure, a camara was mounted on the roof of the test vehicle to measure the amount of weaving of the car (standard deviation of lateral position-SDLP). Drivers were instructed to drive with a steady lateral position while maintaining a constant speed of 95 km/hr (60 mph). The study found that amount of weaving was significantly less with immediate-release methylphenidate (18.8 cm) compared with placebo (21.1 cm; $P=0.004$). Self-reports on various measures of driving quality and driving style were also superior for methylphenidate relative to placebo. However, the study also found that mean lateral position, standard deviation of speed (km/h), and mean speed were not significantly different between the 2 groups.[206] Two additional studies have examined simulator driving performance trials. Results found that immediate-release methylphenidate 10 mg significantly improved an Impaired Driving Score ($P=0.05$),[184] immediate-release methylphenidate 40 mg significantly reduced steering variability,[178] and immediate-release methylphenidate 20 mg significantly improved appropriate use of turn signals.[178] Although promising, results from driving methylphenidate performance trials should be considered preliminary and would be strengthened by further confirmation based on assessment of effects in patients driving their own vehicles in every-day traffic settings, across multiple occasions.

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

Mixed amphetamine salts XR: Driving performance. We identified a small, 3-week, placebo-controlled, crossover trial that measured the effects of mixed amphetamine salts XR on simulated driving performance in 19 young adults (mean age of 22 years, 89% male). mixed amphetamine salts XR was given based on a forced-dose titration schedule of 20 mg in the first week, 40 mg in the second week, and 50 mg in the third week. Improvement in driving ability was measured based on lowering of the numerical overall Driving Safety Score, which reflects the mean of z-scores from each of 8 simulator-derived variables including total citations, total collisions, time to collision, driving out-of-lane incidents, percentage of time above excessive speed threshold, number of times overcornering, number of times tailgating, and response to crash-likely events. Greater improvements in overall simulated driving performances were found for mixed amphetamine salts XR than for placebo both at 7-hours post-dose (–0.31 compared with +0.33; $P=0.013$) and at 12-hours post-dose (–0.29 compared with +0.31; $P=0.005$).[186]

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

inattentive, 34.8%; hyperactive/impulse, 8.7%).[183] Parenting skills were measured using the 42-item, validated Alabama Parenting Questionnaire (APQ) based on mother self-report and collateral reports from individuals who lived with or were close to the mothers. During Phase 1, all mothers were titrated on methylphenidate OROS over 5 weeks for identification of a maximally effective dose. During Phase 2, mothers were then randomized to 2 weeks of treatment with their maximally effective dose of methylphenidate OROS (mean dose 83.7 mg daily) or placebo. Compared with placebo, maximally effective doses of methylphenidate OROS were superior in decreasing the frequency with which mothers used corporal punishment methods and inconsistent discipline. Significant differences were not found between methylphenidate OROS and placebo in effects on involvement, positive parenting, or poor monitoring/supervision behaviors.

Key Question 2. Safety

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

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

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

The Preschool ADHD Treatment Study provides some limited evidence on the short-term safety of methylphenidate.[59, 222] Overall, 21/183 (11%) of Preschool ADHD Treatment Study patients taking methylphenidate withdrew due to adverse events, although there is no data on withdrawals among placebo patients during the phases of the trial that included placebo arms. One serious adverse event, a suspected seizure, was potentially linked to methylphenidate use. No other drug-related serious adverse events were reported. Rates of moderate to severe adverse events ranged from 16% to 30% in methylphenidate groups and 16% to 21% in placebo groups. While numerous severe adverse events are listed in the Wigal publication, only overall rates are provided with no stratification according to intervention, nor is there any indication which adverse events were potentially associated with use of the active intervention.[222]

Parent-rated rates of several specific adverse events were significantly higher with methylphenidate use compared to placebo during the crossover titration phase of the study. These include trouble sleeping ($P \leq 0.005$), appetite loss ($P \leq 0.003$), stomachache ($P \leq 0.03$), dull/tired/listless behavior ($P \leq 0.02$), social withdrawal ($P \leq 0.03$), and buccal-lingual movements ($P \leq 0.01$). Data from the 10-month open-label phase of the study, in which all patients who had previously improved with active treatment received methylphenidate, showed that rates of some adverse events significantly decreased (irritability, crying, sadness/depression, listless/tired behavior; $P \leq 0.03$) while others remained stable (appetite loss, picking, trouble sleeping, anxiety, social withdrawal, stomachache, headache, abnormal movements, and buccal-lingual movements).

Growth effects

An analysis of growth data from the Preschool ADHD Treatment Study found that ADHD patients (N=140; mean age 4.4 years) enrolled in the study were in general larger than average at

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

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

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

Direct evidence

Stimulants. Four of 6 trials of immediate-release dextroamphetamine compared with immediate-release methylphenidate reported no differences between the drugs in adverse events.[37, 93-95] However, 2 short-term crossover trials found immediate-release dextroamphetamine to cause greater weight loss than immediate-release methylphenidate with mean weight change differences of 0.7 kg to 0.97 kg.[47, 96] One of 3 trials of mixed amphetamine salts compared with immediate-release methylphenidate found no difference in adverse event rates,[116] but 2 other studies found differences.[45, 115] Limitations in study design and lack of description of analysis methods make results from these 2 studies less reliable. These studies found that adding additional doses to the daily regimen of either drug increased the reports of loss of appetite and sleep problems,[115] and that mixed amphetamine salts given twice daily caused the highest rates of these adverse events.[45] In a small study, modafinil had similar rates of adverse events as immediate-release methylphenidate, with the exception of decreased appetite and insomnia, where immediate-release methylphenidate resulted in statistically significantly higher rates.[127]

All 3 studies of immediate-release methylphenidate compared with extended release formulations (methylphenidate OROS, SODAS, and SR) reported no significant differences in the incidence of side effects.[66-68] Mixed amphetamine salts and dextroamphetamine SR were found to cause more weight loss than immediate-release dextroamphetamine during the first week of treatment, but weight gain during the second week was greater with these drugs than with immediate-release dextroamphetamine.[118] Since this was such a short-term trial, no conclusions about differential effects on weight can be made from these data. No differences in adverse event rates were found between methylphenidate SR (Ritalin LA®) and methylphenidate OROS (Concerta®)[41] or between methylphenidate CD (Metadate CD®) and methylphenidate OROS (Concerta®).[70] No differences in adverse events were found between multilayer-release methylphenidate (Biphentin®) and immediate-release methylphenidate in 2 studies.[77, 78]

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

Atomoxetine. Atomoxetine consistently caused more vomiting and somnolence than the stimulant comparators in 4 trials and all differences were statistically significant.[133,134, 136, 138] Rates of vomiting were 12% to 13% for atomoxetine, approximately 3 times greater than rates for immediate-release methylphenidate[133,134] or amphetamine salts XR.[138] Rates of somnolence ranged from 6% to 26% with atomoxetine, which was 3 to 4 times greater than rates with methylphenidate OROS[136, 138] and mixed amphetamine salts XR [138] and over 7 times greater than rates with immediate-release methylphenidate.[133,134] Methylphenidate OROS and mixed amphetamine salts XR caused higher rates of insomnia than atomoxetine in 2 trials (7% atomoxetine, 13% methylphenidate OROS, 28% mixed amphetamine salts XR).[133,136] Rates of nausea and anorexia were greater with atomoxetine compared to immediate-release methylphenidate in 1 trial, however the dose comparison (atomoxetine at recommended doses, immediate-release methylphenidate at lower end of recommended) may have contributed to this finding.[134]

Indirect evidence

Dexmethylphenidate ER. Rates of overall adverse events were comparable for dexmethylphenidate ER compared to placebo in the short-term trials, with rates of 16% to 28% with dexmethylphenidate ER compared to 16 to 22% with placebo in the 1-2 week trials.[89-91] The 7-week trial reported much higher, but similar, rates in both groups; 75.5% dexmethylphenidate ER compared with 57.4% placebo.[88] The most frequently reported adverse events were typical of stimulant products and were generally comparable between dexmethylphenidate ER and placebo. These included decreased appetite, anorexia, upper abdominal pain, fatigue, insomnia, headache, and nausea. The only occasion for which rates of a specific adverse event were statistically significantly higher in patients taking dexmethylphenidate ER compared to placebo was for decreased appetite in the 7-week trial (30.2% compared with 8.5%; $P<0.0068$).

Lisdexamfetamine dimesylate. In the study of lisdexamfetamine and mixed amphetamine salts XR, the overall incidence of adverse events were similar.[124] With mixed amphetamine salts XR, the most frequent were insomnia (8%) and decreased appetite (6%), while with lisdexamfetamine the most frequent were upper abdominal pain (4%) and decreased appetite (4%). Significant differences were not found in our chi-square analysis.

In a dose-ranging study, overall adverse event rates were significantly greater ($P\leq0.05$) for patients taking lisdexamfetamine 30 mg (71.8%), 50 mg (67.6%), or 70 mg (83.6%) compared to placebo (47.2%).[125] When compared to placebo, all dosages of lisdexamfetamine were associated with significantly greater rates ($P\leq0.05$) of decreased appetite (39% compared with 4.2%), insomnia (18.8% compared with 2.8%), and irritability (9.6% compared with 0). Weight loss incidence was only greater for patients in the 70 mg group compared to placebo (9.2% compared with 1.4%; $P\leq0.05$). Withdrawals due to any of these adverse events only occurred in <1% of patients, however.[223]

Immediate-release methylphenidate. In a small study (N=21) of children ages 6 to 12 with ADHD, sleep diaries were assessed over 7 days after receiving placebo, immediate-release methylphenidate 15 to 30 mg daily, or immediate-release methylphenidate 30 to 45 mg daily (divided into 3 daily doses) in a crossover study.[224] Based on an analysis of contrasts, there was no difference between the 2 dose levels, but medication periods caused statistically significant increased sleep onset latency (means of 41 and 44 minutes longer; $P<0.001$ for both compared to

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

Adolescents

Placebo-controlled trials of immediate-release methylphenidate[159-168, 171, 225] provide limited evidence of short-term stimulant tolerability in adolescents. Immediate-release methylphenidate was associated with significant appetite and sleep disturbances across some, but not all placebo-controlled trials.[161, 162, 165, 168] Additionally, adolescents taking immediate-release methylphenidate frequently reported increases in dulled affect, social withdrawal, irritability, and stomachache in 2 placebo-controlled trials.[164, 168]

Trials of other stimulants provide no long-term evidence on safety. One 17-day study comparing methylphenidate OROS and mixed amphetamine salts reported a single adverse event – urinary difficulty – in a patient receiving methylphenidate OROS.[169] Another multi-phase, placebo-controlled study of methylphenidate OROS reported no serious adverse events during the 2-week double-blind phase, although 1 serious adverse event (suicidal ideation) was reported during a run-in, open-label dose titration phase. Other adverse events commonly reported during the open-label dose titration phase were headache (25% of patients), decreased appetite (21%), insomnia (15%), and abdominal pain (9%). However, adverse event rates during the double-blind phase were similar for methylphenidate OROS and for placebo and the only withdrawal due to adverse events was reported in a placebo patient.[170] Results from a 4-week trial found that when compared to placebo, mixed amphetamine salts XR was associated with higher rates of anorexia/decreased appetite (35.6% compared with 1.9%), insomnia (12.0% compared with 3.7%), abdominal pain (10.7% compared with 1.9%), and weight loss (9.4% compared with 0%). Five patients taking mixed amphetamine salts XR withdrew from the study due to adverse events. No placebo patients discontinued due to adverse events and no serious adverse events were reported in either group.

Adults

Direct comparisons

Modafinil and immediate-release dextroamphetamine were associated with similar rates of insomnia (38% compared with 19%, *P*=NS), muscle tension (24% compared with 19%; *P*=NS) and appetite suppression (24% compared with 19%, *P*=NS) in the only included head-to-head trial.[51] There were no withdrawals due to adverse effects.

Placebo-controlled trials

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

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

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

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

Abbreviations: ADHD, attention deficit hyperactivity disorder.

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

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

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

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

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

No study was rated good quality. All but 1 was rated fair quality due to biased patient selection processes and/or biased or unspecified outcome ascertainment methods. We did not analyze results from a poor-quality, comparative study of growth rebound in methylphenidate and immediate-release dextroamphetamine due to our concerns about how possible additional biases may have affected the results.[248] We cannot rule out the possibility of between-groups differences in baseline characteristics because no information/analysis was provided. We also cannot rule out the possibility that the results were confounded by time and other relevant factors.

Suicide

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

Using data on file from all clinical trials of atomoxetine in children, the manufacturer conducted an independent meta-analysis of suicidal-related behavior in response to requests from the US Food and Drug Administration and other organizations.[226] Based on 12 short-term clinical trials in children with ADHD or enuresis, 1357 children taking atomoxetine were compared to 851 taking placebo (6 to 18 week trials), finding an increased risk of suicidal ideation (n=5) or suicidal behaviors (n=1) in those taking atomoxetine; 0.44% overall. No suicidal-behavior events occurred in the placebo groups, such that the risk difference between the groups was statistically significant (Mantel-Haenszel Incidence Difference, 0.52; 95% CI, 0.12 to 0.91) indicating an increased risk with atomoxetine compared to placebo. Time to onset of suicidal-related behavior was 9 to 32 days. All children experiencing suicidal-related behaviors were boys, ages 7-12, and 2 of 6 (33%) were African American – whereas the proportion of African American children in these studies was 12%. Two of 6 had comorbid psychiatric disorders. Analysis of data from 2 trials comparing atomoxetine to methylphenidate found 1 case of suicidal ideation in each group (atomoxetine or methylphenidate), with no significant difference. Prior to this analysis, a US Food and Drug Administration analysis of the same data also found an increased risk, but identified one case as a suicide attempt and identified 1 fewer case of suicidal behavior overall. Atomoxetine was associated with significantly higher risk of suicidal ideation than placebo: 0.37% (5/1357) compared with 0% (0/851); Maentel-Haenzel Incidence Difference 0.46; 95% CI, 0.09 to 0.83; *P*=0.016. Suicide attempts were slightly higher with atomoxetine; 0.07% (1/1357) compared with 0% (0/851).[226] A subsequent black box warning is included in Appendix G.

A higher rate was found in an analysis of children taking atomoxetine for at least 3 years.[153] Based on data from 2 extension studies and 3 open label studies, 2% (14 of 714) experienced suicide-related outcomes (11 suicidal ideation, 2 suicide attempts, and 1 suicidal behavior). These events occurred as early as 234 days and as late as 5.8 years of treatment, with only case 1 occurring before 2 years of treatment. Because there is no control group for this analysis, and because much of these data come from extension studies where some level of selection bias exists, these findings must be viewed as suggestive only.

A single before-after study followed 8 adult males (mean age of 27.2 years) that continued on open methylphenidate for 3 to 6 months subsequent to participation in short-term clinical trials.[185] One participant (12.5%) attempted to commit suicide by consuming a month's supply of methylphenidate.

Cardiovascular deaths

Stimulants. In a good-quality case-control study, children (ages 7 to 19) who had died from "sudden unexplained death" during the years of 1985 to 1996 were identified from state vital statistics from each of the 50 United States.[253] A control group was selected from children who died from motor vehicle traffic accidents. The cases and controls were matched on a 1:1 basis, with 564 resulting in each group. The exposure was defined as stimulant use immediately prior to death, based on survey of parents. Ten (1.8%) of those with sudden death were reported to have been taking immediate-release methylphenidate at the time of their death, compared to 2 (0.4%) in the motor vehicle death group, resulting in an odds ratio of 7.4 (95% CI, 1.4 to 74.9).

Sensitivity analyses altering the way exposure was identified or removing children also taking a tricyclic antidepressant did not meaningfully alter the results. Recall bias was raised as a potential limitation of this study, as the time since the child's death to the survey of the parent was longer in the sudden death group (13 years) compared to the motor vehicle death group (10 years).

A good-quality retrospective cohort study based on 10 years of Florida Medicaid claims data and the Vital Statistics Death Registry data identified 55 383 patients with newly diagnosed ADHD.[232] Of these, 32 807 had used a stimulant (either currently or formerly) and 22 576 had never used a stimulant medication. Those who had used a stimulant at any time were more likely to be male, white, non-Hispanic, and to have used other psychoactive drugs. Of 73 children who died over the study period, 5 died of circulatory causes (4 per 100 000 person-years); none of these were sudden cardiac death and numbers were too small to make reliable comparisons among groups. Emergency department and physician office visits due to cardiac causes occurred significantly more often in the group currently using a stimulant compared to non-users (hazard ratio, 1.20; 95% CI, 1.04 to 1.38 and hazard ratio, 1.21; 95% CI, 1.06 to 1.39, respectively). Former use of stimulants was not significantly associated. Using regression analysis, several factors were found to be significantly associated with the increased risk of an emergency department or physician's office visit due to cardiac causes: age ≥15 years compared to <15 years; congenital anomalies; history of circulatory disease; disability; nonblack race; and the use of antidepressants, antipsychotics, and bronchodilators.

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

Table 12. Cardiovascular risks of ADHD drugs

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

Blood pressure, pulse, electrocardiographic changes

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

Methylphenidate OROS. An open-extension of a trial of methylphenidate OROS reported small changes in blood pressure (3.3 mmHg systolic and 1.5 mmHg diastolic) and heart rate (3.9 bpm) over a 1 year study period.[255] During this time, 33% discontinued treatment, but only 1 withdrew due to systolic blood pressure >130 mmHg. ANOVA analyses showed no relationship to dose or age and no tolerance development over time was found, but those children with the lowest blood pressure at baseline had the greatest increases. The final report from this 2 year study found no additional withdrawals due to cardiovascular adverse events.[256]

In a seven-week study of 226 adults (56% male, mean age of 39 years), similar proportions of participants in the methylphenidate OROS and placebo groups, respectively, had systolic blood pressure greater than 140 mm Hg at any post-baseline visit (8% compared with 6%), but greater proportions of participant in the methylphenidate OROS group had diastolic blood pressure greater than 90 mm Hg (10% compared with 3%, *P* not reported) and a pulse rate of greater than 100 bpm (7% compared with 2%, *P* not reported).[176]

Mixed amphetamine salts XR. Four open-label extension studies of mixed amphetamine salts XR, 1 each in children,[257, 258] adolescents,[259] and adults examined the cardiovascular effects over periods of 6 to 24 months.[260] In each of these studies the subjects were populations of patients who were highly selected and were described as being healthy other than the diagnosis of ADHD. The studies in children and adolescents also included a short-term placebo-controlled phase. While no statistically significant differences compared to placebo in any

electrocardiogram measure were found in children in the short-term trial, 2% (11/568) had diastolic blood pressure >90 mmHg, and 9% (50/568) had a systolic blood pressure >130 mmHg at some point during follow-up. Overall, 0.7% (4/586) withdrew from the study due to a cardiovascular adverse event; 1 due to tachycardia (max 121 bpm compared to 108 bpm at baseline), 2 due to chest pain (both had sinus bradycardia at baseline), and 1 due to elevated blood pressure (130/90 mmHg that resolved to 115/80mmHg after 1 month without drug). In a shorter duration open-label study, 2968 children were given mixed amphetamine salts XR for a period of up to 15 weeks.[258] The absolute numbers of patients with cardiovascular adverse events are not clearly reported. It is reported that 0.2% (7/2968) discontinued mixed amphetamine salts XR due to cardiovascular adverse events. Nine patients had treatment emergent cardiovascular adverse events that were moderate or serious in intensity, 5 of which were deemed probably related to mixed amphetamine salts XR.

Thirteen of 79 adolescent patients (16%) experienced adverse events during a 4-week study of mixed amphetamine salts XR compared with placebo that included cardiovascular symptoms such as syncope, tachycardia, and electrocardiogram abnormality.[259] Of these, 2 were withdrawn from study drug, 1 with palpitations and 1 with severe migraine and syncope. During 6-month follow-up there were no serious cardiovascular adverse events reported, although 4% (6/138) reported adverse events with cardiovascular symptoms, however none withdrew due to these adverse events. In a 2-year extension study in adults with ADHD, two-thirds discontinued the study prior to completing 2 years, 22% because of adverse events.[260] Statistically significant, but not considered clinically meaningful, increases in systolic blood pressure and diastolic blood pressure were seen at various points throughout the study (mean increase in systolic blood pressure, 2.3 mmHg; diastolic blood pressure, 1.3 mmHg at endpoint). While a statistically significant increase in QTcB (7.2 msec; $P<0.001$) was found, no patient had a QTcB >480 msec. Three percent withdrew due to cardiovascular events (2 due to palpitations or tachycardia – extent not reported, and 5 due to hypertension).

Atomoxetine. Open-label extension studies of atomoxetine have reported on cardiovascular adverse events in children or teens[238] and in adults.[261] One report involved 169 children and adolescents that continued on open or blinded atomoxetine (max dose of 2 mg/kg divided into twice daily) for at least 1 year following 3 short-term, placebo-controlled trials.[238] The timing of electrocardiogram measurements is not stated, but is presented by increasing dose. Linear regression suggests that there is no evidence of an increase in QTc with increasing dosage of atomoxetine.[238] An interim analysis of an open-label extension study in adults reports no "clinically relevant changes in QTc" after a mean of 97 months of follow-up.[261]

Height and weight effects

A non-systematic review, using estimation techniques, graphing, and qualitative synthesis, found that stimulants (amphetamines and methylphenidate) caused growth delays in both height and weight but that these were attenuated over time.[227] Their qualitative analysis indicated that there may be a dose effect, that there are no important differences between amphetamines and methylphenidate, and that discontinuing treatment results in resumption of normal growth. Because this review was not systematic and pooled data from a wide variety of study designs, we suggest caution in interpreting these findings.

A frequently cited nonsystematic review concluded that effects on weight and height associated with immediate-release methylphenidate vary across short-term clinical trials and

long-term observational studies and are mostly transient.[262] We reached similar conclusions based on our analysis of a larger number of primarily long-term observational studies that compared immediate-release methylphenidate to immediate-release dextroamphetamine,[239, 240, 246] or unmedicated hyperactive control groups.[242, 246, 247] Height and weight changes associated with immediate-release methylphenidate[235, 237, 241, 243, 244] and OROS were also observed in long-term noncomparative studies.[243] A noncomparative study of mixed amphetamine salts (Adderall XR®) found a low overall rate of withdrawal due to weight loss (4.8%), however weight loss was the most common reason for withdrawal from this 24-month extension of placebo-controlled trials.[263] Multiple noncomparative study findings provide inconclusive evidence regarding immediate-release methylphenidate effects on children's height and weight. Analysis of 2- and 5-year data from open-label extensions of 13 trials of atomoxetine assessed the effect on height and weight. [230, 233]

Table 13. Direct comparisons of long-term height and weight outcomes

Study	Interventions (mean dose) Duration Sample size	Age Gender Population	Height	Weight
Gross 1976	DEX 16.5 mg, n=12 6.8 years follow-up MPH 34 mg, n=60 5.8 years follow-up	Mean age=9 82% male Children/adolescents with hyperkinetic syndrome or minimal brain dysfunction	Change in percentile: +10.9, *P*<0.01 vs. +12.8, *P*<0.001	Change in percentile: +16.0, *P*<0.02 vs. +11.4, *P*<0.001
Safer 1972	DEX 11.7 mg, n=3 11.8 mg, n=8 MPH 37.5 mg, n=4 24.0 mg, n=5 9 months follow-up	Mean age=9.8 Gender NR	NR	Weight gain (kg): 0.23 vs. 0.12, t=1.8, *P*<0.05 Weight gain (excluding patients taking low-dose MPH, n=16) (kg): 0.13 vs. 0.12, t=0.137, NS ON vs. OFF Weight gain (kg) over a 3-month summer period: MPH= 0.29 vs. 0.41, t=0.526, *P*=NS; DEX= 0.14 vs. 0.47, t=2.523, *P*<0.01
Safer 1973	DEX, n=29 MPH, n=20 Unmedicated controls, n=14 ≥ 2 years follow-up Mean dosages NR	Mean age NR 89.8% male in children on medication; 100% male in unmedicated control group 100% White	Change in percentile: DEX: –13.45 MPH > 20 mg: –9.40 All MPH: –5.20 MPH ≤ 20 mg: –1.00 Controls: +1.29 DEX > MPH all-dose, low-dose and control groups DEX=MPH high-dose group MPH high-dose > controls MPH all-dose and low-dose=controls	DEX; MPH: high-dose (> 20 mg), all, low-dose (≤ 20 mg); controls Percentile changes in: Weight: –20.38; –10.0, –6.35, –2.7, +6.79 DEX > all MPH dosage groups and controls; MPH high-dose and all doses > controls; MPH low-dose=controls
Pliszka 2006	MPH, n=113 2.7 years follow-up MAS, n=66 2.4 years follow-up Mean dose NR	Mean age 9 81% male	Change in z-score: MPH 0.1 MAS 0.1	Change in z-score: MPH 0 MAS 0.3

Abbreviations: NR, not reported.

Height

Comparative studies. The only comparative evidence comes from 2 studies of immediate-release dextroamphetamine and methylphenidate,[239, 246] and 1 of methylphenidate and mixed amphetamine salts.[251] Results are mixed across the methylphenidate compared with immediate-release dextroamphetamine studies (Table 14). Both reported changes in height percentiles using the outdated Iowa City norms. Immediate-release dextroamphetamine and methylphenidate were both associated with similar height *increases* at final follow-up (mean 6 years) in 1 study,[239] and immediate-release dextroamphetamine was associated with significantly greater height *decreases* than methylphenidate after at least 2 years in the other.[246] It is impossible to establish whether heterogeneity in group characteristics across studies may possibly contribute to the contradictory

findings, as 1 of the studies did not report mean age, dosage, or duration.[246] The study of methylphenidate (any formulation) compared with mixed amphetamine salts (any formulation) did not find statistically significant differences in the z-score for height change over 3 years of continuous treatment.[251] Mixed amphetamine salts appeared to have a small negative impact at year 1, but this difference was not statistically significant. The authors found that the adjusted cumulative dose showed a statistically significant negative relationship to height (both drugs combined) (r = –0.26, *P*=0.001), but when 3 outlier values were removed from the regression the findings were no longer statistically significant.

Noncomparative studies: Immediate-release methylphenidate. In summary, studies of children taking immediate-release methylphenidate at various doses for 1-4 years showed inconsistent suppression of growth in height as compared to children who were unmedicated,[264,236, 242, 247] and those in noncomparative studies that reported varied analyses including differences between expected and actual growth,[235] change in percentile,[237] percent of expected growth,[241] and proportion of patients with decreased growth rates.[244]

A study of children previously enrolled in a study of immediate-release methylphenidate were followed for 5 years, and a negative relationship between stimulant (any) dose and z-scores for height was found.[250] Further analysis indicated that the impact on height occurred after the dose reached ≥2.5 mg/kg methylphenidate equivalent and a duration of treatment of ≥4 years. Extrapolation from the regression model indicates that a 13 year old boy receiving 2.5 mg/kg methylphenidate for >4 years would have 1.9 cm less increase in height compared to norms. This study is based on small numbers of patients (N=91 at baseline, N=68 at year 5) and many patients did not have height and weight data available for all years.

A before-after study followed 407 children with ADHD taking methylphenidate OROS 40 mg daily for 12 months.[256] Absolute height increased by a mean of 10.2 cm at 21 months. Analysis of z-scores for height change indicates the final height to be a mean of 0.23 cm less than expected.

A 3-year randomized controlled trial (N=62) of withdrawing immediate-release methylphenidate during summer months compared with not withdrawing found no significant difference in height after summer 1 (0.1 cm), but a significant difference after summer 2 (1.3 cm, *P*=0.02).[264] Serious limitations of this study, in design and conduct, limit the likelihood that the findings are valid. Overall, 42% of those randomized withdrew, with data available for 58 children at the end of summer 1 (ON n=32, OFF n=26) and 34 at the end of summer 2 (ON n=20, OFF n=14). Weight and height were collected by unblinded secretaries, but not for the purposes of this study.

Based on the Preschool ADHD Treatment Study trial, preschool-aged children treated with immediate-release methylphenidate were found to be taller at baseline than age-based norms (+2.04 cm).[265] Children who remained on methylphenidate had reduced growth, a mean of 1.38 cm/year.

Noncomparative studies: Atomoxetine. Based on 412 patients (children and adolescents) who had received atomoxetine for at least 2 years and had at least 1 post-baseline height measurement, atomoxetine resulted in a mean decrease in expected height of 0.44 cm.[233] Height changes appeared to regress toward the mean by 2 years. In an extension of this study, 1312 children (ages 6-17 at study entry) were followed under open-label conditions.[230] Of those enrolled in the study, 16% discontinued due to lack of efficacy and 5% due to adverse events.

Based on the data from the small subset (N=53) that had reached 5 years of follow-up and had height data, analysis indicated that there was a negative impact on expected height up to 18 months of treatment. At baseline, the children's mean height percentile was 55.7, and at 18 months it was 49.0; $P<0.001$. However, the difference at 2 years was no longer statistically significant, and by 5 years patients were at the 59th percentile. The largest decrease in height percentile occurred in the group in the 3rd quartile (50th to 75th percentile), but this analysis was based on very few patients.

Weight

Comparative studies: Immediate-release methylphenidate and immediate-release dextroamphetamine. Results from 3 comparative studies suggest that immediate-release dextroamphetamine is associated with significantly greater suppression of weight gain than methylphenidate, at least in the first 1 to 2 years (Table 14).[239, 240, 246] Immediate-release dextroamphetamine was associated with a significantly lower mean weight gain (kg) than methylphenidate after 9 months in 1 study,[240] significantly greater declines in weight percentiles after the first of 5 years another study,[239] and at end of treatment (≥ 2 years) in yet another.[246] In the 5-year, partly retrospective and partly prospective study that involved 84 children (mean age at initiation of drug therapy, 9 years; 82% male), however, differences in decreased weight percentiles between immediate-release dextroamphetamine and methylphenidate resolved by the second year and resulted in significantly greater than expected mean increases in weight percentiles at final follow-up (+10.9; $P<0.01$ and +12.8; $P<0.001$, respectively).[239]

The 9-month study also reported subgroup analyses.[240] The first suggests that comparison of mean weight gain between immediate-release dextroamphetamine and methylphenidate may have been confounded by dosage disparities. Apparently, the difference between immediate-release dextroamphetamine and methylphenidate resolved when 4 patients taking lower-dose methylphenidate (20 mg daily) were removed from the analysis (0.13 kg compared with 0.12 kg per month). Weight gain in children who continued medication over the summer compared with those who discontinued medication during the summer was also reported. In patients taking immediate-release dextroamphetamine, medication continuation was associated with significantly lower mean weight gain than in children who discontinued medication (0.14 compared with 0.47 kg per month, $P<0.01$). Medication continuation status did not have an effect on weight gain in the group of patients taking methylphenidate.

Comparative studies: Immediate-release methylphenidate and mixed amphetamine salts. A study of methylphenidate compared to mixed amphetamine salts (any formulation) found no statistically significant differences in z-scores for weight change over a 3 year period between the 2 drugs, but did find a significant negative association of duration of treatment with mixed amphetamine salts and z-score ($P=0.029$), indicating a greater impact on weight over time.[251] Overall, the children in the study were heavier than average, such that the mean final weights were not below average for age.

Noncomparative studies: Immediate-release methylphenidate. Noncomparative studies[235, 237, 241, 244] provide mixed evidence about the association between immediate-release methylphenidate and suppression of weight gain in school-aged children. In the earliest study (1977), only 2 of 36 boys with minimal brain dysfunction (5.5%) lost weight while taking methylphenidate (maximum dose 20 mg) over 16 months.[244] The other 34 boys gained weight. The next study,

published in 1979, involved 72 boys (age range 6-12) with hyperactivity that were taking methylphenidate for up to 2 years.[241] A significant growth weight deficit (30%; $P<0.05$) was associated with methylphenidate 24.2 mg daily (0.47 mg/kg) in the 72 boys who completed the first year. The growth weight deficit associated with methylphenidate 0.59 mg/kg of 10% was insignificant for the 48 boys who completed the second year of treatment. Results of a subgroup analysis suggest that the deficit in weight gain was only significant in patients that continue to use medication over the summer months compared to those who did not. The third study, published in 1983, involved relatively higher mean dosages of methylphenidate (39.9 to 41.3 mg) and followed children with hyperactivity over the longest observation period (4 years).[237] methylphenidate was associated with significant declines in weight percentiles in all 4 years of the study (Year 1 [–9.7] compared with Year 2 [–15.9] compared with Year 3 [–18.6] compared with Year 4 [–20.8]; $P<0.001$ for all). The final study, published in 1999, found an insignificant difference (0.72 kg) between expected compared with actual weight gain in 29 patients who took methylphenidate 34.5 mg for 2 years.[235]

In a study following children taking stimulants for 5 years, described above, stimulant dose ≥2.5 mg/kg methylphenidate equivalent was found to be negatively associated with weight gain ($P<0.001$).[250] Comparing the models for height and weight, the authors find that the impact of increased dose is greater on weight than height. Using the change in z-score based on dose, the estimated difference in weight gain in a 10-year-old boy using a stimulant for more than 1 year was found to be 1.41 kg at 1.5 mg/kg daily, 2.17 kg at 2 mg/kg daily, and 2.89 kg at 2.5 mg/kg daily compared to age-based norms. Again, these results are based on small numbers of children and could be subject to change in a larger sample were used.

A 3-year randomized controlled trial (N=62) of withdrawing immediate-release methylphenidate during summer months compared with not withdrawing found that after summer 1, the immediate-release methylphenidate ON group gained significantly less (0.9 kg, $P=0.005$) than the immediate-release methylphenidate OFF group. However, in summer 2 the difference was non-significant (0.6 kg).[264] Serious limitations of this study, in design and conduct, limited the likelihood that the findings were valid. Overall, 42% of those randomized withdrew, with data available for 58 children at the end of summer 1 (ON, n=32; OFF, n=26); and 34 at the end of summer 2 (ON, n=20; OFF, n=14). Weight and height were collected by unblinded secretaries, but not for the purposes of this study.

Results were mixed across 2 studies that compared children taking methylphenidate to unmedicated hyperactive children, however.[236, 247] In 1 study, methylphenidate was associated with significantly greater declines in weight percentiles than in the unmedicated children after 1 year.[236] The differences between the methylphenidate groups and the unmedicated group increased numerically along with the dosages (<20 mg, –6.88; 20.56 mg, –8.81; >20 mg, –15.40, all $P<0.005$). In the other study, the methylphenidate group and the unmedicated group demonstrated similar absolute weight gain (kg) after 364 days.[247]

Based on data from the Preschool ADHD Treatment Study study, preschool-aged children were heavier than age-based norms by 1.78 kg.[265] After a year of treatment, those who stayed on immediate-release methylphenidate experienced less weight gain than those who did not complete by 1.32 kg/year.

Noncomparative studies: Methylphenidate OROS. In the before-after study of 407 children (above), absolute weight increased a mean of 6.0 kg during 21 months, with the baseline weight

being slightly above expected and the final weight being slightly below expected for age. The final weight was 1.23 kg (2.64 pounds) less than expected for age.[256]

Noncomparative studies: Mixed amphetamine salts XR. Twenty-seven of 568 (4.7%) children withdrew due to weight loss in a 24-month before-after study of mixed amphetamine salts XR.[263, 266] Eligibility for this study was restricted to patients that completed either of 2 placebo-controlled trials without any clinically relevant adverse events or withdrew for any other reasons. Overall, the children had a mean weight deficit at endpoint (change in age-adjusted weight quartile, –15.15). The deficit was greatest among those in the highest quartiles at baseline, and among those who were stimulant naïve. Weight change was greatest during the first year, with change in the second year not statistically significant. A second open-label study of mixed amphetamine salts XR-treated adolescents (mean age 14 years; N=138) reports that 25% (34/138) experienced weight loss as an adverse event over 6 months, 2 of whom discontinued drug for this reason.[215] The mean weight decreased by 2.4 kg (5.2 lbs), with approximately 9.2 lb weight loss being the mean among mixed amphetamine salts XR-naïve patients. The study also found that those in the 75th percentile for weight lost more weight (mean 4.2 kg) compared to those in the 25th to 75th percentile (1.5 kg), while those below the 25th percentile gained 0.5 kg (mean).

Noncomparative studies: Atomoxetine. Based on 412 patients (children and adolescents) who had received atomoxetine for at least 2 years and had at least 1 post-baseline weight measurement, atomoxetine resulted in a mean decrease in expected weight of 0.87 kg.[233] Analysis of change over time indicated that weight changes were greatest in the early months of treatment, with some regression toward the mean percentile at 2 years. In an extension of this study, 1312 children (ages 6-17 at study entry) were followed under open-label conditions.[230] Of those enrolling in the study, 16% discontinued due to lack of efficacy and 5% due to adverse events. Based on the data from the small subset (N=62) that had reached 5 years of follow-up and had weight data, analysis indicated that there was a negative impact on weight up to 18 months of treatment. At baseline, the children's mean weight percentile was 68. After only 1 month the mean weight percentile had dropped to 66 (P<0.001), and by 15 months it was 58 (P<0.001). This change was statistically significant up to 3 years of treatment, when the percentile had risen to 65. At 5 years, the mean percentile was 71. Analysis indicated that the modal dose did not impact the change in weight. At 5 years, those children with who were in the 4th quartile (75th to 100th percentile) at baseline had lost weight (–8 percentiles; P<0.048), while those in the lower quartiles had gained weight. Those in the 1st quartile gained the most, followed by those in the 2nd and then the 3rd quartile. However, this analysis is based on very few patients.

Insomnia, decreased appetite, and headaches

A small (N=150), 24-month, retrospective cohort study examined rates of insomnia, decreased appetite, and headache reported by children attending a single clinic database.[229] Using a one-way ANOVA analysis, the rates of insomnia across immediate-release methylphenidate, methylphenidate OROS, mixed amphetamine salts, mixed amphetamine salts XR, and atomoxetine were not statistically significantly different, although the crude rate in the mixed amphetamine salts group (22%) was numerically greater than in the other groups (range 4% to 13%). Similarly, rates of decreased appetite were not found to be different, although the rates in the immediate-release mixed amphetamine salts, mixed amphetamine salts XR, and

methylphenidate OROS groups (range 15% to 22%) were also higher than the atomoxetine and immediate-release methylphenidate groups (range 9% to 10%). Atomoxetine had lower rates of headache compared to mixed amphetamine salts XR (0% and 12%, *P*=0.001), immediate-release mixed amphetamine salts (0% and 11%, *P*=0.001), or methylphenidate OROS (0% and 10%, *P*=0.002). Dose was not controlled for in these analyses, and because the data were sparse a Boneronni correction was used, thus we suggest caution in interpreting these findings.

Tics

Five studies and 1 meta-analysis reported tic-related outcomes.[229, 235, 243, 245, 256, 267, 268] One of these is a long-term placebo-controlled trial[267] of immediate-release methylphenidate. Table 14 summarizes the characteristics and outcomes from these studies. Although the 1-year study started out with similar numbers assigned to placebo and methylphenidate, by the study end 72 were on methylphenidate and only 18 on placebo. Development of new tics or worsening of pre-existing tics was not different between the 2 groups. The studies do not provide any information about how different pharmacologic treatments for ADHD compare in safety with regard to tic-related outcomes. A meta-analysis of data from 3 short-term trials found similar rates of tics reported as an adverse event among the groups.[268] This same publication also reported on 2 open-label studies of methylphenidate OROS, 1 of which was already included here,[243] the other is a report on a 9-month community-use study in children, adolescents, and adults, for which no reference is given (see table 14).

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

Table 14. Tic-related outcomes in observational studies

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

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

Seizures

In an analysis of post-marketing data and clinical trials data, the manufacturer of atomoxetine found that the rate of seizure was 01.% to 0.2%, with no statistically significant difference in rate between atomoxetine, methylphenidate, and placebo, although the comparative data were limited.[231]

Injuries

A retrospective database study analyzed an association between childhood behavioral disorders and common childhood injuries by using the British Columbia Linked Health Data Set to identify injuries. Children with behavioral disorders were identified using methylphenidate prescriptions as a proxy for diagnosis using data in a Triplicate Prescription Program.[234] Injury frequencies in children prescribed methylphenidate at least once between January 1, 1990 and December 31, 1996 (n=16 806) were compared to those in children not taking methylphenidate (n=1,010,067). Children were 51.4% male and less than 19 years in age. Mean duration of exposure was not identified. Odds of any injury (fractures, open wounds, poisoning/toxic effect, intracranial, concussion, and burns) were significantly higher in children taking methylphenidate than for those not taking methylphenidate (odds ratio, 1.67; 95% CI, 1.54 to 1.81), even after

adjusting for baseline age, sex, socioeconomic status, and region. This study design clearly suffers from lack of sensitivity to diagnosis, in that an unknown number of children with behavioral disorders are included in the group not taking methylphenidate. Since methylphenidate was used simply as a proxy for behavioral disorders, the relationship between the drug and the increase in injuries is not necessarily clear.

Hepatotoxicity

Atomoxetine. Two case reports (via the US Food and Drug Administration MedWatch system) of hepatotoxicity in patients taking atomoxetine (1 adult, 1 child) have resulted in the addition of a warning in the product labeling: "Postmarketing reports indicate that Strattera® can cause severe liver injury in rare cases. Although no evidence of liver injury was detected in clinical trials of about 6000 patients, there have been 2 reported cases of markedly elevated hepatic enzymes and bilirubin, in the absence of other obvious explanatory factors, out of more than 2 million patients during the first 2 years of postmarketing experience. In 1 patient, liver injury, manifested by elevated hepatic enzymes (up to 40 times the upper limit of normal) and jaundice (bilirubin up to 12 times the upper limit of normal), recurred upon re-challenge and was followed by recovery upon drug discontinuation, providing evidence that Strattera® caused the liver injury. Such reactions may occur several months after therapy is started, but laboratory abnormalities may continue to worsen for several weeks after drug is stopped. Because of probable under reporting, it is impossible to provide an accurate estimate of the true incidence of these events. The patients described above recovered from their liver injury and did not require a liver transplant. However, in a small percentage of patients, severe drug-related liver injury may progress to acute liver failure resulting in death or the need for a liver transplant. Strattera® should be discontinued in patients with jaundice or laboratory evidence of liver injury, and should not be restarted. Laboratory testing to determine liver enzyme levels should be done upon the first symptom or sign of liver dysfunction (pruritus, dark urine, jaundice, right upper quadrant tenderness, or unexplained "flu-like" symptoms").[269]

Raynaud's Syndrome

A small (N=64) case-control study found a statistically significant association between current or past stimulant (methylphenidate or immediate-release dextroamphetamine) use and Raynaud's Syndrome in children, mean age 16 years with a chi square of 5.00; P=0.01.[228] This study was not high quality, with only limited description of the cases and controls selected, particularly potentially confounding factors, and only chart review determination of exposure to stimulant medications. However, these findings suggest that further research is needed.

Key Question 2c. Evidence on the risk of abuse, misuse or diversion of drugs used to treat ADHD in patients with no previous history of misuse/diversion

Because the potential for misuse and/or diversion crosses the lines of childhood to adulthood, the evidence is considered as 1 body here. Also, because development of abuse and diversion are longer-term issues, we did not examine short-term trial evidence regarding apparent misuse based on tablet counts. We did not include studies of abuse potential in persons who did not have ADHD.[270]

Direct evidence

We found only 1 poor-quality study attempting to compare methylphenidate OROS to other formulations of methylphenidate.[271] This study used combinations of data from the Drug Abuse Warning Network, Drug Enforcement Administration claims of theft or losses, and the US Food and Drug Administration Adverse Event Warning System to evaluate the risk of abuse or diversion with methylphenidate OROS for 2000 (the year of its US Food and Drug Administration approval) to 2002 or 2003. The authors found that methylphenidate OROS had a lower risk of emergency room visits (Drug Abuse Warning Network), reports to the Adverse Event Warning System, and theft or losses reported to the Drug Enforcement Administration compared to methylphenidate in general (combined data for any other formulation). The study is based on groups of cross-sectional data, each of which has flaws. For example, the Drug Abuse Warning Network data do not report product specific information, but the authors report small numbers of cases from Drug Abuse Warning Network where methylphenidate OROS is specifically mentioned, and then use this in part as a basis for their conclusions.

Indirect evidence

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

This is a much-discussed topic in the literature,[272-280] but a clear conclusion has not yet been reached. The evidence is largely limited to longitudinal studies assessing the relationship of treatment with a stimulant during childhood and later substance use in adolescence or adulthood. None of these studies were comparative in terms of the specific stimulant drugs used during treatment, with most reporting immediate-release methylphenidate as the most commonly used drug. We did not find any evidence assessing the impact of nonstimulant drugs or extended release stimulants on later substance use/abuse in patients with ADHD. In general these studies suffered from methodologic flaws that hinder clear conclusions from being drawn. Some depend on data that appear to have been collected for other purposes, or at least not for the specific purpose of assessing future substance abuse, and definition or methods of determination of substance abuse is not consistent across studies. There is general agreement that the rate of substance use in adolescence or adulthood is higher among those diagnosed with ADHD in childhood, compared to healthy controls, and that age of diagnosis (younger ages), severity of symptoms, and presence of conduct disorder increase the likelihood of later substance use. However, the impact of drug treatment during childhood on later substance use is not clear, and in fact there is distinctly conflicting evidence. The major concern raised regarding these studies is the lack of controlling for potential confounding, particularly severity of ADHD, age at follow-up (assessment during adolescence not allowing enough time for exposure to illicit substances), the definition of substance use (for example “ever use” compared with substance use disorder), and exposure to substances during childhood (for example cigarette smoking by parents or other relatives). We have rated all of these studies as fair quality and suggest caution in interpreting the results of any one study as conclusive.

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

further. There are 7 studies that made relevant comparisons.[155, 281, 290-292, 294, 302] Below is a summary of the findings of these studies (Table 15). These are generally small studies, with limited ability to control for all important confounding factors. Importantly, differences among the groups at baseline that may have lead to 1 group receiving a stimulant and the other not well identified particularly in the older studies where these data may not have been recorded. Therefore, the findings should be interpreted as suggestive and require further research to confirm. Overall, the studies of stimulant use in childhood and later abuse or dependence on nicotine, alcohol or illicit drugs compared to children with ADHD but not exposed to stimulants did not indicate an increased risk. Some indicate a protective effect, but it appears that conduct disorder may be an important modifying factor.

Rates of nicotine abuse and dependence were assessed in 4 studies,[290, 292, 294, 302] with 1 finding stimulant use in girls protective against nicotine abuse (regular smoking) as adolescents (hazard ratio, 0.28; 95% CI, 0.14 to 0.60).[294] Another found no association with the rate of or timing of the first cigarette, but did find that stimulant exposure delayed the time to regular smoking by 2 years and 1 month.[292] Two other studies, in males, however found no associations after controlling for confounding factors including conduct disorder.[290, 302]

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

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

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

Study	Nicotine
Huss 2008 N=215 Children with ADHD Mean age at follow-up: 21.75 years Mean years to follow-up: 12.6 years	No difference in rate or age of first cigarette, or rate of nicotine abuse or nicotine dependence. Time to nicotine abuse significantly greater in stimulant group, by 2 years, 1 month (*P*=0.049)
Wilens 2008 N=114 Females with ADHD Mean age at follow-up: 16.2 years Mean years to follow-up: 5 years	Stimulant use found protective; hazard ratio, 0.28; 95% CI, 0.14 to 0.60
Biederman 2008 N=112 Males with ADHD Mean age at follow-up: 22 years Mean years to follow-up: 10 years	Controlling for conduct disorder; nicotine dependence hazard ratio, 1.1; 95% CI, 0.6 to 2.1
Burke 2001 N=164 Boys with disruptive behavior disorders Mean age at follow-up: 13-15 years Mean years to follow-up: NR	Regression did not find stimulant use to significantly associated with tobacco use in adolescence (odds ratio, 2.19; *P*=0.061)

Study	Alcohol
Blouin 1978 N=42 Hyperactive children Follow-up age 13-14 years Mean years to follow-up: 5 years	39.3% of those MPH IR group had used alcohol once or twice vs. 21.4% of untreated group. Current users: MPH IR group 46. 4% vs. untreated 26.4%.
Biederman 1997 and 2003 N=212 Children with ADHD Follow-up >5 years	Stimulants found protective; alcohol abuse or dependence OR 0.16 (confidence intervals not given)
Biederman 2008 N=112 Males with ADHD Mean age at follow-up: 22 years Mean years to follow-up: 10 years	Controlling for conduct disorder: Alcohol abuse hazard ratio, 1.1; 95% CI, 0.6 to 2.1; dependence hazard ratio, 1.0; 95% CI, 0.5 to 2.4. Duration of alcohol abuse was longer in those who had received stimulant treatment.
Paternite 1999 N=121 Children with hyperactivity follow-up = age 21-23	Holding age at diagnosis and childhood symptoms constant, no statistically significant correlations with alcoholism, although authors indicate a trend towards higher dose of MPH may be related to lower rates of alcoholism
Goksoyr 2008 N=91 Mean age stimulant group: 21.6	Stimulant exposed 23% vs. non-exposed 38%; *P*=NS

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

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

Misuse and diversion of ADHD medications

In a fair- to poor-quality systematic review, 21 studies of misuse or diversion of methylphenidate or amphetamine reported from 1995 to 2006 were included.[304] The review did not adequately describe inclusion criteria and did not include a quality assessment of studies. The majority of studies were surveys or questionnaires, involving 113 145 participants, with 12 studies including college students and smaller numbers including children from elementary, middle, and high schools or mixed populations. The review found that the rate of misuse of methylphenidate or amphetamine was 5% to 8% among children up through high school and 5% to 35% among college students. Among college students, 2 small studies found that higher rates of misuse (30% to 35%) were for enhancement of academic performance. The review reported on the findings of a study of data from of the National Survey on Drug Use and Health from 2000, 2001, and 2002 and indicated that of all respondents, 0.9% in the 12- to 17-year-old age group and 1.3% in the 18- to 25-year-old age group had misused an ADHD stimulant (nonmedically) in the past year.[305] We review this study in more detail below.

In looking at the evidence on diversion of these stimulants, the systematic review found that among children up through high school aged, 15% to 24% gave them away, 7% to 19% sold them, and 4% to 6% had them stolen at some time in the past. Among college students, 23% had been asked to give, to trade, or to sell their ADHD medications, and in another study 29% of those surveyed had reported selling them. In a longitudinal follow-up study of adults, 11% reported having sold their ADHD medications in the last 4 years. These studies did not report specific products or formulations of stimulants.

Using data collected as part of the National Survey on Drug Use and Health from 2000, 2001, and 2002, 34.7% of respondents had ever misused a prescription stimulant intended for use to treat ADHD.[305] As noted in the systematic review (above), no psychiatric diagnosis information is available from the survey, so it is not known what proportion of respondents had ADHD. The most commonly misused stimulants in this survey were methylphenidate and

dexamphetamine, with smaller numbers reporting use of other drugs, including mixed amphetamine salts and methylphenidate OROS. Similarly, 30% had misused an ADHD stimulant in the past year, with significantly higher rates among those aged 12- 25 years compared to older participants, and among Whites compared to other races. Using combined data from 2000 and 2001 (due to low numbers in each survey), 4.7% were determined to be dependent or abusing a prescription ADHD stimulant drug, with rates highest again among those 12 -25 years old. Rates of dependence were higher among women, whereas rates of abuse were higher among men. This study indicates a serious problem with dependence and abuse of ADHD stimulant drugs, but does not provide insight into the course of development of abuse or dependence, or the medical history of those found to be abusing or dependent on stimulants.

Two studies not included in the systematic review are also relevant.[306, 307] Similar to the studies included, a small study of 66 adults prescribed methylphenidate found that 29% reported inappropriate use during the past month, with 84% using it orally, 74% using it nasally, and 11% smoking it.[306] Regression analysis indicated that misuse of methylphenidate was associated with illicit use of cocaine or amphetamines. Forty-four percent reported diverting their medication to someone else, with 97% giving it away, 17% selling it, and 14% doing both. Regression analyses indicated that diversion was associated with younger age both at the time of the survey and at the time methylphenidate was first prescribed. This was a very small study, however, and such regression analyses should be interpreted with caution.

A study of the Texas Poison Control Network revealed that 8.5% (322 of 3789) of calls about human exposures to methylphenidate during 1998 to 2004 were cases of abuse.[307] The database did not record the formulation of methylphenidate involved, although they report that the number of calls regarding methylphenidate had reduced during 1998 to 2000, then increased during 2001 to 2004.

Reinforcing effects of ADHD medications

We found 2 very small studies (1 in 5 children with ADHD, 1 in 10 adults with ADHD) that used a choice procedure as a proxy measurement of abuse potential.[308, 309] The logic behind this is that choice of 1 treatment over another may be reflective of the reinforcing effects of a drug, which is often considered to be predictive of abuse potential. The trials involved short-term administration of blinded drug (sampling days) and then allowing them to choose their preferred condition on other days (choice days). In the adult study, ADHD symptom improvement was self-assessed using a 5-point scale (1="not effective" and 5="extremely effective"). The main findings were that Immediate-release methylphenidate was chosen significantly more often than placebo (50% compared with 32.5%; $P<0.001$), but that perceived effectiveness ratings for patients who reliably chose methylphenidate were also significantly greater than non-methylphenidate choosers (4.8 compared with 3.2 points; $P=0.04$). Based on these findings, authors concluded that the higher methylphenidate preference demonstrated by these patients was more reflective of therapeutic efficacy rather than abuse potential.

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

Key Question 3. Subgroups

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

ADHD subtypes, comorbidities, and race or ethnicity were not recorded in most randomized controlled trials and observational studies. For example, only one-quarter of all studies of school-aged children reported ADHD subtype prevalence rates. Importantly, of those that did record demographic information, only 1 poor-quality trial reported results of a subgroup analysis of Black children with ADHD.[310] While the data available from the studies that do report this information can be useful in determining the generalizability of results, the lack of attention to assessing the impact of these factors means there is almost no evidence on potential differences in response or adverse events.

Race or ethnicity

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

A subgroup analysis conducted specifically to evaluate the comparative efficacy and safety of *open-label* methylphenidate OROS and atomoxetine in 183 Black children with ADHD (out of 1323 children that participated in the overall trial) found treatment outcomes to be similar to those for the overall study population.[310] Main findings from the subgroup analysis are summarized in Evidence Table 3, but will not be discussed in detail here due to concerns about study quality. This trial (the FOCUS trial) was rated poor quality based on a combination of flaws including undescribed methods of randomization and allocation concealment, significant between-groups baseline differences in ADHD severity, and lack of information about attrition and number of patients included in analyses (Evidence Table 4).

Immediate-release methylphenidate. Immediate-release methylphenidate 0.15, 0.30 and 0.50 mg/kg was studied in a placebo-controlled, crossover trial (2 weeks in each arm) of 11 Black male adolescents (mean age=13.6 years).[159, 225] Immediate-release methylphenidate had a positive effect on 75% of efficacy measures. This response rate is similar to that seen in other placebo-controlled trials of immediate-release methylphenidate. Immediate-release methylphenidate was associated with significant linear elevations diastolic blood pressure among these patients.

An analysis of California Medicaid claims data suggests that mean persistence (days of treatment without any 30-day gaps) was longer for children taking methylphenidate ER formulations (OROS and SODAS) than for those taking immediate-release methylphenidate regardless of ethnicity (White, Black, Hispanic).[43] This same data indicates that mean treatment durations overall (methylphenidate OROS, SODAS, and immediate release) were significantly shorter for Black children (survival time ratio, 0.77; 95% CI, 0.73 to 0.80), Hispanic children

(survival time ratio, 0.81; 95% CI, 0.78 to 0.84), and other ethnicities (survival time ratio, 0.81; 95% CI, 0.75 to 0.87) than for white children.

Methylphenidate OROS. A 4-week, noncomparative trial evaluated the efficacy and tolerability of methylphenidate OROS in 119 Korean children with ADHD.[311] Significant improvements were seen in the children's scores on both the parent and teacher versions of the IOWA Conners' Rating Scale, as well as on the investigator-rated Clinical Global Impression-Severity Scale. Only 2 (1.7%) patients withdrew due to adverse events of decreased appetite and insomnia. However, these findings do not provide reliable information about how methylphenidate OROS treatment effects in Korean children compare to those in children of different ethnic descent.

Lisdexamfetamine. Subgroup analyses of ethnic origin (Caucasian compared with Non-Caucasian) were performed using data from 2 double-blind, randomized controlled trials of lisdexamfetamine and results were reported in the Center for Drug Evaluation and Research Medical Review[223] In the 1-week, crossover study (#201), average Swanson, Kotlin, Agler, M-Flynn and Pelham - Deportment Subscale (SKAMP-DS) scores for lisdexamfetamine were similar to mixed amphetamine salts XR and superior to placebo, regardless of ethnic origin. In the 4-week, parallel-group study (#301), mean changes in ADHD rating scale IV for lisdexamfetamine 30 mg compared with placebo appeared less robust for the subgroup of non-Caucasians (–18.5 compared with –10.1; P=0.0754) compared to the population overall (–21.8 compared with –6.2 points; P<0.0001). Treatment effects for the lisdexamfetamine 50 mg and 70 mg dosage groups also appeared less robust in non-Caucasians, but mean changes in the ADHD rating scale IV scores remained statistically significantly greater than placebo.

Atomoxetine. A placebo-controlled study of atomoxetine was undertaken in Taiwanese children with ADHD.[312] This study reported statistically significantly greater improvements on the ADHD-Rating Scale-IV scale with atomoxetine compared to placebo (–17.15 compared with –9.31; P<0.01). The mean change in score is slightly greater than those seen in trials of atomoxetine conducted in the United States (–12.8 to –16.7 with atomoxetine compared with –5.0 to –7.0 for placebo). The most frequently reported adverse event was decreased appetite (36% compared with 17%; P=0.002), followed by somnolence (22% compared with 9%, NS), and nausea (17% compared with 0; P<0.01).

A sub-group analysis of 1198 participants from 2 multi-center, open-label trials of atomoxetine with follow-up periods of 10 and 11 weeks was performed to assess response to atomoxetine among Latinos compared to Caucasians in children age 6 to < 18 years with ADHD.[313] There were 5 significant differences between the 2 groups at baseline (mean age, ADHD subtype, previous substance use, percent of slow metabolizers, and ADHD rating scale IV-PI total mean score). The study reported significant and similar improvements in ADHD (ADHD rating scale IV-PI) with an improved score of 54% for the Latino population (N=107) and an improved score of 52% for the Caucasian population (–22.10 compared with –19.55; P=0.47). The only significant between-group difference was a greater decrease in the ADHD rating scale IV-PI hyperactive/impulsive subscale during the last 4 weeks of treatment for Latinos (effect size=0.35). Latinos, however, had higher baseline scores than Caucasians. The incidence of treatment-emergent adverse events was comparable among the 2 groups with the following exceptions: Caucasians reported significantly more abdominal and throat pain

(P=0.006; P=0.037, respectively), whereas Latinos reported significantly more decreased appetite and dizziness (P=0.03; P=0.023, respectively).

Gender

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

Direct comparisons

Subgroup analyses based on gender were performed based on data from 2 double-blind, randomized controlled trials of lisdexamfetamine[223] The average SKAMP-DS scores for lisdexamfetamine were similar to mixed amphetamine salts XR and superior to placebo regardless of gender in the 1-week, crossover study (#201). In the 4-week, parallel-group trial, treatment effects appeared less robust in subgroups of girls for all dosage groups of lisdexamfetamine compared to placebo, but changes in ADHD rating scale IV lost statistical significance only in the 30 mg treatment group (–19 compared with –8.1; P=0.0537). Results from the subgroups of girls in study #301 must be interpreted with caution, however, due to the small sample sizes (N=88).

A post hoc subgroup analysis of the START study, comparing mixed amphetamine salts XR and atomoxetine, examined the effects in the 57 girls enrolled.[314] Similar to the overall study analysis, mixed amphetamine salts XR was found to have greater improvements in symptoms based on the SKAMP deportment and attention subscale scores compared to atomoxetine. In the original analysis, 71.9% of the children enrolled were boys.

A post hoc analysis of data from the COMACS study, comparing methylphenidate OROS and methylphenidate CD, found differences between boys and girls, but not between drugs. At baseline, more girls had comorbid anxiety disorder and girls had superior response rates at 1.5 hours post-dose, but inferior response rates at 12 hours post-dose compared with boys.[315]

Indirect comparisons

We found 3 studies examining differences in response to stimulants (primarily immediate-release methylphenidate) between boys and girls.[47, 316, 317] Two found no differences between boys and girls,[47, 317] while the third found that during the task period, boys were significantly more compliant and mothers gave fewer commands and more praise comments than in the girls group.[316] All 3 studies suffer from design and conduct flaws, including important differences between the groups at baseline and not accounted for in the analysis, and comparison to historical controls.

Data from girls enrolled in 2 separate placebo-controlled trials of atomoxetine with identical protocols were analyzed post hoc to assess the effects in this subgroup of children.[318] This analysis of 52 girls reported similar efficacy to that reported for the whole trial group (atomoxetine superior to placebo on most measures) but did not make a comparison of the effects in boys compared with girls.

A pooled analysis of two 10-week, placebo-controlled trials (N=536; 35% female, 65% male) of atomoxetine in adults examined gender differences.[319] The study found that when compared to baseline, a statistically significant change favoring atomoxetine was observed among both genders on the multiple ADHD rating scales (P<0.05). This study conducted multiple exploratory analyses of differences in gender based on treatment effects. At endpoint, atomoxetine resulted in better scores in women on emotional dysregulation (temper + mood

lability + emotional overactivity) items on the Wender-Reimherr Adults Attention Deficit Disorder Scale compared with men. The Sheehan Disability social life subscale demonstrated a significant gender-by-treatment effect (P=0.042), with women showing a stronger treatment effect than men, but there was no significant difference on the total score. No other analyses showed a gender difference. Considering the post hoc, exploratory nature of these analyses and the smaller number of women than men in these studies, these findings are preliminary.

Age

Subanalyses of persistence and compliance outcomes based on age were conducted using data from a Texas Medicaid Vendor Drug Program database on children taking immediate-release methylphenidate, immediate-release mixed amphetamine salts, or methylphenidate OROS.[79] More details of this database review are discussed under Key Question 1. Findings suggest that patients aged 5-9 years (0.43) had significantly higher rates of persistence than children aged 10-14 years (0.41) and children aged 15-18 (0.41). There were also higher rates of compliance (Medication Possession Ratio) in children aged 5-9 years (0.73) and aged 10-14 years (0.73) than in children aged 15-18 (0.67). This, however, doesn't provide any information about how persistence and compliance rates compared between the long-acting and shorter-acting stimulants within each age group.

A sub-group analysis of adults with ADHD[175] showed that age demonstrated a trend towards interacting with treatment (P=0.057) and that younger patients (ages 18-30) showed more functional improvement when compared to placebo (mean change 19.4 compared with 10.4; P=0.010) than older age groups who did not differ by treatment.

ADHD subtypes

The potentially moderating effects of ADHD subtypes (inattentive, hyperactive/impulsive, or combined) in children have been examined in 4 small, short-term placebo-controlled trials of immediate-release methylphenidate,[320, 321] methylphenidate OROS,[322] and modafinil.[323] Results from all trials suggest that these drugs have superior efficacy relative to placebo in children with ADHD, but that response or dose-response differs by diagnostic subtype. One trial each of immediate-release methylphenidate (N=40)[320] and methylphenidate OROS (N=47)[322] examined the potential relationship between stimulant dose and ADHD subtype. Although very preliminary, there were findings in both trials suggesting that the greatest symptom improvements may occur at higher dosages of immediate-release methylphenidate or methylphenidate OROS (≥30 mg daily) in children diagnosed with ADHD of the combined subtype or attention deficit disorder with hyperactivity, whereas greater symptom improvements may occur at lower dosages (≤18 mg daily) in children with ADHD of the inattentive type or attention deficit disorder without hyperactivity.

Immediate-release methylphenidate. In a small study (N=41), children were stratified into 2 subtypes, combined or inattentive. After 6 weeks of treatment, immediate-release methylphenidate had a significant effect on parent and teacher ratings of inattention and hyperactivity in both ADHD subtypes. Ratings of hyperactivity and aggression were improved in more the group with combined subtype, while task-incompatible behavior, arithmetic performance, and inattention were improved in both subtypes.[321]

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

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

Methylphenidate OROS. In another small trial (N=47) analyses based on linear and higher-order dose-response curves were used to evaluate the impact of dose on response in subtypes with methylphenidate OROS.[322] In this trial, significant relationships between ADHD subtype and methylphenidate OROS were detected for some, but not all, efficacy outcomes. When parent-ratings of the Inattention and Hyperactivity subscales from the ADHD rating scale IV were considered, it was noted that children with the combined type of ADHD had the greatest decreases in symptoms between the 36 mg and 54 mg dosages of methylphenidate OROS, whereas children with the inattentive type of ADHD had the greatest decreases in symptoms between placebo and the 18 mg dosages of methylphenidate OROS. We recommend using caution when interpreting this finding, however, as differences in appearance between placebo and methylphenidate OROS capsules may have increased parents' awareness of medication condition and could have affected efficacy ratings. Also, a similar pattern in subtype differences based on dosage was not observed when Clinical Global Impression Scale-related ratings were considered.

Modafinil. In a pooled analysis of data from 3 placebo-controlled trials, 638 children age 6 to 17 years, 30% with inattentive subtype, 27% with combined subtype, and only 4% with hyperactive-impulsive subtype, were stratified.[323] Results indicated a statistically significant improvement on the ADHD rating scale IV for both the combined and inattentive subtypes, but no statistically significant difference for the hyperactive-impulsive subtype. However, as this subgroup was very small, this finding may have been due to lack of statistical power rather than a true difference.

Comorbidity

Rates of commonly occurring comorbidities were only reported in around half of all studies. With the exception of depression, the ranges of comorbidities reported in these trials encompass the American Academy of Pediatrics estimates on prevalence of common comorbidities: Oppositional defiant disorder, 35%; conduct disorder, 26%; anxiety disorder, 26%; and depressive disorder, 18%.[63] The American Academy of Child and Adolescent Psychiatry estimate somewhat higher proportions; 54% to 84% with comorbid oppositional defiant disorder, 0% to 33% with depressive disorders, up to 33% with an anxiety disorder, and 25% to 35% with learning disabilities.[26] The comorbidities considered here are oppositional defiant disorder, conduct disorder, learning disabilities, anxiety disorders, depression, bipolar disorders, and tic disorders, and substance use (see methods section for discussion of selection).

In a small study (N=90), immediate-release methylphenidate 10 to 30 mg daily was given for 15 days, with outcome assessment for adverse events evaluated using the Barkley Stimulants Side Effects Rating Scale (BSSERS).[324] Post hoc analyses indicated that gender, age, dose, and baseline severity of ADHD symptoms were not associated with an increase in the BSSERS, but

presence of a comorbidity was significantly associated with an increase (61% "not affected" and 85% "affected"; $P<0.05$). However, analysis of individual comorbidities did not result in significant differences. The small size and post hoc nature of this analysis indicates a need for further research to confirm and expand these findings.

Oppositional defiant disorder

Atomoxetine. The impact of comorbid oppositional defiant disorder on treatment of ADHD in children has been most widely studied for atomoxetine.[146, 325-328] Meta-analyses of data from 2 earlier[146] and 3 more recent[327] placebo-controlled trials of atomoxetine were respectively designed to evaluate the efficacy and adverse effects of atomoxetine in children with ADHD and comorbid oppositional defiant disorder . Additionally, findings are available from post hoc analyses of data from single placebo-controlled trials.[325, 326] Collectively, these studies consistently found that the presence of oppositional defiant disorder does not impact the effectiveness of atomoxetine in treating children with ADHD. One analysis, pooling data from placebo-controlled trials found children with ADHD and oppositional defiant disorder taking atomoxetine demonstrated similar or greater improvements than placebo on all quality-of-life-related subscales of the Child Health Questionnaire except 'parental impact-emotional', 'parental impact-time', and 'self-esteem'.[327] Evidence to date is not conclusive that there is a benefit in oppositional defiant disorder symptoms with atomoxetine.[328]

In a post hoc analysis of a placebo-controlled trial, findings suggest that response to treatment of ADHD in children with comorbid oppositional defiant disorder (N=113) may be related to dose.[325] Improvements in ADHD symptoms and quality of life measures after 8 weeks were significantly greater for atomoxetine than placebo for the group of children with oppositional defiant disorder taking 1.8 mg/kg, but not for the 1.2 mg/kg or 0.5 mg/kg groups.

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

Mixed amphetamine salts XR. The efficacy and adverse effects of mixed amphetamine salts XR 10-40 mg has also been studied in 235 children with ADHD and oppositional defiant disorder.[330] This 4-week placebo-controlled trial focused on oppositional defiant disorder as the primary diagnosis, with only 79.2% of the original 308 children having comorbid ADHD. In the oppositional defiant disorder plus ADHD subgroup population, improvements in ADHD symptoms were significantly greater for mixed amphetamine salts XR compared to placebo on the parent- and teacher-ratings on the ADHD subscale of the SNAP-IV. Although these findings are encouraging, there are some limitations to consider. Mean change from baseline on the

ADHD subscale of the SNAP-IV was included as a secondary outcome measure and it is unclear if the analysis was adequately powered to measure between-group differences.

Conduct disorder

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

Learning disabilities

We identified 1 study that examined whether children with and without learning disabilities benefit from immediate-release methylphenidate to the same extent when treated for ADHD.[331] This study was based on outcome data from 95 children with ADHD (85% male; mean age, 9.2 years) who participated in a 2-week, placebo-controlled, crossover trial of immediate-release methylphenidate twice daily 0.5 mg/kg. ADHD-related symptoms before and after immediate-release methylphenidate were primarily assessed based on the Restricted Academic Situation Scale, the Continuous Performance Test, and personal impressions of parents, teachers, clinicians and researchers. Data from the placebo-control phase were not reported. Ultimately, children were assigned consensus clinical response scores (0=nonresponder, 1=mild response, 2=moderate response, 3=large response) to reflect overall degree of ADHD symptom control while taking immediate-release methylphenidate. Children with consensus clinical response scores of 0-1 were categorized as "nonresponders" and children with consensus clinical response scores of 2-3 were categorized as "responders." When compared to children without learning disabilities, the number of "responders" to immediate-release methylphenidate were significantly fewer in children with learning disabilities overall (75% compared with 55%; P=0.034) and when the disability was specific to mathematics (72% compared with 50%; P=0.034), but not when the disability was specific to reading (68% compared with 59%; P=NS).

Anxiety disorders

Children

Overall, 6 head-to-head trials and 10 placebo-controlled trials reported symptoms of anxiety or nervousness as an adverse event and 1 head-to-head comparison and 1 placebo-controlled trial reported it as a symptom of ADHD. In the head-to-head comparisons (immediate-release methylphenidate compared with immediate-release dextroamphetamine, mixed amphetamine salts, methylphenidate SR, methylphenidate OROS, or atomoxetine), no statistically significant differences were found, although for some comparisons numerical differences were apparent.[68, 72, 73, 114, 116, 133, 332] For example, compared to immediate-release methylphenidate, rates were higher with atomoxetine (15.8% compared with 10% nervousness) and immediate-release dextroamphetamine (68% compared with 61%), but lower compared to Adderall® (10% compared with 5%) or methylphenidate OROS (31.3% compared with 18.7% in 1 study, 12% compared with 13% in another). Placebo-controlled trial evidence was conflicting; some studies showed higher rates of anxiety or nervousness with methylphenidate, indicating a dose-dependent effect, while others showed no increase over placebo rates.[54, 130, 131, 140, 142, 333-338] Reports of anxiety were similar between placebo and atomoxetine in 2 studies[140, 142] and placebo and modafinil in 2 others.[130, 131] Because most of these studies reported these as spontaneously reported adverse events, we do not believe that the quality of the data warrants a conclusion. The 2 trials that assessed anxiety symptoms as part of ADHD did not find a difference between

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

A 12-week fair-quality placebo-controlled study of atomoxetine in children with both ADHD and anxiety disorder diagnoses examined the affect on both ADHD and anxiety symptoms.[339] In the intention to treat analysis, atomoxetine was superior to placebo in both improvements on ADHD symptoms and anxiety symptoms (–4.5 compared with –2.4 points on the Pediatric Anxiety Rating Scale; $P<0.010$). This study had a high drop-out rate; 25% overall. Ten percent dropped out during a 2-week placebo run-in phase, and another 16% dropped out during the 10-week treatment phase. The last observation carried forward method was used to include patients who discontinued the study early in the analysis. With a high drop-out rate, we recommend caution in interpreting these findings.

Adults

For adults, we found 1 publication that reported findings from exploratory, post hoc analyses of the effects of *lifetime*, but not current, diagnoses of DSM-IV comorbidity on response to atomoxetine compared to placebo.[340] The main finding of these subanalyses was that compared to adults with "pure" ADHD (no comorbidities), adults with ADHD and post-traumatic stress disorder had greater improvements on atomoxetine compared to placebo when based on Investigator ratings, but not when based on patient self-report measures. While these findings provide rationale for design of future prospective research, they must be viewed in light of their limitations. These were post hoc analyses of subgroups of unknown size and it was unclear as to whether they involved comparisons of atomoxetine and placebo groups that were well-matched on important baseline characteristics or whether there was any adjustment for potential confounders. Results from the primary analyses of these data were reported in an earlier, separate publication [194] and are discussed under Key Question 1.

Additionally, numerous placebo-controlled trials examined whether treatment with ADHD drugs improves comorbid anxiety symptoms.[178, 181, 185, 187-189, 194, 203, 205, 208, 214] However, only immediate-release methylphenidate was consistently associated with improvements in anxiety symptoms in adults with ADHD.[181, 203, 210] Finally, in terms of adverse effects, only methylphenidate OROS has been associated with significantly greater adverse anxiety effects in adults than placebo across 2 trials.[179, 196]

Depression

In adolescents with DSM IV diagnoses of ADHD and Major Depression, 9 weeks of atomoxetine treatment resulted in significantly greater improvement in ADHD symptoms (change in ADHD rating scale IV was –13.3; atomoxetine, –5.1; placebo; $P<0.001$).[341] No statistically significant differences in depression scale scores or rates of treatment emergent mania were found.

For adults, the only evidence regarding the effects of depressive disorders on response to medication comes from the 1 publication that reported findings from exploratory, post hoc analyses using pooled data from 2 placebo-controlled trials of atomoxetine discussed above in the section on anxiety.[340] Here, the main relevant findings were that compared to adults with "pure" ADHD (no comorbidities), adults with ADHD and major depression, but not adults with ADHD and depression not otherwise specified, consistently had greater improvements on

atomoxetine compared with placebo across multiple rating scale scores. As noted previously, however, methodological weaknesses limit interpretation of these findings.

Bipolar disorder

When added to divalproex, mixed amphetamine salts (Adderall®) was associated with significantly greater improvements in ADHD symptoms than placebo after 4 weeks, but had no effect on bipolar disorder symptoms in 30 pediatric patients with comorbid ADHD and bipolar disorder (mean age 9.8 years).[342] This fair-quality study included 30 children who achieved a significant response to 8 weeks of open-label divalproex out of 40 enrolled in the run-in phase.

A 4-week placebo-controlled, cross-over study of methylphenidate twice a day (5 mg, 10 mg, or 15 mg compared with best dose week) added to mood stabilizers including 20 euthymic youths (ages 5-17) found that best dose week was superior to placebo in improving ADHD symptoms (ADHD rating scale IV) ($P<0.02$; effect size= 0.90).[343] However, no single dose level of methylphenidate was found to be superior to placebo in the study population. No suicidal behaviors were observed or reported.

Psychiatric comorbidities

One placebo-controlled trial of atomoxetine[201] in adults reported results of subgroup analyses stratified by comorbidities. Atomoxetine treatment effects were not altered by the presence or absence of "psychiatric comorbidity" in a 3-week trial of 22 adults.[201] This trial does not provide evidence of comparative efficacy among subgroups of patients with comorbidities.

Tic disorders including Tourette's Disorder

There is concern that stimulant drugs may be contraindicated in ADHD patients with comorbid tic disorders due to possible tic exacerbation. There has also been uncertainty about whether stimulants treat ADHD symptoms as well in children with ADHD and established tic disorders as they do in children with primary ADHD. Several placebo-controlled trials of primarily immediate-release methylphenidate have examined these issues.[49, 98, 344-350] Immediate-release dextroamphetamine and atomoxetine treatments for ADHD have also been studied in children with tic disorders.[98, 347, 349, 351]

The majority of these trials were of short duration and involved very small numbers of children.[98, 344-346, 348] Children participating in these trials were mostly male (≥ 85%), with a range in age of 8.3 years to 11.2 years. Motor and verbal tic frequency and severity were assessed in classroom, lunchroom, and playground settings using a variety of different rating scales. The most common tic rating scale used was the Yale Global Tic Severity Scale.

Overall, there was very little evidence across these trials to indicate that immediate-release methylphenidate, immediate-release dextroamphetamine, or atomoxetine were associated with any tic exacerbation effects. Paradoxically, in one 2-week trial of 34 children, only the lowest dose of immediate-release methylphenidate (0.1 mg/kg daily) was associated with any tic worsening, characterized by an increase in motor tics only in the classroom setting.[344, 346] In another 3-week trial of 12 children, only the higher dosages of immediate-release methylphenidate (0.67 mg/kg daily or 1.20 mg/kg daily) were associated with tic exacerbations.[98] Otherwise, compared to placebo, immediate-release methylphenidate, immediate-release dextroamphetamine, and atomoxetine were all consistently associated with improved tic severity in these trials. Furthermore, children also showed greater improvements in

ADHD symptoms with immediate-release methylphenidate, immediate-release dextroamphetamine, and atomoxetine compared to placebo. Observational evidence of the impact of immediate-release methylphenidate treatment indicates that the baseline frequency and severity of motor and vocal tics was significantly higher than during the placebo phase of the study, and no differences were found among the placebo and 12, 18, and 24 month immediate-release methylphenidate treatment follow-up periods.[235]

Substance use disorder

Adolescents

We identified 1 trial of methylphenidate-SODAS focusing on the subpopulation of substance use disorder.[352] This 6-week, single-blind, placebo-controlled crossover study assessed the efficacy of escalated doses of methylphenidate SODAS on ADHD symptoms in 16 adolescents with ADHD and comorbid substance use disorder (marijuana N=16 and cocaine N=7). Medication dose was titrated to 1.2 mg/kg per day. The trial found that methylphenidate SODAS was superior to placebo in reducing ADHD symptoms and improving global functioning for all main outcome measures (SNAP-IV and Clinical Global Impression Scale scores; *P* values for all measures were $\leq$0.001). There was no significant treatment effect on drug use (number of marijuana cigarettes per day; urine tests for either cannabis or cocaine).

Adults

Placebo-controlled trials of atomoxetine, immediate-release methylphenidate, and methylphenidate SR have evaluated treatment of ADHD in adults with comorbid substance abuse. Atomoxetine treatment has been assessed in a 12-week placebo-controlled trial of 147 adults with ADHD and comorbid alcohol use disorders.[353] In this trial, reductions in ADHD symptoms, as measured by reductions in the Total Score on the ADHD Investigator Symptom Rating Scale (AISRS), were significantly greater for atomoxetine (–13.6 points; *P*=0.007) compared with placebo (–8.3 points).

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

Two trials each of immediate-release methylphenidate[182, 198] and methylphenidate SR[190, 191] focused only on patients with ADHD and comorbid substance abuse disorders. One trial of immediate-release methylphenidate involved a broader population of patients with any alcohol or drug dependence,[182]while the others focused on either patients with cocaine dependence[191, 198] or methadone-maintained patients.[190] The primary objectives of these trials were to investigate (1) whether use of immediate-release methylphenidate or methylphenidate SR in adult substance abusers with ADHD reduces ADHD symptoms to a similar extent as in non-substance abusers and with ADHD, and (2) what kind of impact immediate-release methylphenidate or methylphenidate SR use may have on the course of the substance abuse disorder. Overall, although use of immediate-release methylphenidate or methylphenidate SR in adult substance abusers with ADHD did not appear to negatively influence the course of the substance abuse disorder recovery process (cravings, abstinence duration, proportion of days of substance use, amount of money spent on substances, or number of days until first negative urine sample),[190, 191, 198] immediate-release methylphenidate or methylphenidate SR also did not appear to offer much of a benefit in the reduction of these patients' ADHD symptoms.[182, 190, 191, 198] In all but 1

of these trials, not only were there less robust treatment response rates in substance abusers with ADHD compared to non-substance abusers (34% to 47% compared with 38% to 78%), but the placebo response rates in the substance abuser trials were also substantially greater (ranges 21% to 55% compared with 4% to 16%).[182, 190, 191] Trial authors noted several possible factors that may have led to these abnormally negative findings, including that methylphenidate treatment-resistance may be characteristic of substance abusers in general and/or that patients in substance abuse treatment may be more eager to please research staff and have a tendency to over-endorse improvements in any areas of functioning.

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

Adolescents

A retrospective chart review of 450 teens treated at a substance abuse center in Canada from 1993 to 1999 examined the prevalence of abuse of methylphenidate or immediate-release dextroamphetamine.[354] Twenty-three percent had ever used, and 6% were currently using methylphenidate or immediate-release dextroamphetamine, most often reported to be used as crushed tablets taken intranasally. Further assessment of covariates indicated that higher rates of abuse of methylphenidate or immediate-release dextroamphetamine were associated with the teen being out of school or having an eating disorder ($P<0.01$), but not with a diagnosis of ADHD; 36% of abusers had a diagnosis of ADHD compared with 24% of non abusers (not statistically significant). An assessment of correlation of abuse of methylphenidate or immediate-release dextroamphetamine with abuse of other substances did not reveal any statistically significant results. The authors note that this population had a higher psychiatric comorbidity rate than the general adolescent population, which may have affected the results.

Adults

Two trials each of immediate-release methylphenidate[182, 198] and methylphenidate SR[190, 191] focused only on patients with ADHD and comorbid substance abuse disorders. One trial of immediate-release methylphenidate involved a broader population of patients with any alcohol or drug dependence,[182] while the others focused on either patients with cocaine dependence[191, 198] or methadone-maintained patients.[190] None reported results of direct assessment of misuse or illicit diversion outcomes. As a potential proxy measure of abuse/diversion, 3 trials reported medication compliance.[190, 191, 198] Patient self-reported compliance rates were similar in treatment and placebo groups across all 3 trials (88.5% to 95%). Additionally, no differences were found between methylphenidate and placebo in the proportions of riboflavin positive fluorescence (range 0.77 to 0.84).[190, 191]

Limitations of this Review

As with other types of research, it is important to recognize the limitations of this systematic review. These can be divided into those relating to generalizability of the results and those relating to methodology within the scope of this review. The generalizability of the results is limited by the scope of the key questions and inclusion criteria, and the generalizability of the studies included. The great majority of studies included narrowly or poorly defined patient

populations who met strict criteria for case definition, had few comorbidities, and used few or no concomitant medications. One concern about this group of studies is the variation in diagnostic criteria, particularly comparing studies conducted recently to those conducted in previous decades. Another concern is the handling of subtypes of ADHD in these studies. While many studies identify the proportions of patients diagnosed with various subtypes, stratification or analysis of the results based on these is lacking. Similarly, common comorbid conditions are not well addressed by the studies. In large part, the failure to address either subtypes or comorbidities may be due to small sample sizes involved in most studies, but these are serious short-comings that should not be ignored. The failure of these studies to assess the effect of prior medication exposure or concurrent treatment with other psychoactive medications on outcomes is another serious issue, particularly when comparing older studies where very few patients had prior exposure to newer studies where large proportions did have exposure. Minorities and the most seriously ill patients were underrepresented.

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

SUMMARY

Key Questions are summarized in Table 16, below.

Table 16. Summary of the evidence

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

	Comparison: Overall strength of the evidence	Conclusion
		in the morning; they had similar effects in the afternoon; and MPH OROS was superior in the evening. d-MPH ER was superior to MPH OROS at 2 to 6 hours post-dose, and MPH OROS was superior at 10 to 12 hours in 1 trial.
IR vs. IR	DEX IR vs. MPH IR: Good	The body of evidence clearly indicates no difference in efficacy between DEX and MPH IR.
	MAS IR vs. MPH IR: Fair	MASIR was superior to MPH IR on a few efficacy outcome measures in 2 trials, but clear evidence of superiority is lacking.
	DEX IR vs. DEX ER vs. MAS: Poor	Evidence on the comparison of DEX IR vs. SR vs. MAS may suggest that measures made in the morning show DEX IR superior to DEX SR, and afternoon measures show DEX SR superior to MAS.
	Modafinil vs. MPH IR: Fair	Based on 1 trial, modafinil was similar to MPH IR in efficacy
	Dexmethylphenidate: NA	Only placebo-controlled evidence was found.
Transdermal MPH	MTS vs. MPH OROS	Based on 1 trial, MTS and MPH OROS had similar efficacy
Lisdexamfetamine	Fair	Lisdexamfetamine was comparable to MAS XR on average SKAMP-DS scores and superior to placebo on same, as well as on ADHD rating scale IV mean changes.
Atomoxetine	Poor	
	Atomoxetine vs. MPH IR	Limited evidence suggests a lack of a difference in efficacy compared to MPH IR.
	Atomoxetine vs. MAS XR	Limited evidence suggests that MAS XR is superior to atomoxetine on most efficacy measures.
	Atomoxetine vs. MPH OROS	MPH OROS was superior to atomoxetine in response rates
Adolescents		
Efficacy	Poor	
	MPH OROS vs. MAS IR	Effectiveness outcomes: NR Short-term improvements in core ADHD symptoms: No differences. Other: MPH OROS > MAS IR on overall simulator driving performance.
	MPH IR vs. MPH OROS	Functional capacity: NR Short-term improvements of core ADHD symptoms: NR. Driving performance: MPH OROS > MPH IR in evening and at night.
	Placebo-controlled studies of MPH IR	Functional capacity: NR Short-term improvements of core ADHD symptoms: MPH IR generally efficacious.
Adults		
Efficacy	Fair	
Direct comparisons	DEX IR vs. modafinil	Limited evidence suggests a lack of a difference in efficacy between DEX IR and modafinil.

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

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

	Comparison: Overall strength of the evidence	Conclusion
	Cardiac events	Emergency room and physician office visits for cardiac causes significantly more frequent among those taking stimulants compared with those not (hazard ratio, 1.20; 95% CI, 1.04 to 1.38 compared with hazard ratio, 1.21; 95% CI, 1.06 to 1.30).
	Suicidal behavior	Increased risk with atomoxetine compared to placebo (risk difference, 0.52; 95% CI, 0.12 to 0.91) based on meta-analysis. Time to onset of behavior 9 to 32 days. Overall rate of suicidal behavior and ideation was 0.44% in this study compared to 1.7% in another meta-analysis of longer-term duration.
	Height	• DEX vs. MPH IR: Mixed findings; DEX=MPH in 6-year height increases in 1 study, DEX>MPH in 2-year height decreases in the other • MPH IR vs. unmedicated controls: No significant differences in 2 studies. • MPH IR in uncontrolled studies: Inconsistent effects across 4 studies • Atomoxetine: Uncontrolled studies suggest that height changes are similar to those reported with MPH IR, and are also transient
	Weight	• DEX vs. MPH: Three studies consistently suggest that DEX>MPH in weight gain suppression in the first 1-2 years. The longest-term (5 years) of these studies also reported that DEX=MPH in exceeding weight gain expectations at final follow-up. These findings are weakened by methodological flaws, however • MPH IR in other comparative (imipramine and unmedicated hyperactives or healthy controls) and noncomparative studies: Evidence does not support an indisputable relationship between MPH and weight gain suppression • MPH OROS and tomoxetine (atomoxetine): Evidence from noncomparative studies (1 each) doesn't suggest weight gain suppression effects • Atomoxetine: Uncontrolled studies suggest that weight changes are similar to those reported with MPH IR, and are also transient
	Tics, seizures, cardiovascular adverse events, injuries, and suicidal behavior	No comparative evidence.
2c. Abuse/diversion		

	Comparison: Overall strength of the evidence	Conclusion
Teens and young adults	Poor	Stimulant use during childhood not associated with alcohol abuse later. May be protective against or delay nicotine dependence, but comorbid conduct disorder may be a significant confounder. Stimulant use may protect against later substance abuse, but again comorbid conduct disorder may be a confounder. Evidence on misuse and diversion reports wide ranges of prevalence with no comparative data.
Key Question 3. Subgroups		
Children	Fair	
	ADHD subtypes or severity	Atomoxetine, MPH IR, MPH OROS all have superior efficacy relative to placebo in children with ADHD, regardless of diagnostic subtype but response may be better in those with combined or inattentive subtype.
	Race/ethnicity	Most trials conducted in primarily White populations. Ethnicity/race only reported in one half of studies. No analyses based on race. Very limited evidence suggests MPH IR in African American boys results in response rates similar to other populations studied. Evidence from subgroup analysis of a placebo-controlled trial suggested that effects of lisdexamfetamine may be less robust in non-Caucasian children.
	Gender	Subgroup analyses based on gender were limited. Evidence from subgroup analysis of a placebo-controlled trial suggested that lisdexamfetamine may be less efficacious in girls. Exploratory analysis indicates atomoxetine may have better response on emotional regulation items in women than men.
	Common comorbidities	Rates on commonly occurring comorbidities reported in only one half of trials. No study analyzed data stratified by these conditions. Rates of prevalence of these among study participants were generally similar to prevalence rates reported by American Academy of Pediatrics for the overall ADHD population.
	Tic disorders	No consistent evidence that atomoxetine, DEX IR or MPH IR increased tic severity or frequency compared to placebo. All of these studies of MPH IR showed a benefit of MPH IR on ADHD outcome measures compared to placebo.
	Oppositional defiant disorder	Very limited evidence suggests that atomoxetine is beneficial on most ADHD outcomes compared to placebo.
	Bipolar disorder	Very limited evidence suggests that MAS IR or MPH IR have benefit on most ADHD outcomes compared to placebo.

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

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Appendix A. Glossary

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

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

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

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

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

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

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

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

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

Applicability: see *External Validity*

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Double-blind: The process of preventing those involved in a trial from knowing to which comparison group a particular participant belongs. While double-blind is a frequently used term in trials, its meaning can vary to include blinding of patients, caregivers, investigators, or other study staff.

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

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

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

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

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

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

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

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

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

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

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

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

The center of the diamond is at the pooled point estimate, and its horizontal tips show the confidence interval.

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

Generalizability: See *External Validity.*

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

Harms: See *Adverse Event*

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

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

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

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

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

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

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

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

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

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

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

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

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

Masking: See *Blinding*

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

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

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

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

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

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

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

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

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

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

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

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

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

Odds ratio: The ratio of the odds of an event in one group to the odds of an event in another group. An odds ratio of 1.0 indicates no difference between comparison groups. For undesirable

outcomes an odds ratio that is <1.0 indicates that the intervention was effective in reducing the risk of that outcome.

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

Outcome: The result of care and treatment and/ or rehabilitation. In other words, the change in health, functional ability, symptoms, or situation of a person, which can be used to measure the effectiveness of care/ treatment/ rehabilitation. Researchers should decide what outcomes to measure before a study begins; outcomes are then assessed at the end of the study.

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

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

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

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

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

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

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

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

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

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

Precision: The likelihood of random errors in the results of a study, meta-analysis, or measurement. The greater the precision, the less the random error. Confidence intervals around

the estimate of effect are one way of expressing precision, with a narrower confidence interval meaning more precision.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Washout period: (In a cross-over trial) The stage after the first treatment is withdrawn, but before the second treatment is started. The washout period aims to allow time for any active effects of the first treatment to wear off before the new one gets started.

Appendix B. Scales used to assess efficacy and adverse events

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The Consensus Clinical Response (CCR) measures the overall improvement of the patient for each week of a trial. It is scored on a 4-point scale ranging from 0 (nonresponder) to 3 (moderate

response). The CCR combines and assesses multiple factors that can possibly affect and be relevant to the patient's improvement.

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

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

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

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

Driver behavior survey (DBS) is a 26-item scale in children and adults with attention deficit hyperactivity disorder (ADHD). Questions are rated on a scale of 1 to 4 with a possible maximum score of 104. The items assess the driving and safety behaviors of the driver with scores ranging from 1 = not at all or rarely and 4= very often. The questionnaire can be completed by the patient or by an individual that is familiar with the patient's driving. Lower scores on the DBS indicates less safe driving behaviors. The survey has been shown to be valid in assessing driver behaviors.[36]

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

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

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

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

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

Inattention/Overactivity With Aggression Conners' Teacher Rating Scale (IOWA CTRS) is revised from the 39-item Conners' Teacher scale. 10 items were devised to determine Inattention-Overactivity (IO) and aggression (A) behaviors. Teachers rate their child's symptoms from zero to three (0=not at all, 1=just a little, 2=pretty much, 3=very much). Coefficient alpha was tested as .89 for the IO scale and .86 for the A scale. They only tested the sensitivity and specificity scores of the IO scale, and the scores depend on the screen score being rated. Therefore, it recommended the use of an IO scale for at least 11 points for research purpose, and 7 points for clinical purpose.[42] The differential validity of IO and A factors had been tested as well.[43]

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

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

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

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

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

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

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

hyperactivity, psychosis, social skills, somatic concern, and withdrawal). The scales are interpreted through actuarial guidelines derived for T-score ranges that vary by scale.[48]

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

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

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

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

The Restricted Academic Situation Scale (RASS) is a tool that measures and assesses 5 specific behaviors (off-task, playing with objects, out of seat, vocalizing and fidgeting) of a child as the child performs specific academic tasks, within a clinical setting, that are appropriate for the

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

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

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

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

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

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

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

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

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

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

Swanson, Kotlin, Agler, M-Flynn and Pelham (SKAMP) scale is a 15-item scale. Ten items describe typical behaviors in a classroom setting and other five items were used for recording specific behavior. [65] Items are rated on a 7-point impairment scale (none, slight, mild, moderate, severe, very severe, and maximal). The reliabilities were from .70 to .78 for the SKAMP Attention ratings, and were from .63 to .73 for the SKAMP Deportment ratings. The concurrent

validity was established by calculating correlations with Conners and the IOWA Conners' Rating scale.[66] SKAMP comprises of two subscales (deportment [SKAMPDS] and attention [SKAMP-AS]).[47]

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

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

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

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

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

Wender-Reimherr Adult Attention Deficit Disorder Scale (WRADDS) is intended to measure the severity of the target symptoms of adults with ADHD using the Utah Criteria, which Wender

developed. It measures symptoms in 7 categories: attention difficulties, hyperactivity/restlessness, temper, affective lability, emotional overreactivity, disorganization, and impulsivity. The scale rates individual items from 0 to 2 (0 = not present, 1 = mild, 2 = clearly present) and summarizes each of the 7 categories on a 0-to-4 scale (0 = none, 1 = mild, 2 = moderate, 3 = quite a bit, 4 = very much). The WRAADS may be particularly useful in assessing the mood lability symptoms of ADHD.[74]

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

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

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Appendix C. Search strategy: Update 3

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

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

34 limit 33 to (clinical trial, all or clinical trial or comparative study or controlled clinical trial or evaluation studies or meta analysis or multicenter study or randomized controlled trial or "review") (270)
35 observational stud$.mp. or exp Cohort Studies/ or cohort$.mp. or exp Retrospective Studies/ or retrospective$.mp. (1052665)
36 35 and 33 (62)
37 34 or 36 (300)
38 from 37 keep 1-300 (300)

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

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

Database: PsycINFO <1806 to December Week 4 2008>
Search Strategy:

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1 exp Amphetamine/ or "amphetamine$".mp. (10362)
2 adderall.mp. (70)
3 atomoxetine.mp. (239)
4 strattera.mp. (18)
5 dexmethylphenidate.mp. (17)
6 focalin.mp. (10)
7 dextroamphetamine.mp. or exp Dextroamphetamine/ (2295)
8 dexedrine.mp. (77)
9 dextrostat.mp. (0)
10 methylphenidate.mp. or exp Methylphenidate/ (2726)
11 concerta.mp. (29)
12 metadate.mp. (6)
13 methylin.mp. (2)

14 Ritalin.mp. (398)
15 biphentin.mp. (0)
16 modafinil.mp. (332)
17 provigil.mp. (11)
18 Alertec.mp. (0)
19 methamphetamine.mp. or exp methamphetamine/ (1996)
20 desoxyn.mp. (2)
21 lisdexamfetamine.mp. (4)
22 vivanse.mp. (0)
23 daytrana.mp. (2)
24 11 or 21 or 7 or 17 or 2 or 22 or 1 or 18 or 23 or 16 or 13 or 6 or 3 or 9 or 12 or 20 or 14 or 15 or 8 or 4 or 19 or 10 or 5 (13662)
25 Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (7459)
26 Attention deficit disorder.mp. (12357)
27 attention deficit$.mp. (15316)
28 adhd.mp. (10299)
29 27 or 25 or 28 or 26 (15800)
30 24 and 29 (1879)
31 limit 30 to yr="2007 - 2009" (313)
32 limit 31 to (human and english language) (258)
33 from 32 keep 1-258 (258)

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

22 vivanse.mp. (0)
23 daytrana.mp. (2)
24 11 or 21 or 7 or 17 or 2 or 22 or 1 or 18 or 23 or 16 or 13 or 6 or 3 or 9 or 12 or 20 or 14 or 15 or 8 or 4 or 19 or 10 or 5 (13662)
25 Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (7459)
26 Attention deficit disorder.mp. (12357)
27 attention deficit$.mp. (15316)
28 adhd.mp. (10299)
29 27 or 25 or 28 or 26 (15800)
30 Central Nervous system Stimulants.mp. or exp Central Nervous System Stimulants/ (59)
31 30 or 24 (13701)
32 31 and 29 (1885)
33 diversion.mp. (1176)
34 substance abuse.mp. or exp Substance-Related Disorders/ (18864)
35 misuse.mp. (4506)
36 addictive behavior.mp. or exp Behavior, Addictive/ (631)
37 35 or 33 or 34 or 36 (24640)
38 32 and 37 (58)
39 limit 38 to yr="2007 - 2009" (17)
40 from 39 keep 1-17 (17)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2008>
Search Strategy:

---

1 exp Amphetamine/ or "amphetamine$".mp. (1008)
2 adderall.mp. (44)
3 atomoxetine.mp. (100)
4 strattera.mp. (6)
5 dexmethylphenidate.mp. (12)
6 focalin.mp. (7)
7 dextroamphetamine.mp. or exp Dextroamphetamine/ (470)
8 dexedrine.mp. (15)
9 dextrostat.mp. (0)
10 methylphenidate.mp. or exp Methylphenidate/ (1098)
11 concerta.mp. (27)
12 metadate.mp. (6)
13 methylin.mp. (0)
14 Ritalin.mp. (97)
15 biphentin.mp. (1)
16 modafinil.mp. (200)
17 provigil.mp. (3)
18 Alertec.mp. (0)
19 methamphetamine.mp. or exp methamphetamine/ (213)
20 desoxyn.mp. (0)
21 lisdexamfetamine.mp. (4)
22 vivanse.mp. (0)

23 daytrana.mp. (0)
24 11 or 21 or 7 or 17 or 2 or 22 or 1 or 18 or 23 or 16 or 13 or 6 or 3 or 9 or 12 or 20 or 14 or 15 or 8 or 4 or 19 or 10 or 5 (2412)
25 Attention Deficit Disorder with Hyperactivity.mp. or exp Attention Deficit Disorder with Hyperactivity/ (995)
26 Attention deficit disorder.mp. (1104)
27 attention deficit$.mp. (1322)
28 adhd.mp. (830)
29 27 or 25 or 28 or 26 (1454)
30 24 and 29 (848)
31 limit 30 to yr="2007 - 2008" (98)
32 from 31 keep 1-98 (98)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2008>
Search Strategy:

---

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

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

Database: EBM Reviews - Cochrane Database of Systematic Reviews <4th Quarter 2008>
Search Strategy:

---

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

31 from 30 keep 1-18 (18)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <4th Quarter 2008>
Search Strategy:

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

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

Appendix D. Methods used to assess quality of studies

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

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

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

Systematic Reviews

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

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

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

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

3. Is the validity of included studies adequately assessed?

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

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

4. Is sufficient detail of the individual studies presented?

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

5. Are the primary studies summarized appropriately?

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

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

Controlled Trials

Assessment of Internal Validity

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

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

Not reported

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

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to treatment allocation?

6. Was the care provider blinded?

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

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

9. Did the study maintain comparable groups?

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

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

Nonrandomized studies

Assessment of Internal Validity

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

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

3. Were the events investigated specified and defined?

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

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

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

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

References

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

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

Appendix E. Excluded trials

Exclusion codes

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

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

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

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

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

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

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

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

Reference:

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

Appendix F. Previous systematic reviews

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

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

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

Summary of good-quality systematic reviews

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

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

References for Appendix F

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Trade name	Active ingredient(s)	Boxed warnings
Methylin®	Methylphenidate hydrochloride	Drug abuse and dependence: Methylin® should be given cautiously to emotionally unstable patients, such as those with a history of drug dependence or alcoholism, because such patients may increase dosage on their own initiative. Chronically abusive use can lead to marked tolerance and psychic dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during drug withdrawal, since severe depression as well as the effects of chronic overactivity can be unmasked. Long-term follow-up may be required because of the patient's basic personality disturbances.
Metadate® ER	Methylphenidate hydrochloride	
Strattera®	Atomoxetine HCL	WARNING: SUICIDAL IDEATION IN CHILDREN AND ADOLESCENTS Strattera® (atomoxetine) increased the risk of suicidal ideation in short-term studies in children or adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD). Anyone considering the use of Strattera® in a child or adolescent must balance this risk with the clinical need. Co-morbidities occurring with ADHD may be associated with an increase in the risk of suicidal ideation and/or behavior. Patients who are started on therapy should be monitored closely for suicidality (suicidal thinking and behavior), clinical worsening, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Strattera® is approved for ADHD in pediatric and adult patients. Strattera® is not approved for major depressive disorder. Pooled analyses of short-term (6 to 18 weeks) placebo-controlled trials of Strattera® in children and adolescents (a total of 12 trials involving over 2200 patients, including 11 trials in ADHD and 1 trial in enuresis) have revealed a greater risk of suicidal ideation early during treatment in those receiving Strattera® compared to placebo. The average risk of suicidal ideation in patients receiving Strattera® was 0.4% (5/1357 patients), compared to none in placebo-treated patients (851 patients). No suicides occurred in these trials.

Drug Class Review

Pharmacologic Treatments for Attention Deficit Hyperactivity Disorder

Final Report
Update 3
Evidence Tables

October 2009

Update 2: November 2007
Update 1: May 2006
Original Report: September 2005

The literature on this topic is scanned periodically.

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

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

Drug Effectiveness Review Project
Marian McDonagh, PharmD, Principal Investigator

Oregon Evidence-based Practice Center
Mark Helfand, MD, MPH, Director

Oregon Health & Science University

OREGON HEALTH & SCIENCE UNIVERSITY
OHSU

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

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
Preschool children			
Barkley 1988 (Fair)	RCT DB crossover	1. Parent and/or teacher complaints of short attention span, poor impulse control and restlessness 2. Age of onset of problem behavior prior to 6 years 3. A duration of problem behavior for at least 12 months 4. Scores on the Hyperactivity Index of the Conners Parent Rating Scale and the Werry-Weiss-Peters Activity Rating Scale greater than two SDs above the mean for same-age, same-sex normal children 5. Scores on the Home Situations Questionnaire indicating that the child posed behavior problems in at least eight of the 16 situations described on the questionnaire to establish pervasiveness of behavior problems 6. Absence of epilepsy, severe language delay, deafness, blindness, autism, psychosis or gross brain damage as established through developmental/medical histories and observation of the children	NR
Conners 1975 (Poor)	RCT DB	Less than 6 years of age and not retarded and have a diagnosis of minimal brain dysfunction as manifested by: 1) hyperkinetic behavior; 2) a medical history of early onset of impulsive, restless, or agitated behavior; and 3) the presence of other symptoms such as short attention span, low frustration tolerance, easy distractibility, early rising from sleep, "driven" type of behavior, destructiveness of property, and aggressive or disruptive play with peers or siblings. In addition, the child had to be physically healthy and free of gross sensory pathology, seizure disorder, and family psychopathology (including alcoholism, drug addiction, psychosis, or mental retardation)	80% of the children showed mild to moderate over-all dysfunction 0% was found to have major(focal) symptomatology 63% were found to have mild to moderate speech and language dysfunction 0% had marked movement disorders (synkinesis, dystonis, tremor, tics), but a majority had difficulty with cross body control. over 80% of the mothers regarded the children as overactive during their first two years of life

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Preschool children			
Barkley 1988 (Fair)	methylphenidate 0.15mg/kg bid or 0.5mg/kg bid Duration: 7-10 days for each condition (baseline, placebo, low dose, high dose) Timing: NR	2 days/NR	NR
Conners 1975 (Poor)	methylphenidate Starting dosage: 5mg, bid (adjusted twice weekly) mean dose: 11.8(6.9)mg/day Duration: 6 weeks Timing: before the morning and midday meals	NR/NR	NR

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Preschool children		
Barkley 1988 (Fair)	A free play (20 mins) and 5 task (20 mins total): mother-child interactions were videotaped and separate coding of the interactions was done using the Response Class Matrix. Timing: the last day of each drug condition	Mean age=3.9 years Gender: 70.3% male Ethnicity: NR
Conners 1975 (Poor)	93-item behavior symptom list (before and after treatment) filled by parents. Clinical evaluation (week 2, 4, 6 after treatment): the Merrill-Palmer Intelligence Scale, the Beery-Buktenica Visual Motor Integration Test (VMI), the Flowers-Costello Test of centrak Auditory Abilities, the Meeting Street School Screening Test (MSST), Continuous Performance Test (CPT), the Harris-Goodenough Draw-a-Man Test, and Kagan's Matching Familiar Figures Test, Seat activity	Mean age=4.81 years Gender: 74.6% male Ethnicity: 100% white

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Preschool children			
Barkley 1988 (Fair)	the Peabody Picture Vocabulary Test: Mean=98.1(2.1), range 81-138 CPRS total: 68.4(25.4) CPRS hyperactivity: 19.6(5.0) Werry-Weiss-Peters Scale: 30(6.0)	NR/NR/27	0/0/27
Conners 1975 (Poor)	100% with upper-middle-class background 11(18.6%) had some prior analeptic therapy 2(3.4%) were able to sit quietly during the medical examination, 45% were extremely unmanageable 52% had a family history of hyperactivity	NR/66/59	3/0/56

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Results
Preschool children	
Barkley 1988 (Fair)	Pairwise Comparison: Free play- only the low dose condition was significantly reduced as compared with the placebo condition, p<0.05 Task interaction -compliance: 15% improvement in high dose compared with placebo, p<0.05 -compete: 45% decrease occurred in off-task, or competing, behavior in high dose compared with placebo, p<0.05 Others: NS
Conners 1975 (Poor)	Parent rating: Selected 18 items to be most related to hyperkinesis were analyzed, 4 out of 18 were significant improved in the drug group: disturbs other children, p<0.03; restless or overactive, p<0.01; throws himself around, p<0.05; always climbing, p<0.025 Activity chair: seat movement decrease, p<0.05; seat rotations, NS; feet movement, NS; total score, NS. Clinical evaluation (n=23, MPH=8, placebo=15): MSST: motor patterning improvement, NS; visual-perceptual-motor scores improvement, p<0.025; language raw score improvement, NS VMI: visual-perceptual-motor integration improvement, p<0.025 CPT: reduction in errors of omission, NS; reduction in errors of commission, NS. Merril-Palmer Intelligence Test: score improvement, p<0.01 Harris-Goodenough Draw-a-Man Test: IQ gain score improvement, NS MFFT: NS Flowers-Costiello Test of Central Auditory Abilities: total score, NS; competing messages test, NS Effects on Cortical Evoked Responses: increased amplitude for all visual and auditory amplitudes in drug condition, p<0.05

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Preschool children				
Barkley 1988 (Fair)	reported by mother	a tend (p<0.1) for the mothers to report more side effects during the medication than placebo conditions, but no in the severity of these side effects.	0	
Conners 1975 (Poor)	Weight, BP, self-report	weight: NS BP: methylphenidate>placebo, p<0.07 other side effects: insomnia, anorexia, ataxia, nausea, headache, vomiting, jitteriness, sadness, cramps, thirst, rash, irritability, nightmares. The number of side effects in the drug group was not statistically exceed that in the placebo group	NR	

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
Greenhill 2006/Kollins 2006/Wigal 2006 (PATS)	One year - 8 phases 1-week, open MPH treatment phase, followed by a 5-week, double-blind, placebo-controlled crossover trial; a 4-week, double-blind, placebo-controlled, parallel design phase; and 10-months' open maintenance. Setting NR	Stimulant naive, children of both sexes, ages 3 to 5.5 years with a DSM-IV consensus diagnosis of ADHD based on the Diagnostic Interview Schedule for Children IV-Parent Version and semistructured interview; combined or predominantly hyperactive subtype; an impairment scale score G55 on the Children`s Global Assessment Scale; hyperactive-impulsive subscale T score of 65 (1.5 SDs above the age- and sex-adjusted means) on both the Revised Conners Parent and Teacher Rating Scales; Full Scale IQ equivalent of 970 on the Differential Ability Scales; participation in a preschool, day care group setting, or other school program at least 2 half-days per week with at least eight same-age peers; and the same primary caretaker for at least 6 months before screening. Children were excluded if there was current evidence of adjustment disorder, pervasive developmental disorders, psychosis, significant suicidality, or other psychiatric disorder in addition to ADHD that required treatment with additional medication; current stimulant or cocaine abuse in a relative living in the home; a confounding medical condition; inability of the parent to understand or follow study instructions, or history of bipolar disorder in both biological parents. To be eligible, patients met both dimensional symptom criteria (scores 91.5 SD above age- and gender-adjusted means on the Hyperactive/Impulsive subscale of both parent and teacher Conners Rating Scales) and categorical diagnostic criteria (positive diagnosis on Diagnostic Interview Schedule for Children-IV and semistructured diagnostic interview).	Oppositional-defiant disorder; Communication disorder; Elimination disorder (i.e., encopresis, enuresis); Specific phobia (i.e., animals, needles, social phobia); Anxiety disorder (i.e., separation, generalized, posttraumatic stress disorder); Developmental coordination disorder; Conduct disorder; Pica; Adjustment disorder; Reactive attachment disorder; Obsessive-compulsive disorder; Sleepwalking disorder

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Greenhill 2006/Kollins 2006/Wigal 2006 (PATS)	Various- Methylphenidate (3.75 to 22.5 mg daily) vs. placebo , 70-week trial	1 Week	none

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Greenhill 2006/Kollins 2006/Wigal 2006 (PATS)	For Phase 5: 5-Week Double-Blind, Placebo-Controlled, Crossover Design Titration Study a composite of parent and teacher ratings on commonly used behavioral scales Phase 6 4-Week, Double-Blind, Placebo-Controlled Parallel Study outcome derived from parent and teacher versions of the Swanson, Nolan, and Pelham Rating Scale, Version IV which measure both ADHD and oppositional defiant disorder symptoms and are sensitive to treatment effects. For adverse effects general clinician inquiry and parents and teachers rated AEs on a checklist based on the Pittsburgh Side Effect Rating Scale	Baseline n= 303 Mean age=4.41 yrs Gender: 76% male Ethnicity: 63% white 19% black 16% Hispanic or Latino 2% Asian 0.7% other Phase 5-Crossover n = 165 Mean age=4.74 yrs Gender: 69% male Ethnicity: 63% white 18% black 18% Hispanic or Latino 1% Asian 0.6% other Phase 6 Parallel n =114 Mean age=4.76 yrs Gender: 70% male Ethnicity: 65% white 17% black 17% Hispanic or Latino 0.9% Asian 0.9% other

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Greenhill 2006/Kollins 2006/Wigal 2006 (PATS)	Conners Teacher rating scale (mean) Baseline 38.52 Phase 5 40.16 Phase 6 39.95 Conners Parent rating scale (mean) Baseline 35.43 Phase 5 35.91 Phase 6 35.48	Screened: 303 Eligible: 261 Enrolled: 183 and 165 randomized	1-week open-label lead-in (*n* = 183); a 5-week placebo-controlled, double-blind phase (*n* = 165); a 5-week double-blind, parallel phase (*n* = 114); and 10 months of open-label maintenance (*n* = 140 entered, 95 completed)

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Results
Greenhill 2006/Kollins 2006/Wigal 2006 (PATS)	Phase 5 - decreases in ADHD symptoms were found on MPH vs. placebo at 7.5 mg ($p < .01$), 15 mg ($p < .001$), and 22.5 mg ($p < .001$) doses, but not for 3.755 mg ($p < .06$). The mean optimal MPH total daily dose for the entire group was 14.2 mg/day Parallel study phase 6, only 21% on best-dose MPH and 13% on placebo achieved MTA-defined categorical criterion for remission

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Greenhill 2006/Kollins 2006/Wigal 2006 (PATS)	NR	Overall AEs per parents: 30% of parents reported moderate to severe AEs during study. MPH 15mg vs. placebo Appetite decrease chi-squared 5.4 P < 0.03 Trouble sleeping chi-squared 5.4 P < 0.03 MPH 22.5mg vs. placebo Weight loss chi-squared 4.0 P < 0.05 Severe AEs at baseline (2), open lead-in (23), titration (38), parallel (2), and maintenance (14) and overall there were 8 serious AEs throughout	Total withdrawals Parallel phase- placebo 45% MPH 15% Due to AEs Overall 11% (21) Open lead-in 11 Titration 3 Parallel Phase 1/114 Open label maintenance 7/140	Withdrawals were not reported well

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
Musten 1997 Firestone 1998 (Fair)	RCT DB crossover	1. A diagnosis of ADHD based on DSM-III-R 2. A score greater than 1 on 8 out of 14 DSM-III-R items 3. A standard score greater than or equal to 80 on the Peabody Picture Vocabulary Test (PPVT) 4. A score equal to or above 1.5 SD above the age and sex mean of the Hyperactivity Index of the Conners Parent Rating Scale-Revised. 5. Attention span of less than 88 seconds on the parent-supervised attention task. 6. Parent and children were fluent in English 7. Subjects did not have any sensory or physical disabilities, developmental disorders, neurologic disease, or obvious central nervous system dysfunction as assessed by a pediatrician. 8. Subjects who had received methylphenidate were considered for the study if they had received methylphenidate for less than 6 months and if the daily dosage administered was less than the mean of dosage used in the current study.	NR
Schleifer 1975 (Fair)	RCT DB crossover	Preschool children diagnosed as hyperactive participated in this study	NR

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Musten 1997 Firestone 1998 (Fair)	methylphenidate 0.3mg/kg or 0.5mg/kg, bid Duration: 7-10 days for each condition (placebo, low dose, high dose) Timing: NR	2 days/ NR	NR
Schleifer 1975 (Fair)	methylphenidate: 2.5 mg - 20mg q.a.m and 10mg at lunch (mean dose = 5mg bid) Duration: 14-21 days	NR/NR	NR

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Musten 1997 Firestone 1998 (Fair)	Cognitive measures (Gordon Diagnostic System Delay and Vigilance Tasks) Behavior rating (CPRS-R) Observed behaviors Time on-Task Productivity Timing: at the end of the each treatment	Mean age=4.84 years Gender: 83.9% male Ethnicity: NR
Schleifer 1975 (Fair)	Observation Hyperactivity Rating Scale Timing: before and after the intervention	Mean age=4.08 years Gender: 89.3% male Ethnicity: NR

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Musten 1997 Firestone 1998 (Fair)	Peabody Picture Vocabulary Test (standard score)=99.26(14.41) Diagnostic Interview for Children and Adolescents (number)=12.03(1.49) Swanson Nolan and Pelham Checklist (number)=11.48(1.91) Conners Hyperactivity Index (T score)=84.61(9.95) Attention Task-Supervised (sec)=30.43(10.36)	109(43 refused, 64 agreed) /54/41	4/6/31
Schleifer 1975 (Fair)	Mean IQ=102 (86-124) Hollingshead scale (socioeconomic class): Mean=2.5	NR/NR/28	0/2/26

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Results
Musten 1997 Firestone 1998 (Fair)	Cognitive tasks: Gordon Delay: no. correct, P<L, P<H, p< 0.001; Efficiency ratio, NS Gordon Vigilance: no. correct, P<L, P<H, p<0.01; commission errors, NS Parent Rating Scale: Conners: learning, P>L, P>H, L>H, p<0.001; Conduct, P>L, P>H, p<0.001; Hyperactivity Index, P>L, P>H, p<0.001 Observed behaviors: Child compliance Task: %compliance, NS; Dot-to-Dot %compliance, NS; Cancellation Task %compliance, NS Time on-Task: Dot-to-Dot Task time, P<H, L<H, p<0.001; Cancellation task time, P<H, L<H, p<0.001 Productivity: Dot-to-Dot Task patterns correct, NS; Cancellation Task rows correct, P<H, L<H, p<0.01
Schleifer 1975 (Fair)	Hyperactivity Rating Scale pre: active: placebo "True" Hyperactives (n=10): 50.80: 40.30:47.40 "Situational" Hyperactives: (n=16): 46.66: 32.75: 42.62 3-way ANOVA (group x condition x order) Active medication: F=29.09; p<0.01

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Musten 1997 Firestone 1998 (Fair)	Side Effects Rating Scale (17 items)	placebo: low dose: high dose (%) <u>Temperament</u> Irritable: 81:75:38, P>H, L>H, p<0.001 Sad/unhappy: 47:56:84, P<H, L<H, p<0.001 prone to crying: 56:66:56, NS Anxious: 66:72:12, P>H, L>H, p<0.001 Euphoric/unusually happy: 19:25:6, NS <u>Somatic</u> Insomnia or trouble sleep: 59:62:42, P>H, L>H, p<0.05 Nightmares: 28:31:62, P<H, L>H, p<0.01 Stares a lot or daydreams: 47:47:52, NS Decreased appetite: 25:56:81, P<L, P<H, L<H, p<0.001 Stomachaches: 31:38:22, NS Headaches: 18.75:21.88:37.50, NS Drowsiness: 12.50:25:65.63, P<H, L<H, p<0.01 Bites fingernails: 12.5:15.63:28.13, NS Dizziness: 0:3.13:3.13, NS Tics or nervous movements: 3.13:9.38:12.50, NS <u>Sociability</u> Talks less with others: 21.88:34.38:50, P<H, p<0.05 Uninterested in others: 31.25:37.5:75, P<H, L<H, p<0.001	NR	
Schleifer 1975 (Fair)	NR	NR	0	

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
Adolescents: Head-to-head trials			
Cox 2006		Male and female active drivers who had ADHD and were aged 16 to 19 years were eligible to participate in the study. To be included in the study, adolescents had to have a diagnosis of current ADHD as determined by parent report, questionnaire, and structured clinical interviews; a positive history of stimulant responsiveness as disclosed by adolescents and parent reports; and current license to drive and reported daily driving activity. Adolescents were excluded when they had a history of tics or any adverse reactions to stimulant medication, a history of substance abuse disclosed by patient or parent, or a coexisting medical condition or medication usage that is known to interfere with the safe administration of stimulant medications.	Comorbid psychiatric diagnoses for 6 participants (1 agoraphobia, 1 conduct disorder with marijuana abuse, 1 with obsessive compulsive disorder, 1 with obsessive compulsive disorder and hypomania, and 2 with nicotine dependence).
Adolescents: Immediate release stimulants vs. placebo			
Ahmann 2001 (Fair)	randomized, DB, cross-over	children aged 5-15 diagnosed with ADHD (DSM-III), ACTeRS Attention score at or below 25th percentile ACTeRS Hyperactivity Score at or below 25th percentile CTRS-28 Inattention/Passivity Scale 2 or more sd above mean CTRS-28 Hyperactivity Index 2 or more sd above mean CPRS-48 Hyperactivity Index 2 or more sd above mean met the criteria of a Ritalin responder: parent reported 1 sd improvement on CPRS-48 Hyperactivity Index, or 1 positive narrative, teacher reported same scores	NR
Brown 1988 (Fair)	RCT DB crossover	1. Receive a sexual maturity rating of at least 3 to thereby ensure postpubertal status 2. Diagnosed as having a long history of symptoms associated with attention deficit disorder based on DSM-III 3. Obtained a score of at least 15 on the Abbreviated Conners Teacher Rating Scale	NR

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Adolescents: Head-to-head trials			
Cox 2006	OROS MPH, se-AMPH ER, or placebo Days 1 through 5, a half dose (36 mg/day OROS MPH or 15 mg/day se-AMPH ER), and on days 6 to 17, the full study dose of active drug (72 mg/day of OROS MPH or 30 mg/day of se-AMPH ER).	NR	21 were taking MPH , and 12 were taking amphetamine formulations.
Adolescents: Immediate release stimulants vs. placebo			
Ahmann 2001 (Fair)	0.3 mg/kg and 0.5 mg/kg doses, and placebo, 3 times per day, in 7 day cycles, in 2 weeks trials.	run-in NR, no washouts due to short half-life of ritalin	NR
Brown 1988 (Fair)	methylphenidate 0.15mg/kg, 0.3mg/kg or 0.5mg/kg, bid (mean=4.38mg, 12.55mg, 21.28mg) Duration: 14 days for each condition (placebo, 0.15mg/kg, 0.3mg/kg and 0.5mg/kg) Timing: 8am and 12pm	none of the subjects had been treated with stimulants during the year proceeding the study/ NR	NR

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Adolescents: Head-to-head trials		
Cox 2006	Driving stimulator at 5:00 PM, 8:00 PM, and 11:00 PM. Driving performance was rated by adolescents and investigators.	Mean Age 17.8 yrs Gender: 54% male Ethnicity: NR
Adolescents: Immediate release stimulants vs. placebo		
Ahmann 2001 (Fair)	Weekly completion of (BSEQ) Barkley Side Effects Questionnaire, by parents.	n=79 ethnicity NR ages 10-15y 79.7% males
Brown 1988 (Fair)	<u>Behavioral (at the end of each 2-week trial)</u> Conners Parent Rating Scale-Revised (CPRS) Abbreviated Conners Parent (ACP) Teacher Hyperactivity Index (ATR) ADD/H Comprehensive Teacher Rating Scale (ACTeRS) <u>Attention and impulsivity (1 hour after medication)</u> Matching Familiar Figures Test(MFFT) Gordon Diagnostic System (GDS) <u>Academic</u> Arithmetic task <u>Physiological (at least 1 hour after medication)</u> Side Effect Rating Scale	Mean age=13.5 year Gender: 100% male Ethnicity: black

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Adolescents: Head-to-head trials			
Cox 2006	Medication before study No medication 2 MPH formulations 21 Amphetamine formulations 12	Screened: NR Eligible: NR Enrolled: 35	35 analyzed
Adolescents: Immediate release stimulants vs. placebo			
Ahmann 2001 (Fair)	NR	NR/NR/NR	NR/NR/79
Brown 1988 (Fair)	WISC-R IQ=92.91(5.28) Parent rating on Conners factorial rating scale(total)=0.91(0.33) Teacher ratings abbreviated Conners hyperactivity Index=2.12(0.36)	NR/NR/11	0/0/11

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Results
Adolescents: Head-to-head trials	
Cox 2006	Overall driving performance was better with active treatment. a significant medication effect vs. placebo (F = 7.16, P < 0.001). Separate contrasts demonstrated that OROS MPH was associated with better driving performance than placebo (t = 3.31, P = .001) and se-AMPH ER (t = 2.15, P = 0.03), se-AMPH ER was not associated with better driving than placebo (t = 1.17, P < 0.24)
Adolescents: Immediate release stimulants vs. placebo	
Ahmann 2001 (Fair)	**Barkley Side Effects Questionnaire Scores** Ritalin vs placebo, p value Insomnia: 51.3 vs 26.3, p<0.001 Decreased appetite: 61.8 vs 25.0, p<0.001 Stomachache: 36.8 vs 14.5, p<0.001 Headache: 38.7 vs 22.7, NS Dizziness: 10.7 vs 1.3, NS Daydreaming: 42.7 vs 52.0, NS Irritability: 62.2 vs 80.3, p<0.01 Anxiety: 50.7 vs 64.0, NS Nail biting: 26.7 vs 36.0, NS
Brown 1988 (Fair)	*28 out of 36 (75%) dependent measures resulted in significant main effects for drug condition Pairwise Comparison: placebo vs. 0.15mg/kg: 12/27(44%) items showed significant difference placebo vs. 0.30mg/kg: 14/27(52%) items showed significant difference placebo vs. 0.50mg/kg: 17/27(63%) items showed significant difference 0.15mg/kg vs. 0.30mg/kg: 5/27(18.5%) items showed significant difference 0.15mg/kg vs. 0.50mg/kg: 16/27(59.2%) items showed significant difference 0.30mg/kg vs. 0.50mg/kg: 6/27(22.2%) items showed significant difference

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Adolescents: Head-to-head trials				
Cox 2006	NR	One AE reported OROS MPH 36 urinary difficulty	No withdrawals but two participants rescheduled due to lack of adherence	
Adolescents: Immediate release stimulants vs. placebo				
Ahmann 2001 (Fair)	patient/parent report	"dazed", with rapid heartbeat and difficulty breathing: n=1 "zombie": n=1 stomachache, headache, decreased appetite and insomnia: n=1 decreased appetite and sleep problems: n=1	4 withdrawals, all due to adverse events.	the study includes the largest group of girls with ADHD reported in the literature (n=45)
Brown 1988 (Fair)	Side Effects Rating Scale	number of side effect: only a significant difference was found in the comparison of 0.15mg/kg and 0.50mg/kg	0	

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
Klorman 1986 Coons 1986 (Fair)	RCT DB crossover	Scored 1.5 on the abbreviated Conners Hyperactivity Questionnaire and 1.02 on the Home Activity Scale	NR
Klorman 1990 Klorman 1991 Klorman 1992 (Fair)	RCT DB crossover	Subjects received a DSM-III diagnosis of ADD in childhood as well as for the period preceding referral in separate interviews by a clinical psychologist of both the patient and his/her parent on the Diagnostic Instrument for Childhood and Adolescence(DICA). Psychiatric diagnoses other than ADD were assigned if the DICA criteria were fulfilled for either the subject's or the parent's interview. The DICA as well as clinical evaluations by the physicians referring the patients to the study ruled out organic brain disorders or syndromes, childhood autism, psychosis, physical handicaps, and uncorrected visual or auditory deficits. Mental deficiency was ruled out by requiring Full Scale WISC-R IQ scores > 80 on a test administered within 6 months of referral. Subjects were in good physical health and free of all medication.	12(25%) Oppositional disorder plus conduct disorder 1(2.1%) tobacco dependence 5(10.4%) alcohol use 2(4.2%) alcohol abuse 1(2.1%) marijuana abuse 1(2.1%) history of major depression 16(33.3%) past or present adjustment disorder with affective mood 5(10.4%) overanxious disorder 5(10.4%) phobia 14(29.2%) enuresis in the present or past 3(6.3%) history of encopresis

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Klorman 1986 Coons 1986 (Fair)	Week 1: 10mg at breakfast and lunch, 5mg at 4pm Week 2: 15mg at breakfast and lunch, 10mg at 4pm Week 3: 15mg at breakfast and lunch, 10mg at 4pm	2-4 weeks/NR	NR
Klorman 1990 Klorman 1991 Klorman 1992 (Fair)	weight <37.5kg: week 1-- 7.5mg bid in the morning and at noon week 2-- 10mg bid in the morning and at noon week 3-- 10mg in the morning and at noon and 5mg at 4pm weight between 37.5-54kg: each of the above doses was incremented by 2.5mg weight >54kg: each of the above doses was incremented by 5mg Duration: 1 week for each condition(baseline, placebo, drug) Mean dosage: 35.33mg/day, or 0.64mg/kg/day	NR/NR	NR

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Klorman 1986 Coons 1986 (Fair)	Abbreviated Conners Questionnaire IOWA scale Sternberg Test Continuous Performance Test (CPT)	Mean age=14.80 years Gender: 84.2% male Ethnicity: NR
Klorman 1990 Klorman 1991 Klorman 1992 (Fair)	Abbreviated Conners Hyperactivity Questionnaire, weekly IOWA scale, weekly Open-end questions, weekly Hyperactivity, Attention, and Aggression Scale of the Time on Task Scale (TOTS), at the end of each phase Global outcome, in the last session Continuous Performance Test (CPT)	Mean age=14.12 years Gender: 87% male Ethnicity: 96% Caucasian

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Klorman 1986 Coons 1986 (Fair)	SES (hollingshead 4-factor): 2.32(1.01) Wechsler Full Scale IQ: 100.58(13.15) Peabody Individual Achievement Test: 93.47(12.43) Retrospective Conners Parent Scale: 1.96(0.48) Retrospective Home Activity Scale: 2.32(1.01) Current Conners Parent Scale: 1.52(0.62) Current Home Activity Scale: 1.76(0.96) Current Conners Teacher Scale: 1.35(0.69)	NR/NR/19	0/0/19
Klorman 1990 Klorman 1991 Klorman 1992 (Fair)	Hollingshead 4-point SES=51.33(14.29) WISC-R full scale IQ=109.54(12.10) PIAT age total score=99.50(12.08) Home Activity Scale by parent: contemporaneous=1.35(0.94); retrospective=1.74(0.89) Conners Hyperactivity scale: contemporaneous(parent)=1.21(0.62); retrospective(parent)=1.39(0.67); contemporaneous=1.28(0.52)	NR/NR/48	NR/NR/48

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Results
Klorman 1986 Coons 1986 (Fair)	Parent rating (mean dose), placebo: methylphenidate Conners Scale= 1.35: 0.89, p<0.03 I/O=1.30: 0.89, p<0.05 A=1.36: 1.02, p<0.09 Teacher rating (mean dose), placebo: methylphenidate, all NS; Teacher rating (Week 3 dose), placebo: methylphenidate Conners Scale= 0.64: 0.50, NS I/O=0.82: 0.64, p<0.02 A=0.29: 0.16, p<0.02 Heart rate: rose under drug condition (100 beats/min), p<0.02 Sternberg Test: methylphenidate decreased errors and reaction time on performance, p<0.0001 CPT: methylphenidate reduced the rate of missed targets on performance, p<0.0001; enhanced the index of sensitivity of detection, p<0.0005; shorten P3b latency, p<0.0001
Klorman 1990 Klorman 1991 Klorman 1992 (Fair)	Significant improvement in drug condition: Abbreviated Conners Hyperactivity Questionnaire, by parent: p<0.0005; by teacher: p<0.0005 I/O scale, by parent: p<0.002; by teacher: p<0.005 Aggression scale, by parent: p<0.006; by teacher: p<0.0002 valence of comments, by parent: p<0.007; by teacher: p<0.0001 *Parents detected significantly less disturbance over week, p<0.003 *Teachers reported greater improvement as dosage increased over the course of the methylphenidate phase, p<0.03 *Teachers reported greater improvement for younger than older patients in aggression ratings. TOTS scales: improvement under drug condition, p<0.02 (over all) -rated by parent, in aggression, p<0.03; hyperactivity, p=0.05; attention, p=0.06 -rated by teacher, in aggression, p<0.03, hyperactivity, p<0.0002; attention, p<0.04 Global outcome: improvement under drug condition, p<0.006 CPT: improvement in accuracy and speeded reaction times to targets, p<0.05

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Klorman 1986 Coons 1986 (Fair)	Subjects' Treatment Emergent Symptom Scale (STESS)	All 23 items showed no significant effect under drug condition: eat less, eat more, drink more, drink less, dry mouth, wet mouth, stomachache, nausea, rashes, headaches, dizziness, shakiness, pronunciation, clumsiness, restlessness, fatigue, sleepiness, sleep problem, crying, irritability, unhappiness, sadness, inattention.	0	
Klorman 1990 Klorman 1991 Klorman 1992 (Fair)	Subjects' Treatment Emergent Symptom Scale (STESS)	Appetite loss: by parent, 0.05; by patient, p<0.001 Increased thirst: NS Dry mouth: by parent, NS; by patient, p<0.1 Stomachaches: NS Nausea: NS Headaches: NS Sleep problem: NS Shakiness: by parent, NS; by patient, p<0.1 Crying: NS Anger: NS Unhappiness: NS Sadness: NS	0	

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
Pelham 1991 (Fair)	RCT DB crossover	Received a primary diagnosis of ADHD	15 met or exceeded criteria for Oppositional/Defiant Disorder (ODD) or Conduct Disorder (CD) based on DSM-III-R

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Pelham 1991 (Fair)	methylphenidate 0.3mg/kg to the nearest 1.25mg, bid mean dosage: 12.13mg (range 6.25mg-11.25mg) Duration: 4-11 days depending on the child Timing: morning at breakfast and midday	2 weeks/ NR	NR

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Pelham 1991 (Fair)	Daily behavior-modification point system Teacher-recorded classroom measures Teacher and counselor Conners rating scale Daily child's individual behavior and academic goals report card	Mean age=12.59 years Gender: 100% male Ethnicity: NR

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Pelham 1991 (Fair)	Mean IQ=97.2(11.0) DSM-III-R Structured Parent Interview: -ADHD symptoms: 10.6(2.5) -ODD symptoms: 5.7(2.3) -CD symptoms: 1.9(1.7) Abbreviated Conners Rating Scale: -Parent: 21.4(4.4) -Teacher: 14.9(6.1) Iowa Conners Teacher Rating Scale: -I/O: 9.5(3.5) -A: 5.2(3.7) Woodcock-Johnson Achievement test: - Reading: 90.2(14.9)	NR/NR/17	0/0/17

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Results
Pelham 1991 (Fair)	Daily behavior-modification point system: 5 out of 6 items show the effect of drug, p<0.05 Teacher-recorded classroom measures: 4 out of 7 items show the effect of drug, p<0.05 Teacher and counselor Conners rating scale: 2 out of 2 items show the effect of drug, p<0.01 Daily child's individual behavior and academic goals report card, 1 out of 1 items show the effect of drug, p<0.01 9 out of 17(53%) adolescent were judged to be positive responders to 0.3mg/kg methylphenidate.

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Pelham 1991 (Fair)	NR	NR	0	

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
Smith 1998 Evans 2001 (Fair)	randomized, DB, cross-over	Adolescents diagnosed with ADHD (DSM-III-R), aged 12 and up, Verbal IQ >80, no conditions that precluded a trial of stimulants.	NR
Varley 1983 (Fair)	RCT DB crossover	Patients with long-standing symptoms of impulsivity, short attention span, distractibility and excitability	100% were considered to have attention deficit disorder without hyperactivity or a conduct disorder.

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Smith 1998 Evans 2001 (Fair)	25, 50 or 75 mg per day methylphenidate or placebo, 3 times per day, during weeks 3-8 of study.	2 week run in/ washout NR	NR
Varley 1983 (Fair)	methylphenidate 0.15mg/kg, 0.3mg/kg, bid Duration: 1 week for each condition (placebo, low dose, high dose) Timing: 8am and 12pm	1 week/ NR	NR

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Smith 1998 Evans 2001 (Fair)	Timing of Assessment NR Omnibus test Linear trend 10-mg plateau 20 mg plateau quadratic trend	n= 46 mean age= 13.8 yrs 89% male 85% Caucasian
Varley 1983 (Fair)	Conners' abbreviated parent/teacher questionnaire Narrative comments regarding the subject Timing: daily	Mean age=14.27 years Gender: 77.3% male Ethnicity: NR

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Smith 1998 Evans 2001 (Fair)	Parent Iowa Conners Rating Scale (mean) Inattention/Overactivity: 10.1 Oppositional/Defiant: 8.5 Teacher IOWA Conners Rating Scale Inattention/Overactivity: 8.7 Oppositional/Defiant: 6.0 Disruptive behavior disorders parent rating scale Attention-deficit hyperactivity disorder: 8.8 Oppositional defiant disorder: 5.2 Conduct disorder: 1.7 Disruptive behavior disorders teacher rating scale Attention-deficit hyperactivity disorder: 7.5 Oppositional defiant disorder: 3.6 Conduct disorder: 1.9	screened NR/49 eligible/46 enrolled	0/0/46
Varley 1983 (Fair)	All subjects had been noted to be stimulant responders. IQ mean=95.91, range 81-128	NR/NR/22	0/0/22

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Results
Smith 1998 Evans 2001 (Fair)	**measure: mean score at 10mg MPH vs 20mg MPH vs 30mg MPH vs placebo** **C**onduct behavior frequency: 1.0 vs 0.21 vs 0.16 vs 3.7 Defiant behavior frequency: 11.4 vs 5.7 vs 4.3 vs 25.0 Teasing peers frequency: 1.1 vs 1.0 vs 0.9 vs 2.3 Impulsive behavior frequency: 8.3 vs 5.3 vs 4.4 vs 17.6 Inattention/Overactivity rating: 3.2 vs 2.7 vs 2.2 vs 4.2 Oppositional/defiant rating: 2.7 vs 2.3 vs 1.7 vs 3.9 Success Ratio (summary of negative behaviors): 92.6 vs 94.3 vs 95.5 vs 86.1 Job performance rating: 2.6 vs 2.4 vs 2.2 vs 2.8
Varley 1983 (Fair)	Dosage effects: Conners' Parent Questionnaire, parent narrative, Conners' Teacher Questionnaire, teacher narrative, all p<0.01 t test for correlated means (Conners/ narrative) <u>Parents</u> -placebo vs low dose: p<0.05/ p<0.05 -placebo vs high dose: p<0.05/ p<0.05 -low dose vs high dose: NS/ p<0.05 <u>Teachers</u> -placebo vs low dose: p<0.05/ p<0.05 -placebo vs high dose: p<0.05/ p<0.05 -low dose vs high dose: NS/ p<0.05

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Smith 1998 Evans 2001 (Fair)	patient, parent report	Dulled affect, social withdrawal, stomachache, loss of appetite- ns at 10 mg, but increased at 20 mg and 30 mg. **Side effect/rater: 10 mg MPH vs 20 mg MPH 30 mg MPH vs placebo; P value** Motor Tics Counselor: 0.3 vs 0 vs 0.4 vs 0; .693 Parent: 0.4 vs 0 vs 0.4 vs 0; .660 Tearful Counselor: 3.0 vs 3.3 vs 3.0 vs 6.4; .695 Parent: 2.2 vs 2.7 vs 2.3 vs 2.0; .943 Worried Counselor: 6.3 vs 4.9 vs 3.8 vs 5.5; .281 Parent: 1.8 vs 0.4 vs 2.7 vs 3.3; .556 Headache Counselor: 3.3 vs 3.4 vs 5.7 vs 3.8; .429 Parent: 1.6 vs 4.2 vs 3.03 vs 0.8; .093 Picking at skin, etc, Counselor: 13.4 vs 12.6 vs 13.4 vs 7.2; .099 Parent: 5.4 vs 4.0 vs 5.9 vs 0.4; .526 Buccal lingual movements Counselor: 4.0 vs 4.3 vs 2.7 vs 7.9; .030 Parent: 1.1 vs 0.4 vs 1.1 vs 8.4; ..848 Crabby Counselor: 13.4 vs 10.5 vs 9.4 vs 24.2; .000 Parent: 6.3 vs 5.0 vs 4.3 vs 8.4; .710 Dull/Tired/Listless Counselor: 6.5 vs 8.2 vs 12.4 vs 4.2; .001 Parent: 4.0 vs 4.4 vs 5.0 vs 1.8; .118 Withdrawn Counselor: 4.1 vs 4.1 vs 7.8 vs 0.7; .001 Parent: 2.2 vs 1.1 vs 1.2 vs 1.6; .909 Stomachache Counselor: 3.0 vs 4.2 vs 4.3 vs 4.6; .804 Parent: 1.5 vs 3.1 vs 3.8 vs 1.5; .005 Ate less than half of lunch Counselor: 19.9 vs 30.4 vs 35.5 vs 12.4; .000 Loss of appetite - Parent: 3.8 vs 8.6 vs 3.9 vs 1.8; .000 Difficulty falling asleep - Parent: 3.3 vs 3.0 vs 3.9 vs 2.3; .269	0	The clinical implications of this study are that, in most cases, the appropriate single dose of MPH for an adolescent with ADHD is between 10 mg-20 mg.
Varley 1983 (Fair)	NR	occasional comments regarding sleep disturbance and appetite suppression but none significant enough to warrant discontinuation of medication. There was a mean rise in the blood pressure of the subjects of 7mmHg in the diastolic, as well as an increase in the heart rate 10 beats/min in the high dose condition.	0	

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
Adolescents: Longer-acting stimulants vs. placebo			
Buitelaar 2007	RCT Europe (24 centers), Israel (2 centers), South Africa (4 centers), and Australia (3 centers)	Patients aged 6 to 15 years who met DSM-IV criteria for ADHD, as assessed by clinical history and confirmed by a structured interview (Schedule for Affective Disorders and Schizophrenia for School-aged Children-Present and Lifetime Version [K-SADS-PL]), and whose symptom severity was at least 1.5 standard deviations above US age and sex norms on the ADHD Rating Scale IV (ADHD RS) were eligible to participate. Patients with bipolar disorder or psychotic illness were excluded, as were patients with unstable medical illness or conditions requiring ongoing administration of a psychoactive medication (other than atomoxetine). Comorbid psychiatric disorders were assessed clinically and by the K-SADS-PL.All subjects had a medical evaluation including physical examination, routine chemistries, liver function tests, complete blood count, urinalysis, and electrocardiogram (ECG).	NR

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule		Run-in/Washout Period	Allowed other medications/ interventions
Adolescents: Longer-acting stimulants vs. placebo				
Buitelaar 2007	Atomoxetine vs. placebo	6 months	NA	None

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Adolescents: Longer-acting stimulants vs. placebo		
Buitelaar 2007	investigator-administered version of the ADHD RS, CGI-S, Child Health Questionnaire, relapse rates	Mean age=10.8 yrs Gender: 90% male Ethnicity: NR

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Adolescents: Longer-acting stimulants vs. placebo			
Buitelaar 2007	Population characteristics at 2nd randomization ADHD RS Total (mean): 40.8 ADHD RS Total T-score (mean): 80 ADHD-RS Inattention score (mean):21.5 ADHD-RS Hyperactivity/Impulsivity score (mean): 19.4 CTRS-RS ADHD Index: 23.7 CPRS-RS ADHD Index: 28.4 CDRS total score: 26.5 MASC Anxiety Disorder Index: 10.9 CHQ Psychological Summary score: 30.5	Screened: NA Eligible: NA Enrolled: 163	41/ NR/ 161

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Results	
Adolescents: Longer-acting stimulants vs. placebo		
Buitelaar 2007	Change from baseline active vs placebo	ADHD-RS 1.7 vs. 7.8 (P < 0.001)
	Rates of relapse 2.5% vs. 12.2% (P = NR)	RR for relapse during placebo trmt 5.6 (95% CI 1.2, 25.6)

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Adolescents: Longer-acting stimulants vs. placebo				
Buitelaar 2007	NR	NR	Total 27% atomoxetine 17.7% placebo 33.3% Due to AEs NR	

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
Spencer 2006	Randomized, DB, parallel study, multicenter	Adolescents aged 13 to 17 years, weighing ≤75 kg (≤165 lb), who satisfied DSM-IV-TR 1 criteria for primary diagnosis of ADHD combined subtype (predominantly inattentive subtype or hyperactive-impulsive subtype), were eligible for the study. Key inclusion criteria were an intelligence quotient score ≥80, normal blood pressure (girls--systolic blood pressure, 128-132 mm Hg; diastolic blood pressure, 84-86 mm Hg; boys--systolic blood pressure, 130-140 mm Hg; diastolic blood pressure, 84-89 mm Hg), electrocardiographic (ECG) findings within the normal range, and a willingness and ability to comply with protocol requirements in conjunction with a parent or caregiver. Adolescents who were known to be nonresponsive to stimulants (defined as no clinical improvement after trials of 2 stimulant medications, taken for at least 3 weeks each) or naive to stimulant treatment were eligible for enrollment. Exclusion criteria included comorbid illness that could interfere with study participation or impact the efficacy and tolerability of MAS XR; a history of nonresponse to stimulant medication; a documented allergy or intolerance to MAS, MAS XR, or amphetamines; and medication use (not including ADHD medication) that could affect blood pressure or heart rate. Other exclusion criteria included a current comorbid psychiatric diagnosis except oppositional defiant disorder, hypertension, history of seizure disorder within the last 2 years, tic disorder, Tourette's syndrome, abnormal thyroid function, cardiac disorder, and significant laboratory abnormalities. In addition, patients with a history of drug abuse or who were current abusers of drugs or other substances or who had a parent or guardian who abused drugs were excluded.	Oppositional defiance disorder not excluded

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Spencer 2006	Forced-dose titration MAS XR (10-40 mg/day); Adderall XR vs. placebo MAS XR groups: 10 mg/day MAS XR for 4 weeks 20 mg/day MAS XR (10 mg/day week 1, 20 mg/day weeks 2-4) 30 mg/day MAS XR (10 mg/day week 1, 20 mg/day week 2, 30 mg/day weeks 3-4) 40 mg/day MAS XR (10 mg/day week 1, 20 mg/day week 2, 30 mg/day week 3, 40 mg/day week 4)	1-4 week washout phase depending on ADHD medication	NR

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Spencer 2006	Change from baseline in ADHD-RS-IV score	Mean age 14.2 years
		65.5% male
	ADHD-RS-IV scores analyzed post hoc in low and high baseline	73.7% white
	ADHD-RS-IV severity groups	15.8% black
		6.8% Hispanic
	Score on CGI-I scale	3.6% other

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Spencer 2006	78.8% patients were treatment naïve	Screened: 287 Eligible: 287 Enrolled: 287 Placebo = 54 MAS XR 10 mg/day = 56 MAS XR 20 mg/day = 56 MAS XR 30 mg/day = 58 MAS XR 40 mg/day = 63	Withdrawn 23; MAS XR 21, placebo 2 Lost to f/u 6 Analyzed 278 Placebo = 52 MAS XR 10 mg/day = 54 MAS XR 20 mg/day = 53 MAS XR 30 mg/day = 58 MAS XR 40 mg/day = 61

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Results
Spencer 2006	Improvement in mean ADHD-RS-IV total scores in all 4 MAS XR groups compared with placebo (p<0.001) at all weeks Mean change from baseline was -17.8 in MAS XR 10 to 40 mg/day groups and -9.4 in placebo group Greater improvements observed in low baseline severity groups for MAS XR 20, 30, and 40 mg/day than placebo (p≤0.01)and in all MAS XR groups with high baseline severity than placebo (p≤0.02) Higher % improved in endpoint CGI-I scale in MAS XR groups than placebo (p<0.01)

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Spencer 2006	AEs, vital signs, and body weight recorded at weekly study visits and 30 days after drug discontinuation AEs categorized as mild, moderate, or severe ECGs at screening and endpoint	MAS XR/ placebo anorexia, decreased appetite 35.6%/ 1.9% headache 16.3%/ 22.2 % insomnia 12.0%/ 3.7% abdominal pain 10.7%/ 1.9% weight loss 9.4%/ 0% 97.5% AEs mild or moderate in intensity	Total withdrawn 23 Withdrawn AE 5 MAS XR, 0 placebo	

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
Wilens 2006	Multisite study (15 sites) consisting of 4 phases. 1-week washout phase, an open-label dose titration phase lasting up to 4 weeks, a 2-week double-blind phase and an 8-week open-label follow-up safety phase assessing treatment	Adolescent outpatients aged 13 to 18 years having a diagnosis of ADHD (any subtype) were eligible for the study. Diagnosis of ADHD was based on a clinical evaluation using Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSMIV) criteria, confirmed by structured interview (using the behavior module of the Kiddie Schedule for Affective Disorders and Schizophrenia) and by a Children's Global Assessment Scale score of 41 to 70. Eligible subjects could be taking no medications for ADHD at the time of enrollment. Subjects using a behavioral modification program at the time of enrollment had to agree not to change the program or initiate a new program during the study period. Participants had to comply with the study visit schedule, and their parents or caregivers had to be willing to complete all assessments. Excluded subjects included any adolescents with a history of nonresponse to methylphenidate treatment, hypersensitivity or significant intolerance to methylphenidate, clinically significant gastrointestinal tract problems, clinically important electrocardiographic or blood pressure measurement abnormalities, or coexisting medical conditions or concurrent medications likely to interfere with the safe administration of methylphenidate. Subjects requiring any of the following medications were excluded: clonidine or other α2-adrenergic receptor agonists, tricyclic antidepressants, selective serotonin reuptake inhibitors, theophylline, warfarin sodium, and anticonvulsant agents. Participants with psychiatric comorbidities were eligible for inclusion, except for those with Tourette syndrome or a family history of Tourette syndrome, an ongoing seizure disorder, bipolar disorder, psychotic disorder, a mood or anxiety disorder requiring drug therapy, alcohol or other drug abuse within the 6 months before study enrollment, an eating disorder, or marked anxiety, tension, or agitation.	Participants with psychiatric comorbidities were eligible for inclusion, except for those with Tourette syndrome or a family history of Tourette syndrome, an ongoing seizure disorder, bipolar disorder, psychotic disorder, a mood or anxiety disorder requiring drug therapy, alcohol or other drug abuse within the 6 months before study enrollment, an eating disorder, or marked anxiety, tension, or agitation.

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule		Run-in/Washout Period	Allowed other medications/ interventions
Wilens 2006	methylphenidate, osmotic-release oral system (OROS) 14 weeks	18-72 mg day 11	1 Week	none

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Wilens 2006	ADHD RS, Conners-Wells Adolescent Self-report of Symptoms Scale, and CCI, as well as changes in heart rate and systolic and diastolic blood pressure from baseline to the end of the double-blind phase of the study CGI -I at end of double blind period only	Mean age=14.6 yrs Gender: 80.2% male Ethnicity: 75.1% white 13.6% black 11.3% other

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Wilens 2006	ADHD RS score investigator 31.26 parent 30.82 Parent Child Conflict Index 0.272 Conners-Wells Adolescent Self-report of Symptoms Scale 91.96	Screened: NR Eligible: NR Enrolled: 220	49/ NR/ 220

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Results
Wilens 2006	Change in measures from baseline to end of double blind period of active vs. placebo DHD RS Investigator -14.93 vs. -9.58 P = 0.001 parent -14.00 vs. -10.14 P = 0.008, Conners-Wells Adolescent Self-report of Symptoms Scale -31.7 vs. -18.7 P= 0.001 and CCI -0.098 vs. -0.016 P= 0.005 CGI-I much or very much improved 51.8% vs. 31.0% P= 0.01

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Wilens 2006	NR	Active vs placebo (%) **headache** 3.4 vs. 6.7 **decreased appetite** 2.3 vs. 0 **insomnia** 4.6 vs. 0 **abdominal pain** 1.1 vs. 2.2 **nausea** 1.1 vs. 2.2 **asthenia** 0 vs. 2.2 **diarrhea** 2.3 vs. 0 for all P = NR	During double-blind phase- Withdrawals active 18% placebo 31% Due to AEs active 1% placebo 0%	

Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

	Internal Validity								
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/high**
Preschool children									
Barkley 1988	NR	NR	n/a	Yes	Yes	Yes	Yes	No No No No	NR NR
Conners 1975	NR	NR	NR	Yes	Yes	Yes	Yes	Yes No No No	No No

Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

				External Validity	
Author, Year Country	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**	**Exclusion criteria**
Preschool children					
Barkley 1988	Unclear	No	Fair	NR/NR/27	NR
Conners 1975	No; different numbers of patients were excluded from analyses at each time point due to "missing data"	No	Poor	NR/66/59	Marked anxiety, tension, or agitation thought to result from current psychological stress in the home; hypersensitivity to MPH; glaucoma; epilepsy; severe organic brain damage; or need during therapy for any other psychotropic drugs; pressor agents, MAO inhibitors, phenylbutazone, or coumarin-type anti-coagulants

Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

Author, Year Country	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Preschool children					
Barkley 1988	NR/NR	No	Yes	NIMG Grant # MH 32334; Department of Neurology, Medical College of Wisconsin	Yes
Conners 1975	NR/NR	No	Yes	In part by U.S. Public Health Service research grant # MH 18909 from the National Institute of Mental Health	Yes

Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

	Internal Validity								
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/high**
Greenhill 2006/Kollins 2006/Wigal 2006 (PATS)	Method not reported	Yes	Unclear	Yes	Yes	NA	Yes	Yes Yes Yes Yes	Yes Enrolled in crossover titration trial: 165 Enrolled in parallel trial: 114

Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

				External Validity	
Author, Year Country	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**	**Exclusion criteria**
Greenhill 2006/Kollins 2006/Wigal 2006 (PATS)	No	Yes	Fair, despite high attrition (due to extra cautious safety measures).	1915/553/303	Child or parent could not understand or follow instructions, evidence of moderate to severe adverse effects or evidence of much improved response to any dose of methylphenidate or another stimulant, >5 week exposure to at least 30 mg/day of methylphenidate or equivalent doses or other stimulants, use of any other psychotropic medication, taken investigational drug in last 30 days, history of motor or vocal tics or Tourette's syndrome, major medical conditions that would interfere with involvement in long-term study or could be negatively affected by study drug, current evidence of adjustment disorder, autism, psychosis, significant suicidality, or other psychiatric disorder in addition to ADHD that requires medication, evidence of current physical, sexual, or emotional abuse, living with anyone abusing stimulants or cocaine, or history of bipolar disorder in both biological parents. Also, ADHD improvement after required parent behavior training.

Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

Author, Year Country	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Greenhill 2006/Kollins 2006/Wigal 2006 (PATS)	No Yes	NR	Yes	National Institutes of Mental Health; Author's relationships with Pharma are disclosed (long list)	Yes

Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

	Internal Validity								
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/high**
Musten 1997	NR	Yes	n/a	Yes	Yes	Yes	Yes	Yes	No
Firestone 1998								No	No
								No	
								No	
Schleifer 1975	NR	NR	n/a	Yes	Yes	Yes	Yes	No	NR
								No	NR
								No	
								No	

Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

				External Validity	
Author, Year Country	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**	**Exclusion criteria**
Musten 1997 Firestone 1998	No; Analysis excluded 10 patients (24%) - 4 "withdrew" and 6 "did not have completed assessment protocols"	No	Fair	109 (43 refused, 64 agreed) /54/41	NR
Schleifer 1975	Yes	No	Fair	NR/NR/28	NR

Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

Author, Year Country	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Musten 1997 Firestone 1998	NR/NR	No	Yes	Health Canada grant 6606-4979-63	Yes
Schleifer 1975	No No	No	Yes	Supported in part by a Dominion-Provincial Mental Health grant to Dr. Gert Morgenstern	Yes

Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

	Internal Validity								
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/high**
Adolescents									
Ahmann 2001	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes No No No	NR NR
Brown 1988	NR	NR	n/a	Yes	Yes	Yes	Yes	No No No No	NR NR
Bostic 2000	NR	NR	NR	Yes	Yes	Yes	Yes	Yes No No No	NR NR
Buitelaar 2007	Yes	NR	Unclear	Yes	Yes	Yes	Yes	Yes NA No No	Yes I: 65/79; C: 54/81

Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

				External Validity	
Author, Year Country	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**	**Exclusion criteria**
Adolescents					
Ahmann 2001	No	No	Fair	NR/NR/234	History of seizures, mental retardation, Tourette's syndrome, or other significant neurologic history
Brown 1988	Unclear	No	Fair	NR/NR/11	Mentally retardation or gross neurological disorders
Bostic 2000	Yes	No	Fair	32/21/21	Clinically significant medical conditions or abnormal baseline laboratory liver function tests, mental retardation, organic brain disorders, unstable psychiatric conditions, bipolar disorder, psychosis, drug or alcohol abuse of dependence within the prior 6 months, or active pregnancy or nursing.
Buitelaar 2007	No	Yes	Fair	604/NR/163	Bipolar disorder, psychotic illness, unstable medical illness, or conditions requiring ongoing administration of psychoactive medication (other than drug under investigation)

Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

Author, Year Country	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Adolescents					
Ahmann 2001	No No	NR	Yes	Marshfield Clinic grants 0844-01-87 and 0844-01-90	Yes
Brown 1988	NR/NR	NR	Yes	NR	Yes
Bostic 2000	No Patients on psychotropics were required to washout at least 2 weeks before the beginning of the study; treatment periods were separated by 2-week washout period	NR	Yes	Eli Lilly, Inc.	Yes
Buitelaar 2007	NR Yes	No	Yes	Eli Lilly and Co.	Is assessment long-term, continuation treatment relevant?

Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

	Internal Validity								
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/high**
Cox 2006	Yes	NR	NR	Yes	Yes	NA	Yes	No No No No	No No
Klorman 1986 Coons 1986	NR	NR	n/a	Yes	Yes	Yes	Yes	No No No No	NR NR
Klorman 1990 Klorman 1991 Klorman 1992	NR	NR	NR	Yes	Yes	Yes	Yes	No No No No	NR NR
Pelham 1991	NR	NR	n/a	Yes	Yes	Yes	Yes	No No No No	NR NR

Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

				External Validity	
Author, Year Country	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**	**Exclusion criteria**
Cox 2006	NR	No	Poor	NR/NR/35	History of tics, any adverse reactions to stimulant medication, history of substance abuse, or coexisting medical condition or medication usage known to interfere with safe administration of stimulant medications
Klorman 1986 Coons 1986	Unclear	No	Fair	NR/NR/19	(1) No evidence of organic brain disorder, psychosis, or uncorrected sensory impairment; (2) Full-Scale WAIS-R or WISC-R IQ scores of at least 74; and (3) no treatment with drugs for a suitable period before entering the protocol, 2 weeks for patients receiving MPH and 4 weeks for those also receiving thioridazine
Klorman 1990 Klorman 1991 Klorman 1992	Unclear	No	Fair	NR/NR/48	CNS involvement, childhood autism, psychosis, physical handicaps, and uncorrected visual or auditory problems, mental deficiency
Pelham 1991	Unclear	No	Fair	NR/NR/34	Mental retardation or gross neurological disorders

Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

Author, Year Country	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Cox 2006	No No, even with cross-over design	NR	NR	McNeil Pediatrics Division of McNeil-PPC, Inc.	Is effect of drug on *driving performance* relevant? All subjects had ADHD.
Klorman 1986 Coons 1986	NR/Yes (see exclusion criteria)	No	Yes	NIMH Grants MH 32103 and MH38118	Yes
Klorman 1990 Klorman 1991 Klorman 1992	NR NR	95.8% treatment naïve	Yes	NIMH grant MH38118	Yes
Pelham 1991	NR/NR	NR	Yes	NR	Yes

Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

	Internal Validity								
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/high**
Spencer 2006	Method not reported	NR	Unclear	Yes	Unclear, although says "double-blind" in title	Unclear, although says "double-blind" in title	Unclear, although says "double-blind" in title	Yes NA Yes No	No No
Smith 1998 Evans 2001	NR	NR	NR	Yes	Yes	Yes	Yes	Yes No No No	NR NR
Varley 1983	Yes	NR	n/a	Yes	Yes	Yes	Yes	Yes No No No	No No

Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

				External Validity	
Author, Year Country	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**	**Exclusion criteria**
Spencer 2006	Yes	Yes	Fair	335/308/297	Comorbid psychiatric diagnosis (except ADHD), diagnosis of conduct disorder, medical history of nonresponse to stimulant medication, seizures, tic disorder, or Tourette's syndrome
Smith 1998 Evans 2001	Unclear	No	Fair	NR/NR49	NR
Varley 1983	Yes	No	Fair	NR/NR/22	Conduct disorder

Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

Author, Year Country	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Spencer 2006	No Yes	NR	NR	Shire Pharmaceuticals Inc.	Is comorbid ADHD and ODD (Oppositional Defiant Disorder) relevant?
Smith 1998 Evans 2001	Run-in: NR Wash-out: 2 weeks prior to randomization	No	Yes	National Institute on Drug Abuse, NIMH, National Institute on Alcohol Abuse and Alcoholism, and the National Institute of Child Health and Human Development	Yes
Varley 1983	NR/NR	No	Yes	NR	Yes

Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

	Internal Validity								
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/high**
Wilens 2006	Yes	Yes	Yes, except more males in C vs I	Yes	Yes	NA	Yes	Yes NA Yes No	Yes I: 16/87 C: 28/90

Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

				External Validity	
Author, Year Country	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**	**Exclusion criteria**
Wilens 2006	Yes	Yes	Good	220/182/175	History of nonresponse to methylphenidate treatment, hypersensitivity or significant intolerance to methylphenidate, clinically significant gastrointestinal tract problems, clinically important electrocardiographic or blood pressure measurement abnormalities, coexisting medical conditions, concurrent medications likely to interfere with safe administration of methylphenidate, Tourette's syndrome, family history of Tourette's syndrome, ongoing seizure disorder, bipolar disorder, psychotic disorder, mood or anxiety disorder requiring drug therapy, alcohol or other drug abuse within 6 months before enrollment, eating disorder, marked anxiety, tension, agitation, or requiring any of the following medications: clonidine or other adrenergic receptor agonists, tricyclic antidepressants, selective serotonin reuptake inhibitors, theophylline, warfarin sodium, and anticonvulsant agents.

Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

Author, Year Country	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Wilens 2006	No Yes	No	Yes	McNeil Consumer and & Specialty Pharmaceuticals	Yes

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria
Dextroamphetamine vs. methylphenidate IR		
Arnold 1978 Huestis 1975 Fair	RCT with crossover Single center	Diagnosis of Minimal Brain Dysfunction with such signs an symptoms as hyperactivity, short attention span, distractibility, irritability, variability, explosiveness, aggression, inability to keep friends or function in a group, underachievement, visual-motor dysfunction, and poor coordination or other minor neurological signs; total score of 24 or more on the first six items of the Davids Hyperkinetic Rating Scale, by parents and teacher; indication for stimulant treatment as determined by the patient's psychiatrist; aged between 5 and 12 years; enrollment in some sort of school setting to obtain teachers' ratings; no psychoactive drug in the preceding month; insufficient benefit from an initial 2-week "placebo washout" to be maintained without active drug

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Comorbidity	Interventions and total daily dose Duration Dosing schedule
Dextroamphetamine vs. methylphenidate IR		
Arnold 1978 Huestis 1975 Fair	NR	Days 1/2/3+: Dextroamphetamine: 5/10/15 mg Methylphenidate: 10/20/30 mg 3 weeks, then crossover Twice daily: morning and noon

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Dextroamphetamine vs. methylphenidate IR				
Arnold 1978 Huestis 1975 Fair	2-week placebo washout	NR	Parents' Symptom Checklist (Arnold and Smeltzer) Conners Teachers' Behavior Checklist; Davids' Hyperkinetic Rating Scale (completed by both parents and teachers); target symptom assessment/quantification using 9-point scale (1=excellent, 5=no change from placebo washout; 9=disastrous)	Mean age=8 75.9% male Race nr

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Dextroamphetamine vs. methylphenidate IR			
Arnold 1978	Mean sum CTRS=91.52	NR	NR
Huestis 1975	CTRS factor I (conduct)=35.83	NR	NR
	CTRS factor IV (hyperactivity)=23.10	29	29
Fair	Mean total items 1-6 DHRS by teachers=29.03 DHRS by teachers Item I (hyperactivity)=5.28 Mean total items 1-6 DHRS by parent=30.76 DHRS by parent Item I (hyperactivity)=5.24 Mean sum Problem Behavior Checklist by parent=190.07 Problem Behavior Checklist by parent factor I (aggression)/factor 4 (hyperactivity)=65.59/24.31 Target symptoms rating by psychiatrists=5.00		

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Dextroamphetamine vs. methylphenidate IR		
Arnold 1978 Huestis 1975 Fair	Mean changes on (p=NS for all): Conners' school behavior checklist by teachers: -21.26 vs -17.97 Sum of first 6 items on Davids' Hyperkinetic Rating Scale by teacher: -6.65 vs -5.89 Item 7 (poor schoolwork) on Davids' Hyperkinetic Rating Scale by teachers: -0.69 vs -0.79 First six items on Davids' Hyperkinetic Rating Scale by parents: -5.45 vs -5.35 Problem checklist by parents: -43.1 vs -37.79 Psychiatrists' ratings of parent-assessed target symptoms: -1.87 vs -1.62	Mean side effects reported by parents on checklist (1=not at all; 4=very much)

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Dextroamphetamine vs. methylphenidate IR	
Arnold 1978	p=NS on all
Huestis 1975	Poor appetite: -0.45 vs 0.35
	Awake at night: 0.07 vs -0.03
Fair	Headaches: -0.27 vs -0.27
	Tummy aches: -0.41 vs -0.31
	Side effects of drug: 0.25 vs 0.25
	Mean change in weight (kg): -1.32 vs -0.92; p=NS

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Dextroamphetamine vs. methylphenidate IR		
Arnold 1978	NR	
Huestis 1975	NR	
Fair		

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria
Borcherding 1990 Poor	RCT with crossover Single center	DSM-III diagnosis of Attention Deficit Disorder with Hyperactivity (ADDH); medically healthy; WISC-R full scale IQ score > 80; score 2 SDs or above their age norms on Factor 4 (hyperactivity) of the CTRS

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Comorbidity	Interventions and total daily dose Duration Dosing schedule
Borcherding 1990 Poor	NR	Mean dosages for weeks 1/2/3: Dexmethylphenidate 0.2/0.5/0.7 mg/kg Methylphenidate 0.5/0.8/1.3 mg /kg 3 weeks then crossover Twice daily: 9 a.m. and 1 p.m.

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Borcherding 1990 Poor	3-week washout	NR	Efficacy nr	Mean age=8.6 years 100% male 71.7% white, 2.2% black, 6.5% Hispanic/Asiatic

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Borcherding	WISC-R Full Scale IQ=106.1	NR	1 (2.2%) withdrawn/lost to
1990	Mean CTRS for Factor 4 (hyperactivity)/Factor 1 (conduct):	NR	fu nr/# analyzed ranged by
	2.5/1.2	46	outcome
Poor	28.3% stimulant naïve		

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Borcherding 1990 Poor	Efficacy nr	STESS (rated by physician/child's parents) + 4 items (orofacial, stereotypic, other tics, tremor) 3 items from CPRS (nervous habits/mannerisms, compulsive actis, obsessive thinking) 20-item Leyton Obsessional Inventory Other observations by teachers, nurses, and other professional staff, and from families (as cued by professional staff)

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Borcherding	Abnormal movements
1990	Abnormal movements "NOTED": 34/45 (76%) overall
	Abnormal movements "OBSERVED": 27/34 (79%)
Poor	Of those n=27 subjects (Dextroamphetamine vs methylphenidate; p=NS on all):
	Abnormal movements: 6 (22%) vs 10 (37%)
	Orofacial movements: 7 (27.9%) vs 7 (27.9%)
	Steretypies: 2 (7.4%) vs 4 (14.8%)
	Compulsive behaviors
	Overall: 23/45 (51.1%)
	Of those 23 subjects (Dextroamphetamine vs methylphenidate; p=NS on all):
	Compulsive behaviors: 13 (56%) vs 5 (22%); p=0.09
	STESS items (mean scores)
	Does things over & over a certain number of times before they seem quite right (n=38): 0.4 vs 0.4; both > placebo
	Meticulous; pays close attention to detail: 0.4 vs 0.3; both > placebo
	Overly neat and clean: 0.2 vs 0.1: only dextroamphetamine > placebo
	Has trouble making up his mind: 0.4 vs 0.5; methylphenidate > placebo
	Jerks/twitches or unusual movements: 0.2 vs 0.2; both = placebo
	CPRS items (mean scores) (all "both > placebo)
	Compulsive acts: 1.7 vs 1.5
	Nervous habits & mannerisms: 1.8 vs 1.7
	Obsessive thinking: 2.0 vs 2.0

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Borcherding 1990 Poor	1 (2.2%) withdrawals withdrawals due to adverse events nr	Compares results of this 100% female trial to trial of 45 boys (Castellanos 1996)

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria
Castellanos	RCT with crossover	(1) DSM-III-R criteria for Tourette's disorder with tics confirmed by a knowledgeable clinician at least
1997	Single center	1 year prior to referral (Tourette Syndrome Classification Study Group, 1993); (2) symptoms of
United States		ADHD present in at least two settings; (3) Conners hyperactivity factor scores from their home teacher were at least 2 SD greater than age norms
Subgroup of Elia 1991		Tourette's syndrome

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Comorbidity	Interventions and total daily dose Duration Dosing schedule
Castellanos 1997 United States Subgroup of Elia 1991	Conduct disorder=1(5%) Oppositional defiant disorder=6(30%) Reading disorder=1(5%) Overanxious disorder=1(5%) Obsessive-compulsive disorder=2(10%) Enuresis=4(20%)	Group 1 (n=12), Low-medium-high Weeks 1, 2, and 3 for children < 30 kg/ > 30 kg: Dextroamphetamine 10, 25, and 40 mg/15, 30, and 45 mg Methylphenidate 25, 40 and 70 mg/30, 50 and 90 mg Placebo Group 2 (n=6), Low-medium-medium Weeks 1, 2, and 3 for children < 30 kg/ > 30 kg: Dextroamphetamine 10, 25, and 25 mg/15, 30, and 30 mg Methylphenidate 25, 40 and 40 mg/30, 50 and 50 mg Placebo Group 3 (n=4), Low-high-high Weeks 1, 2, and 3 for children < 30 kg/ > 30 kg: Dextroamphetamine 10, 40, and 40 mg/15, 45, and 45 mg Methylphenidate 25, 70 and 70 mg/30, 90 and 900 mg Placebo 3 weeks then crossover Twice daily at 9 am and 1 pm Individualized curriculum and instruction provided from 9 am to 12:30 pm in a highly structured classroom. This included a positive reinforcement management program using play money. Children were paid for appropriate behavior and fined for inappropriate behavior. NIMH Research Day Program

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Castellanos 1997 United States Subgroup of Elia 1991	≥ 4 weeks washout	Haloperidol	CTRS Historical and Examiner's Ratings from the Unified Rating Scale provided by the Tourette Syndrome Association (modified from Yale Global Tic Severity Scale)	Mean age=9.4 Gender nr 80% white

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Castellanos	WISC-R Full Scale IQ=98.8	NR	# withdrawn: Group
1997	WISC-R Verbal=102	NR	1=2(9.1%), Group 2=nr,
United States	WISC-R Performance=95.6	Enrolled: Group	Group 3=n4/lost to fu
	Yale Global Tic Severity Scale (0-104)=37.3	1=22, Group 2=6,	nr/Analyzed: Group 1=20,
Subgroup of Elia 1991	CTRS Conduct/Hyperactivity factors=0.59/1.98	Group 3=4	Group 2=nr, Group 3=nr
	C-GAS=42.6		

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Castellanos 1997 United States Subgroup of Elia 1991	Tic severity Dextroamphetamine had greater severity than placebo (+25%), p<0.05 Methylphenidate severity indistinguishable from placebo (-4%), p=NS	NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Castellanos	# cases with dextroamphetamine vs methylphenidate (denominate unclear)
1997	Marked appetite suppression with transient weight loss: 4 vs 3
United States	Initial insomnia: 10 vs 2
	Transient obsessive-compulsive symptoms: 1 vs 5
Subgroup of Elia 1991	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Castellanos 1997 United States Subgroup of Elia 1991	NR NR	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria
Efron 1997 Australia Fair	RCT with crossover Single center	Age between 5 and 15 years; meet DSM-IV criteria for ADHD. The DuPaul ADHD rating scale was used; each DSM-IV ADHD symptom was marked on a 4-point scale: "never or rarely," (0); "sometimes," (1); "often," (2); and "very often," (3). Only symptoms rated 2 or 3 were considered present and counted toward the diagnosis; T-score of at least 1.5 standard deviations (SD) above the mean on the Attention Problems scale of the Child Behavior Checklist or Teacher Report Form. No history of intellectual disability, gross neurologic abnormality, or Tourette's syndrome. Decision made to trial stimulant medication on clinical grounds.

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Comorbidity	Interventions and total daily dose Duration Dosing schedule
Efron 1997 Australia Fair	NR	Dextroamphetamine 0.15mg/kg Methylphenidate 0.3 mg/kg Both rounded off to the nearest capsule size x 2 weeks then crossover

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Efron 1997 Australia Fair	24-hour washout	NR	Wechsler Intelligence Scale for Children, 3rd Edition (WISC-III), 28-item Conners' Teacher Rating Scale-Revised (CTRS-R), 48-item Conners' Parent Rating Scale-Revised (CPRS-R), Continuous Performance Test (CPT), Child Behavior Checklist (CBCL)	8.7 years NR NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Efron	ADHD-mixed type=101(81.8%)	NR	NR
1997	ADHD-predominantly inattentive=22(17.6%)	NR	NR
Australia	ADHD-predominantly hyperactive/impulsive=2(1.6%)	125	125
	Mean IQ=98.9		
Fair			

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Efron 1997 Australia Fair	% subjects rated by their parents as improved overall compared with their usual selves: 86 (68.8%) vs 90 (72%); p=NS (CTRS-R and CPRS-R data generally corroborated with these proportions of global response to the two stimulants)	Side Effects Rating Scale (SERS)

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Efron	Trouble sleeping: 88(70%) vs 79(64%), p=NS
1997	Poor appetite: 74(59%) vs 69(56%), p=NS
Australia	Irritable: 102(82%) vs 100(80%), p=NS
	Proneness to crying: 95(76% vs 89(71%), p=NS
Fair	Anxiousness: 85(68%) vs 76(61%), p=NS
	Sadness/unhappiness: 74(59%) vs 69(56%), p=NS
	Headaches: 38(30%) vs 30(24%), p=NS
	Stomachaches: 50(40%) vs 40(32%), p=NS
	Nightmares: 35(28%) vs 26(21%), p=NS
	Daydreams: 78(62%) vs 77(62%), p=NS
	Talking little with others: 37(30%) vs 35(28%), p=NS
	Uninterested in others: 43(34%) vs 39(31%), p=NS
	Drowsiness: 23(18%) vs 22(18%), p=NS
	Biting fingernails: 50(405) vs 56(45%), p=NS
	Unusually happy: 33(26%) vs 35(28%), p=NS
	Dizziness: 18(14%) vs 15(12%), p=NS
	Tics or nervous movements: 32(26%) vs 35(28%), p=NS
	Severity: dexamphetamine > methylphenidate on trouble sleeping, irritability, prone to crying, anxiousness, sadness/unhappiness, nightmares (data nr)

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Efron 1997 Australia Fair	Total withdrawals nr Withdrawals due to adverse events: 2(1.6%) vs 2(1.6%)	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria
Efron 1998 Australia Fair	RCT with crossover Single center	Age between 5 and 15 years; meet DSM-IV criteria for ADHD. The DuPaul ADHD rating scale was used; each DSM-IV ADHD symptom was marked on a 4-point scale: "never or rarely," (0); "sometimes," (1); "often," (2); and "very often," (3). Only symptoms rated 2 or 3 were considered present and counted toward the diagnosis; T-score of at least 1.5 standard deviations (SD) above the mean on the Attention Problems scale of the Child Behavior Checklist or Teacher Report Form. No history of intellectual disability, gross neurologic abnormality, or Tourette's syndrome. Decision made to trial stimulant medication on clinical grounds.
Elia 1990 United States Fair	RCT with crossover Single center	DSM-III criteria for attention deficit disorder with hyperactivity in at least two settings (home, school, or hospital). A score 2 SD or more above age norms was required on Factor IV (hyperactivity) of the revised 39-item Conners Teacher Rating Scale(CTRS). WISC-R Full scale IQ score of 80 or more
Elia 1991 Schmidt 1994 United States Fair	RCT with crossover Single center	DSM-III criteria for attention deficit disorder with hyperactivity in at least two settings (home, school, or hospital). A score 2 SD or more above age norms was required on Factor IV (hyperactivity) of the revised 39-item Conners Teacher Rating Scale(CTRS). Parents also completed the 48-item Conners Parent Questionnaire (CPQ).

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Comorbidity	Interventions and total daily dose Duration Dosing schedule
Efron 1998 Australia Fair	NR	Dextroamphetamine 0.15mg/kg Methylphenidate 0.3 mg/kg Both rounded off to the nearest capsule size x 2 weeks then crossover
Elia 1990 United States Fair	Comorbid conduct disorder: 7 (22.6%) Comorbid oppositional disorder: 6 (19.4%) Comorbid specific developmental disorders: 9 (29%)	Weeks 1, 2, and 3 for children < 30 kg/ > 30 kg: Dextroamphetamine 10, 25, and 40 mg/15, 30, and 45 mg Methylphenidate 25, 40 and 70 mg/30, 50 and 90 mg 3 weeks then crossover Twice daily at 9 am and 1 pm
Elia 1991 Schmidt 1994 United States Fair	Comorbid conduct disorder: 10 (20.8%) Comorbid oppositional disorder: 12 (25%) Comorbid specific developmental disorders: 11 (22.9%) Comorbid dysthymic disorder: 1 (2%)	Weeks 1, 2, and 3 for children < 30 kg/ > 30 kg: Dextroamphetamine 10, 25, and 40 mg/15, 30, and 45 mg Methylphenidate 25, 40 and 70 mg/30, 50 and 90 mg 3 weeks then crossover Twice daily at 9 am and 1 pm

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Efron 1998 Australia Fair	24-hour washout	NR	Wechsler Intelligence Scale for Children, 3rd Edition (WISC-III), 28-item Conners' Teacher Rating Scale-Revised (CTRS-R), 48-item Conners' Parent Rating Scale-Revised (CPRS-R), Continuous Performance Test (CPT), Child Behavior Checklist (CBCL) Study subjects/parents were also asked to rate how they felt whilst taking each medication, compared to their usual self, at the completion of each cycle using a dichotomized 5-point scale (Nonresponse='worse than usual', 'much worse than usual' or about the same as usual'; Response='better than usual' or 'much better than usual' Children also asked to rate "How helpful was the medication?' on a 5-point scale, from 'very helpful to 'not at all helpful'	Mean age= 9.3 years 91.2% male Race nr
Elia 1990 United States Fair	≥ 3 weeks washout	NR	CTRS CPRS CGI CPT	Mean age=8.5 years 100% male Race nr
Elia 1991 Schmidt 1994 United States Fair	NR	NR	ABTRS CTRS CPRS CPQ CGI C-GAS CPT Palwin Truncal motor activity monitor	Mean age=8.6 years 100% male

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Efron 1998 Australia Fair	ADHD-Mixed type=84(82.4%) ADHD-predominantly inattentive=17(16.7%) ADHD-predominantly hyperactive/impulsive=1(1%) Mean IQ=98.8 Learning disability for reading=30(27.3%) Learning disorder for spelling=36(32.7%)	NR NR 102	NR NR 102
Elia 1990 United States Fair	Mean Full Scale WISC-R IQ=102 Mean CTRS factor I (conduct)/factor IV (hyperactivity): 1.3/2.6 Mean CPRS factor I (conduct)/factor IV (hyperactivity): 1.6/2.4 Stimulant naïve: 18 (37.5%)	NR NR 31	NR NR NR
Elia 1991 Schmidt 1994 United States Fair	Mean Full Scale WISC-R IQ=105.6 Mean CTRS factor I (conduct) - teacher/parent rating: 1.3/1.5 Mean CTRS factor IV (hyperactivity) - teacher/parent rating: 2.6/2.4 Stimulant naïve: 18 (37.5%)	NR NR 48	NR NR NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Efron 1998 Australia Fair	Dextroamphetamine versus methylphenidate: Child's rating: "When I took this medication I felt:" (cases/%) Much worse than usual: 6/5.9 vs 5/4.9 Worse than usual: 13/12.9 vs 8/7.8 About the same as usual: 26/25.7 vs 25/24.5 Better than usual: 23/22.8 vs 35/34.3 Much better than usual: 33/32.7 vs 29/28.4 Child's rating: "How helpful was the medication?" (cases/%) Very helpful: 39/38.6 vs 46/45.1 A bit helpful: 25/24.8 vs 29/28.4 Not sure: 27/26.7 vs 15/14.7 Not very helpful: 5/5 vs 4/3.9 Not at all helpful: 5/5 vs 8/7.8	SERS
Elia 1990 United States Fair	dextroamphetamine=methylphenidate on all measures (limited data provided in graph format) Estimated from graphs (dextroamphetamine vs methylphenidate) <u>Mean changes in (all p=NS):</u> CGI: +2.5 vs +2.8 CPT (# correct): +9 vs +10 CTRS Factor I: -0.4 vs -0.4; CTRS Factor IV: -0.8 vs -0.8 CPRS Factor I: -0.7 vs -0.6; CPRS Factor IV: -1.2 vs -1	STESS CPRS
Elia 1991 Schmidt 1994 United States Fair	dextroamphetamine=methylphenidate on all measures (limited data provided in graph format) Estimated from graphs (dextroamphetamine vs methylphenidate) <u>Mean changes in (all p=NS):</u> CGI: 2.3 vs 2.4; GAS: 5 vs 6 39-item Conners Factor I (conduct): -0.41 vs -0.41 48-item Conners Factor I (conduct): -0.5 vs -0.39 CPT (# omission errors): -11 vs -11 39-item Conners Factor IV (hyperactivity): -0.9 vs -1 48-item Conners Factor IV (hyperactivity): -1.2 vs -1.0 CPT (# commission errors): -13 vs -14	STESS CPRS

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Efron 1998 Australia Fair	NR
Elia 1990 United States Fair	NR
Elia 1991 Schmidt 1994 United States Fair	dextroamphetamine vs methylphenidate (% patients with mild/moderate/severe severity scores on STESS) (all p=NS) Decreased appetite (n=48): 40/42/13 vs 40/35/10 Sleep difficulties (n=48): 31/40/10 vs 40/31/8 Overly meticulous (n=33): 18/12/6 vs 30/3/0 Not happy (n=48): 25/33/4 vs 27/35/6 dextroamphetamine vs methylphenidate (% patients with mild/moderate/severe severity scores on CPRS) (p=NS) Nervous habits and mannerisms: 35/9/0 vs 26/21/3

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Efron 1998 Australia Fair	NR NR	
Elia 1990 United States Fair	NR NR	
Elia 1991 Schmidt 1994 United States Fair	NR NR	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria
Elia 1993 United States Fair	RCT with crossover Single center	DSM-III criteria for attention deficit disorder with hyperactivity in at least two settings (home, school, or hospital). A score 2 SD or more above age norms was required on Factor IV (hyperactivity) of the CTQ-R. A WISC-R full scale IQ score > 80.
Gross 1976 Poor	RCT with crossover Single center	Diagnosis of having Minimal Brain Dysfunction or Hyperkinetic Syndrome, based largely on the criteria of Clements and Peters, and showing a majority of the following traits: restlessness, hyperactivity or excessive daydreaming, short attention span, distractibility, labile emotionality or temper tantrums, overreaction to stimuli, lack of appropriate cautiousness or fear
Kauffman 1981 Fair	RCT with crossover Single center	Children diagnosed as "hyperactive," according to a set of predetermined clinical criteria

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Comorbidity	Interventions and total daily dose Duration Dosing schedule
Elia 1993 United States Fair	Comorbid conduct disorder: 6 (18.2%) Comorbid oppositional disorder: 7 (21.2%) Comorbid developmental disorders: 9 (27.3%)	Weeks 1, 2, and 3 for children < 30 kg/ > 30 kg: Dextroamphetamine 10, 25, and 40 mg/15, 30, and 45 mg Methylphenidate 25, 40 and 70 mg/30, 50 and 90 mg Placebo 3 weeks then crossover Twice daily at 9 am and 1 pm Individualized curriculum and instruction provided from 9 am to 12:30 pm in a *highly structured classroom*. This included a positive reinforcement management program using play money. Children were paid for appropriate behavior and fined for inappropriate behavior.
Gross 1976 Poor	NR	Age group 3-4/5-6/7-8/9-11/12-14: Dextroamphetamine: 2.5/4.5/7.25/10/11.25 mg Methylphenidate: 4.5/10/15/20/22.5 mg 1 week, then crossover AM and noon
Kauffman 1981 Fair	NR	Dextroamphetamine 10-60 mg Methylphenidate 5-30 mg Placebo Twice daily: morning and noon 6 weeks, then crossover

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Elia 1993 United States Fair	≥ 3 weeks washout	NR	Specific Skill Series Reading (Barnell Loft, Ltd) Developing Key Concepts in Math (Barnell Loft, Ltd)ABTRS CTQ-R CGI C-GAS Rosvold's A-X Continuous Performance Task	Mean age= 9.3 years Gender NR
Gross 1976 Poor	None	NR	Parents asked to rate each week in terms of improvements in target symptoms and get similar ratings from the child's teacher(s): =2=much worse, -1=slightly worse, 0=no really significant change, +1=slightly improved, +2=definite improvement but symptoms still pronounced, +3=considerably improved, +4=excellent improvement but some symptoms still present to a significant degree, and +5=outstanding improvement with few residual symptoms	NR NR NR
Kauffman 1981 Fair	NR	NR	Urine sample Returned capsules were recorded	Mean age nr 100% male 100% white

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Elia 1993 United States Fair	Mean Full Scale WISC-R IQ=108.8 Mean CTQ-R factor I (conduct)=1.16 Mean CTQ-R factor IV (hyperactivity)=2.49 Mean CPQ-R factor I (conduct)=1.49 Mean CPQ-R factor IV (hyperactivity)=2.26	NR NR 33	NR/NR/33
Gross 1976 Poor	NR	NR NR 50	2 (4%) withdrawn/lost to fu nr/analyzed: dextroamphetamine=48 vs methylphenidate=46
Kauffman 1981 Fair	NR	NR NR 12	NR/NR/12

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Elia 1993 United States Fair	Combined Reading Scores *Percent correct* Dextroamphetamine vs placebo=89.5 vs 86.1; p<0.01 Methylphenidate vs placebo=89.7 vs 86.1; p<0.01 *Mean number of attempts* Dextroamphetamine vs placebo=11.4 vs 9.5; p<0.01 Methylphenidate vs placebo=10.6 vs 9.5; p<0.01 Dextroamphetamine vs methylphenidate: p<0.05 Combined Arithmetic Scores *Percent correct* Dextroamphetamine vs placebo=97.1 vs 94.0; p<0.05 Methylphenidate vs placebo=96.2 vs 94.0; p=NS *Mean number of attempts* Dextroamphetamine vs placebo=38.3 vs 30.5; p<0.01 Methylphenidate vs placebo=39.2 vs 30.5; p<0.05	STESS
Gross 1976 Poor	Average improvement: 2.3 vs 2.2; p=NS	Use of same 8-point scale used for efficacy (-2=much worse to +5=outstanding improvement)
Kauffman 1981 Fair	% patients with positive urinalysis: 60 vs 67; p=NS % of patient-weeks with missed doses recorded: 18 vs 13; p=NS	Side effects checklist (not specified)

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Elia 1993 United States Fair	% patients (dextroamphetamine vs methylphenidate) Decreased appetite: 43 vs 46 Difficult with sleeping: 42 vs 36 Overly meticulous behavior: 24 and 21 Seemed unhappy: 12 vs 24 Transient tics or other nervous mannerisms: 36 vs 39
Gross 1976 Poor	Average improvement in average side effects: 0.4 vs 0.5; p=NS
Kauffman 1981 Fair	Anorexia (incidence/patient-week): 0.32 vs 0.26; both significantly different from placebo Insomnia (incidence/patient-week): 0.20 vs 0.36; only methylphenidate significantly different from placebo Mean change in weight (kg): -0.86 vs +0.11; significant difference between active drugs (p nr) Mean change in height (cm): +0.4 vs +0.4; neither significantly different from placebo

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Elia 1993 United States Fair	Withdrawals due to adverse events: 0 vs 0	
Gross 1976 Poor	2 (4%) NR	
Kauffman 1981 Fair	NR NR	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria
Sharp 1999 Fair	RCT with crossover Single center	Girls with ADHD symptoms present in at least 2 settings; Conners Hyperactivity factor scores from their home teacher were at least 2 SD greater than age and sex norms
Simpson 1980 United States Fair	DB RCT crossover design Setting: regular elementary classrooms	Boys aged 6-12, for whom 1) hyperactivity that had been long term; 2) complaints of hyperactivity were voiced by both the parents and teachers; 3) each child had at least average intellectual abilities as measured by the WISC-R. Subjects were evaluated for hyperactivity on the basis of a physical exam, classroom observations, and through the completion of teacher, parent, and self-ratings. Medical evaluation was designed to rule out overt brain damage or CNS trauma, cerebral palsy, convulsive disorders, CNS infection, genetic syndromes, metabolic disorders, or other medical conditions incongruous with developmental hyperactivity.

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Comorbidity	Interventions and total daily dose Duration Dosing schedule
Sharp 1999 Fair	NR	Mean doses for weeks 1, 2, and 3: Dextroamphetamine 0.23, 0.43, and 0.64 mg/kg Methylphenidate 0.45, 0.85 and 1.28 mg/kg Twice daily: breakfast and lunch 3 weeks, then crossover
Simpson 1980 United States Fair	NR	MPH, D-amphetamine, placebo for 8 weeks each

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Sharp 1999 Fair	3-week washout	All subjects attended accredited NIMH school 5 days a week for 3 months (academic instruction in the morning and recreation therapy activities in the afternoon)	WISC-RR, Woodcock-Johnson Achievement Battery, Conners Hyperactivity and Conduct factors, CBCL, TRF, C-GAS, CGI-SI, CPT	n=42 (includes 10 girls from another, unpublished pilot trial of sustained release dextroamphetamine vs Adderall) Mean age=8.9 100% female 67% white, 19% black, 14% Latina
Simpson 1980 United States Fair	NR/NR	NR	Each subject was observed daily in his classroom setting for 16 minutes via a modified form of the Direct Observation System. Reliability data was taken by an independent observer simultaneously observing and recording the subjects.	Age 6-12, mean age NR 100% male Ethnicity NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Sharp 1999 Fair	n=42 (includes 10 girls from another, unpublished pilot trial of sustained release dextroamphetamine vs Adderall) SES: 48 WISC-R Full Scale IQ=105.2 WISC-R Verbal IQ=105.6 WISC-R Performance IQ=104.0 WJ Reading/Math standard scores: 95.6/96.6 C-GAS=44.6 CGI-SI=5 Teacher/Parent Conners: Hyperactivity=2.0/2.5; Conduct=0.9/1.4 CBCL: Attention problems=76.0, Externalizing behaviors=70.7, Internalizing behaviors=63.6, Total behaviors=71.0 TRF: Attention problems=70.3, Externalizing behaviors=69.7, Internalizing behaviors=61.0, Total behavior problems=69.3	150/NR/32	1 (3.1%) withdrawn/lost to fu nr/analyzed=32
Simpson 1980 United States Fair	NR	NR/NR/12	NR/NR/12

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Sharp 1999 Fair	% patients with CGI--GI ratings of "very much improved" or "much improved": 85% vs 83%; p=NS	NR
Simpson 1980 United States Fair	Results reported only for each individual child, post-hoc analysis reported to indicate that *where a positive effect was seen*, dextroamphetamine was superior to methylphenidate - but these data are not presented.	Blood count, platelet count, and urinalysis were obtained at beginning and end of each treatment phase. Height, weight, pulse, and blood pressure were recorded at each clinic visit. Urinalysis was conducted at weekly visits to determine compliance. A symptom checklist was completed during each visit to evaluate side effects.

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Sharp 1999 Fair	Mean change in body weight (kg) Dextroamphetamine: -1.1; p=0.01 from baseline Methylphenidate: -0.4; p=NS from baseline
Simpson 1980 United States Fair	NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Sharp 1999 Fair	1 (3.1%) total withdrawals Withdrawals due to adverse events nr	Meta-analysis of this 100% female trial
Simpson 1980 United States Fair	0 withdrawals; 0 withdrawals due to adverse events	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria
Adderall		
Barkley 2000 Poor	RCT with crossover Single center	DSM-IV criteria for ADHD
Chronis 2003 (same as Pelham 1999a) Fair	See Pelham 1999a	See Pelham 1999a

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Comorbidity	Interventions and total daily dose Duration Dosing schedule
Adderall		
Barkley 2000 Poor	NR	Adderall 10 mg and 20 mg Methylphenidate 10 mg and 20 mg Placebo 1 week, then crossover Twice daily: morning and noon
Chronis 2003 (same as Pelham 1999a) Fair	See Pelham 1999a	See Pelham 1999a

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Adderall				
Barkley 2000 Poor	NR	NR	ADHD/ODD Rating Scale, Conners CPT, Stroop Word-Color Association Test, CGI	n=35 Mean age=14 85.7% male Race nr
Chronis 2003 (same as Pelham 1999a) Fair	See Pelham 1999a	See Pelham 1999a	Parent affect: Positive and Negative Affect Schedule (PANAS) - comprised of two 10-item subscales (PA=positive affect, NA=negative affect) Pleasantness, successfulness, and effectiveness ratings: Parents completed a series of questions using a 7-point Likert scale (0=very pleasant/successful/effective to 6=very unpleasant/unsuccessful/ineffective)	See Pelham 1999a

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Adderall			
Barkley 2000 Poor	Mean IQ=103.9	NR NR 46	8 (17.4%) withdrawals/lost to fu NR/31 (89%) analyzed for parent/teen ratings; 13 (37%) analyzed from language arts teacher ratings; 15 (43%) analyzed from math teacher ratings; 33 (94%) analyzed from lab measures
Chronis 2003 (same as Pelham 1999a) Fair	See Pelham 1999a	See Pelham 1999a	See Pelham 1999a

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Adderall		
Barkley 2000 Poor	Mean scores for Adderall 5 mg/10 mg vs methylphenidate 5 mg/10 mg vs placebo: Parent ratings ADHD Total: 21.3/19.0 vs 21.01/16.8 vs 21.9 ODD Total: 10.0/8.2 vs 9.7/8.2 vs 9.4 Teen self-ratings ODD Total: 6.0/5.8 vs 5.6/5.2 vs 5.1 English Teacher ADHD Total: 21.9/18.1 vs 17.9/21.5 vs 22.5 ODD Total: 4.3/3.9 vs 5.2/5.0 vs 5.1 Math Teacher ADHD Total: 17.5/16.4 vs 12.2/14.0 vs 17.7 ODD Total: 4.7/6.1 vs 3.3/3.9 vs 4.8 In-clinic tests Stroop Word Score: 46.5/48.7 vs 46.3/49.5 vs 47.1 Stroop Color Score: 44.5/47.7 vs 45.2/46.2 vs 44.3 Stroop Interference: 52.0/54.8 vs 51.8/53.2 vs 49.7 CPT Omissions: 7.1/15.0 vs 15.5/23.2 vs 14.0 CPT Commissions: 15.2/13.8 vs 16.5/15.2 vs 15.7 CPT Reaction Time (ms): 391.0/408.1 vs 388.3/396.3 vs 417.2	SERS
Chronis 2003 (same as Pelham 1999a) Fair	1) Placebo/Placebo/Placebo 2) MPH .3/.3/.3 3) MPH .3/.3/.15 4) MPH .3/Placebo/Placebo 5) Adderall .3/Placebo/.3 6) Adderall .3/Placebo/.15 7) Adderall .3/Placebo/Placebo All p-values reflect comparison to condition #1 (Placebo/Placebo/Placebo) Positive affect (all p=NS): 1) 28.1; 2) 30.81; 3) 29.17; 4) 29.40; 5) 30.28; 6) 30.29; 7) 29.62 Negative affect (all p=NS): 1) 12.51; 2) 11.43; 3) 12.67; 4) 12.22; 5) 11.90, 6) 11.68, 7) 11.79 Parent task completion (all p=NS): 1) 2.34; 2) 1.94; 3) 2.18; 4) 2.29; 5) 2.25; 6) 1.95; 7) 2.37 Child task completion: 1) 2.46; 2) 1.61, **p<0.01**; 3) 2.47; 4) 2.17; 5) 1.78; 6) 1.77, **p<0.01**; 7) 2.17 Overall effectiveness: 1) 2.52; 2) 1.90, **p<0.01**; 3) 2.27; 4) 2.19; 5) 2.07; 6) 1.75, **p<0.001**; 7) 2.22 Pleasantness of interaction: 1) 2.76; 2) 1.65, **p<0.01**; 3) 2.41; 4) 2.26, **p<0.01**; 5) 1.67, **p<0.01**; 6) 1.44, **p<0.001**; 7) 1.98, **p<0.01**	See Pelham 1999a

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Adderall	
Barkley 2000 Poor	Mean scores for Adderall 5 mg/10 mg vs methylphenidate 5 mg/10 mg vs placebo: Parent ratings Side effects number: 4.8/5.1 vs 5.4/5.5 vs 5.1 Side effects severity: 3.1/2.8 vs 3.0/2.9 vs 2.9 Teen self-ratings Side effects number: 4.7/4.7 vs 4.3/4.8 vs 4.6 Side effects severity: 2.5/2.4 vs 3.3/2.9 vs 2.7; "...teens rated the 10 mg dose of Adderall condition as producing significantly less severe side effects than the 5 mg dose of methylphenidate" English Teacher (n=13) 2.9/3.1 vs 3.2/3.6 vs 3.8 3.3/1.9 vs 3.4/2.7 vs 1.9 Math Teacher Side Effects Number: 3.1/3.9 vs 1.9/3.1 vs 3.2 Side Effects Severity: 2.6/2.3 vs 1.5/2.4 vs 2.2
Chronis 2003 (same as Pelham 1999a) Fair	See Pelham 1999a

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Adderall		
Barkley 2000 Poor	NR NR	
Chronis 2003 (same as Pelham 1999a) Fair	See Pelham 1999a	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria
Pelham 1999a Fair	RCT with daily crossover Summer Treatment Program (STP) at the State University of New York at Buffalo	DSM-IV diagnosis of ADHD

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Comorbidity	Interventions and total daily dose Duration Dosing schedule
Pelham 1999a Fair	NR	MPH=methylphenidate 1) placebo at 7:30 am, 11:30 am, and 3:30 pm 2) 0.3 mg/kg of MPH at 7:30 am, 11:30 am, and 3:30 pm 3) 0.3 mg/kg of MPH at 7:30 am and 11:30 am with 0.15 mg/kg at 3:30 pm 4) 0.3 mg/kg of MPH at 7:30 am only 5) 0.3 mg/kg of Adderall at 7:30 am and at 3:30 pm 6) 0.3 mg/kg of Adderall at 7:30 am with 0.15 mg/kg received at 3:30 pm 7) 0.3 mg/kg of Adderall at 7:30 am only Medication received Monday through Thursday throughout a period of 6 weeks for a 24-day clinical medication assessment; resulting in ~3 days of data in each of the active drug conditions and 6 days in the placebo condition

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Pelham 1999a Fair	First 2 weeks of the program served as a period of baseline observation (unclear if run-in/washout used)	Concurrent behavioral point system	Point system Classroom measures (% of points kept, percentage of assigned seatwork completed, percentage correct of seatwork, behavioral observations during seatwork period) Daily Report Cards (% of behavioral targets met) Counselor and Teacher Ratings (Inattention/Overactivity and Oppositional/Defiant subscales of the IOWA Conners Rating Scale; Pittsburgh Side Effect Rating Scale Parent Ratings: IOWA Conners Rating Scale	Mean age=10.3 90.5% male Race nr

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Pelham 1999a Fair	87% with previous use of stimulant medication 9 (43.8%) with learning problems 14 (66.7%) with comorbid oppositional defiant disorder 5 (23.8%) with comorbid conduct disorder Mean IQ=109.9 Reading achievement standard score=99.1 Math achievement standard score=105.7 ADHD items endorsed in parent structured interview: Inattention (out of 9 items)=6.1, Hyperactivity/impulsivity (out of 9 items)=5.5 oppositional/defiant items endorsed in parent structured interview=4.3 Conduct disorder items endorsed in parent structured interview=2.8 Abbreviated Conners rating scale parent=20.5 Abbreviated Conners rating scale teacher=18.2 IOWA Conners teacher rating scale inattention-overactivity/oppositional-defiant: 9.6/7.5 Disruptive behavior disorders parent rating scale: Inattention=2.2, Hyperactivity/impulsivity=2.0, Oppositional/defiant=1.8, Conduct disorder=0.4 Disruptive behavior disorders teacher rating scale: Inattention=1.7, Hyperactivity/impulsivity=1.7, Oppositional/defiant=1.6	NR/NR/21	NR/NR/NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Pelham 1999a	Adderall qAM vs MPH bid vs MPH qAM b = p<0.05 vs MPH bid; c = p<0.05 vs MPH qAM Counselor measures	Frequency with which raters endorsed any side effect as either moderate or severe on at least 1 day
Fair	Following activity/rules: 73.1c vs 70.6 vs 65.7b Noncompliance: 1.2 vs 0.8 vs 1.2 Interruption: 4.0 vs 5.3 vs 6.9 Complaining: 3.0 vs 3.0 vs 5.8b Positive peer behaviors: 5.5 vs 5.2 vs 6.4 Conduct problems: 1.7 vs 0.9 vs 0.6 Negative verbalizations: 3.6 vs 3.9 vs 6.6 IOWA Conners IQ: 3.0c vs 3.3c vs 4.3 IOWA Conners OD: 1.9c vs 2.2c vs 3.1 Classroom measures: Seatwork rules: 92.7 vs 91.9 vs 84.6 Peer tutoring rules: 93.9 vs 93.6 vs 90.1 Computer rules: 92.3 vs 93.4 vs 89.3 Seatwork complete: 90.2 vs 86.1 vs 86.9 Seatwork correct: 90.9 vs 89.8 vs 87.5 On-task behavior: 97.1 vs 96.1 vs 94.9 Disruptive behavior: 1.9 vs 2.5 vs 3.5 Teacher IOWA Conners IO: 0.8c vs 0.9 vs 2.0b Teacher IOWA Conners OD: 0.7 vs 0.4 vs 1.4b Daily Report Card: 82.8c vs 80.5 vs 69.0	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Pelham 1999a	% children rated by Counselor/Parent/Teacher as displaying side effects at a moderate-severe leve on at least one day: MPH qAM vs MPH 0.3/0.3/0.15 vs MPH 0.3/0.3/0.3 vs Adderall qAM vs Adderall 0.3/-/0.15 vs Adderall 0.3/-/0.3
Fair	Tics: 5/10/5 vs 5/10/0 vs 5/10/5 vs 5/5/0 vs 5/0/5 vs 5/0/5 vs 0/5/0 Appetite loss: 5/25/- vs 57/20/0 vs 33/33/- vs 29/33/- vs 71/15/- vs 62/29/- vs 52/29/- Sleep trouble (only parent ratings): 25 vs 15 vs 20 vs 20 vs 24 vs 38 vs 33

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Pelham 1999a	NR NR	

Fair

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria
Pelham 1999b Fair	RCT with daily crossover Summer Treatment Program (STP) through the psychology department State University of New York at Buffalo	DSM-IV diagnosis of ADHD

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Comorbidity	Interventions and total daily dose Duration Dosing schedule
Pelham 1999b Fair	NR	Adderall 7.5 mg at 7:45 am and 12.5 mg at 12:15 pm Methylphenidate 10 mg at 7:45 am and 17.5 mg at 12:15 pm Medication received Monday through Thursday throughout a period of 6 weeks for a 24-day clinical medication assessment; resulting in ~5 days of data in each of the active drug conditions and 6 days in the placebo condition

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Pelham 1999b Fair	First 2 weeks of the program served as a period of baseline observation (unclear if run-in/washout used)	NR	Point system Classroom measures (% of points kept, percentage of assigned seatwork completed, percentage correct of seatwork, behavioral observations during seatwork period) Daily Report Cards (% of behavioral targets met) Recess Rule violations (rated ~4.5 hours after ingestion of morning dose) Counselor and Teacher Ratings (Inattention/Overactivity and Oppositional/Defiant subscales of the IOWA Conners Rating Scale; Pittsburgh Side Effect Rating Scale Parent Ratings: IOWA Conners Rating Scale	Mean age=9.6 84% male 88% white

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Pelham 1999b Fair	13 (52%) with comorbid oppositional defiant disorder 8 (32%) with comorbid conduct disorder WISC vocabulary scaled score=12.3 WISC block design scaled score=11.2 WIAT spelling scaled score=95.7 WIAT math scaled score=105.7 DSM ADHD items-parent=10.8 DSM ODD items-parent=5.3 DSM CD-parent=1.8 Abbreviated Conners-parent=22.6 Abbreviated Conners-teacher=19.6 Iowa Conners I/O-teacher=11.8 Iowa Conners O/D-teacher=9.6 Disruptive behavior disorders parent/teacher rating scale: ADHD=1.5/2.4 Oppositional/defiant=1.7/2.5 Conduct disorder=1.8/nr	NR/NR/25	NR/NR/NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Pelham 1999b Fair	Adderall 7.5/12.5 vs Methylphenidate 10 mg/17.5 mg; results of ANOVA of methylphenidate vs Adderall; p-value: Classroom variables Rule-following Seatwork: 89.7/90.7 vs 84.3/87.8, 4.06, p=NS Peer tutoring: 95.1/95.0 vs 91.4/94.8, 3.71, p=NS Computer: 91.1/94.4 vs 87.3/92.6, 2.80, p=NS Seatwork completion: 71.6/67.1 vs 69.5/69.2, 0.00, p=NS Seatwork accuracy: 87.6/87.3 vs 87.9/87.1, 0.00, p=NS Observational measures On-task behavior: 89.0/89.9 vs 89.2/89.6, 0.00, p=NS Disruptive behavior: 6.4/6.4 vs 6.9/6.2, 0.15; p=NS Daily report card: 83.8/82.8 vs 76.4/81.7, 6.63, p<0.05 Recess rule violations: 1.0/0.4 vs 1.3/0.7, 3.21, p=NS Counselor ratings I/O: 2.4/2.2 vs 3.4/2.6, 1.4, p<0.001; O/D: 1.0/0.8 vs 2.3/1.1, 13.85, p<0.01 Teacher ratings I/O: 1.2/1.2 vs 1.8/1.1, 0.72, p=NS; O/D: 0.7/0.4 vs 1.3/0.6, 3.22, p=NS 5:00-6:00 parent ratings I/O: 0.9/0.5 vs 1.5/1.0, 5.25, p<0.05; O/D: 0.8/0.6 vs 1.2/1.1, 4.09, p=NS All evening parent ratings I/O: 1.5/1.4 vs 2.6/1.7, 3.33, p=NS; O/D: 1.9/1.2 vs 2.4/1.2, 12.17, p<0.01 Point system measures Following rules: 75.4/79.9 vs 71.4/74.5, 10.38, p=NS Attention: 68.2/68.2 vs 64.0/64.3, 5.47, p=NS Noncompliance: 0.9/1.2 vs 2.2/0.8, 5.65; p=NS Interruption: 6.2/6.8 vs 10.6/6.7, 7.48, p=0.025 Complaining/whining: 2.9/2.0 vs 4.1/2.6, 4.12, p=NS Positive peer behaviors: 8.1/7.8 vs 8.8/8.8, 1.82, p=NS Conduct problems: 0.4/0.2 vs 1.4/0.1, 5.17, p=NS Negative verbalizations: 2.0/2.2 vs 6.1/2.2, 7.89, p=0.01	Frequency with which raters endorsed any side effect as either moderate or severe on at least 1 day

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Pelham 1999b	% children rated by Counselor/Parent as displaying side effects at a moderate-severe leve on at least one day: Adderall 7.5 mg vs Adderall 12.5 mg vs methylphenidate 10 mg vs methylphenidate 17.5 mg
Fair	Motor Tics Counselors: 8 vs 8 vs 8 vs 4 Parents: 4 vs 8 vs 4 vs 0 Trouble sleeping Counselors: n/a Parents: 48 vs 64 vs 32 vs 24 Loss of appetite Counselors: 76 vs 80 vs 60 vs 68 Parents: 40 vs 72 vs 8 vs 20

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Pelham 1999b	1 (4%) withdrawal due to exacerbation of pre-existing motor tics	

Fair

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria
Pliszka 2000	RCT	DISC criteria for ADHD; ≥ 1.5 SD above the mean for his/her age and sex on the IOWA CTRS
Faraone 2001	Parallel	Inattention/Overactivity (I/O) factor; parent Conners Global Index score similarly elevated
Fair		
Manos 1999	CCT (Adderall and methylphenidate protocols run simultaneously)	DSM-IV criteria for ADHD; presence of at least 6 symptoms of inattention and/or at least 6 symptoms of hyperactivity/impulsivity; symptoms significantly interfered with functioning at home and at school as noted during structured (Computerized Diagnostic Interview Schedule for Children) or semistructured clinical interviews; symptom severity on broad-band (Conners ASQ) and narrow-band (ARS) rating scales was at threshold or above (i.e., rated 2 or 3); multiple raters agreed to the presence of the symptoms; empirical comparison to norms indicated at least a 1.5 SD cutoff on at least one rating scale
Poor	Crossover Pediatric Assessment and Evaluation Service (PAES) of a large, urban teaching hospital	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Comorbidity	Interventions and total daily dose Duration Dosing schedule
Pliszka 2000 Faraone 2001 Fair	NR	Adderall < 60 kg = 5-15 mg > 60 kg = 10-30 mg Week1: single am dose Week2: morning dose doubled if no improvement on morning+afternoon or just afternoon teacher ratings; after school dose added if morning+afternoon teacher ratings improved, but parent rating remained impaired Week3: noon dose added if afternoon behavior remained impaired; after school dose added if evening behavior had not been impaired in week 1 but now was Methylphenidate < 60 kg = 5-25 mg > 60 kg = 10-50 mg Week1: single am dose Week2: morning dose doubled if no improvement on morning+afternoon (teacher); noon dose added if no afternoon improvement (teacher); after school dose added if evening rating (parent) remained impaired; morning dose doubled and a noon dose added if morning+afternoon teacher ratings Week3: noon dose doubled if the afternoon ratings (teacher) remained impaired 3 weeks; Flexible dosing and timing
Manos 1999 Poor	Oppositional defiant disorder=21.4%	Adderall (once daily) vs methylphenidate (twice daily) 1-week for each condition Fixed dosage: 4 conditions: (1) placebo; (2) 5 mg; (3) 10 mg; (4) 15 mg Six dose orders were used such that the highest dose (15 mg) was given only when preceded by the moderate dose (10 mg) Dose orders were assigned in a random fashion Parents blind to dosage

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Pliszka 2000 Faraone 2001 Fair	NR/NR	NR	IOWA CTRS, Conners Global Index, CGI	Mean age=8.2 Gender nr Race nr
Manos 1999 Poor	NR/NR	NR	ARS, Conners ASQ, SSQ-R	Mean age=10.1 78.6% male 92.8% white

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Pliszka 2000 Faraone 2001 Fair	IOWA CTRS I/O: 2.2 IOWA CTRS A/D: 1.4 Conners Global: 2.1 ODD=62% CD=10.3% Anxiety disorder=12.1% RCMAS: 15.8% CDI: 12.2% Weight (kg): 33.3	73 screened/eligible unclear/enrolled 58	5 (8.6%) withdrawn/0 lost to fu/58 analyzed Adderall n=20 Methylphenidate n=20 Placebo n=18
Manos 1999 Poor	Inattentive type=45.2% Combined type=54.8% Mood disorder=1.2% Anxiety disorder=4.8% Learning disability=47.6%	Referred=60/eligible=NR/participated=159	MPH n=42 (matched by "hand-selecting" by age, diagnostic category and gender to Adderall group), Adderall n=42

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Pliszka 2000 Faraone 2001 Fair	Adderall vs methylphenidate IOWA CTRS I/O: AM: 0.44 vs 0.78; p=NS PM: 0.54 vs 0.85, p=NS Average: 0.49 vs 0.81, p<0.05 IOWA CTRS A/D AM: 0.25 vs 0.47, p=NS PM: 0.33 vs 0.51, p=NS Average: 0.29 vs 0.49, p<0.05 Conners Global Index: 1.04 vs 1.28, p=NS CGI Improvement: 1.6 vs 2.35, p<0.05 Responders %: 90 vs 65 Final weight (kg): 37 vs 33.2, p=NS Dosing regimen: 70% of Adderall subjects required only an AM dose vs 85% in the methylphenidate group received 2 or more doses per day; p=0.003	Multi-Modality Treatment of ADHD; parents asked to rate severity (none, mild, moderate, severe) of facial tics, tongue movements, picking at skin, anxious, tired, headache, stomach ache, irritable, sad or tearful, appetite loss, and "gets wild when medication wears off"
Manos 1999 Poor	"Best dose" comparisons of Adderall vs methylphenidate <u>Parent ratings (no significant differences, but p-values nr)</u> ASQ: 49.83 vs 50.64 ARS: 11.79 vs 10.10 Composite ratings: 3.50 vs 3.31 <u>Teacher ratings (no significant differences, but p-values nr)</u> ASQ: 51.47 vs 56.12 SSQ-R, total: 1.67 vs 1.92 SSQ-R, part: 2.23 vs 2.68	SE/BMS

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Pliszka 2000	All p=NS
Faraone 2001	
	Facial tics: 1 (5%) vs 0
Fair	Tongue movements: 1 (5%) vs 0
	Picking at skin: 1 (5%) vs 0
	Anxious: 1 (5%) vs 2 (10%)
	Tired: 2 (10%) vs 4 (20%)
	Headache: 2 (10%) vs 0
	Stomach ache: 5 (25%) vs 1 (5%)
	Irritable: 5 (25%) 3 (15%)
	Sad, tearful: 5 (25%) vs 3 (15%)
	Appetite loss: 3 (15%) vs 3 (15%)
	Gets wild when medication wears off: 7 (35%) vs 8 (40%)
Manos	Results described as "no differences", but p-values nr
1999	Insomnia: 5 (11.9%) vs 2 (4.8%)
	Decreased appetite: 0 vs 1(2.4%)
Poor	Tics/nervousness: 0 vs 0

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Pliszka 2000 Faraone 2001 Fair	Total withdrawals=5 (8.6%) Withdrawals due to adverse events: 2 (10%) vs 1 (5%), p=NS	
Manos 1999 Poor	NR NR	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria
McCracken 2003 United States	RCT Crossover Multicenter (4 academic sites)	Potential subjects were screened to meet the following eligibility criteria: age 6 to 12 years; diagnosis of DSM-IV ADHD (combined or hyperactive-impulsive subtype as determined by a comprehensive clinician evaluation and selected modules of the Diagnostic Interview Schedule for Children, Version IV-Lifetime [DISC-IV]) administered by a research staff member with suitable training; no evidence of mental retardation; and history of positive response to psychostimulant medication, or no prior stimulant treatment. Information pertaining to co-occurring psychopathology from the clinical evaluation was supplemented by the Comorbid Disorders Checklist, a parent-report questionnaire composed of DSM-III-R symptom items. All diagnoses were based on DSM-IV criteria. Subjects were excluded if they met criteria for any of the following: comorbid psychiatric conditions including psychosis, pervasive developmental disorder, bipolar disorder; severe obsessive-compulsive disorder, severe depressive or anxiety disorder (severe defined as any comorbid disorder with impairment necessitating concurrent treatment of any type); a clinically significant medical condition (e.g. seizure disorder, hypertension, abnormal laboratory test result); need for ongoing medical treatment; intolerance to psychostimulants; history of nonresponse to Adderall; or history of a tic disorder.

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Comorbidity	Interventions and total daily dose Duration Dosing schedule
McCracken 2003 United States	NR	SLI381 (Adderall XR) 10, 20, or 30mg, placebo, or active control (Adderall 10mg) Mean Dose: NR Subjects who tolerated initial exposure to SLI381 were randomly assigned in crossover design to each of five treatment weeks: SLI381 10mg, SLI381 20mg, SLI381 30mg, Adderall 10mg, and placebo, each administered daily at 7:30 AM

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
McCracken 2003 United States	1 week washout period with discontinuation of previous stimulant medication	NR	Primary Outcome Measure: the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) scale Attention and Deportment variables as completed by the classroom raters Other Measures: Permanent Product Measure of Performance (PERMP), Parent Global Assessment global behavior rating scale	Mean age= 9.5 yrs (SD 1.9) 86.3% male 49% white 15.7% black 23.5% Hispanic 5.9% Asian/Pacific Islander 5.9% other

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
McCracken 2003 United States	ADHD diagnosis: Hyperactive-impulsive=2% Combined=98% Duration of prior stimulant treatment: mean=1.7 yrs (SD 1.7) ADHD treatment before study entry: amphetamine only=33.3% methylphenidate only=58.8% none listed=7.8%	Number screened NR/51 eligible/51 enrolled	2 of 51 withdrawn because of withdrawal of consent; 49 randomized for crossover treatment 2 of 47 withdrawn (1 stomachache, 1 developed an exclusion criterion) 45 completed 5 weeks of double-blind portion of study (all treatment conditions) 3 withdrew in extra or "makeup" week ITT=49

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
McCracken 2003 United States	**p-values for active drug vs placebo:** **Adderall XR 30mg/20mg/10mg/Adderall 10mg** **SKAMP Attention (hours post-dose)** 1.5-hr: 0.0015/0.0513/0.5846/0.0025 4.5-hr: <0.0001/0.0023/0.0269/0.0005 6.0-hr: <0.0001/<0.0001/0.0003/0.0005 7.5-hr: <0.0001/<0.0001/0.0001/0.0002 9.0-hr: 0.0001/0.0072/0.2442/0.8264 10.5-hr: <0.0001/<0.0001/0.0062/0.3250 12.0-hr: 0.0034/0.0077/0.0626/0.3064 **SKAMP Deportment (hours post-dose)** 1.5-hr: 0.0002/0.0031/0.0725/<0.0001 4.5-hr: <0.0001/<0.0001/0.0090/<0.0001 6.0-hr: <0.0001/<0.0001/<0.0001/<0.0001 7.5-hr: <0.0001/<0.0001/0.0083/0.0004 10.5-hr: <0.0001/0.0021/0.0724/0.0246 12.0-hr: 0.0062/0.0531/0.9878/0.7901 **PERMP no. attempted (hours post-dose)** 1.5-hr: 0.0030/0.0283/0.0920/0.0004 4.5-hr: <0.0001/0.0006/0.0136/0.0850 6.0-hr: <0.0001/<0.0001/0.0001/0.0015 7.5-hr: <0.0001/<0.0001/0.0017/0.0157 9.0-hr: <0.0001/0.0001/0.0230/0.0048 10.5-hr: <0.0001/<0.0001/0.0101/0.7626/ 12.0-hr: 0.0017/0.0053/0.9938/0.7508 **PERMP no. correct (hours post-dose)** 1.5-hr: 0.0059/0.0333/0.1121/0.0007 4.5-hr: <0.0001/<0.0001/0.0020/0.0353 6.0-hr: <0.0001/<0.0001/<0.0001/0.0007 7.5-hr: <0.0001/<0.0001/0.0029/0.0667 9.0-hr: <0.0001/<0.0001/0.0128/0.0195 10.5-hr: <0.0001/<0.0001/0.0025/0.3424 12.0-hr: 0.0001/0.0007/0.5420/0.9304	Parents completed weekly Side Effect Rating Scale; teachers completed Teacher Side Effect Rating scale each analog classroom day; adverse events were noted by study physicians or research staff

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
McCracken 2003 United States	Study medications well tolerated overall. No serious side effects reported or observed. Only anorexia displayed a dose-dependent pattern of increases for Adderall XR doses. Placebo (n=49) vs. Adderall 10mg (n=48) vs. SLI381 10mg(n=48) vs. SLI381 20mg (n=50) vs. SLI381 30mg (n=49) Nervousness: 29 (59.2%) vs. 22 (45.8%), 26 (54.2%) vs. 28 (56.0%) vs. 21 (42.9%) Insomnia: 10 (20.4%) vs. 17 (35.4%) vs. 6 (12.5%) vs. 16 (32.0%) vs. 14 (28.6%) Anxiety: 10 (20.4%) vs. 11 (22.9%) vs. 13 (27.1%) vs. 11 (22%) vs. 9 (18.4%) Emotional lability: 5 (10.2%) vs. 10 (20.8%) vs. 13 (27.1%) vs. 9 (18%) vs. 6 (12.2%) Depression: 5 (10.2%) vs. 4 (8.3%) vs. 5 (10.4%) vs 11 (22.0%) vs. 3 (6.1%) Abdominal pain: 12 (24.5%) vs. 16 (33.3%) vs. 14 (29.2%) vs 18 (36.0%) vs. 17 (34.7%) Headache: 12 (24.5%) vs. 12 (25.0%) vs. 12 (25.0%) vs. 15 (30.0%) vs. 12 (24.5%) Anorexia: 11 (22.4%) vs. 22 (45.8%) vs. 13 (27.1%) vs. 20 (40.0%) vs. 27 (55.1%)

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
McCracken 2003 United States	Of the 49 randomized subjects, 3 withdrew due to AE's	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria
IR vs. SR formulations of methylphenidate		
Bergman 1991 United States Poor	CCT Crossover Setting NR	DSM-III diagnosis of Attention Deficit Disorder with Hyperactivity (ADDH)
Cox 2004 Fair	RCT Crossover	Diagnosis of current ADHD as determined by parent-report questionnaire and structured clinical interviews (DuPaul ADHD Rating Scale-IV, Diagnostic Interview Schedule for Children, Standardized Interview for Adult ADHD; positive history of MPH responsiveness disclosed by subject and parent reports; and current daily driving activity

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Comorbidity	Interventions and total daily dose Duration Dosing schedule
IR vs. SR formulations of methylphenidate		
Bergman 1991 United States Poor	11 (26.2%) met criteria for reading disability (ADHD/RD) based on Reading Quotient index which calculated by dividing the Wide Range Achievement Test-Revised (WRAT-R) Reading test score by the WISC-R Full Scale IQ score. If the resulting RQ score was less than 0.85, indicating a discrepancy of more than 1 SD between reading and IQ scores, the subject was categorized as reading disabled (ADHD/RD)	Sustained-release methylphenidate 20 mg (single morning dose) Short-acting (regular) methylphenidate 10 mg (twice daily - morning and afternoon) Placebo 1 day
Cox 2004 Fair	NR	Methylphenidate in equal doses at 8 am, noon, and 4 pm (mean = 60 mg) Methylphenidate osmotic, controlled-release oral formulation (OROS) at 8 am (mean=54 mg) 7 days of dosage maintenance

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
IR vs. SR formulations of methylphenidate				
Bergman 1991 United States Poor	NR/NR	NR	Identical Pairs version of the CPT (CPT-IP)	Mean age nr (between 6 and 12) 100% male Ethnicity nr
Cox 2004 Fair	24 hour washout	NR	Atari Research Driving Simulator Composite Score (Impaired Driving Score) consisting of Off Road, Veering Across Midline, Standard Deviation Steering, Inappropriate Braking, % Missed Stop Signals, % Bumps, and % Crashes	Mean age =17.2 100% male Race NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
IR vs. SR formulations of methylphenidate			
Bergman 1991 United States Poor	NR	NR/NR/42	NR/NR/NR
Cox 2004 Fair	Inattentive type=4(66.7%) Combined type=2(33.3%) Proportion taking medication for ADHD at baseline NR Mean baseline dose of MPH NR	NR/NR/7	1 (14.3%) withdrawn/0 lost to fu/analyzed=6

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
IR vs. SR formulations of methylphenidate		
Bergman 1991 United States Poor	SR methylphenidate = short-acting methylphenidate on all measures (data nr)	NR
Cox 2004 Fair	OROS Methylphenidate vs methylphenidate TID IDS 2 PM: -0.55 vs -0.54, p=NS 5 PM: -2.2 vs -1.04, p=NS 8 PM: -1.98 vs 4.23, p=0.01 11 PM: -1.65 vs 5.1, p=???? (wrote to author - reported as 0.1 in text but I think that's wrong) Individual parameters (F-value/p-value for MPH TID vs MPH OROS) Standard deviation steering: F=0.65, p=0.42 Off Road: 2.50/0.12 Veering across midline: 2.11/0.15 Inappropriate braking: 4.47/0.04 % missed stop signals: 5.76/0.02 % bumps: 1.35/0.25 % crashes: 3.13/0.08 Speeding: 1.60/0.21 Standard deviation speed: 4.19/0.04 Risky Driving Means (daily driving diaries - self reported): 2.6 vs 3.2, p=NS	NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
IR vs. SR formulations of methylphenidate	
Bergman 1991 United States Poor	NR
Cox 2004 Fair	NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
IR vs. SR formulations of methylphenidate		
Bergman 1991 United States Poor	NR NR	
Cox 2004 Fair	1 (14.3%) withdrawals 0 due to adverse events	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria
Dopfner 2004 Germany designed as a non-inferiority trial	RCT, DB, crossover Multicenter Analogue classroom setting, with each group having a trial period of 2.5 weeks; trial phase consisted of three phases: phases 1 and 2 were 4 workdays plus the weekend; and trial phase 3 was 4 workdays).	Children between 8 and 15 years who met ICD-10 diagnosis of Hyperkinetic Disorder (F90) of a DSM-IV diagnosis of ADHD using a diagnostic checklist, DCL-HKS. All patients were methylphenidate responders on the basis of clinical assessment. They also had to have an intelligence IQ ≥85 and a body weight >20 kg.

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Comorbidity	Interventions and total daily dose Duration Dosing schedule
Dopfner 2004 Germany designed as a non-inferiority trial	44% (35 patients) had ODD or CD	Medikinet-Retard (methylphenidate ER) qd Methylphenidate IR (MPH IR) bid Placebo Dosage varied: 9 patients (11%) received 10 mg/d; 54 (68%) patients received 20 mg/d; 14 patients (17%) received 30 mg; and 2 patients (3%) received 40mg.

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Dopfner 2004 Germany designed as a non-inferiority trial	1 workday run-in / No (MPH dose prior to trial had to be unchanged during the previous month)	NR	Primary efficacy: SKAMP (Swanson, Kotkin, Agler, M-Flynn, and Pelham) scores, with subscales of conduct or attention-to-rules index and the attention index; PERMP (Permanent Product Measure of Performance, an age-appropriate math test) was used for academic performance. The PERMP was assessed for number of problems attempted and number correct. SKAMP and PERMP both were assessed daily at 9:30 am, 11:30 am, 13:00 pm, 15:30 pm and 16:45 pm. Secondary measures included an ADHD rating scale (FBB-HKS) assessed at 13:00 for the mornings and 16:45 for the afternoons.	Mean age: 10.0 yrs Gender: 89.9% male Ethnicity NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Dopfner	Mean IQ: 103.0 (+/- 10.4)	NR/ NR/ 82	3/ NR/ 79
2004	DSM-IV diagnosis of ADHD		
Germany	Combined type: 92.4% Predominately inattentive: 7.6%		
designed as a non-inferiority trial			

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Dopfner 2004 Germany designed as a non-inferiority trial	Results of repeated measures analysis of variance of SKAMP and PERMP scores, Treatment effect: SKAMP attention: F 2.77 = 27.4, p<0.000 SKAMP deportment: F 2.77 = 18.8; p<0.000 PERMP no. attempted: F 2.77 = 17.8; p<0.000 PERMP no. correct: F 2.77 = 17.2; p<0.000	NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Dopfner 2004 Germany designed as a non-inferiority trial	NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Dopfner 2004 Germany designed as a non-inferiority trial	NR	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria
Findling 2006 Australia, Canada, United States	RCT Double-blind Parallel Multicenter	Children aged 6–12 years were eligible to participate if they met diagnostic criteria for one of the three subtypes of ADHD as described in the Diagnostic & Statistical Manual of Mental Disorders, 4th Edition and had been on a stable dose of MPH for at least 3 weeks prior to screening. The diagnosis of ADHD was confirmed using the Schedule for Affective Disorders and Schizophrenia for School-Aged Children— Present and Lifetime version (K-SADS-PL). Inclusion Criteria: Male and female children aged 6–12 years (inclusive); On a stable dose of methylphenidate ≥3 weeks prior to screening; diagnosed with ADHD based on DSM-IV criteria for any subtype and confirmed by administration of the K-SADS-PL interview at screening; attending a school setting in which a single teacher could make morning and afternoon assessments of the child's behavior. Exclusion criteria: Female who had experienced menarche; co-morbid psychiatric disorder requiring medication; history of seizure, tic disorder, or a family history of Tourette's disorder; IQ test score below 80, or functioning at a level of intelligence indicative of an IQ below 80; the use of unapproved medication(s); use of an investigational product within 30 days prior to study entry; concurrent chronic or acute illness, disability, or medication, that might confound the results of rating tests; diagnosed with hyperthyroidism, glaucoma, or eating disorder; current substance abuse disorder or living with someone with a current substance abuse disorder; demonstrated lack of response to methylphenidate.
Fitzpatrick 1992 Poor quality	Study design unclear (CCT or RCT?) Crossover Setting NR	Diagnosis of ADD in the Diagnostic Instrument for Childhood and Adolescence (DICA)

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Comorbidity	Interventions and total daily dose Duration Dosing schedule
Findling 2006 Australia, Canada, United States	NR	Mean Dose: NR MPH-IR twice-daily (morning and lunch-time), EqXL once-daily (morning) followed by placebo at lunch-time, or placebo twice-daily (morning and lunch-time) for 3 weeks. The dosages of the active treatments were determined according to the child's pre-study MPH regimen: Children on a previous total daily dose of 10–20 mg IR MPH or 20 mg ER MPH were randomized to receive either 10 mg MPH-IR twice-daily, 20 mg EqXL once-daily, or placebo; children on a previous total daily dose of 25–40 mg IR MPH or >20 mg to £40 mg ER MPH were randomized to receive 20 mg MPH-IR twice-daily, 40 mg EqXL once-daily, or placebo; and children on a previous total daily dose >40 mg IR MPH or >40 mg ER MPH were randomized to receive 30 mg MPH-IR twice-daily, 60 mg EqXL once-daily or placebo.
Fitzpatrick 1992 Poor quality	63.1% oppositional disorder	Per-protocol dosages for patients < 30 kg / > 30 kg / mean dosages: Placebo Sustained-release (SR) methylphenidate 20 mg am / 20 mg am / mean=20 mg Standard (SA) methylphenidate: 7.5 mg in am and pm / 10 mg in am and pm / mean=17.1 mg Combination SA + SR methylphenidate: 5 mg SA+20 mg SR in am and 5 mg SA in pm / 7.5 SA + 20 mg SR in am and 7.5 mg SA in pm / mean=20 mg SR + 11.8 mg SA Each phase lasted 2 weeks

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Findling 2006 Australia, Canada, United States	NR	NR	Primary Outcome Measure: the inattention/ overactivity (I/O) component of the overall Teacher's IOWA Conners' Questionnaire obtained from the SNAP-IV questionnaire Other Measures: IOWA Conners' Rating Scale, the 40-item SNAP-IV (which includes the IOWA Conners' Rating scale as a subscale), the Clinical Global Impression (CGI) Scale and the CGI Improvement scale, the Parent's Global Assessment (PGA)	Mean age=9.5 yrs (Range=6-12 yrs) 79.2% male 85.8% Caucasian 5.3% Afro-Caribbean 0.3% Asian 1.6% Hispanic 6.9% other
Fitzpatrick 1992 Poor quality	NR/NR	NR	Conners Hyperactivity Index; IOWA Inattention/Overactivity and Aggression/Noncompliance Scales; Hyperactivity, Attention, and Aggression Subscales of Time on Task Scale (TOT); parents and teachers answered open-ended questions about child's behavior, academics, relations with others, concentration, and attitude toward school and responses rated by blinded rater as +1=positive, 0=blank/irrelevant/neutral, -1=negative responses; Continuous Performance Test (CPT) - administered 1 and 3 hours after each dose (target=2 identical numbers); Paired-associate learning (PAL) test	Mean age=8.71 89.5% male Race nr

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Findling 2006 Australia, Canada, United States	ADHD Subtype: Inattention: 23% Hyperactive/Impulsivity: 5.7% Combined subtype: 71.4%	346/NR/327 318 received treatment	9 withdrawn due to failure to meet all eligibility criteria 318 analyzed
Fitzpatrick 1992 Poor quality	Weight=31.45 kg Wechsler Scale IQ=114.11 Peabody Individual Achievement Scale=105.68 Conners Hyperactivity Index-Parent/Teacher: 1.79/1.74 IOWA Inattention-Overactivity-Parent/Teacher=2.01/2.09 IOWA Aggression/Noncompliance-Parent/Teacher: 1.27/1.18 TOTS Aggression-Parent/Teacher: 0.88/0.72 TOTS Hyperactivity-Parent/Teacher=0.86/0.56 TOTS Attention Parent/Teacher=0.32/0.46	NR/NR/19	NR/NR/NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Findling 2006 Australia, Canada, United States	Difference from placebo (95% CI) for MPH-IR vs EqXL Teacher's Ratings: I/O component of 10-item IOWA Conners' Rating Scale 1-week: -2.4 (-3.36, -1.39) vs -1.9 (-2.87, -0.91) 2-week: -2.6 (-3.70, -1.43) vs. -2.4 (-3.58, -1.31) 3-week: -3.4 (-4.53, -2.26) vs. -3.1 (-4.26, -2.00) Teacher's Ratings: O/D component of 10-item IOWA Conners' Rating Scale 1-week: -1.7 (-2.54, -0.38) vs. -1.5 (-2.32, -0.62) 2-week: -1.9 (-2.81, -0.93) vs. -1.8 (-2.69, -0.81) 3-week: -2.4 (-3.36, -1.38) vs. -2.5 (-3.47, -1.48) Parent's Ratings: I/O component of 10-item IOWA Conners' Rating Scale 1-week: -2.3 (-3.31, -1.22) vs. -1.3 (-2.33, -0.23) 2-week: -2.6 (-3.65, -1.53) vs. -1.9 (-2.97, -0.86) 3-week: -3.0 (-4.09, -1.85) vs. -1.7 (-2.78, -0.54) Parent's Ratings: O/D component of 10-item IOWA Conners' Rating Scale 1-week: -2.1 (-3.22, -1.04) vs. -1.8 (-2.89, -0.71) 2-week: -2.5 (-3.64, -1.30) vs. -2.1 (-3.26, -0.92) 3-week: -2.3 (-3.46, -1.16) vs. -1.6 (-2.74, -0.44)	Throughout study, safety assessments were performed including hematology measures, biochemistry tests, urinalysis, weight, vital signs, and physical examination. Reported AE's were recorded giving duration, intensity and relationship to study drug, action taken, outcome, and seriousness. In addition, parents and teachers completed the Barkley Side Effects Rating Scale on same days as respective SNAP-IV ratings
Fitzpatrick 1992 Poor quality	SR vs SA vs Combination (SR+SA) p=NS for all All outcomes reported for Parent/Teacher Conners: 0.98/0.77 vs 0.96/0.73 vs 0.81/0.58 Inattention-Overactivity: 0.98/0.92 vs 1.01/0.87 vs 0.79/0.70 Noncompliance: 0.84/0.43 vs 0.80/0.48 vs 0.62/0.25 Aggression: 0.68/0.31 vs 0.56/0.24 vs 0.60/0.26 Hyperactivity: 0.22/-0.12 vs 0.20/-0.16 vs 0.18/-0.29 Attention: 0.72/0.88 vs 0.81/1.01 vs 0.91/1.05 Comments valence: -0.05/0.20 vs 0.17/0.19 vs 0.18/0.40 Other ratings: Parent ranks: 2.16 vs 2.18 vs 1.87 Laboratory rating: 0.13 vs 0.13 vs 0.09 Weight (kg): 31.59 vs 31.41 vs 31.33	Parents interviewed concerning 12 side effects relevant to stimulant therapy and a side effect was counted if it was prevalent to a marked extent during the latter part of the 2-week period

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Findling 2006 Australia, Canada, United States	Adverse events occurring in ≥ 3% of patients [placebo (n=46) vs. MPH-IR (n=133) vs. EqXL (n=139)]: Headache: 4.3% vs. 13.5% vs. 18.0% (p=0.059) Anorexia: 0 vs. 3.0% vs. 6.5% (p=0.131) Abdominal pain, upper: 6.5% vs. 6.8% vs. 5.8% (p=0.951) ADHD: 34.8% vs. 4.5% vs. 5.8% (p<0.001) Nasopharyngitis: 6.5% vs. 1.5% vs. 5.8% (p=0.098) Insomnia: 0 vs. 3.8% vs. 4.3% (p-0.497) Decreased appetite: 0 vs. 2.3% vs. 3.6% (p=0.564) Pyrexia: 6.5% vs. 0.8% vs. 2.9% (p=0.077) Vomiting NOS: 4.3% vs. 3.0% vs. 2.2% (p=0.657) Irritability: 2.2% vs. 3.8% vs. 1.4% (p=0.499)
Fitzpatrick 1992 Poor quality	Percentage of patients with side effects: SR vs SA vs Combination, p=NS for all Sleep problem: 36.8 vs 42.1 vs 63.2 Appetite decrease: 36.8 vs 15.8 vs 26.3 Crying: 21.0 vs 15.8 vs 26.3 Sadness: 0.0 vs 10.5 vs 0.0 Unhappiness: 21.0 vs 5.3 vs 15.8 Anger: 31.6 vs 10.5 vs 26.3 Headaches: 10.5 vs 10.5 vs 5.3 Increased thirst: 5.3 vs 0 vs 0 Dry mouth: 0 vs 0 vs 0 Nausea: 0 vs 5.3 vs 0 Stomachaches: 0 vs 5.3 vs 0 Shakiness: 0 vs 0 vs 5.3

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Findling 2006 Australia, Canada, United States	33/318 (10.4%) withdrew before study completion 21/318 (6.6%) withdrew due to adverse events 9/327 post randomization exclusions	
Fitzpatrick 1992	NR NR	Poor quality

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria
Gau 2006 Taiwan	RCT Open-label University outpatient clinic	Patients, aged 6–15, with a clinical diagnosis of any subtype of ADHD. Patients were included in this study if they were taking MPH on a total daily dose of MPH of 10 mg but not more than 40 mg for past 3 months. They were able to comply with the study visit schedules; and their mothers and teachers were willing and able to complete the weekly assessments. Patients were excluded from participation if they had significant gastrointestinal problems, a history of hypertension, known hypersensitivity to MPH, or a co-existing medical condition or concurrent medication (such as monoamine oxidase inhibitors, and medicines used to treat depression, prevent seizure, or prevent blood clots) likely to interfere with the safe administration of MPH. Patients with glaucoma, Tourette's Syndrome, an active seizure disorder, or a psychotic disorder were excluded, as were girls who had reached menarche.

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Comorbidity	Interventions and total daily dose Duration Dosing schedule
Gau 2006 Taiwan	NR	OROS MPH Mean Dose: 27.7 mg Dose Range: 18-36 mg IR MPH Mean Dose: 26.7 mg Dose Range: 15-30 mg

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Gau 2006 Taiwan	All study subjects washed out MPH for 5-7 days	NR	Chinese version of the Conner's Teacher Rating Scale-Revised: Short Form (CTRS-R:S) Other Measures: Chinese version of the Conner's Parent Rating Scale-Revised: Short Form (CPRS-R:S), Chinese Version of the Swanson, Kotin, Agler, M-Flynn and Pelham (SKAMP) Rating Scale, Chinese version of the Social Adjustment Scale for Children and Adolescents (SAICA), Investigator Clinical Global Impression (CGI), Parent Satisfaction Questionnaire (PSQ)	Mean age=10.5 yrs (Range=6-15 yrs) 90.6% male Ethnicity: NR (study completed in Taiwan)

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Gau 2006 Taiwan	ADHD diagnosis: Combined: 78.1% Inattentive: 18.8% Hyperactive: 3.1% CTRS-R:S, mean (SD): 72.6 (11.5) CPRS-R:s, mean (SD): 77.6 (9.7) SKAMP, mean (SD): 72.5 (15.5) SAICA, mean (SD): 62.6 (12.5) BSEQ, mean (SD): 24.1 (20.6) Vital signs, mean (SD): Systolic pressure : 97.2 (15.3) Diastolic pressure: 58.2 (10.9) Heart rate: 84.9 (14.8)	NR/NR/64	0/0/64

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Gau 2006 Taiwan	Connors' Teaching Rating Scale-Revised, Short Form-C, Day 13-Baseline, mean (SD) OROS vs. IR: Inattention: -1.38 (2.30) vs. -0.84 (1.97) Hyperactivity-Impulsivity: -3.16 (3.76) vs. -3.22 (4.09) Oppositional: -2.13 (2.97) vs. -1.58 (3.55) ADHD-index: -5.58 (6.38) vs. -5.97 (6.59) Connors' Teaching Rating Scale-Revised, Short Form-C, Day 27-Baseline, mean (SD) OROS vs. IR: Inattention: -1.90 (3.00) vs. -1.44 (2.12) Hyperactivity-Impulsivity: -4.94 (4.11) vs. -4.00 (5.13) Oppositional: -3.03 (3.93) vs. -1.91 (3.90) ADHD-index: -9.20 (7.36) vs. -7.13 (7.62) Conners' Parent Rating Scale-Revised: Short Form-C, Day 13-Baseline, mean (SD) OROS vs. IR: Inattention: -4.78 (5.28) vs. -4.72 (5.31) Hyperactivity-Impulsivity: -6.22 (5.13) vs. -5.25 (5.06) Oppositional: -3.69 (3.36) vs. -3.56 (3.53) ADHD-index: -9.97 (8.26) vs. -9.66 (8.23) Conners' Parent Rating Scale-Revised: Short Form-C, Day 27-Baseline, mean (SD) OROS vs. IR: Inattention: -5.63 (5.14) vs. -4.19 (4.84) Hyperactivity-Impulsivity: -7.53 (4.84) vs. -5.84 (5.01) Oppositional: -3.87 (3.32) vs. -3.41 (3.79) ADHD-index: -11.59 (7.82) vs. -9.03 (8.29) SKAMP, Day 13-Baseline mean (SD) OROS vs. IR: Attention: -1.77 (3.16) vs. -1.72 (4.08) Deportment: -2.77 (4.05) vs. -3.25 (4.13) SKAMP, Day 27-Baseline mean (SD) OROS vs. IR: Attention: -3.71 (3.39) vs. -2.98 (5.29) Deportment: -4.65 (5.53) vs. -4.41 (6.71) At final assessment, OROS group had greater proportion of subjects being very much or much improved than the IR MPH group in CGI rating (84.4% vs. 56.3%, p=0.014)	Barkley's Side Effects Questionnaire (BSEQ) was used to measure side effects of MPH. Vital signs (including systolic BP & pulse rate) were checked and any AE was documented if any occurred at each visit.

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Gau 2006 Taiwan	Percentage of side effects with increased BSEQ score from baseline, day 27, OROS vs. IR MPH: Decreased appetite: 46.9 vs. 59.4 (p=0.316) Insomnia/sleep trouble: 40.6 vs. 46.9 (p=0.614) Stomachache: 31.3 vs. 25.0 (p=0.578) Headache: 21.9 vs. 34.4 (p=0.266) Nightmares: 7.8 vs. 25.0 (0.351) Uninterested in others: 28.1 vs. 40.6 (p=0.292) Irritable: 9.4 vs. 21.9 (p=0.169) Dry mouth: 31.3 vs. 17.2 (p=0.79) Sad/unhappy, prone to crying: 31.3 vs. 43.8 (p=0.302) Anxious: 18.7 vs. 31.3 (p=0.248) Bites fingernails: 18.7 vs. 25.0 (p=0.545) Drowsiness: 7.8 vs. 18.8 (p=0.741) Tics or nervous movements: 7.8 vs. 18.8 (p=0.741) No difference in vital signs on day 28 between groups

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Gau 2006 Taiwan	0/0	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria
Pelham 1987 Poor	RCT Crossover Summer Treatment Program	ADD with or without hyperactivity based on a structured parental interview (not described); teacher ratings on the Swanson, Nolan and Pelham rating scale comprised of DSM-III symptoms; ACTRS and IOWA CTRS scales derived from teacher ratings of the CTRS

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Comorbidity	Interventions and total daily dose Duration Dosing schedule
Pelham	4 (30.8%) with Conduct Disorder	Placebo (twice daily)
1987	6 (46.1%) with Oppositional Defiant Disorder	Methylphenidate 20 mg (twice daily)
	3 (23.1%) with Learning Disability	Sustained release methylphenidate 20 mg (once daily)
Poor		
		Condition varied daily and 5 to 9 days of data were gathered per medication condition

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Pelham 1987 Poor	NR/NR	NR	Daily Frequencies=frequencies with which numerous appropriate and inappropriate behaviors occurred daily Time out=average number of time outs per day Classroom measures=rates of on-task behavior and rule-following behavior; 2-minute, timed arithmetic drill, 10-minute, timed reading task (number attempted and percentage correct) Rating scales: Teacher ratings on ACTRS; counselor ratings on Revised Behavior Problems Checklist (35 items rated on a 7-point scale with lower ratings equaling positive evaluations) Daily Report Card=Percentage of days that the child reached daily report criterion Observed Peer Interaction=Percentages of time that children were engaged in positive, negative, or no interactions with their peers were recorded using a modification of the RECESS code	Mean age=8.8 100% male Race NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Pelham	WISC-R IQ=95.3	NR/NR/13	NR/NR/NR
1987	ACRS Parent/Teacher=17.7/19.0		
	IOWA CTRS		
Poor	Inattention/Overactivity=11.9		
	Aggression=8.9		
	Woodcock-Johnson Achievement Test		
	Reading=91.6		
	Mathematics=97.0		
	Language=91.4		

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Pelham 1987 Poor	Methylphenidate vs sustained release methylphenidate, t-test, p-value: Daily frequencies Following rules: 3.5 vs 4.3, t=1.8, p=NS Noncompliance: 3.4 vs 4.3, t=-2.5, p<0.05 Positive peer behaviors=100.2 vs 95.8, t=0.8, p=NS Conduct problems: 0.3 vs 0.4, t=-0.4, p=NS Negative verbalizations=3.4 vs 4.8, t=-2.3, p<0.05 N. of time outs/day: 0.5 vs 0.7, t=-1.2, p=NS Classroom % on task=95.2 vs 96.5, t=-0.6, p=NS % on following rules=93.9 vs 92.2, t=0.6, p=NS Timed math No. attempted=21.0 vs 21.7, t=-0.5, p=NS % correct=9.3 4 vs 94.4, t=-0.5, p=NS Timed reading No. attempted=19.8 vs 18.2, t=1.4, p=NS % correct=79.8 vs 77.9, t=0.4, p=NS Seatwork % completion=86.1 vs 89.1, t=-0.9, p=NS % correct=83.7 vs 82.9, t=0.3, p=NS Teacher rating: 1.9 vs 3.4, t=-1.3, p=NS Counselor rating: 106.4 vs 105.9, t=0.1, p=NS Positive daily report card (% of days received): 83.2 vs 81.8, t=0.2, p=NS Observed interactions Positive peer: 97.9 vs 95.2, t=1.6, p=NS Negative peer: 1.4 vs 1.5, t=-0.2, p=NS No interactions: 0.7 vs 3.3, t=-1.8, p=NS	NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Pelham 1987 Poor	Evidence of anorexia: Standard methylphenidate=4 (30.8%) vs 5 (38.5%); p=NS

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Pelham 1987	NR NR	Poor

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria
Pelham 2001 Fair	RCT, DB, crossover Setting: regular home and school settings Sunday-Friday; study site for Saturday laboratory sessions from 6:45 AM to 8:15 PM	Children between the ages of 6 and 12 with a DSM-IV diagnosis of ADHD (any subtype). Children met DSM diagnostic criteria using a rule in which a symptom was defined as present if either parents or teachers endorsed it, with overlap between raters on at least 1 symptom. Medicated with a stable dose of methylphenidate for at least 4 weeks before the beginning of the study

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Comorbidity	Interventions and total daily dose Duration Dosing schedule
Pelham 2001 Fair	Oppositional defiant disorder=43% Conduct disorder=37%	Placebo Methylphenidate immediate release, three times daily (7:30 AM, 11:30 AM, 3:30 PM), average dose=29 mg (0.88 mg/kg) Methylphenidate extended release (Concerta), once daily in the morning (7:30 AM), average dose=35 mg (1.05 mg/kg) Flexible dosing determined based on that child's MPH dosing before the study Double-dummy placebo design 7 days, then crossover

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Pelham 2001 Fair	NR/NR	4-6 sessions of behavioral parent training was provided (how to use behavioral techniques in the home setting); teacher received 1-4 clinical contacts during which a consulting teacher worked with each child's teacher to establish a daily report card (DRC) and to consult on other classroom management strategies	Primary outcome measures: (1) IOWA inattention/overactivity (I/O) in the natural setting and (2) SKAMP attention in the laboratory classroom Other dependent measures: Natural setting: (1) teacher and parent IOWA Conners ratings, (2) teacher and parent abbreviated Conners ratings, (3) teacher peer relations ratings, (4) teacher and parent global effectiveness ratings, and (5) individualized DRC percentages Laboratory classroom: 1) frequencies of rule violations, 2) math problems completed, 3) math problems percentage correct, 4) teacher SKAMP ratings, 5) observed on-task behavior, 6) observed disruptive behavior, 7) records of individualized target behaviors (DRC goals), and 8(teacher end-of-day IOWA Conners ratings Structured recreation: 1) frequencies of rule violations, 2) frequencies of negative behaviors, 30 observed disruptive behavior, 4) observed on-task behavior, 5) records of individualized target behaviors (DRC), and 6) counselor end-of-day IOWA-Conners ratings Recess: 1) frequencies of rule violations, and 2) observed disruptive behavior Daily behavior: 10 % following activity rules, 2) noncompliance, 3) interrupting, 4) complaining, 5) positive peer behaviors 6) conduct problems, 7) negative verbalizations	Mean age 9.1 89% male 94% white

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Pelham 2001 Fair	Pre-study MPH use: BID dosing=57%; TID dosing=43% Full-scale IQ (WISC-III)=104.8 Reading achievement (WIAT)=104.1 Math achievement (WAIT)=98.8 Spelling achievement (WIAT)=96.3 DISC hyperactive/impulsive symptoms=8.3 DISC inattention symptoms endorsed=7.1 Parent SNAP ratings Inattention=2.26 Hyperactivity/impulsivity=1.96 Oppositional/defiant=1.56 Parent/DBD Ratings Inattention=2.15 Hyperactivity/impulsivity=1.83 Oppositional/defiant=1.28 Conduct disorder=0.26 Parent IOWA Conners ratings Inattention/overactivity=10.42 Oppositional/defiant=7.28 Parent abbreviated Conners rating=18.06 Teacher SNAP ratings Inattention=2.04 Hyperactivity/impulsivity=1.62 Oppositional/defiant=1.56 Teacher DBD ratings Inattention=1.82 Hyperactivity/impulsivity=1.47 Oppositional/defiant=0.75 Teacher IOWA Conners ratings Inattention/overactivity=9.65 Oppositional/defiant=4.07 Teacher abbreviated Conners rating=14.96 Teacher peer relations rating=5.33	NR/NR/70	2 (2.8%) withdrawn/lost to fu nr/analyzed 68 5 children missed one of 3 testing sessions

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Pelham 2001 Fair	Placebo / tid IR MPH / Concerta, p-value = MPH IR vs Concerta Natural setting Teacher ratings Inattention/overactivity: 10.34 vs 5 vs 4.69, p=NS; Oppositional/defiant: 5.09 vs 1.99 vs 1.81, p=NS Abbreviated Conners; 16.40 vs 7.4 vs 7.82, p=NS; Peer interactions: 4.29 vs 4.03 vs 3.41; p=NS Global effectiveness: NS on any classification Daily report card (% positive): 61.17 vs 84.36 vs 86.06 Parent ratings Inattention/overactivity: 10.59 vs 5.93 vs 4.78; p=0.05; Oppositional/defiant: 8.85 vs 5.26 vs 4.82; p=NS Abbreviated Conners: 19.91 vs 11.41 vs 9.49; p=0.05 Global effectiveness: Poor: 73.5% vs 8.8% vs 5.9%; p=NS; Fair: 22.1% vs 26.5% vs 27.9%, p=NS Good: 2.9% vs 50.0% vs 39.7%, p=NS; Excellent: 1.5% vs 14.5% vs 26.5%, p=NS (p=NS for all remaining comparisons of tid IR MPH vs Concerta) Recreational Activities -- Counselor measures Rule violations (mean #)-- 7:45-8:10: 2.52 vs 2.83 vs 2.21; 9:55-10:25: 4 vs 2.58 vs 2.70 1:25-1:55: 5.87 vs 2.17 vs 2.39; 4:35-5:00: 5.21 vs 2.84 vs 2.53 Negative behavior (mean #)-- 7:45-8:10: 1.53 vs 4.86 vs 1.73; 9:55-10:25: 3.62 vs 1.14 vs 1.14 1:25-1:55: 6.25 vs 0.98 vs 2.45; 4:35-5:00: 4.76 vs 2.83 vs 1.58 Individual target goals-- 7:45-8:10: 79.05 vs 69.01 vs 75.13; 9:55-10:25: 65.44 vs 82.30 vs 78.91 1:25-1:55: 56.13 vs 81.25 vs 74.22; 4:35-5:00: 58.82 vs 76.43 vs 80.73 Observer measure negative behavior-- 7:45-8:10: 3.24 vs 4.00 vs 4.21; 9:55-10:25: 6.99 vs 2.13 vs 2.97 1:25-1:55: 8.96 vs 2.17 vs 3.47; 4:35-5:00: 8.91 vs 4.61 vs 2.86 Recess measures (means) Rule violations-- 11:05: 0.81 vs 0.44 vs 0.36; 2:50: 1.10 vs 0.66 vs 0.52; 7:45: 2.07 vs 1.42 vs 1.53; Negative behavior-- 11:05: 10.37 vs 7.48 vs 8.56; 2:50: 14.03 vs 10.13 vs 7.65; 7:45: 13.76 vs 8.88 vs 7.73 Laboratory sessions (means) (overall daily measures) Behavior frequencies Following rules: 47.5% vs 60.2% vs 61.3%; Noncompliance: 5.76 vs 2.73 vs 2.14 Interruption: 21.6 vs 10.5 vs 10.58; Complaining/whining: 15.45 vs 6.95 vs 6.67 Positive peer behaviors: 10.52 vs 9.86 vs 9.20; conduct problems: 3.81 vs 1.53 vs 0.60 Negative verbalizations: 18.27 vs 9.29 vs 7.14 Teacher rating-- Inattention/overactivity: 5.01 vs 2.75 vs 2.59; Oppositional/defiant: 2.18 vs 1.19 vs 1.30 Abbreviated Conners: 7.03 vs 4.03 vs 3.75; Peer interactions: 0.24 vs 0.15 vs 0.15 Counselor rating-- Inattention/overactivity: 7.95 vs 6.31 vs 6.10; Oppositional/defiant: 3.63 vs 2.58 vs 2.36 Abbreviated Conners: 12.70 vs 9.91 vs 9.26; Peer interactions: 0.77 vs 0.56 vs 0.49	Spontaneous reports; parents completed questions regarding AEs, sleep quality, appetite, and tics; sleep quality for the week was rated as poor, fair, good, or excellent; food intake for the week relative to usual food intake was rated as less, usual amount, or more

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Pelham 2001	Placebo vs qd Concerta vs tid IR MPH
	Serious adverse events: 0 vs 0 vs 0
Fair	Motor tics: 0 vs 4/70 (5.7%) vs 0
	Sleep(% patients)
	Excellent: 12% vs 13% vs 7%
	Good: 57% vs 47% vs 65%
	Fair: 21% vs 24% vs 21%
	Poor: 10% vs 16% vs 7%
	Usual appetite: 59% vs 77% vs 66%
	Appetite loss: 4: vs 18% vs 24%
	Headache: 16 (23.2%) vs 8 (11.8%) vs 11 (15.9%)
	Abdominal pain: 8 (11.6%) 9 (13.2%) vs 12 (17.4%)
	Upper respiratory tract infection: 3 (4.3%) vs 2 (2.9%) vs 3 (4.3%)
	Accidental injury: 2 (2.9%) vs 1 (1.5%) vs 3 (4.3%)
	Vomiting: 2 (2.9%) vs 2 (2.9%) vs 2 (2.9%)
	Twitching: 0 vs 0 vs 4 (5.8%)
	Diarrhea: 1 (1.4%) vs 0 (0.0%) vs 2 (2.9%)
	Pharyngitis: 0 (0.0%) vs 1 (1.5%) vs 2 (2.9%)
	Rhinitis: 0 (0.0%) vs 1 (1.5%) vs 2 (2.9%)
	Dizziness: 0 (0.0%) vs 2 (2.9%) vs 1 (1.4%)
	Urinary incontinence: 2 (2.9%) vs 0 (0.0%) vs 1 (1.4%)

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Pelham 2001	2 (2.8%) withdrawals overall (group assignment unclear)	
Fair	Withdrawals due to adverse events: none reported	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria
Steele 2006 Canada	RCT Open-label Parallel Multicenter	Physically healthy, male and female outpatients, aged 6 - 12 years inclusive, with a documented Diagnostic Statistical Manual-Fourth Edition (DSM-IV) diagnosis of Attention-Deficit/Hyperactivity Disorder. These criteria were confirmed by a clinical and structured interview (the Kiddie-Schedule for Affective Disorders and Schizophrenia -Present and Lifetime Version, K-SADS-PL, version 1.0). Subjects were medication naïve or currently on ADHD medication therapy; had a baseline Clinical Global Impression-Severity (CGI-S) score of 4 or greater (at least “moderate” severity); and had to demonstrate significant after-school/evening behavioral difficulties as assessed by the clinician via parent/child interviews. To approximate clinical practice settings, psychotropic medications to treat non-ADHD disorders and psychological interventions were permitted as long as the treatment/intervention had been stable for a minimum of 4 weeks prior to entry and did not change nor newly commence during the trial. Exclusion criteria included: known MPH non-responders, hypersensitivity, or adversely affected by methylphenidate; concomitant use of contraindicated medication likely to interfere with the safe administration of study medication; marked anxiety, tension, aggression/agitation; glaucoma; ongoing seizure disorder; psychotic disorder; diagnosis or family history of Tourette’s disorder; bipolar disorder; suspected mental retardation or significant learning disorder; medication/alcohol abuse/dependence by either the child or parent; history of, or current eating disorder; severe gastrointestinal narrowing; inability to swallow study medications; and any serious/unstable medical illness.

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Comorbidity	Interventions and total daily dose Duration Dosing schedule
Steele 2006 Canada	Oppositional Defiant Disorder: 43.1%, 38.4% Conduct Disorder: 1.4%, 0 Anxiety disorder: 5.5%, 2.7%	OROS-MPH: Mean Dose: 37.8 mg/day (SD 11.9) Initiated on 18 mg once daily. Over 4 weeks, the subjects were titrated by weekly increases, at the investigators' discretion; to the next dose level (27 mg, then 36 mg) to a maximum of 54 mg. IR-MPH: Mean Dose: 33.3 mg/day (SD 13.2) Initiated at whatever dose the clinician felt was appropriate. Over 4 weeks each individual dose was titrated weekly by 5 mg or 10 mg increments, according to the manufacturer's recommendations and the investigator's clinical judgment, to a suggested maximum daily dose of 60 mg.

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Steele 2006 Canada	Minimum 3-day washout from stimulant or non-stimulant medication to treat ADHD	Psychotropic medications to treat non-ADHD disorders and psychological interventions permitted as long as treatment/intervention had been stable at least 4 weeks prior to entry and did not change nor newly commence during the trial	Primary Outcome Measure: parent completed 26 item Swanson, Nolan and Pelham–Fourth Edition (SNAP-IV) rating scale Other Measures: 10-item Inattention/Overactivity with Aggression (IOWA) Conners Parent Rating Scale, 27-item Conners Parent Rating Scale (short), 36-item Parent Stress Index (PSI), Physician-rated Clinical Global Impression of Severity (CGI-S) and Clinical Global Impression of Improvement (CGI-I), Parent/caregiver report of satisfaction with ADHD treatment, 100 mm Visual Analog Scale (VAS) of homework and for social play ability scored by the parent/caregiver, Resource Use Questionnaire (RUQ)	Mean age=9.1 yrs (Range=6-12 yrs) 83.4% male 86.9% Caucasian 3.4% black 9% other

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Steele 2006 Canada	ADHD diagnosis: predominantly inattentive=18.6% combined type=79.3% predominantly H/I=2.1%	187/NR/147	2 withdrawn (didn't receive study medication) ITT n=143 Safety analysis n=145

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Steele 2006 Canada	Achieved remission (SNAP-IV-18) at endpoint: 44% vs. 16%; p=0.0002 Remission rates higher in OROS-MPH group than in IR-MHP group at week 4 (33% vs, 14%; p=0.01) and at week 8 (47% vs. 16%; p=0.0003) Mean change from baseline score (SD) at study endpoint (OROS-MPH vs. IR-MPH): SNAP-IV 26-item (ADHD + ODD items) Scale: -25.5 (18.7) vs. -17.5 (15.2) SNAP-IV 18-item (ADHD items) Scale: -19.6 (13.9) vs. -14.3 (11.6) IOWA Conners Parent Rating Scale, Total: -9.4 (8.5) vs. -6.0 (5.9) IOWA Conners Parent Rating Scale, Inattention/Overactivity Sub-scale: -5.4 (4.5) vs. -3.9 (3.2) Conners Parent Rating Scale: -27.5 (21.9) vs. -19.2 (15.6) Parent Stress Index, Short Form: +14.0 (19.2) vs. +6.1 (14.8) Visual analog scale (mm): homework: -31.8 (29.6) vs. -23.0 (33.8) Visual analog scale (mm): social play: -17.9 (30.4) vs. -7.5 (27.0) CGI-I: mean rating (SD): 2.0 (1.2) vs. 2.6 (1.4); p=0.0008 CGI-S: mean change from baseline rating (SD): -2.2 (1.2) vs. -1.6 (1.4); p=0.0005 Parent satisfaction with current ADHD medication: mean rating (SD): 4.0 (1.3) vs. 3.4 (1.3); p=0.003	Safety assessments collected included adverse events, physical examination, vital signs, and body weight

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Steele 2006 Canada	Adverse events were reported for 82% of subjects in both groups. No serious adverse events were reported. Any event: 82% vs. 82% Any possibly medication related event: 64% vs. 52% Decreased appetite: 24% vs. 32% Headache: 19% vs. 16% Insomnia: 17% vs. 14% Abdominal pain: 14% vs. 12% Nervousness: 13% vs. 12% Emotional lability: 13% vs. 3% Agitation: 11% vs. 7% Fatigue: 10% vs. 3% Flu-like symptoms: 10% vs. 10% Sleep disorder: 4% vs. 10%

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Steele 2006 Canada	Total =24 (16.6%) AEs=8 (5.5%)	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria
Wolraich 2001 United States Fair	RCT Parallel Multicenter	Boys and girls, ages 6 to 12 years, with a clinical diagnosis of any subtype of ADHD; patients who were taking MPH or had taken it in the past had to have been on a total daily MPH dose (IR or IR/SR combination) of at least 10 mg but not more than 60 mg)

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Comorbidity	Interventions and total daily dose Duration Dosing schedule
Wolraich 2001 United States Fair	46.5% ODD 11.3% Conduct Disorder 5.3% Tic Disorder 1.4% Anxiety Disorder 0.7% Depression	Methylphenidate (MPH) mean dose=29.5 (three times daily at 7:30, 11:30 and 3:30) Methylphenidate osmotic, controlled-release, oral dosage form (OROS MPH) mean dose=34.3 (once daily at 7:30) Duration=4 weeks Patients that had not been receiving MPH during 4 weeks prior to study entry started in a 4-week open titration phase where they were ALL given OROS MPH at 18 mg QD and this was increased to 36 mg QD and then to 54 mg QD as necessary

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Wolraich 2001 United States Fair	NR/NR	NR	1) IOWA CTRS 2) SNAP-IV (18 items that reflect ADHD symptoms in the DSM-IV and 8 items that reflect oppositional defiant disorder) 3) Children's Global Assessment Scale (C-GAS) - parent rating 4) Clinical Global Impressions-Improvement (CGI-I) - investigator rated 5) Global Assessment of Efficacy rating by parents/teachers (4-point scale of 0=poor, 1=fair, 2=good, 3=excellent) in response to question: "What is your opinion of the effectiveness of treatment this week?" 6) Peer Interaction: On day 27, teachers rated 6 items from the SNAP-IV and 1 item from the IOWA Conners Rating Scale 7) Parent Satisfaction Questionnaire: based on questionnaire used in the NIMH Multimodal Treatment Study of Children with ADHD (MTA)	Mean age=9 82.6% male 84.4% White 7.4% Black 0.4% Asian 3.5% Hispanic

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Wolraich 2001 United States Fair	ADHD Diagnosis 73.4% combined 19.5% inattentive 7.1% hyperactive/impulsive Previous stimulant therapy 20.2% None 6.4% Not in previous 4 weeks 5.7% Non-MPH 67.7% MPH	Screened=500/Enrolled=405/Randomized=312	Withdrawn=206 (66%)/Lost to follow-up=1(0.3%)/Analyzed=277 (MPH n=94, MPH OROS n=94, Placebo n=89)

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Wolraich 2001 United States Fair	Mean change in IOWA Conners Scores (OROS MPH vs IR MPH) (p-values NR, but narrative states there are NS differences): Teacher/Parent scores: Inattention/Overactivity: -3.76/-4.79 vs -3.59/-3.73 Oppositional/Defiance: -1.6/-3.24 vs -1.3/-2.36 Mean changes in secondary measures of efficacy (teacher ratings) Peer Interaction: -0.33 vs -0.21 SNAP-IV Inattention: -0.69 vs -0.80 SNAP-IV Hyperactivity/Impulsivity: -0.64 vs -0.69 SNAP-IV Oppositional Defiant Disorder: -0.36 vs -0.32 Global Efficacy at end of study: 1.42 vs 1.43 Mean change in secondary measures of efficacy (parent ratings) SNAP-IV Inattention: -0.91 vs -0.77 SNAP-IV Hyperactive/Impulsive: -0.91 vs -0.74 SNAP-IV Oppositional Defiance Disorder: -0.65 vs -0.41 Global Efficacy at end of study: 1.47 vs 1.28 Investigator ratings Mean CGI at end of study: 4.24 vs 4.19 % of patients on CGI rated as "much" or "very much" improved: 46.7% vs 47.2% Other Global assessment of efficacy, % patients teachers/parents rated as "good or excellent": 42.9%/54.0% vs 46.9%/46.5% CGI, % patients rated as "very much improved or much improved": 46.7% vs 47.2% Parent Satisfaction Questionnaire (% pleased/very pleased/extremely pleased): 62.6% vs 64%	AEs collected at days 7, 14 and 28 by asking parents whether any new development in the child's health had occurred since the last clinic visit. Spontaneously reported AEs also were recorded. Sleep quality rated by parents for previous 2 weeks on days 0, 14, and 28 as Excellent, good, fair, or poor Food intake rated by parents for previous 2 weeks on days 14 and 28 as more than before, about the same amount as before, or less than before Motor and verbal tics: parents asked about presence of and/or any changes in severity or specificity on days 0, 14, and 28

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Wolraich 2001 United States Fair	Any adverse event: 42.3% vs 46.2%, p-value nr Sleep: no differences (data nr) Appetite (% of patients who were eating less than usual during the previous two weeks): day 14=22.5% vs 18.8%, p=NS; day 28=data nr but described as "similar" New onset tics (# patients): 0 vs 1 (1%), p=NS

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Wolraich 2001 United States Fair	Withdrawals due to adverse events: 1% vs 1% Total withdrawals: 15 (16%) vs 13 (13.8%)	Although the numbers enrolled vs analyzed are described in the text and in a figure, they are confusing and difficult to reconcile with each other.

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria
Whitehouse 1980 United States Fair	RCT Parallel Double-blind Setting NR	Children of both sexes, 6-14 years of age, with a diagnosis of minimal brain dysfunction (MBD); symptoms of MBD had been satisfactorily controlled by methylphenidate 10 mg given twice daily for at least 1 month prior to study-no medication changes were made during this period; the children were outpatients attending school, in good health, taking no other chronic medications

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Comorbidity	Interventions and total daily dose Duration Dosing schedule
Whitehouse 1980 United States Fair	NR	Standard methylphenidate 20 mg (twice daily) Sustained-release methylphenidate 20 mg (once daily) Duration=2 weeks Dosing schedule: 30 minutes prior to breakfast; 30 minutes before lunch

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Whitehouse 1980 United States Fair	Run-in: one month of standard methylphenidate 20 mg (twice daily) prior to study/no washout	NR	Bender Visual Motor Gestalt Goodenought-Harris Drawing psychometrics tests Physician questionnaire (not described) completed at visits 1 , 2 and 3 Teacher questionnaire (not described) completed within 4 days prior to the patients entering the study and again 4 days before the final visit	Mean age=8.5 83.3% male 86.7% white 13.3% black

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Whitehouse 1980 United States Fair	Height (inches)=50 Weight (pounds)=57.8 Right-handedness=90% Physician Questionnaire Overt Signs of Tension: 1.63 (2.00 vs 1.21; p<0.05) Teacher questionnaire Tension/Anxiety: 10.9 (10.00 vs 12.00; p<0.05)	NR/NR/34	4 (11.8%) withdrawn/0 lost to fu/30 analyzed

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Whitehouse 1980 United States Fair	Mean change scores (visit 3 compared to visit 1) for sustained release vs standard: Teacher Total score: -1 vs -8, p<0.05 Conduct Problem: 0 vs -3, p<0.05 Inattentive/Passive: 0 vs 0 Tension/Anxiety: -1 vs -1 Hyperactivity: 0 vs -2 Social ability: 0 vs 0 Parent/teacher questionnaire: 0 vs -1 Parent Questionnaire Total score: -11 vs -8 Conduct Problem: -2 vs 0; p<0.05 Anxiety: -1 vs -2 Impulsive/Hyperactive: -2 vs 0 Learning problem: 0 vs 0 Psychosomatic: -1 vs 0 Perfectionism: 0 vs 0 Antisocial: 0 vs 0 Muscular tension: -1 vs 0 Parent/Teacher Questionnaire: -2 vs -1	NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Whitehouse 1980 United States Fair	Adverse reactions: 5 (31.3%) vs 2 (14.3%), p=NS (consisted of headache, hyperactivity and restlessness)

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Whitehouse 1980 United States Fair	4 (11.8%) (group assignment NR) No withdrawals due to adverse events	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria
Extended release formulations of Methylphenidate		
Lopez 2003 Fair	RCT Crossover Simulated school setting (18 children per classroom) Single-blind (medicating nurse unblinded; but all other study personnel and patients were blinded)	Children who met ADHD criteria based on the Diagnostic Interview Schedule for Children

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Comorbidity	Interventions and total daily dose Duration Dosing schedule
Extended release formulations of Methylphenidate		
Lopez 2003 Fair	NR	Methylphenidate osmotic controlled release delivery system (MPH OROS) 18 mg or 36 mg Methylphenidate spheroidal oral drug absorption system (MPH SODAS) 20 mg Placebo 5-single dose test sessions (one practice visit, three active treatments and placebo)

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Extended release formulations of Methylphenidate				
Lopez 2003 Fair	NR/NR	NR	(1) Swanson, Kotkin, Agler, M-Flynn and Pelham Rating Scale (SKAMP): Attention, Deportment, and Combined Ratings subscales (2) Paper/pencil math tests: written assignments administered as four pages of 100 math problems each in ascending order of difficulty over a 10-minute period (difficulty altered for each participant's skill level); math test-attempted and math test-correct	Mean age=9.0 80.5% male 36% White 27% African American 36% Hispanic

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Extended release formulations of Methylphenidate			
Lopez 2003 Fair	NR	NR/NR/36	0 withdrawn/0 lost to fu/36 analyzed

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Extended release formulations of Methylphenidate		
Lopez 2003 Fair	MPH SODAS 20mg vs MPH OROS 18mg vs MPH OROS 36mg vs Placebo; p=values reflect comparison to MPH SODAS Mean change from baseline for SKAMP-attention $AUC_{(0-4)}$: -2.48 vs -1.36 (p=0.015) vs -1.55 (p=0.043) vs 1.24 (p<0.001) $AUC_{(0-8)}$: -4.48 vs -2.72 (p=NS) vs -3.24 (p=NS) vs 3.79 (p<0.001) Greatest improvement: 54% at 2 hrs vs 35% at 1 hour vs 35% at 3 hrs Mean change from baseline for SKAMP-deportment $AUC_{(0-4)}$: -1.67 vs -0.28 (p<0.001) vs -0.55 (p=0.004) vs 0.95 (p<0.001) $AUC_{(0-8)}$: -2.81 vs -0.82 (p=0.018) vs -1.34 (p=0.078) vs 2.85 (p<0.001) Greatest improvement: 63%/2 hrs vs 32%/8 hrs vs 40%/6 hrs Mean change from baseline for SKAMP-combined $AUC_{(0-4)}$: -2.05 vs -0.78 (p<0.001) vs -1.01 (p=0.003) vs 1.09 (p<0.001) $AUC_{(0-8)}$: -3.58 vs -1.70 (p=0.01) vs -2.22 (p=0.061) vs 3.28 (p<0.001) Math test-attempted $AUC_{(0-4)}$: 112 vs 62 (p=0.066) vs 69 (p=NS) vs -39 (p<0.001) $AUC_{(0-8)}$: 202 vs 115 (p=NS) vs 137 (p=NS) vs -123 (p<0.001) Greatest improvement: 52%/2 hrs/41% at 1 hr; 26%/8 hrs Math Test Correct $AUC_{(0-4)}$: 104.07 vs 45.44 (p=0.026) vs 58.55 (p=0.080) vs -40.6 (p<0.001) $AUC_{(0-8)}$: 183 vs 100 (p=NS) vs 117 (p=NS) vs -124.7 (p<0.001) Greatest improvement: 52%/2 hrs vs 39%/1 hr vs 26%/8 hrs	NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Extended release formulations of Methylphenidate	
Lopez 2003 Fair	Number (proportion) patients with at least one adverse event: 1 (2.7%) vs 1 (2.7%) vs 1 (2.7%)

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Extended release formulations of Methylphenidate		
Lopez 2003 Fair	Total withdrawals=0 Withdrawals due to adverse events=0	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria
Silva 2005 United States	Single-blind RCT Placebo-controlled Crossover Multicenter	Eligible participants were children 6–12 years of age who met DSM-IV (C-DISC-4 1997) criteria for a primary diagnosis of ADHD and whose parents provided written consent for their participation in the study. Assent to participate was also obtained from all children. Inclusion criteria required that children were treated and stabilized on a total daily dose of 20–40 mg MPH for at least 2 weeks prior to enrollment. Female participants were required to be premenarchal, sexually abstinent, or using an approved method of contraception; those of childbearing potential were required to have a negative urine pregnancy test prior to enrollment. Children were ineligible to participate if they were functioning at an IQ level of 80 or below, based on the investigator's clinical judgment; if they were diagnosed with Tourette syndrome or a tic disorder; if they had a history of a seizure disorder; or if they were deemed by the investigator to be unable to understand or comply with study instructions. Children with significant concurrent medical or psychiatric illness or substance-abuse disorder, as evidenced by abnormal laboratory values, medical and psychiatric history, or physical examination, were not permitted to participate. Also excluded were patients with a history of sensitivity to MPH, those with a history of substance abuse or dependence, those currently taking atomoxetine, and those who had taken, were currently taking, or were planning to take any investigational drug within 30 days of the study start date.

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Comorbidity	Interventions and total daily dose Duration Dosing schedule
Silva 2005 United States	NR	single doses of extended-release MPH (ER-MPH) 20 and 40 mg, modified-release MPH (OROS-MPH) 18 and 36 mg, and placebo Mean Dose: NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Silva 2005 United States	NR	NR	Primary Outcome Measure: SKAMP-Attention subscale score Other Measures: SKAMP-Deportment subscale, SKAMP-Combined (Attention and Deportment) scores, and written math tests	Mean age: 9.4 yrs (SD 1.9) 63% male 63% Caucasian 14.8% African American 0% Asian 22.2% other

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Silva	ADHD subtype	NR/NR/54	1 withdrew
2005	Inattentive: 27.8%		
United States	Hyperactive/impulsive: 1.9%		
	Combined inattentive/hyperactive: 70.4%		

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Silva 2005 United States	Mean (SD) Postdose Scores (ER-MPH 20mg/ER-MPH 40mg/OROS-MPH 18mg/OROS-MPH 36mg/placebo) SKAMP-Attention (hours postdose) 0.5-hr: 1.70 (0.73)/1.78 (0.94)/1.97 (0.97)/1.79 (0.93)/1.86 (1.03) 1.0-hr: 1.37 (1.04)/1.37 (1.03)/1.70 (1.07)/1.76 (1.13)/2.26 (1.17) 2.0-hr: 1.08 (0.78)/0.89 (0.81)/1.31 (0.97)/1.63 (1.10)/1.79 (1.17) 3.0-hr: 1.30 (0.85)/1.01 (0.80)/1.50 (1.01)/1.65 (1.16)/2.08 (1.03) 4.0-hr: 1.31 (0.81)/1.28 (0.88)/1.57 (1.02)/1.49 (0.86)/1.95 (1.00) 6.0-hr: 1.47 (0.85)/1.21 (0.98)/1.55 (0.94)/1.60 (0.99)/2.09 (0.93) 8.0-hr: 1.75 (0.84)/1.41 (1.01)/1.64 (1.04)/1.62 (0.97)/2.18 (1.07) 10.0-hr: 1.84 (0.93)/1.74 (1.04)/1.56 (0.91)/1.81 (1.14)/2.20 (1.10) 12.0-hr: 2.13 (0.98)/1.89 (0.83)/1/73 (1.09)/1.53 (1.06)/2.22 (0.98) SKAMP-Deportment (hours postdose) 0.5-hr: 1.37 (1.29)/1.19 (1.16)/1.48 (1.21)/1.46 (1.38)/1.74 (1.49) 1.0-hr: 1.12 (1.17)/0.79 (1.08)/1.39 (1.31)/1.33 (1.42)/2.10 (1.52) 2.0-hr: 0.91 (0.95)/0.48 (0.65)/1.07 (1.12)/1.19 (1.30)/2.06 (1.46) 3.0-hr: 0.96 (0.93)/0.58 (0.74)/1.27 (1.15)/1.09 (1.10)/2.15 (1.52) 4.0-hr: 1.12 (1.05)/0.63 (0.77)/1.36 (1.24)/1.12 (1.13)/2.19 (1.41) 6.0-hr: 1.20 (1.02)/0.70 (0.83)/1.37 (1.13)/1.16 (1.25)/2.14 (1.24) 8.0-hr: 1.36 (1.29)/0.92 (1.04)/1.35 (1.09)/1.39 (1.33)/2.00 (1.30) 10.0-hr: 1.65 (1.23)/1.25 (1.18)/1.40 (1.28)/1.27 (1.24)/2.06 (0.98) 12.0-hr: 1.94 (1.21)/1.54 (1.19)/1.54 (1.25)/1.33 (1.17)/2.14 (1.29) SKAMP-Combined (hours postdose) 0.5-hr: 1.52 (0.89)/1.46 (0.94)/1.70 (0.95)/1.61 (1.03)/1.79 (1.17) 1.0-hr: 1.24 (0.96)/1.04 (0.95)/1.53 (1.08)1.53 (1.17)/2.18 (1.21) 2.0-hr: 0.99 (0.71)/0.67 (0.58)/1,18 (0.93)/1.40 (1.11)/1.94 (1.18) 3.0-hr: 1.12 (0.74)/0.78 (0.67)/1.37 (0.98)/1.35 (0.98)/2.12 (1.14) 4.0-hr: 1.21 (0.82)/0.93 (0.74)/1.46 (1.04)/1.29 (0.91)/2.08 (1.08) 6.0-hr: 1.32 (0.82)/0.93 (0.82)/1.46 (0.92)/1.37 (1.01)/2.12 (0.96) 8.0-hr: 1.54 (0.98)/1.15 (0.94)/1.48 (0.94)/1.49 (1.04)/2.08 (1.05) 10.0-hr: 1.74 (1.02)/1.48 (1.01)/1.47 (0.96)/1.52 (1.06)/2.13 (0.90) 12.0-hr: 2.03 (1.00)/1.67 (0.92)/1.63 (0.96)/1.42 (1.02)/2.17 (0.96) Math Test-Attempt (hours postdose) 0.5-hr: 80.9 (51.8)/78.4 (53.7)/71.5 (46.6)/72.7 (51.7)/62.1 (42.0) 1.0-hr: 93.2 (55.3)/96.2 (53.9)/84.8 (50.6)/72.1 (42.5)/56.0 (41.2) 2.0-hr: 104.7 (60.0)/115.2 (60.4)/96.3 (58.4)/81.8 (48.4)/70.8 (49.4) 3.0-hr: 92.3 (58.9)/109.9 (60.4)/81.9 (45.3)/80.3 (47.5)/57.6 (39.5) 4.0-hr: 96.5 (52.7)/97.9 (62.9)/79.8 (51.4)/81.2 (47.5)/60.9 (42.0) 6.0-hr: 86.7 (52.6)/104.1 (64.9)/83.9 (52.5)/78.1 (50.4)/56.1 (46.4) 8.0-hr: 78.0 (57.4)/98.3 (64.1)/77.7 (56.5)/78.6)/53.5)/57.9 (49.5) 10.0-hr: 82.0 (55.8)/89.8 (67.1)/88.6 (56.6)/73.0 (48.2)/63.2 (52.5)	During each lab classroom day, vital signs and AE's were assessed. All AE's were recorded and described in terms of start and stop dates, severity of event, relationship to study drug, and any action taken for the event.

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Silva 2005 United States	Small number of AE's (18) were reported. Total AE's (ER-MPH 20mg/ER-MPH 40 mg/OROS-MPH 18 mg/OROS-MPH 36 mg/placebo: 3.7%/5.6%/9.4%/11.3%/3.8% Headache: 3.7%/1.9%/1.9%/5.7%/1.9%

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Silva 2005 United States	1 post-randomization exclusion 53/54 completed study receiving all 5 treatment conditions according to protocol	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Comorbidity	Interventions and total daily dose Duration Dosing schedule

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
	12.0-hr: 65.1 (54.4)/79.5 (60.5)/80.5 (53.1)/85.7 (54.4)/53.6 (40.8) Math Test-Correct (hours postdose) 0.5-hr: 70.8 (43.1)/69.3 (48.1)/63.0 (46.3)/60.6 (42.8)/54.0 (39.1) 1.0-hr: 83.8 (50.0)/86.3 (47.4)/74.7 (48.7)/63.8 (41.0)/47.0 (35.3) 2.0-hr: 97.0 (58.9)/104.6 (54.7)/89.2 (57.6)/70.3 (48.1)/63.4 (48.6) 3.0-hr: 86.8 (57.9)/97.7 (54.0)/76.2 (44.0)/68.9 (47.3)/50.3 (37.8) 4.0-hr: 88.3 (47.8)/83.4 (47.7)/69.9 (45.3)/70.5 (43.6)/52.9 (38.3) 6.0-hr: 79.3 (49.3)/89.7 (51.2)/75.1 (48.2)/67.4 (47.0)/46.6 (38.8) 8.0-hr: 68.6 (51.0)/84.4 (53.5)/68.9 (52.8)/69.7 (50.0)/48.0 (40.8) 10.0-hr: 71.4 (52.1)/76.9 (55.9)/77.5 (53.3)/65.9 (46.8)/54.4 (47.3) 12.0-hr: 55.5 (44.8)/66.3 (45.3)/74.1 (53.2)/76.5 (53.8)/45.6 (34.8)	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria
Swanson 2004 Sonuga-Burke 2004 United States COMACS Study	RCT, DB, crossover multicenter	Children 6-12 years old with diagnoses of a DSM-IV subtype of ADHD (inattentive type, hyperactive-impulsive type, or combined type) who were being treated with methylphenidate (MPH) 10 to 60 mg/d. Children were deemed otherwise healthy by medical history, physical examination, vital sigh measurements, and by clinical laboratory assessments. Children also had to demonstrated the ability to swallow PLA study-treatment capsules whole and without difficulty.

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Comorbidity	Interventions and total daily dose Duration Dosing schedule
Swanson 2004 Sonuga-Burke 2004 United States COMACS Study	~25% had a comorbid condition, with anxiety and ODD the most frequently reported conditions	Methylphenidate extended release (Metadate CD®) vs methylphenidate extended release (Concerta®) vs placebo Dose level assigned according to preexisting MPH dose requirements: Low (≤ 20 mg): 20 mg vs 18 mg Medium (> 20 to 40 mg): 40 mg vs 36 mg High (> 40 mg): 60 mg vs 54 mg Duration 7 days

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Swanson 2004 Sonuga-Burke 2004 United States COMACS Study	No run-in or washout	NR	SKAMP Written 10-minute math test	9.6 years 73.8% male 68.9% white 11.5% black 1.7% Asian 12.4% Hispanic 5.4% other

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Swanson 2004 Sonuga-Burke 2004 United States COMACS Study	Subtype of ADHD Inattentive: 13% Hyperactive/Inattentive: 4.8% Combined: 82.1%	214 / 184 / 184	27 (14.7%) withdrawn/lost to fu NR/184 analyzed (Metadate n=174; Concerta n=181; placebo n=183)

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Swanson 2004 Sonuga-Burke 2004 United States COMACS Study	Effect sizes: Metadate CD® vs Concerta® SKAMP deportment Hours post-dose 0.0: -.23 vs -.18 1.5: 0.82 vs 0.52 3.0: 0.89 vs 0.50 4.5: 0.80 vs 0.50 6.0: 0.76 vs 0.66 7.5: 0.54 vs 0.51 12: 0.06 vs 0.25 SKAMP attention 0.0: -0.59 vs -0.58 1.5: 0.70 vs 0.41 3.0: 0.72 vs 0.48 4.5: 0.66 vs 0.42 6.0: 0.65 vs 0.64 7.5: 0.50 vs 0.53 12: 0.06 vs 0.25 PERMP - # correct math problems 0.0: -0.27 vs -0.33 1.5: 0.57 vs 0.42 3.0: 0.56 vs 0.42 4.5: 0.59 vs 0.40 6.0: 0.58 vs 0.54 7.5: 0.50 vs 0.53 12: 0.10 vs 0.28	Adverse events reported by patient, parent, or guardian were characterized by an investigator as being mild (requires minimal or no treatment), moderate (result in low level inconvenience or concern) or severe (interrupt a patient's usual daily activity and may require drug or other therapy); parent or guardian completed the Barkley Side Effect Rating Scale

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Swanson 2004	Parent ratings of side effects on the Barkley Scale: no differences (data NR)
Sonuga-Burke 2004	
United States	Metadate CD® vs Concerta® vs placebo
	Gastrointestinal disorders: 4.6% vs 6.1% vs 7.1%
COMACS Study	Abdominal pain upper: 3.4% vs 4.4% vs 3.3%
	Vomiting NOS: 0.6% vs 0.6% vs 2.2%
	Infections and infestations: 0.6% vs 2.8% vs 1.1%
	Injury, poisonings, and procedural complications: 3.4% vs 1.7% vs 2.7%
	Metabolism and nutrition disorders: 4.6% vs 6.1% vs 2.2%
	Anorexia: 2.9% vs 2.8% vs 1.1%
	Appetite decreased NOS: 1.7% vs 3.3% vs 0.5%
	Nervous system disorders: 3.4% vs 5.5% vs 5.5%
	Headache NOS: 1.7% vs 3.9% vs 3.3%
	Psychiatric disorders: 6.9% vs 7.2% vs 9.3%
	Insomnia: 1.7% vs 1.7% vs 3.3%
	Irritability: 1.7% vs 1.1% vs 2.7%

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Swanson 2004	Total withdrawals: NR	
Sonuga-Burke 2004	Withdrawals due to adverse events: 0 vs	
United States	0.5% vs 1%	
COMACS Study		

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria
Other comparisons to methylphenidate		
Barrickman 1995 United States Fair quality	RCT Crossover Single center: ADHD outpatient clinic	Diagnosis of ADHD (DSM-III-R) and be between 7 and 17 years old

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Comorbidity	Interventions and total daily dose Duration Dosing schedule
Other comparisons to methylphenidate		
Barrickman 1995 United States Fair quality	Conduct disorder = 2 (13.3%) Oppositional defiant disorder = 2 (13.3%) Developmental learning disorders = 5 (33.3%)	Bupropion 1.5 mg/kg per day in first week, 2.0 mg/kg per day in second week, then titrated to optimal dose (mean final=140 mg) and fixed for last 3 weeks Methylphenidate 0.4 mg/kg per day during the first week, then titrated to optimal dose during next 2 weeks and fixed for final 3 weeks (mean final=31 mg/day) Duration: 6 weeks, then 2-week washout, then crossover for 6 more weeks Dosing schedule: Bupropion=active second dose was added at 4 pm and an active third dose was added at noon if needed; Methylphenidate=active second dose was added at noon and a third dose was added at 4 pm if needed

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Other comparisons to methylphenidate				
Barrickman 1995 United States Fair quality	No run-in/Washout of 14 days	NR	Iowa Conners Abbreviated Parent and Teacher Questionnaire (ICQ); physician-rated Clinical Global Impression (CGI)	Mean age of 11.8 80% male 100% Caucasian

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Other comparisons to methylphenidate			
Barrickman 1995 United States Fair quality	Treatment-naïve=5 (33.3%) WISC-R Full Scale IQ score=106 WISC-R Verbal score=104 WISC-R Performance score=108	NR/NR/18	3 (16.7%) withdrawn/0 lost to fu/15 analyzed

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Other comparisons to methylphenidate		
Barrickman 1995 United States Fair quality	Bupropion vs methylphenidate ICQ change scores (between-group differences not significant unless otherwise noted) Total Teachers: -12.7 vs -14.5; Parents: -11.2 vs -15 Attention Teachers: -6.3 vs -7.6; Parents: -5.9 vs -8.5 ("significant", but no p-value provided) Conduct Teachers: -6.7 vs -7.5; Parents: -5.5 vs -6.4 CDI: -4.1 vs -3.9; R-CMAS: -9 vs -8.1 Kagen errors: -5.5 vs -7; Kagen latency: -6.3 vs -4.8 CPT omission errors: -3.1 vs -4; CPT commission errors: -5.5 vs -6.9 AVLT: -6.1 vs -8.8; CGI (week 5): -2.1 vs -2.6; p<0.05, changes from baseline to other weeks similar for both drugs	NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Other comparisons to methylphenidate	
Barrickman 1995 United States Fair quality	Bupropion vs MPH % patients with any adverse event: 9 (60%) vs 5 (33.3%); p=NS Drowsiness: 4 (26.7%) vs 1 (6.7%) Fatigue: 3 (20%) vs nr Nausea: 3 (20%) vs 1 (6.7%) Anorexia: 2 (13.3%) vs nr Dizziness: 2 (13.3%) vs nr Spaciness: 2 (13.3%) vs nr Anxiety: 1 (6.7%) vs 1 (6.7%) Headache: 1 (6.7%) vs 1 (6.7%) Tremor: 1 (6.7%) vs nr Anger/crying: nr vs 1 (6.7%) Insomnia: nr vs 1 (6.7%) Irritability: nr vs 1 (6.7%) Low mood: nr vs 1 (6.7%) Stomachache: nr vs 1 (6.7%)

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Other comparisons to methylphenidate		
Barrickman 1995 United States Fair quality	Total withdrawals: 3 (16.7%) (group assignments nr) Withdrawals due to adverse events: none reported	Significant treatment order effects were reported

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria
Conners, 1980	RCT DB, parallel. Setting:	Children aged 6-11.75 years, IQ >80 on WISC, physician diagnosed hyperkinesis due to minimal brain dysfunction, visual and auditory acuity was sufficient for normal learning process, family was stable, no obsessive, compulsive, or phobic behavior, child had normal laboratory values, no current medical illness or medical history that contraindicated prescribed drug therapy, no need for antiseizure medication, no concurrent therapy for a chronic illness, current ratings by parents and teachers indicating moderate to severe symptoms of restlessness, inattentiveness, impulsivity, emotional lability, and distractibility, and family physician or pediatrician consented to participate.
Stephens 1984 United States Poor quality	CCT Crossover Patients recruited from (1) Psychology Clinic at Florida State University and (2) Hope Haven Children's Hospital in Jacksonville, Florida	DSM-III diagnosis of attention-deficit disorder with hyperactivity

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Comorbidity	Interventions and total daily dose Duration Dosing schedule
Conners, 1980	NR	Pemoline in 18.75mg tablets was increased weekly, by 37.5mg/day, from an initial dose of 37.5mg/day to a maximum dose of 112.5mg/day. MPH in 5mg tablets was increased weekly, by 5mg/day, from an initial dose of 10mg/day to a maximum dose of 60mg/day. Placebo. Patients were stabilized on their dose between weeks 4 and 8. The trial was 10 weeks long.
Stephens 1984 United States Poor quality	NR	Medication was prescribed by each child's physician (method nr) Pemoline 1.9 mg/kg (mean=8.7 mg) Methylphenidate 0.3 mg/kg (mean=55.5 mg) Placebo Flexible dosing Eight 2-day treatment periods over three weeks

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Conners, 1980	None/8 day washout for hyperkinesis medications and 6 months for phenothiazines	None	Parent and Teacher Conner's questionnaires, Abbreviated Parent and Teacher Conner's questionnaires, Global assessment by physician (administered at baseline, weeks 2, 4, 6, 8, and 10) and parents and teachers (administered at baseline, weeks 4 and 8), psychiatric tests which include the continuous performance test (CPT), Rutter-Graham Standardized Evaluation	Age: 7.9 years (range 6-11 years) Male: 57 (95%) White: 59 (98%) African-American: 1 (2%)
Stephens 1984 United States Poor quality	NR/NR	NR	Paired-associate learning task: Child required to give particular response (numbers 1-11) to each of a list of items (pictures of animals presented on 3 x 5 cards) Spelling task: nonsense words Testing sessions administered 2 hours after pemoline and 1 hour after methylphenidate	Mean age=8.8 86.1% male Race NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Conners, 1980	NR	88/NR/60	NR/NR/60
Stephens 1984 United States Poor quality	ACRS mean score=17.9	NR/NR/31	NR/NR/NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Conners, 1980	**Pemoline vs MPH vs Placebo** CPT-- For Week 0 Total trials: N=15 vs N=15 vs N=16 For Week 0 all others: N=16 vs N=16 vs N=16; For Week 8 all categories: N=18 vs N=19 vs N=17 *Total Trials:* 3.75 (327.47-323.72) vs 8.72 (331.40-322.68) vs -0.44 (324.50-324.94) *Total signals:* 0.12 (50.12-50.00) vs 0.12 (50.12-50.00) vs 0 (50.00-50.00) *Total responses,:* -9.1 (52.12-61.22) vs -7.04 (62.38-69.42) vs 7.82 (68.88-61.06) *Correct responses:* -6.44 (27.62-34.06) vs -10.62 (28.75-39.37) vs -2.09 (30.44-32.53) *Errors of omission:* 4.36 (20.75-16.39) vs 9.36 (21.31-11.95) vs 0.97 (19.56-18.59) *Errors of commission:* 1.00 (22.44-21.44) vs 4.84 (27.31-22.47) vs 9.47 (34.00-24.53) Parent Questionnaire Factors-- For Week 0: N=19 vs N=20 vs N=21; For Week 8: N=18 vs N=20 vs N=20 *Conduct problem:* 0.37 (1.14-0.77) vs 0.52 (1.16-0.64) vs 0.17 (1.00-1.17) *Anxiety:* 0.23 (0.64-0.41) vs 0.40 (0.89-0.49) vs 0.09 (0.70-0.61) *Impulsivity:* 0.54 (1.21-0.70) vs 0.84 (1.53-0.69) vs 0.14 (1.45-1.31) *Immaturity:*0.32 (0.67-0.35) vs 0.30 (0.73-0.43) vs 0.15 (0.79-0.64) *Psychosomatic:* 0.20 (0.37-0.17) vs 0.18 (0.46-0.28) vs 0.15 (0.40-0.25) *Obsessional:* -0.18 (0.39-0.57) vs 0.20 (0.77-0.57) vs 0.07 (0.60-0.53) *Antisocial:* 0.16 (0.22-0.06) vs 0.16 (0.24-0.08) vs 0.09 (0.20-0.11) *Hyperactivity:* 0.39 (0.80-0.41) vs 0.53 (0.99-0.46) vs 0.23 (0.98-0.75) Teacher Questionnaire Factors-- For Week 0: N=19 vs N=20 vs N=21; For Week 8: N=16 vs N=19 vs N=19 *Conduct problem:* 0.58 (1.11-0.53) vs 0.61 (1.29-0.68) vs 0.11 (0.82-0.71) *Inattentive-passive:* 0.80 (1.87-1.07) vs 0.66 (1.86-1.20) vs 0.40 (1.65-1.25) *Anxiety:* 0.09 (0.65-0.56) vs 0.25 (0.96-0.71) vs 0.23 (0.81-0.58) *Hyperactivity:* 0.86 (1.90-1.04) vs 0.96 (2.24-1.28) vs 0.45 (1.90-1.45) *Sociability:*0.121 (0.53-0.41) vs 0.17 (0.88-0.71) vs -0.14 (0.76-0.90)	An ongoing record was obtained from twice-weekly phone calls to parents and physician completed a 49-item checklist of side effects on the Physician's Rating Sheet (done at weeks 4 and 8). Parents also rated their child on a 50-item checklist.
Stephens 1984 United States Poor quality	Pemoline vs methylphenidate (p=NS for all comparisons) Mean number of total errors: Paired associates learning Learning: 37.80 vs 38.64 Retention: 20.67 vs 20.58 Spelling Learning: 27.33 vs 26.19 Retention: 14.39 vs 16.42	NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Conners, 1980	Insomnia and sleep problems (N=29, 48%), anorexia and appetite problems (N=24, 40%), increased crying (N=20, 33%), stomachache (N=19, 32%), headache (N=13, 22%), and increased irritability (N=6, 10%). The following were reported by 4 (7%) subjects each: increased nervousness, nausea, dizziness, and rash. Moodiness was reported by 3 (5%) subjects. The following were reported by 2 (3%) subjects each: temper tantrums, thirsty, itching, depression, increased appetite, glassy eyed, nose bleed, and enuresis. The following were reported by 1 (2%) subject each: argumentative, sensitive to light, night terrors, stares glassily, fine tremors, dilated pupils, leg cramps, odd mannerism of mouth, bad dreams, increased sensitivity, diarrhea, palpitations, stuttering, negativism, nocturnal fears, eyes reddened, speech incoherent, eating erratic, grouchy, pains in ribs, and sluggishness.
Stephens 1984 United States Poor quality	NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Conners, 1980	NR	
Stephens 1984 United States Poor quality	NR NR	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria
Multiple Comparisons		
James 2001 United States Poor	RCT Crossover Double-blind Setting: Research school 5 days per week	DSM-IV criteria for combined-type ADHD; ADHD symptoms present in at least two settings

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Comorbidity	Interventions and total daily dose Duration Dosing schedule
Multiple Comparisons		
James 2001 United States Poor	Oppositional defiant disorder=10 (28.6%) Anxiety disorder=12 (34.3%) Enuresis=3 (8.6%) Dysthymic disorder=2 (5.7%) Learning disorder=6 (17.1%)	Adderall Dextroamphetamine, immediate release Dextroamphetamine spansules Placebo 2 weeks each Dosages were based on age, weight, prior medication experience, and symptom severity. Overall mean low dose was 7.8 mg and mean high dose was 12.8 mg. Dose order was randomized across subjects, but the same order, either increasing (n=18) or decreasing (n=17) was used for a given subject. The last 11 subjects received equal doses of both immediate-release formulations, but received increased dextroamphetamine spansules by 5 mg to more closely approximate clinical use patterns.

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Multiple Comparisons				
James 2001 United States Poor	Run-in NR/3-week washout	NR	Hyperactive/Impulsive factor of the Conners Teacher Rating Scale: teacher Hyperactivity factor of the Children's Psychiatric Rating Scale: recreation therapist scored weekly Academic measures: 5-minute timed math task Conners Parent Behavior Rating Scale for the hours 4 pm to 7 pm Actometer to assess motor activity	Mean age=9.1 60% male 18 (51.4%) White 9 (25.7%) African Americans 7 (20%) Latinos 1 (2.8%) Asian Americans

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Multiple Comparisons			
James 2001 United States Poor	15 (42.8%) naïve to stimulant treatment WISC-III Verbal standard score=102.5 Performance standard score=96.6 Full scale standard score=99.8 CBCL Attention Problems T score=72.5 TRF Attention Problems T score=72.3	NR/38 enrolled/35 randomized	0/0/35

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Multiple Comparisons		
James 2001 United States Poor	Adderall vs dextroamphetamine spansules vs immediate release dextroamphetamine vs placebo; differences are insignificant unless otherwise noted CTRS Hyperactivity T score obtained from 9 AM to 12:30 PM: 50.6 vs 53.7 vs 50.5 vs 63.1; DEX IR > DEX span, p<0.025 CPRS Hyperactivity factor score obtained between 1 PM and 3 PM: 2.8 vs 2.3 vs 2.5 vs 3.8; DEX span > ADL, p=0.04 CPS Hyperactivity T score obtained between 4 PM and 7 PM (only available for n=15): 58.6 vs 60.0 vs 60.5 vs 68.0; Dex span > placebo (p=0.007), ADL > placebo (p=0.03), DEX IR = placebo Total attempted math problems: 171.6 vs 187.0 vs 177.4; DEX IR > placebo (p=0.01), DEX span > placebo (p=0.003), ADL = placebo Total correct math problems: 164.6 vs 177.6 vs 167.6 vs 140.2; DEX IR > placebo (p=0.01), DEX span > placebo (p=0.003), ADL=placebo Sleep (hr): 7.6 vs 7.2 vs 7.4 vs 7.8; DEX span and DEX IR decreased sleep > placebo (p<0.001 and p=0.02), ADL=placebo	Stimulant Side Effect Rating Scale: rated by nurse coordinator Barkley Side Effect Rating Scale: rated by parents

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Multiple Comparisons	
James	SERS N#: 3.3 vs 2.9 vs 2.6 vs 2.0
2001	SERS-N sev: 2.7 vs 3.1 vs 2.7 vs 1.8
United States	SERS-P#: 6.3 vs 6.7 vs 6.4 vs 5.9
	SERS-P sev: 3.2 3.7 vs 3.2 vs 2.8
Poor	Weight (kg): 32.6 vs 32.5 vs 32.7 vs 33.3
	Mean magnitude of adverse effects rated by parents (n=20); staff nurse (n=29) for adderall, immediate-release dextroamphetamine, dextroamphetamine spansules and placebo, uncorrected p-values from ANOVA
	Trouble sleeping: 3.5 vs 3.0 vs 3.3 vs 2.5, p=0.55; nurses didn't rate
	Nightmares: 0.6 vs 0.6 vs 0.3 vs 0.3, p=0.24
	Stomach aches: 1.0 vs 0.9 vs 1.1 vs 1.0, p=0.97; 0.5 vs 0.5 vs 0.8 vs 0.4, p=0.59
	Headaches: 0.9 vs 0.8 vs 0.7 vs 1.0, p=0.89; 0.1 vs 0.2 vs 0.2 vs 0.1; p=0.41
	Tics: 0.8 vs 1.2 vs 1.4 vs 0.9; p=0.16; 0.4 vs 0.3 vs 0.3 vs 0.2, p=0.34

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Multiple Comparisons		
James 2001 United States Poor	0 withdrawals; 0 withdrawals due to adverse events	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria
Pelham 1990 Poor	RCT Crossover 1988 Western Psychiatric Institute and Clinic Attention Deficit Disorder Program's Summer Treatment Program	Diagnosis of ADHD based on structured parental interview and parent and teacher rating scales (not specified)
Atomoxetine		
Amiri 2008 Iran	RCT, DB Parallel Outpatient child and adolescent clinic	Patients were 6-15 years old who met the DSM-IV-TR diagnostic criteria for ADHD. They had total and/or subscale scores on ADHD-RS-IV, school version at least 1.5 SD above norms for patient's age and gender. Patients were excluded if they had a history or current diagnosis of pervasive developmental disorders, schizophrenia or other psychiatric disorders; any current psychiatric comorbidity that required pharmacotherapy; any evidence of suicide risk and mental retardation; they had a clinically significant chronic medical condition, including organic brain disorder, seizures and current abuse or dependence on drugs within 6 months; hypertension, hypotension and habitual consumption of more than 250mg/day of caffeine.

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Comorbidity	Interventions and total daily dose Duration Dosing schedule
Pelham 1990 Poor	Oppositional/defiant disorder = 9 (40.9%) Conduct Disorder = 4 (18.2%) Discrepancy between their Wechsler Intelligence Scale for Children-Revised IQ and their Woodcock-Johnson Achievement scores of at least one full standard deviation in either reading, arithmetic, or written language, suggesting the presence of a learning disability = 13 (59.1%)	Methylphenidate IR 20 mg (dosed twice daily) Sustained release methylphenidate 20 mg (dosed once daily) Pemoline 56.25 mg (dosed once daily) Sustained release dextroamphetamine (Dexedrine spansule) 10 mg (dosed once daily) All conditions accompanied by "behavior modification intervention" as the "primary treatment modality" 8 weeks total, data collected for 3 to 6 days for each condition Dosage time NR
Atomoxetine		
Amiri 2008 Iran	NR (excluded most comorbidities)	Modafinil Dependant on weight: 200mg/day for <30 kg and 300mg/day for >30 kg Methylphenidate Dependant on weight: 20mg/day for <30 kg and 30mg/day for >30 kg

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Pelham 1990 Poor	NR/NR	NR	Daily Frequencies=frequencies with which numerous appropriate and inappropriate behaviors occurred daily Classroom measures=rates of on-task behavior and rule-following behavior; 2-minute, timed arithmetic drill, 10-minute, timed reading task (number attempted and percentage correct) Rating scales: Teacher ratings on ACTRS; counselor ratings on Revised Behavior Problems Checklist (35 items rated on a 7-point scale with lower ratings equaling positive evaluations) Daily Report Card=Percentage of days that the child reached daily report criterion Continuous Performance Task="H" followed by letter "T"	Mean age=10.39 100% male Race NR
Atomoxetine				
Amiri 2008 Iran	None	NR	Primary Outcome Measure: Parent and Teacher ADHD Rating Scale-IV, assessed at baseline, and 21 and 42 days after medication started Other measures: self-report of adverse events using checklist at days 7, 21, and 42; hematology tests were collected at baseline and weeks 2, 4 and 6; serum chemistry and UA were evaluated at baseline and week 6; body weight and vital signs were measured at baseline and weeks 1, 2, 4, and 6; and 12-lead EEG and physical exams were evaluated at baseline and week 6.	Mean age: 9.2 years (Modafinil) vs 8.96 years (Methylphenidate) 78.3% male 100% Persian

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Pelham 1990 Poor	WISC-R IQ=105.68 ACRS - Parent/Teacher: 15.50/19.32 IOWS CTRS Inattention/Overactivity=9.59 Aggression=5.86 DSM-II-R Structured Interview for Parents Attention deficit disorder items=11.36 Oppositional/defiant disorder items=5.36 Conduct disorder items=1.68 Woodcock-Johnson Achievement Test Reading=96.45 Mathematics=99.82 Language=99.00	NR/NR/22	NR/NR/NR
Atomoxetine			
Amiri 2008 Iran	NR	NR/NR/60	5 withdrew: 2 from modafinil group vs 3 from methylphenidate group Lost to FU=NR Analyzed=60

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Pelham 1990 Poor	Placebo vs Methylphenidate vs sustained release methylphenidate vs pemoline vs sustained release dextroamphetamine, ALL results significant compared to PLACEBO unless otherwise noted (p=NS): Daily frequency measures: % following activity rules: 75.2 vs 80.9 vs 78.1 vs 79.0 vs 81.0 Noncompliance: 5.5 vs 2.3 vs 2.3 vs 2.0 vs 1.7 Positive peer interactions: 82.8 vs 92.6 (p=NS) vs 104.5 vs 111.1 vs 100.0 Conduct problems: 0.73 vs 0.25 (p=NS) vs 0.18 vs 0.18 vs 0.21 Negative verbalizations: 5.4 vs 1.6 vs 2.0 (p=NS) vs 1.6 vs 1.4 Classroom measures: % following rules: 85 vs 92 (p=NS) vs 94 vs 95 vs 95 Timed reading # attempted: 14.3 vs 18 vs 16.4 vs 15.7 vs 17.5 % correct: 69 vs 73 vs 73 vs 75 vs 74 Seatwork % completed: 70 vs 78 vs 77 vs 79 (p=NS) vs 76 % correct: 84 vs 84 vs 87 (p=NS) vs 87 vs 86 Teacher rating (ACTRS): 3.8 vs 2.3 vs 2.3 vs 1.5 vs 1.7 Counselor rating (ACTRS): 6.3 vs 4.8 vs 5.0 vs 5.1 vs 4.5 Positive daily report (% days rec'd): 51 vs 63 (p=NS) vs 64 vs 71 vs 67	NR
Atomoxetine		
Amiri 2008 Iran	Modafinil vs Methylphenidate Change in Parent ADHD-RS-IV from baseline at day 42: -24.36 vs -22.66 % of responders based on Parent ADHD-RS-IV: 73.33% vs 70% Change in Teacher ADHD-RS-IV from baseline at day 42: -20.53 vs -21.33 % of responders based on Teacher ADHD-RS-IV: 73.33% vs 73.33%	Checklist comprised of 20 side effects, patients self-reported results

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Pelham	Placebo vs Methylphenidate vs sustained release methylphenidate vs pemoline
1990	vs sustained release dextroamphetamine, measures of significance NR:
	Teacher ratings
Poor	Withdrawn: 0 vs 10.0 vs 0 vs 0 vs 13.6
	Dull, not alert: 4.5 vs 14.3 vs 4.3 vs 0 vs 9.0
	Stomachaches, nausea: 13.6 vs 14.3 vs 9.1 vs 10.0 vs 22.7
	Headaches: 9.1 vs 0 vs 0 vs 0 vs 22.7
	Loss of appetite: 45.0 vs 61.9 vs 76.2 vs 75 vs 77.3
	Eye/Muscle twitches: 4.5 vs 4.8 vs 9.1 vs 4.89 vs 4.5
	Repetitive tongue movements: 9.1 vs 4.8 vs 0 vs 5.0 vs 4.5
	Picking: 0 vs 0 vs 0 vs 0 vs 4.5
	Parent ratings
	Difficulty falling asleep: 5.3 vs 5.9 vs 18.8 vs 42.1 vs 20.0
	Awake during the night: 5.3 vs 12.5 vs 13.3 vs 11.1 vs 14.3
Atomoxetine	
Amiri	Modafinil vs Methylphenidate
2008	Abdominal pain: 4 vs 7
Iran	Anxiety, nervousness: 3 vs 4
	Decreased appetite: 18 vs 26 (p=0.03)
	Sadness: 4 vs 6
	Difficulty falling asleep: 2 vs 8 (p=0.05)
	Weight loss: 3 vs 7
	Nausea: 2 vs 4
	Dry mouth: 7 vs 10
	Irritability: 4 vs 6
	Headaches: 4 vs 7

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Pelham 1990	NR NR	
Poor		
Atomoxetine		
Amiri 2008 Iran	5 withdrew: 2 from modafinil group and 3 from methylphenidate group Withdrawals due to AEs: NR	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria
Biederman 2006 StART substudy (Wigal 2005)	See Wigal 2005	Subgroup of girls from Wigal 2005. See for eligibility criteria
Biederman 2007 United States	RCT, DB Crossover Multicenter	Children 6-12 years old with DSM-IV-TR diagnosis of combined or predominantly hyperactive-impulsive subtype of ADHD. History of treatment with a stable regiment of stimulant medication, ability to follow classroom instructions, and functioning at age-appropriate academic levels

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Comorbidity	Interventions and total daily dose Duration Dosing schedule
Biederman 2006 StART substudy (Wigal 2005)	N/A	See Wigal 2005
Biederman 2007 United States	NR, though most comorbidities excluded	Lisdexamfetamine dimesylate (LDX) Mixed amphetamine salts extended-release (MAS XR) - reference arm Initial dose: 10mg/day

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Biederman 2006 StART substudy (Wigal 2005)	See Wigal 2005	See Wigal 2005	See Wigal 2005	Mean age=8.7 years Subgroup of 100% girls 59.1% white 22.8% black 17.5% Hispanic 1.8% Asian/pacific islander 8.8% other
Biederman 2007 United States	NR/3 day washout - Adderall titration	NR	Primary Outcome Measure: Least squares (LS) mean of the average scores from the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) Deportment Rating Scale across a treatment day Other measures: SKAMP-Attention Rating Scale, Permanent Product Measure of Performance-Attempted (PERMP-A) and Correct Scores (PERMP-C), and Clinical Global Impressions (CGI) Scale scores	Mean age: 9.1 years 63.5% male 55.8% White 23.1% Black 15.4% Hispanic 5.8% other

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Biederman 2006 StART substudy (Wigal 2005)	Mean weight (lb): 71.98 ADHD subtype Hyperactive/impulsive: 0% Combined: 100%	NR/NR/57	NR/NR/57
Biederman 2007 United States	100% ADHD-combined subtype Mean age of ADHD onset: 5.8 years Mean time since diagnosis: 3.3 years Prior treatment Amphetamine: 44.2% Methylphenidate: 26.9% Stimulant NOS: 11.5% Stimulants with Atomoxetine: 9.6% Other: 1.9% Not listed: 5.8%	NR/NR/52	2 withdrew 1 was lost to follow-up 50 analyzed

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Biederman 2006 StART substudy (Wigal 2005)	MAS XR vs atomoxetine SKAMP scale mean changes Deportment: -0.48 vs -0.04; p<0.001 Attention: -0.45 vs -0.05; p<0.001 Math problems (mean number) Attempted: 135.27 vs 119.72; p<0.04 Completed correctly: 94.4% vs 96%; NS	See Wigal 2005
Biederman 2007 United States	**LS Mean SKAMP-DS scores at endpoint** LDX: 0.8 vs Placebo: 1.7 (p<0.0001) MAS XR: 0.8 vs Placebo: 1.7 (p<0.0001) **LS Mean SKAMP-AS scores at endpoint** LDX: 1.2 vs Placebo: 1.8 (p<0.0001) MAS XR: 1.2 vs Placebo: 1.8 (p<0.0001) **LS Means PERMP-A scores** LDX: 133.3 vs Placebo: 88.2 (p<0.0001) MAS XR: 133.6 vs Placebo: 88.2 (p<0.0001) **LS Means PERMP-C scores** LDX: 129.6 vs Placebo: 84.1 (p<0.0001) MAS XR: 129.4 vs Placebo: 84.1 (p<0.0001) **CGI-I scale at endpoint** LDX: 2.2 vs Placebo: 4.2 (p<0.0001) MAS XR: 2.3 vs Placebo: 4.2 (p<0.0001)	Spontaneous report and labs

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Biederman 2006 StART substudy (Wigal 2005)	MAS XR vs atomoxetine (p-values NR) Appetite decrease: 40.7% vs 12.5% Upper abdominal pain: 29.6% vs 15.6% Insomnia: 25.9% vs 3.1% Headache: 14.8% vs 9.4% Weight decrease: 7.4% vs 0 Anorexia: 7.4% vs 6.3% Nausea: 3.7% vs 12.5% Vomiting: 3.7% vs 15.6% Somnolence: 3.7% vs 28.1% Fatigue: 0 vs 6.3% Any adverse event: 78% vs 66%
Biederman 2007 United States	AEs occurring at an incidence of ≥ 2% during the double-blind period were: **LDX** Insomnia: 8% Decreased appetite: 6% Anorexia: 4% Upper respiratory infection: 2% **MAS XR** Decreased appetite: 4% Upper abdominal pain: 4% Upper respiratory infection: 2% Vomiting: 2% Insomnia: 2% **Placebo** Vomiting: 4% Insomnia: 2% Upper abdominal pain: 2%

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Biederman 2006 StART substudy (Wigal 2005)	Overall withdrawals: NR AE withdrawals: 7% vs 3%	
Biederman 2007 United States	2 withdrew 1 withdrew due to viral gastroenteritis	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria
Findling 2008 United States	RCT, DB Parallel Multicenter	Patients were aged 6-12 years, who were diagnosed with ADHD according to the DSM-IV-TR. Participants had a Kaufman Brief Intelligence Test IQ score of ≥80, a total score of ≥26 on the ADHD-RS-IV while unmedicated, and normal lab parameters and vital signs. Patients were excluded if they had any comorbid psychiatric diagnosis; a history of seizures during the last 2 years; a tic disorder; or any concurrent illness or skin disorder that might compromise safety or the study assessments.
Kemner 2005 United States Poor FOCUS	Open-label Parallel Multicenter Outpatient	Children 6 to 12 years of age; meet criteria for a primary diagnosis of ADHD (any subtype) according to the DSM-IV-TR; investigator-rated ADHD-RS score of at least 24 and a Clinical Global Impression-Severity of Illness scale (CGI-S) score of at least 4 ("moderately ill" or worse)

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Comorbidity	Interventions and total daily dose Duration Dosing schedule
Findling 2008 United States	NR (excluded most comorbidities)	Methylphenidate Transdermal System (MTS) Initial dose: 10mg/9 hour (range: 10-30mg) Methylphenidate Oral System (MOS) Initial dose: 18mg (range: 18-54mg) Placebo
Kemner 2005 United States Poor FOCUS	NR	Mean dosages for weeks 1/2/3: Atomoxetine: 32.1 mg/36.8 mg/36.7 mg OROS MPH: 26.8 mg/32.7 mg/32.7 mg (Investigators were allowed to select starting doses and adjust dosages as deemed necessary) Duration: 3 weeks

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Findling 2008 United States	30 day washout of clonidine, atomoxetine, antidepressants, antihypertensives, investigational medications, hepatic or cytochrome P450 enzyme altering agents, medications with CNS effects, sedatives, antipsychotics, or anxiolytics	NR	Primary Outcome Measure: ADHD-RS-IV total score at endpoint, assessed at baseline and at each study visit. Other measures: Conners' Teacher Rating Scale-Revised: Short Form (CTRS-R), assessed on 2 days each week, at least 48 hours apart, throughout the study. Global impressions of ADHD severity and improvement by clinicians and parents throughout the study included the Conners' Parent Rating Scale-Revised: Short Form (CPRS-R), Clinical Global Impressions-Severity of Illness and Improvement Scales (CGI-S and CGI-I), and the Parent Global Assessment (PGA).	Mean age: 8.8 years 66.3% males 77.3% Caucasian 14.5% African American 0.7% Asian 7.5% other
Kemner 2005 United States Poor FOCUS	NR/Wash-out: 3 days or 5 half-lives	NR	Primary measure: Mean change from baseline in investigator-rated ADHD RS Secondary measures: ADHD-RS and CGI-I scores assessed at weeks 1 and 2; proportion of treatment responders at each evaluation point, defined as those patients who achieved a 25% or greater reduction from baseline ADHD-RS score, as well as those receiving an investigator-rated CGI-I score of 2 or less ("much improved" or "very much improved"); treatment response further evaluated on basis of ADHD-RS baseline score reductions of 30% or greater, 50% or greater, and 70% or greater; parent ratings of a nonvalidated, newly developed diary, the Parental Satisfaction Questionnaire (PSQ) (9 statements regarding the patient's behavior, each rated by parents on a 5-point scale ranging from 1=strongly agree to 5=strongly disagree; maximum score=45)	Mean age=8.9 years 74% male 76.74 white

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Findling 2008 United States	ADHD Subtype Combined: 227 (80.5%) Inattentive: 48 (17.0%) Hyperactive/impulsive: 4 (1.4%) Unclassified: 3 (1.1%)	NR/NR/282	113 withdrew total; 8 after randomization but prior to receiving medication; 27 in MTS group vs 25 in MOS group vs 53 in Placebo group 4 lost to follow-up 274 analyzed
Kemner 2005 United States Poor FOCUS	ADHD subtype Combined: 72% Hyperactive-impulsive: 15% Inattentive: 13% ADHD RS-Investigator-scored (mean): 39.3	NR/NR/1323	NR/NR/NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Findling 2008 United States	ADHD-RS-IV Total Score (MTS vs MOS vs Placebo) Baseline: 43.0 vs 43.8 vs 41.9 Endpoint: 18.8 vs 21.8 vs 32.1 (p<0.0001 for both interventions vs placebo, no difference between treatment groups) CTRS-R Total Score (MTS vs MOS vs Placebo) Baseline: 34.9 vs 34.9 vs 39.1 Endpoint: 19.4 vs 18.3 vs 31.6 (p<0.0001 for both interventions vs placebo, no difference between treatment groups) CPRS-R at 11am Total Score (MTS vs MOS vs Placebo) Baseline: 52.6 vs 51.2 vs 49.6 Endpoint: 24.6 vs 28.4 vs 37.0 (p=0.0001 for MTS vs Placebo and p=0.0032 for MOS vs Placebo, no difference between treatment groups) CPRS-R at 3pm Total Score (MTS vs MOS vs Placebo) Baseline: 53.7 vs 51.4 vs 49.8 Endpoint: 24.1 vs 29.1 vs 37.7 (p=0.0001 for MTS vs Placebo and p=0.0288 for MOS vs Placebo, no difference between treatment groups)	Mostly spontaneous self-report by patients. Lab results were used as well as the Children's sleep habits questionnaire (CSHQ)
Kemner 2005 United States Poor FOCUS	OROS MPH vs atomoxetine: ADHD RS Total score (mean change in points): -20.24 vs -16; mean difference=4.24 (p<0.001) ADHD-RS responder rates (% pts with 25% or greater reduction in ADHD-RS): 80.2% vs 68.7%; p<0.001 CGI-I responder rates (% pts with scores of 2 or lower): 68.6% vs 52.8%; p<0.001 PSQ mean reductions (points): -9.1 vs -8.7; p<0.001	Spontaneous patient reports and/or parents; identification by investigators during scheduled study visits

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Findling 2008 United States	Most frequently reported AEs (MTS vs MOS vs Placebo) Decreased appetite: 25 vs 17 vs 4 Insomnia: 13 vs 7 vs 4 Nausea: 12 vs 7 vs 2 Vomiting: 10 vs 9 vs 4 Weight decreased: 9 vs 7 vs 0 Tic: 7 vs 1 vs 0 Affect lability: 6 vs 3 vs 0 Nasal congestion: 6 vs 3 vs 1 Anorexia: 5 vs 3 vs 1 Nasopharyngitis: 5 vs 4 vs 2	113 withdrew total; 8 after randomization but prior to receiving medication; 27 in MTS group vs 25 in MOS group vs 53 in Placebo group Withdrawals due to AEs: MTS=7 vs MOS=2 vs Placebo=1	
Kemner 2005 United States Poor FOCUS	OROS MPH vs atomoxetine (%) - NS unless otherwise noted: Overall AE incidence: 26.3% vs 28.3% Serious AEs (resulting in prolonged inpatient hospitalization, significant disability or incapacity, onset of life-threatening conditions: 0.8% vs 0.2% Abdominal pain: 0.4 vs 1.1 Abdominal pain, upper: 3.5 vs 4.2 Abnormal behavior: 1.4 vs 1.5 Aggression: 1.2 vs 0.6 Crying: 1.5 vs 0.4 Decreased appetite*: 5.8 vs 3.0 Dizziness: 0.8 vs 1.5 Emotional disturbance: 0.6 vs 1.1 Fatigue*: 0.4 vs 3.0 Headache: 3.9 vs 4.2 Initial insomnia: 1.1 vs 0.2 Insomnia: 6.2 vs 2.3 Irritability: 0.8 vs 1.5 Mood alteration: 1.2 vs 1.3 Nausea*: 1.1 vs 4.9 Somnolence*: 0.9 vs 4.2 Vomiting: 1.3 vs 2.1 *=difference noted in text, but p-value NR	Withdrawals due to adverse events: 4.8% vs 5.5%, p-value NR Overall withdrawals NR	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria
Kratochvil 2002 United States/Canada Fair	Open-label Parallel Multicenter Outpatient	Boys aged 7 to 15 years and girls aged 7 to 9 years who met DSM-IV diagnostic criteria for ADHD. Diagnosis was confirmed by clinical interview and by structured interview with the Schedule for Affective Disorders and Schizophrenia for School-Age Children ADHD module. All patients had a severity score of at least 1.5 standard deviations above age and gender norms on the ADHD-IV Rating Scale-Parent Version: Investigator Administered (ADHD RS)

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Comorbidity	Interventions and total daily dose Duration Dosing schedule
Kratochvil 2002 United States/Canada Fair	Oppositional/defiant disorder = 52.6% Major depressive disorder = 6.6% Elimination disorder = 16.7%	Atomoxetine CYP 2D6 extensive metabolizers: titrated to a maximum of 2 mg/kg per day and administered as a divided dose in the morning and late afternoon (mean=1.40 mg/kg per day) CYP 2D6 poor metabolizers: Initiated at 0.2 mg/kg per day and titrated to 1.0 mg/kg per day (mean=0.48 mg/kg per day) Methylphenidate: Beginning at 5 mg from one to three times daily with an ascending dose titration based on the investigators assessment of clinical response/tolerability; maximum dose of 60 mg (mean dose=0.85 mg/kg per day) 10 weeks

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Kratochvil 2002 United States/Canada Fair	NR/NR	NR	Primary measure: Investigator-rated ADHD RS Secondary measures: Parent-rated version of the ADHD RS; Conners Parent Rating Scale-Revised: Short Form (CPRS-R); Clinical Global Impression-ADHD-Severity scale	Mean age=10.4 92.5% male 76.7% white

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Kratochvil 2002 United States/Canada Fair	ADHD subtype Combined: 75.9% Hyperactive-impulsive: 1.3% Inattentive: 22.8% ADHD RS-Parent scored (mean): 76.7	319/NR/228	85 (37.3%) withdrawn/5 (2.2%) lost to fu/218 analyzed (atomoxetine n=178; methylphenidate n=40)

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Kratochvil	Atomoxetine vs methylphenidate (mean changes) (p=NS for all)	Administration of open-ended questions and
2002	ADHD RS Total score: -19.44 vs -17.78	collection of ECG and laboratory data
United States/Canada	ADHD RS Hyperactivity/Impulsivity: -9.50 vs -8.48	
	ADHD RS Inattention subscale: -9.94 vs -9.30	
Fair	CGI-ADHD-Severity score: -1.67 vs -1.70	
	CPRS-R ADHD Index: -11.36 vs -11.97	
	CPRS-R Cognitive: -6.17 vs -5.69	
	CPRS-R Hyperactive: -5.56 vs -4.78	
	ADHD RS-Parent Total T score: -18.83 vs -18.38	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Kratochvil 2002 United States/Canada Fair	Atomoxetine vs methylphenidate; p=NS unless otherwise noted Headache: 57 (31%) vs 13 (32.5%) Abdominal pain: 43 (23.4%) vs 7 (17.5%) Anorexia: 35 (19%) vs 6 (15%) Rhinitis: 33 (17.9%) vs 8 (20%) Nervousness: 29 (15.8%) vs 4 (10%) Vomiting: 22 (12%) vs 0, p=0.017 Fever: 20 (10.9%) vs 4 (10%) Somnolence: 20 (10.9%) vs 0, p=0.029 Nausea: 19 (10.3%) vs 2 (5%) Insomnia: 17 (9.2%) vs 7 (17.5%) Asthenia: 14 (7.6%) vs 1 (2.5%) Diarrhea: 13 (7.1%) vs 1 (2.5%) Emotional lability: 11 (6%) vs 2 (5%) Pharyngitis: 11 (6%) vs 3 (7.5%) Tachycardia: 11 (6%) vs 2 (5%) Accidental Injury: 10 (5.4%) vs 5 (12.5%) Cough increased: 10 (5.4%) vs 2 (5%) Dyspepsia: 10 (5.4%) vs 2 (5.0%) Pain: 10 (5.4%) vs 1 (2.5%) Flu syndrome: 9 (4.9%) vs 4 (10%) Infection: 8 (4.3%) vs 3 (7.5%) Rash: 7 (3.8%) vs 3 (7.5%) Depression: 5 (2.7%) vs 2 (5%) Weight loss: 5 (2.7%) vs 2 (5%) Hyperkinesia: 3 (1.6%) vs 2 (5%) Palpitation: 3 (1.6%) vs 2 (5%) Thinking abnormal: 0 vs 2 (5%); p=0.031	Total withdrawals: 66 (35.9%) vs 19 (43.2%); p=NS Withdrawals due to adverse events: 10 (5.4%) vs 5 (11.4%); p=NS	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria
Muniz 2008 United States	RCT, DB 5-period crossover Multicenter	Patients were 6-12 years with ADHD according to the DSM-IV-TR, who had been stabilized on a total daily dose or the nearest equivalent dose of 40 to 60 mg of *d,l*-MPH or 20 to 30 mg *d*-MPH for at least 2 weeks prior to screening. Children were excluded if they had a tic disorder or Tourette's syndrome, history of seizures, psychiatric illness or substance abuse disorder, taking prohibited concomitant medications or ADHD medication other than methylphenidate, taking antidepressant or psychotropic medications, had begun psychotherapy within 3 months prior to randomization or who were home schooled.

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Comorbidity	Interventions and total daily dose Duration Dosing schedule
Muniz	NR	*d*-MPH-ER 20-30mg/day
2008		*d,l*-MPH-ER 36-54mg/day
United States		Placebo

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Muniz 2008 United States	6 days of washout of their regular ADHD medication	NR	Primary Outcome Measure: change from pre-dose Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) Rating Scale-Combined score at 2 hours post-dose Other measures: change from pre-dose in SKAMP-Combined scores and -Attention and -Deportment subscores at specified intervals post-dose (0.5, 1, 2, 3, 4, 6, 8, 10, 11, and 12 hours). Academic productivity was assessed using math tests developed by Swanson, number of questions attempted and number of questions answered correctly was assessed during the practice visit and each subsequent classroom assessment at specified intervals (0.5, 1, 2, 3, 4, 6, 8, 10, 11, and 12 hours). Conners' Parent Rating Scale (CPRS) was completed by parents on the practice day and at each subsequent assessment day.	Mean age: 9.5 years 65.5% male 42.9% Caucasian 27.4% Black 28.6% Hispanic 1.2% other

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Muniz	DSM-IV ADHD diagnosis	NR/NR/84	3 withdrew
2008	Inattentive type: 9 (10.7%)		
United States	Combined type: 75 (89.3%)		0 lost to fu
			84 analyzed

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Muniz 2008 United States	d-MPH 20mg/day vs d,l-MPH 36mg/day; d-MPH 30mg/day vs d,l-MPH 54mg/day SKAMP-Combined score change from pre-dose to 2-hours post-dose -10.65 vs -5.94 (p<0.001); -11.17 vs -7.52 (p=0.001) d-MPH 20mg vs Placebo: p<0.05; d-MPH 30mg vs Placebo: p<0.001 d,l-MPH 36mg and d,l-MPH 54 mg vs Placebo: p<0.001 SKAMP-Attention score change from pre-dose d-MPH 20mg/day vs d,l-MPH 36mg/day: p<0.001 at 1 and 3 hours; p<0.05 at 2 and 6 hours d,l-MPH 36 mg/day vs d-MPH 20mg/day: p<0.05 at 10 hours; p<0.001 at 11 and 12 hours d-MPH 30mg/day vs d,l-MPH 54mg/day:p<0.001at 1 and 3 hours; p<0.05 at 2, 4, and 6 hours d,l-MPH 54mg/day vs d-MPH 30mg/day: p<0.05 at 11 and 12 hours SKAMP-Deportment score change from pre-dose d-MPH 20mg/day vs d,l-MPH 36mg/day: p<0.001 at 1, 2, 3, and 4 hours d,l-MPH 36mg/day vs d-MPH 20mg/day: p<0.1 at 10, 11 and 12 hours d-MPH 30mg/day vs d,l-MPH 54mg/day: p=0.019 at 0.5 hours; p<0.001 at 1 and 2 hours; p<0.05 at 3 and 4 hours d,l-MPH 54mg/day vs d-MPH 30mg/day: p<0.05 at 11 and 12 hours Change in number of attempted math problems d-MPH 20mg/day vs d,l-MPH 36mg/day: p<0.05 at 1 and 3 hours d,l-MPH 36mg/day vs d-MPH 20mg/day: p=0.01 at 11 hours; p=0.001 at 12 hours d-MPH 30mg/day vs d,l-MPH 54mg/day: p<0.05 at 1, 3, and 4 hours Change in number of accurate math problems d-MPH 20mg/day vs d,l-MPH 36mg/day: p<0.05 at 1, 2, and 3 hours d,l-MPH 36mg/day vs d-MPH 20mg/day: p<0.05 at 11 and 12 hours d-MPH 30mg/day vs d,l-MPH 54mg/day: p<0.05 at 1, 2, 3, and 4 hours d,l-MPH 54mg/day vs d-MPH 30mg/day: p<0.05 at 11 and 12 hours	Self-report by patients and lab tests

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Muniz 2008 United States	*d*-MPH 20mg/day vs *d*-MPH 30mg/day vs *d,l*-MPH 54mg/day vs *d,l*-MPH 36mg/day vs Placebo Total: 8 vs 15 vs 5 vs 12 vs 3 Headache: 4 vs 6 vs 2 vs 5 vs 0 Nausea: 1 vs 1 vs 1 vs 0 vs 0 Nasal congestion: 1 vs 1 vs 0 vs 1 vs 0 Decreased appetite: 0 vs 1 vs 1 vs 1 vs 0 Vomiting: 0 vs 1 vs 1 vs 0 vs 0 Skin laceration: 0 vs 1 vs 0 vs 1 vs 0 Somnolence: 1 vs 1 vs 0 vs 0 vs 0 Insomnia: 0 vs 1 vs 0 vs 1 vs 0 Abdominal pain upper: 1 vs 1 vs 0 vs 0 vs 0 Abdominal pain: 0 vs 1 vs 0 vs 1 vs 0	3 withdrew consent, none withdrew due to AEs	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria
Newcorn 2008 United States	RCT, DB Parallel, followed by a crossover design 20 sites in the US	Patients aged 6-16 years, who met DSM-IV criteria for ADHD, any subtype, symptom severity was ≥1.5 SD above the US age and gender norms as assessed by the ADHD-RS-IV - Parent version. Patients were excluded if they had seizures, bipolar disorder, a psychotic illness, or a pervasive development disorder or who were taking concomitant psychoactive medications; and those with anxiety and tic disorders.

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Comorbidity	Interventions and total daily dose Duration Dosing schedule
Newcorn 2008 United States	Oppositional defiant disorder: 37% Major depressive disorder: 0% General anxiety disorder: 0%	Atomoxetine 0.8-1.8 mg/kg per day (administered as divided twice-daily dose) - mean final dose was 1.45 mg/kg per day or 53mg/day Osmotically released methylphenidate 18-54 mg/day (administered as a single morning dose) - mean final dose was 39.9 mg/day or 1.16 mg/kg per day for patients <12 years and 41.7 mg/day or 0.88 mg/kg per day for patients ≥12 years Placebo

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Newcorn 2008 United States	Discontinue any psychoactive medication for at least five times the medication's plasma half-life (or at least 5 days) before entering the study	NR	Primary Outcome Measure: ADHD-RS-IV total score at endpoint. Other measures: CGI ADHD severity scare, Conners Parent Rating Scale ADHD index, Daily Parent Ratings of Evening and Morning Behavior - Revised, and the Child Health Questionnaire	Mean age: Atomoxetine=10.3 years; Methylphenidate=10.2 ; Placebo=10.1 74.2% male Ethnicity: NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Newcorn 2008 United States	ADHD Subtype Hyperactive/impulsive: 2% Inattentive: 28% Combined: 70%	635/516/516	93 withdrew from acute phase; 42 withdrew from crossover phase 16 lost to follow up from acute phase; no lost to follow up in crossover phase 516 analyzed in acute phase; 178 analyzed in crossover phase

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Newcorn 2008 United States	Atomoxetine vs methylphenidate vs placebo (mean change) ADHD-RS total score: -14.4 vs -16.9 vs -7.3 (p=0.003 for Atomoxetine vs Placebo; p≤0.001 for methylphenidate vs Placebo; p=0.02 for Atomoxetine vs methylphenidate) ADHD-RS total score for prior stimulant users: -12.4 vs -15.1 vs -6.2 (p=0.02 for methylphenidate vs placebo; p=0.03 for methylphenidate vs atomoxetine) ADHD-RS total score for those naïve to stimulants: -17.9 vs -19.7 vs -9.0 (p=0.004 for atomoxetine vs placebo; p≤0.001 for methylphenidate vs placebo) ADHD-RS inattentive subscale: -7.3 vs -9.0 vs -4.1 (p=0.006 for methylphenidate vs atomoxetine) ADHD-RS inattentive subscale for prior stimulant users: -5.9 vs -7.8 vs -3.3 (p=0.02 for methylphenidate vs atomoxetine) ADHD-RS inattentive subscale for those naive to stimulants: -9.7 vs -11.0 vs -5.2 ADHD-RS impulsivity/hyperactivity subscale: -7.1 vs -7.9 vs -3.2 ADHD-RS impulsivity/hyperactivity subscale for prior stimulant users: -6.5 vs -7.3 vs -2.8 ADHD-RS impulsivity/hyperactivity subscale for those naive to stimulants: -8.2 vs -8.7 vs -3.8 CGI ADHD severity index: -1.2 vs -1.5 vs -0.7 CGI ADHD severity index for prior stimulant users: -0.9 vs -1.3 vs -0.6 CGI ADHD severity index for those naive to stimulants: -1.5 vs -1.8 vs -0.8 Conners Parent Rating Scale ADHD Index: -7.8 vs -10.2 vs -2.3 Conners Parent Rating Scale ADHD Index for prior stimulant users: -5.9 vs -8.2 vs -1.1 Conners Parent Rating Scale ADHD Index for those naive to stimulants: -10.9 vs -13.5 vs -3.9 Daily Parent Ratings of Evening and Morning Behavior - Revised; Morning: -0.31 vs -0.25 vs 0.61 Daily Parent Ratings of Evening and Morning Behavior - Revised; Evening: -0.48 vs -0.53 vs 0.60 Child Health Questionnaire psychosocial summary score: 11.9 vs 12.7 vs 12.0 Child Health Questionnaire psychosocial summary score for prior stimulant users: 11.4 vs 13.1 vs 12.1 Child Health Questionnaire psychosocial summary score for those naive to stimulants: 9.9 vs 9.8 vs 12.0 **After Crossover: Response to either treatment arm** 60 of 178 (34%) responded to either atomoxetine or methylphenidate, but not both 78 of 178 (44%) responded to both treatments 40 of 178 (22%) did not respond to either treatment Of 70 patients who did not respond to methylphenidate in the acute phase, 30 (43%) subsequently responded to atomoxetine Of 69 patients who did not respond to atomoxetine in the crossover phase, 29 (42%) had previously	Open-ended questions to patients and measurement of vitals

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Newcorn 2008 United States	Atomoxetine vs methylphenidate vs placebo Any: 149 (67%) vs 146 (67%) vs 40 (54%) Headache: 39 (18%) vs 25 (11%) vs 7 (10%) Decreased appetite: 31 (14%) vs 37 (17%) vs 2 (3%) Pain in upper abdomen: 24 (11%) vs 22 (10%) vs 4 (5%) Any report of insomnia: 15 (7%) vs 29 (13%) vs 1 (1%) Irritability: 14 (6%) vs 13 (6%) vs 1 (1%) Nausea: 9 (4%) vs 13 (6%) vs 6 (8%) Insomnia: 9 (4%) vs 17 (8%) vs 1 (1%) Vomiting not otherwise specified: 15 (7%) vs 8 (4%) vs 4 (5%) Somnolence: 14 (6%) vs 4 (2%) vs 3 (4%) Cough: 7 (3%) vs 8 (4%) vs 4 (5%) Fatigue: 12 (5%) vs 5 (2%) vs 1 (1%) Initial insomnia: 6 (3%) vs 12 (6%) vs 0 (0%)	93 withdrew from acute phase; 12 for AEs 42 withdrew from crossover phase; 3 for AEs	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria
Prasad 2007	Randomised, controlled, open-label 20 UK outpatient centers	Patients were children and adolescents who met DSM-IV criteria for ADHD by clinical investigator assessment and confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Present and Lifetime Versions (K-SADS-PL). Children were 7–15 years of age, and were not intellectually impaired in the viewpoints of the investigators. They were required to have a symptom severity score ≥ 1.5 standard deviations above the investigator-rated ADHD-Rating Scale-IV (ADHD-RS) age norm for their ADHD subtype to be eligible for enrolment. Patients were assessed for other psychiatric disorders by clinical assessment and by the K-SADS-PL (disruptive behaviors, anxiety, and affective disorders modules). Patients were excluded if they weighed < 20 kg; had a history of bipolar disorder, psychotic disorders, pervasive development disorder (autistic spectrum disorder), any seizure disorder or alcohol/drug abuse; were with significant prior/current medical conditions or at serious suicidal risk; or were taking medication that could potentially interfere with study outcomes. Females who were pregnant/breastfeeding or sexually active and not using contraception were also excluded.
Sangal 2006 United States	RCT, DB Crossover 2 sleep disorder centers	Patients were 6 to 14 years old at study entry. They were diagnosed with ADHD using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria as well as severity criteria. Diagnosis was assessed by the investigator's clinical evaluation and by the administration of several modules of the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version structured interview. In addition, patients had an ADHD Rating Scale-IV-Parent Version: Investigator-Administered and Scored (ADHD RS) score at least 1.0 standard deviation above normative values for age and sex for either the inattentive or hyperactive/impulsive subscore, or for the combined score. All patients scored at least 80 on the Wechsler Intelligence Scale for Children -3rd edition. Important exclusion criteria included serious medical illness, a history of symptoms suggestive of a primary sleep disorder – such as obstructive sleep apnea (OSA) (e.g., habitual snoring), periodic limb movement disorder (PLMD, e.g., kicking movements during sleep), or insufficient sleep syndrome (e.g., voluntary sleep restriction resulting in sleep duration habitually significantly shorter than expected age norms}--that could potentially result in a daytime symptom constellation similar to ADHD, and abnormal laboratory values or electrocardiogram (ECG) readings. Patients agreed not to use caffeinated beverages during the duration of the study.

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Comorbidity	Interventions and total daily dose Duration Dosing schedule
Prasad 2007	Comorbidity assessed by the Kiddie-SADS at study entry shows nearly two thirds (61.7%) of all patients with ADHD also had a diagnosis of oppositional defiant disorder and ten patients (5 each arm) had some form of comorbid aniety disorder (typically a specific phobia or separation anxiety disorder). One patient has both dysthymia and another had a depressive disorder and a number of anxiety disorders.	Atomoxetine: Mean Dose: 1.5 mg/kg/day. commenced on 0.5 mg/kg/day. After a minimum of 7 days, patients who, in the judgment of the investigator, had clinically significant residual symptoms and who were tolerating atomoxetine, could have a dose increase to approximately 1.2 mg/kg/day. After a minimum of two further weeks, a dose increase to a maximum of 1.8 mg/kg/day was permitted, if required, based on the investigator's assessment of clinical response (efficacy and tolerability) SCT: Mean daily dose of single therapy short acting MPH was 0.80 mg/kg/day, and for long-acting OROS MPH was 1.03 mg/kg/day. SCT was defined as any intervention regarded by the investigator/treating physician that would benefit the patient, and that they would use as appropriate in their standard clinical practice, including the option of no therapy. SCT could include any combination of medicines (apart from atomoxetine) and/or simple behavioral counseling approaches
Sangal 2006 United States	NR	Atomoxetine Mean final dose: 58.27 mg/day (range = 15-100), or 1.56mglkg per day Methylphenidate: Mean final dose was 42.29 mg/day (range = 15-60), or 1.12 mglkg per day

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Prasad 2007	Washout/evaluation period: 3-28 days	NR	Primary Outcome Measure: Parent-Rated Child Health and Illness Profile-Child Edition (CHIP-CE) total (global) t-score Other Measures: the five CHIP-CE domains; parent-rated Family Burden of Illness Module (FBIM); investigator-rated ADHD-Rating Scale; investigator-rated Clinical Global Impression (CGI)-Severity/Improvement scales; and child rated Harter Self-Perception Profile (HSPP)	Mean age: 10.9 yrs (SD 2.2) (Range: 6.9-15.9 yrs) 88.6% male 99% Caucasian
Sangal 2006 United States	10-20 day study-drug washout	NR	Primary Outcome Measure: change from baseline to endpoint in sleep-onset latency, as measured by actigraphy Other Measures: ADHD RS (Visit 1 and at the end of each study period), the Clinical Global Impression-Severity scale (Visits 1 and 3-12), the Conners' Parent Rating Scale-Revised: Short Form (CPRS-R:S) (Visit 1 and at the end of each study period), and the Daily Parent Ratings of Evening and Morning Behavior (DPREMB) (Visits 1-3,6,7, 11, and 12)	Mean age: 10.1 yrs (SD 2.0) 75.3% male 72.9% Caucasian

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Prasad 2007	Atomoxetine vs SCT Previously treated with stimulants: 59.6% vs 70.1%, p=0.140 patients that have not previously taken any medication: 27.96% vs 19.6%, p=0.187 Pts that have taken medications other than stimulants: 13 pts vs 10 pts, p=0.663 ADHD subtype: Combined: 181(90.5%), p=0.055 Hyperactive: 4(2%), p= >0.999 Inattentive: 15(7.5%), p=0.030 Other disorders in >5% patients: Oppositional defiant disorder: 124(61.7%), p=0.563 Conduct disorder: 14(7%), p= >0.999	208/208/201	7 withdrew in study period I, 26 in atomoxetine group withdrew in study period II, 6 SCT pts withrdrew in study period II,
Sangal 2006 United States	ADHD Subtype: Hyperactive/Impulsive: 2.4% Inattentive: 29.8% Combined: 67.9% Present Comorbid Conditions: ODD: 48.2% Conduct Disorder: 3.5% Anxiety Agoraphobia: 1.2% Prior stimulant exposure: 56.5%	107/85/85	6 withdrew after 1st acute treatment phase; 4 withdrew after 2nd acute treatment phase 50 analyzed (25 excluded from analysis) n=79 for safety

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Prasad 2007	No differential treatment effect between SCT and atomoxetine. LS mean ± SE of the total score of the CHIP-CE increased to 38.4± 1.3 for atomoxetine and to 30.8±1.3 for the SCT group patients treated with atomoxetine was superior in health compared with SCT patients. Atomoxetine patients was just greater than one SD below the US norm of 50. Overall treatment effect for atomoxetine was significant (p<0.001) No significant difference in reduction of FBIM total score between atomoxetine vs SCT Improved investigator-rated ADHD-RS score was higher for atomoxetine pts at wk 10 (p<0.001)	NR
Sangal 2006 United States	Actigraphic Sleep Measures Change from Baseline (SD) Atomoxetine vs. Methylphenidate; [95% CI] Sleep-onset latency, min: 12.06 (27.07) vs. 39.24 (40.77); p<0.001 [-12.82, -6.49] Total nap time, min: 4.49 (10.41) vs. 3.04 (7.92); p=0.475 [-1.68, 3.55] Total sleep interval, min: -15.00 (45.10) vs. -35.89 (56.10); p=0.004 [6.81, 34.15] Assumed sleep time, min: -15.26 (44.25) vs. 29.61 (53.00); p=0.016 [2.73, 25.73] Interrupted sleep time, min: 0.26 (15.04) vs. -6.28 (17.48); p=0.025 [0.80, 11.69] Sleep interruptions, no.: -1.31 (6.83) vs. -4.36 (6.33); p=0.011 [0.70, 5.19]	NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Prasad 2007	Atomoxetine vs SCT headache: 22(21.2%) vs 8(8.2%), p=0.016 Nausea: 18 (17.3%) vs 3(3.1%), p= <0.001 Weight decreased: 8 (7.7%) vs 8(8,2%), p= >0.999 Decreased appetite: 8(7.7%) vs 6(6.2%), p=0.784 Vomiting: 9(8.7%) vs 2(2.1%), p=0.059 Abdominal pain upper: 7(6.7%) vs 3(3.1%), p=0.334 Cough: 6(5.8%) vs 4(4.1%), p=0.749	Total withdrawals depends on the phase of the study; 6 withdrawals due to adverse events	
Sangal 2006 United States	TEAs occurring in at least 10% of the 79 patients in either treatment group (Atomoxetine vs. Methylphenidate) Decreased appetite: 11.4% vs. 24.1% (p=0.30) Headache: 19.0% vs. 15.2% (p=0.698) Insomnia: 6.3% vs. 26.6% (p<0.001) Appetite decreased: 11.4% vs. 15.2% (p=0.357) Irritability: 11.4% vs. 15.2% (p=0.263) Pharyngitis: 15.2% vs. 8.9% (p=0.173) Cough: 12.7% vs. 8.9% (p=0.625) Somnolence: 15.2% vs. 3.8% (p=0.057) Abdominal pain, upper: 11.4% vs. 5.1% (p=0.248) Fatigue: 11.4% vs. 3.8% (p=0.121)	No withdrawals due to adverse events; total withdrawals depends on which phase of the study	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria
Schachar 2008 Canada	RCT, DB 3 way crossover Single center	Patients were aged 6-15 years with a diagnosis of ADHD according to the DSM-IV, with an IQ of ≥85 on the Wechsler Intelligence Scales for Children within the previous 12 months, must be mentally and physically competent to give consent. Patients were excluded if they were allergic to MPH or amphetamines or had a history of serious adverse reactions to MPH or had a lack of response to MPH; if they had serious or unstable medical illness, co-morbid psychiatric illness of sufficient severity to require treatment, or currently receiving psychotropic medications or herbal treatments; and if they had disorders of the sensory organs, autism, psychosis, or any unstable psychiatric conditions.
Starr 2005 United States Subanalysis of FOCUS	Open-label Parallel Multicenter Outpatient	See Kemner 2005; African American group only

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Comorbidity	Interventions and total daily dose Duration Dosing schedule
Schachar 2008 Canada	None	MPH 1.2mg/kg per day (average daily dose=31.2mg/day; range: 20-60mg/day) Multi-layer release was given as a single morning dose, with placebo at lunch-time (MLR MPH) Immediate release was given as two equal doses at morning and lunch-time (IR MPH) Placebo was given at both morning and lunch-time (Placebo)
Starr 2005 United States Subanalysis of FOCUS	See Kemner 2005	Mean dosages: 32.5 mg vs 1.1 mg/kg/day

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Schachar 2008 Canada	NR	NR	Inattention/Overactivity with Aggression Conners Scale (IOWA); the Child's Behavior in Problem Situations scale (CBPS), and the Communicative Pragmatics scale (CP); Stop Signal Paradigm; the Conners' Continuous Performance Task (CPT); and an arithmetic test The CGI-Improvement scale	Mean age: 11.3 years 88% male Ethnicity: NR
Starr 2005 United States Subanalysis of FOCUS	See Kemner 2005	See Kemner 2005	See Kemner 2005	Mean age=8.8 years 82% male 100% African American

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Schachar 2008 Canada	NR	NR/NR/18	1 withdrew, none were lost to follow-up 17 analyzed
Starr 2005 United States Subanalysis of FOCUS	ADHD subtype Hyperactive-impulsive: 14.1% Inattentive: 9.1% Combined: 14.7% Family history of ADHD: 47% Prior treatment for ADHD: 52% Duration of ADHD: 27 months Baseline ADHD-RS: 40.6 Baseline CGI-SI: 4.9	NR/NR/183 (OROS MPH n=125; atomoxetine n=58)	NR/NR/NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Schachar 2008 Canada	Placebo vs IR MPH vs MLR MPH (mean) Stop task - go task (msec): 721.8 vs 670.9 vs 673.1 Stop task - mean delay (msec): 349.6 vs 409.3 vs 426.1 Stop task - stop signal reaction time (msec): 372.2 vs 261.6 vs 247.1 Continuous performance test - errors of omission (n): 60 vs 31 vs 47.7 Continuous performance test - errors of commission (n): 24.1 vs 25.6 vs 24.5 Arithmetic test - number completed: 22.9 vs 26 vs 20.5 Arithmetic test - number correct: 17.6 vs 20.7 vs 20.5 Arithmetic test - percent correct: 75.8% vs 77.5% vs 81.2% IOWA-C - overall change from baseline: 2.03 vs -0.66 vs -1.38 IOWA-C - Inattention/overactivity subscale change from baseline: 3.20 vs -0.98 vs -1.26 IOWA-C - Aggression/defiance subscale change from baseline: 0.86 vs -0.33 vs -1.5 Problem situations change from baseline: 1.49 vs -0.35 vs -0.47 Communicative pragmatics change from baseline: 2.91 vs -0.27 vs -0.89 CGI of "much improved" or "very much improved": 17.6% vs 58.8% vs 76.5%	Used an instrument called CASE, consists of 26 possible AEs common to stimulant medications
Starr 2005 United States Subanalysis of FOCUS	OROS MPH vs atomoxetine: ADHD RS Total score (mean change in points): Week 1: -9.8 vs -7.5, NS Week 2: -14.5 vs -11.4; NS Week 3: -20.4 vs -15.9; p<0.03 ADHD-RS responder rates ≥ 30% reductions (% pts): 77.4% vs 61.1%; p<0.03 ≥ 50% reductions (% pts): 58.3% vs 35.2%: p<0.006 CGI-I responder rates (% pts with scores ≤2): 68.4% vs 49.1%; p<0.01 PSQ total scores: 19.8 vs 23.4; p<0.009 % parents stating that their child was doing "better than" or "somewhat better than" before treatment: 85.1% vs 63.8%; p-value NR	See Kemner 2005

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Schachar 2008 Canada	MLR MPH vs IR MPH vs Placebo Headache: 1 vs 1 vs 1 Tremor: 0 vs 1 vs 1 Somnolence: 1 vs 1 vs 0 Asthenia: 1 vs 0 vs 0 Psychosis: 0 vs 0 vs 1 Anorexia: 0 vs 1 vs 0 Rhinitis: 0 vs 1 vs 0 Infection: 0 vs 0 vs 1 Pruritus: 0 vs 1 vs 0	1 withdrew, none due to AEs	
Starr 2005 United States Subanalysis of FOCUS	Treatment-related adverse events: 19.2% vs 19% Upper abdominal pain: 4.8% vs 1.7% Decreased appetite: 4% vs 1.7% Headache: 4.0% vs 1.7% Insomnia: 3.2% vs 0 Nausea: 0.8% vs 3.4% Somnolence: 0.8% vs 5.2% Sedation: 0 vs 5.2% p-values NR	Withdrawals due to adverse events: 0.8% vs 1.7%; p-value NR Overall withdrawals NR	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria
Wang 2007 China, Korea and Mexico	RCT, DB Parallel Multicountry, multicenter	Patients aged 6-16 years weighing between 20 and 60 kg, who met DSM-IV criteria for ADHD, had a severity of ≥25 for boys and ≥22 for girls, or >12 for a specific subtype, on the ADHD-RS-IV- Parent Version: INV, as well as the CGI-ADHD-S. Patients were excluded if they had a history of bipolar, psychotic or pervasive development disorders; suicidal risk; ongoing use of psychoactive medications other than the study drug; those with motor tics, a diagnosis or family history of Tourette's syndrome or those who met DSM-IV criteria for anxiety disorder.
Weiss 2007 Canada	RCT, DB Crossover 7 centers	Patients aged 6-17 years with DSM-IV diagnosis of ADHD, with an intelligence quotient of ≥80 on the WISC-III within the previous 12 months, score of ≥1.5 SD from norm on the Conners' ADHD index. Patients were excluded if they were allergic to MPH or amphetamines or had ah history of serous adverse reactions to MPH or had a lack of response to MPH; had a serious or unstable medical illness, co-morbid psychiatric illness of sufficient severity to require treatment, or currently receiving psychotropic medications or herbal treatments; history of drug abuse, alcohol abuse, disorder of the sensory organs, autism, psychosis, or any unstable psychiatric conditions.

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Comorbidity	Interventions and total daily dose Duration Dosing schedule
Wang 2007 China, Korea and Mexico	NR	Atomoxetine Initial dose: 0.8mg/kg per day (once daily in morning) Range: 0.8-1.8mg/kg per day Methylphenidate (MPH) Initial dose: 0.2mg/kg per day (twice daily in morning and at lunch) Range: 0.2-0.6mg/kg per day
Weiss 2007 Canada	None	MLR MPH (administered once daily) IR MPH (administered twice daily) Initial dose: 10mg for ≤20kg, 20mg for 20-35kg, 30mg for >35kg up to 40mg for ≤20kg, 50mg for 20-35kg, 60mg for <35kg

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Wang 2007 China, Korea and Mexico	1 week washout period with discontinuation of previous stimulant medication	Limited OTC use	Primary Outcome Measure: Reduction of ≥ 40% on the ADHD-RS-IV Parent: Invs Total Score Other measures: ADHD-RS-IV Parent: Invs Total and Inattention and Hyperactivity/Impulsivity subscales; ADHD Index, Oppositional, Cognitive Problems/Inattention and Hyperactivity subscales of the CPRS-R:S; and the CGI-ADHD-S	Mean age: 9.7 years 83% male 91.5% East/Southeast Asian 8.5% Hispanic
Weiss 2007 Canada	1 week washout period	NR	Primary Outcome Measure: CGI-I Other measures; CTRS-R; CPRS-R, TIP;	Mean age: 11.0 years 82% male 83% White 6% Black 4% Asian 7% other

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Wang 2007 China, Korea and Mexico	DSM-IV subtype Combined: 196 (59.4%) Inattentive: 124 (37.6%) Hyperactive/Impulsive: 10 (3%) Previous exposure to stimulants: 80 (24.2%)	361/330/330	40 withdrew 330 analyzed for safety 326 analyzed for efficacy
Weiss 2007 Canada	MPH naïve: 59%	110/90/90	11 withdrew 1 lost to follow-up 90 analyzed

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Wang 2007 China, Korea and Mexico	Atomoxetine vs MPH Completion rate: 84.1% vs 91.6% (p=0.044) Response rate: 77.4% vs 81.5% (p=0.404) ADHD-RS-IV Parent:Inv total mean change from baseline: -21.1 vs -21.6 ADHD-RS-IV Parent:Inv inattentive subscale mean change from baseline: -11.3 vs -12.0 ADHD-RS-IV Parent:Inv hyperactivity/impulsivity subscale mean change from baseline: -9.7 vs -9.5 CPRS-R:S ADHD index mean change from baseline: -11.1 vs -11.0 CPRS-R:S Cognitive problems/inattention mean change from baseline: -5.8 vs -6.0 CPRS-R:S Hyperactivity mean change from baseline: -5.9 vs -4.9 CPRS-R:S Oppositional mean change from baseline: -3.0 vs -3.4 CGI-ADHD-S mean change from baseline: -2.3 vs -2.5	Spontaneous reports and open-ended questions
Weiss 2007 Canada	MLR MPH vs IR MPH (mean questionnaire results at end of double-blind phase) CGI - therapeutic effect-investigator: 2.8 vs 2.9 CGI - adverse events-investigator: 1.6 vs 1.7 CGI - global improvement-investigator: 2.3 vs 2.3 CGI - global improvement-parent: 2.5 vs 2.6 CGI - global improvement-teacher: 2.4 vs 2.4 CPRS - ADHD index: 56.6 vs 56.8 CPRS - Cognitive/inattention: 56.7 vs 56.3 CPRS - hyperactivity: 56.9 vs 57.2 CPRS - Oppositional: 56.9 vs 56.8 CTRS - ADHD index: 56.3 vs 52.8 CTRS - Cognitive/inattention:51.8 vs 51.1 CTRS - hyperactivity: 55.4 vs 52.0 CTRS - Oppositional: 53.5 vs 51.5	CASE Questionnaire

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Wang	Atomexetine vs MPH	40 withdrew	
2007	Anorexia: 61 (37.2%) vs 42 (25.3%) p=0.024	24 withdrew due to AEs (18 in	
China, Korea and Mexico	Decreased appetite: 46 (28.0%) vs 32 (19.3%)	Atomoxetine group vs 6 in MPH group)	
	Nausea: 33 (20.1%) vs 17 (10.2%) p=0.014		
	Somnolence: 43 (26.2%) vs 6 (3.6%) p<0.001		
	Headache: 25 (15.2%) vs 16 (9.6%)		
	Dizziness: 25 (15.2%) vs 12 (7.2%) p=0.024		
	Abdominal pain: 15 (9.1%) vs 15 (9.0%)		
	Pyrexia: 11 (6.7%) vs 17 (10.2%)		
	Vomiting: 19 (11.6%) vs 6 (3.6%) p=0.007		
	Cough: 11 (6.7%) vs 10 (6.0%)		
	Upper respiratory tract infection: 9 (5.5%) vs 11 (6.6%)		
	Fatigue: 13 (7.9%) vs 5 (3.0%)		
	Irritability: 7 (4.3%) vs 10 (6.0%)		
	Rhinorrhea: 7 (4.3%) vs 10 (6.0%)		
	Insomnia: 5 (3.0%) vs 9 (5.4%)		
Weiss	MLR MPH vs IR MPH	11 withdrew	
2007	Anorexia: 20% vs 24.4%	4 withdrew due to AEs	
Canada	Insomnia: 20% vs 16.7%		
	Nervousness: 17.8% vs 17.8%		
	Headache: 13.3% vs 12.2%		
	Somnolence: 8.9% vs 4.4%		
	Abdominal pain: 6.7% vs 8.9%		
	Depression: 6.7% vs 4.4%		
	Emotional liability: 3.3% vs 6.7%		

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria
Wigal 2005 United States Fair StART study	Double-blind Parallel Multicenter Simulated classroom setting	Male or female aged 6 to 12 years; diagnosis of DSM-IV-TR ADHD combined subtype or predominantly hyperactive/impulsive subtype; weight between 40 lb and 120 lb at enrollment; and capable of understanding and following classroom instruction and generally functioning academically at age-appropriate levels

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Comorbidity	Interventions and total daily dose Duration Dosing schedule
Wigal 2005 United States Fair StART study	NR	Atomoxetine: wk1=0.5 mg/kg/d; wk2-3=1.2 mg/kg/d Mixed amphetamine salts (MAS) XR: wk1=10 mg; wk2=20 mg; wk3=30 mg (mean dosages NR) Duration=3 weeks (wk)

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Wigal 2005 United States Fair StART study	4-day single-blind placebo lead-in period/washout of previous medications, but no details provided	NR	Primary: Change in mean SKAMP deportment subscale scores Secondary: mean SKAMP deportment subscale scores; 10-minute age-appropriate math tests (absolute number of problems attempted and the absolute number of problems completed correctly); CGI; CGI-S; CGI-I; 10-item Conners' Global Index Scale-Parent version (CGIS-P); Medication Satisfaction Survey (Med-SS); Pediatric Quality of Life Inventory (PedsQL)	Mean age=8.7 years 71.9% male 55.6% white 16.2% black 19.7% Hispanic 2.0% Asian or pacific islander 6.4% other

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Wigal 2005 United States Fair StART study	ADHD subtype Hyperactive/impulsive: 0.5% Combined: 99.5% CGI-S category: Borderline impairment: 2.5% Mildly impaired: 3.9% Moderately impaired: 60.1% Markedly impaired: 25.6% Severely impaired: 9.3%	NR/NR/215	25 (12.3%) withdrawn/LTFU NR/203 (94.4%) (MAS XR n=102; atomoxetine n=101)

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Wigal 2005 United States Fair StART study	MAS XR vs atomoxetine SKAMP scale mean changes Deportment: -0.56 vs -0.13; p<0.0001 Attention: -0.49 vs -0.08; p<0.0001 SKAMP scale responders Deportment (≥ 25% improvement): 70% vs 38%; p≤0.0001 Attention (≥ 25% improvement): 68% vs 28%; p<0.0001 Math problems (mean number) Attempted: 62.6 vs 30.5; p<0.0001 Completed correctly: 61.6 vs 29.0; p<0.0001 CGIS-P mean decrease in unit points: -8.3 vs -6.63; p=NS CGI-I ratings of very much improved/much improved (% pts): 74.5% vs 35.6%; p<0.0001 PedsQL total score mean increase in unit points: +7.1 vs +7.9; p=NS PedsQL school functioning score increase in unit points (% increase): +34% vs +25%; p=0.0026 Parent-Rated Med-SS: MAS XR=atomoxetine (data NR)	Assessed by spontaneously reported adverse events

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Wigal 2005 United States Fair StART study	MAS XR vs atomoxetine (p-values NR for all; those reported below reflect Oregon EPC calculations using StatsDirect) Overall AE incidence: 85% vs 73.1%; NS Upper abdominal pain: 18.7% vs 14.8% Vomiting: 4.7% vs 13%; p=0.035 Fatigue: 1.9% vs 7.4% Nausea: 6.5% vs 9.3% Weight decrease: 5.6% vs 3.7% Anorexia: 16.8% vs 9.3% Appetite decrease: 28% vs 17.6% Dizziness: 5.6% vs 1.9% Headache: 15% vs 10.2% Somnolence: 4.7% vs 18.5%; p=0.0015 Insomnia: 28% vs 7.4%; p<0.0001	Overall withdrawals: 13.1% vs 10.2%; NS AE withdrawals: 6.5% vs 3.7%; NS	

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

Internal Validity

Study	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition, adherence
Amiri 2008	Yes	Yes	Unclear (inadequate data presented)	Yes	Yes	Yes	Yes	Y/NR
Arnold 1978 Huestis 1975	NR	NR	Crossover	Yes	Yes	Yes	Yes	NR NR NR NR
Barkley 2000	NR	NR	Crossover	Yes	Yes	Yes	Yes	Reported that 20 - 31% completed each randomized order of drug administration

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

					External Validity	
Study	**Loss to followup: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/ enrolled**	**Exclusion criteria**
Amiri 2008	N/N	Yes	No	Fair	NR/NR/60	Patients were excluded if they had a history or current diagnosis of pervasive developmental disorders, schizophrenia or other psychiatric disorders; any current psychiatric comorbidity that required pharmacotherapy; any evidence of suicide risk and mental retardation; they had a clinically significant chronic medical condition, including organic brain disorder, seizures and current abuse or dependence on drugs within 6 months; hypertension, hypotension and habitual consumption of more than 250mg/day of caffeine.
Arnold 1978 Huestis 1975	NR	Yes	No	Fair	NR/NR/29	NR
Barkley 2000	NR	No	1 excluded due to low IQ	Poor	NR/NR/46	History of (1) motor/vocal tics or Tourette's Syndrome; (2) cardiac surgery, high blood-pressure (sustained blood-pressure levels above the 95th percentile for age and sex) at baseline, or cerebral vascular accident, given the known cardiac presser effects of stimulant medication; (3) adverse reactions to stimulant medications; (4) hyperthyroidism; (5) pregnancy/lactation.

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

Study	Run-in/ Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Amiri 2008	No/No	NR	No	Tehran University of Medical Sciences	Yes
Arnold 1978 Huestis 1975	2-week placebo washout	65.5% were psychopharmacologically "virgin"	Yes	Grant from Ohio Department of Mental Health and Mental Retardation; matched dosage forms were furnished by Ciba-Geigy Pharmaceutical Corp.	No; high proportion of class naïve patients
Barkley 2000	NR/NR	NR	Yes	Shire	Yes

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

	Internal Validity							
Study	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**	**Attrition, adherence**
Barrickman 1995	NR	NR	n/a - crossover	Yes	Yes	Yes	Yes	Yes NR NR NR
Bergman 1991	Inadequate (counterbalanced order)	NR	n/a - crossover	No	Yes	Yes	Yes	NR NR NR NR
Biederman 2007	Randomization stated, but method NR	Unclear	Yes	Yes	Unclear; "double-blind" stated	Unclear; "double-blind" stated	Yes	Y/NR
Borcherding 1990	NR	NR	Crossover	Yes	Yes	Yes	Yes	NR NR NR NR

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

					External Validity	
Study	**Loss to followup: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/ enrolled**	**Exclusion criteria**
Barrickman 1995	NR/NR	No; 3 (16.7%) excluded from analysis that were dropped due to failure to cooperate	No	Fair	NR/NR/18	IQ < 70 (mental retardation) and any other major Axis I, II, or III diagnoses; seizure disorder; eating disorder.
Bergman 1991	NR	Unclear	Unclear	Poor	NR/NR/42	NR
Biederman 2007	N/N	Yes	No	Fair	NR/NR/52	Presence of comorbid illness that could interfere with study participation or impact the efficacy and tolerability of LDX or MAS XR, documented allergy or intolerance to MAS XR, history of drug abuse, concomitant medications with CNS effects, current comorbid psychiatric diagnosis that would contraindicate treatment with MAS XR or LDX or confound efficacy or safety assessments, history of seizures within the last 2 years, tic disorders, hyperthyroidism, cardiac disorders, and significant lab abnormalities.
Borcherding 1990	NR	No	Unclear	Poor	NR/NR/46	Medical or neurological disease, including chronic motor tics or Tourette's syndrome, or other primary Axis I psychiatric disorder were exclusionary.

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

Study	Run-in/ Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Barrickman 1995	No run-in; 14-day washout	No	Yes	NR	Yes
Bergman 1991	NR/NR	NR	Yes	NIMH Grants (MH 38838-05 and MH 30906-09)	Unclear
Biederman 2007	NR/3 day washout	No	Yes	New River Pharmaceuticals and Shire Development Inc	Yes
Borcherding 1990	No/Yes	28.30%	Yes	NR	Yes

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

Internal Validity

Study	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition, adherence
Castellanos 1997	NR	NR	Crossover	Yes	Yes	Yes	Yes	NR NR NR NR
Conners 1980	NR	NR	No	Yes	Yes	Yes	Yes	NR NR NR NR
Connor 2000	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes NR NR NR
Cox 2004	Yes, random numbers table	NR; Use of a random number table without a 3rd party may indicate lack of allocation concealment	n/a - crossover	Yes	Unclear (abstract states study was single-blind, no other details)	Unclear (abstract states study was single-blind, no other details)	Unclear (abstract states study was single-blind, no other details)	Yes NR NR NR
Efron 1997	NR	NR	Crossover	Yes	Yes	Yes	Yes	NR NR NR NR
Efron 1998	NR	NR	Crossover	Yes	Yes	Yes	Yes	NR NR NR NR

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

					External Validity	
Study	**Loss to followup: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/ enrolled**	**Exclusion criteria**
Castellanos 1997	NR	No	Unclear	Poor	NR NR Enrolled: Group 1=22, Group 2=6, Group 3=4	WISC-R Full Scale IQ score less than 75; evidence of medical or neurological diseases; any other Axis I psychiatric disorder, except obsessive-compulsive disorder, conduct or oppositional disorder, overanxious disorder, and specific developmental disorders.
Conners 1980	Unclear	Unclear	No	Fair	88/60/60	NR
Connor 2000	No	Yes	No	Fair	NR/NR/24	NR
Cox 2004	No/No	No	No	Fair	NR/NR/7	History of tics or other adverse reactions to MPH, or a history of substance abuse disclosed by subject or parent.
Efron 1997	NR	Yes	No	Fair	NR/NR/125	NR
Efron 1998	NR	Yes	No	Fair	NR/NR/102	NR

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

Study	Run-in/ Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Castellanos 1997	≥ 4 weeks washout	No	Yes	NR	No
Conners 1980	NR	Unclear	Yes	NIMH and Abbott	
Connor 2000	NR	No	Yes	UMMS Small Grants Project	Yes
Cox 2004	24-hour washout	No	Yes	McNeil Consumer and Specialty Pharmaceuticals	Yes Yes
Efron 1997	24-hour washout	NO	Yes	NR	Yes
Efron 1998	24-hour washout	NO	Yes	NR	Yes

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

	Internal Validity							
Study	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**	**Attrition, adherence**
Elia 1990	NR	NR	Crossover	Yes	Yes	Yes	Yes	NR NR NR NR
Elia 1991	NR	NR	Crossover	Yes	Yes	Yes	Yes	NR NR NR NR
Elia 1993	NR	NR	Crossover	Yes	Yes	Yes	Yes	NR NR NR NR

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

					External Validity	
Study	**Loss to followup: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/ enrolled**	**Exclusion criteria**
Elia 1990	NR	Unclear	Unclear	Fair	NR/NR/31	Evidence of medical or neurologic diseases, or any other Axis I psychiatric disorder (with the exception of conduct disorder or oppositional disorder), specific developmental disorder, or mental retardation.
Elia 1991	NR	Unclear	No	Fair	NR/NR/48	WISC-R full scale IQ < 80; evidence of medical or neurological diseases, or any other Axis I psychiatric disorder, with the exception of conduct disorder, oppositional disorder, mild overanxious disorder, and specific developmental disorders.
Elia 1993	NR	Yes	No	Fair	NR/NR/33	Evidence of medical or neurological disease, or any other Axis I psychiatric disorder, with the exception of conduct disorder or oppositional disorder, and/or specific developmental disorders.

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

Study	Run-in/ Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Elia 1990	≥ 3 weeks washout	NO	Yes	NR	Yes
Elia 1991	NR	No	Yes	NR	Yes
Elia 1993	NR	No	Yes	NR	No

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

Internal Validity

Study	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition, adherence
Findling 2006	Unclear; randomized in a ratio of 3:3:1 (p 452)	NR	Yes, for tx arms; O/D component of IOWA Conners' Scale lower (better) in placebo group compared to either tx group	Yes	NR	Yes	Yes	Y NR NR NR

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

					External Validity	
Study	**Loss to followup: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/ enrolled**	**Exclusion criteria**
Findling 2006	N/N; Placebo group had a high % of study withdrawal compared to the two tx arms; withdrawal data on page 454.	Yes; stated in results, no data provided	Yes; 6 based on clinician's judgment (5 in placebo; 1 in MPH-IR)	Fair	346/327/318	Female who had reached menarche, co-morbid psychiatric disorder requiring medication, history of seizure, tic disorder, or a family history of Tourette's disorder, IQ test <80, or functioning at a level of intelligence indicative of an IQ <80, the use of unapproved medication(s), use of an investigational product within 30 days prior to study entry, concurrent chronic or acute illness, disability, or medication, that might confound the results of rating tests, diagnosed with hyperthyroidism, glaucoma, or eating disorder, current substance abuse disorder or living with someone with a current substance abuse disorder, demonstrated lack of response to methylphenidate

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

Study	Run-in/ Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Findling 2006	NR/NR; children were taking pre-study methylphenidate (MPH) medication at baseline	No	Yes	Celltech Americas, Inc	Yes

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

Internal Validity

Study	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition, adherence
Findling 2008	Yes	Unclear	Mostly, except for prior ADHD medication use, which was slightly higher in the MTS group	Yes	Yes	Yes	Yes	Y/NR
Fitzpatrick 1992	Unclear. No use of "randomized" terminology; No description whatsoever of group assignment	NR	n/a - crossover	No	Yes	Yes	Yes	NR NR NR NR

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

					External Validity	
Study	**Loss to followup: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/ enrolled**	**Exclusion criteria**
Findling 2008	Y (62% of placebo group withdrew compared to 27.5% in both MTS group and MOS group) Y (all groups >20% withdrew)	Not true ITT but small # not included. However, numbers in text and on figure disagree on how many not included.	Several patients withdrew after being randomized, but prior to having at least 1 primary efficacy assessment (planned for 1 week after dose optimization) = 3-4% of total. Not reported which groups these had been randomized to.	Fair-Poor	NR/NR/282	Patients were excluded if they had any comorbid psychiatric diagnosis; a history of seizures during the last 2 years; a tic disorder; or any concurrent illness or skin disorder that might compromise safety or the study assessments.
Fitzpatrick 1992	NR	Unclear	Unclear	Poor	NR/NR/19	NR

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

Study	Run-in/ Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Findling 2008	30 day washout of clonidine, atomoxetine, antidepressants, antihypertensives, investigational medications, hepatic or cytochrome P450 enzyme altering agents, medications with CNS effects, sedatives, antipsychotics, or anxiolytics	Naïve to stimulants or known to be responsive to stimulants	Yes	All authors have received grants or research money from multiple pharmaceutical companies	Somewhat
Fitzpatrick 1992	NR	94.7% naïve to psychotropic medication	Yes	NIMH Grant MH38118, CIBA GEIGY provided placebo tablets	No

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

Internal Validity

Study	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition, adherence
Gau 2006	NR	NR	Yes	Yes	Partial; parent reporters knew which medication, teachers reporters did not	NR	N	Y Y Y N IR MPH group had less adherence than the OROS MPH group (p < 0.0001); report states this did not change the results
Gross 1976	NR	NR	Crossover	Yes	Yes	Yes	Yes	NR NR NR NR
James 2001	NR - order of dose random, but order of drug not clear	NR	n/a - crossover	Yes	Unclear - dose of DEX SR increased part way through study	Yes	Yes	Yes NR NR NR
Kauffman 1981	NR	Yes	Crossover	Yes	Yes	Yes	Yes	NR NR NR NR

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

					External Validity	
Study	**Loss to followup: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/ enrolled**	**Exclusion criteria**
Gau 2006	N/N	Y	N	Fair	NR/NR/64	Significant gastrointestinal problems, a history of hypertension, known hypersensitivity to MPH, or a co-existing medical condition or concurrent medication (such as monoamine oxidase inhibitors, and medicines used to treat depression, prevent seizure, or prevent blood clots) likely to interfere with the safe administration of MPH. Glaucoma, Tourette's Syndrome, an active seizure disorder, or a psychotic disorder, girls who had reached menarche.
Gross 1976	NR	No	Unclear	Poor	NR/NR/50	NR
James 2001	NR/NR	Yes for some efficacy measures; No for CPS and side effects	No	Poor	NR/38/35	WISC-III Full Scale IQ less than 80; presence of a chronic medical or neurological disease including Tourette's disorder, chronic tic disorder, pervasive developments disorders, and mood anxiety disorders requiring current treatment.
Kauffman 1981	NR	Yes	No	Fair	NR/NR/12	No evidence of any neurological disorder, convulsive disorder, mental retardation, metabolic disorder, degenerative neurological disease, or deficit of hearing or sight.

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

Study	Run-in/ Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Gau 2006	NR/Y washed out MPH for 5-7 days	NR	Yes	Jansessen-Cilag, Taiwan.	Unclear; 64 participants from one medical center in Taipei
Gross 1976	No/No	NR	Yes	NR	Unclear
James 2001	No run-in; 3-week washout	42.8% class naïve	Yes	NR	No, research school setting
Kauffman 1981	NR/NR	NR	Yes	Ciba-Geigy Corp.	Yes

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

	Internal Validity							
Study	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**	**Attrition, adherence**
Kemner 2005	NR	NR	No; OROS patients with greater severity of illness at baseline (ADHD-RS 39.9 vs 38.6; p=0.006); adjusted for this difference in the analysis	Yes	NR	No	No	NR Yes NR NR
Kratochvil 2002	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes NR NR NR
Lopez 2003	NR	NR	n/a - crossover	Yes	Yes	Yes	Yes	Yes NR NR NR

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

					External Validity	
Study	**Loss to followup: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/ enrolled**	**Exclusion criteria**
Kemner 2005	NR	NR	NR	Poor	NR/NR/1323	Eating disorders, substance use disorders, comorbid psychiatric conditions other than oppositional defiant disorder; history of seizure, tic disorder, mental retardation, or severe developmental disorder; personal or family history of Tourette's syndrome; previous diagnosis of hyperthyroidism or glaucoma; use of medications contraindicated for coadministration with OROS MPH or atomoxetine; known nonresponse to treatments indicated for ADHD; and occurrence of menarche in girls.
Kratochvil 2002	No/No	No; 10 (4.4%) excluded from analysis due to not having a postbaseline visit	No	Fair	319/NR/228	History of bipolar or psychotic disorders, motor tics or a family history of Tourette syndrome, substance abuse, non-response to a previous trial of MPH (significant residual symptoms after at least 2 weeks of treatment with at least 1.2 mg/kg per day) and serious medical illness.
Lopez 2003	None	Yes	No	Fair	NR/NR/36	Children with concurrent significant medical or psychiatric illness, or substance use disorder were not permitted in the study.

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

Study	Run-in/ Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Kemner 2005	NR/3 days or 5 half-lives	No	Yes	McNeil Consumer and Specialty Pharmaceuticals	Yes
Kratochvil 2002	NR/NR	No	Yes	Eli Lilly	Yes
Lopez 2003	NR/NR	All patients had been stabilized on an equivalent dose of 10 mg twice daily of MPH prior to study entry	Yes	Novartis Pharmaceuticals	Yes

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

Internal Validity

Study	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition, adherence
Manos 1999	No, each child's pediatrician determined whether MPH or Adderall was to be used (based on familiarity, as well as whether they wanted a child to receive a single dose or twice-daily dose)	NR	Yes	Yes	No	No	No	NR NR NR NR
McCracken 2003	Unclear; Latin square design;	Y; randomization schedules generated by the sponsor and distributed to the onsite pharmacist	n/a - crossover	Yes	Yes; states double blind but no details	Yes; states double blind but no details	Yes; states double blind but no details	Y Y Y N

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

					External Validity	
Study	**Loss to followup: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/ enrolled**	**Exclusion criteria**
Manos 1999	NR	Yes	No	Poor	Referred=60/eligible= NR/participated=159	NR
McCracken 2003	N/N	Yes	N	Fair	NR/51/47	Comorbid psychiatric conditions including psychosis, pervasive developmental disorder, bipolar disorder; severe obsessive-compulsive disorder, severe depressive or anxiety disorder (severe defined as any comorbid disorder with impairment necessitating concurrent treatment of any type); a clinically significant medical condition (e.g., seizure disorder, hypertension, abnormal laboratory test result); need for ongoing medical treatment; intolerance of psycho stimulants; history of nonresponse to Adderall; or history of a tic disorder.

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

Study	Run-in/ Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Manos 1999	NR/NR	NR	Yes	NIDA, Maternal and Child Health Program	No
McCracken 2003	NR/Y 1 week washout	N	Yes	Supported by a grant from Shire Pharmaceutical Development Inc.	Unclear

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

Internal Validity

Study	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition, adherence
Muniz 2008	Yes	Yes	NR (only means for whole group given, not separated by group to see how they compare)	Yes	Unclear - "double blind"	Yes	Yes	Y/NR
Newcorn 2008	Randomization stated, but method NR	Yes	Yes	Yes	Yes	Yes	Yes	Y/NR
Pelham 1987	NR	NR	n/a - crossover	Yes	Yes	Yes	Yes	NR NR NR NR
Pelham 1990	NR	NR	n/a - crossover	Yes	Yes	Yes	Yes	NR NR NR NR
Pelham 1999a	NR	NR	Crossover	Yes	Yes	Yes	Yes	NR NR NR NR

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

					External Validity	
Study	**Loss to followup: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/ enrolled**	**Exclusion criteria**
Muniz 2008	N/N	Yes	No	Fair	NR/NR/84	Children were excluded if they had a tic disorder or Tourette's syndrome, history of seizures, psychiatric illness or substance abuse disorder, taking prohibited concomitant medications or ADHD medication other than methylphenidate, taking antidepressant or psychotropic medications, had begun psychotherapy within 3 months prior to randomization or who were home schooled.
Newcorn 2008	N/N	Yes	No	Good-Fair	635/516/516	Patients were excluded if they had seizures, bipolar disorder, a psychotic illness, or a pervasive development disorder or who were taking concomitant psychoactive medications; and those with anxiety and tic disorders.
Pelham 1987	NR	Unclear	Unclear	Poor	NR/NR/13	NR
Pelham 1990	NR	Unclear	Unclear	Poor	NR/NR/22	NR
Pelham 1999a	NR	Unclear	Unclear	Fair	NR/NR/21	No medical history that prohibited them from taking psychostimulant medication or participating in the STP academic or recreational activities.

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

Study	Run-in/ Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Muniz 2008	6 days of washout of their regular ADHD medication	NR	Yes	All authors have received grants or research money from multiple pharmaceutical companies	Yes
Newcorn 2008	Discontinue any psychoactive medication for at least five times the medication's plasma half-life (or at least 5 days) before entering the study	Naïve to stimulants or known to be responsive to stimulants	Yes	Eli Lilly	Yes
Pelham 1987	NR	NR	Yes	NR	No, Summer Treatment Program
Pelham 1990	NR	NR	Yes	NR	No, Summer Treatment Program+behavior modification intervention
Pelham 1999a	NR/NR	24%	Yes	Shire	No; Summer Treatment Program with behavioral training for both children and parents

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

	Internal Validity							
Study	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**	**Attrition, adherence**
Pelham 1999b	NR	NR	Crossover	Yes	Yes	Yes	Yes	NR NR NR NR
Pelham 2001	Yes	Yes for patients	n/a - crossover	Yes	Yes	Yes	Yes	Yes, NR, Yes (virtually 100%), NR
Pliszka 2000 Faraone 2001	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes NR NR NR
Prasad 2007	NR	NR	No, higher proportion with inattentive subtype in Atomoxetine grp (11.5%) vs control (3.1%)	Yes	No	No	No	Y NR NR NR

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

					External Validity	
Study	**Loss to followup: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/ enrolled**	**Exclusion criteria**
Pelham 1999b	NR	Yes	No	Fair	NR/NR/25	NR
Pelham 2001	NR/NR	No; 2 patients excluded (2.8%)	No	Fair	84/NR/70	Presence of any medical condition that would contraindicate the use of stimulant medication; presence of any physical condition or severe learning difficulty that would interfere with participation in the laboratory classroom assessment (WISC IQ < 80); receiving additional medication (beyond MPH) for ADHD; receiving any medication having CNS effects, anticonvulsants, or investigational medications; having reached menarche; and having blood pressure at or above the 95th percentile for age and height.
Pliszka 2000 Faraone 2001	No	Yes	No	Fair	73/Unclear/58	DISC criteria for major depression episode, manic episode, or tic disorder; history of psychosis or have signs of psychosis or significantly depressed mood on the mental status examination; BIT composite IQ < 75.
Prasad 2007	Y (discontinuation from trial 25% atomoxetine, 6% control N	Unclear - modified ITT stated, appears only 75% of atomoxetine grp included in analysis, while 94% of control grp	Y;N	Poor	NR/208/201	Weight < 20 Kg, history of bipolar disorder, psychotic disorders, PDD, seizure disorders, alcohol/drug abuse, significant prior/current medical conditions, at risk of suicide, taking medications that may interfere with study outcomes.

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

Study	Run-in/ Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Pelham 1999b	NR/NR	NR	Yes	Shire	No; Summer Treatment Program with behavioral training for both children and parents
Pelham 2001	NR/NR	No	Yes	Alza	Yes
Pliszka 2000 Faraone 2001	NR/NR	46 (79.3%)	Yes	Shire	Yes
Prasad 2007	Y/N 3-28 days	No	Yes	Eli Lilly	Relevant to outpatient centers in UK, patients without other psychological or medical conditions.

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

Internal Validity

Study	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition, adherence
Sangal 2006	NR	NR	n/a - crossover; reported no differences at baseline	Yes	Yes; states double blind but no details	Yes; states double blind but no details	Yes; states double blind but no details	Y Y Y N
Schachar 2008	Yes	Yes	NR	Yes	Unclear - "double blind"	Unclear - "double blind"	Yes	Y/NR
Sharp 1999	NR	NR	Crossover	Yes	Yes	Yes	Yes	NR NR NR NR

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

					External Validity	
Study	**Loss to followup: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/ enrolled**	**Exclusion criteria**
Sangal 2006	N/N	NO	Y; 35 due to low actigraphy scores or equipment malfunction	Poor	107/85/85 (75 completed) Only 50 cases analyzed due to low actigraphy scores	Inconsistent adherence to 'bed-time' as scheduled; serious medical illness, a history of symptoms suggestive of a primary sleep disorder-such as obstructive sleep apnea (OSA) (e.g., habitual snoring), periodic limb movement disorder (PLMD, e.g., kicking movements during sleep), or insufficient sleep syndrome (e.g., voluntary sleep restriction resulting in sleep duration habitually significantly shorter than expected age norms}--that could potentially result in a daytime symptom constellation similar to ADHD, and abnormal laboratory values or electrocardiogram (ECG) readings.
Schachar 2008	N/N	Yes	No	Fair	NR/NR/18	Patients were excluded if they were allergic to MPH or amphetamines or had a history of serious adverse reactions to MPH or had a lack of response to MPH; if they had serious or unstable medical illness, co-morbid psychiatric illness of sufficient severity to require treatment, or currently receiving psychotropic medications or herbal treatments; and if they had disorders of the sensory organs, autism, psychosis, or any unstable psychiatric conditions.
Sharp 1999	NR	Yes	No	Fair	NR/NR/32	WISC-R Full Scale IQ < 80 and chronic medical or neurological diseases, including Tourette's disorder and chronic tic disorders.

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

Study	Run-in/ Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Sangal 2006	Yes - 22 of 107 (21%) excluded during screening/Y Phase II of study: 10-20 day study drug washout	N (mixed)	Yes	Sponsored by Eli Lilly; data were analyzed by statisticians at Eli Lilly.	Unclear
Schachar 2008	NR	NR	Yes	Some authors are employed by or receive money from Purdue Pharma, but study was not sponsored by Purdue Pharma	Yes
Sharp 1999	No/Yes	NR	Yes	NR	Unclear

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

Internal Validity

Study	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition, adherence
Silva 2005	Unclear; For counterbalancing, 10 crossover treatment sequences used; Williams design to control for effects of treatment order and relative position.	NR	NR; only data on entire study group	Yes	Yes	No; those dispensing medication not blinded	Yes; although states some might have known what they were taking	N N N N
Simpson 1980	NR	NR	n/a - crossover	Yes	Yes	Yes	Yes	NR NR NR NR

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

					External Validity	
Study	**Loss to followup: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/ enrolled**	**Exclusion criteria**
Silva 2005	N/N	Unclear	N	Fair	NR/NR/54	Functioning at an IQ level of 80 or below, based on the investigator's clinical judgment; diagnosed with Tourette syndrome or a tic disorder; history of a seizure disorder; or unable to understand or comply with study instructions. Significant concurrent medical or psychiatric illness or substance-abuse disorder. A history of sensitivity to MPH, those with a history of substance abuse or dependence, those currently taking atomoxetine, and those who had taken, were currently taking, or were planning to take any investigational drug within 30 days of the study start date. Post menarchal females.
Simpson 1980	No	Yes	No	Fair	NR/NR/12	Excluded severe emotional disorder, organic brain disease, and major medical problems (e.g., sensory impairment, chronic illness, etc.).

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

Study	Run-in/ Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Silva 2005	NR/NR; 12 hour post dose observations	N; Patients were instructed to continue taking their regularly prescribed medication for 5 days of the week; administered study drug on Saturdays	Yes	Novartis Pharmaceuticals Corporation	N; Saturday school - 12 hour observation post tx
Simpson 1980	NR/NR	No	Yes	NR	Yes

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

Internal Validity

Study	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition, adherence
Steele 2006	Yes; Site randomization lists	Yes	Yes	Yes	N	N	Y	Y/NR/Y/NR % of subjects who missed any dose during the trial was higher with IR-MPH (84%) than OROS-MPH (56%).
Stephens 1984	Not randomized; medication was prescribed by each child's physician (method nr)	n/a	n/a - crossover	No	Yes	Yes	Yes	NR NR NR NR

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

					External Validity	
Study	**Loss to followup: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/ enrolled**	**Exclusion criteria**
Steele 2006	N/N	Yes	NR	Poor	187/147/145	Known MPH non-responders, hypersensitivity, or adversely affected by methylphenidate; concomitant use of contraindicated medication likely to interfere with the safe administration of study medication; marked anxiety, tension, aggression/agitation; glaucoma; ongoing seizure disorder; psychotic disorder; diagnosis or family history of Tourette's disorder; bipolar disorder; suspected mental retardation or significant learning disorder; medication/alcohol abuse/dependence by either the child or parent; history of, or current eating disorder; severe gastrointestinal narrowing; inability to swallow study medications; and any serious/unstable medical illness.
Stephens 1984	NR/NR	Unclear	Unclear	Poor	NR/NR/36	NR

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

Study	Run-in/ Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Steele 2006	Y/Y 3 day washout at study commencement of any drug for ADHD	N	Y	Janssen-Ortho Inc., Canada	Yes
Stephens 1984	NR/NR	Unclear for 25 (69.4%); reported that 11 were taking stimulants at time of study	Yes	NR	Unclear

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

	Internal Validity							
Study	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**	**Attrition, adherence**
Swanson 2004	NR	NR	n/a - crossover	Yes	Yes	Yes	Yes	Yes NR NR NR
Tourette's Syndrome Study Group 2002	Yes, computer-generated randomization	Yes, central coordinating center	No, differences in age, proportions of ADHD subtype, ASQ-Teacher scores, and gender	Yes	Yes	Yes	Yes	Yes NR NR NR
van der Meere 1999	NR	NR	Boys and girls were not equally distributed among the groups	No	Yes	Yes	Yes	NR NR NR NR

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

					External Validity	
Study	**Loss to followup: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/ enrolled**	**Exclusion criteria**
Swanson 2004	NR/NR	Yes	No	Fair	NR/NR/214	Intelligence quotient < 80 or the inability to follow or understand study instructions; pregnancy; a history of seizure or tic disorder; a family history of seizure or Gilles de La Tourette's syndrome; congenital cardiac abnormality, a history of cardiac disease including myocardial infarction within 3 months of study entry, glaucoma, or hyperthyroidism; a history of substance abuse or a caretaker with a history of substance abuse; concurrent chronic or acute illness or other condition that might confound the study rating measures; a documented allergy or intolerance to MPH; the use of an investigational drug within 30 days of study entry; and the use of concomitant medication that could interfere with the assessment of efficacy and safety of the study treatment.
Tourette's Syndrome Study Group 2002	No/No	Yes	No	Fair	NR/148/136	NR
van der Meere 1999	NR/NR	Yes	No	Fair	NR/NR/53	NR

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

Study	Run-in/ Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Swanson 2004	No/No	No; only patients BEING treated with MPH	Yes	Celltech	Yes
Tourette's Syndrome Study Group 2002	No/No	No	Yes	NIH grant #1R01NS33654	Yes
van der Meere 1999	NR/NR	NR	Yes	Sophia Foundation for Medical Research and Boehringer Ingelheim BV, The Netherlands	Yes

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

	Internal Validity							
Study	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**	**Attrition, adherence**
Wang 2007	Randomization stated, but method NR	Yes	Yes	Yes	Yes	Yes	Yes	Y/NR
Weiss 2007	Yes	Yes	NR	Yes	Yes	Yes	Yes	Y/NR
Whitehouse 1980	NR	NR	No, SR/IR on Overt signs of tension and IR>SR on tension/anxiety	Yes	Yes	Yes	Yes	Yes NR NR NR

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

					External Validity	
Study	**Loss to followup: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/ enrolled**	**Exclusion criteria**
Wang 2007	N/Y MPH group had more complete than atomoxetine group (91.6% vs 84.1%; p=0.044)	Yes	NR	Fair	361/330/330	Patients were excluded if they had a history of bipolar, psychotic or pervasive development disorders; suicidal risk; ongoing use of psychoactive medications other than the study drug; those with motor tics, a diagnosis or family history of Tourette's syndrome or those who met DSM-IV criteria for anxiety disorder.
Weiss 2007	N/N	Yes	NR	Fair	110/90/90	Patients were excluded if they were allergic to MPH or amphetamines or had ah history of serous adverse reactions to MPH or had a lack of response to MPH; had a serious or unstable medical illness, co-morbid psychiatric illness of sufficient severity to require treatment, or currently receiving psychotropic medications or herbal treatments; history of drug abuse, alcohol abuse, disorder of the sensory organs, autism, psychosis, or any unstable psychiatric conditions.
Whitehouse 1980	None/None	No, 4 (11.8%) excluded from analysis; not stated which groups these 4 were assigned to	Yes, 4 excluded from analysis for: 2 dosage deviations, 1 viral illness, 1 "other reasons"	Fair	NR/NR/34	The presence of glaucoma, epilepsy, severe organic brain damage, mental retardation, cultural deprivation, or psychosis; hypersensitivity to methylphenidate, blindness, deafness, and marked anxiety and tension as the sole manifestations of behavior disorders were excluding factors as well.

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

Study	Run-in/ Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Wang 2007	1 week washout period with discontinuation of previous stimulant medication	NR	No	NR, but corresponding author is from Eli Lilly	Yes
Weiss 2007	1 week washout period	NR	No	Purdue Pharma	Yes
Whitehouse 1980	Run-in: one month of standard methylphenidate 20 mg (twice daily) prior to study/no washout	No	Yes	NR	Yes

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

	Internal Validity							
Study	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**	**Attrition, adherence**
Wigal 2005	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes NR NR NR
Wolraich 2001	Yes	Yes	Small differences (NS) : proportions with comorbidities, prior MPH IR use, inattentive vs combined ADHD	Yes	Yes	Yes	Yes	Yes NR NR NR

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

					External Validity	
Study	**Loss to followup: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/ enrolled**	**Exclusion criteria**
Wigal 2005	None	No; 12 (5.6%) excluded from analysis; reasons for exclusion unclear	NR	Fair	NR/NR/215	DSM-IV-TR diagnosis of ADHD, predominantly inattentive subtype; current controlled or uncontrolled comorbid psychiatric diagnosis, except ODD, with significant symptoms such as pervasive developmental disorder, post-traumatic stress disorder, psychosis, bipolar illness, severe obsessive-compulsive disorder, severe depression, or severe anxiety disorder; documented history of aggressive behavior serious enough to preclude participation in regular classroom activities, or a DSM-IV-TR diagnosis of conduct disorder; documented allergies, adverse reactions, or intolerance of stimulants, including MAS XR, atomoxetine, or tricyclic antidepressants, or a history of failure to respond clinically to adequate doses of these medications; history of suspected substance abuse of drug abuse (excluding nicotine) or living with someone with such history of suspicion; taking any prohibited medication including antidepressants, antipsychotics, neuroleptics, anxiolytics, and anticonvulsants; or history of seizure during the past 2 years, a tic disorder, or a family history of Tourette's Disorder.
Wolraich 2001	No/No	Yes	No	Fair	500/405/312 randomized	Acute or serious chronic disease, were hypersensitive to methylphenidate, were having significant adverse experiences from methylphenidate, or were taking a medication that would interfere with the safe administration of methylphenidate; patients with glaucoma, Tourette's syndrome, an ongoing seizure disorder, or a psychotic disorder, as were girls who had reached menarche.

Evidence Table 4. Quality assessment of head-to-head trials in children with ADHD

Study	Run-in/ Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Wigal 2005	4-day single-blind placebo lead-in period/washout of previous medications, but no details provided	No	Yes	In part by NIMH award MH02042 and a grant from Shire	Yes
Wolraich 2001	NR/NR	No	Yes	Alza	Yes

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Atomoxetine			
Biederman 2002 Subgroup Analysis of Girls from Michelson 2001	RCT, DB	51 girls who met the diagnostic criteria for ADHD based on DSM-IV and as assessed by clinical interview and the Kiddie Schedule for Affective Disorders and Schizophrenia and with normal intelligence based on WISC, 3rd edition. Exclusionary criteria: poor metabolism of cytochrome P450 2D6 isoenzyme, weight <25kg at initial visit; a documented history of bipolar I or II or of psychosis; history of organic brain disease or a seizure disorder; currently taking psychotropic medicine; history of alcohol or drug abuse in past 3 months; positive screening for drugs of abuse; or significant previous or current medical conditions (e.g., HIV positive, surgically corrected congenital heart defects, leukemia in remission).	Oppositional/defiant disorder: 38.5% Phobias: 13.5%

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Atomoxetine				
Biederman 2002 Subgroup Analysis of Girls from Michelson 2001	Randomized to receive atomoxetine or placebo, dosed in the morning and in the late afternoon/early evening. 9-weeks duration. Atomoxetine was titrated up to a maximum daily dose of 2.0 mg/kg per day (max. total daily dose = 90 mg/day)	2-week washout, screening, and assessment period	No	Primary efficacy measure: ADHD Rating Scale - IV-Parent Version (ADHD RS), an 18-item scale. Secondary measures: Conners' Parent Rating Scale-Revised: Short Form (CPRS-R) and the Clinical Global Impressions of ADHD Severity (CGI-ADHD-S). The ADHD RS was given at every weekly visit (it assessed the severity of symptoms in the previous week) to parents.

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Atomoxetine				
Biederman 2002 Subgroup Analysis of Girls from Michelson 2001	Mean age in years: 9.66 Males = 0% Ethnicity = NR	Diagnostic subtypes: -Inattentive = 21.2% -Hyperactive/impulsive = 0% -Combined = 78.8% Mean Scores: WISC Full Scale IQ = 105.2 ADHD RS Total T-Score = 88.9 ADHD RS (Total) = 38.2 ADHD RS Inattentive subscale = 21.4 ADHD RS Hyperactive/Impulsive subscale = 16.7 CPRS-R ADHD index = 26.9 CGI-ADHD-S = 4.8	NR/NR/291 (52 total girls)	1/NR/51

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Atomoxetine	
Biederman 2002 Subgroup Analysis of Girls from Michelson 2001	ADHD RS Total score decrease - Atomoxetine-treated vs. placebo: -15.8 vs. -5.8, p=0.002 ADHD RS Inattentive subscale decrease - Atomoxetine-treated vs. placebo: -8.8 vs. -3.4, p=0.001 ADHD RS Hyperactivity/Impulsive subscale decrease - Atomoxetine-treated vs. placebo: -7.0 vs. -2.3 p=0.006 A visit-wise analysis found that atomoxetine-treated patients experienced significant efficacy over placebo that was evident every week of treatment (p<0.05 for Weeks 1,2,5, and 6; p<0.01 for Weeks 3,4,7,8, and 9) CPRS-R ADHD Index scores decrease - Atomoxetine-treated vs. placebo: -10.3 vs. -1.0, p<0.001 CGI-ADHD-S score decrease - Atomoxetine-treated vs. placebo: -1.5 vs. -0.6, p<0.001

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported			Total withdrawals; withdrawals due to adverse events	Comments
Atomoxetine						
Biederman 2002 Subgroup Analysis of Girls from Michelson 2001	AE's reported by patients		Atom.(n=31)*	Placebo(n=21)*	3 withdrawals/ 2 due to AE's	
		Rhinitis	25.8%	38.1%		
		Abdominal pain	29.0%	14.3%		
		Headache	25.8%	14.3%		
		Pharyngitis	19.4%	19.0%		
		Decreased appetite	19.4%	19.0%		
		Vomiting	19.4%	0%		
		Cough increased	16.1%	4.8%		
		Nervousness	6.5%	14.3%		
		Somnolence	6.5%	14.3%		
		Nausea	6.5%	14.3%		
		Emotional lability	3.2%	14.3%		
		Fever	9.7%	4.8%		
		Insomnia	3.2%	9.5%		
		Diarrhea	3.2%	4.8%		
		Dizziness	3.2%	4.8%		
		*(no statistically significant differences between these two groups)				
		1 patient withdrew from each group due to AE's - one had chest pain, the other had somnolence				

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Kaplan 2004 U.S. ODD/ADHD subset analysis of Spencer 2002	DB, PCT	Patients were 7-13 years and met diagnostic criteria for ADHD as defined by DSM-IV and met diagnostic criteria for ODD as characterized by DICA-IV and confirmed by clinical assessment according to the DSM-IV criteria. All children had an IQ in the normal range, as measured by the WISC-III.	All patients (n=98) in this subset had ODD

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Kaplan 2004 U.S. ODD/ADHD subset analysis of Spencer 2002	see Spencer 2002 above Atomoxetine (n=53) Placebo (n=45) Max dose was the lower of either 2 mg/kg/d or 90 mg/d Mean total daily dose: 55.3 mg (SD = 19.0) Treatment as follows: 2 week medication washout (visits 1-3), then a 9-week DB treatment phase (visits 3-12) and then a 1 week single blind discontinuation phase (visits 12-13).	NR / 2-week washout	NR	Primary efficacy measure: ADHD RS - IV-Parent Version, an 18-item scale. The Inattention and Hyperactivity/Impulsivity subscales were also computed. Secondary measures: Conners' Parent Rating Scale-Revised: Short Form (CPRS-R) and the Clinical Global Impressions of ADHD Severity (CGI-ADHD-S).

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Kaplan 2004 U.S. ODD/ADHD subset analysis of Spencer 2002	Mean age: 9.98 years 79.6% male Ethnicity: NR	Mean WISC-III Full scale IQ: 104.9 Mean ADHD-RS Total score: 42.1 ADHD-RS Inattentive subscale: 22.0 ADHD Hyperactive/Impulsive subscale:20.0 CGI-ADHD-S: 5.15 Conners Parents RS: ADHD Index: atomoxetine 27.3 vs placebo 28.6	see above Spencer 2002	in this subset, 24 / NR / 98

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Kaplan 2004 U.S.	Mean change in scores, baseline to endpoint, atomoxetine vs placebo: ADHD RS Total : -17.0 vs -7.5, p<0.001 (effect size=0.72) Inattentive subscale: -8.7 vs -3.9, p<0.001 (effect size=0.71) Hyperactive/Impulsive subscale: -8.3 vs -3.6, p=0.002 (effect size=0.66)
ODD/ADHD subset analysis of Spencer 2002	CGI-ADHD-Severity: -1.5 vs -0.7, p=0.003 Conners' Parent rating scale and subscale scores: ADHD Index: -7.7 vs -3.2, p=0.005 Cognitive: -4.1 vs -1.6, p=0.006 Hyperactive: -4.3 vs-1.3, p=0.003 Oppositional: -2.4 vs -1.8 p=0.796

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Kaplan 2004 U.S. ODD/ADHD subset analysis of Spencer 2002	See Spencer 2002	AEs with significant differences, atomoxetine vs placebo: Decreased Appetite: 18.9% vs 2.2%, p<0.01 Emotional Lability: 11.3% vs 0.0%, p=0.03 Other AEs: atomoxetine vs placebo: Abdominal pain: 28.3% vs 22.2%, p=0.643 Headache: 28.3% vs 28.9%, p>0.99 Rhinitis: 24.5% vs 35.6%, p=0.271 Pharyngitis: 18.9% vs 15.6%, p=0.791 Nausea: 15.1% vs 11.1%, p=0.766 Nervousness: 15.1% vs 6.7%, p=0.271 Vomiting: 15.1% vs 15.6%, p>0.99 Cough increased: 11.3% vs 8.9%, p=0.75 Diarrhea: 11.3% vs 8.9%, p=0.75 Somnolence: 11.3% vs 6.7%, p=0.501 Fever: 7.5% vs 13.3%, p=0.505	24 (12 per group) ; 5 (3 in atomoxetine and 2 in placebo)	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Kelsey 2004	RCT, DB	Children 6 to 12 years of age who met Diagnostic and Statistical Manual of Mental Disorders (4th ed.) criteria for ADHD, as assessed in clinical interviews and confirmed in parent interviews using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged children-Present and Lifetime Version. All patients were required to meet a symptom severity threshold, with a symptom severity score at least 1.5 SDs above age and gender normative values, as assessed with the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored (ADHD RS), for the total score or either of the inattentive or hyperactive/impulsive subscales.	Oppositional/defiant disorder: 37.6% of atomoxetine group; 29.7% of placebo group Conduct disorder: 5.3% of atomoxetine group; 1% of placebo group

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Kelsey 2004	randomized to receive atomoxetine or placebo, dosed once daily in the mornings. Patients in atomoxetine group were given 0.8mg/kg/day for 3 days, with the dose increasing to 1.2mg/kg/day. Dose never to exceed 120 mg/kg/day. This was a 8 week treatment study.	5 day washout period.	NR/NR	ADHD RS, Daily parent Ratings of Evening and Morning Behavior Revised (DPREMB-R), Conners Global Index; Parent-Evening (GIPE), CGI ADHD-S.

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Kelsey 2004	Children aged 6-12 years/71% enrolled were male/ ethnicity NR.	ADHD Subtypes Combined: 37.6% of atomoxetine, 67.2 % of placebo Hyperactive/impulsive: 3.8% atomoxetine, 3.1% of placebo Inattentive: 26.3% of atomoxetine, 29.7% of placebo	260 screened/197eligible/197 enrolled	Atomoxetine: 26 withdrawn 4 lost to fu 107 analyzed Placebo: 17 withdrawn 3 lost to fu 47 analyzed

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Kelsey 2004	Source: Atomoxetine: baseline vs endpoint vs change; Placebo: baseline, endpoint, change; 95%CI for Difference From Placebo ADHD RS (atomoxetine: n=126; placebo: n=60) Total score: 42.1 (9.2) vs 25.3 (14.3) vs -16.7 (14.5)*; 42.3 (7.1) vs 35.2 -12.3) vs -7.0 (10.8); -13.8, -5.9 Inattentive subscore: 22.6 (3.9) vs 14.3 (7.6) vs -8.3 (8.0)*; 23.0 (3.4) vs 19.0 (6.5) vs -4.1 (6.1); -6.7, -2.3 Hyperactive/impulsive subscore: 19.5 (6.8) vs 11.0 (7.7) vs -8.5 (7.5)*; 19.2 (5.9) vs 16.3 (7.5) vs-2.9 (5.8); -7.5, -3.4 DPREMB-R (atomoxetine: n= 113; placebo: n=50) Total Score: 17.1 (7.2) vs 9.4(6.3) vs -7.7 (5.8); 15.4 (6.7) vs 10.9 (6.1) vs -4.5 (5.3) vs -4.0, -0.9 Evening subscore: problems with homework/tasks: 1.8(0.8) vs 1.0(0.7) vs -0.8 (0.7)*; 1.6(o.8) vs 1.2 (0.7) vs -0.4 (0.6) ; -0.4,-0.1 difficulty sitting through dinner: 1.4(0.8) vs 0.8(0.7) vs -0.6(0.7); 1.3(0.8) vs 0.8(0.7);-0.5 (0.6); -0.3, 0.1 Difficulty playing quietly: 1.7(0.9) vs 0.9 (0.7) -0.9(0.7)*; 1.5(0.8) vs 1.1 (0.8) vs -0.4 (0.7) ; -0.6, -0.2) Inattentive and distractible: 1.9(0.7) vs 1.1 (0.7) vs -0.9 (0.7)*; 1.8 (0.7) vs 1.3 (0.7) vs -0.5(0.6) ; -0.4, -0.1 Difficulty transitioning: 1.6(0.7) vs 0.9(0.6) vs -0.7(0.7); 1.5(0.7) vs 1.1(0.6) vs -0.5(0.7); -0.4,-0.1 Arguing or struggling: 1.7(0.8) vs 1.0(0.7) vs-0.79).7); 1.6(0.8) vs 1.1(0.8) vs -0.5(0.7); -0.4,0.0 Difficulty settling at bedtime: 1.7(0.8) vs 0.8(0.7) vs -0.8(0.7)*; 1.5(0.8) vs 1.0(0.7) vs-0.5, -0.7); -0.5,-0.1 Difficulty falling asleep: 1.2(0.7) vs 0.6(0.7) vs -0.6(0.7); 1.1(0.9) vs0.7(0.7) vs -0.4(0.7); -0.3, 0.0 Morning subscore Difficulty getting out of bed: 1.2(90.8) vs 0.7(0.7) vs -0.5(0.6); 1.3 (0.7) vs 1.0(0.6) vs -0.3(0.6); -0.4, -0.0 Difficulty getting ready: 1.5(90.7) vs 0.9(0.7) vs -0.6(0.6)*; 1.3(0.7) vs 1.0(0.6) vs-0.3(0.6); -0.4, -0.0 Arguing or struggling: 1.3(0.8) vs 0.7(0.7) vs -0.6(0.7)*; 1.2 (0.8) vs 0.9(0.7) vs -0.3(0.7); -.4, -0.0 Conners GIPE (atomoxetine: n=127, placebo: n=60) Total Score: 20.1(6.1) vs 13.3(7.3) vs -6.8(6.8)*; 20.1(5.5) vs 16.9(7.3) vs -3,2(6.9); -5.7, -1.8 Restless-impulsive subscale total: 15.8(4.2) vs 10.1(5.6) vs -5.7(5.3)8; 15.5(4.1) vs 13.5(5.3) vs-2.0(5.2); -5.2,-2.1 Emotional liability subscale total: 4.3(2.6) vs 3.2(2.5) vs -1.2(2.4)*; 4.6(2.4) vs 3.4(2.7) vs-1.3(2.4); -0.7, 0.6 CGI-ADHD-S (atomoxetine: n=126; placebo: n=60): 5.0(0.8) vs 3.5(1.3) vs -1.6(1.4)*; 5.0(0.8) vs -0.7(1.1) ; -1.2; 5 * p<.05

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Kelsey 2004	measuring vital signs, ECK's, open-ended questioning about negative physical symptoms and laboratory tests.	**Event: Atomoxetine (n=131) vs Placebo (n=63)** Decreased appetite: 23 (17.6)* vs 4(6.3) Abdominal Pain: 20(15.3) vs 4(6.3) Nausea: 15(11.5) vs 5(7.9) Somnolence: 19(14.5)* vs 1(1.6) Headache: 9(6.9) vs9(14.3) Fatigue: 13(9.)* vs 1 (1.6) Dyspepsia: 8(6.1) vs 1(1.6) Vomiting: 8(6.1) vs 1(1.6) Diarrhea: 2(1.5) vs 4 (6.3) *=p<.05	Atomoxetine: 6 Placebo: 1	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Michelson 2002	RCT, DB, parallel, setting: NR	Children and adolescents, 6-16 years of age, who met DSM-IV criteria for ADHD, as assessed by clinical interview and confirmed by the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL)(7), were eligible to participate. All patients were required to meet a symptom severity threshold: a score at least 1.5 standard deviations above age and gender norms as assessed by the investigator-administered and -scored parent version of the ADHD Rating Scale -IV. Comorbid psychiatric conditions were assessed clinically and with the K-SADS-PL.	Co-morbidity trait: placebo n vs atomoxetine n Oppositional defiant disorder: 21.2% vs 18.8% Depression: 1.2% vs 2.4% Generalized Anxiety Disorder: 0% vs 1.2% Specific Phobia: 2.4% vs 3.5%.

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Michelson 2002	Patients in Atomoxetine treatment group began at 0.5mg/kg/day for 3 days, followed by 0.75mg/kg/day for the remainder of the first week. The daily dose was then increased to 1.0mg/kg/day. This was a 6 week treatment.	NR	5 day washout	Primary outcome measure was total score on ADHD Rating Scale-IV. Other outcome assessment tools included: Connor's Parent Rating Scale-Revised: Short Form, Connor's Teacher Rating Scale-Revised: Short Form, CGI severity score, 13-item parent-rated diary assessing efficacy rates with a Likert scale. Laboratory exams were also conducted at baseline and endpoint.

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Michelson 2002	children aged 6-16 years/ 70.6% male, 29.4 female/ ethnicity NR.	**ADHD subtypes** mixed: 60% of placebo, 55.3% of atomoxetine group hyperactive/impulsive: 0% of placebo, 3.5% of atomoxetine group inattentive: 40% of placebo, 41.2 of atomoxetine	NR/ 171/170	3%/NR/ 170

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Michelson 2002	Placebo(N=83) baseline mean vs mean of change from baseline; Atomoxetine(N=84) baseline mean vs mean of change from baseline; analysis of variance p-value ADHA rating scale-IV: 36.7 vs -5; 37.6 vs -12.8; p=<0.001 Inattentive symptoms: 21.4 vs -2.9; 21.9 vs -7.1; p=<0.001; Hyperactive/impulsive score: 15.3 vs -2.1; 15.7 vs -5.7; p=<0.001 CGI severity score: 4.6 vs -0.5; 4.7 vs -1.2; p=<0.001 Conners Parent rating scale: 26.5 vs -2.4; 27 vs -7.6; p=<0.001 Connors Teacher rating scale: 21.6 vs -1.6; 21.5 vs -5.1; p=0.02 Parent ratings of offspring behavior problems with homework/tasks: 1.8 vs -0.3; 1.8 vs-0.5; p=0.49 sitting thorough dinner: 1.0 vs -0.1; 1.3 vs-0.4; p=0.18 difficulty playing quietly: 1.4 vs -0.3; 1.5 vs -0.5; p=0.15 inattentive and distractible: 1.8 vs -0.3; 1.9 vs -0.7; p=.003 arguing or struggling-evening: 1.4 vs -0.3; 1.5 vs -0.4; p=0.89 irritability-evening: 1.3 vs -0.3; 1.6 vs -0.6; p=0.43 difficulty with transitions: 1.5 vs -0.3; 1.6 vs -0.6; p=0.13 difficulty settling at bedtime: 1.7 vs -0.3; 1.8 vs -0.6; p=0.30 difficulty falling asleep: 1.6 vs -0.4; 1.8 vs -0.6; p=0.30 difficulty getting out of bed: 1.1 vs -0.2; 1.1 vs -0.3; p=0.53 difficulty getting ready: 1.4 vs -0.2; 1.1 vs -0.3; p=0.53 arguing or struggling-morning: 1.0 vs -0.2; 1.0 vs-0.2; p=0.63 irritability-morning: 0.8 vs -0.1; 0.8 vs -0.1; p=0.74

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Michelson 2002	reports from patient/parent of negative physical symptoms	**Event: Placebo: N, % vs Atomoxetine: N, %; Fisher's Exact p** Headache: 15, 17.6% vs 17, 20.0%; 0.85 Rhinitis: 18, 21.2% vs 14, 16.5%; 0.56 Decreased appetite: 5, 5.9% vs 17, 20.0%; 0.02 Abdominal pain: 7, 8.2% vs 14, 16.5%; 0.17 Pharyngitis: 13; 15.3% vs 6, 7.1%; 0.15 Increased coughing: 11, 12.9% vs 6, 7.1%; 0.31 Somnolence: 6, 7.1%; 9, 10.6; 0.59 Vomiting: 1, 1.2% vs 13, 15.3%; 0.001 Nausea: 2, 2.4% vs 10, 11.8%; 0.04 Asthenia: 1, 1.2%, 9, 10.6%; 0.02 Emotional lability: 4, 4.7%, 6, 7.1%; 0.50 Rash: 4, 4.7%; 5, 7.1; 0.75 Accidental injury: 4, 4.7%; 5, 5.9%; 0.99 Fever: 3, 3.5%; 6,7.1%; 0.50 Dyspepsia: 0, 0%; 8, 9.4%; 0.007 Dizziness: 0, 0%; 5,5.9%; 0.06	3 subjects/2 subjects	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Michelson 2001 Good quality	RCT, DB, parallel, Setting: 13 outpatient sites in the United States, Patient visits were weekly for the first 4 weeks of study, and bi-weekly for the remaining 4 weeks of study.	Patients aged 8-18 years of age, meeting the DSM-IV criteria for ADHD by clinical assessment and confirmed by structured interview (behavioral module of the Kiddie Schedule for Affective disorders and Schizophrenia for School-Aged Children-Present and Lifetime Versions).	ADHD subtypes: mixed: 67%, hyper-active/impulsive: 2%, inattentive: 31%, unspecified: less than 1%. Co-morbid conditions: oppositional/defiant disorder: 38%, depression: less than 1%, generalized anxiety disorder: less than 1%.
Michelson 2004	RCT, DB Setting: 33 academic investigative centers in Europe (24 centers), Israel (two centers), South Africa (four centers), and Australia (three centers)	Patients aged 6 to 15 years who met DSM-IV criteria for ADHD assessed by clinical history and confirmed by a structured interview (schedule for affective disorders and schizophrenia for school-age children-present and life-time version [K-SADS-PL]) and whose symptom severity was at least 1.5 SD above US age and gender norms	Atomoxetine: n=292 Comorbid condition oppositional defiant disorder: 42.1% depression: 2.1% generalized anxiety disorder: 2.7% Placebo: n=124 Comorbid condition oppositional defiant disorder: 45.2% depression: 1.6% generalized anxiety disorder: 2.4%

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Michelson 2001 Good quality	Placebo Atomoxetine doses randomized to .5mg/kg/day, 1.2mg/kg/day, or 1.8mg/kg/day. Amounts were divided equally to patients to 2 daily doses, for 4 weeks.	12-18 day evaluation and washout period. Sizes NR.	NR	ADHD RS (semistructured interview with patient's caregiver), Conner's Parent Rating Scale: revised: short-form, Clinical Global Impressions of Severity. Affective symptoms were assessed using Children's Depression Rating Scale. Social and family functioning assessed with Child health Questionnaire. Binary measure assessed with Fisher's exact test. Dose-response relationships assessed with Cochran-Armitage trend test.
Michelson 2004	atomoxetine 1.2mg/kg/day-1.8mg/kg/day for the first 10 weeks then atomoxetine or placebo for 9 months Duration: 9 months	NR	NR	ADHD RS and Clinical Global Impressions of Severity (CGI-S): primary assessments, bi-weekly. Child Health Questionnaire, Children's Depression Rating Scale, Conners Parent Rating Scale-Revised: Short, Conners Teacher Rating Scale-Revised: Short, WISC-III, and the Multidimensional Anxiety Scale.

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Michelson 2001 Good quality	mean age 11.2 male: 71% female: 29% ethnicity NR.	Placebo vs Atomoxetine 0.5mg/kg/day vs 1.2 mg/kg/day vs 1.8 mg/kg/day **Total ADHD subtype (%)** Inattentive: 682 (23.1) Hyperactive/impulsive: 197 (6.7) Combined: 2072 (70.2) **Comorbidity (%)** ODD: 31(36.9) vs 21 (47.7) vs 25 (29.8) vs 36 (42.4) Generalized anxiety disorder: 1 (1.2) vs 0 vs 0 vs 0 Depression:0 vs 0 vs 0 vs 1 (1.2)	381/297/297	16 (16.5%) withdrawn/ 10 (3.3%) lost to fu/292 . Placebo n=83, ATMX .05 n=43; ATMX 1.2 n=84; ATMX 1.8 n=82.
Michelson 2004	Atomoxetine: n=292 Mean age: 10.6 years 89.4% male Ethnicity: NR Placebo: n=124 Mean age: 10.1 years 90.3% male Ethnicity: NR	Atomoxetine: n=292 ADHD subtype combined: 72.6% hyperactivity/impulsive: 4.5% Inattentive: 22.9% Previous stimulant treatment: 53.8% Placebo: n=124 ADHD subtype combined: 74.2% hyperactivity/impulsive: 4.8% Inattentive: 21.0% Previous stimulant treatment: 50.0%	NR/NR/604	10/NR/414

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Michelson 2001 Good quality	Placebo vs Atomoxetine 0.5 mg/kg (n=43) vs Atomoxetine 1.2 mg/kg (n=84) vs Atomoxetine 1.8 mg/kg (n=82) (all with 95% CI for difference from placebo ADHD RS Total: -5.8 vs -9.9 (-8.9, 0.9) vs -13.6 (-12.1, -4.0, p<0.05) vs -13.5 (-11.9, -3.7; p<0.05) Inattention subscale: -2.5 vs -5.1 (-5.2, 0.3) vs -7.0 (-6.8, -2.2, p<0.05) vs -6.8 (-6.6, -2.0, p<0.05) Hyper/Imp Subscale: -3.2 vs -4.8 (-4.1, 1.0) vs -6.6 (-5.6, -1.4, p<0.05) vs -6.7 (-5.7, -1.4, p<0.05) CPRS-R ADHD Index: -1.5 vs -7.2 (-9.2, -2.1, p<0.05) vs -8.9 (-10.3, -4.5, p<0.05) vs -8.8 (-10.0, -4.2, p<0.05) Hyperactive Subscale: -1.1 vs -4.1 (-4.5, -1.2, p<0.05) vs -4.1 (-4.4, -1.6, p<0.05) vs -4.3 (-4.5, -1.8, p<0.05) Cognitive Subscale: -0.4 vs -2.4 (-4.7, -0.6, p<0.05) vs -4.8 (-6.0, -2.6, p<0.05) vs -4.6 (-5.8, -2.4, p<0.05) Oppositional Subscale: 1.1 vs -0.3 (-4.0, 1.6) vs -1.5 (-5.0, -0.5, p<0.05) vs -2.0 (-5.2, -0.7, p<0.05) CDRS-R: 1.1 vs -0.3 (-4.0, 1.6) vs -1.5 (-5.0, -0.5, p<0.05) vs -2.0 (-5.2, -0.7, p<0.05) CHQ Physical: 0.4 vs -.6 (-4.1, 0.25 vs -1.1 (-4.0, 1.4) vs -2.0 (-4.9, 0.5) Psychosocial Summary Score Behavior: -0.4 vs 8.2 (1.7, 15.7, p<0.05) vs 13.0 (7.9, 19.5, p<0.05), 16.3 (10.9, 22.4, p<0.05) Family activity: 0.7 vs 8.7 (-0.6, 17.9) vs 14.6 (6.3, 21.5, p<0.05), 15.2 (7.3, 22.2, p<0.05) Parent impact-emotional: 3.0 vs 5.7 (-6.1, 11.1) vs10.1 (-0.3, 14.0) vs 11.0 (1.2, 15.2, p<0.05) Child emotional: -4.4 s 7.6 (-3.2, 26.1) vs 7.9 (-0.4, 23.9) vs 15.9 (7.7, 31.6, p<0.05) Child mental health: -1.9 vs 7.7 (3.7, 15.1, p<0.05) vs 4.5 (1.6, 11.1, p<0.05) vs 8.9 (5.6, 15.0, p<0.05) Child self-esteem: 1.4 vs 1.4 (-4.7, 9.3) vs 5.4 (-3, 11.9, p<0.05) vs 8.4 (4.2, 15.6, p<0.05)
Michelson 2004	Survival curve, proportion not relapsing: atomoxetine>placebo, p<0.001 Atomoxetine baseline: change from baseline vs. placebo baseline: change from baseline *ADHD RS*- 15.8: 6.8 vs 15.7: 12.3, p<0.001 *CGI-S score*- 2.3: 0.9 vs 2.2: 1.4, p=0.003 *CPRS*- oppositional, 6.5: 1.6 vs 5.4: 2.7, p=0.027; cognitive problems, 7.3: 1.9 vs 6.8: 3.7, p<0.001; hyperactivity- 4.5: 1.5 vs 4.6: 3.1, p=0.001; ADHD index, 13.7: 3.7 vs 13.3: 6.9, p<0.001 *CTRS*- all NS *CHQ*- 43.4: -5.6 vs 44.0: -9.5, p=0.016

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Michelson 2001 Good quality	The following vital signs were tracked throughout the study: Blood Pressure Systolic, Diastolic, Pulse, Weight. Patient self-reports of negative health symptoms were noted at appointments.	**Symptom: placebo vs ATMX .5mg/kg/day vs ATMX 1.2mg/kg/day vs ATMX 1.8 mg/kg/day.** Headache: 19 vs 11 vs 20 vs 20. Rhinitis: 18 vs 7 vs 10 vs 12. Abdominal pain: 9 vs 5 vs 12 vs 12. Pharyngitis: 12 vs 4 vs 9 vs 9. Anorexia: 4 vs 3 vs 10 vs 10. Vomiting: 5 vs 3 vs 6 vs 9. Cough increased: 4 vs 6 vs 6 vs 7. Somnolence: 3 vs 2 vs 6 vs 9. Insomnia: 5 vs 4 vs 5 vs 4. Rash: 3 vs 3 vs 5 vs 7. Nausea: 5 vs 2 vs 6 vs 4. Nervousness: 4 vs 3 vs 5 vs 5. Fever: 5 vs 1 vs 7 vs 3. Pain: 5 vs 4 vs 2 vs 5. Accidental injury: 7 vs 1 vs 3 vs 3. Asthenia: 4 vs 3 vs 2 vs 4. Infection: 1 vs 0 vs 5 vs 6. Dizziness: 1 vs 4 vs 2 vs 4. Diarrhea: 5 vs 0 vs 4 vs 0. Depression: 5 vs 1 vs 0 vs 2. Pruritus: 0 vs 0 vs 1 vs.5	Less than 1% of withdrawals were due to adverse events.	
Michelson 2004	Self-report	atomoxetine: placebo number of adverse events- 191(65.6%): 66(53.7%), p=0.027 mean weight gain- 1.2: 3.3, p<0.001 mean height gain- 2.5: 2.9, p=0.088 NS in routine chemistry, liver function tests, hematological measures, or cardiac QT intervals(corrected for heart rate)	atomoxetine: 9(3.1%) placebo: 1(0.8%) p=0.293	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Spencer 2002	RCT DB	Patients were at least 7 years of age but less than 13 years of age at the initial visit and were determined to be of normal intelligence based on the Weschler Intelligence Scale for Children-Third Edition (WISC-III). Patients were required to meet DSM-IV diagnostic criteria for ADHD, as assessed by clinical interview and the Kiddie Schedule for Affective Disorders and Schizophrenia, and have a score on the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored (ADHD RS) at least 1.5 standard deviations above the age and gender norms for their diagnostic subtype (primarily inattentive or primarily hyperactive/impulsive) or the total score for the combined subtype.	Atomoxetine: Oppositional defiant disorder-53(41.1%) Elimination disorders-10(7.8%) Phobias-16(12.4%); Dysthymia-7(5.4) Generalized anxiety disorder-4(3.1) Major depressive disorder-4(3.1) Placebo: Oppositional defiant disorder-45(36.3%) Elimination disorders-15(12.1%) Phobias-13(10.5%); Dysthymia-5(4.0) Generalized anxiety disorder-3(2.4) Major depressive disorder-4(3.2)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Spencer 2002	atomoxetine 2mg/kg/day or a total 90mg/day based on therapeutic response and tolerability for 9 weeks	2 weeks	NR/NR	ADHD Rating Scale (ADHD RS) rated by trained clinicians during every visit based on an interview with the parent and child. Responders are defined as having a minimum 25% reduction in ADHD RS total score and also the change in Clinical Global Impression-ADHD-Severity (CGI-ADHD-S) and Conners Parent Rating Scale-Revised: Short Form (CPRS-R:S)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Spencer 2002	Atomoxetine: Age- mean=9.7 Gender- 98(76%) male Placebo: Age- mean=10 Gender- 103(83%) male Race: NR	Mean IQ: Atomoxetine=103, placebo=106.9, p=0.021	409 screened/ 291 eligible/ 253 enrolled	59 withdrawn/ 0 lost to fu/ 253 analyzed

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Spencer 2002	*atomoxetine: placebo= mean-study1, p value; mean-study2, p value* ADHD RS Total= -15.6:-5.5, p<0.001; -14.4:-5.9, p<0.001 ADHD RS sub-- Inattentive= -7.5:-3.0, p<0.001; -7.6:-3.0, p<0.001 Hyperactivity/impulsive= -8.0:-2.5, p<0.001; -6.9:-2.9, p=0.002 CGI-ADHD-severity= -1.2:-0.5, p=0.003; -1.5:-0.7, p=0.001 CPRS-ADHD Index= -5.7:-2.6, p=0.023; -8.8:-2.1, p<0.001 *ADHD RS total score deduction percentage* Study1-- atomoxetine: placebo= 64.1%: 24.6%, p<0.001 Study2-- atomoxetine: placebo= 58.7%: 40.0%, p=0.048

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Spencer 2002	vital sign assessment NR for symptoms	*Atomoxetine: placebo* Headache, abdominal pain, rhinitis, pharyngitis, vomiting, cough increased, nervousness, somnolence, nausea: NS Decreased appetite= 21.7%: 7%, p<0.05 Systolic blood pressure, temperature: NS Diastolic blood pressure= 9.6:8.3, p=0.008 Heart rate, bmp=9.2:1.5, p<0.001	atomoxetine: total withdrawals=27 due to adverse events=6(4.7%) placebo: total withdrawals=32 due to adverse events=3(2.4%)	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Weiss 2005 International	RCT, DB parallel	Children aged 8-12 years with ADHD (any subtype as defined by DSM-IV were eligible. Symptom severity had to be >1.0 standard deviation (SD) above age and sex norms on the ADHD Rating Scale -IV-Teacher Version: Investigator administered and scored (ADHDRS-IV-Teacher: Inv). Patients were also required to have a mean Conners Parent Rating Scale (CPRS-R:S) ADHD index score at least 1.5 SD above age and sex norms.	ODD: 33.3% Generalized anxiety disorder: 2.6% Learning disorder: 29.8% Motor skills disorder: 6.5% Communications disorder: 8.1%

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Weiss 2005 International	Atomoxetine 1.2 to 1.8 mg/kg/d (n=101) Placebo (n=52) 2:1 7-weeks' treatment Mean dose: 1.33 mg/kg of atomoxetine	NR / 5 days	No	Primary efficacy measure: ADHDRS-IV-Teacher: Inv; interviews with primary classroom teacher within 4 days before each clinical visit. Secondary measures: Conners Global Index-Teacher; the Social Skills Rating System-Teacher (SSRS-T); the Brown Attention-Deficit Disorder Scales: Teacher version; the Academic Performance Rating Scale; the Behavioral Grade Measure, CGI-I and CGI-S; and the Conners Parent Rating Scale (CGI-I and CGI-S completed at each visit by investigator; parents completed Conners Parent Rating scale at each visit). All measures were tested at baseline and endpoint.

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Weiss 2005 International	Mean age: 9.9 years 80.4% male Ethnicity: NR	Mean baseline CGI-S score: 4.9 (SD=0.8)	241 / 153 / 153	21 / 3 / 132

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Weiss 2005 International	Atomoxetine vs placebo: Responders, defined as a 20% reduction in ADHDRS-IV-Teacher: Inv : 69% vs 43.1%, p=0.003 Responders, defined as endpoint ADHDRS-IV_Teacher:Inv score within 1 SD of the mean for age and sex: 68% vs 51%, p=0.51 Change in scores from baseline: ADHDRS-IV-Teacher: Inv, Total: -14.5 vs -7.2, p=0.001 Inattentive subscale: -7.5 vs -4.3, p=0.16 Hyperactive/impulsive subscale: -7.0 vs -3.0, p<0.001 CGI-S: -1.5 vs -0.7, p=0.001 CGI-I: +2.6 vs +3.4, p<0.001 Conners Global Index-Teacher: -3.7 vs -0.8, p=0.008 Brown ADD Scale: Teacher: Combined T score: -5.0 vs -2.9, p=0.072 Effort T score: -4.6 vs -1.9, p=0.046 Action T score: -5.7 vs -2.9, p=0.052 APRS, total: +4.8 vs +2.2, p=0.106 Social Skills Rating-Teacher: Problem behavior: -5.3 vs -2.0, p=0.025 Social skills: +4.0 vs +2.4, p=0.196 Conners Parent Rating Scale-Revised Oppositional subscale: -5.4 vs -1.6, p=0.276 Cognitive Problems subscale: -11.8 vs -3.8, p<0.001 Hyperactivity subscale: -12.2 vs -4.2, p<0.001 ADHD Index: -12.1 vs -4.1, p<0.001

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Weiss 2005 International	Assessed by open-ended discussion at each clinic visit	Atomoxetine vs placebo: Decreased appetite: 24.0% vs 3.8%, p=0.001 Somnolence: 17.0% vs 3.8%, p=0.020 Change in weight: -0.67 vs +1.21, p<0.001 Change in heart rate: +3.3 bpm vs -0.1 bpm, p=0.67 Vomiting: differences were not statistically significant Discontinuations (n=6) due to AEs in Atomoxetine group were due to: abdominal pain (n=2), emotional disturbance (n=1), feeling abnormal (n=1), irritability (n=1), vomiting (n=1)	21 ; 6 (all in atomoxetine group) 83.2% of atomoxetine patients completed the study (84 of 101) 92.3% of placebo patients complete study (48 of 52)	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Dexmethylphenidate XR			
Greenhill 2006	RCT DB	Eligible participants were males and females 6 to 17 years of age who met DSM-IV criteria for ADHD of any type, as established by a psychiatric examination and a semistructured diagnostic interview (the ADHD module of the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version). For boys, baseline scores on the Conners ADHD/DSMIV Scale-Teacher version (CADS-T) DSM-IV total subscale were required to be ≥27 for those 6 to 8 years old, ≥24 for those 9 to 11 years old, ≥19 for those 12 to 14 years old, and ≥14 for those 15 to 17 years old. For girls, the respective baseline cutoff scores on the CADS-T were ≥16, ≥13, ≥12, and ≥6. All of the patients were attending school in a classroom setting and had the same teacher for the duration of the study who was able and willing to perform symptom assessments. Patients had to be functioning at age-appropriate levels academically, and female patients who had reached menarche were required to have a negative pregnancy test and to be using adequate and reliable contraception throughout the study. Excluded were those patients with clinically significant abnormalities in vital signs, physical examinations, or laboratory tests; those with a history of seizures or use of anticonvulsant medication, comorbid psychiatric conditions (obtained by clinical interview); those with any medical condition that could interfere with study participation or assessments or that may pose a danger with administration of methylphenidate; those taking psychotropic medications; and those who initiated psychotherapy within the past 3 months. Patients with a positive urine drug screen or with a history of poor response or intolerance to methylphenidate were also excluded, as were those who were pregnant or nursing or were taking any other investigational drug within 30 days of study entry.	None

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Dexmethylphenidate XR				
Greenhill 2006	d-MPH-ER: Mean Final Dose = 24.0 mg/day (SD 7.1) ; Dose Range: 5-30 mg/day Placebo: Mean Final Dose: 26.9 mg/day (SD 7.1)	5-week dose titration phase/NR	NR/NR	Primary Outcome Measure: Conners ADHD/DSM-IV Scale - Teacher version (CADS-T) total subscale score Other Measures: CADS-T Inattentive and Hyperactive-Impulsive subscale scores, CADS-P DSM-IV total subscale score and Inattentive and Hyperactive-Impulsive subscale scores, Clinical Global Impressions-Improvement (CGI-I) and CGI-Severity (CGI-S) scale scores, and Child Health Questionnaire Parent Form 50 scores

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Dexmethylphenidate XR				
Greenhill 2006	Mean age= 10 yrs (Range: 6-17 yrs) 64% male 60.1% white	D-MPH-ER vs. Placebo, NS between groups **DSM-IV ADHD diagnosis N(%)** Inattentive: 22 (21.4) Hyperactive/impulsive: 2 (1.9) Combined Type: 79 (76.7) **Duration of ADHD symptoms, yr** Mean (SD): 5.3 **Received Medication for ADHD in the past N(%)** Yes: 40 (38.8) No: 63 (61.2) **Baseline CADS-T total subscale score** Mean: 34.3 **Baseline CADS-P total subscale score** Mean: 39.5 **Baseline CGI-S rating N(%)** 4: 65 (63.1) 5: 35 (34.0) 6: 3 (2.9)	NR/NR/103	NR/NR/97

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Dexmethylphenidate XR	
Greenhill 2006	**d-MPH-ER vs. Placebo** Conners ADHD/DSM-IV Scale - Teacher version (CADS-T) total subscale score: 16.3 vs. 5.7, p<0.001 CADS-T Inattentive: 8.1 vs. 3.3, p=0.001 CADS-T Hyperactive-Impulsive: 8.2 vs. 2.5, p<0.001 CADS-P DSM-IV total subscale score: 17.6 vs. 6.5, p<0.001 CADS-P Inattentive: 9.5 vs. 3.2, p<0.001 CADS-P Hyperactive-Impulsive: 8.2 vs. 3.3, p<0.001 CGI-I, very much improved or much improved at final visit: 67.3% vs. 13.3%, p<0.001 CGI-S at final visit: moderately ill: 32.0% vs. 64.0% markedly ill: 4% vs. 21.4% severely ill: 0% vs. 2.4% CHQ physical component: NS CHQ psychological component:11.9 vs. 4.3, p<0.001

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Dexmethylphenidate XR				
Greenhill 2006	spontaneously reported	D-MPH-ER vs. placebo (%) Total Adverse Events: 75.5 vs. 57.4, NS Decreased appetite: 30.2 vs. 8.5, p=0.0068 Headache: 24.5 vs. 10.6, NS Abdominal Pain, Upper: 13.2 vs. 12.8, NS Nausea: 11.3 vs. 6.4, NS Nasopharyngitis: 9.4 vs. 6.4, NS Upper respiratory tract infection: 9.4 vs. 6.4, NS Dyspepsia: 7.5 vs. 4.3, NS Insomnia: 7.5 vs. 6.4, NS Abdominal Pain: 5.7 vs. 0, NS Initial Insomnia: 5.7 vs. 4.3, NS Affect lability: 3.8 vs. 0, NS Anorexia: 3.8 vs. 2.1, NS Diarrhea: 3.8 vs. 2.1, NS Fatigue: 3.8 vs. 4.3, NS Gastroenteritis: 3.8 vs. 0, NS Influenza: 3.8 vs. 8.5, NS Irritability: 3.8 vs. 2.1, NS Otitis media: 3.8 vs. 2.1, NS Stomach Discomfort: 3.8 vs. 0, NS Vomiting: 3.8 vs. 4.3, NS	19/1	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Silva 2006	RCT DB crossover	Boys and girls 6–12 years of age who had been diagnosed with ADHD were eligible for enrollment. Patients eligible for inclusion were required to fulfill the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria for ADHD of any type, as established by the Computerized Diagnostic Interview Schedule for Children (C-DISC-4). Patients must also have been stabilized on 20–40 mg/day of MPH for at least 1 month prior to screening. Only those patients whose parents and/or guardians provided written, informed consent were enrolled. Assent was also obtained from all children (documented by signature of those older than 9 years). Girls were required to be premenarchal, sexually abstinent, or using a reliable contraceptive method. Sexually active girls were required to show negative results on a urine pregnancy test. At screening (days –14 to –7), all prospective patients underwent a physical examination, an electrocardiogram (ECG), blood and urine sampling for routine laboratory tests, urine drug screening, and, for girls, a urine pregnancy test. Informed consent was also documented. A complete medical and psychiatric history was obtained, and the C-DISC-4 was conducted to confirm ADHD diagnosis. Children were excluded if the investigator deemed the child's IQ was below average or if there was evidence of an IQ below 80, or if they were home schooled, were diagnosed with Tourette syndrome or a tic disorder, had a concurrent or history of a significant medical or psychiatric illness (schizophrenia, bipolar disorder, or autism) or substance abuse disorder, or if they or their parents or guardians were unable to understand or follow instructions necessary to participate in the study. Patients taking antidepressants, those who had initiated psychotherapy within 3 months preceding screening, and those with a positive urine drug screen, were also ineligible. Children with poor response or intolerance to MPH, currently taking other medications for ADHD, taking or planning to take another investigational drug within 30 days of study start, or who had previously participated in d-MPH-ER studies were also excluded.	None

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Silva 2006	d-MPH-ER 20 mg/day or placebo	NR/NR	NR/NR	Primary Outcome Measure: the Swanson, Kotkin, Agler, M-Flynn, and Pelham rating scale (SKAMP)-Combined scores Other Measures: SKAMP Deportment and Attention subscales, Math—Attempted, and Math—Correct scores

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Silva 2006	Mean age= 9.4 yrs (SD 1.6) (Range: 6-12 yrs) 70.4% male Ethnicity NR ("predominantly Caucasian")	**DSM-IV ADHD diagnosis N(%)** Inattentive: 5 (9.3) Hyperactive/impulsive: 0 Combined Type: 49 (90.7) **ADHD mean duration, years (SD**): 4.6 (1.6)	54/NR/54	1/0/53

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Silva 2006	modafinil vs. placebo SKAMP-Combined scores adjusted mean: -10.014 vs. 0.878, p<0.001 SKAMP Deportment scores, mean change at 12 h postdose: -0.3 vs. 3.6, p=0.001 -estimated from graphic SKAMP Attention score, mean change at 12 postdose: 1.7 vs. 2.6, p=0.046 -estimated from graphic Math—Attempted, mean change at 12 postdose: 20 vs. -11, p< 0.001 -estimated from graphic Math—Correct scores, mean change at 12 postdose: 18 vs. -10, p< 0.001 -estimated from graphic

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Silva 2006	spontaneous reporting by subjects and parents	decreased appetite anorexia: 9.4% vs. 0% fatigue: 3.85% vs. 0% insomnia: 3.85% vs. 0% headache: 1.9% vs. 5.6% irritability: 0% vs. 5.6%	1-Jan	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Lisdexamphetamine			
Biederman 2007	RCT DB	Male and female children aged 6 to 12 years who met DSM-IV criteria for ADHD and ADHD-RS-IV score >= 28	None

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Lisdexamphetamine				
Biederman 2007	LDX 30, 50, or 70 mg with forced-dose titration, or placebo 1 week screening 1 week wash out and 4 weeks treatment 30 mg for 4 weeks, 50 mg (30 mg/d for week 1, with forced-dose escalation to 50 mg/d for weeks 2-4), or 70 mg (30 mg/d for week 1, with forced-dose escalation to 50 mg/d for week 2 and 70 mg/d for weeks 3 and 4), or placebo all 4 weeks	1 week wash out	None	Weekly assessments of ADHD-RS Conners' Parent Rating Scale-Revised: Short Form (CPRS-R) CGI-I

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Lisdexamphetamine				
Biederman 2007	Mean age: 9 yrs. 69% male 53% white	LDX 30 mg vs LDX 50 mg vs LDX 70 mg vs Placebo Combined n(%): 67 (94.4) vs 71 (95.9) vs 71 (97.3) vs 69 (95.8) Hyperactive n(%): 4 (5.6) vs 3 (4.1) vs 2 (2.7) vs 3 (4.2) Mean age of ADHD onset, yrs (SD): 6.9(2.2) vs 7 (2.3) vs 2 (2.2) vs 7.6 (2.2) Prior treatment, n (%) Amphetamine: 7 (9.9) vs 7 (9.5) vs 2 (2.7) vs 6 (8.3) MPH: 14 (19.7) vs 13 (17.6) vs 8 (11) vs 12 (16.7) Stimulant: 3(4.2) vs 3(4.1) vs 5 (6.8) vs 2 (2.8) Atomoxetine: 2 (2.8) vs 0 vs 2 (2.7) vs 1 (1.4) Stimulant/atomoxetine: 1 (1.4) vs 2 (2.7) vs 3 (4.1) vs 4 (5.6) Other: 2 (2.8) vs 1 (1.4) vs 2 (2.7) vs 1 (1.4) None (past 12 mo.): 42 (59.2) vs 48 (64.9) vs 51 (69.9) vs 46 (63.9)	NR/NR/297/290 randomized	60 withdrawals/ 11 / 285 analyzed

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Lisdexamphetamine	
Biederman 2007	At 4 weeks of treatment ADHD-RS-IV total score) was significantly greater with each of the 3 LDX doses compared with placebo (P < 0.001, d[= 3256, F = 35.16) (Data in graphs) Effect sizes based on the ADHD-RS-IV were LDX30 1.21, LDX50 1.34, and LDX70 1.60 (by the corresponding between-group differences and the model-based SD of 12.84). CPRS-R scores were significantly better in active groups than Placebo throughout study (P< 0.01, Data=NR) CGI-I ratings were either "very much improved" or "much improved" in _>70% of patients in the active-treatment groups, compared with 18% of patients receiving placebo. (Data= NR)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Lisdexamphetamine				
Biederman 2007	Observation and asking a non-leading question	Treatment Emergent AEs (%) Any Events **LDX30 71.8 LDX50 67.6 LDX70 83.6** Placebo 47.2 Decreased appetite **LDX30 36.6 LDX50 31.1 LDX70 49.3** Placebo 4.2 Insomnia LDX30 15.5 LDX50 16.2 LDX70 24.7 Placebo 2.8 Irritability **LDX30 11.3 LDX50 8.1 LDX70 9.6** Placebo 0 Dizziness **LDX30 7.0** LDX50 5.4 LDX70 2.7 Placebo 0 Vomiting LDX30 7.0 LDX50 5.4 **LDX70 13.7** Placebo 4.2 Weight loss LDX30 5.6 LDX50 2.7 **LDX70 19.2** Placebo 1.4 Dry mouth LDX30 2.8 LDX50 2.7 **LDX70 8.2** Placebo 0 **P=< 0.05 compared to placebo**	LDX30 15 LDX50 14 LDX70 13 Placebo 18; LDX30 4 LDX50 4 LDX70 10 Placebo 1	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Methamphetamine			
Hall 1973	RCT DB	Male outpatients; with pre-drug age 72-132 months; normal IQ (WISC 80 or above); personality and adjustment difficulties as indicated by one or more combinations of the following behaviors: excitable, impulsive, poor judgment, learning achievement not commensurate with measures of general intelligence, restless or immature, low frustration tolerance, distractibility, short attention span emotional lability, mood changes quickly, clumsy, poor motor coordination; free of observable psychotic behaviors; general diagnostic category due to minimal brain dysfunction; no medical illness which contraindicated stimulant therapy; no concurrent medication during the study; no sever seizures or significant sensory and/or gross motor deficits; any previous stimulant therapy must be discontinued.	None

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Methamphetamine				
Hall 1973	Desoxyephedrine (time released formula) 5 mg/day taken in morning for first 2 weeks Dose increase to 10 mg/day for following 2 weeks (one child required 15mg dose)	NR/NR	NR	Wechsler Intelligence Scale for Children (WISC, 1955) on either pre- or on-drug, Matching Familiar Figures Test (MFFT)Porteus Maze Test (PM), Paired Associate Learning Test (PALT), Werry-Weiss-Peters Activity Scale (WW)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Methamphetamine				
Hall 1973	Mean age: 6.9 yrs. 100% male 93% white	**Class placement, N (%)** regular: 21 (65.6) educationally handicapped: 4 (12.5) limited day: 3 (9.4) aphasia: 2 (6.3) home teacher: 2 (6.3) previously medicated, N (%) Yes: 8 (25) No: 24 (75)	40/32/32	NR/NR/32

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Methamphetamine	
Hall 1973	**desoxyephedrine vs. placebo, mean change** **PALT** Trials: 0.37 vs 1.82 Errors: -1.94 vs. 11.13 **MFFT** Latency: 2.47 vs. -1.50 Errors: -6.75 vs. -0.87 **PM** TA: 1.25 vs. 0.60 TQ: 8.19 vs. 4.75 **Digit Span:** 0.44 vs. 0.76 **WISC** Verbal IQ: 7.17 vs. -0.75 Perf. IQ: 10.31 vs 5.25 FS IQ: 8.19 vs. 2.43 **WW:** -8.62 vs. -1.25

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Methamphetamine				
Hall 1973	NR	NR	NR/NR	dissertation

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
MPH ER (Metadate®)			
Greenhill 2002	RCT, DB (randomized 1:1 to MPH MR vs. placebo)	Children 6-16 years old with a primary diagnosis (based on parent interview using the NIMH Diagnostic Interview Schedule for Children - version 4.0) of AHDH, combined subtype or the predominately hyperactive-impulsive subtype as defined in DSM-IV (diagnostic code 314.01), who were in first grade or higher with a single teacher who could assess their behavior in the morning and afternoon on specified days. Exclusion criteria: comorbid psychiatric diagnosis; history of seizure, tic disorder, or family history of Tourette's syndrome; female having undergone menarche; use of amphetamines, pemoline, or an investigational drug within 30 days of study entry; concomitant use of clonidine, anticonvulsant drugs, or medications known to affect blood pressure, heart rate, or central nervous system function; hyperthyroidism or glaucoma; any concurrent chronic or acute illness (e.g., allergic rhinitis, severe cold) or disability that could confound the study results. Also excluded were children who had failed a previous trial of stimulants for ADHD, had required a third daily dose in the afternoon or evening, had a documented allergy or intolerance to MPH, or were living with anyone who currently had substance abuse disorder (excluding dependency).	None reported

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
MPH ER (Metadate®)				
Greenhill 2002	3-week treatment period. Doses taken at breakfast. Doses began at 20 mg/day and were to be individually titrated up to be: Week 1: 20 mg/day of MPH MR or 20 mg/day for placebo Week 2: 40 mg/day of MPH MR or 36.8 mg/day for placebo Week 3: 60 mg/day of MPH MR or 51.6 mg/day for placebo Mean total daily dose (MPH MR) for week 1: 20 mg/d (0.64 mg/kg/day); mean total daily dose (MPH MR) for week 2: 32.3 mg/d (1.02 mg/kg/day); mean total daily dose (MPH MR) for week 3: 40.7 mg/d (1.28 mg/kg/day). By week 3, 25% (n=38) were taking 20 mg/day of MPH MR; 38% (n=59) were taking 40mg/day; and 28% (n=43) were taking 60 mg/day.	1-week, single-blind run-in period with placebo. 45 (n=24%) of children screened were found to be placebo-responders and were disqualified.	No	Primary efficacy measure: Conners' Teachers Global Index (10 items), completed by phone interview in the morning (~10am) and afternoon (~2 pm) of three alternating days of each treatment week. Secondary efficacy measures: Conners' Parent Global Index (10 item) completed on 1 day of each weekend during the morning, afternoon, and evening. Parents were also asked to complete a global assessment at the final visit, using a diary of observations they had kept during the run-in placebo week.

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
MPH ER (Metadate®)				
Greenhill 2002	Mean age =9 years Male=81.8% White = 81.4% African American = 15.3% Hispanic = 10.2% Other = 3.5%	Previously treated for ADHD = 64 .0%(n=201) Mean Conners' Global Index - Teacher = 12.1 Mean Conners' Global Index - Parent = 13.2 Mean CGI Severity of Disorder = 4.45	507 screened/ 321 eligible /321 enrolled	45 withdrawn (n=28 from placebo, n=17 from MPH MR) /NR /314 analyzed (n=155 MPH MR; n=159 placebo)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
MPH ER (Metadate®)	
Greenhill 2002	At endpoint, investigators rated 64% of children as moderately or markedly improved with MPH MR treatment, compared with 27% of the placebo group. Conners' Global Index - Teacher's Scores (MPH MR vs. placebo): Baseline mean (Standard deviation): 12.7 (7.2) vs. 11.5 (7.35) (p=0.1309) Week 1 mean (SD): 7.3 (4.93) vs. 10.9 (6.56) (p=0.0001) Week 2 mean (SD): 5.8 (4.71) vs. 10.4 (6.75) (p=0.0001) Week 3 mean (SD): 4.7 (4.77) vs. 9.2 (6.30) (p=0.0001) Least squares mean changes between treatment groups differed significantly in favor of MPH MR group (95% CI: 5.26-8.09, t=9.27, df=311, p<0.001). Effect size (calculated from teacher assessment) = 0.78 for MPH MR vs. placebo during last week of treatment. Conners' global index - Teacher's scores (MPH MR vs. placebo) Baseline mean (Standard deviation): 13.6 (6.6) vs. 12.9 (7.6) (p=NR) Weeks 1 and 2: data not specified Week 3 mean (SD): 7.4 (5.9) vs. 10.1 (6.7) (p=NR) Least squares mean change between treatment groups differed significantly in favor of MPH MR group (95% CI: 1.7-4.9, t=3.97, df=297, p<0.001). Effect size (calculated from parent assessment) = 0.4 for MPH MR vs. placebo during last week of treatment.

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
MPH ER (Metadate®)				
Greenhill 2002	Reported and observed AE's. Vital signs were collected at baseline and weekly thereafter. Parents completed the Pittsburgh 11-item side effect questionnaire the same day they completed the Conners' Global Index. Teachers also filled out a similar side effect questionnaire 3 times per week near the end of the school day, on the same days they filled out the Conners' Global Index.	Any Adverse Event (AE) reported: 51.6%(n=80) in MPH MR; 37.9% (n=61) in placebo Headache: 14.8% (n=23) in MPH MR; 10.6% (n=17) in placebo Anorexia: 9.7% (n=15) in MPH MR; 2.5% (n=4) in placebo [anorexia more significant in MPH MR group than in placebo; p=0.007] Abdominal Pain: 9.7% (N=15) in MPH MR; 5.0% (n=8) in placebo Insomnia: 7.1 %(n=11) in MPH MR: 2.5% (n=4) in placebo (these AE's are spontaneous AE's occurring at an incidence >=5% in either treatment group) AE's determined by investigator to be related to study medicine: 32.9% of MPH MR and 17.4% of placebo (Of the two withdrawals due to AE's, one child developed a pruritic, no erythematous, periumbilical rash on the 6th day of MPH MR treatment; whereas the other children developed a headache on Day 4 and dizziness + stomachache on Day 5 of MPH MR treatment.)	45 withdrawals; 2 withdrawals due to adverse events	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
MPH transdermal patch			
McGough 2006	RCT DB crossover	Eligible participants were children between the ages of 6 and 12 years, inclusive, diagnosed with ADHD by Diagnostic and Statistical Manual of Mental Disorders (4th edition) criteria. Diagnosis of ADHD and screening for co-occurring psychopathology was based on the Schedule for Affective Disorders and Schizophrenia for School-Age Children: Present and Lifetime Version (KSADS-PL) and comprehensive clinical psychiatric interviews. The Kaufman Brief Intelligence Test (KBIT) was used to assess mental capacity. Participants were not permitted to enroll if they had a comorbid psychiatric diagnosis (with the exception of oppositional defiant disorder), a history of seizures or tic disorders, mental retardation, or any illness or skin disorder that might jeopardize safety or compromise study assessments. Participants were required to have a total score of ≥ 26 on the ADHD Rating Scale–Fourth Edition at baseline (unmedicated), normal laboratory parameters and vital signs including electrocardiogram (ECG) results, and could not have taken clonidine, atomoxetine, antidepressants, investigational medications, hepatic, P450 enzyme altering agents, medications with central nervous system effects, sedatives, anxiolytics, or antipsychotics within the 30 days prior to screening. Participants were either known to be responsive to stimulants or naïve to stimulant treatment.	patients with concurrent ODD allowed, proportion of ODD patients not reported

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
MPH transdermal patch				
McGough 2006	Methylphenidate: Total daily doses of 10, 16, 20, or 27 mg, delivered over the 9-hour patch wear time Mean Dose: NR	lead-in open label dose optimization phase/NR	NR/NR	Primary Outcome Measure: the Deportment subscale of the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) Teacher Rating Scale measured at multiple time points (predose and 2, 3, 4.5, 6, 7.5, 9, 10.5, and 12 hours postdose) Other Measures: Permanent Product Measure of Performance (PERMP) Derived Measures, the ADHD Rating Scale IV completed by investigators after parental interviews, and the Conners' Parent Rating Scale–Revised Short Version (CPRS-R), Clinical Global Impressions (CGI-S and CGI-I) and Parent Global Assessment (PGA)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
MPH transdermal patch				
McGough 2006	Mean age= 9.1 yrs (SD .7) 72% male 70% white	**ADHD subtypes n (%)** Inattentive: 13 (17) Hyperactive/Impulsive: 4 (5) combined: 62 (79) **ADHD Rating Scale, Mean (SD):** 41.8 (7.6) **CGI-S, Mean (SD)**: 4.4 (0.7)	NR/NR/93	13/2/79

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
MPH transdermal patch	
McGough 2006	**Teacher Rating Treatment/Period/Sequence/Subject-within-sequence,** SKAMP-D, F(1.77): 71.48(p<.0001)/1.25(p=.2664)/.79(p=.3767)/3.26(p<.0001) SKAMP-A, F(1.77): 83.04(p<.0001)/.97(p=.3266)/1.56(p=.2156)/4.98(p<.0001) PERMP-number attempted, F(1.77): 46.34(p<.0001)/3.81(p=0544)/1.42(p=2365)/8.98(p<.0001) PERMP-number correct, F(77.77): 56.24(p<.0001)/6.15(p=.0153)/1.33(p=.2520)/9.97(p<.0001) **Other Measures, MTS vs. placebo** LS Mean SKAMP-D (+/-SE): 3.2 (0.58) vs. 8.0 (0.58), p<0.0001 LS Mean SKAMP-A (+/-SE): 6.2 (0.50) vs. 9.9 (0.50), p<0.0001 ADHD Rating Scale IV: 16 vs. 32, p<0.0001 [estimated from graphic] CPRS-R: 19 vs. 35, p<0.0001 [estimated from graphic] CGI-I: 79.8% vs. 11.6%, p<0.0001 Parent Global Assessment: 71.1% vs. 15.8%, p<0.0001

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
MPH transdermal patch				
McGough 2006	open-ended investigator inquiry at onset, every visit and study ending	**MPH vs. placebo, n (%)** Any adverse event: 24 (30.0) vs. 18 (22.5) Headache: 3(3.8) vs. 3(3.8) Anorexia: 2(2.5) vs. 0 Pharyngolaryngeal Pain: 2(2.5) vs. 1(1.3) Rash: 1(1.3) vs. 2(2.5) Nasopharyngitis: 1(1.3) vs. 2(2.5) Nausea: 3(3.8) vs. 0 Rhinitis allergic: 2(2.5) vs. 0 Blood Pressure Increased: 2(2.5) vs. 0 Lymphadenopathy: 2(2.5) vs. 0 Upper Respiratory Tract Infection: 0 vs. 3(3.8)	13/7	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Modafinil			
Biederman 2005	RCT DB	Patients were 6 to 17 years of age and had a diagnosis of ADHD on the basis of criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) for ADHD at screening, as manifested by a psychiatric/clinical evaluation and the Diagnostic Interview Schedule for Children, Fourth Edition, with a Clinical Global Impression Severity of Illness (CGI-S) rating of 4 or higher ("moderately ill" or worse). In addition, patients were attending full-time school (i.e., they were not being homeschooled); had a teacher-/investigator-rated Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) School Version total and/or subscale score at least 1.5 SDs above normal values for age and gender, were between the 5th and 95th percentile for weight and height on the basis of National Center for Health Statistics guidelines, had an IQ of at least 80 as estimated by the Wechsler Intelligence Scale for Children–Third Edition, and had a score of at least 80 on the Wechsler Individual Achievement Test–Second Edition–Abbreviated. Patients were excluded when they had a history or current diagnosis of pervasive developmental disorder, schizophrenia, or other psychotic disorders (DSM-IV Axis I); evidence of suicide risk; current psychiatric comorbidity that required pharmacotherapy; or other active clinically significant disease. To avoid potential ethical concerns, patients whose ADHD was well controlled and who were satisfied with current ADHD therapy (with low levels of side effects) were also excluded, as were those who had failed to respond to 2 or more adequate courses (dose and duration) of stimulant therapy for ADHD. Other exclusion criteria included a clinically significant drug sensitivity to stimulants, a history of alcohol or substance abuse as defined by DSM-IV criteria, consumption of >250 mg/day caffeine, absolute neutrophil count <1 x 109/L, hypertension (systolic blood pressure [SBP] of ≥122 mm Hg or diastolic blood pressure [DBP] of ≥78 mm Hg for patients aged 6–9 years; SBP of ≥126 mm Hg or DBP of ≥82 mm Hg for patients aged 10–12 years; SBP of ≥136 mm Hg or DBP of ≥86 mm Hg for patients aged 13–17 years), hypotension (sitting SBP <50 mm Hg for patients younger than 12 years or <80 mm Hg for patients 12 years and older), and resting heart rate outside the range of 60 to 115 beats per minute. Concomitant use of prescription or nonprescription agents with psychotropic properties, including ADHD treatments and dietary supplements, was prohibited within 1 week of the baseline visit (within 2 weeks for monoamine oxidase inhibitors and selective serotonin reuptake inhibitors) and during the study.	None

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Modafinil				
Biederman 2005	Modafinil Mean Dose: 368.5 mg Dose Range: 170–425 mg once daily	1- to 4-week washout period prior to randomization	none/NR	Primary Outcome Measure: ADHD-RS-IV School Version total score Other Measures: subscale scores for inattention and hyperactivity-impulsivity for the ADHD-RS-IV School Version and the total, inattention, and hyperactivity-impulsivity scores on the Home Version, the Clinical Global Impression of Improvement scale (CGI-I), Conners' Parent Rating Scale–Revised, Short Form (CPRS-R:S), Social Skills Rating System (SSRS), and Child Health Questionnaire (CHQ)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Modafinil				
Biederman 2005	Mean age=10.3 years 71% male Ethnicity NR	**No Statistically significant between-group differences were observed for any characteristic at baseline.** **CGI-S Score, N (%)** Moderately ill: 115 (47) Markedly ill: 93 (38) Severely ill: 37 (15) Among the most extremely ill: 1 (0.4) **Current ADHD subtype, N (%)** Inattentive: 94 (38) Hyperactive-Impulsive: 7 (3) Combined: 145 (59) **Previous ADHD treatment, N (%)** Methylphenidate-Methylphenidate Hydrochloride: 83 (34) Dexamphetamine Sulfate: 64 (26) Atomoxetine Hydrochloride: 35 (14) Other: 12 (5) **No previous ADHD treatment:** 133 (54) **Most frequently co-administered agents in >10% of patients N (%)** Non-opioid analgesics/Anti-inflammatories: 76 (31) Respiratory Agents: 49 (20) Anesthetics: 41 (20) Antihistamines: 34 (14) Other: 95 (39) **ADHD-RS-IV Total score Mean** School Version: 35.7 Home Version: 37.43	372/NR/248	118/7/244

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Modafinil	
Biederman 2005	**Modafinil vs. Placebo, change (p value)** **No Statistically significant between-group differences were observed for any characteristic at baseline** **CGI-S Score, N (%)** Moderately ill: 115 (47) Markedly ill: 93 (38) Severely ill: 37 (15) Among the most extremely ill: (0.4) **Current ADHD subtype, N (%)** Inattentive: 94 (38) Hyperactive-Impulsive: 7 (3) Combined: 145 (59) **Previous ADHD treatment, N (%)** Methylphenidate-Methylphenidate Hydrochloride: 83 (34) Dexamphetamine Sulfate: 64 (26) Atomoxetine Hydrochloride: 35 (14) Other: 12 (5) **No previous ADHD treatment:** 133 (54) **Most frequently co-administered agents in >10% of patients N (%)** Non-opioid analgesics/Anti-inflammatories: 76 (31) Respiratory Agents: 49 (20) Anesthetics: 41 (17) Antihistamines: 34 (14) Other: 95 (39) **ADHD-RS-IV Total score Mean** School Version: 35.7 Home Version: 37.43 **Modafinil vs. Placebo, change (p value)** **ADHD-RS-IV School Version** Total Score: -15 vs. 7.3(<.0001) Inattention: -8.8 vs. -5.0(<.0001) Hyperactivity-impulsivity: -6.3 vs. -2.3(<.0001) **ADHD-RS-IV Home Version** Total Score: -14.3 vs. -7.0(<.0001) Inattention: -7.9 vs. 3.8(<.0001) Hyperactivity-impulsivity: -6.4 vs. -3.3(.001)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Modafinil				
Biederman 2005	spontaneously reported	Modafinil vs. Placebo N(%) Insomnia: 48(29) vs. 3(4), P<0.05 Headache: 32(20) vs. 12(15), NS Decreased Appetite: 26(16) vs. 3(4), P<0.05 Infection: 19(12) vs. 12(15), NS Rhinitis: 16(10) vs. 9(11), NS Pharyngitis: 14(9) vs. 5(6), NS Cough Increased: 13(8) vs. 7(9), NS Abdominal Pain: 12(7) vs. 9(11), NS Rash: 10(6) vs. 2(4), NS Vomiting: 10(6) vs. 7(9), NS Accidental Injury: 8(5) vs. 5(6), NS Nervousness: 7(4) vs. 5(6), NS Fever: 8(5) vs. 2(2), NS Pain: 8(5) vs. 1(1), NS Asthenia: 6(4) vs. 4(5), NS Somnolence: 4(2) vs. 4(5), NS	118/8	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Biederman 2006	RCT DB	Children aged 6 to 13 years whose height and weight corresponded to greater than the fifth percentile in standardized growth charts and who were attending full-day kindergarten, elementary school, or middle school were eligible. Participants met complete criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), for ADHD (combined type, predominantly inattentive type, or predominantly hyperactive-impulsive type) at screening, as determined by a psychiatric/clinical evaluation and confirmed by the Diagnostic Interview Schedule for Children, Fourth Edition. Eligibility was restricted to those children who were stimulant-naïve (i.e., who had not received stimulant medication in the past) or who had manifested an unsatisfactory response to stimulant therapy. At screening, an intelligence quotient (IQ) of at least 80, as estimated on the Wechsler Intelligence Scale for Children, Third Edition, and a score of 80 or higher on the screener version (for learning disabilities) of the Wechsler Individual Achievement Test were used to rule out low IQ or learning disabilities as contributing causes of symptoms and were required for inclusion. At the baseline visit, children were required to have a clinician-rated Clinical Global Impressions of Severity (CGI-S) score of 4 or more, reflecting their overall clinical condition (moderately ill or worse). For each child, availability of a parent and a weekday teacher who were willing to participate in the study was required. Main exclusion criteria included active, clinically significant gastrointestinal, cardiovascular, hepatic, renal, hematologic, neoplastic, endocrine, neurologic, immunodeficiency, pulmonary, or other major clinically significant disorder or disease; any current psychiatric comorbidity, including but not limited to depression and other mood disorder, anxiety disorder, or pervasive mental disorder that required pharmacotherapy use of any prescription (e.g., clonidine, guanfacine) or nonprescription medication with psychoactive properties (e.g., over-the-counter medications or dietary supplements containing ephedrine, pseudoephedrine,caffeine, or phenylpropanolamine) within 1 week of the start of the washout period; and a history or evidence of substance abuse.	None

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Biederman 2006	Modafinil: Dose Range: Divided doses of 300/0 (300mg/day total), 200/100 (300mg/day total), 100/200 (300mg/day total), 200/200 (400mg/day total), or placebo	7-10 day placebo run-in phase that served as a washout for those patients previously taking psychostimulants	None/NR	Primary Outcome Measure: NR Other Measures: Teacher-rated School Version and clinician-rated Home Version of the ADHD Rating Scale-IV, parent completed Conners' ADHD/DSM-IV Rating Scales (CADS-P), Clinical Global Impressions of Improvement

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Biederman 2006	Mean age=9.2 yrs (Range: 6 to 14 yrs) 75% male 81.4% Caucasian	**NS for all characteristics** **Current ADHD subtype N(%)** Combined: 190 (77) Inattentive: 51 (21) Hyperactive-impulsive: 5 (2) **CGI-S N(%)** Moderately ill: 107 (43) Markedly ill: 118 (48) Severely ill: 21 (8) Among the Most Extremely ill: 2 (0.8) **ADHD—RS-IV Mean, Score** **School Version** Total: 25.6 Inattention: 14.6 Hyperactivity-impulsivity: 11.4 **Home Version** Total: 36.1 Inattention: 19.8 Hyperactivity-impulsivity: 16.2 **CADS-P, Mean, Score** (t score) Total: 74.6 ADHD Index: 73.1 Inattentive: 72.1 Hyperactive-Impulsive: 73.8	343/NR/248	22/4/196

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Biederman 2006	**RESULTS ESTIMATED FROM GRAPHIC** **Mean (SEM) Changes From Baseline to the Final Visit on ADHD Rating Scales for the 300-mg Modafinil dosing groups. (MG) 300/0 vs. 200/100 vs. 100/200 vs. Placebo (p value)** **ADHD-RS-IV, School Version** Total: -8.7(≤.01)/-7.9(<.05)/-5.3(NS)/-2.1(NS) Inattention: -4.8(≤.01)/-4(NS)/-2.7(NS)/-.5(NS) Hyperactivity-impulsivity: -4(<.05)/-3.9(<.05)/-2.7(NS)/-1.2(NS) **ADHD-RS-IV, Home Version** Total: -11.4(≤.001)/-8.1(NS)/-8(NS)/-3.8(NS) Inattention: -6(≤.01)/-4.1(NS)/-4.3(NS)/2(NS) Hyperactivity-impulsivity: -6.7(≤.001)/-4(<.05)/-3.8(NS)/-1.8(NS) **CADS-P** ADHD Index: -7.9(<.05)/-4.3(NS)/-7(NS)/4(NS) Total: -7.1(≤.01)/-6.2(NS)/-7.9(≤.01)/-2(NS) Inattentive: -7(<.05)/-4.8(NS)/-6.4(<.05)/-2.9(NS) Hyperactive-impulsive: -6.4(<.05)/-7(<.05)/-7(≤.01)/-1.6(NS) **Mean (SEM) Changes From Baseline to the Final Visit on ADHD Rating Scales for the 400-mg Modafinil dosing group. (Mg) 200/200 vs. Placebo (P Value)** **ADHD-RS-IV, School Version** Total: -5.4(NS) vs. -2.3(NS) Inattention: -3(NS) vs. -0.3(NS) Hyperactivity-impulsivity: -2.3(NS) vs. -2.1(NS) **ADHD-RS-IV, Home Version** Total: -10.2(.01) vs. -3.8(NS) Inattention: -5.4(.01) vs. -1.8(NS) Hyperactivity-impulsivity: -5(<.05) vs. -2(NS) **CADS-P** ADHD Index: -8.1(NS) vs. -4.1(NS) Total: -8.2(<.05) vs. -2.3(NS) Inattentive: -6.8(NS) vs. -2.9(NS) Hyperactive-impulsive: -8.8(<.05) vs. -2(NS)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Biederman 2006	monitoring reported or observed at 1-week intervals	**(MG) 200/200 vs. 200/100 vs. 100/200 vs. 300/0 vs. Placebo** Headache: 7(14)/6(12)/6(13)/7(14)/11(22) Insomnia: 5(10)/7(14)[p<.05]/6(13)/5(10)/1(2) Infection: 3(6)/1(2)/3(6)4(8)/6(12) Pain (Abdominal): 3(6)/5(10)/6(13)/4(8)/4(8) Cough: 2(4)/2(4)/3(6)/6(12)/2(4) Rhinitis: 2(4)/0(0)/5(10)/2(4)/2(4) Decreased Appetite: 1(2)/4(8)/3(6)/6(12)/1(2) Fever: 0(0)/5(10)/5(10)/2(4)/2(4)	22/9	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Greenhill 2006	RCT DB	Eligible patients met the following inclusion criteria: 6 to 17 years of age, inclusive; the National Institute of Mental Health Diagnostic Interview Schedule for Children, Fourth Edition (DISC-IV) was used to establish the patients' diagnosis of ADHD using the full DSM-IV diagnostic criteria; Clinical Global Impression of Severity of Illness (CGI-S) rating of 4 or higher (moderately ill or worse); weight and height between the 5th and 95th percentile based on the National Center for Health Statistics; intelligence quotient of at least 80; absence of learning disabilities, with a score of at least 80 on the Wechsler Individual Achievement Test, Second Edition, Abbreviated; attending a full-time school (not home school), with a teacher and parent or legal guardian willing to participate; and total and/or factor scores on the teacher-/investigator-rated Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) School Version at least 1.5 standard deviations (SD) above the norm for the patient's age and gender. Patients were excluded if they had a history or current diagnosis of pervasive developmental disorder, schizophrenia, or other psychotic disorders (DSM-IV axis I); any current psychiatric comorbidity that required pharmacotherapy; any evidence of suicide risk; or ADHD symptoms well controlled on current therapy with tolerable side effects. Patients who had failed to respond to two or more adequate courses (dose and duration) of stimulant therapy for ADHD were also excluded. Additional exclusion criteria were absolute neutrophil count (ANC) below 1 X 109/L; hypertension (defined as systolic blood pressure [SBP] ≥122 mmHg or diastolic blood pressure [DBP] ≥78 mmHg for children 6 to 9 years old; ≥126 mmHg or ≥82 mmHg, respectively, for ages 10 to 12; and ≥136 mmHg or ≥86 mmHg, respectively, for ages 13 to 17); hypotension (defined as sitting SBP <50 mmHg for children <12 years of age, <80 mmHg for children ≥12 years of age); resting heart rate outside the range of 60 to 115 beats per minute; a history of alcohol or substance abuse as defined by DSM-IV criteria; and consumption of >250 mg/day of caffeine. Concomitant use of prescription or nonprescription agents with psychotropic properties, including ADHD treatments and dietary supplements, was prohibited within 1 week of the baseline visit and during the study. Monoamine oxidase inhibitors and selective serotonin reuptake inhibitors were prohibited within 2 weeks of baseline testing and throughout the study.	NR

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Greenhill 2006	Modafinil: Mean Dose: 361.4 mg (SD 90.9) Dose Range: 85 to 425mg Placebo: Mean Dose: 383.1 mg (SD 85.5) Dose Range: 85 to 425mg	washout 7d before baseline testing	none/NR	Primary Outcome Measure: total score on the teacher-/investigator-rated ADHD-RS-IV School Version Other Measures: the ADHD-RS-IV Home Version, Clinical Global Impression of Improvement (CGI-I), factor scores derived from the Test of Variables of Attention (TOVA), factor scores for inattention and hyperactivity derived from the Conners' Parent Rating Scale-Revised, Short Form (CPRS:R-S), factor scores from the Social Skills Rating Scale (SSRS), and Child Health Questionnaire (CHQ)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Greenhill 2006	Mean age= 9.9 yrs (Range: 6 - 16 yrs) 73% male 72% white	Modafinil vs. Placebo **CGI-S Score, N(%)** Moderately ill: 76 (38) Markedly ill: 87 (44) Severely ill: 34 (17) Not Assessed: 1 (0.5) **Current ADHD Subtype, N(%)** Inattentive: 47 (24) Hyperactive/impulsive: 10 (5) Combined: 139 (70) **Previous ADHD Treatment, N(%):** 109 (55) MPH: 73 (37) Amph. Salts: 64 (32) ATX: 27 (14) Other: 22 (11) **Most Frequently Coadministered Agents N(%)** Nonopioid analgesics/anti-inflammatories: 65 (33) Respiratory agents: 33 (17) Antihistamines: 28 (14) Anti-infectives: 24 (12) **ADHD-RS-IV total score, mean** School Version: 38.5 Home Version: 40.8	295/NR/200	59/5/194

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Greenhill 2006	Modafinil vs. placebo , mean change **ADHD-RS-IV School version** Total score: -17.5 vs.-9.8, p<.0001 Inattention: -9.7 vs. -4.9, p<.0001 Hyperactivity/impulsivity: -7.9 vs. -4.8, p=.003 **ADHD-RS-IV Home version** Total score: -17.6 vs. -7.7, p<.0001 Inattention: -9.2 vs. -3.5, p<.0001 Hyperactivity/impulsivity: -8.3 vs. -4.2, p=.0001 TOVA **ADHD score**: -0.4 vs. 1.1, p=.001 **CPRS:R-S** **ADHD index**: -12.7 vs. -6.3, p=.001

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Greenhill 2006	general inquiry and spontaneous reporting	Modafinil vs. Placebo, N(%) Insomnia : 37(28) vs. 5(7), p<.05 Headache : 29(22) vs. 6(9), p<.05 Decreased appetite: 23(18) vs. 2(3), p<.05 Abdominal pain: 16(12) vs. 3(4), NS Infection: 14(11) vs. 6(9), NS Increased cough: 12(9) vs. 6(9), NS Pharyngitis: 11(8) vs. 9(13), NS Rhinitis: 10(8) vs. 7(10), NS Vomiting: 8(6) vs. 4(6), NS Emotional Lability: 7(5) vs. 4(6), NS Nervousness: 7(5) vs. 3(4), NS Weight Loss: 7(5) vs. 0(1), p<.05 Accidental Injury:6(5) vs. 3(4), NS Fever: 6(5) vs. 3(4), NS Gastroenteritis: 6(5) vs. 3(4), NS Somnolence: 6(5) vs. 3(4), NS Nausea: 6(5) vs. 2(3), NS	59/10	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Rugino 2003 Fair	RCT, DB, Parallel groups Setting: Regional development center	(1) reliable transportation to and from the development center; (2) regular school attendance; (3) an average Conners Teacher Rating Scale ADHD index t score of 70 or higher; (4) an average percentile score for the ADHD Rating Scale IQ of 70 or higher; and (5) a verbal intelligence quotient of 80 or higher.	ODD/Conduct=6 (27.3%) Separation anxiety=13.6% Specific phobia=18.2% Enuresis=13.6% Learning disorder=18.2% Borderline intelligence quotient=9.1% Adjustment disorder=9.1% Selective mutism=4.5%

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Rugino 2003 Fair	Modafinil mean dose=264 mg Placebo Flexible dosing Dosing schedule=once each morning Mean study duration=5.6 weeks	NR/NR	NR	Test of Variables of Attention (TOVA) ADHD Rating Scale IV Conners' Parents Ratings Scales Revised-L (CPRS) Conners' Teachers Rating Scales Revised-L (CTRS)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Rugino 2003 Fair	Mean age=7.9 62.5% male 100% white	ADHD type Combined=72.7% Inattentive=18.2% Hyperactive-impulsive=4.5%	NR/NR/24	2 (8.3%) withdrawn/0 lost to fu/analyzed=22 (modafinil=11, placebo=11)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Rugino 2003 Fair	Modafinil vs placebo (t scores representing post-treatment improvement) DSM-IV symptoms (CTRS and CPRS): 68.2 vs 76, p<0.05 Other Conners ADHD Scales (% of 14 scales with mean t score difference more negative than -5): 13 (92.8%) vs 1 (7.1%), p<0.001 ADHD Rating Scale raw scores: 14 vs 14.7, p=NS % parents rating "significant" overall improvement: 10 (90.9%) vs 8 (72.7%), p<0.004

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Rugino 2003 Fair	NR	Delayed sleep onset: 4 (36.4%) vs 4 (36.4%) Modafinil (n=11) Transient stomachache=2 (18.2%) Occasional transient headache=1 (9.1%) Transient mood disorder with tearfulness=1 (9.1%) Placebo (n=11) Sleepiness=1 (9.1%) Irritability=1 (9.1%) Decreased appetite=1 (9.1%) Tonsillitis/pharyngitis=1 (9.1%)	Total withdrawals: 2/13 (15.4%) vs 0 Withdrawals due to adverse events: nr	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Swanson 2006	RCT DB	Male or female patients aged 6 to 17 years who met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria for ADHD were eligible for enrollment. Additional inclusion criteria included a Clinical Global Impressions-Severity of Illness scale (CGI-S) rating of 4 or higher ("moderately ill" or worse), total and/or subscale cores on the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) School Version at least 1.5 standard deviations above norms for the patient's age and gender, an intelligence quotient of at least 80 as estimated by the Wechsler Intelligence Scale for Children-Third Edition, and a score of at least 80 on the Wechsler Individual Achievement Test, Second Edition, Abbreviated. Patients were eligible if they were attending a full-time school (i.e., they were not eligible if receiving home schooling) and if a teacher and parent (or legal guardian) were willing and able to participate for the duration of the study. Patients with a history or current diagnosis of pervasive developmental disorder, schizophrenia, or other psychotic disorders (DSM-IV-TR Axis I) were excluded from the study, as were those with a clinical assessment of current suicide risk or other psychiatric comorbidities requiring pharmacotherapy. To avoid potential ethical concerns, patients whose symptoms were very well controlled and who were satisfied with current therapy for ADHD (with low levels of adverse events) were also excluded, as were those who had failed to respond to 2 or more adequate courses of stimulant therapy for ADHD with trials on a range of doses and immediate- and controlled-release formations. Patients were excluded if their height or weight was below the 5th or above the 95th percentile based on National Center for Health Statistics growth charts. Additional exclusion criteria were hypertension (defined as systolic blood pressure [SBP] ≥122 mm Hg or diastolic blood pressure [DBP] ≥78 mm Hg for children aged 6-9 years; ≥126 mm Hg or ≥82 mm Hg, respectively, for ages 10-12; and ≥136 mm Hg or ≥86 mm Hg respectively, for ages 13-17), hypotension (defined as sitting SBP <50 mm Hg for children <12 years of age or <80 mm Hg for children ≥12 years of age), resting heart rate outside the range of 60 to 115 beats per minute, absolute neutrophil count below 1 x 10^9/L, history of alcohol or substance abuse, and habitual consumption of more than 250 mg/day of caffeine. Patients were not allowed to use prescription or nonprescription medications with psychotropic activity, including other treatments for ADHD and dietary supplements, within 1 week of baseline (within 2 weeks for monoamine oxidase inhibitors and selective serotonin reuptake inhibitors) or throughout the study.	None

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Swanson 2006	Modafinil: Mean Dose: 395 mg Dose Range: 340 mg, 425 mg, or placebo (Titrated during first 7 - 9 days)	NR/NR	NR	Primary Outcome Measure: ADHD-RS-IV (teacher-/investigator-rated School Version) Other Measures: total, inattention, and hyperactivity-impulsivity scores on the ADHD-RS-IV School Version and the parent-/investigator-rated ADHD-RS-IV Home Version, Clinical Global Impressions-Improvement scale (CGI-I), Test of Variables of Attention (TOVA), Conners' Parent Rating Scale-Revised, Short form (CPRS:R-S), Social Skills Rating Scale (SSRS), and Child Health Questionnaire (CHQ)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Swanson 2006	Mean age= 10 yrs (Range: 6 - 17 yrs) 71% male 80% white	Modafinil vs. Placebo NS for all between group differences **CGI-S Score, N(%)** Moderately ill:117 (62) Markedly ill: 55 (29) Severely ill: 17 (9) **Current ADHD Subtype, N(%)** Inattentive: 51 (27) Hyperactive/impulsive: 10 (5) Combined: 126 (67) **Previous ADHD treatment N(%)** Total: 104 (55) Methylphenidate hydrochloride: 69 (37) Amphetamine salts: 58 (31) Atomoxetine Hydrochloride: 35 (19) Other: 12 (6) **Patients Receiving Coadministered agents N(%)** Respiratory Agents: 20 (11) Vitamins/nutritional supplements: 5 (3) Nonopioid analgesics/anti-inflammatories: 39 (21) Antihistamines: 11 (6) Anti-infectives: 12 (6) Other: 22 (12) **ADHD-RS-IV total score, mean** School version: 37.5 Home Version: 38.8	316/NR/190	69/1/183

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Swanson 2006	Modafinil vs. placebo **ADHD-RS-IV School version** Total score: 17.1 vs. 8.2, p<.0001 Inattention: 9.4 vs. 6.6, p<.001 Hyperactivity/impulsivity: 7.7 vs. 2.8, p<.0001 **ADHD-RS-IV Home version** Total score: 13.9 vs. 7.9, p=.001 Inattention: 7.1 vs. 4.0, p<.001 Hyperactivity/impulsivity: 6.5 vs. 3.9, p=.004 **CPRS:R-S** ADHD index: 10.7 vs. 5.2, p<.001 Cognitive problems/inattention: 10.0 vs. 4.1, p<.0001 Hyperactivity: 11.8 vs. 4.6p<.001

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Swanson 2006	**Modafinil vs. Placebo, N (%)** **During 7-week Double-Blind period** **Modafinil/Modafinil vs. Modafinil/placebo vs. placebo/placebo, N (%)** **During 2-week Observation period**	**Modafinil vs. Placebo** Insomnia: 30(24) vs. 0(0), p<0.0001 Headache: 21(17) vs. 9(14) Decreased Appetite: 18(14) vs. 1(2), p=0.0042 Infection: 13(10) vs. 10(16) Abdominal Pain: 12(10) vs. 5(8) Fever: 7(6) vs. 2(3) Increased Cough: 7(6) vs. 3(5) Rhinitis: 5(4) vs. 5(8) **AE during the 2-week Observation Period Modafinil/Modafinil vs. Modafinil/Placebo vs. Placebo/Placebo** Headache: 2(5)/2(5)/0(0) Abdominal Pain: 1(2)/3(5)/1(3) Contact Dermatitis: 0(0)/2(5)/0(0)	74/12	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Subgroup Comorbidity: Epilepsy			
Gross-Tsur 1997 Israel Poor	Between testing sessions: Open, unblinded, uncontrolled intervention During testing sessions: DB, single-dose crossover of methylphenidate and placebo (1/2 of children received placebo during the first testing session, and 1/2 during the second)	Children with epilepsy, aged 6.4 to 16.4 years, with a diagnosis of ADHD made by a pediatric neurologist using the criteria of the DSM-III-R, cognitive testing, and a behavioral questionnaire (Child Behavior Checklist (CBCL).	Epilepsy

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Subgroup Comorbidity: Epilepsy				
Gross-Tsur 1997 Israel Poor	First 8 weeks: antiepileptic drugs (AEDs) Second 8 weeks: AEDs+methylphenidate 0.3 mg/kg (observational study) Testing session #1 (after first eight weeks): assigned to a single dose of either methylphenidate 0.3 mg/kg or placebo Testing session #2 (after second eight weeks): crossed over to a single dose of either methylphenidate 0.3 mg/kg or placebo	NR/NR	NR	(1) neurologic examination (2) electroencephalography (3) AED trough level and 2 hours after dosing with AED and with methylphenidate or placebo (4) CPT

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Subgroup Comorbidity: Epilepsy				
Gross-Tsur 1997 Israel Poor	Mean age=9.8 18 (60%) male Ethnicity NR	Mean IQ=92.8 Complex partial seizures=15 (50%) Primary tonic-clonic seizures=7 (23.3%) True absences=6 (20%) Multiple seizure type=2 (6.7%) Monotherapy=26 (86.7%) Combination therapy=4 (13.3%) Abnormal brain computed tomography=4 (13.3%)	NR/NR/30	NR/NR/30 for all but AED drug levels (n=27)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Subgroup Comorbidity: Epilepsy	
Gross-Tsur 1997 Israel Poor	Speed of response: MPH>placebo [F(1, 30)=10.1 (p<0.003) Performance decrement over time: less pronounced with MPH [interaction time-on-task by drug condition was F(2,60)=3.8 (P<0.03)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Subgroup Comorbidity: Epilepsy				
Gross-Tsur 1997 Israel Poor	NR	AE's reported only for the observational study periods.	NR NR	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Subgroup Comorbidity: Tourette's Disorder/Tics			
Allen 2005	RCT DB crossover	Study subjects were children or adolescents at least 7 years of age but less than 17 years and 6 months and weighing between 20 and 80 kg at the time informed consent was obtained. All study subjects met DSM-IV criteria for ADHD and had concurrent Tourette syndrome or chronic motor tic disorder, as diagnosed by clinical interview and examination by the investigator and confirmed by the Schedule for Affective Disorders and Schizophrenia for School-age Children–Present and Lifetime Version16 (K-SADSPL). Subjects' scores on the ADHD Rating Scale-IV-Parent Version: Investigator Administered and Scored (ADHDRS-IV-Parent:Inv) had to be at least 1.5 standard deviations above the age and sex norm for diagnostic subtype (predominantly inattentive or predominantly hyperactive–impulsive), or for the total score for the combined subtype (if DSM-IV criteria were met for the combined subtype), using published norms for the ADHDRS-IV-Parent:Inv at Visits 1 (enrollment) and 2 (randomization). Subjects' Yale Global Tic Severity Scale (YGTSS) total scores had to be at least 5 at both Visits 1 and 2. Exclusion criteria included a Children's Yale–Brown Obsessive–Compulsive Scale19 (C-YBOCS) total score 15 or diagnosis of obsessive-compulsive disorder severe enough, in the investigator's opinion, to require pharmacotherapy; a Children's Depression Rating Scale–Revised20 (CDRS-R) total score 40 or diagnosis of depression severe enough to require pharmacotherapy; a history of bipolar disorder or psychosis; seizure disorder; or current use of any psychotropic medication other than study drug.	100% ADHD and either chronic motor tic disorder, chronic vocal tic disorder or Tourette disorder {some patients list more than one diagnosis) Tourette disorder: 117 (79%) Chronic motor tic disorder: 44 (29.7%) Chronic vocal tic disorder: 26 (17.6%)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Subgroup Comorbidity: Tourette's Disorder/Tics				
Allen 2005	Atomoxetine for up to 18 weeks: Mean Dose = 1.33 mg/kg/day (SD 0.22) Dose Range = 0.5 to 1.5 mg/kg/day (maximum total daily dose of 110 mg)	3-week dose titration phase and 2-week discontinuation period	diphenhydramine allowed for insomnia	Primary Outcome Measure: Yale Global Tic Severity Scale (YGTSS) total score Other Measures: Tic Symptom Self-Report (TSSR), CGI-Tic/Neuro-S, ADHDRS-IV-Parent:Inv, the CGI-Overall-S, and the CGI-ADHD/Psych-S (a subscale rating of the clinician's global assessment of the severity of ADHD and other psychiatric symptoms)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Subgroup Comorbidity: Tourette's Disorder/Tics				
Allen 2005	Mean age=11.2 yrs (SD 2.5 yrs), range 6.6 - 17.4 yrs 88.5% male 87.8% white	n(%), all NS ADHD subtype combined: 90(60.8), inattentive: 53 (35.8), hyperactive/impulsive: 5(3.4) Oppositional Defiance Disorder: 32(21.6) Major Depression: 1(0.7) Generalized anxiety disorder 5(3.4) Obsessive Compulsive Disorder 4 (2.7) previous exposure to stimulant therapy 101(68.2)	166/148/148	83/2/148

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Subgroup Comorbidity: Tourette's Disorder/Tics	
Allen 2005	Tics efficacy, Atomoxetine vs. Placebo, change mean Yale Global Tic Severity Scale (YGTSS) total score: -5.5 vs. -3.0, p=0.063 YGTSS Motor: -3.1 vs. -1.7, p=0.119 YGTSS Phonic: -2.4 vs. -1.3, p=0.168 TSSR: -4.7 vs. -2.9, p=0.095 CGI-Tic/Neuro-S: -0.7 vs. -0.1, p=0.002 ADHD/Behavior Efficacy, change mean ADHD-RS Total: -10.9 vs. -4.9, p=0.002 ADHD-RS Inattentive: -5.7 vs. -2.7, p=0.019 ADHD-RS hyperactive/impulsive: -5.2 vs. 2.1, p=0.002 CGI-ADHD/Psych-S, -0.8 vs. -0.3, p=0.015 CGI-Overall-S, -0.6 vs. -0.2, p=0.014

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Subgroup Comorbidity: Tourette's Disorder/Tics				
Allen 2005	NR	No serious AE Atomoxetine vs. Placebo, N (%) Headache, 16 vs. 14, p=0.840 Vomiting, 12 vs. 6, p=0.211 Upper abdominal pain 7 vs. 9, p=0.601 decreased appetite 12 vs. 2, p=0.01 Cough 4 vs. 9, p=0.151 Nausea 12 vs.1, p=0.002 Fatigue 9 vs.3, p=0.131 Pharyngitis 3 vs. 9, p=0.073 Diarrhea 3 vs. 8, p=0.123	Atomoxetine vs. Placebo 50 vs. 53; 2 vs. 1 withdrawals due to AE	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Nolan 1999	RCT DB crossover Withdrawal effect on tic disorders	Subjects were 19 children (18 boys and 1 girl) between the ages of 6.6 and 17.4 years old who met Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised, diagnostic criteria for ADHD and either chronic motor tic disorder or Tourette's disorder (established based on a clinical interview with the parent). To be considered eligible for the study, each child had to be receiving maintenance stimulant drug therapy for a minimum of 1 year. (No attempt was made to determine the total number of days each child actually ingested medication.) In addition, subjects could not be receiving any other medication for ADHD, tics, or other emotional or behavioral disorders.	100% ADHD and either chronic motor tic disorder or Tourette disorder Tourette disorder: definite=11, by history=7 Chronic motor tic disorder: definite=1
Sverd 1992	RCT DB crossover	Boys between the ages of 6.1 and 11.9 years old. All subjects met Diagnostic and Statistical Manual (3rd ed) revised (DSM-III-R) diagnostic criteria for ADHD and either chronic motor tic disorder or Tourette disorder (established on the basis of clinical interview with the parent) and were above cut-off on two out of three parent-and teacher-completed hyperactivity/ADHD behavior rating scales.	100% ADHD and either chronic motor tic disorder or Tourette disorder Tourette disorder: definite=7(63.6%), by history=3(27.3%) Chronic motor tic disorder: definite=1(9.1%)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Nolan 1999	Methylphenidate: Mean dose = 26mg (SD 10mg) Dose range = 10 - 50mg Dextroamphetamine: Mean dose = NR Dose range = 10mg - 20mg	first 2 weeks: subjects received their maintenance dose as typically administered	NR/NR	Primary Outcome Measure: NR Other Measures: Clinically evaluated using Yale Global Tic Severity Scale (YGTSS), Tourette Syndrome Clinical Global Impression Scale, the Shapiro Tourette Syndrome Severity Scale, and the Tourette Syndrome Unified Rating Scale Parent evaluation using Hyperactivity Index of the Revised Conners Parent Rating Scale, the Hyperactivity and Aggression subscales of the Mother's Method for Subgrouping (MOMS) checklist, the Peer Conflict Scale, the ADHD category of the Child Symptom Inventory-3R: Parent Checklist (CSI-3R) Teacher evaluation using Abbreviated Parent-Teacher Questionnaire, IOWA Conners Teacher's Rating Scale, and the ADHD category of the CSI-3R Teacher Checklist
Sverd 1992	methylphenidate (MPH): placebo, 0.1mg/kg, 0.3mg/kg, and 0.5mg/kg, bid, for 2 weeks each. * for any given 0.1mg/kg dose, the minimum=2.5mg, the maximum=20mg	at least 1 week for stimulants and 3 weeks for neuroleptic (pimozide)	NR	Physician evaluation: Yale Global Tic Severity Scale (YGTSS) and Tourette Syndrome Unified Rating Scale (TS unified RS) Clinic observation: playroom procedure Parent Rating Scale: Abbreviated Parent Rating scale (APRS), Primary Secondary Symptom Checklist (PSSC), Global Tic Rating Scale (GTRS), Peer Conflict Scale

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Nolan 1999	Mean age=12.3 yrs (SD 3.0 yrs), range 6.6 - 17.4 yrs 95% male Ethnicity: NR	Mean (SD) **Parent ADHD Measures** CGI-3R ADHD category (>7): 10.0 (4.1) CHI (>15): 16.3 (4.7) MOMS Hyperactivity scale (>2): 3.6 (1.3) **Teacher ADHD Measures** CGI-3R ADHD category (>7):10.5 (3.5) CHI (>15): 18.2 (7.7) MOMS Hyperactivity scale (>6): 9.7 (3.0) **Aggression measures** MOMS Aggression scale (>2): 2.0 (1.8) IOWA Aggression scale (>3): 5.5 (4.0) **Clinician Tic measures** YGTSS Motor Tic score:11.6 (3.7) YGTSS Phonic Tic score: 9.4 (4.9) YGTSS Overall Impairment Rating scores: 14.3 (12.7) YGTSS Global Severity score: 35.0 (17.2) Methylphenidate: 17 subjects and Dextroamphetamine: 2 subjects	NR/NR/19	NR/NR/19
Sverd 1992	Mean age=8.3(1.96), range 6.1-11.9 years. Gender=11(100%) male Race: NR	Overall Impairment Rating scores from the Yale Global Tic Severity Scale: 2(18.2%): none 4(36.4%): minimal 4(36.4%): mild 1(9.1%): severe Global Severity Scores: mean=40.6(16.6), range 16-79	NR/ NR/ 11 enrolled	0/0/0

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Nolan 1999	Placebo (blind) VS. Drug (blind) **Clinician Ratings** **YGTSS** Total Motor Tics: 10.1(7.2) vs. 8.3(4.4) NS Total Phonic Tics: 5.6(5) vs. 3.8(5.3) NS Overall Impairment Rating: 12.1(12.3) vs. 6.8(11.1) NS Global Severity Score: 29(19.5) vs. 19(18.4) NS **STSSS**: 1.6(1.1) vs. 1.5(1.2) NS **TS-CGI**: 2.1(.7) vs. 1.8(.9) NS **TS Unified Rating Scale** Shapiro Symptom Checklist Number of Motor Tics: 4(2.5) vs. 4(4.5) NS Number of Vocal Tics: 1.5(1.6) vs. 1.3(2.2) NS 2-Minute Tic Count Motor Tic Count: 4.3(2.9) vs. 5(4.3) NS Vocal Tic Count: .4(.8) vs. 1.2(1.8) p=.0037 **GTRS** Motor Tic Index: 2.6(1.4) vs. 2.7(1.5) NS Vocal Tic Index: 1.1(1.2) vs. 1(1.4) NS Tic Severity: 1.8(2.3) vs. 1.4(2.2) NS **CGI-OC**: 1.1(.7) vs. 1(.8) NS **Parent Ratings** GTRS Motor Tic Index: 2.5(1.4) vs. 2.9(1.7) NS Vocal Tic Index: 1.5(1.4) vs. 1.2(1.7) NS Tic Severity Index: 2(2.3) vs. 1.8(2.6) NS **Classroom Observations** Motor Tic Frequency: 20.4(13.1) vs. 17.8(13.8) NS Vocal Tic Frequency: 1(3) vs. 1(1.8) NS
Sverd 1992	Placebo vs. 0.1mg/kg; Placebo vs. 0.3mg/kg; Placebo vs. 0.5mg/kg Physician evaluation-- a. YGTSS: NS b. TS unified RS: NS Observations-- a. % on task: p<0.01; p<0.01; p<0.01 b. worksheets no. of completed: p<0.05; p<0.05; p<0.01 Parent rating-- a. APRS: p<0.01; NS; p<0.05 b. PSSC: NS c. GTRS: NS d. Peer Conflict Scale: p<0.05; p<0.05; p<0.05

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Nolan 1999	parent reported	none	none	
Sverd 1992	Stimulant Site Effects Checklist (SSEC) by parents	Placebo vs. 0.1mg/kg vs. 0.3mg/kg vs. 0.5mg/kg (no post hoc) SSEC-- a. Mood index: p=0.0086 b. Attention-arousal index: NS c. Somatic complaints index: NS d. Unusual motor movement: NS	none	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Subgroup Comorbidity: Mental Retardation			
Gadow 1992	RCT DB crossover	Boys between the ages of 6.1 and 11.9 years old. Potential subjects had to meet Diagnostic and Statistical Manual (3rd ed) revised (DSM-III-R) diagnostic criteria for ADHD and either chronic motor tic disorder or Tourette disorder (established on the basis of clinical interview with the parent) and had to be above cut-off on two out of three Parent-and teacher-completed hyperactivity/ADHD behavior rating scales.	100% ADHD and either chronic motor tic disorder or Tourette disorder Tourette disorder: definite=7(63.6%), by history=3(27.3%) Chronic motor tic disorder: definite=1(9.1%)
Gadow 1995	RCT DB crossover	Children with ADHD and either chronic motor tic disorder or Tourette disorder were above cutoff on two out of three parent-completed and two out of three teacher-completed hyperactivity/ADHD behavior rating scale	100% ADHD and either chronic motor tic disorder or Tourette disorder Tourette disorder: definite=22(64.7%), by history=12(35.3%)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Subgroup Comorbidity: Mental Retardation				
Gadow 1992	methylphenidate (MPH): placebo, 0.1mg/kg, 0.3mg/kg, and 0.5mg/kg, bid, for 2 weeks each. * for ease of administration, individual milligram-doses were rounded off to the nearest 5mg. The upper limit for the moderate dose was 20mg.	at least 1 week for stimulants and 3 weeks for neuroleptic (pimozide)	NR	Classroom: Classroom Observation Codes Lunchroom: Code for Observing Social Activity (COSA) Playground: Code for Observing Social Activity (COSA) *Observers followed subjects while they were in the classroom, lunchroom and playground Rating Scale: Abbreviated Teacher Rating Scale (ATRS), IOWA Conners Teacher's Rating Scale, Peer Conflict Scale Global Tic Rating Scale
Gadow 1995	methylphenidate (MPH): placebo, 0.1mg/kg, 0.3mg/kg, and 0.5mg/kg, bid, for 2 weeks each * for ease of administration, individual milligram-doses were rounded off to the nearest 2.5mg. The upper limit for the 0.5mg/kg dose was 20mg.	at least 1 week for stimulants and 2 to 3 weeks for clonidine and neuroleptics	NR	Direct observations-- Classroom: Classroom Observation Codes Lunchroom: Code for Observing Social Activity (COSA) Playground: Code for Observing Social Activity (COSA) *Observers followed subjects while they were in the classroom, lunchroom and playground Physician Measures-- Yale Global Tic Severity Scale (YGTSS) and Shapiro Symptom Checklist from the Tourette Syndrome Unified Rating Scale

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Subgroup Comorbidity: Mental Retardation				
Gadow 1992	Mean age=8.3(1.96), range 6.1-11.9 years. Gender=11(100%) male Race: NR	Overall Impairment Rating scores from the Yale Global Tic Severity Scale: 2(18.2%): none 4(36.4%): minimal 4(36.4%): mild 1(9.1%): severe Global Severity Scores: mean=40.6(16.6), range 16-79 ADHD index: mean=8.7(1.77) Conners Hyperactivity index: mean=17.6(3.53) PSSC Hyperactivity subscale: mean=4.2(1.25)	NR/ NR/ 11 enrolled	0/0/0
Gadow 1995	Mean age=8.8(1.9), range 6.1-11.9 years. Gender=31(91.2%) male Race: NR	NR	NR/ NR/ 34 enrolled	0/0/0

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Subgroup Comorbidity: Mental Retardation	
Gadow 1992	Placebo vs. 0.1mg/kg; Placebo vs. 0.3mg/kg; Placebo vs. 0.5mg/kg; 0.1mg/kg vs. 0.5mg/kg Classroom observation-- a. Interference: NS; p<0.01; p<0.01; p<0.05 b. Motor: p<0.01; p<0.01; p<0.01; p<0.05 c. Off-task: NS; NS; p<0.01; NS d. Noncompliance: p<0.01; p<0.01; p<0.01; NS Lunchroom observation-- a. Noncompliance: p<0.05; p<0.01; NS; NS b. Physical aggression: p<0.05; p<0.05; p<0.05; NS Playground observation: a. Noncompliance: p<0.05; p<0.05; p<0.05; NS b. Physical aggression: NS; p<0.05; NS; NS Rating Scales: a. ATRS: p<0.01; p<0.01; p<0.01; NS b. IOWA I-O: p<0.01; p<0.01; p<0.01; NS c. IOWA A: p<0.01; p<0.01; p<0.01; NS d. Peer Conflict: NS; NS; p<0.01; NS In classroom, vocal tics were significantly less frequent (p<0.01) on the 0.3mg/kg and the 0.5mg/kg doses compared with placebo Minimal effective dose: mean=0.26mg/kg or 8.4mg (range 0.1-0.5mg/kg or 2.5-20mg)
Gadow 1995	Placebo vs. 0.1mg/kg; Placebo vs. 0.3mg/kg; Placebo vs. 0.5mg/kg; 0.1mg/kg vs. 0.5mg/kg Classroom observation-- a. Interference: p<0.05; p<0.05; p<0.01; p<0.05 b. Motor: p<0.05; p<0.01; p<0.01; p<0.05 c. Off-task: p<0.01; p<0.01; p<0.01; p<0.01 d. Noncompliance: p<0.01; p<0.01; p<0.01; p<0.05 e. Nonphysical aggression: NS; NS; NS; NS Lunchroom observation-- a. Noncompliance: NS; p<0.05; p<0.01; NS b. Physical aggression: NS; NS; p<0.01; NS c. Nonphysical aggression: NS; p<0.01; <0.05; NS Playground observation: a. Nonphysical aggression: p<0.01; p<0.05; p<0.05; NS School tic observations: a. Motor tic observation: p<0.05; NS; NS; NS Minimal effective dose: mean=0.29mg/kg/bid or 8.8mg (range 2.5mg-20mg)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Subgroup Comorbidity: Mental Retardation				
Gadow 1992	Stimulant Site Effects Checklist (SSEC) by parents	NS in SSEC * no other side effect information	none	
Gadow 1995	NR	NR	none	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Handen 1991	RCT DB crossover	1. Intellectual functioning within the mild to borderline range of mental retardation (IQ 48-74, mean=64), as measured either by the Wechsler Intelligence Scale for Children-Revised (Full-Scale IQ Score) or the Stanford-Binet Intelligence Scale: Fourth Edition (Composite Index), and educable mental retardation in class placement 2. Adaptive functioning within the mild to borderline range of mental retardation, based upon the Vineland Adaptive Behavior Scale-Parent Version 3. A score of 15 or more on Hyperactivity Index of both the Conners Abbreviated Teacher Rating Scale and the Conners Abbreviated Parent Rating Scale 4. A diagnosis of ADHD based upon a semistructured interview with parents using DSM-III-R criteria	100% mental retardation and ADHD
Handen 1997	RCT DB	An initial diagnosis of ADHD was made prior to entry into the double-blind MPH trial. This was based upon either (a) a score at or above the 98th percentile for age and gender on the Hyperactivity Index of both the Conners Parent and Teacher Rating Scales, or (b) a score of 15 points or more on the Hyperactivity Index of both the Conners Parent and Teacher Rating Scales.	mental retardation and ADHD
Handen 1999	RCT DB crossover	All subjects scored at or above the 90th percentile on both a teacher-completed Preschool Behavior Questionnaire and the Hyperactivity Index of the Conners Parent Rating Scale. In addition, all subjects had been previously evaluated by an interdisciplinary team of developmental specialists, during which time either a diagnosis of ADHD was confirmed or long-term concerns with inattention and overactivity were documented.	9(82%) ADHD, 2(18%) oppositional defiant disorder.

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Handen 1991	week3-5: 0.3mg/kg methylphenidate (MPH), 0.6mg/kg MPH, or placebo: bid (breakfast and lunch) for a 7-days period.	2 weeks	NR	Side Effect Checklist (6 point Likert Scale) by teachers: motor movement, drowsy, sad, staring, social withdrawal, irritability, poor appetite, anxiety, dizzy, moody, high activity, stomachache, headache
Handen 1997	methylphenidate (MPH) *no dosage, duration and schedule information	NR	NR	Baseline Home Measures: Conner Parent Rating Scale Baseline Weekday Classroom Measures: Conners Teacher Rating Scale and Classroom Assignment 1-5 years Follow-up Measures: age, length of follow-up, classroom assignment, medication history, nonpharmacologic interventions, inpatient treatment, school suspensions, police involvement, Conners parent rating scale.
Handen 1999	week2-4: 0.3mg/kg methylphenidate (MPH), 0.6mg/kg MPH, or placebo: bid with breakfast and 3.5-4 hours later with lunch for a 7-days period.	1 week before intervention	NR	Preschool Classroom Measures at the last day of each phase (weekly): Conners Teacher Rating Scale, Preschool Behavior Questionnaire, Side Effects Checklist Laboratory Measures (weekly): Waiting Task, Resistance to Temptation, Play Session, Compliance Task, Clean-up Task.

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Handen 1991	Mean age=8.6, range 6.7-12.1 years Gender=22(81.5%) male Race: NR	NR	NR/ NR/ 27 enrolled	13 withdrawn/ o lost to fu/ 27 analyzed
Handen 1997	Age (months): mean=130.4, range 86-178 Gender: 32(62.7%) male Race: 37(72.5%) Caucasian, 13(25.5%) Black, 1(2%) Hispanic	Mean IQ =64(8.6), range 48-77 Hollingshead four-factor Index for social-economic status (Level): I -- 3(5.9%) II -- 10(19.6%) III -- 14(27.5%) IV -- 6(11.8%) V -- 18(35.3%)	NR/NR/51 enrolled	0/0/0
Handen 1999	Age: mean=4.9, range 4-5.11 years Gender: 9(82%) male Race: NR	Mean IQ=60(11.6), range 40-78	NR/NR/11 enrolled	1 withdraw/ 0 lost/ 10 analyzed

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Handen 1991	18(67%) were identified as responders to methylphenidate. Placebo vs. 0.3mg/kg (N=27); Placebo vs. 0.6mg/kg (N=25) Irritability: NS; 14(51.8%): 3(12%), p<0.05 Anxiety: NS; 11(40.7%): 3(12%), p<0.05 High activity: 21(77.8%): 9(33.3%), p<0.05; 21(77.8%): 10(40%), p<0.05 *Other side effects: NS; NS Placebo vs. 0.3mg/kg (N=14); Placebo vs. 0.6mg/kg (N=14) Staring: 2.0: 0.93, p<0.05; 2.0: 0.75, p<0.05 Irritability: 1.21:0.43, p<0.05; 1.21: 0.33, p<0.05 Anxiety: 1.0: 0.86, NS; 1.0: 0.50, p<0.05 Moody: 0.79: 0.36, NS; 0.79: 0.00, p<0.05 High activity: 3.0: 1.50, p<0.05; 3.0: 0.75, p<0.05 *Other side effects: NS; NS
Handen 1997	Initial vs. follow-up: Conduct problem (CA), p=0.041 Conduct problem (MA), p=0.097 Anxiety (CA), p=0.295 Anxiety (MA), p=0.041 Impulsivity-Hyperactivity (CA), p=0.003 Impulsivity-Hyperactivity (MA), p=0.007 Learning problem (CA), p<0.005 Learning problem (MA), p<0.005 Psychosomatic (CA), p=0.947 Psychosomatic (MA), p=0.569 Hyper. Index (CA), p<0.005 Hyper. Index (MA), p<0.005
Handen 1999	8(73%) responded to the drugs (based on a 40% or more decrease in Teacher-rated Conners Hyperactivity Index and/or Hyperactive-Distractible subscale) Dull, social withdrawal, poor appetite, anxiety, and drowsiness were reported more in the drugs than placebo (mean): Dull -- placebo(0.4), 0.3mg/kg(1.5), 0.6mg/kg(2.2) Social withdrawal -- placebo(0.4), 0.3mg/kg(1.3), 0.6mg/kg(2.1) Poor appetite -- placebo(0.1), 0.3mg/kg(1.9), 0.6mg/kg(3.2) Anxiety --placebo(0), 0.3mg/kg(0.1), 0.6mg/kg(0.3) Drowsiness -- placebo(0), 0.3mg/kg(1.1), 0.6mg/kg(0.6)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Handen 1991	Side Effect Checklist (6 point Likert Scale) by teachers: motor movement, drowsy, sad, staring, social withdrawal, irritability, poor appetite, anxiety, dizzy, moody, high activity, stomachache, headache	18(67%) were identified as responders to methylphenidate. Placebo vs. 0.3mg/kg (N=27); Placebo vs. 0.6mg/kg (N=25) Irritability: NS; 14(51.8%): 3(12%), p<0.05 Anxiety: NS; 11(40.7%): 3(12%), p<0.05 High activity: 21(77.8%): 9(33.3%), p<0.05; 21(77.8%): 10(40%), p<0.05 *Other side effects: NS; NS Placebo vs. 0.3mg/kg (N=14); Placebo vs. 0.6mg/kg (N=14) Staring: 2.0: 0.93, p<0.05; 2.0: 0.75, p<0.05 Irritability: 1.21:0.43, p<0.05; 1.21: 0.33, p<0.05 Anxiety: 1.0: 0.86, NS; 1.0: 0.50, p<0.05 Moody: 0.79: 0.36, NS; 0.79: 0.00, p<0.05 High activity: 3.0: 1.50, p<0.05; 3.0: 0.75, p<0.05 *Other side effects: NS; NS	13 withdrawals due to adverse events	
Handen 1997	NR	NR	NR	
Handen 1999	Parents or teachers reported	5(4.5%) patients were reported with severe adverse side effects with 0.6mg/kg dose. Dull, social withdrawal, poor appetite, anxiety, and drowsiness were reported more in the drugs than placebo (mean): Dull -- placebo(0.4), 0.3mg/kg(1.5), 0.6mg/kg(2.2) Social withdrawal -- placebo(0.4), 0.3mg/kg(1.3), 0.6mg/kg(2.1) Poor appetite -- placebo(0.1), 0.3mg/kg(1.9), 0.6mg/kg(3.2) Anxiety --placebo(0), 0.3mg/kg(0.1), 0.6mg/kg(0.3) Drowsiness -- placebo(0), 0.3mg/kg(1.1), 0.6mg/kg(0.6)	1 (9%)	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Subgroup comorbidity: Learning disorders			
Grizenko 2006	RCT DB, crossover	Diagnoses of ADHD according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSMIV), 31 that were based on clinical examination, information collected from different sources and a structured interview using the Diagnostic Interview Schedule for Children Version IV (DISC-IV). Children with an IQ lower than 70 on the Wechsler Intelligence scale for Children-III,32 a history of Tourette's syndrome, pervasive developmental disorder or psychosis were excluded from the study. Those with previous intolerance or allergic reaction to MPH were also excluded.	44% with learning disability and 56% without learning disability LD determined using the Wide range Achievement Test (WRAT) and if there was a difference in reading or math grade level >/= 2 years with respect to the expected grade level, the child was considered to have an LD in that subject.

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Subgroup comorbidity: Learning disorders				
Grizenko 2006	Placebo or 0.5 mg/kg of body weight of MPH divided in 2 equal doses (morning and noon)	none	NR	Primary Outcome Measure: Consensus Clinical Response Other Measures: Conners Global Index–Teacher's Version and Parent Version (CGI-T and CGI-P), Clinical Global Impression Scale, the Restricted Academic Situation Scale (RASS), the Conners' Continuous Performance Task (CPT), Wide Range Achievement Test, Revised (WRAT), and the Test de rendement pour francophones (TRF)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Subgroup comorbidity: Learning disorders				
Grizenko 2006	Mean Age: 9.2 yrs (Range: 6 - 12 yrs) Male: 85.3% Ethnicity: NR	IQ Mean: 96.45 CBCL ext. mean: 70.0 CBCL int. mean: 63.5 RASS Mean: 43.8 CPT overall index: 10.6	NR/100/95	NR/NR/95

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Subgroup comorbidity: Learning disorders	
Grizenko 2006	Responders=CCR of 2 or 3 and Non-responders=CCR of 0 or 1, number(%) Non-responders with LD: 19 (45) [with RD and MD: 10 (45), with RD only: 4 (33), with MD only: 5 (63)], without LD: 13 (25), p=0.034 Responders with LD: 23 (55) [with RD and MD: 12 (55), with RD only: 8 (67), with MD only: 3 (37)], without LD: 40 (75) Reading: with RD non-responders: 14(41), responders: 20(59) and without RD nonresponders: 19(31), responders 41(68), p=0.33 Math: with MD non-responders: 15(50), responders: 15(50) and without MD nonresponders: 18(28), responders 47(72), p=0.034

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Subgroup comorbidity: Learning disorders				
Grizenko 2006	NR	No important AE or side effects were noted	NR; none	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Subgroup comorbidity: Disruptive Behavior Disorders			
Biederman 2007	Randomized, double-blind, placebo-controlled	Children and adolescents, aged 6–16, who met the criteria for ADHD in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), as confirmed by clinical assessment and structured interview [behavioral module of the Schedule for Affective Disorders and Schizophrenia for School-aged Children—Present and Lifetime Versions (K-SADS-PL)]. Subjects were required to have a symptom severity score that was at least 1.0 (study LYAW) or 1.5 (studies LYAT and LYBG) standard deviations above age and sex norms on the ADHDRS-IV parent version: investigator-administered and -scored scale (ADHDRS-IV-Parent:Inv) for either the total score or the inattention or hyperactivity/impulsivity subscale scores, corresponding to the combined, primarily inattentive, and primarily hyperactive/impulsive subtypes of ADHD, respectively. Subjects were assessed for lifetime psychiatric disorders, including ODD, by clinical history and structured interview, using the K-SADS-PL. Subjects with learning disabilities were not excluded. However, subjects were required to be of normal intelligence (IQ ≥80), as assessed by either the full Wechsler Intelligence Scale for Children, third edition (WISC-III), or the four specified subtests of the WISC-III (block design, picture arrangement, similarities, and vocabulary). Other exclusion criteria included any serious medical illness, comorbid psychosis, or bipolar disorder, history of a seizure disorder, or ongoing use of psychoactive medications other than the study drug. Comorbidity was not a contraindication to participation, with the exception that children were not permitted to enroll if they were receiving treatment of a coexisting disorder that took precedence over, or otherwise mitigated, their treatment for ADHD.	ODD-Comorbid vs noncomorbid, n (%) Hyperactive/impulsive: 1 (0.6) vs 8 (2.3) Inattentive: 22 (13.9) vs 141 (39.8) Combined: 135 (85.4) vs 205 (57.9)
Hazell 2006	RCT DB	Children and adolescents aged 6–15 years who met DSM-IV criteria for ADHD, as assessed by clinical interview and confirmed by a structured diagnostic interview [Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime (K- ADSPL)]. In addition, all patients had symptom severity at least 1.5 standard deviations above expected age and sex norms on the ADHD Rating Scale-IV (ADHD RS) for the patients' ADHD subtype (predominantly inattentive, predominantly hyperactive/impulsive, combined). Children and adolescents were randomly assigned in the double-blind, placebo-controlled relapse prevention study period if they were deemed responders to 10 weeks of open-label treatment with atomoxetine. Important exclusion criteria included a history of bipolar or psychotic illness, substance abuse, serious medical illness, use of concomitant psychoactive medications, and low IQ.	ADHD only: 236 ADHD + ODD: 179

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Subgroup comorbidity: Disruptive Behavior Disorders				
Biederman 2007	Once-daily atomoxetine (up to 1.8 mg/kg/day) or placebo Mean Dose: NR In two of the three studies, subjects assigned to atomoxetine received 0.8 mg/kg/day in the morning for 3 days, after which the dose was increased to 1.2 mg/kg/day. In the other study, subjects assigned to atomoxetine received 0.5 mg/kg/day for 3 days, followed by 0.75 mg/kg/day for the remainder of the first week; then, the dose was increased to 1.0 mg/kg/day. After 3–4 weeks, subjects with significant residual symptoms [defined by a clinical global impressions of severity (CGI-S) score of 3 or greater] and for whom there was no safety or tolerability contraindication could have their dose increased to 1.5–1.8 mg/kg/day.	NR	NR	Primary Outcome Measure: ADHDRS-IV Other Measures: Conners' Parent RS, revised: short form (CPRS-R:S), which includes a subscale assessing oppositional behavior; the CGI-S, keyed to ADHD severity (CGI-ADHD-S); child health questionnaire (CHQ)
Hazell 2006	ATX: Minimum dose of 0.5mg/kg/day to a maximum of 1.8 mg/kg/day Mean Dose = NR	Run-in: 10-week open-label trial to determine responsiveness and titrate optimal dose/NR	NR/NR	Primary Outcome Measure: Relative Risk of Relapse

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Subgroup comorbidity: Disruptive Behavior Disorders				
Biederman 2007	Mean age: 9.9 yrs 73.4% male Ethnicity: NR	ODD-comorbid vs noncomorbid, n(%) Conduct disorder: 13/151 (8.6) vs 0 (0), p = <.001 General anxiety disorder: 4/150 (2.7) vs 3/353 (0.9), p = 0.205 Major depressive disorder: 4/151 (2.7) vs 7/352 (2), p = 0.741	512/512/512	NR/NR/512
Hazell 2006	Mean Age: NR (Range: 6–15 yrs) Male: 90% Ethnicity: 98% Caucasian	ODD vs. non-ODD **ADHD Subtype, No.(% of total in ODD or non-ODD group)** Hyperactive/impulsive: 19(4.6) Inattentive: 93 (22.4) combined: 303 (73) **previous stimulant therapy, No.(% of total in ODD or non-ODD group)**: 218 (52.5)	604/NR/416	211/5/415

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Subgroup comorbidity: Disruptive Behavior Disorders	
Biederman 2007	Youth with ODD exhibited greater ADHD severity than noncomorbid youth according to ADHDRS-IV-Parent: Inv total scores (ODD-comorbid: 5.2+0.8 vs noncomorbid: 38.3+9.5) ADHD with ODD vs ADHD without ODD CGI-ADHD-S: 5.2+0.8 vs 4.7+0.7, p = 0.001 CPRS-R:S: 12.2+4.1 vs 7.4+4.5, p<0.001 CHQ Psychosocial summary scores: 27.9+10.2 vs 34.4+10.1, p<0.001
Hazell 2006	**ADHD with ODD vs. ADHD without ODD taking Atomoxetine: RR 0.67, 95% CI 0.42-1.06** Mean days to relapse: 215 vs. 211, p=0.08 **ADHD with ODD vs. ADHD without ODD taking Placebo: RR 1.27, 95% CI 0.81-1.99** Mean days to relapse: 136 vs. 151, p=0.22

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Subgroup comorbidity: Disruptive Behavior Disorders				
Biederman 2007	NR	NR	NR	
Hazell 2006	NR in this study	NR	211/10	original "parent study" reports detailed outcomes and safety data, Michelson et al 2004

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Newcorn 2005	RCT DB	Children and adolescents, 8 to 18 years of age, who met DSM-IV criteria for ADHD by clinical assessment and confirmed by structured interview (behavioral module of the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime versions (K-SADS-PL). Patients were also required to have a symptom severity score ≥1.5 SDs above age and gender norms on the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent version, investigator administered and -scored scale (ADHDRS-IV-Parent:Inv) for either the total score or the Inattentive or Hyperactive/Impulsive subscale scores, corresponding to the combined, primarily inattentive, and primarily hyperactive/impulsive subtypes of ADHD, respectively. Patients were assessed for lifetime psychiatric disorders, including ODD, by clinical history and structured interview, using the K-SADS-PL. Patients with learning disabilities were not excluded. However, patients were required to be of normal intelligence (IQ ≥80) as assessed by either the full WISC-III or the four specified subtests of the WISC-III (Block Design, Picture Arrangement, Similarities, and Vocabulary). Other exclusion criteria included any serious medical illness, comorbid psychosis or bipolar disorder, history of a seizure disorder, or ongoing use of psychoactive medications other than the study drug. Comorbidity was not a contraindication to participation, with the exception that children were not permitted to enroll if they were receiving treatment of a coexisting disorder that took precedence over or otherwise mitigated their treatment for ADHD.	115 (39.3%) with ODD 178 (60.8%) without ODD

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Newcorn 2005	ATX: Fixed dosing of 0.5, 1.2, or 1.8 mg/kg/day or placebo (began treatment at 0.5 mg/kg/day. In the higher dose arms, drug was titrated with intermediate steps of 0.8 mg/kg/day and 1.2 mg/kg/day at 1-week intervals) Mean Dose = NR	initial 12- to 18-day medication washout period	NR	Primary Outcome Measure: ADHDRS-IV-Parent:Inv Other Measures: Conners' Parent Rating Scale-Revised Short Form (CPRS-R:S), the Clinical Global Impressions of Severity (CGI-ADHD-S). Child Health Questionnaire (CHQ)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Newcorn 2005	Mean Age: 11.1 yrs (Range: 8–18 yrs) Male: 72.5% Ethnicity: NR	ODD vs. non-ODD **ADHD Subtype No.(%) all NS** Hyperactive/impulsive: 5 (2.8) Inattentive: 92 (31.4) combined: 196 (66.9)	NR/NR/293	NR/NR/NR

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Newcorn 2005	**1.8 vs. 1.2 vs. 0.5 vs. placebo** **ADHDRS-IV-Parent Total mean change:** ODD: -13.4 (p=0.030)/-11.5(p=0.092)/-10.8(p=0.185)/-5.1 non-ODD: -13.6 (p=0.050)/-14.9(p=0.009)/-9.1(p=0.690)/-5.1 **ADHDRS-IV-Parent inattentive mean change:** ODD: -6.9 (p=0.020)/-5.7(p=0.105)/-5.4(p=0.194)/-2.2 non-ODD: -6.8 (p=0.098)/-7.8(p=0.010)/-4.8(p=0.688)/-3.1 **ADHDRS-IV-Parent hyperactive/impulsive mean change:** ODD: -6.6 (p=0.091)/-5.8(p=0.131)/-5.4(p=0.252)/-2.9 non-ODD: -6.8 (p=0.066)/-7.1(p=0.034)/-4.3(p=0.798)/-3.7 **CGI-ADHD-S mean change:** ODD: -1.2 (p=0.040)/-0.9(p=0.207)/-1.0(p=0.149)/-0.4 non-ODD: -1.3 (p=0.038)/-1.5(p=0.002)/-0.6(p=0.930)/-0.6 **CPRS-R:S, ADHD Index mean change:** ODD: -7.2 (p=0.018)/-6.6(p=0.030)/-7.5(p=0.016)/-0.3 non-ODD: -9.9 (p<0.001)/-10.0(p<0.001)/-7.0(p=0.125)/-2.4 **CPRS-R:S, oppositional mean change:** ODD: -3.4 (p=0.027)/-2.2(p=0.321)/-3.4(p=0.040)/-0.6 non-ODD: -2.3 (p=0.229)/-2.7(p=0.057)/-1.5(p=0.884)/-0.7 **CDRS-R:** ODD: -1.6 (p=0.255)/-1.9(p=0.209)/-1.4(p=0.300)/1.3 non-ODD: -2.2 (p=0.077)/-1.8(p=0.108)/0.6(p>0.999)/0.8 **Measures of QOL** **Psychosocial Summary mean change:** ODD: 10.8(p=0.003)/7.1(p=0.07)/4.4(p=0.238)/-0.4 non-ODD: 7.8(p=<.001)/5.8(p=.006)/4.5(p=0.124)/-0.9 **Behavior mean change:** ODD: 18.6(p=<.001)/13.0(p=.036)/9.1(p=.077)/-2.3 non-ODD: 14.6(p=<.001)/14.0(p=<.001)/7.5(p=0.250)/0.8 **Family Activity Mean Change:** ODD: 16.7(p=.006)/13.9(p=.021)/6.4(p=.269)/-0.9 non-ODD: 14.1(p=.094)/15.7(p=<.054)/10.6(p=0.495)/0.9 **Parent Impact-Emotional Mean Change:** ODD: 7.1(p=.955)/13.0(p=.627)/6.1(p=.269)/8.4 non-ODD: 13.8(p=.023)/9.3(p=.281)/5.4(p=.883)/0.7 **Parent Impact-Time Mean Change:** ODD: 13.0(p=.091)/5.8(p=.313)/2.6(p=.499)/-2.3

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Newcorn 2005	NR	NR	NR;NR	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Spencer 2006	RCT DB	Children and adolescents aged 6 to 17 years with ODD as defined according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria. Key inclusion criteria included normal blood pressure (e.g., within the 95th percentile for their age, height, and sex), an electrocardiographic (ECG) finding within normal range, and no comorbid illness that could affect the efficacy or tolerability of MAS XR. Patients were excluded if they had another psychiatric diagnosis (except ADHD); a diagnosis of conduct disorder; or a medical history of nonresponse to stimulant medication, seizures, tic disorder, or Tourette's syndrome.	ADHD +ODD: 235 (79.1%) ODD only: 70 (23.6%)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Spencer 2006	MAS XR 10, 20, 30, or 40 mg/d or placebo (All doses were given in the morning. Forced-dose-titration design: in which patients randomized to the 10-mg/d group received 1 dose of 10 mg/d for 4 weeks. Patients randomized to the 20-mg/d group received 1 dose of 10 mg/d for the first week and 1 dose of 20 mg/d for the remaining weeks; patients randomized to the 30-mg/d group received 1 dose of 10 mg/d for the first week, 1 dose of 20 mg/d for the second week, and 1 dose of 30 mg/d for the remaining 2 weeks; and patients randomized to the 40-mg/d group received 1 dose of 10 mg/d for the first week, 1 dose of 20 mg/d for the second week, 1 dose of 30 mg/d for the third week, and 1 dose of 40 mg/d for the fourth week.) Mean Dose: NR	NR/1- to 4-week washout phase at beginning to stop all current psychotropic medication	bronchodilators and inhaled corticosteroids as needed, also allowed antibiotics and over-the-counter medications that do not affect blood pressure, heart rate, or central nervous system activity./NR	Primary Outcome Measure: ODD subscale of the Swanson, Nolan, and Pelham-IV (SNAP-IV) parent rating Other Measures: ODD subscale of the SNAP-IV teacher rating, the ADHD subscales of the SNAP-IV parent and teacher ratings, the Child Health Questionnaire Parent Form 50 (CHQ-PF50), the self-esteem module from the CHQ-CF87, and the Clinical Global Impressions (CGI)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Spencer 2006	Mean age: 10.6 yrs Male: 69.2% Ethnicity: 70.8% Caucasian 16.2% Black 6.5% Hispanic 6.5% Other	**Pure ODD**: 64 (20.8%) **ODD with comorbid ADHD: 79.2%** **Subtype, No.(% of total)** Hyperactive/impulsive: 17 (5.5) Inattentive: 49 (15.9) Combined: 186 (60.4) Not available: 56 (18.2) **Mean years since ODD diagnosis**: 1.46 (SD=2.5) **Mean years since ADHD diagnosis:** 2.52 (SD=3.3**)**	335/NR/308	46/13/297

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
	non-ODD: 5.8(p=.740)/7.4(p=.637)/1.1(p=.999)/1.3 **Mental Health Mean Change:** ODD: 12.1(p=.017)/7.0(p=.401)/6.4(p=.237)/0.0 non-ODD: 6.5(p=.022)/3.7(p=.086)/8.8(p=.015)/-2.3 **Role-Emotional Mean Change:** ODD: 19.7(p=.071)/8.3(p=.241)/11.6(p=.200)/-5.6 non-ODD: 13.1(p=.051)/7.8(p=.161)/4.2(p=.695)/-5.4 **Self-Esteem Mean Change:** ODD: 9.6(p=.048)/7.6(p=.417)/-2.7(p=.990)/-1.4 non-ODD: 7.4(p=.031)/4.9(p=.222)/5.0(p=.274)/-0.2
Spencer 2006	MAS XR 40mg vs. 30mg vs. 20mg vs. 10mg vs. placebo **ODD subscale of the (SNAP-IV) teacher rating, mean change (SD):** -0.49 (0.78) vs. -0.46 (0.57) vs. -0.45 (0.91) vs. -0.43 (0.77) vs. 0.09 (0.62) **ODD subscale of the (SNAP-IV) parent rating, LS mean difference:** -0.30 (NS) vs. -0.43(p<0.005) vs. -0.26 (NS) vs. -0.23 (NS) **ADHD subscales of the SNAP-IV parent:** improvements were significant in MAS XR 10mg (p=0.02), 30mg (p=0.002) and 40mg (p=0.009) groups compared with placebo **ADHD subscales of the SNAP-IV teacher:** improvements were significant in MAS XR 10mg (p=0.03), 30mg (p=0.01) and 40mg (p=0.006) groups compared with placebo **CGI-S, % much or very much improved** 61% (p<0.001) vs. 60.9% (p<0.001) vs. 55.4% (p<0.006) vs. 36.2% (p=0.122) vs. 26.7% **CHQ-PF50, change in positive treatment effects for patients treated with MSA XR:** Behavior, p=0.006 Self-Esteem, p=0.04 General health perceptions, p=0.037 Physical summary, p=0.009 Psychosocial summary, p=0.02

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Spencer 2006	self report **severe,** if it was incapacitating and the patient was unable to engage in usual activity or work **serious** if it resulted in death, hospitalizations or significant or persistent incapacity	**MAS XR 40mg vs. 30mg vs. 20mg vs. 10mg vs. placebo** **No. (%)** Anorexia/Decreased Appetite: 21(34.4)/22(31.9)/22(37.9)/10(16.7)/3(5.0) Insomnia: 17(27.9)/16(23.2)/14(24.1)/8(13.3)/5(8.3) Headache: 16(26.2)/11(15.9)/10(17.2)/11(18.3)/9(15.0) Abdominal Pain: 7(11.5)/10(14.5)/6(10.3)/7(11.7)/3(5.0) Weight Loss: 9(14.8)/8(11.6)/6(10.3)/2(3.3)/0(0), p,0.001 Pharyngitis: 7(11.5)/2(2.9)/3(5.2)/6(10.0)/3(5.0) Nervousness: 5(8.2)/5(7.2)/4(6.9)/3(5.0)/0(0) Emotional Lability: 3(4.9)/6(8.7)/3(5.2)/2(3.3)/1(1.7) Accidental Injury: 4(6.6)/2(2.9)/4(6.9)/1(1.7)/3(5.0)	46/14	study reports ITT and PP results

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Subgroups: ADHD Subtypes			
Gorman 2006	RCT DB crossover	Eligibility: ages 6 to 12; WISC-III (Wechsler, 1991) Full Scale IQ ≥80; no history of neurological disorder, chronic medical illness, bipolar disorder, schizophrenia, or pervasive developmental disorder; no episode of major depressive disorder in the preceding 6 months; normal/corrected vision and hearing; no current medication; and no physical disabilities. To confirm the diagnosis of ADHD, ≥6 inattention and/or hyperactivity/impulsivity symptoms on the Parent Interview for Child Symptoms-4, a semistructured DSM interview administered by the second author and ≥4 symptoms of inattention and/or ≥4 symptoms of hyperactivity/impulsivity on the teacher ADHD scale, a Likert scale comprising of 18 DSM-IV symptoms for ADHD were required. The count of inattention or hyperactivity/impulsivity symptoms endorsed by the parent was supplemented by up to two ADHD symptoms for each symptom cluster reported by the teacher.	ADHD subtypes: mixed: 22 (29.3%), inattentive: 19 (25.3%), control group 34 (45.3%)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Subgroups: ADHD Subtypes				
Gorman 2006	Methylphenidate: Mean Dose: 33.1 mg/day Dose Range: Terminal daily doses from 25 to 50 mg	NR/NR	none/NR	Primary Outcome Measure: IOWA Conners scales (parent and teacher ratings) of: Inattention/Overactivity, Hyperactivity, Attention, Aggression/Oppositionality, Aggression, and Valence of interview responses/comments

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Subgroups: ADHD Subtypes				
Gorman 2006	Mean age: 9.1 yrs (Range: 6 to 12 yrs) Male: 52% Ethnicity: 91% Caucasian	**Frequency or mean** Socioeconomic status: 50.60, NS Anxiety disorders:7 lifetime affective disorder: 2 ODD:18, p<0.001 Wechsler full-scale IQ: 113.86, p<0.001 Basic Reading Skills Index: 113.44, p<0.001 Broad Mathematics Index: 115.98, p<0.001 Kaufman Test of Academic Achievement, Spelling: 107.91, p<0.001	NR/NR/75	NR/NR/NR

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Subgroups: ADHD Subtypes	
Gorman 2006	Mean change from pretrial (+/- SD) Parent ratings [placebo or matched session vs. MPH or matched session] / teacher ratings [placebo or matched session vs. MPH or matched session] **Inattention/Overactivity** Controls: 0.13(0.09) ADHD/I: -0.08 vs. -0.40 / -0.13 vs. -0.67, p<0.05 ADHD/C: -0.17 vs. -1.06 / -0.08 vs -0.94, p<0.001 **Hyperactivity** Controls: -.98(.06) ADHD/I: 0.05 vs. 0.12 / 0.08 vs. -0.13, p<0.05 ADHD/C: -0.04 vs. -0.44 / 0.11 vs -0.45, p<0.001 **Attention** Controls: .72(.06) ADHD/I: -.07 vs 0.21 / -0.17 vs 0.21, p<0.05 ADHD/C: 0.10 vs 0.49 / -0.07 vs. 0.46, p<0.001 **Aggression/Oppositionality** Controls: .25(.09) ADHD/I: 0.05 vs -0.03 / -0.10 vs -0.22, NS ADHD/C: 0.25 vs -0.47 / -0.10 vs. -0.58, p<0.001 **Aggression** Controls: .21(.06) ADHD/I: 0.03 vs 0.01 / 0.05 vs 0.04, NS ADHD/C: 0.15 vs -0.16 / -0.06 vs -0.27, p<0.001 **Valence of interview responses/comments,** ADHD/I: 0.26(.32) vs 1.10(.37) / -0.76(.42) vs 0.50(.43) ADHD/C: -0.15(.30) vs 1.80(.34) / -0.96(.39) vs 0.97(.40)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Subgroups: ADHD Subtypes				
Gorman 2006	NR	MPH vs. Placebo, mean of body weight and counts of side effects (+/-SE) Body Weight (Kg): 36.09(1.99) vs. 36.54(2.01), p=0.18 Somatic Complaints: 1.14(.15) vs. 0.29(.10), p=0.001 Behavioral Complaints: 1.18(.19) vs. 1.30(.21), NS	NR/NR	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Subgroups: Race			
Gau 2007	RCT DB Parallel	Children and adolescents aged 6-16 years; met DSM-IV criteria for diagnosis of ADHD, confirmed by Chinese version of K-SADS-E; ADHDRS-IV-Parent Version: Investigator Administered and Scored Total Score of at least 25 for boys and 22 for girls, or greater than 12 for their diagnostic subtype at both visit 1 and visit 2; normal intelligence; no ADHD medication or completion of the washout procedures	Taiwanese children
Comorbidity: Bipolar Disorder			
Scheffer 2005 U.S.	DB PCT crossover (after 8 weeks of open treatment with divalproex sodium)	Study subjects were recruited from a university-based outpatient pediatric psychiatry clinic and the community. Eligible subjects were males and females 6-17 years of age, who met the DSM-IV criteria for both bipolar I or bipolar II disorder (in either the mixed, manic, of hypomanic phase) and ADHD. All subjects had to score >= 14 on the Young Mania rating scale at baseline, to have scores exceeding 2 standard deviations from normal on the hyperactivity index of the Conners' Teachers and Parents Rating Scales, and to be of normal intelligence (IQ>70) on the basis of clinical impression or formal testing.	Bipolar I or II Disorder

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Subgroups: Race				
Gau 2007	Study period I: Medication-free screening/assessment Study period II: Atomoxetine 1.4 mg/kg QD (mean final dose) vs placebo x 6 weeks	No run-in/wash-out procedures not described	Concomitant use of other psychoactive medications not allowed	Primary: Total score of ADHDRS-IV Secondary: ADHDRS-IV Inattention and Hyperactivity/Impulsivity subscales; CGI-ADHD-S, Chinese version of Connors' Parent Rating Scale-Revised: Short Form (CPRS-R:S), Chinese version of Connors' Teacher Rating Scale-Revised: Short Form (CTRS-R:S)
Comorbidity: Bipolar Disorder				
Scheffer 2005 U.S.	Adderall 5 mg po bid Placebo 4 weeks of treatment DB (A follow-up of 12 weeks of open label Adderall+divalproex after the 4 weeks of DB also briefly assessed)	NR / NR for Adderall part (2 week washout for psychotropics before the 8-week divalproex open label trial (fluoxetine=4 week washout)	Divalproex sodium given concomitantly.	Primary Outcome Measure: Clinical Global Impression Improvement (GCI-I) subscale Other Measures: Young Mania Rating Scale, Conners' Teachers and Parents Rating Scales

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Subgroups: Race				
Gau 2007	Mean age=9.2 years 89% male 100% Taiwanese	Height (cm): 133.6 Weight (kg): 31.5 Previous psychostimulants (# pts): 57.5% Family ADHD history: 15.1% ADHD Subtype Combined: 73% Inattentive: 27% Comorbid conditions ODD: 16% Conduct Disorder: 8.5% ADHDRS-IV, total score: 36.8 points CGI-ADHD-S: 5.3 CPRS-R:S, total score: 44 CTRS-R:S, total score: 30.6	NR/NR/106	8 (7.5%) withdrawn/LTFU NR/98 (92%) analyzed
Comorbidity: Bipolar Disorder				
Scheffer 2005 U.S.	for DB crossover trial only, n=31 Mean age: 9.8 years 83.3% male 93.3% white 6.7% Hispanic	Mean Young Mania Rating score: 28.8 (SD: 5.2) Mixed phase: 83.3% Manic phase: 16.7% Bipolar I: 73.3% Bipolar II: 26.7%	NR / NR / 31	1 / NR / 30

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Subgroups: Race	
Gau 2007	**Atomoxetine vs placebo: Mean change scores** ADHDRS-IV Total Score: -17.3 vs -9.3, p=0.002 CGI-ADHD-S: -2 vs -1; p<0.001 CPRS-R:S Total Score: -12.8 vs -3.5; p<0.001 CTRS-R:S Total Score: -6.8 vs +0.8; p=0.028 Oppositional subscale: -0.1 vs +0.1; NS
Comorbidity: Bipolar Disorder	
Scheffer 2005 U.S.	Mean score Adderall (n=14) vs placebo (n=16): At the end of the first 2 week period of the trial, CGi-I: 1.7 (SD=0.6) cs 3.4 (SD=1.0), p<0.0001 At the end of the 4 week DB trial (i.e., after crossover): 1.8(SD=0.6) vs 3.7 (SD=1.0), p=NR % patients with treatment response according to CGI Improvement Score CGI=1 or 2): 89.6 % on Adderall vs 10 % on placebo

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Subgroups: Race				
Gau 2007	Open-ended questions	**Atomoxetine vs placebo** Decreased appetite: 26 (36.1%) vs 5 (17.4%); p=0.02 Somnolence: 16 (22.2%) vs 3 (8.8%); NS Nausea: 12 (16.6%) vs 0; p<0.01 Cough Increased: 9 (12.5%) vs 7 (20.6%); NS Insomnia: 8 (11.1%) vs 1 (2.9%); NS Headache: 7 (9.7%) vs 2 (5.9%); NS Dizziness: 7 (9.7%) vs 1 (2.9%); NS Asthenia: 7 (9.7%) vs 0; p=0.09 Rhinitis: 6 (8.3%) vs 0; NS Abdominal pain: 6 (8.3%) vs 0; NS Pharyngitis: 5 (6.9%) vs 3 (8.8%); NS Vomiting: 5 (6.9%) vs 3 (8.8%); NS Diarrhea: 4 (5.6%) vs 0; NS Weight loss: 4 (5.6%) vs 0; NS Fever: 3 (4.2%) vs 5 (14.7%); NS	Total withdrawals: NR separated by group Withdrawals due to AE's: 1 (1.4%) vs 0; NS	
Comorbidity: Bipolar Disorder				
Scheffer 2005 U.S.	Side Effects Form for Children and Adolescents	4 week DB phase, which treatment not specified: Abdominal pain n=2 Diarrhea, n=1 Nausea, n=1 Appetite decrease, n=2 Headache, n=1 Drowsiness, n=2 Difficulty falling asleep, n=1 Irritability, n=1 Rash, n=1 AEs not specified for 12 week follow-up period	1 ; NR	During the 12-week follow-up period (n=23), the average dose was 14.5 mg/day

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Comorbidity: Anxiety Disorders			
Geller 2007	RCT DB Parallel	Children and adolescents ages 8 to 17 years who met DSM-IV criteria for ADHD and for at least one of the following anxiety disorders: separation anxiety disorder, generalized anxiety disorder or social phobia; at visits 2 and 3, patients must have had a total or subscale score on the ADHDRS-IV-PI of at least 1.5 SDs above age and sex norms for ADHD subtype, and a total score on the Pediatric Anxiety Rating Scale (PARS) of at least 15 (max score=25); ADHD diagnoses were confirmed clinically, and anxiety and ADHD diagnoses were confirmed using the K-SADS-PL administered to parent and child	Separation anxiety disorder, generalized anxiety disorder or social phobia
Comorbidity: MDD			
Bangs 2007	RCT DB Parallel	Adolescents aged 12-18 years who met the criteria for both ADHD and MDD per the DSM-IV as confirmed by the K-SADS-PL; score of at least 1.5 SD's above age and sex norms on ADHD-RS-IV; Children's Depression Rating Scale-Revised (CDRS-R) total score of at least 40 at every visit prior to randomization	Major Depressive Disorder

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Comorbidity: Anxiety Disorders				
Geller 2007	Study period I: Single-blind placebo run-in x 2 weeks Study period II: Atomoxetine 1.3 mg/kg/day (mean final dose) or placebo x 12 weeks	2-day washout prior to visit 2 (eligibility assessment of ADHD symptom severity); 2-week SB placebo run-in	NR	Primary: ADHDRS-IV-PI and PARS Secondary: Multidimensional Anxiety Scale for Children (MASC), CGI-S, CGI-I, Life Participation Scale for ADHD-Revised (LPS-ADHD-R), Child Health Questionnaire-Parent-Completed Full Length (CHQ-PF50)
Comorbidity: MDD				
Bangs 2007	Study period I: screening/baseline assessment Study period II: 1-week placebo lead-in (blinding unclear) Study period III: Atomoxetine 1.51 mg/kg QD (mean final dose) vs placebo x 9 weeks	Study period II: 1-week placebo lead-in (blinding unclear)/Washout N/A	No other psychotropics allowed	Primary: ADHDRS-IV-Parent:Inv, CDRS-R Secondary: MADRS, CGI-I, CGI-S, Young Mania Rating Scale (YMRS)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Comorbidity: Anxiety Disorders				
Geller 2007	Mean age= 12 years 64.8% male 80.7% white	Prior stimulant exposure: 62% ADHD subtype Combined: 75% Inattentive: 24% Hyperactive/Impulsive: 1% Height (mean cm): 150.1 Weight (mean kg): 46.8	269/NR/176	44 (25%)/1 (0.5%)/176 (100%)
Comorbidity: MDD				
Bangs 2007	Mean age=14 73% male 82% white	ADHD Subtype Combined: 43% Inattentive: 57% Prior stimulant exposure: 81% Height (cm): 163.7 Weight (kg): 61	NR/NR/141	22 (15%) withdrawn/4 (2.8%) LTFU/140 analyzed

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Comorbidity: Anxiety Disorders	
Geller 2007	Lisdexamfetamine vs placebo Mean change from baseline ADHDRS-IV-PI: -9 vs -0.7, p<0.001 PARS: -4.5 vs -2.4, p<0.01 CGI-S: -0.9 vs -0.4; p=0.002 MASC: -4.6 vs 2.1; p=0.009 LPS-ADHD-R: 9.5 vs 3.1; p=0.002 CHQ-PF50: 6.9 vs 3.3; 0.019
Comorbidity: MDD	
Bangs 2007	Atomoxetine vs placebo ADHDRS-IV-Parent: Inv Mean Change: -13.3 vs -5.1; p<0.001 CDRS-R mean change: 53.4 vs 52; NS CGI-I score of 1 or 2 (% pts): 33 (48%) vs 12 (18%); p<0.001 CGI-S score of 1 or 2 (% pts): 13 (19%) vs 7 (10%), NS

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Comorbidity: Anxiety Disorders				
Geller 2007	Open-ended discussion at end of each visit	Mean weight loss (kg): -0.55 vs +1.39; p<.001 Decreased appetite: 11 (14.3%) vs 3 (3.8%); p=0.025 Headache: 11 (14.3%) vs 7 (8.8%), NS Upper abdominal pain: 9 (11.7%) vs 4 (5%), NS Vomiting: 8 (10.4%) vs 4 (5%), NS Irritability: 5 (6.5%) vs 3 (3.8%), NS Nasopharyngitis: 5 (6.5%) vs 5 (6.3%), NS Nausea: 5 (6.5%) vs 2 (2.5%), NS Cough: 4 (5.2%) vs 5 (6.3%), NS Influenza: 4 (5.2%) vs 1 (1.3%), NS Sinusitis: 4 (5.2%) vs 3 (3.8%), NS	Overall withdrawals: 12 (15%) vs 14 (16%) Withdrawals due to AE's: 1 (1%) vs 1 (1%)	
Comorbidity: MDD				
Bangs 2007	NR	Atomoxetine vs placebo (% pts) Headache: 12 (17%) vs 7 (10%), NS Nausea: 16 (22%) vs 4%), p=0.002 Vomiting: 9 (12%) vs 6 (9%), NS Fatigue: 9 (12%) vs 3 (4%), NS Upper abdominal pain: 6 (8%) vs 5 (7%), NS Dizziness: 9 (12%) vs 2 (3%), NS Decreased appetite: 9 (12%) vs 0; p=0.003 Diarrhea: 1 (1%) vs 6 (9%), NS Influenza: 3 (4%) 4 (6%), NS Pyrexia: 2 (3%) vs 5 (7%), NS Weight decreased: 6 (8%) vs 1 (1%), NS Irritability: 4 (6%) vs 1 (1%), NS Weight increased: 1 (1%) vs 4 (7%), NS	Overall withdrawals: 13 (18%) vs 9 (13%), NS Withdrawals due to AE: 1 (1%) vs 1 (1%), NS	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Withdrawal of Medication			
Arnold 2004 Poor	RCT placebo controlled withdrawal Setting: 7-center US	Children and adolescents with ADHD based on DSM-III-R	d-MPH: placebo ADHD type Inattentive- 7(20%): 8(20%) combined- 28(80%): 32(80%) Stimulant naïve- 29(82.9%): 25(62.5%)
Klein 1988 Poor	Randomized experimental study; unblinded	Cross-situational, pervasive hyperactive behavior of long duration. When they entered treatment, all were between the ages of 6 and 12 years, had Wechsler Intelligence Scale for Children IQs of 85 or above, were free of neurological disorders and psychosis, and had received a diagnosis of DSM-II hyperkinetic reaction of childhood	NR

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Withdrawal of Medication				
Arnold 2004 Poor	Dexmethylphenidate 5-20mg/day Duration: 6 weeks	NA	NR	Swanson, Nolan and Pelham- ADHD scale (SNAP-ADHD) rated by parents
Klein 1988 Poor	Condition (A)="ON", remain "ON" a methylphenidate regimen all throughout up to 3-years, including summers Condition (B)="OFF", go "OFF" methylphenidate during each of two consecutive summers, with reinstatement between summers for up to 3 years Dosage ranges/mean dosages NR Dosing schedule NR	NR/NR	NR	NR

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Withdrawal of Medication				
Arnold 2004 Poor	MPH group: n=35 Mean age=10.1 years Gender: 85.7% male Ethnicity: 80% Caucasian, 14.3% African-American, 5.7% Hispanic Placebo group: n=40 Mean age=9.9 years Gender: 77.5% male Ethnicity: 75% Caucasian, 12.5% African-American, 12.5% Hispanic	d-MPH: placebo Teacher SNAP-ADHD- 0.7: 0.7 Parent SNAP-ADHD- 0.65: 0.55	116/89/89	5/3/75 6 with other reasons
Klein 1988 Poor	Mean age=9 years 91% male Ethnicity NR	Height=133.4 cm Weight=27.9 kg	NR/NR/62	26 (41.9%) withdrawn/0 lost to fu/analyzed: One summer=58 (ON n=32, OFF n=26); Two summers=34 (ON n=20, OFF n=14)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Withdrawal of Medication	
Arnold 2004 Poor	d-MPH patients continued to demonstrate the stable benefit obtained during the open-label titration phase (baseline vs. 3pm, p=0.0025), and the magnitude of the effect at 6 hours after the noon dose was similar to the effect at 3 hours (baseline vs. 6pm, p=0.038).
Klein 1988 Poor	NR

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Withdrawal of Medication				
Arnold 2004 Poor	reported by patients	46% of d-MPH patients and 38% of placebo patients experienced at least one AE, which is generally mild.	NR	
Klein 1988 Poor	Height and weight were obtained routinely by secretaries in all clinic children before and after the summer with a medical scale	ON vs OFF, t-score, p-value <u>Height (cm)</u> One summer: 134.3 vs 134.4, t=0.73, p=NS Two summers: 138.3 vs 139.8, t=2.57, p=0.02 <u>Weight (kg)</u> One summer: 28.6 vs 29.5, t=2.98, p=0.005 Two summers: 32.2 vs 32.8, t=0.88, p=NS	NR	Retrospective analysis of height/weight data from a study designed to measure efficacy

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Sleator 1974 Poor	Long-term continuous follow-up	Children who had previously been in a DB, placebo-controlled study. These children scored >=15 (2 standard deviations above the mean) on the Conners' Teacher Abbreviated Symptom Questionnaire (ASQ) (the highest possible score is 30 and represents a maximum of hyperactive behavior).	NR
Zeiner 1999 Fair	RCT, DB, crossover	a)boys between 7-12 years who fulfilled diagnostic criteria for ADHD; b) IQ of 70 or more; c) did not fulfill criteria for pervasive developmental disorder, psychosis, or mood disorder; d) did not have any acute or chronic medical or neurologic disease; and e) had never used stimulants or any other psychotropic drug	4(19%) had developmental reading disorder 5(24%) showed delayed development of motor functions 13(62%) was diagnosed as oppositional defiant disorder

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Sleator 1974 Poor	Mean daily dose: 0.66 mg/kg or 20.5 mg (41 subjects took doses once a day, in the morning) Children were taking MPH for a year (n=29) or two years (n=13), with a month of placebo to which the teacher and subject were both blinded. MPH was usually given on school days only.	Not applicable	NR	ASQ ratings were obtained from each subject's teacher at the end of each school month. Report cards and written reports from teachers were also obtained.
Zeiner 1999 Fair	Methylphenidate mean dose=22.4mg/day, range 15mg-35mg duration: 3 weeks dosage schedule: NR	NR/1 week	NR	Parental Account of Childhood Symptoms (PACS) Conners' Teacher Rating Scale (CTRS) Children's Checking Task (CCT) Continuous Performance Test (CPT) Paced Auditory Serial-Addition Task (PASAT) Maze Coordination Test (MCT) Grooved Pegboard Test (GPT) Reliable Change Index (RCI)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Sleator 1974 Poor	NR	NR	NR/NR/42	NR/NR/28
Zeiner 1999 Fair	Mean age=8.8 years 100% male Ethnicity NR	NR	NR/NR/21	NR/NR/21

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Sleator 1974 Poor	17/42 patients showed deterioration during the placebo month. Of these 17, 5 could not continue receiving placebo for an entire month because their restlessness threatened their successful completion of the school-year, and 7 needed an increased dose over the original recommended dose to achieve scores below 15 on the ASQ. These 7 are called the "increased-dose" subgroup. The remaining 10/17 are called the "drug-benefited" group. 11/42 scored adequate functioning (ASQ score <15) during the placebo month (the "remission" group) and were thought to be able to function adequately once taken off medication. No significant differences were found in mean age or IQ between the children who needed treatment versus the "remission" group (no data given). Mean ASQ Rating (placebo, 0.1 mg/kg, 0.3 mg/kg, and 0.7 mg/kg): 17, 15.8, 15.0, 11.8 (estimated from graph). Mean ASQ Score (pre-placebo, placebo, post placebo - estimated from graph): Drug-Benefited Group: 8, 17.5, 8.5 Increased Dose Group: 17, 23.8, 14 Remission Group: 7.8, 7.0, 7.7 Mean ASQ for all subjects when receiving medication (placebo eliminated) for Sep, Oct, Nov, Dec, Jan, Feb, Mar, Apr, May: 10, 9.5, 11, 12, 11, 12.5, 11.3, 11.3, 10.8 (estimated from graph)
Zeiner 1999 Fair	methylphenidate: placebo PACS hyperactivity- 3.8: 4.5, NS; PACS defiance- 7.4: 11.8, p<0.05 CTRS hyperactivity- 11.2: 16.8, p<0.0001; CTRS defiance- 10.4: 17.6, p<0.0001 CCT commission errors- 1.1: 1.0, NS; CCT omission errors- 2.7: 4.6, p<0.05 CPT commission errors- 4.6: 7.6, NS; CPT omission errors- 7.8: 13.8, p<0.05 PASAT R version- 8.8: 8.4, NS; PASAT S version- 8.2: 7.4, NS MCT dominant hand- 3.9: 12.0, p<0.05; MCT non-dominant hand- 30.8: 35.5, NS GPT dominant hand- 67.7: 74.9, p<0.05; GPT non-dominant hand- 83.7: 91.6, NS RCI showed significant improvement in methylphenidate treatment

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Sleator 1974 Poor	NR	NR	NR	
Zeiner 1999 Fair	NR	NR	NR	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Young Children (6 years and under)			
Bangs 2008 Europe & Australia	RCT, DB parallel	Patients were 6-12 years and met DSM-IV criteria for ADHD (any subtype) and comorbid ODD. If other comorbid conditions were present, either ADHD or ODD was the primary diagnosis.	**Atomoxetine vs Placebo** ADHD combined type: 84.6% vs 84.3% ADHD inattentive type: 9.0% vs 11.4% ADHD hyperactive/impulsive type: 6.4% vs 4.3%
Brams 2008 United States	RCT, DB Crossover	Males and females aged 6-12 years, who met the DSM-IV criteria for ADHD of any type, subjects must have been stabilized on a total daily dose or the nearest equivalent dose of methylphenidate 40-60mg or dexmethylphenidate 20-30mg for >2 weeks prior to screening.	ADHD combined type: 87.2% ADHD inattentive type: 2.8% ADHD hyperactive-impulsive type: 0%
Chacko 2005 U. S.	DB PCT crossover Summer Treatment Program (STP) which was attended 8-5 M-F.	5-6 year olds who met DSM-IV ADHD criteria and who were enrolled in the STP conducted at the Western Psychiatric Institute and Clinic or the University at Buffalo, SUNY.	50% met DSM-III-R or DSM-IV criteria for ODD 27.8% met DSM-III-R or DSM-IV criteria for conduct disorder (CD)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Young Children (6 years and under)				
Bangs 2008 Europe & Australia	Atomoxetine 1.2mg/kg; once daily Placebo 8 weeks	3- to 28-day washout period	NR	Primary Outcome Measure: SNAP-IV ODD subscale Other Measures: CGI-S, CGI-I, Conners' Global Index-Parent Version (CGI-P), Social Readjustment Rating Scale, ADHD Impact Module (AIM)
Brams 2008 United States	Dexmethylphenidate ER 20mg/day Placebo	No/No	NR	Primary Outcome Measure: Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) Rating scale (change from pre-dose to 0.5 hours post dose) Other measures: Change in SKAMP at 1, 2, 4, 6, and 8 hours post dose, Permanent Product Measure of Performance (PERMP), Conner's ADHD/DSM-IV scales for parents (CADS-P)
Chacko 2005 U. S.	Methylphenidate 0.3 mg/kd and 0.6 mg/kg (given bid) Placebo Medication given at 7:45 am and 11:45 am Monday-Thursday 6-week study Each treatment occurred 1-2 times/week, with the order randomized on a daily basis.	NR / NR	Medications: NR; in addition to medication, the children also had behavioral treatment in the STP.	Assessed by counselors throughout each day Point system: % of time following activity rules; noncompliance; conduct problems; negative verbalization Classroom measures: % of time following classroom rules; productivity; seatwork accuracy

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Young Children (6 years and under)				
Bangs 2008 Europe & Australia	Atomoxetine vs Placebo Mean age (years): 9.5 vs 9.7 91.7% vs 97.1% males Ethnicity: NR	Atomoxetine: n=156 Previous stimulant exposure: 66.7% Mean height: 136.6cm Mean weight: 33.2kg Placebo: n=70 Previous stimulant exposure: 74.3% Mean height: 139.3cm Mean weight: 36.3kg	257/226/226	29 total (24, 15% from atomoxetine group and 5, 7% from placebo group) 1 lost to follow-up from placebo group 257 analyzed
Brams 2008 United States	Mean age: 9.5 years 61.6% male 48.8% Caucasian 24.4% Black 2.3% Oriental 23.3% Hispanic 1.2% other	Mean height: 137.8cm Mean weight: 37.0kg Duration of ADHD symptoms: 4.7 years	92/86/86	NR
Chacko 2005 U. S.	Mean age: 6.13 years 89% male 86% white	Full scale IQ (SD): 102 (15.50) Parent-rated vs teacher-rated abbreviated Conners: 19.5 vs 18.8 IOWA Conners Rating (SD) Inattention/overactivity: 10.9 (3.9) Oppositional/defiant: 7.0 (4.5)	NR / NR/ 36	0 / 0 / 36

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Young Children (6 years and under)	
Bangs 2008 Europe & Australia	**Atomoxetine vs Placebo (mean change)** SNAP-IV ODD: -3.7 vs -2.9 Combined: -9.6 vs -4.4 (p<0.001) Inattentive: -5.0 vs -2.2 (p<0.001) Hyperactivity/impulsivity: -4.6 vs -2.2 (p=0.003) CGI-I: 3.5 vs 3.9 (p=0.037) CGI-S: -0.7 vs -0.3 (p=.013) ADHD impact module Child: 10.2 vs 2.5 (p=.002) Child self-control: 0.13 vs 0.17 (NS) Family: 9.4 vs 3.5 (p=0.018) CGI-P Total: -4.7 vs -1.6 (p=0.002) Restless/impulsive: -3.7 vs -1.2 (p<0.001) Emotional lability: -1.0 vs -0.4 (NS)
Brams 2008 United States	**Dexmethylphenidate ER vs Placebo** Mean change in SKAMP-Combined score 0.5 hours post dose: -0.969 vs 3.336 (p<0.001) Mean change in SKAMP-Combined score 1, 2, 4, 6, and 8 hours post dose was greater in dexmethylphenidate ER vs placebo (p<0.001 for all timepoints) Mean change in SKAMP-Attention and SKAMP-Deportment scores 0.5, 1, 2, 4, 6, and 8 hours post dose was greater in dexmethylphenidate ER vs placebo (p=0.012 and p=0.003 for 0.5 hours post dose for SKAMP-Attention and SKAMP-Deportment scores, respectively and p<0.001 for all other timepoints) Dexmethylphenidate ER was significantly more effective than placebo at all timepoints for both Math Test-Correct (p=0.001 at 0.5 hours post dose and p<0.001 at all other time points) and Math Test-Attempted (p=0.003 at 0.5 hours post dose and p<0.001 at all other timepoints)
Chacko 2005 U. S.	Dose effects were significant for 2 of the 4 point system measures: % following activity rules, p<0.001 Non-compliance, p<0.001 Dose effect was significant for 1 of the 3 classroom measures: % following activity rules, p<0.05 For the point system, these measures were statistically significant for both doses vs. placebo (p<0.05) % following activity rules, non compliance, conduct problems, and negative verbalizations For the classroom measures, % following classroom rules and seatwork completed were statistically significant for both doses vs. placebo (p<0.05) but % seatwork correct was not significantly different for either dose vs placebo.

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Young Children (6 years and under)				
Bangs 2008 Europe & Australia	Open-ended questions	NR	29 withdrawals 6 (3.8%) for AEs in Atomoxetine group 0 for AEs in placebo group	
Brams 2008 United States	Spontaneous report of AEs and laboratory tests	Total: 17.4% while taking dexmethylphenidate ER and 22.1% while taking placebo Common AEs (dexmethylphenidate ER vs Placebo): abdominal pain: (upper) 3.5% vs 4.7% headache: 3.5% vs 2.3% increased appetite: 0% vs 3.5% gastroenteritis (viral): 0% vs 2.3%	NR	
Chacko 2005 U. S.	AEs were reported by parents, counselors, and teachers.	The only common side effect was appetite loss at lunch, with counselors reporting it for 2 in placebo vs. 8 in the 0.3 mg/kg and 10 in the 0.6 mg/kd group No child had a side effect such that a decrease in medication dose or discontinuation in medication was required. Reduced appetite was noted for a substantial portion of the sample.	0 ; 0	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Corkum 2008 Canada	RCT, DB parallel	Stimulant medication-naive, meet DSM-IV criteria for one of the three ADHD subtypes, receive a recommendation to initiate a trial of MPH following the assessment, and have parents/caregivers who agreed to initiate a stimulant medication trial through the clinic pediatrician. Children were excluded if they had an IQ <1 SD below the mean on the Wechsler Intelligence Scale for Children–IV (WISC-IV), had a known neurological, metabolic, or seizure disorder, were currently taking other psychotropic medications or medications for sleep disturbances, evidenced symptoms of an intrinsic sleep disorder [i.e., sleep apnea, restless leg syndrome (RLS)/PLMS)] or a sleep-onset disorder based on parent report, or reached criteria for another mental health disorder that was considered primary to the ADHD diagnosis (e.g., autism).	11 (52.4%) had combined type 2 (9.5%) had hyperactive-impulsive type 8 (38.1%) had inattentive type

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Corkum 2008 Canada	MPH and placebo were in identical capsules. 21 days; drug or placebo was administered at 8 a.m., 12 p.m., and 4 p.m Children ≥25kg received 5 and 10mg doses Children >25kg received 10 and 15mg doses	NR	NR	Sleep diary completed by parent just after child goes to sleep and just after he/she woke up each day. Actigraph worn by children Conners' Parent (CPRS) and Teacher (CTRS) Rating Scales Sleep disturbances scale for children (SDSC)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Corkum 2008 Canada	Mean age: 8.5 years (range: 6-12 years) 71.4% male	Learning disabilities: 6 (29%) Oppositional defiant disorder 2 (10%) Baseline scores CTRS - ADHD index: 71.10 CTRS - Inattention: 58.85 CTRS - Hyperactivity/Impulsivity: 67.90 CTRS - Oppositional: 62.55 CPRS - ADHD index: 68.90 CPRS - Inattention: 67.19 CPRS - Hyperactivity/Impulsivity: 65.43 CPRS - Oppositional: 61.00	28/28/28	7/0/21

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Corkum 2008 Canada	Placebo vs Low dose vs Moderate dose Sleep diary at 3 weeks Time in bed: 585.97 vs 547.12 vs 547.56 (p<0.000 for placebo vs low dose and placebo vs moderate dose) Sleep onset latency: 24.71 vs 52.10 vs 51.14 (p<0.001 for placebo vs low dose and placebo vs moderate dose) Night awakenings: 0.16 vs 0.25 vs 0.23 (NS) Bedtime resistance: 29.42 vs 32.44 vs 30.13 (NS) Lights out: 21:13:05 vs 21:15:14 vs 21:15:02)NS) Sleep onset: 21:37:59 vs 22:02:45 vs 22:00:08 (p<0.002 for placebo vs low dose and placebo vs moderate dose) Sleep offset: 7:20:35 vs 7:15:57 vs 7:07:36 (NS) Sleep Disturbance Scale for Children at 3 weeks DIM: 57.71 vs 59.76 vs 62.05 SDB: 52.76 vs 53.71 vs 52.14 DA: 52.81 vs 51.00 vs 51.67 SWTD: 54.71 vs 57.14 vs 55.86 DOES: 53.86 vs 51.38 vs 52.24 SHY: 50.43 vs 50.43 vs 49.86 Total: 54.89 vs 55.40 vs 58.02 CTRS at 3 weeks ADHD Index: 67.40 vs 59.95 vs 59.65 (p<0.003 for placebo vs low dose and placebo vs moderate dose) Inattention: 57.00 vs 54.95 vs 52.85 (p<0.007 for placebo vs low dose and placebo vs moderate dose) Hyperactivity/impulsivity: 63.85 vs 57.45 vs 59.35 (p<0.01 for placebo vs low dose and placebo vs moderate dose) Oppositional: 59.25 vs 55.30 vs 55.15 (p<0.02 for placebo vs low dose and placebo vs moderate dose) CPRS at 3 weeks ADHD Index: 69.38 vs 63.05 vs 62.14 (p<0.005 for placebo vs low dose and placebo vs moderate dose) Inattention: 68.19 vs 62.86 vs 61.05 (p<0.007 for placebo vs low dose and placebo vs moderate dose) Hyperactivity/impulsivity: 64.00 vs 58.95 vs 59.67 (NS) Oppositional: 62.38 vs 55.57 vs 55.24 (NS)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Corkum 2008 Canada	NR	NR	NR	Sleep is focus of study

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Findling 2007 United States	RCT, DB Crossover	Youths ages 5-17 years, meeting DSM-IV criteria for a diagnosis of a bipolar spectrum disorder and a comorbid diagnosis of ADHD and the use of a psychostimulant was clinically indicated for the treatment of dysfunctional residual symptoms of ADHD. Patients were required to be treated with fixed doses of mood stabilizers at the time of study enrollment for at least 5 days before receiving study medication.	ADHD combined type: 94% ADHD inattentive type: 6% ADHD hyperactivity/impulsivity type: 0%

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Findling 2007 United States	MPH twice a day (morning and midday): either 5mg, 10mg, or 15mg Placebo	Patients required to be on fixed dose of mood stabilizer at least 5 days before receiving study medication	Mood stabilizers required Lithium and Divalproex sodium allowed	Primary Outcome Measure: ADHD Rating Scale-IV (ARS-IV) Other Measures: Conners Parent Rating Scale (CPRS), Children's Depression Rating Scale-Revised (CDRS-R), Young Mania Rating Scale (YMRS), Clinical Global Impressions-Severity Scale (CGI-S)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Findling 2007 United States	Mean age: 10.43 years 75% male 75% Caucasian 19% Hispanic 6% African American	Bipolar I disorder: 88% Bipolar II disorder: 6% Bipolar disorder not otherwise specified: 6%	NR/NR/20	4/0/16

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Findling 2007 United States	**Placebo vs 5 mg vs 10 mg vs 15 mg vs Best Dose Week** ARS-IV Inattentive: 17.81 vs 15.94 vs 13.87 vs 10.88 vs 11.25 (p<0.05 for 10mg and 15mg vs baseline and for best dose week vs placebo) ARS-IV Impulsivity/Hyperactivity: 14.38 vs 14.25 vs 12.47 vs 8.94 vs 9.56 (p<0.05 for 10mg and 15mg vs baseline and for best dose week vs placebo) ARS-IV local scores: 32.19 vs 30.19 vs 26.33 vs 19.81 vs 20.81 (p<0.05 for 10mg and 15mg vs baseline and for best dose week vs placebo) CPRS-48 Conduct Problem subscale T score: 73.9 vs 71.9 vs 60.2 vs 56.0 vs 62.8 (p<0.05 for 10mg and 15mg vs baseline and for best dose week vs placebo) CPRS-48 Learning Problem subscale T score: 77.0 vs 75.0 vs 64.2 vs 60.0 vs 65.3 (p<0.05 for 10mg and 15mg vs baseline and 15mg vs placebo) CPRS-48 Impulsive-Hyperactive subscale T score: 64.0 vs 64.5 vs 53.1 vs 54.0 vs 54.2 (p<0.05 for 10mg and 15mg vs baseline and for best dose week vs placebo) CPRS-48 Hyperactivity Index subscale T score: 73.1 vs 69.8 vs 57.3 vs 55.8 vs 59.2 (p<0.05 for 10mg vs baseline and for 15mg and best dose week vs placebo) CGI-Severity: 3.50 vs 3.07 vs 2.69 vs 2.19 vs 2.50 (p<0.05 for 5mg and 10mg vs baseline and for 15mg and best dose week vs placebo) YMRS: 3.03 vs 3.56 vs 2.44 vs 1.25 vs 0.94 (NS) CDRS-R: 18.19 vs 18.31 vs 17.75 vs 17.75 vs 17.69 (NS)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Findling 2007 United States	Side Effects Behavior Monitoring Scale (completed by patients and parents) Labs	**Placebo vs 5 mg vs 10 mg vs 15 mg vs Best Dose Week** Insomnia or trouble sleeping: 2 vs 1 vs 2 vs 5 vs 0 Stares or daydreams: 2 vs 1 vs 1 vs 2 vs 1 Talks less with others: 2 vs 0 vs 0 vs 0 Uninterested in others: 1 vs 2 vs 0 vs 0 vs 0 Decreased appetite: 1 vs 4 vs 4 vs 5 vs 4 Irritable: 6 vs 5 vs 3 vs 3 vs 0 Stomachaches: 1 vs 2 vs 4 vs 3 vs 1 Headaches: 0 vs 0 vs 1 vs 0 vs 0 Drowsiness: 4 vs 3 vs 0 vs 0 vs 1 Sad/unhappy: 1 vs 2 vs 1 vs 1 vs 0 Prone to crying: 0 1 vs 1 vs 0 vs 1 Anxious/worried: 3 vs 2 vs 1 vs 3 vs 1 Perseveration verbal/behavior: 2 vs 0 vs 0 vs 0 vs 0 Bites fingernails: 2 vs 3 vs 4 vs 3 vs 4 Euphoric/unusually happy: 1 vs 1 vs 0 1 vs 0 Dizziness: 0 vs 0 vs 0 vs 1 vs 0 Tics or nervous movements: 0 vs 0 vs 2 vs 2 vs 2 Over focused: 0 vs 3 vs 2 vs 2 vs 1 Rebound effects: 1 vs 3 vs 5 vs 4 vs 3	4 withdrawals 2 due to AEs	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Gadow 2008 United States	RCT, DB parallel	Potential subjects had to meet DSM-III-R (American Psychiatric Association, 1987) or DSM-IV (American Psychiatric Association, 1994) diagnostic criteria for ADHD and either chronic motor tic disorder or Tourette's syndrome. Children who exhibited one or more of the following were excluded from consideration for the study if they were too severely ill (dangerous to self or others), psychotic, or mentally retarded (IQ < 70), or had a seizure disorder, major organic brain dysfunction, major medical illness, medical or other contraindication to medication (other than tics), or pervasive developmental disorder. Children were also excluded if their tics were so severe at intake that either the parent or child requested immediate intervention, which was rarely the case, or were extremely mild because in both cases symptoms would likely change in only one direction. This rule did not appear to markedly bias our sample because our patients_ mean YGTSS symptom ratings were certainly comparable with those of other studies. Children were not excluded if previous treatment with stimulants had purportedly induced or exacerbated their tics.	NR

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Gadow 2008 United States	MPH and placebo given in identical pills 3 dosage regimes of MPH by weight: 0.1mg/kg (mean 4.5mg) 0.3mg/kg (mean 9.3mg) 0.5mg/kg (mean 14.3mg) Maximum dose: 20mg	NR/washout of prior stimulants 1 week, prior neuroleptic or SSRIs 3 weeks, and clonidine 2 weeks	NR	Primary Outcome Measure: Yale Global Tic Severity Scale (YGTSS) Other measures: Shapiro Tourette Syndrome Severity Scale, Tourette's Syndrome-Clinical Global Impressions (TS-CGI), Global Tic Rating Scale, the 2-minute Tic and Habit Count, AP/TRS, IOWA Conners Teacher's Rating Scale, MOMS

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Gadow 2008 United States	Mean age: 8.95 years 80% male 87% European 6% Hispanic 6% African 1% Asian	Mean age at tic onset: 5.6 years Receiving special education full time: 27% Receiving special education part time: 31% Not receiving special education: 42%	NR/NR/71	NR

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Gadow 2008 United States	Placebo vs 01.mg/kg MPH vs 0.3mg/kg MPH vs 0.5mg/kg MPH Teacher Ratings ATRS: 11.6 vs 8.0 vs 7.3 vs 5.7 (p=0.0001 for all doses compared to placebo) Factor 1: 9.3 vs 6.5 vs 5.9 vs 4.6 (p=0.0001 for all doses compared to placebo) Factor 2: 2.2 vs 1.5 vs 1.6 vs 1.1 (p=0.0001 for all doses compared to placebo) IOWA Conners I-O Scale: 7.4 vs 5.2 vs 4.7 vs 3.8 (p=0.0001 for all doses compared to placebo) O/D Scale: 3.4 vs 1.9 vs 1.7 vs 1.1 (p=0.0001 for all doses compared to placebo) Peer Conflict Scale: 3.7 vs 2.0 vs 1.6 vs 1.1 (p=0.0001 for all doses compared to placebo) Parent ratings APRS: 11.0 vs 8.2 vs 10.0 vs 7.8 (p=0.0249 for all doses compared to placebo) Factor 1: 7.3 vs 5.4 vs 5.1 vs 4.3 (p=0.0001 for all doses compared to placebo) Factor 2: 3.4 vs 2.7 vs 2.9 vs 2.5 (p=0.0721 for all doses compared to placebo) MOMS Hyperactivity scale: 2.9 vs 2.3 vs 2.3 vs 1.7 (p=0.0001 for all doses compared to placebo) Aggression scale: 2.1 vs 1.4 vs 1.6 vs 1.3 (p=0.0003 for all doses compared to placebo) Peer Conflict Scale: 4.6 vs 3.2 vs 3.2 vs 2.5 (p=0.0001 for all doses compared to placebo) CPT Inattention: 7.3 vs 6.0 vs 5.1 vs 5.1 (p=0.0010 for all doses compared to placebo) Impulsivity: 3.1 vs 3.2 vs 1.8 vs 2.4 (p=0.0001 for all doses compared to placebo) Dyscontrol: 6.5 vs 7.3 vs 2.7 vs 3.6 (p=0.0001 for all doses compared to placebo) Clinic Classroom On-task: 79.8 vs 85.8 vs 90.5 vs 89.8 (p=0.0001 for all doses compared to placebo) Fidgets: 22.8 vs 20.8 vs 18.4 vs 16.9 (p=0.0064 for all doses compared to placebo) Worksheet items: 242 vs 281 vs 281 vs 285 (p=0.0001 for all doses compared to placebo) Physician ratings YGTSS - total motor: 12.7 vs 12.8 vs 12.7 vs 12.8 vs (NS) YGTSS - total phonic: 8.5 vs 7.7 vs 8.1 vs 8.7 (NS) YGTSS - Impairment: 10.7 vs 9.7 vs 11.5 vs 10.4 (NS) YGTSS - Global Severity: 31.8 vs 30.3 vs 32.2 vs 30.5 (NS) Shapiro TSSS: 2.0 vs 1.9 vs 1.9 vs 1.9 (NS) GTRS - Motor: 5.0 vs 5.1 vs 5.0 vs 5.1 (NS) GTRS - Vocal: 1.3 vs 1.2 vs 1.3 vs 1.3 (NS) GTRS - Total: 3.1 vs 1.1 vs 2.8 vs 2.4 (NS)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Gadow 2008 United States	Stimulant Site Effects Checklist (SSEC) by parents and teachers	Placebo vs 0.1mg/kg MPH vs 0.3mg/kg MPH vs 0.5mg/kg MPH Teacher SSEC Mood index: 3.5 vs 2.7 vs 2.6 vs 2.6 (p=0.0047) Attention/arousal index: 1.8 vs 1.5 vs 1.5 vs 1.2 (p=0.0021) Somatic index: 0.4 vs 0.3 vs 0.4 vs 0.5 (NS) Motor movements: 1.1 vs 0.7 vs 0.8 vs 0.7 (p=0.0110) Parent SSEC Mood index: 2.1 vs 1.8 vs 1.9 vs 1.9 (NS) Attention/arousal index: 0.6 vs 0.8 vs 0.8 vs 0.9 (NS) Somatic index: 1.1 vs 1.5 vs 1.8 vs 2.0 (p=0.0001) Motor movements: 1.2 vs 1.0 vs 1.0 vs 0.8 (p=0.0572) Cardiovascular Systolic: 99.0 vs 100.6 vs 102.3 vs 104.3 (p=0.0999) Diastolic: 60.0 vs 61.4 vs 61.0 vs 64.5 (p=0.0386) Heart rate: 86.0 vs 88.8 vs 91.7 vs 91.6 (p=0.0326) Weight: 79.3 vs 78.3 vs 78.1 vs 77.8 (p=0.0040)	NR	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Silva 2008 United States	RCT, DB Crossover	Males and females ages 6 to 12 years and diagnosed with ADHD. Al of the subjects had to be clinically and behaviorally stable in the opinion of the referring physician and the site's principal investigator. They also had to have been taking their current dose of medication without adjustment for at least 2 weeks. This was required to be a total daily dose or nearest equivalent of MPH 40 mg or immediate-release D-MPH 20 mg (Concerta 36 mg was allowable) before screening.	ADHD combined type: 82.4% ADHD inattentive type: 17.6% ADHD hyperactive-impulsive type: 0%
Sinzig 2007 Germany	RCT, DB parallel	Children and adolescents aged 6–16 years who met diagnostic criteria for ADHD according to the DSM-IV. Teacher ratings on an ADHD-symptom checklist had to be above the 90th percentile.	DSM-IV Diagnosis of ODD/CD: 58.1% (MPH) vs 71.4% (Placebo)
Szobot 2008 Brazil	RCT, Single-blind Crossover	Inclusion criteria were age between 15 and 21 years, male gender, current diagnosis of abuse of or dependence on marijuana or cocaine, current diagnosis of ADHD, and stimulant-naive subjects.	Group A Conduct disorder: 100% ODD: 25% Depression: 12.5% Group B Conduct disorder: 75% ODD: 37.5% Depression: 25% ADHD-combined type: 75% ADHD-inattentive type: 18.75% ADHD-hyperactive/impulsive type: 6.25%

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Silva 2008 United States	Dexmethylphenidate ER 20mg/day Placebo	No/No	NR	Primary Outcome Measure: Change from pre-dose on the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) rating scale (timepoints being 1, 3, 4, 5, 7, 9, 10, 11 and 12 hours post-dose) Other measures: the Permanent Product Measure of Performance
Sinzig 2007 Germany	MPH-MR Initial dose: 20mg Depending on weight and symptoms, medication was titrated up to 40mg or 60mg Weight guidance was as follows: 20-30kg, max 20mg MPH-MR; 31-50kg, max 40mg MPH-MR; >50kg, max 60mg MPH-MR Placebo	NR/NR	NR	Primary Outcome Measure: ADHD Symptom Checklist Other measures: ODD/CD-symptom-checklist
Szobot 2008 Brazil	Long acting methylphenidate (MPH-SODAS) Placebo Group A: MPH-SODAS followed by placebo Group B: Placebo followed by MPH-SODAS	NR/NR	NR	Primary Outcome Measure: Swanson, Nolan, and Pelham Scale, version IV (SNAP-IV) and the Clinical Global Impression (CGI) scale Other measures: # of days with drug use

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Silva 2008 United States	Mean age: 9.5 years 66.2% male 50% white 22.1% black 0% Asian 19.1% Hispanic 8.8% other	Mean height: 138.2cm Mean weight: 34.4kg Duration of ADHD symptoms: 4.5 years Received medication for ADHD in the past: 100%	NR/NR/68	1 withdrew, no lost to follow-up 68 analyzed for safety 67 analyzed for efficacy
Sinzig 2007 Germany	MPH group: n=43 mean age: 9.8 years 86.1% male Placebo group: n=42 mean age: 9.8 ears 90.5% male Ethnicity: NR	Duration of ADHD: 5.5 years (MPH) vs 5.2 years (Placebo)	102/85/85	NR
Szobot 2008 Brazil	Group A Mean age: 17.50 years 100% male 37.5% European-Brazilian Group B Mean age: 17.38 years 100% male 87.5% European-Brazilian	Group A SUD: Marijuana: 100% SUD: Cocaine: 50% SUD: days of cannabis use, last month: 30 SUD: # of cannabis cigarettes per day: 3 Group B SUD: Marijuana: 87.5% SUD: Cocaine: 37.5% SUD: days of cannabis use, last month: 38.57 SUD: # of cannabis cigarettes per day: 2.71	32/29/16	2 withdrew from Group A/none were lost to follow-up/16

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Silva 2008 United States	**Mean change in Scores** SKAMP-Combined - 0.5 hours post-dose: -2.242 (d-MPH-ER) vs 3.493 (Placebo); p=0.001 (8.6% improvement for d-MPH-ER and 66.7% worsening with placebo) - 1, 3, 4, 5, 7, 9, 10, 11, and 12 hours post-dose: d-MPH-ER significantly greater improvement compared to placebo (p≤0.001) SKAMP-Attention - 0.5, 1, 3, 4, 5, 7, 9, 10, 11, and 12 hours post-dose: d-MPH-ER significantly greater improvement compared to placebo (p≤0.001) SKAMP-Deportment - 0.5, 1, 3, 4, 5, 7, 9, 10, 11, and 12 hours post-dose: d-MPH-ER significantly greater improvement compared to placebo (p=0.003 for 0.5 hours, p=0.013 for 12 hours and p≤0.001 for all other time points) Math Test - Attempted: significantly more improvement with d-MPH-ER compared to placebo (p<0.001) Math Test - Correct significantly more improvement with d-MPH-ER compared to placebo (p<0.001)
Sinzig 2007 Germany	**MPH-MR vs Placebo** ODD/CD Symptom Checklist mean scores at week 4 Teacher - total: 0.31 vs 0.82 (effect size=1.0) Parent - total: 0.80 vs 1.04 Teacher - Part A: 0.41 vs 1.13 (effect size=1.0) Parent - Part A: 1.05 vs 1.34 Teacher - Part B: 0.15 vs 0.36 Parent - Part B: 0.43 vs 0.54 Responders after 4 weeks of treatment: Teacher - total: 23.3% vs 31.0% Parent - total: 51.2% vs 40.5% Teacher - Part A: 23.3% vs 31.0% Parent - Part A: 51.2% vs 40.5% Teacher - Part B: 23.3% vs 47.6% Parent - Part B: 58.1% vs 52.4%
Szobot 2008 Brazil	MPH-SODAS was significantly more effective at reducing ADH symptoms and on subjective functioning compared to placebo, according to both the SNAP-IV and CGI scores (p≤0.001 for all analyses) No significant sequence or period effect. Baseline SNAP-IV and CGI severity scores were significantly associated with response to treatment (p≤0.001 for all analyses) No significant differences between treatment, period or order effect in terms of number of days with drug use. However, subjects presented a slight decrease in the number of days with drug use while doses of medication were increased: 5.94 days at 0.3mg/kg/day; 5.87 days at 0.7mg/kg/day; 5.56 days at 1.2mg/kg/day

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Silva 2008 United States	Spontaneous report of AEs and laboratory tests	**d-MPH-ER vs Placebo** Total: 11 (16.2%) vs 11 (16.2%) Upper respiratory tract infection NOS: 3 (4.4%) vs 5 (7.4%) Abrasion NOS: 1 (1.5%) vs 0 Asthma aggravated: 1 (1.5%) vs 0 Folliculitis: 1 (1.5%) vs 0 Gastroenteritis NOS: 1 (1.5%) vs 3 (4.4%) Headache: 1 (1.5%) vs 1 (1.5%) Lymphadenitis NOS: 1 (1.5%) vs 0 Pharyngitis: 1 (1.5%) vs 0 Proteinuria: 1 (1.5%) vs 0 Rhinitis allergic NOS: 1 (1.5%) vs 2 (2.9%) Scabies infestation: 1 (1.5%) vs 0 Toothache: 1 (1.5%) vs 0 Rhinorrhea: 0 vs 1 (1.5%)	1 withdrew due to AE	
Sinzig 2007 Germany	NR	NR	NR	
Szobot 2008 Brazil	Barkley Side Effect Rating Scale (SERS)	Treatment with MPH-SODAS significantly reduced appetite ($p \leq 0.001$), no treatment effect was found for insomnia or headache No additional information provided	2 withdrew, 0 for AEs	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Wilens 2008 United States	RCT, DB Crossover	Subjects, 6 to 12 years of age, diagnosed with ADHD according to DSM-IV-TR criteria were eligible for the study. Subjects were required to be able to complete the Permanent Product Measure of Performance (PERMP) math test assessment and to have a minimum IQ score of 80. Subjects could not have conduct disorder or comorbid illnesses that contraindicated or could confound MTS treatment.	NR

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Wilens 2008 United States	MPH Transdermal System (MTS) worn for 9 hours (7am-4pm) Initial dose of 10mg, titration up to 15mg, 20mg and 30mg patches Placebo	No study medication for 30 days prior to screening/7-day washout period	Investigator monitored concomitant therapies	Primary Outcome Measure: Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) Teacher Rating scale (every 2 hours after patch application in week 6, 7 and 8) Other outcomes: SKAMP at 4 and 6 hours after application, the Permanent Product Measure of Performance (PERMP), ADHD Scale-IV (ADHD-RS-IV), Clinical Global Impressions-Improvement (CGI-I), Parent Global Assessment (PGA)< Conners Parent Rating Scale-Revised (CPRS-R), Clinical Global Impressions-Severity (CGI-S)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Wilens 2008 United States	Mean age: 8.8 years 64.1% male 63.2% white 15.4% black 0% Pacific Islander 0% Asian 0% American Indian 21.4% other	Mean CGI-S score at baseline: 4.8 < moderately ill: 0.9% > moderately ill: 99.1%	148/NR/128	11 withdrew/none lost to follow up/ 117 analyzed

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Wilens 2008 United States	SKAMP-Deportment scores averaged over the 4 and 6 hours that the patches were worn during the Analog Classroom sessions were significantly lower for MTS than for placebo (p<0.0001) - Least square mean deportment scores were 11.5, placebo; 5.7, 4-hours after application; 5.9, 6-hours after application SKAMP-Attention scores averaged over the 4 and 6 hours that the patches were worn during the Analog Classroom sessions were significantly lower for MTS than for placebo (p<0.0001) - Least square mean attention scores were 6.3, placebo; 4.0, 4-hours after application; 4.2, 6-hours after application SKAMP-Total scores averaged over the 4 and 6 hours that the patches were worn during the Analog Classroom sessions were significantly lower for MTS than for placebo (p<0.0001) - Least square mean deportment scores were 24.5, placebo; 14.7, 4-hours after application; 15.4, 6-hours after application

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Wilens 2008 United States	Spontaneous report of AEs and laboratory tests	326 treatment-emergent AEs were reported 62% were mild intensity and 37% were moderate intensity, only 4 patients (1%) had severe intensity **Most Frequent AEs** Decreased appetite: 28% Headache: 21% Insomnia: 20% Abdominal pain: 12% No serious AEs were reported	11 withdrew, NR how many due to AEs	

Evidence Table 6. Quality of placebo-controlled trials in children

Internal Validity

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Atomoxetine							
Kelsey 2004	NR	NR	Yes	Yes	Yes	Yes	Yes
Spencer 2002	NR	NR	No	Yes	Yes	Yes	Yes
Michelson 2001 Biederman 2002	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Michelson 2002 Newcorn 2005	NR	NR	Yes	Yes	Yes	Yes	Yes
Michelson 2004 Hazell 2006	NR	NR	Yes	Yes	Yes	Yes	Yes

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential /high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating	*External Validity* Number screened/eligible/enrolled
Atomoxetine						
Kelsey 2004	Yes, NR, NR, NR	No	No	No	Fair	260/197/197
Spencer 2002	Yes, NR, NR, NR	NR	No	No	Fair	409/291/291
Michelson 2001 Biederman 2002	Yes, NR, NR, NR	No	Yes	No	Good	381/297/297
Michelson 2002 Newcorn 2005	Yes, NR, NR, NR	No	No	No	Fair	NR/NR171
Michelson 2004 Hazell 2006	Yes, NR, NR, NR	No	Yes	No	Fair	NR/NR/604

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Exclusion criteria	Run-in/Washout	Class naïve patients only	Control group standard of care
Atomoxetine				
Kelsey 2004	Serious medical illness, a history of psychosis or bipolar disorder, alcohol or drug abuse within the past 3 months, and ongoing use of psychoactive medications other than the study drug	5-day washout	No	Yes
Spencer 2002	Poor metabolizers of CYP2D6; weight < 25 kg; documented history of bipolar I or II disorder or any history of psychosis; organic brain disease or a history of any seizure disorder, were taking any psychotropic medication; had any history of alcohol or drug abuse within the past 3 months; significant prior or current medical conditions	2-week washout	No	Yes
Michelson 2001 Biederman 2002	IQ<80 as assessed by the WISC-III; serious medical illness, comorbid psychosis or bipolar disorder, history of a seizure disorder, or ongoing use of psychoactive medications other than the study drug	12-18 day washout	No	Yes
Michelson 2002 Newcorn 2005	Serious medical illness, a history of psychosis or bipolar disorder, alcohol or drug abuse within the past 3 months, and ongoing use of psychoactive medications other than the study drug	5-day washout	No	Yes
Michelson 2004 Hazell 2006	Bipolar disorder; psychotic illness; unstable medical illness or patients with a condition that would require ongoing administration of a psychoactive medication	Washout of at least 5 times the plasma half-life	No	Yes

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Funding
Atomoxetine	
Kelsey 2004	Lilly
Spencer 2002	Lilly
Michelson 2001 Biederman 2002	Lilly
Michelson 2002 Newcorn 2005	Lilly
Michelson 2004 Hazell 2006	Lilly

Evidence Table 6. Quality of placebo-controlled trials in children

Internal Validity

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Bupropion							
Casat 1987	NR	NR	Yes	Yes	NR	Yes	Yes
Connors 1996	NR	NR	Yes	Yes	Yes	Yes	Yes
Daviss 2001 United States Poor Quality	NR	NR	NR	Yes	Yes	Yes	Yes
Clonidine							
Hunt 1985	NR	NR	NR	Yes	Yes	Yes	Yes
Gross-Tsur 1997	Non-random assignment. Methods for assignment NR	NA	n/a-crossover	Yes	NR	Yes	Yes

Evidence Table 6. Quality of placebo-controlled trials in children

						External Validity
Author, Year Country	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential /high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**
Bupropion						
Casat 1987	NR, NR, NR, NR	No	Unclear	No	Poor	NR/NR/31
Connors 1996	NR, NR, NR, NR	Unclear	Unclear	No	Fair	NR/NR/109
Daviss 2001 United States Poor Quality	Yes, NR, Yes, NR	No	Unclear	No	Poor	NR/29/25
Clonidine						
Hunt 1985	Yes, NR, NR, NR	NR	No	No	Poor	NR/NR/12
Gross-Tsur 1997	NR, NR, NR, NR	Unclear	Yes	No	Poor	NR/NR/30

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Exclusion criteria	Run-in/Washout	Class naïve patients only	Control group standard of care
Bupropion				
Casat 1987	IQ < 70 on WISC-R; history of seizure disorder, tic disorder, any unstable medical conditions, and known hypersensitivity to psychotropic medications	14-day washout	No	Yes
Connors 1996	WISC-R IQ < 70; body weight < 20 kg; girls who had passed menarche; known hypersensitivity to psychotropic medications; history or presence of seizure or tic disorders	14-day washout	No	Yes
Daviss 2001 United States Poor Quality	Pervasive developmental disorders, mental retardation, bipolar disorders, psychosis, bulimia or anorexia nervosa, current alcohol or drug abuse/dependence, Tourette's disorder, and history of a seizure disorder; serious medical problems, weight M 25 kg; known hypersensitivity to bupropion; females sexually active without contraception	2-week single blind placebo lead-in	No	Yes
Clonidine				
Hunt 1985	NR	NR/NR	No	Yes
Gross-Tsur 1997	NR	NR/NR	NR	Yes

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Funding
Bupropion	
Casat 1987	Burroughs-Wellcome Company
Connors 1996	NIMH grant; 2 authors are Glaxo-Wellcome scientists
Daviss 2001 United States	Glaxo-Wellcome
Poor Quality	
Clonidine	
Hunt 1985	NR
Gross-Tsur 1997	NR

Evidence Table 6. Quality of placebo-controlled trials in children

Internal Validity

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Greenhill 2002	NR	NR	Yes	Yes	Yes	Yes	Yes
Scahill 2001	NR	NR	Yes	Yes	Yes	Yes	Yes
Singer 1995	NR	Yes	NR	No	Yes	Yes	Yes

Evidence Table 6. Quality of placebo-controlled trials in children

						External Validity
Author, Year Country	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential /high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**
Greenhill 2002	Yes, NR, NR, NR	No	No	No	Fair	507/321/321
Scahill 2001	Yes, NR, NR, NR	None	Yes	No	Fair	50/40/34
Singer 1995	Yes, NR, NR, NR	No	Unclear	No	Fair	58/37/37

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Exclusion criteria	Run-in/Washout	Class naïve patients only	Control group standard of care
Greenhill 2002	Exclusion criteria: comorbid psychiatric diagnosis; history of seizure, tic disorder, or family history of Tourette's syndrome; female having undergone menarche; use of amphetamines, pemoline, or an investigational drug within 30 days of study entry; concomitant use of clonidine, anticonvulsant drugs, or medications known to affect blood pressure, heart rate, or central nervous system function; hyperthyroidism or glaucoma; any concurrent chronic or acute illness (e.g., allergic rhinitis, severe cold) or disability that could confound the study results. Also excluded were children who had failed a previous trial of stimulants for ADHD, had required a third daily dose in the afternoon or evening, had a documented allergy or intolerance to MPH, or were living with anyone who currently had substance abuse disorder (excluding dependency).	1-week SB placebo washout - excluded any that responded to placebo during these phase	No	Yes
Scahill 2001	Evidence of current major depression, generalized anxiety disorder, separation anxiety disorder, or psychotic symptoms; WISC-R IQ < 70; prior adequate trial of guanfacine (dose of >/= 1.5 mg/day for at least 2 weeks)	Placebo washout of 7-14 days	100% guanfacine naïve	Yes
Singer 1995	NR	1-week washout between periods	No	Yes

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Funding
Greenhill 2002	Celltech Pharmaceuticals, Inc.
Scahill 2001	M01-RR-06022 from the Children's Clinical Research Center, mental Health Research Center grant MH-30929 and a grant from the Tourette Syndrome Association
Singer 1995	Tourette Syndrome Association and US

Evidence Table 6. Quality of placebo-controlled trials in children

Internal Validity

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Rugino 2003	NR	NR	Yes	Yes	Yes	Yes	Yes
Tourette's Disorder							
Sverd 1992	NR	NR	NR	Yes	Yes	Yes	Yes
Mental Retardation							
Agarwal 2001	NR	NR	NR	Yes	Yes	Yes	Yes

Evidence Table 6. Quality of placebo-controlled trials in children

						External Validity
Author, Year Country	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential /high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**
Rugino 2003	Yes, NR, NR, NR	None	No, 2 patients excluded	No	Fair	NR/NR/24
Tourette's Disorder						
Sverd 1992	NR, NR, NR, NR	Unclear	Unclear	No	Fair	NR/NR/11
Mental Retardation						
Agarwal 2001	Yes, NR, NR, NR	No	Yes	No	Fair	NR/NR/10

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Exclusion criteria	Run-in/Washout	Class naïve patients only	Control group standard of care
Rugino 2003	(1) acute medical or uncontrolled psychiatric illness; (2) allergy to modafinil or any of the components of the tablet; (3) mitral valve prolapse, left ventricular hypertrophy, cardiac ischemia, clinically significant cardiac arrhythmia, or history of syncope; (4) use of the following medications within 30 days before the study: psychoactive medications other than stimulants prescribed to manage ADHD, antiepileptics, or medications metabolized primarily through the hepatic cytochrome P450 system; (5) more than 3 migraine headaches within 3 months before the study; (6) female with potential of becoming pregnant during the study; (7) uncontrolled seizure disorder; (8) sleep disorder with insomnia; and (9) history of manic episodes or psychosis	NR/NR	NR	Yes
Tourette's Disorder				
Sverd 1992	Children who were believed to be too severely ill, psychotic, or mentally retarded (IQ < 75), or who had a seizure disorder, major organic brain dysfunction, major medical illness, medical or other contraindication to medication (other than tics), or pervasive developmental disorder	NR/NR	No	Yes
Mental Retardation				
Agarwal 2001	NR	NR/NR	No	Yes

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Funding
Rugino 2003	NR
Tourette's Disorder	
Sverd 1992	NR
Mental Retardation	
Agarwal 2001	NR

Evidence Table 6. Quality of placebo-controlled trials in children

Internal Validity

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Gadow 1992	NR	NR	NR	Yes	Yes	Yes	Yes
Gadow 1995	NR	NR	NR	Yes	Yes	Yes	Yes
Handen 1990	NR	NR	NR	Yes	Yes	Yes	Yes
Handen 1991	NR	NR	NR	Yes	Yes	Yes	Yes

Evidence Table 6. Quality of placebo-controlled trials in children

						External Validity
Author, Year Country	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential /high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**
Gadow 1992	NR, NR, NR, NR	Unclear	Unclear	No	Fair	NR/NR/11
Gadow 1995	NR, NR, NR, NR	Unclear	Unclear	No	Fair	NR/NR/34
Handen 1990	NR, NR, NR, NR	Unclear	Unclear	No	Fair	NR/NR/12
Handen 1991	NR, NR, NR, NR	Unclear	Unclear	No	Fair	NR/NR/27

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Exclusion criteria	Run-in/Washout	Class naïve patients only	Control group standard of care
Gadow 1992	Children who were believed to be too severely ill; tics were the major clinical management concern; psychotic or mentally retarded (IQ < 75); seizure disorder; major organic brain dysfunction; major medical illness, medical or other contraindication to medication, or pervasive developmental disorder	NR/NR	Unclear	Yes
Gadow 1995	Children who were believed to be too severely ill; tics were the major clinical management concern; psychotic or mentally retarded (IQ < 75); seizure disorder; major organic brain dysfunction; major medical illness, medical or other contraindication to medication, or pervasive developmental disorder	NR/NR	Unclear	Yes
Handen 1990	NR	NR/NR	Unclear	Yes
Handen 1991	Severe motor deficits; use of other medication (anticonvulsants, antipsychotics); diagnosis of major depression or psychosis	NR/NR	No	Yes

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Funding
Gadow 1992	Tourette Syndrome Association and NIMH grants; CIBA supplied MPH and placebo
Gadow 1995	Tourette Syndrome Association and NIMH grants; CIBA supplied MPH and placebo
Handen 1990	Edith L. Trees Foundation and Research Advisory Committee of Children's Hospital of Pittsburgh
Handen 1991	National Institute of Child Health and Human Development; US DHHS; Edith L. Trees Foundation; Research Advisory Committee of Children's Hospital of Pittsburgh

Evidence Table 6. Quality of placebo-controlled trials in children

Internal Validity

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Handen 1992	NR	NR	NR	Yes	Yes	Yes	Yes
Handen 1994	NR	NR	NR	Yes	Yes	Yes	Yes
Handen 1995	NR	NR	NR	Yes	Yes	Yes	Yes
Handen 1996	NR	Inadequate - hospital pharmacist	NR	Yes	Yes	Yes	Yes
Handen 1997	NR	NR	NR	Yes	Yes	Yes	Yes

Evidence Table 6. Quality of placebo-controlled trials in children

						External Validity
Author, Year Country	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential /high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**
Handen 1992	NR, NR, NR, NR	Unclear	Unclear	No	Fair	NR/NR/14
Handen 1994	NR, NR, NR, NR	Unclear	Unclear	No	Fair	NR/NR/47
Handen 1995	NR, NR, NR, NR	Unclear	Yes	No	Fair	NR/NR/22
Handen 1996	NR, NR, NR, NR	Unclear	Yes	No	Fair	NR/NR/44
Handen 1997	Yes, NR, NR, NR	No	Unclear	No	Fair	NR/NR/52

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Exclusion criteria	Run-in/Washout	Class naïve patients only	Control group standard of care
Handen 1992	NR	NR/NR	No	Yes
Handen 1994	NR	NR/NR	No	Yes
Handen 1995	Diagnosis of autism or pervasive developmental disorder	NR/NR	No	Yes
Handen 1996	Autism or pervasive developmental disorder	NR/NR	No	Yes
Handen 1997	Autism or pervasive developmental disorder	NR/NR	No	Yes

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Funding
Handen 1992	National Institute of Child Health and Human Development; US DHHS; Edith L. Trees Foundation; Research Advisory Committee of Children's Hospital of Pittsburgh
Handen 1994	National Institute of Child Health and Human Development; US DHHS; Edith L. Trees Foundation; Research Advisory Committee of Children's Hospital of Pittsburgh
Handen 1995	National Institute of Child Health and Human Development; US DHHS; Edith L. Trees Foundation
Handen 1996	National Institute of Child Health and Human Development; US DHHS
Handen 1997	National Institute of Child Health and Human Development; US DHHS

Evidence Table 6. Quality of placebo-controlled trials in children

Internal Validity

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Handen 1999	NR	NR	NR	Yes	Yes	Yes	Yes
Handen 2000	NR	NR	NR	Yes	Yes	Yes	Yes
Varley 1982	NR	NR	NR	Yes	NR	Yes	Yes
Withdrawal of medication							
Allen 2005	Yes - computerized interactive voice response system	Yes	Yes, for most characteristics. Higher mean ADHDRS - IV - Parent: Inv total score and hyperactivity/impulsivity subscale score at baseline in atomoxetine group (described in text; p values not given)	Yes	Unclear, reported as double-blind	Yes	Yes
Anonymous 2005/Posey 2007`	Yes	Yes	No data stratified by tx group	Yes	Yes	Yes	Yes

Evidence Table 6. Quality of placebo-controlled trials in children

						External Validity
Author, Year Country	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential /high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**
Handen 1999	Yes, NR, NR, NR	No	No	No	Fair	NR/NR/11
Handen 2000	NR, NR, NR, NR	Unclear	Yes	No	Fair	NR/NR/13
Varley 1982	Yes, NR, NR, NR	No/No	Yes	No	Fair	15/10/10
Withdrawal of medicat						
Allen 2005	No No No No	No	Yes	No	Good	NR/166/148
Anonymous 2005/Posey 2007`	No N/A No No	No	No	No	Fair	117/72/66

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Exclusion criteria	Run-in/Washout	Class naïve patients only	Control group standard of care
Handen 1999	Autism or pervasive developmental disorder	NR/NR	No	Yes
Handen 2000	NR	NR/NR	Unclear	Yes
Varley 1982	Psychotic disorders, undersocialized aggressive conduct disorders	NR/NR	80% naïve	Yes
Withdrawal of medicat				
Allen 2005	C-YBOCS score>15 or diagnosis of OCD requiring pharmacotherapy; CDRS-R score >40 or diagnosis of depression requiring pharmacotherapy; history of bipolar disorder or psychosis; seizure disorder; use of psychotropic drug other than study drug	10 to 18-day screening period	NR	Yes
Anonymous 2005/Posey 2007`	Neuropsychiatric disorders requiring alternative medical management, significant medical condition (heart or liver disease), uncontrolled (<6 mos) seizure disorder, hypertension, use of methylphenidate within 2 yrs of trial, previous adverse response to methylphenidate	Washout psychotropic drugs 1-3 weeks dependant on medication; 1 week test dose run-in	No	N/A

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Funding
Handen 1999	Fanny Pushin Rosenberg Research Foundation
Handen 2000	Fanny Pushin Rosenberg Research Foundation
Varley 1982	NR
Withdrawal of medicat	
Allen 2005	Eli Lilly
Anonymous 2005/Posey 2007`	NIH, NIMH, Korczak Foundation

Evidence Table 6. Quality of placebo-controlled trials in children

Internal Validity

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Arnold 2004 Poor	NR	NR	No	Yes	Yes	Yes	Yes
Arnold 2006	Method NR	Method NR	Yes, at initial randomization (crossover study)	Yes	Unclear, reported as double-blind	Unclear, reported as double blind	Yes
Bangs 2007	Method NR	Method NR	No- Mean weight (kg) significantly greater in ATX group: 63.1 vs 58.4; p=0.04	yes	Unclear, reported as double-blind	Unclear, reported as double blind	Unclear, reported as double-blind

Evidence Table 6. Quality of placebo-controlled trials in children

						External Validity
Author, Year Country	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential /high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**
Arnold 2004 Poor	Yes, NR, NR, NR	No	No	No	Fair	116/89/89
Arnold 2006	No N/A No No	No	Yes	No	Good	NR/NR/16
Bangs 2007	Yes, NR, NR, NR	No/No: LTFU 4.2% vs 1.4%, NS	1 patient of 142 total excluded from analysis	no	Fair	NR/NR/142

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Exclusion criteria	Run-in/Washout	Class naïve patients only	Control group standard of care
Arnold 2004 Poor	Cardiovascular, renal, respiratory (other than asthma/allergy), endocrine, or immune system disease; history of substance abuse; hypersensitivity to d,l-MH or other stimulants; treatment with any investigational drug within 30 days of screening; other significant central nervous system disorders; and treatment with antidepressants, neuroleptics/antipsychotics, mood stabilizers, anticonvulsants, beta blockers, alpha-2 agonists, other stimulants, thyroid medications, chronic oral steroids, or sedatives/hypnotics	NR/NR	Unclear	Yes
Arnold 2006	Cardiovascular disease, glaucoma, unstable seizure disorder, other significant physical illness, psychosis, severe mood disorder, substance abuse, pregnancy	1 week unblinded washout between crossovers; 2 week washout catecholaminergic psychoactive drugs at beginning of study	NR	N/A
Bangs 2007	Beginning structured psychotherapy for ADHD and/or depression less than 1 month before trial entry	1 week placebo lead-in (blinding unclear); washout N/A	No	Yes

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Funding
Arnold 2004 Poor	Celgene
Arnold 2006	Eli Lilly; General Clinical Research Center Ohio State University
Bangs 2007	Eli Lilly & Company

Evidence Table 6. Quality of placebo-controlled trials in children

Internal Validity

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Bangs 2008	Randomization mentioned, but methods NR	NR	Yes	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Unclear, reported as double-blind
Biederman 2005	Yes	Method NR	Yes	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Yes

Evidence Table 6. Quality of placebo-controlled trials in children

						External Validity
Author, Year Country	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential /high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**
Bangs 2008	Yes, NR, NR, NR	No/No	Yes	8 (5.1%) from Atomoxetine group withdrawn after randomization for protocol violations	Fair	257/226/226
Biederman 2005	No No No No	No	No	Yes (2 in placebo group)	Fair	372/281/248

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Exclusion criteria	Run-in/Washout	Class naïve patients only	Control group standard of care
Bangs 2008	History of bipolar I or II disorder, psychosis, or pervasive developmental disorder were excluded, current diagnosis of major depressive disorder, posttraumatic stress disorder, a Children's Depression Rating Scale-Revised total raw score 40 at visit 1, or if they were determined to be at serious suicidal risk, history of any seizure disorder (other than febrile seizures), a history of alcohol or drug abuse within the past 3 months, current cardiovascular disease or other conditions that could be aggravated by an increased heart rate or increased blood pressure, a medical condition that would markedly increase sympathetic nervous system activity, or severe gastrointestinal narrowing, and those who, in the investigator's judgment, were likely to need psychotropic medications apart from the drug under study or who at any time during the study were likely to begin structured psychotherapy.	3- to 28-day washout period	No	Yes
Biederman 2005	History or current diagnosis of pervasive developmental disorder, schizophrenia, other psychotic disorders, suicide risk, current psychiatric comorbidity requiring pharmacotherapy, other active clinically significant disease, well controlled ADHD, previous failure to respond to 2 or more adequate courses of stimulant therapy, clinically significant drug sensitivity to stimulants, history of alcohol or substance abuse, consumption of >250 mg caffeine/day, ANC <1x10-9th/L, hypertension, hypotension, resting heart rate 60-115 bpm	MAOI and SSRI 2 wk washout; Prescription or nonprescription medications w/psychotropic properties 1 wk washout; at least 1 wk washout for all patients	No	Yes

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Funding
Bangs 2008	Many authors receive funding from Eli Lilly
Biederman 2005	Cephalon Inc

Evidence Table 6. Quality of placebo-controlled trials in children

Internal Validity

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Biederman 2006	Method NR	Method NR	No - due to prespecified randomization procedure, pts randomized to modafinil 400 mg had higher body weight and were older (in text; p values NR)	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Yes
Biederman 2007	Method NR	Method NR	N/A (crossover study)	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Unclear, reported as double-blind

Evidence Table 6. Quality of placebo-controlled trials in children

						External Validity
Author, Year Country	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential /high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**
Biederman 2006	No No No No	No	Yes	No	Good	343/NR/248
Biederman 2007	Yes, NR, NR, NR	No/No	4% excluded	No	Fair	NR/52/52

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Exclusion criteria	Run-in/Washout	Class naïve patients only	Control group standard of care
Biederman 2006	Active, clinically significant GI, CV, hepatic, renal, hematologic, neoplastic, endocrine, immunodeficiency, pulmonary or other major clinically significant disorder or disease, current psychiatric comorbidity including depression or other mood disorder, anxiety disorder, pervasive mental disorder requiring pharmacotherapy, use of any prescription medication with psychoactive properties w/in 1 wk of study entry, history or evidence of substance abuse	7-10 day placebo washout	Yes	Yes
Biederman 2007	Presence of comorbid illness that could interfere with study participation or impact the efficacy and tolerability of LDX or MAS XR; documented allergy or intolerance to MAS XR; drug abuse history; concomitant medications with CNS effects; history of seizures with last 2 years, tic disorders, hyperthyroidism, cardiac disorders, significant laboratory abnormalities	3 weeks of open MAS XR; no washout between treatment periods	No	Yes

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Funding
Biederman 2006	Cephalon Inc
Biederman 2007	New River Pharmaceuticals and Shire

Evidence Table 6. Quality of placebo-controlled trials in children

Internal Validity

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Brams 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Corkum 2008	Yes	Yes	NR	Yes	Yes	Yes	Yes

Evidence Table 6. Quality of placebo-controlled trials in children

						External Validity
Author, Year Country	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential /high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**
Brams 2008	No, NR, NR, NR	NR/NR	Yes	No withdrawals reported	Fair	92/86/86
Corkum 2008	Yes, NR, NR, NR	No/No	7 of 28 excluded (25%)	Yes	Fair	28/28/28

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Exclusion criteria	Run-in/Washout	Class naïve patients only	Control group standard of care
Brams 2008	If children or parents were unable to understand or follow instructions necessary to participate in the study, if they were deemed by the investigator to have below-average cognitive capacity, or if they were home schooled, had been previously diagnosed with Gilles de la Tourette's syndrome or a tic disorder, had a history of seizure disorder, or had a history of , or concurrent, significant medical or psychiatric illness or substance abuse disorder, those taking antidepressant or other antipsychotic medication, those who initiated psychotherapy within 3 months of screening, those with poor response or known sensitivity to all methylphenidate or dexmethylphenidate formulations based on past medical history, those currently taking other medications for ADHD, prospective subjects taking or planning to take any other investigational drug within 30 days of study start and those who had previously participated in an analogue classroom study within 6 months prior to screening.	NR/NR	No	Yes
Corkum 2008	Children were excluded if they had an IQ <1 SD below the mean on the Wechsler Intelligence Scale for Children–IV (WISC-IV), had a known neurological, metabolic, or seizure disorder, were currently taking other psychotropic medications or medications for sleep disturbances, evidenced symptoms of an intrinsic sleep disorder [i.e., sleep apnea, restless leg syndrome (RLS)/PLMS)] or a sleep-onset disorder based on parent report, or reached criteria for another mental health disorder that was considered primary to the ADHD diagnosis (e.g., autism).	NR/NR	Yes	Yes

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Funding
Brams 2008	Novartis Pharmaceuticals Corporation
Corkum 2008	IWK Health Centre in Halifax, Nova Scotia

Evidence Table 6. Quality of placebo-controlled trials in children

Internal Validity

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Findling 2007	Yes	NR	Yes	Yes	Unclear	Unclear	Yes
Hall 1972	Yes	Yes	Yes	Yes	Yes	Unclear, reported as double-blind	Yes

Evidence Table 6. Quality of placebo-controlled trials in children

						External Validity
Author, Year Country	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential /high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**
Findling 2007	Yes, Yes, NR, NR	No/No	NR	4 withdrew (20%)	Fair	NR/NR/20
Hall 1972	No No No No	No	Yes	No	Good	40/32/32

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Exclusion criteria	Run-in/Washout	Class naïve patients only	Control group standard of care
Findling 2007	Patients with clinical evidence of mental retardation, a pervasive developmental disorder, an inability to swallow pills, a history of alcohol or other substance abuse or dependence within 6 months before enrollment, or an active neurological or other medical condition suspected to be related to mood symptoms were also excluded from participation. In addition, pregnant females, those intending to become pregnant, and those sexually active female patients who were on an inadequate form of birth control were not permitted to participate. Additional exclusion criteria included significant symptoms of mania (YMRS ≥ 13) or depression (CDRS-R ≥ 40) during the week before enrollment and anticipated dosing changes for mood-stabilizing agents. Patients receiving a tricyclic antidepressant or antipsychotic agent and those with symptoms of psychosis or suicidal ideation were also excluded. Females who were nursing an infant as well as those patients experiencing any significant medical or neurological illness were not permitted to participate.	Patients required to be on fixed dose of mood stabilizer at least 5 days before receiving study medication	No	N/A
Hall 1972	Current medical illness or past medical history which contraindicated stimulant therapy, required other concurrent medication, free of gross organic involvement, severe recurring seizures or significant sensory and/or gross motor deficits use of phenothiazine two months preceding study entry.	NR	No	Yes

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Funding
Findling 2007	Many authors have financial ties to pharmaceutical companies, but no direct funding was given from pharmaceutical companies to this study
Hall 1972	Abbott Labs (partial funding)

Evidence Table 6. Quality of placebo-controlled trials in children

Internal Validity

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Gadow 2008	Randomization mentioned, but methods NR	Yes	NR	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Yes
Gau, 2007	Yes: Computer-generated random sequence	Yes: Assignment using interactive voice response system	Unclear - typographical error in table makes interpretation difficult; some differences exist	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Unclear, reported as double-blind
Geller, 2007	Method NR	Method NR	Unclear - some differences, other important parameters not reported	Yes	Unclear, reported as double-blind	Unclear, reported as double blind	Unclear, reported as double-blind

Evidence Table 6. Quality of placebo-controlled trials in children

						External Validity
Author, Year Country	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential /high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**
Gadow 2008	NR, NR, NR, NR	NR	Unclear	NR	Fair-Poor	NR/NR/71
Gau, 2007	Yes, NR, NR, NR	No	No: Excluded 8 patients (7%)	No	Fair	NR/NR/106
Geller, 2007	Yes, NR, NR, NR	Yes - 0.6% were LTFU (1 patient in ATX group during placebo run-in), and 25% for all-cause noncompleters	Yes, using LOCF	No	Fair	269/NR/176

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Exclusion criteria	Run-in/Washout	Class naïve patients only	Control group standard of care
Gadow 2008	Children who exhibited one or more of the following were excluded from consideration for the study if they were too severely ill (dangerous to self or others), psychotic, or mentally retarded (IQ < 70), or had a seizure disorder, major organic brain dysfunction, major medical illness, medical or other contraindication to medication (other than tics), or pervasive developmental disorder. Children were also excluded if their tics were so severe at intake that either the parent or child requested immediate intervention, which was rarely the case, or were extremely mild because in both cases symptoms would likely change in only one direction. Children were not excluded if previous treatment with stimulants had purportedly induced or exacerbated their tics.	NR/washout of prior stimulants 1 week, prior neuroleptic or SSRIs 3 weeks, and clonidine 2 weeks	No	Yes
Gau, 2007	Weight less than 20 kg or more than 60 kg; serious medical illness, such as a CV disease; history of bipolar I or II disorder, psychosis, or PDD; DSM-IV anxiety disorder at study entry; history of seizure disorder or prior EEG abnormalities related to epilepsy, or had taken/were taking anticonvulsants for seizure control; history of alcohol or drug abuse within past 3 months; potential for need for other psychoactive medications other than the study drug during the study period	No/No	No	Yes
Geller, 2007	Significant abnormalities in baseline laboratory or ECT results; met diagnostic criteria for current PTSD, panic disorder, specific phobias, or OCD; scored 15 or greater on CYBOCS; history of hypertension or bipolar, psychotic, pervasive developmental or seizure disorders; pregnant and lactating females, use of MAOI's within 2 weeks of visit 2, recent substance abusers, serious suicidal risk or with medical or personal conditions likely to affect the trial or health outcomes; cc use of drugs that inhibit the CYP2D6 enzyme pathway	14 d placebo run-in resulted in 18 exclusions	Not sure about this. Only 2 more pts in ATX group were tx-naïve; chi-square test using statsdirect was NS	Unclear

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Funding
Gadow 2008	None
Gau, 2007	Eli Lilly & Company
Geller, 2007	Eli Lilly & Company

Evidence Table 6. Quality of placebo-controlled trials in children

Internal Validity

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Gorman 2006	Method NR	Method NR	Yes except for concomitant ODD	Yes	Unclear, reported as double-blind	Unclear, reported as double blind	Yes
Greenhill 2006	Method NR	Method NR	Yes	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Unclear, reported as double-blind
Greenhill 2006	Method NR	Method NR	Yes	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Unclear, reported as double-blind
Grizenko 2006	Method NR	Method NR	Yes, at initial randomization (crossover study)	No	Unclear, reported as double-blind	Unclear, reported as double blind	Yes

Evidence Table 6. Quality of placebo-controlled trials in children

						External Validity
Author, Year Country	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential /high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**
Gorman 2006	No No No No	No	No	Yes; 2 (one in each group)	Fair	NR/NR/75
Greenhill 2006	No No No No	No	No	No	Fair	295/240/200
Greenhill 2006	No No No No	No	No	No	Fair	NR/NR/103
Grizenko 2006	No N/A No No	No	Yes	NR	Fair	NR/NR/95

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Exclusion criteria	Run-in/Washout	Class naïve patients only	Control group standard of care
Gorman 2006	History of neurological disorder, chronic medical illness, bipolar disorder, schizophrenia, pervasive developmental disorder, episode of major depressive disorder in the 6 months prior to study entry, current medication use, physical disabilities	NR	No	Yes
Greenhill 2006	History or current diagnosis of pervasive developmental disorder, schizophrenia or other psychotic disorders, psychiatric comorbidity that required pharmacotherapy, evidence of suicide risk, ADHD symptoms well controlled on current therapy with tolerable side effects, failure to respond to two or more adequate courses (dose and duration) of stimulant therapy, ANC <1x10-9th/L, hypertension, hypotension, history of alcohol or substance abuse, caffeine consumption >250mg/day	MAOI and SSRI 2 wk washout; Prescription or nonprescription medications w/psychotropic properties 1 wk washout; at least 1 wk washout for all patients	No	Yes
Greenhill 2006	Clinically significant abnormalities in vital signs, physical examinations, laboratory tests, history of seizures or use of anticonvulsants, comorbid psychiatric conditions, any medical condition that could interfere with study participation or assessments or that may pose a danger with administration of methylphenidate, use of psychotropic medications, initiation of psychotherapy within 3 mos, positive urine drug screen, history of poor response or intolerance to methylphenidate, pregnant/nursing, use of other investigational drug w/in 30 days of current study	At least 7 days washout existing ADHD therapy	No	Yes
Grizenko 2006	NR	1 week run-in	Unclear	N/A

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Funding
Gorman 2006	NIMH grant # MH56571
Greenhill 2006	NR
Greenhill 2006	Novartis Pharmaceuticals Corporation
Grizenko 2006	Canadian Institutes of Health Research

Evidence Table 6. Quality of placebo-controlled trials in children

Internal Validity

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Klein 1988	NR	NR	Yes	Yes	NR	Unblinded study	Unblinded study
McGough 2006	Method NR	Method NR	Yes	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Unclear, reported as double-blind
Nolan 1999	Method NR	Method NR	N/A (crossover study)	Yes	Unclear, reported as double-blind	Unclear, reported as double blind	Yes
Silva 2006	Yes	Method NR	Yes (reported in text; no comparative table)	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Yes

Evidence Table 6. Quality of placebo-controlled trials in children

						External Validity
Author, Year Country	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential /high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**
Klein 1988	Yes, NR, NR, NR	None	No	No	Poor	NR/NR/62
McGough 2006	No No No No	No	Yes	No	Good	NR/NR/93
Nolan 1999	No N/A No No	NR	Unclear	NR	Fair	NR/NR/19
Silva 2006	No No No No	No	Yes	No	Fair	54/54/54

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Exclusion criteria	Run-in/Washout	Class naïve patients only	Control group standard of care
Klein 1988	NR	NR/NR	NR	Yes
McGough 2006	Comorbid psychiatric diagnosis (except ODD) history of seizures or tic disorders, mental retardation, any illness or skin disorder that might jeopardize safety or compromise study assessments.	Up to 28 days washout existing medications	No	Yes
Nolan 1999	NR	2 wk run-in regular medication (methylphenidate or dextroamphetamine)	No	N/A
Silva 2006	Below average IQ at screening or preexisting evidence of IQ <80, home schooled, diagnosis of Tourette's or tic disorder, concurrent history of significant medical or psychiatric illness , substance abuse disorder, parents/guardians unable to understand or follow instructions	NR	No	Yes

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Funding
Klein 1988	Supported in part by Public Health Service grant MH 18579
McGough 2006	Shire Pharmaceuticals
Nolan 1999	Tourette Syndrome Association; US Public Health Service Grant MH45358; NIMH
Silva 2006	Novartis Pharmaceuticals Corporation

Evidence Table 6. Quality of placebo-controlled trials in children

Internal Validity

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Silva 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sinzig 2007	Randomization mentioned, but methods NR	Yes	Yes	Yes	Yes	Yes	Yes
Sleator 1974	n/a - nonrandomized	n/a - nonrandomized	NR	Yes	NR	Yes	Yes
Spencer 2005	Method NR	Method NR	Yes	Yes	Unclear, reported as double-blind	Unclear, reported as double blind	Yes

Evidence Table 6. Quality of placebo-controlled trials in children

						External Validity
Author, Year Country	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential /high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**
Silva 2008	Yes, Yes, NR, NR	No/No	Yes	No	Good	NR/NR/68
Sinzig 2007	No, NR, NR, NR	NR/NR	Unclear	No withdrawals reported	Fair	102/85/85
Sleator 1974	NR, NR, NR, NR	NR	NR	NR	Poor	NR/NR/42
Spencer 2005	No No No No	No	No for efficacy: 297/308 randomized pts included in efficacy analysis; Yes for safety	No	Good	NR/335/308

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Exclusion criteria	Run-in/Washout	Class naïve patients only	Control group standard of care
Silva 2008	Children were excluded if they or their parents/guardians were unable to understand or follow instructions necessary to participate in the study, if they were deemed by the investigator to have below-normal cognitive capacity, or if they were home schooled, diagnosed with Tourette disorder or a tic disorder, or had a history of, or concurrent, significant medical or psychiatric illness or substance abuse disorder. Children taking an antidepressant medication, those who initiated psychotherapy within the 3 months preceding screening, and those with a positive urine drug screen were ineligible. Also excluded were any children with poor response or intolerance to MPH, currently taking other medications for ADHD, taking or planning to take any other investigational drug within 30 days of study start, or who had previously participated in D-MPH-ER studies.	No/No	No	Yes
Sinzig 2007	Noted elsewhere (Dopfner et al 2003)	NR/NR	NR	Yes
Sleator 1974	NR	NR/NR	NR	Yes
Spencer 2005	Psychiatric diagnosis other than ADHD, diagnosis of conduct disorder, medical history of nonresponse to stimulant medication, seizures, tic disorder, Tourette's syndrome	1-4 wk washout of current psychotropic medication and replaced with placebo	No	N/A

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Funding
Silva 2008	Novartis Pharmaceuticals Corporation
Sinzig 2007	Medice Arzneimittel Putter GMBH & Co
Sleator 1974	NIMH grant; MPH supplied by Ciba-Geigy
Spencer 2005	Shire Pharmaceuticals

Evidence Table 6. Quality of placebo-controlled trials in children

Internal Validity

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Swanson 2006	Method NR	Method NR	Yes	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Yes
Szobot 2008	Randomization mentioned, but methods NR	Yes	Yes	Yes	No	No	Yes
Wilens 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Zeiner 1999 Fair	NR	NR	NR	Yes	Yes	Yes	Yes

Evidence Table 6. Quality of placebo-controlled trials in children

						External Validity
Author, Year Country	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential /high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**
Swanson 2006	No No No No	No	Yes	Yes (1 pt in modafinil group)	Fair	316/232/190
Szobot 2008	Yes, Yes, NR, NR	No/No	Yes	No	Fair	32/29/16
Wilens 2008	Yes, NR, NR, NR	No/No	Yes	No	Good	148/NR/128
Zeiner 1999 Fair	Yes, NR, NR, NR	No	Yes	No	Fair	NR/NR/21

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Exclusion criteria	Run-in/Washout	Class naïve patients only	Control group standard of care
Swanson 2006	History or current diagnosis of pervasive developmental disorder, schizophrenia or other psychotic disorders, suicide risk, other psychiatric comorbidities requiring pharmacotherapy, well controlled ADHD , previous failure to respond to 2 or more adequate courses of stimulant therapy for ADHD, height or weight below 5th or above 95th percentile	Prior ADHD medication 1-4 wk washout	No	Yes
Szobot 2008	Exclusion criteria were the lack of a responsible adult to inform about possible childhood psychopathology or to take responsibility for the medication, the need for inpatient treatment for drug abuse or psychiatric comorbidities, and the presence of a primary psychiatric condition that required immediate outpatient treatment (like moderate/severe depression).	NR/NR	Yes	Yes
Wilens 2008	Subjects could not have conduct disorder or comorbid illnesses that contraindicated or could confound MTS treatment. Subjects with a history of failing to respond to psychostimulant treatment were also excluded. Subjects were not permitted to have taken another investigational product within 30 days of screening or to participate in other research trials involving drug treatment during the course of the study.	No study medication for 30 days prior to screening/7-day washout period	No	Yes
Zeiner 1999 Fair	NR	NR/NR	Unclear	Yes

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Funding
Swanson 2006	Cephalon Inc
Szobot 2008	CNpq (No. 307780/2004-0) and Hospital de Clinicas de Porta Alegre
Wilens 2008	Shire Pharmaceuticals
Zeiner 1999 Fair	Norwegian Medical Research Council, Norwegian Public Health Association, and the Legacy of Haldis and Josef Andresen

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Eligibility criteria	Comorbidity	Interventions and total daily dose Duration Dosing schedule
PCT > 6 mos			
DEX			
Conrad 1971 (Poor)	Children from low-income neighborhood, in grades kindergarten-second grade, with rating from teacher as hyperactive (19th percentile or lower), and with sings of significant perceptual-cognitive impairment as defined by: perceptual age one year or more below on Bender-Gestalt, Frostig Perceptual Quotient of 90 or less, 3 or more errors on Bender-Gestalt, discrepancy between verbal IQ and Performance IQ on WISC of 15 or more points, variability among subscores on WISC of 6 or more points	NR	n=68 randomized into 1 of 4 groups: Grp A: placebo/no tutoring (n=18) Grp B: placebo/tutoring (n=17) Grp C: dextroamphetamine/no tutoring (n=17) Grp D: dextroamphetamine/tutoring (n=16) duration 4-6 months doses increased/decreased at 5mg/day, until undesirable side effects, or maximum positive response achieved. Average dose: 10-20 mg/day.

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
PCT > 6 mos				
DEX				
Conrad 1971 (Poor)	NR NR NR	NR	1350/262/106/68	NR

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Results
PCT > 6 mos	
DEX	
Conrad 1971 (Poor)	**Mean difference scores between baseline and post-testing** reported as variable: grp A (placebo/no tutor); grp B (placebo/tutor); grp C (dextroamphetamine/no tutor); grp D (dextroamphetamine/tutor); (p-Value) Motor Coordination: -.17; 24; 18; .25; (.20) Repeating a Motor Pattern: .00; 1.00; .71; 1.50; (.02) Visual Tracking: .00; .59; .18; .31; (.12) Motor Activity: -.06; .18; .65; .69; (.01) Distractibility: .22; .35; .59; .44; (.50) Hyperkinetic Score: 2.28; 5.59; .9.29; 6.25; (.08) Behavior Rating By Teacher: 3.00; 2.77; 2.59; 2.19; (.001) Behavior Rating By Parent: 2.94; 2.77; 2.06; 1.94; (.001) Spatial Orientation: 1.33; 1.65; .71; 2.00; (.50) Koppitz Errors: 1.44; 2.18; 3.06; 4.25; (.07) Frostig I: -.56; -.18; .53; -.25; (.30); Frostig II: -.39; -.18; 1.00; .00; (.12) Frostig III: .06; 1.29; 1.47; 1.69; (.25); Frostig IV: -.56; -.47; 1.18; .31; (.02) Frostig V: -.39; .53; 1.00; .69; (.02); Frostig PQ: -4.61; 2.18; 10.41; .69; (.02) Frostig Stars: .56; .53; .88; .56; (.50) WISC Subtests Information: -1.17; .88; -.06; 1.06; (.005); Comprehension: -.33; .06; -.29; 1.00; (>.50) Arithmetic: .28; .59; .47; -.31; (>.50); Similarities: .72; -.24; .82; -.06; (>.50) Digit Span: 1.39; .77; 2.18; 1.69; (>.50); Picture Completion: .02; -.06; .71; .06; (>.50) Picture Arrangement: .89; 1.41; .41; 1.75; (>.50); Block Design: -.50; 1.29; -.06; .56; (>.50) Object Assembly: .67; .88; 1.06; 2.75; (.17); Coding: .72; .82; 3.35; 2.00; (.07) WISC Verbal IQ: .89; 2.18; 4.53; 3.94; (>.50) WISC Performance Scale: 2.94; 6.06; 6.88; 9.19; (.30) WISC Full-Scale IQ: 2.11; 4.41; 6.24; 7.43; (.12) Temporal Order: 1.44; 2.00; 1.53; 2.19; (>.50) Bender Recall: .80; .93; 1.00; 1.38; (>.50) WRAT Reading: 6.33; 5.59; 5.29; 4.94; (>.50) WRAT Arithmetic: 3.06; 3.47; 5.41; 4.44; (.18)

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events
PCT > 6 mos			
DEX			
Conrad 1971 (Poor)	NR	NR	NR

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Eligibility criteria	Comorbidity	Interventions and total daily dose Duration Dosing schedule
MPH			
Ialongo 1993 Fair	Children had to meet DSM-III-R criteria for ADHD, based on a) Conners Parent and Teacher Hyperkinesis Indices scores >=2 SD's above published means; b) a clinical interview with the parents; and c) the results of psychometric testing. A pediatrician and psychiatrist had to both agree with ADHD diagnosis in their review of available data. Children with a comorbid anxiety and/or depressive disorder and with gross physical impairments, intellectual deficits, and psychosis in either child or parent(s) were excluded.	Original study of n=107: Conduct disorder: 7.5% (n=8) Oppositional defiant disorder: 43.0% (n=46)	All MPH and behavioral treatments had been discontinued 9 months prior to follow-up. In short-term portion of study, children were randomly assigned to: placebo alone; low-dose MPH=0.4 mg/kg/day; high dose MPH=0.8 mg/kg/day; placebo + behavioral parent training (PT) and child self-control instruction (SC); low-dose MPH+PT+SC; high dose MPH+PT+SC

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
MPH				
Ialongo 1993 Fair	Average Age = 8.27 years Male = 77.4% White = 84.9% African-American = 9.4% Hispanic = 3.8% Asian American = 1.9%	NR	117/107/96	18/7/71 analyzed

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Results
MPH	
Ialongo 1993 Fair	Overall trend (the exception was the parent report data) towards an erosion of treatments gains seen across treatments. ("A table of means and standard deviations by condition and over time for each of the outcome measures is available from the senior author.") -Only significant contrast seen for PT+SC treatment effect for posttest to follow-up (fu) : F[5,56]=3.69, p=0.006. Univariate F for PT+SC treatment effect was significant for each of the parent report measures: CPRS, F[1,64]=14.31, p<0.001; SNAP, F[1,62]=4.89, p=0.031 CBCL total problems, F[1,61]=12.03, p=0.001; CBCL externalizing F[1,61]=11.07, p=0.001 CBCL aggression F[1,60]=6.29, p=0.015 -Medication alone condition: modest deterioration or no gain from posttest to fu; in contrast, children in PT+SC showed improvements from posttest to fu on Conners Hyperkinesis Index, SNAP total score, and CBCL (total problems, externalizing, and aggression) (no data given). -Multivariate Fs for pretest to posttest and posttest to fu contrasts were significant for medication by period effect: pretest to posttest:F[4,120]=5.05, p=0.001; posttest to fu: F[4,121]=3.37, p=0.012 Univariate Fs for off-task behavior: pretest to posttest:F[2,62]=10.36, p<0.001; posttest to fu: F[2,60]=7.18, p=0.002 -Children receiving stimulant medication showed a significantly greater deteriorization in posttest to fu scores than did children receiving placebo. (explanation: the non-medicated children showed virtually no change pretest to posttest or posttest to fu, whereas medicated children did show significant improvement from prettest to posttest and deterioration of those gains from posttest to fu.) (no data given) -No evidence of greater maintenance of treatment gains at fu were found with children receiving PT+SC+medication. (no data given).

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events
MPH			
Ialongo 1993 Fair	NR for follow-up group	NR for follow-up group AE details not specified for short-term group, though 3 withdrew because of them and 13 dropped out "owing to concerns about the medication, or insufficient time to attend the groups, or dissatisfaction with treatment efficiency".	18 withdrawals/3 withdrew to AE's during the short-term part of the trial; 7 lost to follow-up

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Eligibility criteria	Comorbidity	Interventions and total daily dose Duration Dosing schedule
Kupietz 1987 Fair	Children between 7 and 13 inclusive, with an IQ>=80, meeting DSM-III criteria for ADD with Hyperactivity (ADDH) and Developmental Reading Disorder, whose parents confirmed in an interview that hyperactivity had been present for >=2 years, a teacher rating of >=2.5 (on a 1 to 4 scale) on the Hyperactivity factor of the Conner's TRS. Children with an additional Axis I psychiatric diagnosis or uncorrected hearing or visual deficits were excluded.	Developmental Reading Disorder	0.3 mg/kg, 0.5 mg/kg, 0.7 mg/kg or placebo per day Duration was a total of 28 weeks: 14 weeks of treatment, 1 wk placebo, 12 wks treatment, 1 wk placebo

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Kupietz 1987 Fair	Mean age = 9.7 years Male = NR White = NR	**At baseline:** Conner's TRS mean Hyperactivity score = 3.08 Reading Grade Level = 4.5 (mid fourth-grade) FSIQ mean score = 93.8 VIQ mean score = 91.5 PIQ mean score= 97.8	NR/NR/58	11 withdrew before completing the 28-week drug protocol/NR/47, but sample size varies across dependent measures due to missing forms from parents or teachers

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Results
Kupietz 1987 Fair	Conners TRS scores with the adjusted means for Aggressiveness (I), Inattentiveness (II), and Hyperactivity (IV) Factors analyzed together: Mean ratings for dosage (all weeks combined): placebo, 0.3mg, 0.5mg, 0.7mg, and 0.7mg: 2.43, 1.93, 1.85, 1.62* *Post-hoc analysis: 0.7 mg/kg group received significantly lower ratings than placebo (p=NR) Mean ratings for week (all dosages combined): week 2, week 14, week 27: 1.96, 1.89, 2.05* *Post-hoc analysis: Means for Week 14 compared to Week 2 was considered unchanged (p-value NR); but the increase between Week 14 and Week 27 was considered significant (p-value NR). DESB Scale: adjusted mean ratings for placebo, 0.3 mg, 0.5 mg, 0.7mg (all weeks combined): 140.3, 128.0, 112.6, 104.9 *Post-hoc Analysis: only 0.7mg and placebo groups were found to differ significantly (p-value NR) Conners ARS scores, Combined Adjusted Mean ratings for dosage (all weeks combined): placebo, 0.3mg, 0.5mg, 0.7mg, and 0.7mg: 2.51, 2.39, 2.36, 1.80 *Post-hoc analysis: 0.7 mg were rated significantly less hyperactive than placebo (p=NR) DCB Scale: Mean parent ratings for weeks 2, 14, 27 (all dose groups combined): 185.6, 180.0, 132.2* *Post hoc analysis: Week 27 results were significantly lower than Week 2 or 14 results. At each study week, 0.7mg were lowest; only at week 14 was 0.7mg significantly lower than placebo or 0.3mg (p-value NR) WWPAS: No dose group effects were obtained; the main effect for weeks only approached significance as a main effect (p=0.058). Mean activity ratings for weeks 2, 14, 27 (all dosages combined) were 18.5, 16.5, 16.4 Paired-Associate Learning (PAL): Neither dose group nor study week was significant, but there was a significant interaction between these variables (F=3.34, p<0.05). Adjusted error scores show a tendency for errors to decrease as a function of MP dosage across the 0.5mg and 0.7mg groups (p-value NR). Post-hoc analysis: at Week 27, 0.7mg group made significantly fewer errors than placebo or 0.3mg (p-value NR). STM Task: no drug effects were obtained on latency of correct response measure; thus, these data not reported. A main effect of matrix (F=51.51, p<0.001) and a significant interaction between dose group and study week (F=3.68, p<0.02). Post-hoc analysis: significantly more correct responses were made to matrix size 3 than to 9 or 15 (p-value NR); at week 2 the 0.7mg group made significantly more correct responses than placebo, but not at week 27 (p-values NR).

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events
Kupietz 1987 Fair	NR	NR	11 withdrawals; study states that some withdrew due to side effects, but does not give a specific number

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Eligibility criteria	Comorbidity	Interventions and total daily dose Duration Dosing schedule
ADHD Drug Versus Non-Drug Treatment			
MTA Cooperative Group 1999. 2004	Children between 7 and 9.9 years (grades 1-4), in residence with same primary caretaker >=last 6 months, who met the DSM-IV criteria for ADHD Combined Type, using the Diagnostic Interview Schedule for Children (DISC) parent report version 3.0, supplemented with up to 2 symptoms identified by children's teachers for cases falling just below DISC threshold. Exclusion criteria: situations that would prevent families' full participation in assessments or treatment, or that might require additional treatment incompatible with study treatments (ex. child currently in hospital, child currently in another study, child with =<80 on all WISC-III scales and SIB, bipolar disorder, psychosis, or personality disorder, chronic serious tics or Tourette syndrome, OCD serious enough to require separate treatment, neuroleptic medication in previous 6 months, major neurological or medical illness, history of intolerance to MTA medications, ongoing or previously unreported abuse, parental stimulant abuse in previous 2 years, same classroom as child already in MTA study, non-English-speaking primary caretaker, no telephone, suicidal or homicidal, another child in same household in MTA study)	ODD: 39.9% (n=231) Conduct Disorder: 14.3% (n=83) Anxiety Disorder: 33.5% (n=194) Tic Disorder: 10.9% (n=63) Affective Disorder: 3.8% (n=22) Mania/hypomania: 2.2% (n=13)	4 different arms of treatment: medication management [MM] only (n=144), behavioral treatments [BT] (no medication) (n=144), combined medication and behavioral treatment [CT] (n=145), and standard community care [CC] (in which community doctors decided the best mode of treatment for their individual patients) (n=146). -Blinded physicians agreed on best dose of medication for subjects in both the MM and CT groups after a 28-day titration (the only DB part of study) - at which point blind was broken and this agreed-on dose became the subject's initial maintenance dose. -MM and CT subjects originally given MPH: 77.3% (n=198 of 256 who completed titration) MM and CT subjects originally given Dex: 10.2 % (n=26) MM and CT subjects originally given no medication: 12.5% (n=32) average initial dose of MPH = 30.5 mg/day -At the end of 14 months, MM and CT subjects taking MPH: 73.4% (n=212 of 289 completing both MM and CT) MM and CT subjects taking Dex: 10.4% (n=30) MM and CT subjects on other drugs: 3.1% (n=9) MM and CT subjects on no medication: 13.1% (n=38) CT subjects received 31.2 mg of MPH versus MM=37.7 mg of MPH by treatment end point -At the end of 14 months, CC subjects taking MPH: 57.5% (n=84 of 146 CC subjects) CC subjects taking Dex: not specified CC subjects on other drugs: 16.4% (n=24) CC subjects on no medication: not specified Mean total daily dose for CC subjects=22.6 mg of MPH at treatment end point 14 Month Duration for all treatment arms

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
ADHD Drug Versus Non-Drug Treatment				
MTA Cooperative Group 1999. 2004	Mean Age = 8.5 (range: 8.4-8.6) years Male = 80.3% (n=465) White = 60.6% African American = 19.9% Hispanic = 8.3%	WISC-III IQ, mean score= 100.9 Conners Teacher Rating Scale, mean score = 1.32 Conners Parent Rating Scale, mean score = 0.83 Welfare recipients = 19.0% Subjects living with 2-parent family = 68.4%	4541/609/579	NR/NR/526 analyzed (number gotten from test score subject numbers at 14 months)

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Results
ADHD Drug Versus Non-Drug Treatment	
MTA Cooperative Group 1999. 2004	For all results, significance is taken after Bonferroni-corrected p-values 1) ADHD symptoms a) Inattention rated by teacher: MM>BT (p=0.001); CT vs.MM (p=ns); CT>BT (p=0.005); CT>CC (p=0.001); MM>CC (p=0.001); BT vs.CC (p=ns) b) Inattention rated by parent: MM>BT (p=0.001); CT vs.MM (p=ns); CT>BT (p=0.001); CT>CC (p=0.001); MM>CC (p=0.001); BT vs.CC (p=ns) c) Hyperactive-impulsive rated by teacher: MM vs.BT (p=ns); CT vs.MM (p=ns); CT vs.BT (p=ns); CT>CC (p=0.001); MM>CC (p=0.001); BT vs.CC (p=ns) d) Hyperactive-impulsive rated by parent: MM>BT (p=0.001); CT vs.MM (p=ns); CT>BT (p=0.001); CT>CC (p=0.001); MM>CC (p=0.001); BT vs.CC (p=ns) e) Classroom rated by classroom observer: MM vs.BT (p=ns); CT vs.MM (p=ns); CT vs.BT (p=ns); CT vs.CC (p=ns); MM vs.CC (p=ns); BT vs.CC (p=ns) 2) Aggression-ODD a) Rated by teacher: MM vs.BT (p=ns); CT vs.MM (p=ns); CT vs.BT (p=ns); CT>CC (p=0.004); MM>CC (p=0.004); BT vs.CC (p=ns) b) Rated by parent: MM vs.BT (p=ns); CT vs.MM (p=ns); CT>BT (p=0.001); CT>CC (p=0.002); MM vs.CC (p=ns); BT vs.CC (p=ns) c) Rated by classroom observer: MM vs.BT; CT vs.MM; CT vs.BT; CT vs.CC; MM vs.CC; BT vs.CC (p=ns for all 6 comparisons) 3) Internalizing symptoms- SSRS Internalizing rated a) by teacher: MM vs.BT; CT vs.MM; CT vs.BT; CT vs.CC; MM vs.CC; BT vs.CC (p=ns for all 6 comparisons) b) by parent: MM vs.BT (p=ns); CT vs. MM (p=ns); CT>BT(p=0.001); CT>CC (p=0.001); MM vs.CC (p=ns); BT vs. CC (p=ns) c) MASC rated by child: MM vs.BT; CT vs.MM; CT vs.BT; CT vs.CC; MM vs.CC; BT vs.CC (p=ns for all 6 comparisons) 4) Social Skills- SSRS rated a) by teacher: MM vs.BT; CT vs.MM; CT vs.BT (p=ns for all three); CT>CC (p=0.001); MM almost equivalent to CC (p=0.009); BT vs.CC (p=ns) b) by parent: MM vs.BT; CT vs.MM; CT vs.BT; CT vs.CC; MM vs.CC; BT vs.CC (p=ns for all 6 comparisons) 5) Parent-child relations a) Power assertion rated by parent: MM vs.BT; CT vs.MM; CT vs.BT (p=ns for all three); CT>CC (p=0.003); MM vs.CC (p=ns); BT almost equivalent to CC (p=0.005) b) Personal closeness rated by parent: MM vs.BT; CT vs.MM; CT vs.BT; CT vs.CC; MM vs.CC; BT vs.CC (p=ns for all 6 comparisons) 6) Academic achievement a) Reading: CT>BT and CT>CC in pairwise comparisons (p=0.001) b) Mathematics: no significant main effects for treatment group, so no pairwise comparisons were performed c) Spelling: no significant main effects for treatment group, so no pairwise comparisons were performed 24-Month Outcomes: CT vs MM vs BT vs CC 1) Medication use (%)- 14-24 months: 86 vs 85 vs 44 vs 69, p<0.001; 24 month: 70 vs 72 vs 38 vs 62 2) Mean dosage (mg/day): 30.4 vs 37.5 vs 25.7 vs 24, p<0.0001 3) the advantage of CT/MM over BT/CC remained significant (p=0.002) for ADHD symptoms and almost significant (p=0.016) for ODD symptoms 4) The proportion of children with SNAP item means < (near normalization or "excellent responders") at 24 months: 48 vs 37 vs 32 vs 28

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events
ADHD Drug Versus Non-Drug Treatment			
MTA Cooperative Group 1999. 2004	Side-effects were monitored monthly using parent-completed 13-item Pittsburgh Side Effects Rating Scale (ratings=not present, mild, moderate, severe)	245 combined treatment/medication families reported side effects: No side-effects: 88 (35.9%) Mild side effects: 122 (49.8%) Moderate side effects: 28 (11.4%) Severe side effects: 7 (2.9%) (6 of 11 reported server side effects (depression, worrying, or irritability) could have been due to non-medication factors)	20 complete dropouts by 14 months = 3.5%; Withdrawals due to AE's: not specified

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Eligibility criteria	Comorbidity	Interventions and total daily dose Duration Dosing schedule
MPH vs. Parent training			
Firestone 1986	Children aged 5-9 years, with DSM-III diagnosis of ADHD, and with rating of 1.5 or higher on Teacher's Activity Index.	NR	Subjects randomly assigned to one of three grps: parent trg and meds (PTMEDS), parent trg and placebo (PTPL) or meds only (MED). Doses: raised or lowered by % mg steps, based on reports of symptoms, until individual optimal dosages were established (decrease in problematic behavior and absence of negative side effects), average dose was 22 mg/day. Duration: 24 months. Dosing schedule NR.

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
MPH vs. Parent training				
Firestone 1986	ages: 5-9 yrs gender: NR ethnicity: NR	NR	NR/NR/73	NR/ 21 lost to fu/ 52 analyzed for entire 2 yr period

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Results
MPH vs. Parent training	
Firestone 1986	**Test scores at 3 mos: (mean scores; SD; n)** Hyperactivity Index: MED: .81; .44; (n=11); PTPL: 1.12; .56; (n=9); PTMED: 1.03; .46; (n=10) Conduct Problems: MED: 6.45; 4.42; (n=11); PTPL: 6.89; 4.23; (n=9); PTMED: 5.8; 2.81; (n=10) Reaction Time: MED: .64; .19; (n=12); PTPL: .75; .22; (n=8); PTMED: 5.8; 2.81; (n=10) Verbal Grade: MED: 3.42; 1.54; (n=10); PTPL: 2.51; 1.62; (n=8); PTMED: 3.36; 1.22; (n=9) **Test Scores at 10-12 mos: (mean scores; SD; n)** Hyperactivity Index: MED: .96; .59; (n=11); PTPL: 1.07; .55; (n=9); PTMED: .92; .36; (n=10) Conduct Problems: MED: 5.91; 3.61; (n=11); PTPL: 6.44; 4.02; (n=9); PTMED: .92; .36; (n=10) Reaction Time: MED: .59; .13; (n=12); PTPL: .70; .15; (n=8); PTMED: .63; .25; (n=10) Verbal Grade: MED: 3.56; 1.62; (n=10); PTPL: 3.23; 2.16; (n=8); PTMED: 3.97; 1.34; (n=9) **Test Scores at 22-24 mos: (mean scores; SD; n)** Hyperactivity Index: MED:1.09; .60; (n=11); PTPL: 1.09; .63; (n=9); PTMED: 1.06; .59; (n=10) Conduct Problem: MED: 6.97; 4.41; (n=11); PTPL: 4.51; 3.57; (n=9); PTMED: 1.06; .59; (n=10) Reaction Time: MED: .60; .11; (n=12); PTPL: .64; .14; (n=8); PTMED: .52; .12; (n=10) Verbal Grade: MED: 4.56; 1.70; (n=10); PTPL: 4.29; 2.74; (n=8); PTMED: 5.14; 1.92; (n=9)

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events
MPH vs. Parent training			
Firestone 1986	report of symptoms from teachers.	NR	NR

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Eligibility criteria	Comorbidity	Interventions and total daily dose Duration Dosing schedule
Brown 1985	40 boys whose parents and teachers agreed that he demonstrated, in serious and persistent form (symptoms demonstrated from infancy or early childhood for a duration of >=12 months prior to referral), symptoms associated with ADHD. Parent and teacher interviews were conducted to ascertain the child's symptoms and emotional climate in the home after health care or special education personnel referred the boy to the study. Each boy also demonstrated a reading deficit of at least two grade levels. Excluded were boys with symptoms that seemed to stem from stress at home or from inconsistent child management practices; with major diseases; with obvious physical defects; with gross neurological, sensory, or motor impairment; or with psychosis.	Reading deficits	MPH Doses were 0.3 mg/kg - twice daily: in the morning and at lunch Individual doses ranged from 5 to 15 mg/day Cognitive training: individual twice-weekly one hour sessions over a total of 12 weeks (24 session total/individual). Modeling, self-verbalization, and strategy training were taught. Mothers observed several training sessions with another trainer from behind a one-way mirror and were instructed on how these procedures could be applied at home. There were four treatment groups: no treatment (n=10); MPH only (N=10); Cognitive Training only (n=10) [CTO]; and Combined Cognitive Training and MPH treatment (n=10) [Combined] Cognitive training lasted 12 weeks; MPH continued for the "duration of study"

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Brown 1985	Mean age = 11.36 years Male = 100% Ethnicity NR	Mean IQ score (obtained from WISC-R): 101.92 (range: 91-136) Mean ACRS score: 18.55 (range: 17-22) Separate ANOVAs for these variables show that none of the four groups differed in age, IQ, or ACRS (no data given) Since 10 boys were non-random, a one-way multiple ANOVA was performed on pre-treatment scores; result was nonsignificant F ratio, F(3,36)=0.47, n.s.; these results indicate equality prior to treatment between subgroups.	NR/NR/40	NR/NR/40

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Results
Brown 1985	F ratios determined using separate MANOVAs to determine differences in the effectiveness of treatment and to determine the persistence of each treatment at delaye posttesting (DPT): MPH only; Combined; CTO; No Treatment: F(2,34)=3.95, p<0.001; F(2,34)=5.06, p<0.0001; F(2,34)=1.88, p<0.69; F(2,34)=0.53, p<0.95 **Comparisons of Univariate Measures by Condition** *p-values* for: MPH only; Combined Therapy; Cognitive Training only (CTO); and No Treatment* CCT Omissions: p<0.0001; p<0.0001; p<0.07 (as); ns CCT Commissions: ns; p<0.08 (as); ns; ns MFFT Error: p<0.0001; p<0.008; p<0.08 (as); ns MFFT Latency: ns; p<0.00001; p<0.001; p<0.01 CEFT Total correct: p<0.01; ns; p<0.005; ns WISC-R Attention factor: p<0.004; p<0.06; p<0.03; ns WRAT Arithmetic: p=ns for all four subgroups WRAT Reading: p=ns for all four subgroups Durrell Listening Comprehension: p<0.005; p<0.006; p<0.03; ns Detroit Subtests (3): p=ns for all four subgroups on all 3 subtests Conners Teacher: p<0.0001; p<0.004; ns; ns Conners Parent: p<0.05; p<0.002; ns; ns Teacher Rating Attention: p<0.005; p<0.05: ns; ns Teacher Rating Impulsivity: p<0.02;p<0.02; p<0.07 (as); ns Self-rating Impulsivity: p<0.0001; p<0.0001; ns; ns *p-values: significance when p<0.05; not significant = ns, approached significance=as [value given] Duncan's Multiple Range Test post-hoc analyses were performed by condition for each of the significant univariate dependent measures. Differences between pretest and posttest (p<0.05) and pretest and DPT (p<0.05) were significant, but differences between posttest and DPT were ns (no p-value given). Canonical correlation coefficients (Rc2) for the multivariate analyses for MPH Only; Combined; CTO 0.963; 0.971; 0.926 (amount of variance in dependent measures across pre-, post-, and DPT accounted for by the differences in MPH only and Combined treatments was virtually the same).

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events
Brown 1985	NR	NR	NR

Evidence Table 8. Quality in long-term efficacy trials

Internal Validity

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Brown 1985	NR	NR	NR	Yes	NR	No	No
Conrad 1971	NR	NR	NR	Yes	Yes	Yes	Yes
Firestone 1986	NR	NR	NR	Yes	Yes	Yes	Yes
Kupietz 1987	NR	NR	NR	Yes	Yes	Yes	Yes
Ialongo 1993	NR	NR	No, more non-white children in placebo group	Yes	Yes	Yes	Yes

Evidence Table 8. Quality in long-term efficacy trials

						External Validity
Author, Year Country	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/ high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality rating**	**Number screened/eligible/ enrolled**
Brown 1985	NR, NR, NR, NR	NR	NR	NR	Poor	NR/NR/40
Conrad 1971	Yes, NR, NR, NR	No/No	No	NR	Poor	NR/96/96
Firestone 1986	Yes, NR, NR, NR	NR	No	No	Fair	NR/NR/73
Kupietz 1987	Yes, NR, NR, NR	No/No	No, sample size varied across dependent measures, based on incomplete data	No	Fair	NR/NR/58
Ialongo 1993	Yes, NR, NR, NR	No/No	Yes	No	Fair	117/107/96

Evidence Table 8. Quality in long-term efficacy trials

Author, Year Country	Exclusion criteria	Run-in/ Washout	Class naïve patients only	Control group standard of care	Funding
Brown 1985	Gross neurological, sensory, or motor impairment or psychosis	NR/NR	NR	Yes	NR
Conrad 1971	NR	NR/NR	NR	Yes	NY State Department of Mental Hygiene Contract No. C36725
Firestone 1986	Definite signs of brain damage, epilepsy, or psychosis	NR/NR	NR	Yes	Ontario Ministry of Health grants
Kupietz 1987	Additional Axis I psychiatric diagnosis or uncorrected hearing or visual deficits	NR/NR	NR	Yes	NIMH grant MH 36004
Ialongo 1993	Comorbid anxiety and/or depressive disorder; gross physical impairments, intellectual deficits or psychosis	NR/NR	NR	Yes	NR

Evidence Table 8. Quality in long-term efficacy trials

Author, Year Country	Relevance
Brown 1985	
Conrad 1971	
Firestone 1986	
Kupietz 1987	
Ialongo 1993	

Evidence Table 8. Quality in long-term efficacy trials

Internal Validity

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
MTA	NR	Yes	No, significant differences across treatment groups in age	Yes	Yes	No	No

Evidence Table 8. Quality in long-term efficacy trials

						External Validity
Author, Year Country	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/ high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality rating**	**Number screened/eligible/ enrolled**
MTA	Yes, Yes, Yes, Yes	NR	No	No	Fair	4541/609/579

Evidence Table 8. Quality in long-term efficacy trials

Author, Year Country	Exclusion criteria	Run-in/ Washout	Class naïve patients only	Control group standard of care	Funding
MTA	ex. child currently in hospital, child currently in another study, child with =<80 on all WISC-III scales and SIB, bipolar disorder, psychosis, or personality disorder, chronic serious tics or Tourette syndrome, OCD serious enough to require separate treatment, neuroleptic medication in previous 6 months, major neurological or medical illness, history of intolerance to MTA medications, ongoing or previously unreported abuse, parental stimulant abuse in previous 2 years, same classroom as child already in MTA study, non-English-speaking primary caretaker, no telephone, suicidal or homicidal, another child in same household in MTA study	NR/NR	No	Yes	NIMH grants

Evidence Table 8. Quality in long-term efficacy trials

Author, Year Country	Relevance
MTA	

Evidence Table 9. Head-to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, regimen, duration)	Run-in/ Washout Period
Dextroamphetamine vs modafinil				
Taylor, 2000 U.S. (Fair)	DB RCT, crossover study	Subjects were older than 21, and from a single local community. Subjects had to meet DSM-IV criteria for ADHD by age 7 as well as currently, with chronic course, with at least moderate impairment from the symptoms, and provide corroborating history from at least one parent or older sibling, with evidence from schoolwork or prior psychologic testing. Subjects were required to score above the 93rd percentile of symptom severity.	DAMP 10-49 mg/day in 5 mg capsules; mean dose 21.8 mg/day Modafinil 100-400 mg/day in 50 mg capsules; mean dose 206.8 mg/day Placebo (lactose) Daily dosing was on awakening and again 5 hours later. Titration occurred over 4-7 days, with fixed dose thereafter for another 7-10 days. 2-week treatment phases of placebo, modafinil, and DAMP, separated by 4-day washouts.	Run-in NR; 4-day washout between treatments

Evidence Table 9. Head-to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Dextroamphetamine vs modafinil			
Taylor, 2000 U.S. (Fair)	NR	At baseline and on the last day of each treatment phase within 3 hours of the last dose: self-rated ADHD behavior checklist for adults; self-rated BDI; clinician-administered Ham-A. Clinician-administered cognitive tests: letters C, F, and L of the COWAT; Wechsler Adult Intelligence Scale-Revised; Stroop-Color-Word Interference Test	Mean age 40.8 59% male Ethnicity NR

Evidence Table 9. Head-to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Dextroamphetamine vs modafinil			
Taylor, 2000 U.S. (Fair)	100% completed high school; 55% completed college 91% had family history of ADHD 73% had child or sibling with ADHD Comorbidities: 46% had at least 1 episode of depression 14% anxiety disorder and past history of alcohol dependence	29/22/22	1 withdrawn 0 lost to fu; 21 analyzed, all exposed to both DAMP & modafinil

Evidence Table 9. Head-to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Results
Dextroamphetamine vs modafinil	
Taylor, 2000 U.S. (Fair)	Cognitive mean scores, DAMP vs modafinil: COWAT Test 86.5 vs 87.7 (ns) Digit Span forward 10.3 vs 10.3 (ns); backward 7.6 vs 7.5 (ns) Stroop Color 50.2 vs 48.0 (ns); Word 48.8 vs 48.8 (ns); Color-Word 52.0 vs 51.6 (ns) DSM-IV ADHD behavior checklist mean scores, DAMP vs modafinil: Total 20.0 vs 18.3 (ns); Hyperactivity subscore 9.0 vs 7.3 (ns); Inattention subscore 11.0 vs 10.5 (ns) Drug preference: 48% chose DAMP, 43% chose modafinil, 10% chose placebo

Evidence Table 9. Head-to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals by treatment; withdrawals due to adverse events
Dextroamphetamine vs modafinil			
Taylor, 2000 U.S. (Fair)	Side effect checklist, elicited by investigator on the last visit of each drug trial	DAMP vs modafinil: Insomnia 38 vs 19% (ns) Irritability 14 vs 19% (ns) Muscle tension 24 vs 19% (ns) Appetite suppression 24 vs 19% (ns) Anxiety 19 vs 10% (ns) Headaches 10 vs 10% (ns) Dizziness 10 vs 0% (ns) Lingual dyskinesia 5 vs 10% (ns)	1 withdrew before receiving treatment; No withdrawals due to AEs

Evidence Table 9. Head-to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Comments
Dextroamphetamine vs modafinil	
Taylor, 2000 U.S. (Fair)	The report provides outcomes that are the averaged data collected at baseline and at the end of each treatment phase. Data from the first phase was not made separately available.

Evidence Table 9. Head-to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, regimen, duration)	Run-in/ Washout Period
Dextroamphetamine vs methylphenidate				
Matochik, 1994 U.S. (Fair)	DB, RCT	Subjects had to be adults who met following: 1) DSM-II criteria for ADHD 2) Utah criteria for attention deficit disorder in adulthood 3) a childhood history of ADHD 4) no history of an other major psychiatric disorders.	DAMP 5 mg/day, up to 5-15 mg/day OR methylphenidate 5 mg/day, up to 5-25 mg/day. Duration: 6-15 weeks	1 month washout before starting meds

Evidence Table 9. Head-to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Dextroamphetamine vs methylphenidate			
Matochik, 1994 U.S. (Fair)	NR	PET scan, (schedule NR) "How I Feel" Questionnaire administered on PET scan days Subject's Treatment Emergent Symptom Scale (schedule NR) modified Conner's Parent Rating Scale for Spouse/Close friend to complete (schedule NR) NIMH Clinical Global Impressions scale administered at tend of study period.	mean age 35.5 y 21 males, 16 females Ethnicity NR

Evidence Table 9. Head-to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Dextroamphetamine vs methylphenidate			
Matochik, 1994 U.S. (Fair)	**Characteristic: methylphenidate vs d-amphetamine** had parents with attention-deficit disorder, residual type: 11/19 vs 12/18 had children with ADHD: 10/19 vs 10/18 WAIS IQ mean score: 108 vs 107 Wide Range Achievement Test scores Reading: 106.1 vs 102.7 Spelling: 105.6 vs 101.9 Arithmetic: 100.1 vs 97.2 Years of education: 15.4 vs 15.5 Socioeconomic status: 61.2 vs 56.6	NR/NR/37	NR/NR/ 37 analyzed: methylphenidate: n=19 DAMP: n=18

Evidence Table 9. Head-to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Results
Dextroamphetamine vs methylphenidate	
Matochik, 1994 U.S. (Fair)	**Behavioral Effects of methylphenidate vs d-amphetamine** measure; Mean score at end of drug treatment (methylphenidate); p-Value vs d-amphetamine; p-Value Conner's rating scale Self: 5.0; 0.0001 vs 4.6; 0.0001 Spouse/Other: 5.7; 0.0001 vs 8.3; 0.0001 "How I Feel" Questionnaire Feel cranky or tired: 0.5; 0.02 vs NR; NR Have trouble keeping my mind on things: 0.5; 0.0001 vs 0.6; 0.0001 Feel like something bad might happen: 0.1; 0.008 vs NR; NR Feel restless, like moving around: 0.8; 0.0002 vs NR; NR Feel things may get messed up today: 0.0; NR vs NR; NR Feel I'm not much good at things: 0.3; 0.007 vs 0.2; 0.05 Feel sad: NR;NR vs 2.2; 0.008 Feel like I don't want to play with anyone: NR; NR vs 0.1; 0.01 Feel in a good mood: NR; NR vs 2.2; 0.008 Feel like my thoughts are going fast: NR; NR vs 0.2; 0.05 Feel tired and slow: NR; NR vs 0.0; NR Subject's Treatment Emergent Symptom Scale Trouble with sitting still: 0.7; 0.0001 vs 0.7; 0.002 Feeling sleepy: 0.4; 0.007 vs 0.2; 0.05 Not being happy: 0.3; 0.02 vs NR;NR Trouble with paying attention: 0.4; 0.0001 vs 0.6; 0.0001 Colds or sniffles: NR;NR vs 0.1; 0.01 Headaches: NR;NR vs 0.2; 0.03 Tiredness: NR;NR vs 0.3; 0.03 Trouble getting or staying asleep: NR;NR vs 0.3; 0.04 Getting along with parents: NR;NR vs 04; 0.007 Crying: NR; NR vs 0.1; 0.04 Being sad: NR; NR vs 0.1; 0.04

Evidence Table 9. Head-to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals by treatment; withdrawals due to adverse events
Dextroamphetamine vs methylphenidate			
Matochik, 1994 U.S. (Fair)	NR	1 subject reported adverse events (not specified) within first 2 weeks, and was immediately switched to other drug	None

Evidence Table 9. Head-to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Comments
Dextroamphetamine vs methylphenidate	
Matochik, 1994 U.S. (Fair)	

Evidence Table 10. Quality assessment of head-to-head trials in adults with ADHD

	Internal Validity						
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Bupropion SR vs methylphenidate							
Kuperman, 2001 U.S.	Method not reported	Method not reported	Yes	Yes	Yes but method not described	Not reported	Yes
Dextroamphetamine vs guanfacine							
Taylor, 2001 U.S.	Method not reported	Method not reported	Not reported	Yes	Yes but method not described	Not reported	Yes
Dextroamphetamine vs guanfacine							
Taylor, 2000 U.S.	Method not reported	Method not reported	Not reported	Yes	Yes but method not described	Not reported	Yes

Evidence Table 10. Quality assessment of head-to-head trials in adults with ADHD

Author, Year Country	*Internal Validity* Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential / high	Intention-to-treat analysis	Post-randomization exclusions	Quality rating
Bupropion SR vs methylphenidate					
Kuperman, 2001 U.S.	Yes NR NR NR	No/ no	No: 81.1%	No	Fair
Dextroamphetamine vs guanfacine					
Taylor, 2001 U.S.	Yes NR NR NR	No/ no	Yes	No	Fair
Dextroamphetamine vs guanfacine					
Taylor, 2000 U.S.	Yes NR NR NR	No/ no	No: 95.4%	No	Fair

Evidence Table 10. Quality assessment of head-to-head trials in adults with ADHD

	External Validity	
Author, Year Country	**Number screened/ eligible/ enrolled**	**Exclusion criteria**
Bupropion SR vs methylphenidate		
Kuperman, 2001 U.S.	NR/NR/37	Patients were excluded if they had a clinically significant chronic medical condition, another current Axis 1 diagnosis, a history of tic disorders, mental retardation (IQ <80), organic brain disorders, clinically unstable psychiatric symptoms (suicidal behaviors, psychosis, violence, criminality), or substance abuse within 6 months; if taking other psychotropic medications. Any patient with a seizure history was excluded. Patients with eating disorders were excluded since they are predisposed to bupropion-induced seizures. Females of child-bearing potential were included only if using a medically approved form of contraception.
Dextroamphetamine vs guanfacine		
Taylor, 2001 U.S.	NR/NR/17	Excluded conditions already associated with frontostriatal pathology, including organic brain disorders, schizophrenia, and Tourette disorder; also excluded subjects with psychopathology possibly caused by neurologic insult. Also excluded medical conditions likely to affect mood or cognition, such as metabolic disorders, CNS conditions, mental retardation, untreated endocrine disorders, and pregnancy. Subjects using substances such as cannabis, amphetamines, cocaine, and heroin within 6 months of beginning drug trials were excluded. Subjects taking tricyclics, venlafaxine, or bupropion within 3 months, or stimulants within 2 weeks, before study were excluded.
Dextroamphetamine vs guanfacine		
Taylor, 2000 U.S.	29/22/22	Excluded narcolepsy and conditions associated with altered cognitive abilities including schizophrenia, Tourette's disorder, and diagnosable neurologic conditions; also excluded subjects with neurological soft signs that may be associated with frontal lobe cognitive deficits. Also excluded medical conditions likely to affect mood and condition, such as metabolic disorders, mental retardation, untreated endocrine disorders, and pregnancy. Also excluded the following: subjects using any cannabis, cocaine, heroin, or nonprescription amphetamines within 6 months of trial; subjects taking tricyclic antidepressants, venlafaxine, or bupropion within 3 months of trial; subjects taking prescription stimulants within 2 weeks prior to trial.

Evidence Table 10. Quality assessment of head-to-head trials in adults with ADHD

	External Validity				
Author, Year Country	**Run-in / washout**	**Class naïve patients only**	**Control group standard of care**	**Funding**	**Relevance**
Bupropion SR vs methylphenidate					
Kuperman, 2001 U.S.	Lead-in yes; Washout NR	No	Yes	Glaxo Wellcome	Yes
Dextroamphetamine vs guanfacine					
Taylor, 2001 U.S.	Run-in NR; 4-day washout between treatments	No	Yes	Not reported	Yes
Dextroamphetamine vs guanfacine					
Taylor, 2000 U.S.	Run-in NR; 4-day washout between treatments	No	Yes	Not reported	Yes

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, regimen, duration)	Run-in/ Washout period	Allowed other medications/ interventions
Amphetamine mixture					
Spencer, 2001 U.S. (Fair)	DB RCT crossover design	Outpatient adults with ADHD aged 19-60, satisfying full diagnostic criteria for DSM-IV ADHD based on clinical assessment confirmed by structured diagnostic interview. ADHD diagnoses, with onset in childhood by age 7, chronic course until time of assessment, and associated with significant distress and disability.	Each medication was prescribed bid, taken at 7:30 AM and 2:30 PM. Amphetamine mixture (Adderall) was titrated up to 20 mg/day by week 1, 40 mg/day by week 2, and 60 mg/day by week 3. Mean dose at end of week 3 was 53.7 mg/day at end of week 3 (1st drug phase) Placebo mean dose 59.3 mg/day at end of week 3 Randomized crossover design with 1 week washout between treatment phases; Total trial duration 7 weeks	Run-in NR; 1-week blinded placebo washout between phases	Not reported (NR)
Atomoxetine					
Adler 2008 U.S. Atomoxetine	DB, RCT	Ages 18-50 years old who met DSM-IV criteria for current ADHD and a historical childhood diagnosis of ADHD; have a severity of at least 4 (moderate) on the Clinician Global Impressions Severity Scale; employed 20/per week for 6 months prior to study.	Atomoxetine vs placebo Atomoxetine or placebo titrated from 40 mg to 80 mg per day. Dose flexible from 40 mg to 100 mg / day based on tolerability. Treatment phase = 6 months open-label extension phase = up to 4 months	No psychotropic medications for $\geq$ 1 week prior to randomization. Washout period up to 28 days.	NR
Barkley 2007 United States	DB, RCT Within group crossover	Ages 21-65, composite IQ > 80, corrected or uncorrected visual acuity o no worse than 20/30, valid driver's license, no evidence of deafness, blindness, severe language delay, cerebral palsy, epilepsy, autism, or psychosis. DSM-IV ADHD diagnosis. DSM criteria met for both current functioning and using retrospective reports of childhood behavior between ages 5-7.	Placebo for 4 weeks w/ sham upward titration after 1 week Atomoxetine 0.6 mg/kg for 1 week and upward titration to 1.2 mg/kg daily for 3 weeks.	Not reported	NR

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics
Amphetamine mixture			
Spencer, 2001 U.S. (Fair)	HAM-D, HAM-A, BDI before and after each arm of the study. CGI and ADHD rating scale administered weekly. Neuropsychological test battery was administered 3 times, at baseline and after each study arm, and included an auditory version of the CPT, the Stroop test, and the Rey-Osterrieth Complex Figure. Improvement was defined as either a 30% reduction in the ADHD rating scale or "much" or "very much improved" on the CGI scale.	56% male Mean age 38.8 96% white	93% had at least 1 lifetime comorbid psychiatric disorder 67% had 1 or more first- or second-degree relatives with ADHD
Atomoxetine			
Adler 2008 U.S. Atomoxetine	Primary functional outcome: Endicott Work productivity Scale (EWPS) (25-item, self report questionnaire that assesses work attendance, lost hours, presenteeism --feelings, behaviors) Use of a 5-point scale for frequency of occurrence (0=never, 4=always) Higher scores=higher impairment Secondary functional outcome: ADHD Quality of Life Measure (29 questions evaluated by 5-point Likert-type scale for frequency of occurrence). Four sub-scores are derived: productivity, life outlook, relationships, psychological health. Lower scores=greater impairment in functioning Driving Behavior Survey (26 item questionnaire) Likert-type scale 1=not at all, 4=very often. Low scores indicate more problematic driving behaviors Illness severity measures: Conners Adult Attention Deficit/Hyperactivity Disorder Rating Scale (CAARS) ADHD Inattention and Hyperactivity-Impulsivity sub-scales (higher scores=greater distress/ impairment) Adult Self-Report Scale (ASRS) used for efficacy. (higher scores=greater severity of symptoms) Timing: Following randomization, patients were seen monthly for two visits then bimonthly for two visits (6 month follow-up)	Mean age 36.5 59.7% male 81.8% Caucasian 8.6% Hispanic 6.2% African American 1.25% Asian 2.2% Other	ADHD subtype Inattentive subtype: 31% Hyperactive-impulsive subtype: .35% Combined subtype: 68% Prior stimulant treatment: 23.3% History of depression: 14.9% Substance abuse disorder: 7.3% Anxiety disorder: 1.9%
Barkley 2007 United States	Driving evaluations at baseline, placebo and atomoxetine completed by subjects ADHD Rating Scale Safe Driving Behavior Survey Driving Anger Scale (DAS) Driving simulator (12 minutes) -- also completed by examiner Simulator driving behavior scale and global simulator performance evaluation -- also completed by examiner Driving evaluations at baseline, placebo and atomoxetine completed by significant other ADHD Rating Scale Safe Driving Behavior Survey	Mean age 36.1 44% male ethnicity: 94% white 6% African American	ADHD subtypes: combined type: 72% inattentive type: 28% Mean education in years: 15.2 IQ (Shipley): 110.8

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Number screened/ eligible/ enrolled N per drug	Number withdrawn/ lost to fu/ analyzed: N per drug
Amphetamine mixture		
Spencer, 2001 U.S. (Fair)	103/41/30 Same subjects exposed to both treatments; N per drug in first treatment phase not reported.	3 (10%) withdrawals; 0% lost to fu; 27 (90%) analyzed. N per drug not reported
Atomoxetine		
Adler 2008 U.S. Atomoxetine	NR/NR/410 Atomoxetine n=271 Placebo n=139	Atomoxetine: 167 (62%) withdrawn; 48 (18%) lost to fu Placebo: 71 (51%) withdrawn; 16 (12%) lost to fu Number analyzed per drug: atomoxetine n=NR placebo n=NR
Barkley 2007 United States	32/22/20	4/ 0 Analyzed: rating scale: 18 subjects simulator data: 16 subjects

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Results	Method of adverse effects assessment
Amphetamine mixture		
Spencer, 2001 U.S. (Fair)	Mean change in ADHD rating scale during first treatment phase (Weeks 1-3), Adderall vs placebo: -12 vs +1 (p<0.001) Mean change in score, data combined from 1st and 2nd drug phases, Adderall vs placebo: Stroop Test: Word T-score +5.6 vs +4.0 ; Color T-score +5.0 vs +2.6; Color-Word T-score +1.4 vs +0.7; Interference T-score +1.2 vs +1.0 Rey-Osterrieth Complex Figure: copy organization -0.8 vs +0.1; copy accuracy +0.4 vs -0.1; delay organization +1.1 vs +1.5; delay accuracy +8.8 vs +9.5 CPT: number of hits +9 vs +7.8, number of omissions -7.9 vs -6.2; number late -1.39 vs -1.74 % of patients who improved, i.e., >30% reduction on ADHD rating scale: 70.4% vs 7.4% % of patients who were "much" or "very much" improved on CGI scale: 66.7% vs 3.7% Decrease in ADHD symptoms: tomoxetine: (11/21 subjects)-- week 2: p< 0.01; week 3: p<0.001 (3 week study) placebo: (2/10 subjects). Results from scales and tests at end of study reported as: paired tests of tomoxetine scores vs placebo scores; p-v	Elicited by investigator; HAM-D, HAM-A, BDI
Atomoxetine		
Adler 2008 U.S. Atomoxetine	Atomoxetine vs. placebo EWPS (Work productivity) Mean reduction in impairment 16.2 points (atomoxetine) vs. 15.6 points (placebo) (NS) Quality of Life: mean change productivity 17.3 (Atomoxetine); 14.7 (placebo) (NS) relationships 12.2 (Atomoxetine); 11.8 (placebo) (NS) life outlook 10.4 (Atomoxetine); 6.8 (placebo) (P=.025) psych health 12.9 (Atomoxetine); 9.8 (placebo) (NS) DBS (Driving behavior) Self report total score NR observer ratings subsample: mean improvement (Atomoxetine) 6.1; (placebo) 2.0 (P=.011) ADHD Efficacy measures CAARS-S:SV (mean change -- baseline to endpoint (Atomoxetine) -11.5; (placebo) -9.9 (P=.027) Other efficacy measures (NS)	Patients were queried regarding any possible AEs.
Barkley 2007 United States	ADHD rating scale (placebo vs. atomoxetine) self -- symptoms: P=.011; Cohen's d: 0.94 self -- impairment: P=.005; Cohen's d: 0.94 other -- symptoms: NS other -- impairment: NS Side effects number (placebo vs. atomoxetine): P<.001; Cohen's d 1.62 Driving rating scales (difference from baseline): Driving Anger Scale -- self: NS Safe Driving Behavior -- self: P=.029; Cohen's d 0.72 Safe Driving Behavior -- other: NS Simulator ratings (placebo vs. atomoxetine): Driving behavior -- self: . P=.042 Cohen's d 0.39 Driving behavior / driving performance -- other: NS Simulator Scores (NS)	NR

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Adverse Effects Reported	By treatment, total withdrawals; withdrawals due to adverse events
Amphetamine mixture		
Spencer, 2001 U.S. (Fair)	Adderall vs placebo: Insomnia 37 vs 14.8% (ns) Loss of appetite 29.6 vs 11.1% (p=0.03) Anxiety 25.9 vs 14.8% (ns) Headache 11.1 vs 7.41% (ns) Agitation 22.2 vs 7.4% (p=0.05)	Adderall vs placebo: Total withdrawals: 0 vs 3 (10%) Withdrawals due to AEs not reported
Atomoxetine		
Adler 2008 U.S. Atomoxetine	Atomoxetine vs placebo Nausea 28.4%; 5.8% (P<.001) Other adverse events that occurred in ≥ 5% sample and were statistically sig. Dry mouth, fatigue or insomnia, decreased appetite, constipation, erectile dysfunction, and urinary hesitation (individual rates were not reported)	Atomoxetine: 167 (62%); Placebo: 71 (51%) withdrawals due to AE 14% atomoxetine vs. 2.2% placebo (P< .001)
Barkley 2007 United States	drug effects number: Difference from baseline Atomoxetine 2.5 vs. .1 placebo individual adverse effects not reported	2 atomoxetine/ 2 placebo 0 withdrawals due to AE

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Comments
Amphetamine mixture	
Spencer, 2001 U.S. (Fair)	The mean ADHD rating scale score did not fully return to baseline after 1st phase of Adderall and 1-week washout, but the order effect was not significant.
Atomoxetine	
Adler 2008 U.S. Atomoxetine	Week 9: Participants not responding to treatment (no change or worsening of Sx) using the CAARS-S:SV total score were discontinued from the study.
Barkley 2007 United States	

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, regimen, duration)	Run-in/ Washout period	Allowed other medications/ interventions
Kay 2009 United States (see note in comments section)	RCT, DB, Crossover	Age 19-25 with the following criteria satisfied. DSM-IV diagnosis of ADHD Score of ≥ 24 (severity worse to moderate range) on ADHD-RS rating scale Normal intellectual functioning (score ≥ 89 on Wechsler abbreviated Scale of Intelligence) Demonstrated no greater than average performance on at least two standardized measures of executive function (Stroop Color and Word Test; Halstead-Reitan Category Test)	Atomoxetine: titrated up to 80 mg/day x 3 weeks Placebo titrated up to 80 mg/ day x 3 weeks	Washout period for other drugs was 7-28 days. No washout between crossover.	NS
Michelson, 2003/Reimherr 2005/Faraone 2005/Spencer 2006 31 outpatient sites in North America, country not otherwise specified (Fair)	2 identical, concurrent DB parallel group RCTs multi-site	Adults who met DSM-IV criteria for ADHD as assessed by clinical interview and confirmed by the Conners' Adult ADHD Diagnostic Interview were recruited from clinics and by advertisement. Patients were required to have at least moderate symptom severity, and the diagnosis had to be corroborated by a second reporter for either current symptoms (by a significant other) or childhood symptoms (by a parent or older sibling).	Atomoxetine mean dose 94.4 mg/day; administered in evenly divided doses in the morning and late afternoon/early evening, beginning at 60 mg/day. Patients with residual symptoms had dose increased to 90 mg/day after 2 weeks, and to 120 mg/day after 4 weeks. Placebo Duration 10-week	1-week washout, followed by 2-week placebo lead-in phase	NR

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics
Kay 2009 United States (see note in comments section)	Primary outcome measure: Driving Safety Score consisting of 8 variables (traffic tickets, total collisions, time to collision, driving out-of-lane incidents, percentage of time above excessive speed threshold, number of times over cornering, number of times tailgating). The eighth variable is the rating of the driver's response to crash-likely events. DSS test scores were standardized using population based z-scores. Subjects were tested at 2,7,and 12 hours after dose on test day (3 weeks after the start of drug treatment). The mean z-score for the three tests is reported for visits 3 and 4. Lower score=better driving Subjects returned 3 weeks later and were tested again (visit 4) this time either placebo or Mixed amphetamine salts extended release (50 mg). Secondary Efficacy Assessments: Above mentioned measures ADHD symptom severity assessed by ADHD-RS and CGI scale (clinician's assessment of baseline condition severity and change in improvement)	Mean age: 22.4 Male: 87.5% Caucasian: 56.3% African American: 18.8% Hispanic: 12.5% Asian 12.5%	Mean Weight (lbs): 178.3 Mean Height (inches): 70.3
Michelson, 2003/Reimherr 2005/Faraone 2005/Spencer 2006 31 outpatient sites in North America, country not otherwise specified (Fair)	Self-rated version of CAARS and WRAADDS at baseline and endpoint; HAM-A and HAM-D; social and occupational functioning were assessed using the self-rated Sheehan Disability scale Primary outcome: sum of the Inattention and Hyperactivity/Impulsivity subscales of the investigator-rated CAARS	Mean age 40.2 63.6% male Ethnicity NR Mean age 42.1 66.4% male Ethnicity NR	Study I / Study II, ADHD subtype: Combined 71.8% / 60.5% Inattention 27.5% / 35.1% Hyperactive/Impulsive 0.7% / 4.3%

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Number screened/ eligible/ enrolled N per drug	Number withdrawn/ lost to fu/ analyzed: N per drug
Kay 2009 United States (see note in comments section)	NR/NR/16 8 atomoxetine 8 placebo	2/0/8 each drug
Michelson, 2003/Reimherr 2005/Faraone 2005/Spencer 2006 31 outpatient sites in North America, country not otherwise specified (Fair)	448/329/280 Atomoxetine n=141 Placebo n=139 388/325/256 Atomoxetine n=129 Placebo n=127	71 (25%) withdrew; 22 (7.8%) lost to fu; 267 (95%) analyzed (atomoxetine n=133, placebo n=134) 79 (30.9%) withdrew; 12 (4.7%) lost to fu; 248 (96.9%) analyzed (atomoxetine m=124, placebo n=124)

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Results	Method of adverse effects assessment
Kay 2009 United States (see note in comments section)	**Mean Driving Scores (driving safety score = z score)** 2 hr. test: Pla 0.021; Atomoxetine -0.024 P=NS 7 hr. test: Pla 0.066; Atomoxetine -0.075 P=NS 12 hr. test: Pla 0.037; Atomoxetine -0.032 P=NS Mean total score: pla 0.018; Atomoxetine -0.021 P=NS ADHD-RS and CGI-I scores: ADHD-RS score: Improved from baseline: pla 25%; Atomoxetine 40% (P=NS) CGI-I: subjects rated as very much/ much improved: pla 6.3%; Atomoxetine 13.3% (P=NS)	At each study visit and during a follow-up phone interview 30 days after study completion, "subjects could volunteer information" about AEs.
Michelson, 2003/Reimherr 2005/Faraone 2005/Spencer 2006 31 outpatient sites in North America, country not otherwise specified (Fair)	***Mean change in score, atomoxetine vs placebo, Study I // Study II:*** CAARS-INV total ADHD symptom score -9.5 vs -6.0 (p=0.005) // -10.5 vs -6.7 (p=0.002) CAARS-INV Inattentive -5.0 vs -3.1 (p=0.010) // -5.8 vs -3.5 (p=0.001) CAARS-INV Hyperactive/Impulsive -4.5 vs -2.9 (p=0.017) // -4.7 vs -3.2 (p=0.013) CAARS-Self total ADHD Symptom score -16.0 vs -9.3 (p=0.002) // -17.3 vs -11.6 (p=0.008) CAARS-Self inattentive -15.9 vs -8.6 (p<0.001) // -12.5 vs -8.8 (p=0.025) CGI-ADHD-S -0.8 vs -0.4 (p=0.010) // -0.9 vs -0.5 (p=0.002) WRAADDS -5.3 vs -2.9 (p=0.002) // -4.5 vs -2.8 (p=0.041) HAM-D-17 -0.3 vs -0.6 (ns) // +0.2 vs -1.0 (p=0.013) HAM-A -1.0 vs -1.2 (ns) // -0.7 vs -1.0 (ns) Sheehan Disability total -4.5 vs -2.9 (p=0.022) // -4.4 vs -4.0 (ns) Sheehan Disability work life -1.6 vs -1.0 (p=0.007) // -1.8 vs -1.2 (ns) Sheehan Disability family life -1.5 vs -1.0 (ns) // -1.4 vs -1.6 (ns) Sheehan Disability social life -1.3 vs -0.9 (ns) // -1.2 vs -1.2 (ns) ***Spencer 2006 subanalyses of effects of comorbidities*** Predictor of outcome specific to atomoxetine on CAARS subscales: t test/df/p-value Investigator-rating Index Subscale: Depression NOS: 1.6/494/.121 MDD: -2.2/500/.028 Investigator-rating Hyperactivity subscale: Depression NOS: 3.9/494/.051 MDD: -2.1/500/.033 PTSD: -2.3/505/.020 Self-rating Hyperactivity Subscale PTSD: 3.3/424/.069 Depression NOS: 2.0/415/.049 Investigator-rating Inattention subscale Depression NOS: -2.1/495/0.35 PTSD: -2.2/505/.031 Investigator-rating Total Score Depression NOS: 2.2/495/.028 MDD: -2.0/500/.046 PTSD: -2.4/505/.016 Self-rating Total Score PTSD: 1.8/422/.069 Depression NOS: 2.0/413/.045	Elicited by investigator

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Adverse Effects Reported	By treatment, total withdrawals; withdrawals due to adverse events
Kay 2009 United States (see note in comments section)	Total AE reported: Atomoxetine (68%); pla (56.3%) gastrointestinal: 43.8; 12.5% abdominal pain: 18.8%; 0 dry mouth: 12.5; 6.3% nausea: 18.8%; 6.3% general: 18.8; 12.5% weight decrease: 6.3%; 0 metabolism/ nutrition: 18.8%; 0 anorexia: 12.5%; 0 nervous system: 25; 12.5% headache:12.5; 12.5% somnolence: 12.5%; 0 Psychiatric: 12.5%; 0 Anger: 0; 6.3% Anxiety: 6.3%; 0 Insomnia: 0; 6.3% Irritability: 0; 6.3%	Atomoxetine 1; Pla 0 Withdrawals due to AE 1 (atomoxetine); 0 (placebo).
Michelson, 2003/Reimherr 2005/Faraone 2005/Spencer 2006 31 outpatient sites in North America, country not otherwise specified (Fair)	Atomoxetine vs placebo Dry mouth 21.2 vs 6.8% (p<0.001) Insomnia 20.8 vs 8.7% (p<0.001) Nausea 12.3 vs 4.9% (p=0.003) Decreased appetite 11.5 vs 3.4% (p<0.001) Constipation 10.8 vs 3.8% (p=0.002) Libido decreased 7.1 vs 1.9% (p=0.006) Dizziness 6.3 vs 1.9% (p=0.015) Difficulty attaining or maintaining erection (among males) 9.8 vs 1.2% (p<0.001) Sweating 5.2 vs 0.8% (p=0.004)	Atomoxetine vs placebo: Total withdrawals: 73 (27%) vs 55 (20.7%), (ns) Withdrawals due to AEs: 23 (8.5%) vs 9 (3.4%), (p=0.03)

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Comments
Kay 2009 United States (see note in comments section)	This study included two separate placebo controlled studies within a crossover study. Cohort 1: MAS XR vs. placebo Cohort 2: Atomoxetine vs. placebo
Michelson, 2003/Reimherr 2005/Faraone 2005/Spencer 2006 31 outpatient sites in North America, country not otherwise specified (Fair)	

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, regimen, duration)	Run-in/ Washout period	Allowed other medications/ interventions
Spencer, 1998 U.S. (Fair)	DB, crossover design, parallel groups	Adults whom met full DSM-III criteria for ADHD by the age of 7 yrs, , with current, chronic symptoms, and endorsed impairment with the disorder.	Tomoxetine vs placebo. Patients randomized to Tomoxetine 40 mg/day in week 1, and 80 mg/day in weeks 2 and 3; or placebo.	Run-in NR/ 1 week of washout between the two 3 week periods.	NR
Wernicke, 2004 U.S. (Fair)	DB RCT parallel design with treatment and discontinuation phases	Adults who met DSM-IV criteria for ADHD as assessed by clinical interview and confirmed by the Conners' Adult ADHD Diagnostic Interview (CAAR-D) were randomized to acute treatment (approx. 10 weeks) with atomoxetine or placebo in 2 identical double-blind studies.	Atomoxetine vs placebo. For patients randomized to atomoxetine, dose was initiated at 60 mg/day (30 mg bid), titrated based on clinical response to a maximum of 120 mg/day (60 mg bid). After approximately 10 weeks, a 4-week double-blind discontinuation phase. Atomoxetine patients were randomized to either abrupt or tapered discontinuation, in which dose was reduced weekly.	NR/NR	NR
Bupropion					
Wilens, 2001 U.S. (Fair)	DB RCT parallel groups	Subjects were outpatient adults with ADHD aged 20-59, recruited from advertisements and clinical referrals to a psychopharmacology clinic. To obtain a full diagnosis of adult ADHD, the subject had to have 1) fully met the DSM-IV criteria for ADHD by age 7 as well as currently (within the past month); 2) described a chronic course of ADHD symptoms from childhood to adulthood, and 3) endorsed a moderate or severe level of impairment attributed to those symptoms.	Bupropion SR 200-400 mg/day, taken upon awakening and 6 hours later. Dose was titrated over 4 weeks, beginning at 100 mg bid, and increased by 100 mg weekly up to 200 mg bid in week 4. Bupropion mean dose at week 6: 362 mg/day. Weekly supplies of bupropion and placebo were dispensed in 100-mg capsules. Placebo mean dose at week 6: 379 mg/day Duration 6 weeks	NR/NR	NR

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics
Spencer, 1998 U.S. (Fair)	Improvement was defined as a reduction in ADHD Rating scale score of 30% or more. Following tests after each arm: ADHD Rating Scale (6) (weekly) Hamilton Depression Rating Scale Beck Depression Inventory Hamilton Anxiety Rating Scale Continuous Performance Test Stroop Tests Wisconsin Card Sorting Test Rey-Osterrieth Complex Figure	n=21 Adults aged 19-60 yrs, 11 women, 10 men, ethnicity NR.	1 lifetime comorbid psychiatric disorder (n=13) current ratings of severe depression or anxiety (n=2) family history of ADHD (n=20) average to above-average intelligence (n=21).
Wernicke, 2004 U.S. (Fair)	Visits at weekly intervals assessed CAARS, HAM-D, HAM-A	NR NR NR	Not reported
Bupropion			
Wilens, 2001 U.S. (Fair)	CGI Severity and Improvement scales, and the ADHD Rating Scale were administered at baseline and weekly visits. HAM-D, BDI, and HAM-A were administered at baseline and end of study. Categorical improvement was defined as a reduction in ADHD Rating Scale score of 30% or better.	Mean age 38.3 55% male Ethnicity NR	Inattentive subtype 58% Combined subtype 35% Hyperactive or impulsive subtypes 8% Major depression: past 59%, current 19% Two or more anxiety disorders: past 19%, current 8% Substance abuse/dependence: past 35%, current 0% Smoking: past 33%, current 10% Alcohol abuse/dependence: past 33%, current 10% Antisocial personality disorder: past 16%, current 0%

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Number screened/ eligible/ enrolled N per drug	Number withdrawn/ lost to fu/ analyzed: N per drug
Spencer, 1998 U.S. (Fair)	screened NR 22 enrolled Tomoxetine: n=11 Placebo: n=10	1 withdrawn/ 0 lost to fu 21 analyzed Tomoxetine: n=11 Placebo: n=10
Wernicke, 2004 U.S. (Fair)	NR/NR/380 Atomoxetine with abrupt discontinuation n=90; Atomoxetine with tapered discontinuation n=94; Placebo n=196	2 (0.5%) withdrawn; lost to fu NR; 377 (99.2%) analyzed (atomoxetine-abrupt discontinuation n=89, atomoxetine-tapered discontinuation n=93, placebo n=195)
Bupropion		
Wilens, 2001 U.S. (Fair)	154/NR/40 Bupropion n=21 Placebo n=19	2 (5%) withdrawn; 0% lost to fu; 40 (100%) analyzed: Bupropion n=21, Placebo n=19

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Results	Method of adverse effects assessment
Spencer, 1998 U.S. (Fair)	Decrease in ADHD symptoms: tomoxetine: (11/21 subjects)-- week 2: p< 0.01; week 3: p<0.001 (3 week study) placebo: (2/10 subjects). **Results from scales and tests at end of study** reported as: paired tests of tomoxetine scores vs placebo scores; p-value McNemar test: (x= 7.4, df=1; p<0.01) Stroop Color Word test: (z=2.6, n=21, p<0.05) Interference T test scores: (z=2, n=21, p<0.05) ADHD rating scale: p-value= ns Parallel-groups comparison during the first 3 weeks of protocol (z= 3.2, n=21, p<0.01)	self-report from patients
Wernicke, 2004 U.S. (Fair)	Change in symptom severity from pretreatment phase to end of treatment phase :: from end of treatment phase to end of discontinuation phase, in atomoxetine abrupt discontinuation vs tapered discontinuation vs placebo: CAARS total score -11.2::5.1 vs -11.4::3.6 vs -7.0::2.7 (ns) HAM-A -0.5::-0.5 vs -1.8::0.2 vs -1.5::0.0 (ns) HAM-D 0.4::-0.5 vs -1.1::0.0 vs -0.9::0.4 (ns) During the discontinuation phase, changes in ADHD symptom ratings did not differ significantly between treatment groups. Depressive or anxiety symptoms did not significantly increase following drug discontinuation, compared with placebo.	Elicited by investigators, via open-ended questioning, and the Association for Methodology and Documentation in Psychiatry-5: Somatic Signs
Bupropion		
Wilens, 2001 U.S. (Fair)	Bupropion vs placebo: CGI improvement rating of 1 (much improved) or 2 (very much improved): 52 vs 11%, p=0.007 Improved by 30% or more reduction in DSM-IV ADHD symptom checklist score: 76 vs 37% (p=0.02) Mean change from baseline to 6 weeks in ADHD symptom checklist score: -42% vs -24% (p=0.05) Proportion of the 18 DSM-IV ADHD-specific symptoms that improved: 100 vs 44% (p<0.001) Depression and anxiety (HAM-D, BDI, HAM-A): no difference between groups	Elicited by investigator at each visit

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Adverse Effects Reported	By treatment, total withdrawals; withdrawals due to adverse events
Spencer, 1998 U.S. (Fair)	no serious adverse events observed, 1 subject withdrawn after becoming ery anxious on tomoxetine.	tomoxetine: 1/21 (due to increased anxiety in patient) placebo: 0 withdrawals;
Wernicke, 2004 U.S. (Fair)	% in atomoxetine-abrupt vs atomoxetine-tapered vs placebo: Headache 4.4 vs 10.6 vs 4.1% (ns) Pain in limb 3.3 vs 1.1 vs 0% (p=0.019) Diarrhea 2.2 vs 5.3 vs 2.6% (ns) Sinusitis 2.2 vs 4.3 vs 0.5 (ns) Insomnia 1.1 vs 5.3 vs 3.1 (ns) Irritability 0 vs 4.3 vs 0% (p=0.007) Dyspepsia 0 vs 4.3 vs 0.5% (ns) Allergic reactions: 1.1 vs 6.5 vs 1.5% (p=0.036)	Atomoxetine-abrupt vs atomoxetine-taper vs placebo: Total withdrawals: 0 vs 1 (1%) vs 1 (0.5%) Withdrawals due to AEs: 1 (1%) in atomoxetine-taper discontinuation phase, due to headache
Bupropion		
Wilens, 2001 U.S. (Fair)	Bupropion vs placebo: Headache 19 vs 16% (ns) Aches or pains 10 vs 5% (ns) Dry mouth 10 vs 0% (ns) Chest pain 10 vs 0% (ns)	Bupropion vs placebo, Total withdrawals: 2 (9.52%, noncompliance) vs 0% Due to AEs: 0 vs 0

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Comments
Spencer, 1998 U.S. (Fair)	3 week study period.
Wernicke, 2004 U.S. (Fair)	Depressive or anxiety symptoms did not significantly increase following drug discontinuation.
Bupropion	
Wilens, 2001 U.S. (Fair)	

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, regimen, duration)	Run-in/ Washout period	Allowed other medications/ interventions
Dexamphetamine					
Paterson, 1999 Australia (Fair)	DB RCT parallel groups	Patients were eligible if they reported the presence of at least 4 inattentive and/or 5 hyperactive symptoms during the previous 6 months. Screening for illicit substance use among eligible patients was conducted by urinalysis.	Dexamphetamine mean dose 4.77 tablets per day (23.85 mg/day); Placebo. Dose was titrated gradually throughout the study. Week 1: 1 tablet in AM, Week 2: 1 tablet in AM and 1 tablet at noon, Week 3: 1 tablet in AM and 2 tablets at noon, Weeks 4-6: up to 6 tablets per day, but increased by no more than 1 tablet per day, with 2 days between increases. Duration 6 weeks	NR/NR	NR
Dextroamphetamine					
Weiss 2006	DB RCT	Outpatients age 18 to 66 years diagnosed ADHD via DSM IV	Placebo , Paroxetine (Par), Dextroamphetamine (Dex) and Par + ex, titrated for 4 weeks up to Par 40 mg/day and Dex 40 mg day Duration 20 weeks	1 week washout	No but all received psychotherapy
Lisdexamfetamine					
Adler 2008 U.S. Lisdexamfetamine	DB RCT	Outpatients age 18 to 55 years with a primary diagnosis of ADHD via DSM IV. All subjects were required to meet at least 6 of the 9 DSM-IV-TR subtype criteria and to have moderate to severe ADHD as rated by a clinician at baseline (score of $\geq$28). Other inclusion criteria included 12-lead electrocardiogram with QT/QTc-F interval < 450 ms for men and < 470 ms for women, resting heart rate 40 to 100 bpm, PR interval < 200 ms, and QRS interval < 110 ms.	Lisdexamfetamine: 30 mg/day; 50 mg/day (forced dose escalation 30 mg/day week 1, 50 mg/day weeks 2-4); 70 mg/day (forced dose escalation 30 mg/day week 1, 50 mg/day week 2; 70 mg/day weeks 3 and 4), or placebo. Duration: 4 weeks	7 to 28 days	NR
Methylphenidate IR					
Barkley 2005 United States	DB RCT crossover	Not clear	Methylphenidate 10 mg, single dose (low dose) Methylphenidate 20 mg, single dose (high dose) Placebo Subjects were crossed over to each dose one time (i.e., all subjects took one dose of each of the three interventions), 75 minutes before testing began	NR/ at least a 24 hr washout period for stimulant medication before testing	allowed all other medications but stimulants

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics
Dexamphetamine			
Paterson, 1999 Australia (Fair)	DSM-IV ADHD criterion list with modified thresholds (see comments) were administered at baseline, 3 weeks, and 6 weeks. Patients' relatives were also asked to fill out these questionnaires for comparison. Patients completed the BSI, a 53-item self-report symptom inventory, at baseline and weeks 3 and 6. Three CGI subscales were used at baseline and week 6: Severity at baseline, Improvement at 6 weeks, and an Efficacy Index was calculated by using a ratio of benefits against side effects. Patient satisfaction was measured at the end of the trial on a 5-point Likert Scale.	Mean age 35.5 60% male Ethnicity NR	51% were inattentive type 46.7% were combined inattentive and hyperactive types 2% were hyperactive type
Dextroamphetamine			
Weiss 2006	ADHD-RS Investigator version CGI-I	Mean age 37.5 64% male Ethnicity 85% white	53% lifetime mood or anxiety disorder
Lisdexamfetamine			
Adler 2008 U.S. Lisdexamfetamine	Primary Efficacy Measure ADHD-RS total score with adult prompts. (0= no symptoms, 3=severe symptoms) Secondary Efficacy Measure Change in ADHD-Rs total score at endpoint and at each study week. Clinical Global Impression scale (CGI-S and CGI-I)	mean age: 35.1 male: 54% White: 82.5%	ADHD-RS mean total score at baseline: 40.5 CGI-S score at baseline, percentage in each group Moderate: 35% Marked: 50.75% Severe: 14% Extreme: 0.25%
Methylphenidate IR			
Barkley 2005 United States	These results were measured at baseline, and at the end of each of the three drug conditions (i.e., on the same day as the testing occurred): *Conners continuous performance test (measuring number of omissions and reaction time for inattentiveness and false hits and reaction time for impulsiveness) *FAAC virtual reality driving simulator: each time a series of 5 tests were given (daytime course #1, nighttime course #1, daytime course #2, nighttime course #2, and an obstacle course). Courses #1 and #2 took approximately 12 minutes to complete. *Examiner rating of simulator driving performance *Patient self-rating of simulator driving performance	Mean age: 31.3 years (SD: 11.3) 74% male White: 83.3% African American: 3.7% Hispanic: 5.6% Native American: 5.6% Other: 1.9%	Combined subtype: 87% Predominantly Inattentive subtype: 11% Predominantly Hyperactive-Impulsive subtype: 0% ADHD not otherwise specified: 2% Never married: 67% Mean IQ: 104.7 (SD=9.7) Average number of years of driving experience: 14.5 years (SD: 11.1) Mean number of miles driven/week: 252 miles (SD: 203)

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Number screened/ eligible/ enrolled N per drug	Number withdrawn/ lost to fu/ analyzed: N per drug
Dexamphetamine		
Paterson, 1999 Australia (Fair)	68/51/45 24 dexamphetamine 21 placebo	1 (2.2%) withdrawn 0% lost to followup 45 (100%) analyzed: Dexamphetamine n=24, Placebo n=21
Dextroamphetamine		
Weiss 2006	144/129/98 Placebo 26 Par 24 Dex 23 Par + Dex 25	34/NR/98 Placebo 26 Par 24 Dex 23 Par + Dex 25
Lisdexamfetamine		
Adler 2008 U.S. Lisdexamfetamine	NR/NR/420 lisdexamfetamine 30 mg: 119 lisdexamfetamine 50 mg: 117 lisdexamfetamine 70 mg: 122 placebo: 62	71/2/414 lisdexamfetamine 30 mg: 115 lisdexamfetamine 50 mg: 117 lisdexamfetamine 70 mg: 120 placebo: 62
Methylphenidate IR		
Barkley 2005 United States	56 / 56 / 54 Same subjects exposed to all treatments	2 / 0 / 52 had complete data

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Results	Method of adverse effects assessment
Dexamphetamine		
Paterson, 1999 Australia (Fair)	Mean change in score from 0 to 6 weeks, p-values signifying change from baseline, dexamphetamine vs placebo: ADHD score, Hyperactive -2.0 (p=0.004) vs -1.0; Inattentive -3.83 vs -1.57 (ns); Total -5.83 (p<0.0001) vs -3.57 (p=0.042) BSI mean T-score, Anxiety -8.2 (p<0.001) vs -5.43 (p<0.001); Depression -3.59 (ns) vs -2.76 (ns); Global Severity Index -5.5 (ns) vs -6.19 (ns) Efficacy Index at week 6: 95% of placebo had equal levels of benefits and side-effects; 75% of dexamphetamine had greater benefits than side-effects (p<0.001)	Weight loss and evaluation of blood pressure were assessed at weeks 3 and 6. Urinalysis was conducted at baseline and weeks 6 to ensure compliance and exclude drug abuse. Patients kept a diary of side effects.
Dextroamphetamine		
Weiss 2006	Response CGI-I Much or very much improved Placebo 28% Par 65.2% Dex 63.6% Par+Dex 56% Response CGI-I-ADHD Much or very much improved Placebo 16% Par 63.6% Dex 44% Par+Dex 44% Response CGI-I for mood and anxiety disorder Much or very much improved Placebo 36% Par 69.6% Dex 45.5% Par+Dex 48%	Collected at study visits, rated as mild, moderate and severe
Lisdexamfetamine		
Adler 2008 U.S. Lisdexamfetamine	Change (LS mean) in ADHD-RS scores from baseline to endpoint: ITT population (N= 414) placebo: -8.2 (NS) lisdexamfetamine 30 mg: -16.2 (P<.0001) lisdexamfetamine 50 mg: -17.4 (P<.0001) lisdexamfetamine 70 mg: -18.6 (P<.0001) Post hoc analysis: > 30% reduction in ADHD_RS scores (% responding) -- data displayed on a graph, percentages are approximate. placebo: 35% lisdexamfetamine 30 mg: 60% lisdexamfetamine 50 mg: 68% lisdexamfetamine 70 mg: 70% CGI-I Score: % improved or very much improved: placebo: 29% lisdexamfetamine 30 mg: 57% lisdexamfetamine 50 mg: 62 % lisdexamfetamine 70 mg: 61%	Collected at study visits. Included PSQI.
Methylphenidate IR		
Barkley 2005 United States	Mean results for 1-baseline vs 2-MPH low vs 3-MPH high vs 4-placebo Standard course: Simulator self-rating: 55.7 vs 60.6 vs 61.9 vs 61.4 (p<0.001; pair-wise contrasts: 1<2,3,4) Simulator observer rating: 54.4 vs 60.1 vs 59.7 vs 59.2 (p<0.001; pair-wise contrasts: 1<2,3, 4) Number of crashes: 1.7 vs 0.9 vs 0.7 vs 0.9 (p<0.001; pair-wise contrasts: 1>2, 3, 4) Average speed and speed variability were not significantly different between groups; steering variability, course driving time, and number of turn signals given were significant between groups, but none showed a significant difference between MPH low and MPH high Only 44 of 54 patients could complete the obstacle course Conners Continuous performance test: Comission Errors: 13.3 vs 7.5 vs 7.2 vs 8.5 (p<0.001; pair-wise contrasts: 1>2, 3, 4; 4>3) Omission Errors: 4.2 vs 3.2 vs 2.0 vs 2.8 (not significantly different) Reaction time and reaction time variability did not differ significantly between the four groups	Self-rated and observer rated simulator sickness

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Adverse Effects Reported	By treatment, total withdrawals; withdrawals due to adverse events
Dexamphetamine		
Paterson, 1999 Australia (Fair)	Dexamphetamine vs placebo, number of patients: Sleep disturbance: 9 vs 1 Headache: 6 vs 3 Dry mouth: 7 vs 0 Thirst: 3 vs 0 Mean weight loss: -3.6 kg (p<0.001) vs -0.286 kg (ns)	Dexamphetamine vs placebo, Total withdrawals: 1 (4.2%) vs 0% Due to AEs: 1 (4.2%, depression) vs 0%
Dextroamphetamine		
Weiss 2006	83% of patients reported at least one AE	Total withdrawals: Placebo 5 Par 9 Dex 9 Par+Dex 10 Due to AEs: Placebo 2 Par 6 Dex 3 Par+Dex 7
Lisdexamfetamine		
Adler 2008 U.S. Lisdexamfetamine	Placebo vs Lisdexamfetamine 30mg/d vs Lisdexamfetamine 50mg/d vs Lisdexamfetamine 70mg/d Anorexia: 0 vs 4(3%) vs 8(7%) vs 6(5%) Anxiety: 0 vs 5(4%) vs 7(6%) vs 9(7%) Decreased appetite: 1(2%) vs 34(29%) vs 33(28%) vs 28(23%) Diarrhea: 0 vs 8(7%) vs 12(10%) vs 4(3%) Dry mouth: 2(3%), 25(21%) vs 29(25%) vs 38(31%) Feeling Jittery: 0 vs 2(2%) vs 4(#%) vs 9(7%) Insomnia: 3(5%) vs 23(19%) vs 20(17%) vs 26(21%) Nausea: 0 vs 10(8%) vs 7(6%) vs 8(7%)	Total withdrawals: 10 (16%) placebo 16 (13%) Lisdexamfetamine 30mg/d 21 (18%) Lisdexamfetamine 50mg/d 24 (20%) Lisdexamfetamine 70mg/d Due to AEs: 1 (2%) Placebo 4 (3%) Lisdexamfetamine 30mg/d 8 (7%) Lisdexamfetamine 50mg/d 9 (7%) Lisdexamfetamine 70mg/d
Methylphenidate IR		
Barkley 2005 United States	the only AE reported was for simulator sickness.	Crossover design, thus withdrawals by treatment not given; unclear if patients who withdrew for part of a test completed the rest of the crossovers

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Comments
Dexamphetamine	
Paterson, 1999 Australia (Fair)	The report does not state the dose of dexamphetamine, only the number of tablets. The dose of 5 mg in each tablet was inferred from other publications using Sigma's preparation of dexamphetamine in Australia.
Dextroamphetamine	
Weiss 2006	
Lisdexamfetamine	
Adler 2008 U.S. Lisdexamfetamine	
Methylphenidate IR	
Barkley 2005 United States	All subjects were paid $150 at the end of the protocol.

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, regimen, duration)	Run-in/ Washout period	Allowed other medications/ interventions
Boonstra 2004 Netherlands cognitive outcomes from Kooij 2004	DB RCT crossover	see Kooij 2004	see Kooij 2004. For the 43 patients analyzed in this paper, the mean daily dose of MPH was 70.6 mg (SD: 16.7) Mean dose mg/kg/d was 0.93 mg/kg/d (SD: 0.18)	see Kooij 2004	NR
Bouffard, 2003 Canada (Fair)	DB RCT crossover design	DSM-IV diagnosis of ADHD; 1.5 or more on at least 1 ADHD self-report questionnaire (either CAARS or AAPBS); IQ >=80 on abbreviated WAIS-R	Methylphenidate or placebo (sugar pill) 30 mg/day for 2 weeks (10 mg tid,) followed by 45 mg/day for 2 weeks (15 mg tid). Subjects were randomly assigned to start either methylphenidate or placebo.	3-day run-in of increasing dosages (15/30/45 mg/day); 5 to 7-day washout btw. active & placebo phases	NR
Carpentier 2005	DB RCT double cross-over in in-patients at open addiction trmt facility	positive diagnosis of ADHD w/ 6 criteria from DSM IV	Day 1–3 1 tablet t.i.d. 15 mg Day 4–7 2 tablets t.i.d. 30 mg Day 8–14 3 tablets t.i.d. 45 mg and two weeks placebo repeated (so 4 rounds) Duration 8 weeks	Detoxification of 3 weeks if necessary	one patient on methadone
Cox, 2000 U.S. (Fair)	DB RCT crossover design	ADHD and non-ADHD male subjects with no other current comorbidity were recruited from the local community from TV and computer bulletin board notices, as well as direct physician referrals. ADHD subjects were required to have previously taken Ritalin, but could not be taking any medication for their condition within the past 6 months. To confirm DSM-IV criteria for ADHD, participants were interviewed using Barkley's structured interview for ADHD and the DSM-III-R criteria. ADHD subjects had current and childhood symptoms, consistent with DSM-III-R criteria.	Methylphenidate 10 mg/day, single dose Placebo (vitamin C), single dose Subjects were admitted to the research center to control for diet and sleep conditions. On the following day at 8AM, subjects received either placebo or methylphenidate at 8AM. 1.5 hours after taking the medication, subjects drove for 30 minutes on a simulator. At 3:30PM, subjects received the alternative treatment (placebo or methylphenidate) than that received at 8AM. 1.5 hours after taking the medication, subjects drove for 30 minutes on a simulator using an alternative driving scenario.	NR/NR	NR

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics
Boonstra 2004 Netherlands cognitive outcomes from Kooij 2004	Conners' Continuous Performance Test (CPT) Change Task (ChT) of Logan and Burkell (computerized) Tests were given at the end of week 3 and the end of week 7 (i.e., when MPH was at its highest). Tests were given in random order, and were given 75 minutes after tablet intake.	(these are statistics for the 43 who completed the trial without protocol violations) Mean age: 38.9 years 48.8% male Ethnicity: NR	(these are statistics for the 43 who completed the trial) 95.3% had ADHD combined subtype 4.7% had ADHD hyperactive / impulsive subtype Average IQ: 100.3 (SD: 17.9) Sheehan Disability scale (min 0, max 30): 22.8 (SD: 3.3) Global Assessment of Functioning (min 0, max 100): 57.3 (SD: 6.1) Antisocial Personality Disorder: 9.3% Borderline Personality Disorder: 16.3%
Bouffard, 2003 Canada (Fair)	2 self-rating questionnaires (CAARS & AAPBS); SCL-90, BDI, HAM-A; GAF	Mean age 34 80% male Ethnicity NR	Mean IQ 101
Carpentier 2005	ADHD-RS Clinical Observation Scale Clinical Global Impression Scale Assessed at baseline and weekly	Mean age=31.9 88% male race nr	Type of substance abuse Alcohol 52.0% Drug 92%
Cox, 2000 U.S. (Fair)	The Atari Research Driving Simulator had 2 equivalent driving courses with similar driving demands. The 16-mile courses take approximately 30 minutes to complete when following posted speed limits. The simulator quantifies steering, braking, and crash variables. After completing the simulation, subjects were asked to rate their driving performance on a 5-point scale (1=poor, 5=well).	Mean age 22.0 100% male 77% white 15% black 7.7% Asian	ADHD patients vs non-ADHD controls: Mean # motor vehicle violations, 2.6 vs 1.5 (p=0.06) Mean # automobile crashes, 2.7 vs 0.8 (p=0.018)

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Number screened/ eligible/ enrolled N per drug	Number withdrawn/ lost to fu/ analyzed: N per drug
Boonstra 2004 Netherlands cognitive outcomes from Kooij 2004	NR / 108 / 45	2 / 0 / 43 43 subjects exposed to both treatments. This analysis excluded two patients who were included in the Kooij analysis.
Bouffard, 2003 Canada (Fair)	93/NR/38 Same subjects exposed to both treatments	8 (21%) withdrawn Loss to followup NR 30 (79%) analyzed, same subjects exposed to both treatments (phases were combined in analysis)
Carpentier 2005	NR/NR/25	6/3/19
Cox, 2000 U.S. (Fair)	NR/NR/13 Same subjects exposed to both treatments	0% withdrawn; 0% loss to followup; 13 (100%) analyzed, same subjects exposed to both treatments (phases were combined in analysis)

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Results	Method of adverse effects assessment
Boonstra 2004 Netherlands cognitive outcomes from Kooij 2004	Mean test results, MPH vs placebo: CPT: Mean hit reaction time: 342.6 vs 333.5, p=0.029 Standard error: 4.9 vs 6.0, p=0.11 Commission errors: 10.7 vs 13.6, p=0.002 Attentiveness: 3.4 vs 3.1, p=0.007 Risk taking: 0.7 vs 0.6, p=0.837 Change Task variables, over all 7 weeks: (univariate tests revealed significant interactions of treatment condition and treatment order for mean reaction time (p=0.001) and standard deviation of reaction times (p=0.000)) Stop signal reaction time: 202.3 vs 220.0, p=0.87 Change response mean reaction time: 457.1 vs 475.3, p=0.033 Change response standard deviation reaction time: 113.2 vs 117.0, p=0.615 data for the first point of measurement (after 3 weeks) for the variables showing the significant interactions between treatment order and treatment condition: Mean reaction time: 407.4 vs 434.1, p=0.346 Standard deviation reaction time: 78.2 vs 96.9, p=0.52	see Kooij 2004
Bouffard, 2003 Canada (Fair)	Mean change in condition from baseline, methylphenidate 30 mg/day vs methylphenidate 45 mg/day vs placebo (*p-values compare placebo with methylphenidate*): Adult behavior problems -1 vs -1 -0.7 (p<0.005) CAARS -0.8 vs -0.9 vs -0.5 (p<0.01) CPT% commission error -17.1 vs -19.4 vs -9.8 (p<0.001) CPT% omission error -3.3 vs -3.0 vs -0.5 (p<0.1) Stop-signal task vs -35.8 vs -47 vs -29.05 (ns) HAM-R -0.4 vs -0.5 vs -0.35 (p<0.05) BDI -5.5 vs -5.5 vs -4.4 (ns) SCL-90-R -9.8 vs -11 vs -7.45 (ns) Obsessive-compulsive scale -12 vs -13 vs -7.5 (p<0.05) Hostility scale -6.0 vs -6.8 vs -3.5 (ns)	Self-rated
Carpentier 2005	Mean (SD) ADHD rating scale Placebo 31.8 (12.7) MPH 27.6 (15.3) (P = 0.352) Clinical Observation scale Placebo 17.8 (8.1) MPH 14.0 (9.2) (P = 0.211) Clinical Global Impression scale Placebo 8.3 (3.9) MPH 6.5 (4.3) (P = 0.184) Responders 30% reduction in in all 3 trmt scales Placebo 5 MPH 9	NR
Cox, 2000 U.S. (Fair)	Placebo vs ritalin, mean Impaired Driving Score (score of 0 would be average, +1 would be one standard deviation worse than the mean): ADHD patients +0.5 vs +2.4 (p=0.05) Non-ADHD controls +0.6 vs -1.0 Mean self-rated driving performance, ADHD patients vs non-ADHD controls: Placebo: 3.0 vs 3.9 (p=0.05) Ritalin: 3.5 (+0.5 better than placebo) vs 3.6 (-0.3 worse than placebo), (ns)	NR

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Adverse Effects Reported	By treatment, total withdrawals; withdrawals due to adverse events
Boonstra 2004 Netherlands cognitive outcomes from Kooij 2004	see Kooij 2004	see Kooij 2004
Bouffard, 2003 Canada (Fair)	Change from baseline in % of subjects reporting condition, methylphenidate 45 mg/day vs placebo: Mild appetite loss +23 vs +5% (ns) Mild trouble sleeping -2 vs -7% (ns) Moderate trouble sleeping -13 vs -9% (ns) Mild headache -4 vs +5% (ns)	Methylphenidate vs placebo, Total withdrawals unclear by treatment group; 4 enrolled withdrew on methylphenidate "because they were not blind" to treatment. Withdrawals due to AEs (n=1, (2.6%), treatment group unclear.
Carpentier 2005	MPH showed significantly more side effects than placebo (F = 4.30, df = 1.87, P = 0.03).	Total withdrawals 6 1 withdrawal due to AEs on placebo
Cox, 2000 U.S. (Fair)	NR	Methylphenidate vs placebo, Total withdrawals: 0 vs 0 Withdrawals due to AEs: 0 vs 0

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Comments
Boonstra 2004 Netherlands cognitive outcomes from Kooij 2004	This analysis did not analyze data from 2 non-compliant patients who were included in the original paper (see Kooij 2004).
Bouffard, 2003 Canada (Fair)	Data from the first treatment phase was not reported separately. Concealment of allocation is a concern: "Not blind to methylphenidate," caused 6 pre-enrollment and 4 post-enrollment exclusions. The hospital pharmacy used a numbered list for allocation; subjects gave their number to the pharmacist when picking up prescriptions. Run-in rapidly titrated to maximum trial dose in 3 days, but withdrawals from side effects was not high (n=1).
Carpentier 2005	
Cox, 2000 U.S. (Fair)	Data from the first treatment phase was not reported separately. Author concludes that Ritalin improved ADHD driving performance to the non-ADHD level.

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, regimen, duration)	Run-in/ Washout period	Allowed other medications/ interventions
Gualtieri, 1985 U.S. (Fair)	DB RCT crossover design	Eight male subjects who met the diagnostic criteria for ADD-RT. Subjects had clinical histories consistent with ADHD during their primary school years, which were confirmed by parents and by review of medical or school records. All subjects continued to have difficulty with poor attention span and distractibility, restlessness and fidgety behavior, impulsiveness, emotional lability (especially temper outbursts), unsatisfactory level of efficiency at work, and difficult interpersonal relationships.	MPH (0.3 mg/kg) or Placebo were given on a bid schedule (8AM and 12 noon) for 5 days (Monday through Friday). On the second Monday, following a 68-hr washout period, the procedure was repeated with the alternative treatment.	Run-in NR; 68-hr washout between treatment phases	NR
Kinsbourne, 2001 U.S. (Fair)	DB RCT crossover design	Subjects were selected from consecutive adult clinic referrals based on the following: 1) history of symptoms meeting DSM-IV ADHD (at least 6 of 9 inattentive and/or hyperactive/impulsive symptoms); 2) full DSM-IV criteria for ADHD met in childhood, in retrospect; 3) have no other psychiatric disorder that would explain their symptoms of ADHD; 4) gave informed consent.	Methylphenidate 5, 10, and 20 mg/day Placebo Each dose of MPH or placebo was administered in a single dose, in a randomized sequence, in the morning on each of four days. Duration 4 days	NR/NR	NR
Kooij 2004 Netherlands	DB RCT crossover	Outpatient adults with ADHD aged 20 to 56 years, with current ADHD (at least 5 of 9 symptoms of inattention and/or hyperactivity /impulsivity) and childhood onset with at least 6 of 9 symptoms in one or both symptom domains.	Methylphenidate and placebo. MPH was started at 0.5 mg/kg/day by week 1, increased to 0.75 mg/kg/d by week 2, and was uptitrated to 1.0 mg/kg/d by week 3 unless adverse events emerged. Treatment was 3 weeks long. There were two 3-week treatment periods with 1 week of washout in-between the crossover.	NR / 1 week washout between treatment crossover	NR
Mattes, 1984 U.S. (Fair)	DB RCT crossover design	Subjects were drawn from a psychiatric outpatient clinic and via newspaper ads and given a questionnaire of 5 ADD symptoms (restlessness, difficulty concentrating, excitability, impulsivity, irritability). Subjects were aged 18-45, who met questionnaire criteria and received a psychiatrist rating of at least 2 on at least 3 of the 5 adult ADD symptoms. Subjects with history of childhood ADHD were assigned to experimental group; subjects with no childhood history were assigned to control group.	Methylphenidate or placebo: dosage began at 5 mg bid (8AM and 12 noon), increased to 10 mg bid every 2 days, to a maximum of 30 mg bid. Methylphenidate mean dose: 48.2 mg/day Placebo mean dose: 57 mg/day Sequence of drug phases was randomized. Each phase lasted three weeks, with no intervening washout period.	NR/NR	NR; drug or alcohol abuse was allowed

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics
Gualtieri, 1985 U.S. (Fair)	On the first day of each treatment phase, a nurse measured pulse and blood pressure in seated subjects, and a blood sample was drawn to measure baseline growth hormone (GH) levels. 1 hour after the first dose of MPH or placebo, pulse and blood pressure were again measured, followed by a second blood sample for MPH serum levels and GH. Subjects then completed the CPT with a wristwatch actometer on the nondominant arm. At the end of each treatment phase, subjects filled out the AAS, ZSDS, and ZSAS and reported their subjective experiences. Before the drug code was broken, subjects were asked to guess which drug was MPH and which was placebo.	Mean age 27.2 100% male Ethnicity NR (represents n=22, of which 8 were included in the placebo-RCT)	In the total sample (n=22, of which 8 participated in the DB RCT), previous diagnoses included depressive neurosis (n=3), personality disorder (n=3), and alcoholism (n=1). Two subjects had narcolepsy.
Kinsbourne, 2001 U.S. (Fair)	CPALT - 30-minute test, 4 sessions. On each day of assessment, patient was tested at time zero (baseline), 2 hours after drug administration, in a randomized sequence, counterbalanced across subjects. Favorable response was defined as performance on one of the drug conditions 25% or more above that on placebo. Adverse response was 25% below placebo. Outcomes between those extremes was recorded as non-response.	Mean age 34 41.2% male Ethnicity NR	None of the subjects had been previously diagnosed with ADHD, and none were currently taking psychoactive drugs.
Kooij 2004 Netherlands	Symptoms of ADHD measured with Dutch self-report version of the DSM-IV ADHD rating scale Severity of ADHD measured with CGI - ADHD Depression was measured with Hamilton Depression Scale (HAM-D) Anxiety was measured with Hamilton Anxiety Scale (HAM-A) Functional impairment measured using the Dutch version of the Sheehan Disability Scale (SDS) and the Global Assessment of Functioning scale (GAF) All assessments were made at baseline and at the end of the first and second treatment period, except for the DSM-IV ADHD rating scale, the CGI-ADHD and the adverse events list (all of these were administered weekly). The primary outcome was a decrease of ≥2 points on the CGI-ADHD scale over the total treatment period (3 weeks) + a ≥30% symptom reduction in the DSM-IV ADHD rating scale.	Mean age: 39.1 years 53.3% male Ethnicity: NR	95.5% had ADHD combined subtype 4.5% had ADHD hyperactive / impulsive subtype Average IQ: 101 (SD: 18) School failure: 76% Sheehan Disability scale (min 0, max 30): 22.8 (SD: 3.3) Global Assessment of Functioning (min 0, max 100): 57.3 (SD: 6.1) Co-morbid Antisocial or Borderline Personality Disorder: 33% Baseline HAMD: 8.0 (SD: 5.8) Baseline HAMA: 7.8 (SD: 6.0) Any substance use disorder: 51%
Mattes, 1984 U.S. (Fair)	To determined childhood history of ADHD, patients completed questionnaires including items from CTQ; if a parent was accessible, the parent was asked to quantitate the patient's childhood behavior (CPQ); a relative was asked to complete a modified version of the adult ADD questionnaire; and school records were requested. Patient and psychiatrist rated global improvement weekly; self-rated adult ADD questionnaire, SCL-90, POMS completed at weeks 3 and 6. A study psychiatrist completed a structured interview form of 23 ratings of adult ADD symptoms.	NR NR NR	29 patients with childhood ADHD 37 patients without childhood ADHD DSM-III diagnoses of subjects: ADD residual type 42.4% Antisocial personality disorder 7.6% Alcoholism 10.6% Drug abuse 24.2% Borderline personality disorder 24.2% Major depressive episode (mild) 28.8% Generalized anxiety disorder 10.6% Other 68.2%

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Number screened/ eligible/ enrolled N per drug	Number withdrawn/ lost to fu/ analyzed: N per drug
Gualtieri, 1985 U.S. (Fair)	NR/NR/8 Same subjects exposed to both treatments	NR/NR/8 N per drug not reported (phases were combined in analysis).
Kinsbourne, 2001 U.S. (Fair)	NR/NR/17 Same subjects exposed to all treatments	0% withdrawn 0% lost to followup 17 (100%) analyzed; N per drug not reported (phases were combined in analysis)
Kooij 2004 Netherlands	NR / 108 / 45 same subjects exposed to both treatments	0 / 0 / 45 same subjects exposed to both treatments
Mattes, 1984 U.S. (Fair)	2829/116/66 Same subjects exposed to both treatments	5 (7.6%) withdrawn; Loss to followup NR; 61(92.4%) analyzed; N per drug not reported (phases were combined in analysis).

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Results	Method of adverse effects assessment
Gualtieri, 1985 U.S. (Fair)	Placebo vs MPH: AAS: 27.7 vs 25.8, NS ZSDS: 45.3 vs 37.5, NS ZSAS: 38.3 vs 33.8, NS CPT correct: 121.8 vs 128.5, p <0.05 CPT errors: 5.3 vs 2.1, NS Actometer: 98.6 vs 60.3, NS Growth hormone: 1.3 vs 6.0, NS MPH significantly improved correct responses on the CPT. All subjects accurately guessed the active drug condition.	NR
Kinsbourne, 2001 U.S. (Fair)	12% were non-responders; their best performance was on placebo. 88% were favorable responders; 41% performed optimally at 5 mg; 12% at 10 mg; 35% at 20 mg	NR
Kooij 2004 Netherlands	% of responders at end of treatment periods, methylphenidate vs placebo: DSM-IV ADHD rating scale combined with CGI-S: 38% vs 7%, p=0.003 DSM-IV ADHD rating scale only: 42% vs 13%, p=0.011 CGI-S scale only: 51% vs 18%, p=0.011 Compliance data (taking medicine >80% of time; for 41 patients): 68.3% compliant 31.7% non-compliant Mean decrease in scores for methylphenidate vs placebo, p-value: DSM-IV ADHD: -0.19, p=0.064 CGI-S: -0.72, p=0.026 SDS: -0.93, p=0.029 GAF score: +2.5, p=0.104 HAMD: +2.4, p=0.002 (i.e., MPH is associated with higher symptom leves of depression) HAMA: +2.9, p=0.002 (i.e., MPH is associated with higher symptom leves of anxiety)	Side effects measured using a modified version of the Side Effects Rating Scale from Barkley (Barkley and Murphy 1998)
Mattes, 1984 U.S. (Fair)	No response to methylphenidate occurred in either patients with or without childhood ADHD. Results among patients without childhood ADHD were not shown. Psychiatrist-rated improvement (1=completely recovered; 8=much worse) among patients with varying certainties of having had childhood ADHD, methylphenidate vs placebo: Definitely (at least 90% certainty), N=2: 5.0 vs 4.00 (ns) Very likely (at least 70% certainty), N=16: 4.19 vs 4.31 (ns) Probably (at least 50% certainty), N=26: 4.42 vs 4.58 (ns)	SADS-C elicited by investigator

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Adverse Effects Reported	By treatment, total withdrawals; withdrawals due to adverse events
Gualtieri, 1985 U.S. (Fair)	AEs were not reported among the 8 subjects who participated in the short-term DB RCT.	Methylphenidate vs placebo, Total withdrawals 0 vs 0 Withdrawals due to AEs 0 vs 0
Kinsbourne, 2001 U.S. (Fair)	NR	Methylphenidate (5/10/20 mg/day) vs placebo, Total withdrawals: 0/0/0 vs 0. Withdrawals due to AEs: 0/0/0 vs 0
Kooij 2004 Netherlands	Methylphenidate vs placebo: % of patients on treatment reporting any AEs: 82% vs 69% (p=0.11) Loss of appetite: 22% vs 4 % (p=0.039) Sleeping problems: 33% vs 22% (p=0.27) Headache: 16% vs 4% (p=0.18) Tachycardia: 9% vs 2% (p=0.25) Dizziness: 16% vs 7% (p=0.34) Abdominal complaints: 13% vs 4% (p=0.22) Dry mouth: 24% vs 7% (p=0.06) Tics: 7% vs 2% (p=0.5) 18% of patients lowered their MPH dose due to AEs; none dropped out due to AEs Systolic blood pressure: +0.13 mmHg after MPH (p=0.954) compared to placebo Diastolic pressure "virtually unchanged" Mean heart rate: +4.8 beats/min higher after MPH (p=0.002) compared to placebo Mean body weight: -1.7kg after MPH (p<0.001) compared to placebo	0 / 0
Mattes, 1984 U.S. (Fair)	The following AEs occurred significantly (p<0.05) with methylphenidate: more anorexia, headaches, late-afternoon depression, and less psychiatrist-rated impulsivity. Numeric results for AEs were not shown.	Methylphenidate vs placebo: Total withdrawals unclear by treatment group; Withdrawals due to AEs not reported.

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Comments
Gualtieri, 1985 U.S. (Fair)	Despite small sample size (n=8), MPH improved correct responses on CPT to a statistically significant degree. Levels of growth hormone were non-significantly higher on MPH than placebo.
Kinsbourne, 2001 U.S. (Fair)	Data from the first treatment phase was not reported separately.
Kooij 2004 Netherlands	Exclusion criteria included: clinically unstable psychiatric conditions, current use of psychotropics, prior use of methylphenidate or amphetamines, and a history of tic disorders.
Mattes, 1984 U.S. (Fair)	This study included adults with ADD symptoms, with or without ADHD in childhood. Outcomes represent 26 patients with childhood ADHD; AEs reflect the experience of all study subjects. Data from the first phase was not reported separately.

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, regimen, duration)	Run-in/ Washout period	Allowed other medications/ interventions
Schubiner, 2002 U.S. (Fair)	DB RCT parallel groups	Between the ages of 18 and 55 years; DSM-IV criteria for current cocaine dependence; provide a urine specimen with a positive urine toxicology result for cocaine metabolite; meet criteria for the diagnosis of ADHD as a child and as an adult	Methylphenidate 30 mg/day for first 2 or 3 days; 60 mg/day for the next 4 to 5 days; 90 mg/day by day 8 Placebo Plus twice-weekly cognitive-behavioral group therapy (CBT) for cocaine dependence Pemoline arm dropped after the first year because of recruitment difficulties Dosing: three times daily (times nr) Duration: 13 weeks	NR/NR	NR
Spencer, 1995 U.S. (Fair)	DB RCT crossover design	Male or female aged 18-60, with at least 8 of 14 DSM-III-R criteria for ADHD (assessed by psychiatric evaluation and structured diagnostic interview), with onset in childhood by age 7, chronic course until time of assessment, and associated with significant distress and disability. Adults were self-referred or referred by other clinicians for life-long histories of inattention and underachievement.	Randomized crossover design of methylphenidate vs placebo, with 1 week washout between treatment phases; total trial duration 7 weeks. Study medication was titrated up to 0.5 mg/kg per day by week 1, 0.75 mg/kg/day by week 2, and up to 1.0 mg/kg/day by week 3.	Run-in NR; 1-week washout between phases	NR
Spencer, 2005 U.S. (Poor)	Double-blind Randomized Parallel	Subjects aged between 19 and 60 years recruited from clinical referrals and advertisements in the local media. Subjects had to satisfy full diagnostic criteria for DSM-IV ADHD based on clinical assessment and confirmed by structured diagnostic interview.	Randomized parallel design of methylphenidate vs placebo. Total trial duration: 6 weeks. Study medication was titrated up to 0.5 mg/kg per day by week 1, 0.75 mg/kg/day by week 2, and 1.0 mg/kg/day by week 3.	NR/NR	Other psychoactive medications were not permitted

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics
Schubiner, 2002 U.S. (Fair)	ADHD outcome measures (administered at weeks 5, 9 and 13) ADHD Symptom Checklist Global Improvement Scale Beck Depression Inventory Substance use outcomes Urinalysis Addiction Severity Index (ASI) - every visit Tiffany Cocaine Craving Scale - monthly Self-report - beginning of each study week	Mean age=37.5 89.6% male 70.8% white	No. days using cocaine in last 30 days=13.52 No. hyperactive symptoms=5.8 No. inattentive symptoms=4.8 Mean BDI scores=22.4 ASI Drug use=0.2242 Alcohol use=0.1605 Illegal activity=0.1172 Medical condition=0.1080 Family relations=0.3047 Psychiatric status=0.3324 Employment=0.4503 Affective disorders=56% Anxiety disorders=12.5% Other Axis I disorders=4.1%
Spencer, 1995 U.S. (Fair)	Improvement defined as CGI score less than 2 and a reduction of at least 30% in individual rating scale scores. HAM-D, HAM-A, BDI before and after each arm of the study. CGI and ADHD rating scale administered weekly.	Mean age 40 43.5% male 100% white non-Hispanic	74% had at least one past comorbid psychiatric disorder 56% had a current comorbid psychiatric disorder
Spencer, 2005 U.S. (Poor)	Primary outcome: Adult ADHD Investigator System Report Scale (AISRS) and Clinical Global Impression (CGI) Scale. Responder status was defined as a 30% reduction in the AISRS plus "much" or "very much improved" in the CGI. Timing: weekly Secondary outcome: Hamilton Depression Scale; Beck Depression Inventory; Hamilton Anxiety Scale. Timing: at the beginning and end of the study	Mean age 37 58.2% male Ethnicity: NR	38% major depression 9% multiple (>2) anxiety disorders

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Number screened/ eligible/ enrolled N per drug	Number withdrawn/ lost to fu/ analyzed: N per drug
Schubiner, 2002 U.S. (Fair)	932/338/59 Methylphenidate n=24 Placebo n=24 Pemoline n=11 (dropped from analysis)	34 (57.6%) withdrawn; 11 (18.6%) dropped due to being in the pemoline group; Lost to fu NR; 48 (100% for MPH vs placebo comparison) for most efficacy measures MPH n=24, placebo n=24
Spencer, 1995 U.S. (Fair)	85/25/25 N per drug during first phase not reported.	2 (8%) withdrawn 0% lost to followup 23 (92%) analyzed. N per drug in 1st treatment phase not reported.
Spencer, 2005 U.S. (Poor)	289/NR/146 104 in MPH; 42 in placebo	36/NR/110 26(25%) in MPH; 10(24%) in placebo dropout

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Results	Method of adverse effects assessment
Schubiner, 2002 U.S. (Fair)	MPH vs placebo (mean change); differences NS unless otherwise specified No. inattentive symptoms=2.13 (-2.79) vs 2.83 (-1.96) No. hyperactive symptoms=3.42 (-2) vs 4.78 (-1.47) No. days using cocaine in past 30 days=15.42 (+2.13) vs 14.58 (+0.83) Amount spent on cocaine in past 30 days=$62.54 vs $97.19 Longest continuous abstinence=5.17 vs 5.17 % Urine samples tested negative for cocaine=0.5 vs 0.42 Physician efficacy ratings showing moderate improvement: 77% vs 21%, p<0.05 at 4 weeks: 77% vs 44% at 8 weeks: 60% vs 36% at 12 weeks: 50% vs 56% last visit: 73% vs 42%, p<0.05 Mean participant efficacy ratings at last visit: 1.88 vs 2.68; p<0.05 at 4 weeks: 2.57 vs 3.00 at 8 weeks: 2.08 vs 3.08 at 12 weeks: 1.75 vs 2.64	Side effects checklist based on Barkley's (1990) version with the addition of cardiac symptoms
Spencer, 1995 U.S. (Fair)	Mean change in score during first treatment phase (Weeks 1-3), methylphenidate vs placebo: ADHD Rating Scale -18 vs -2.5 (p<0.0001) Global Severity subscale of the CGI Scale -1.8 vs 0 (p<0.0001) Mean change in ADHD symptom cluster score, using 1st and 2nd treatment phases combined, methylphenidate vs placebo: Hyperactivity overall -1.2 vs -0.16 (p<0.001) Impulsivity overall -1.3 vs -0.44 (p<0.001) Inattentiveness -0.62 vs -0.26 (p<0.001) % of patients who improved, i.e.. CGI score <2 and reduction >=30% in individual rating score: 78% vs 4% (p<-0.001)	Elicited by investigator; HAM-D, HAM-A, BDI
Spencer, 2005 U.S. (Poor)	Methylphenidate vs placebo, CGI rated "much" or "very much" improved: 63(68%) vs 6(17%), p<0.001	self-report

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Adverse Effects Reported	By treatment, total withdrawals; withdrawals due to adverse events
Schubiner, 2002 U.S. (Fair)	MPH vs placebo (*differences NS unless otherwise specified*) (*% worst occurrence during study*) Chest pain=0 vs 2 (8%) Palpitations=0 vs 1 (4%) Dizzy=2 (8%) vs 1 (4%) Stomachaches=3 (13%) vs 3 (13%) Nightmares=5 (21%) vs 3 (13%) Headaches=6 (25%) vs 6 (25%) Nausea or upset stomach=8 (33%) vs 5 (21%) Euphoria, unusually happy=10 (42%) vs 7 (29%) Drowsiness=6 (25%) vs 10 (42%) Tics or nervous movement=5 (17%) vs 5 (21%) Decreased appetite=12 (50%) vs 6 (25%) Insomnia or trouble sleeping=15 (63%) vs 8 (33%); p<0.05 Irritability=14 (58%) vs 13 (54%) Sadness=15 (63%) vs 9 (38%) Talk less with others=11 (46%) vs 12 (50%) Stare a lot or daydream=12 (50%) vs 17 (71%) Anxious=19 (79%) vs 15 (63%)	Methylphenidate vs placebo: Total withdrawals: 13 (54.2%) vs 10 (41.7%) Withdrawals due to adverse events: 0 vs 1 (4.2%)
Spencer, 1995 U.S. (Fair)	Loss of appetite 26% Insomnia 22% Anxiety 22% Methylphenidate vs placebo: Mean heart rate 80 vs 76 beats/min (p<0.05) Mean weight 73.2 vs 74.3 kg (p<0.05)	Methylphenidate vs placebo, Total withdrawals 2 (8%) vs 0%; Withdrawals due to AEs: 2 (8%, chest pain in 1, agitation/irritability in another) vs 0%
Spencer, 2005 U.S. (Poor)	Methylphenidate vs placebo, Life events: 2(2%) vs 0(0%), p=0.37 Psychiatric adverse events: 7(7%) vs 0(0%), p=0.085 Somatic complaints: 2(2%) vs 0(0%), p=0.37	Methylphenidate vs placebo, Total withdrawals 26 (25%) vs 10(24%); Withdrawals due to AEs: 11(11%) vs 0(0%)

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Comments
Schubiner, 2002 U.S. (Fair)	Comorbid for cocaine dependence Pemoline arm dropped (n=11) due to low enrollment after 1 year
Spencer, 1995 U.S. (Fair)	Outcomes from the first phase of treatment (MPH vs placebo) are presented separately, but number of patients in each group is not reported.
Spencer, 2005 U.S. (Poor)	

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, regimen, duration)	Run-in/ Washout period	Allowed other medications/ interventions
Tenenbaum, 2002 U.S. (Fair)	DB RCT crossover design	Participants were recruited via newspaper ads, outpatient therapy practices, support groups, and posted notices. Respondents with symptoms of ADHD, defined as either: (i) two of the primary subscales of the ADSA (both Attention-Focus/Concentration Scale and Behavior-Diagnosed Activity Scale) or (ii) both of the subscales of Barkley's ADHD Rating Scale (inattention and hyperactivity/impulsivity). ADSA ratings were significant when subscale scores were >=1.5 standard deviations above the mean. Ratings on Barkley's scale were significant according to age/gender normative scores per by Barkley & Murphy 1998. Diagnosis of ADD, combined type was determined using DSM-IV criteria, clinical interviews and standard rating scales. A significant other attended each of 3 assessment/baseline sessions to provide collateral information.	All study medications were administered quid, at morning, noon, 4PM, and evening. Methylphenidate (up to 45 mg/day) dosed as follows, with placebo given at evening dose: Day 1-2: 5 mg AM and 5 mg noon, placebo 4PM Day 3-4: 5 mg AM, 5 mg noon, 5 mg 4PM Day 5-7: 10 mg AM, 10 mg Noon, 5 mg 4PM Day 8-10: 10 mg AM, 10 mg Noon, 10 mg 4PM Day 11-13: 15 mg AM, 15 mg noon, 10 mg 4PM Day 14-21: 15 mg AM, 15 mg noon, 15 mg 4PM Pycnogenol was administered qid, to a total dosage of 1 mg/lb body weight. Placebo qid Duration of each treatment phase: 3 weeks Duration of total trial: 17 weeks, including 1 week baseline phase, washout periods between treatment phases, and 3-week follow-up	Run-in NR; 1-week washout between treatment phases	NR
Turner, 2005	DB PCT crossover	Adult patient with ADHD who scored ≥172 on the attention-deficit scales for adults (ADSA) and who also were assessed with the Global Severity Index (GSI)	Methylphenidate 30 mg single dose and placebo. Dose given 75 minutes before testing started.	NR / 12-hour washout for alcohol or caffeine	NR

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics
Tenenbaum, 2002 U.S. (Fair)	Self-report rating scales, rating scales completed by the individual's significant other, and a computerized continuous performance test, conducted at baseline and end of each 3-week treatment phase, as well as 1 month after the final treatment condition. Self-reported rating scales: Barkley's ADHD rating scale, Attention Deficit Scales for Adults, Copeland Symptom Checklist for Adult Attention Deficit Disorders, Barratt Impulsiveness Scale, Conners' CPT, Brown ADD scales Other-reported data: Barkley's ADHD Scale, Attention Deficit Scales for Adults, Copeland Symptom Checklist for Adult ADD, Brown ADD Scales Composite scores for each scale were calculated as follows: the mean baseline score was subtracted from each subject's score at the end of each 3-week treatment phase, divided by standard deviation at baseline for the entire sample. For each research instrument the standardized scores for the subscales were then summed to provide one composite score for each participant for each treatment condition.	Mean age 42 45.8% male 100% white	Not reported
Turner, 2005	Patients completed a Visual Analogue Scale (Bond and Lader 1974) that measured their feelings in terms of 16 dimensions before administration of the drug and on completion of testing. Patients were tested using the computerized Cambridge Neuropsychological Test Automated Batter (CANTAB) for Patter Recognition Memory (PRM), Spatial Working Memory (SWM), Spatial Span (SSP) and Rapid Visual Information Processing (RVIP). Testing sessions were separated by at least a week and lasted approximately 1 hour.	Mean age (for n=18 patients with DSM-IV ADHD): 28.5 70.4% male (of original 27 patients; no data specified for smaller group)	Mean baseline GSI =1.4 (SD:0.6) 18 of 24 patients met DSM-IV criteria for ADHD; 5 of these had a diagnosis of "inattentive type" and 7 of "combined type". 6 of 24 patients did not meet DSM-IV ADHD criteria; they were classified as patients with "attentional difficulties" and were not included in the main analysis of the effects of MPH .

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Number screened/ eligible/ enrolled N per drug	Number withdrawn/ lost to fu/ analyzed: N per drug
Tenenbaum, 2002 U.S. (Fair)	128/85/33 Same subjects exposed to all treatments.	9 (27%) withdrawn due to non-compliance 0% lost to fu 24 (72.7%) analyzed, N per drug not reported (phases were combined in analysis).
Turner, 2005	NR / 27/ 27 same subjects exposed to both treatments	3 / NR / 24 (24 per drug)

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Results	Method of adverse effects assessment
Tenenbaum, 2002 U.S. (Fair)	Composite score effect size, self-reported data; other-reported data: Barkley's ADHD Rating Scale 0.18/ 0.13; Attention Deficit Scales for Adults 0.19/0.09 Copeland Checklist for Adult ADD 0.20/0.23; Barratt Impulsiveness Scale 0.25/other na Conners' CPT 0.13/other na; Brown ADD Scales 0.25/0.22 Mean change from baseline in MPH vs placebo [Cohen's d effect size] from self-reported data; from other-reported data: Barkley's Inattention -2.75 v -2.79 [-.02] ; -1.18 v -1.57 [-.15] Barkley's hyperactivity -1.79 v -1.79 [.00] ; -.96 v -1.35 [-.17] ADS Attention-Focus -7.10 v -4.80 [.33] ; -2.50 v -3.50 [-.16] ADS Behavior-Disorganized Activity -9.00 v -7.80 [.13] ; -6.60 v -5.80 [.08] ADS Emotive Scale -4.90 v -5.10 [-.04] ; -3.50 v -3.00 [.07] Copeland Inattention/Distractibility -15.10 v -9.40 [.30] ; -1.90 v -8.20 [-.40] Copeland Impulsivity Scale -15.00 v -11.20 [.21] ; -5.10 v -7.80 [-.12] Copeland Overactivity/Hyperactivity -8.40 v -16.50 [-.42] ; -3.60 v -7.90 [-.20] Copeland Underactivity -12.50 v -8.20 [.22] ; -4.80 v -5.20 [-.03] Barratt Total scale -5.60 v -6.00 [-.04] ; Other-reported data n/a Barratt Cognitive impulsiveness scale -1.70 v -1.40 [.10] ; Other-reported data n/a Barratt motor impulsiveness -3.00 v -2.70 [.07] ; Other-reported data n/a Barratt non-planning impulsivity -.90 v -2.00 [-.22] ; Other-reported data n/a CPT: Standard Error of Hit Rate -1.27 v -1.25 [.01] ; Other-reported data n/a CPT: SE of variability in reaction times -.30 v -1.89 [-.40] ; Other-reported data n/a CPT: Hit rate minus interstimulus interv -.01 v -.01 [.10] ; Other-reported data n/a CPT: Intertrial interval -.01 v -.01 [-.02] ; Other-reported data n/a Brown total score -15.60 v -15.10 [.02] ; -12.80 v -18.80 [-.35] Brown: Activating and organizing to work -3.60 v -3.30 [.05] ; -3.80 v -3.80 [-.15] Brown: Sustaining attention and concentr -3.90 v -3.30 [.13] ; -2.70 v -4.70 [-.34] Brown: Sustaining effort and energy -3.60 v -3.20 [.07] ; -2.70 v -3.80 [-.21] Brown: Managing affective interference -2.13 v -2.67 [-.14] ; -1.80 v -2.30 [-.13] Brown: Utilizing working memory and reca -2.30 v -2.70 [-.09] ; -2.00 v -3.30 [-.41] Beck Depression -1.68 v -3.68 [-.31] ; Other-reported data n/a Beck Anxiety .12 v -2.17 [-.54] ; Other-reported data n/a Avg.effect size [-.02] ; [-.18]	NR
Turner, 2005	No significant differences were seen between placebo and methylphenidate for the PRM, and the SSP, and none were seen for 3 of 4 parts of the SWM and for 1 of 3 parts of the RVIP. For the significant differences on the SWM, methylphenidate vs placebo: Between errors 6-box stage scores (SD) were: 2.3 (3.1) vs 6.8 (6.7), p = 0.0026 For the significant differences on the RVIP, methylphenidate vs placebo: Mean latency in milliseconds: 416.5 (67.7) vs 468.3 (85.1), p=0.006 Target sensitivity scores: 0.931 (0.006) vs 0.908 (0.06), p=0.026 On the VAS assessing patient's feelings, of the 16 different domains, the increases between methylphenidate vs placebo on these 7 feelings were significant: Alert, well-coordinated, contented, tranquil, quick-witted, attentive, interested	NR

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Adverse Effects Reported	By treatment, total withdrawals; withdrawals due to adverse events
Tenenbaum, 2002 U.S. (Fair)	NR	Methylphenidate vs placebo: Total withdrawals unclear by treatment group. Withdrawals due to AEs 0 vs 0
Turner, 2005	NR	3 enrolled patients did not have complete data, but no information was given about these patients.

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Comments
Tenenbaum, 2002 U.S. (Fair)	Data from the first treatment phase was not reported separately. The effect sizes in the composite scores ANOVAs were uniformly small (0.09-0.25), accounting for no more than 6% of the variance, indicating that treatment effects of MPH and Pycnogenol were not superior to those of placebo. Most of the effect sizes for all measures comparing MPH with placebo were very small and mostly negative. Only 3 of the 80 effect sizes reached the criterion of 0.50 for a moderate effect size, and in each of these cases the effect size was negative. These results show that MPH and pycnogenol were no better, and perhaps even slightly worse, than placebo.
Turner, 2005	

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, regimen, duration)	Run-in/ Washout period	Allowed other medications/ interventions
Wender, 1985 U.S. (Fair)	DB RCT crossover design	Clinics were asked to refer white patients aged 21-45 with prominent complaints of impulsivity, irritability restlessness, and emotional lability. Included patients whose mothers were available and willing to fill out the Parent Rating Scale, with IQ >90. Patients were interviewed with a semistructured personal and family history instrument. Utah criteria for ADD, residual type; subject must first have had a history of ADHD in childhood as well as both hyperactivity and ADD persisting from childhood, and additionally have affective lability; inability to complete tasks; hot or explosive temper; impulsivity; and stress intolerance. Mothers of prospective patients rated the behavior of their offspring between ages 6 and 10, using a modified Conners Teacher's Rating Scale.	Methylphenidate or placebo were dispensed in 10-mg tablets. Initial dose was 5 mg bid, at 8AM and 12 noon, increased by 5 mg per dose every 2-3 days on the basis of patient's report. Maximum dose was set at 3 tablets tid (90 mg/day). Methylphenidate mean dose at end treatment phase 43.2 mg/day. Placebo mean dose at end treatment phase 50.2 mg/day Randomized crossover design with 1-week washout between 2-week treatment phases; total duration 5 weeks.	Run-in NR; 1-week washout between treatment phases	NR
Wood, 1976 (Fair)	DB, crossover design	Adults who had a rating, as children, of hyperactivity from parents' report (Conner Abbreviated Rating Scale) scoring over the 95th percentile, with prominent complaints of no change in adulthood.	Methylphenidate for 2 weeks twice daily, at variable, NR dose amounts, gradually increased to max of 60mg. Crossover: to methylphenidate, doses varying to 20-60 mg/day (specifics NR)of: Methylphenidate or Pemoline	Run-in NR. No washout given due to short duration of drug	Imipramine, 10mg, was used with 1 subject, who did not respond to Pemoline,
Methylphenidate SR					
Biederman 2006	DB RCT parallel design	Outpatients 19–60 years. To be included, subjects had to satisfy full diagnostic criteria for DSM-IV ADHD on the basis of clinical assessment and confirmation by structured diagnostic interview	Osmotic release oral system methylphenidate (OROS MPH) vs. placebo titrated to optimal response (a maximum daily dose of 1.3 mg/kg; initial dose of 36 mg 6 weeks	NR	No
Boonstra 2007 Netherlands (companion to Kooij 2004)	DB RCT crossover design	Adults (age not specified) with current diagnosis of ADHD and childhood diagnosis of ADHD using DSM-IV.	Placebo (dose not reported) and Methylphenidate (MPH) dosing was initiated at .5 mg/kg/d week 1, .75 mg/kg/d week 2, and up to 1 mg/kg/d in week 3. Medication was dosed 4 or 5 times daily. Last dose given at 20:00 (8:00 PM).	one week between placebo and MPH crossover	Not reported (NR)

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics
Wender, 1985 U.S. (Fair)	Clinical status was evaluated at beginning of each treatment phase, 1 week following initiation, and at end of 2-week drug or placebo phase. Physician's target symptom rating scale Physician's Global Rating Scale Medicine response sheet (self-rating instrument) Global Assessment Scale Profile of Mood States SCL-90	Mean age 31.1 54% male Ethnicity NR	Comorbidities: 68% dysthymic disorder 22% cyclothymic disorder
Wood, 1976 (Fair)	12 month assessment self-report of symptoms from patients, completion of self-report questionnaire	N=15 but only 11 in cross-over Age Range: 21-60 Ethnicity: Caucasian Male: 40% (of the 15 total)	RDC diagnoses: generalized anxiety disorder: n=8 cyclothymic disorder: n=4 drug/alcohol abuse: n=2 antisocial disorder: n=2 minor depressive disorder: n=4 N>15, as patients as patients over-lapped in these diagnoses
Methylphenidate SR			
Biederman 2006	CGI-I CGI-S Adult ADHD Investigator System Report Scale score. Assessed baseline, weekly and endpoint	Placebo/OROS MPH Age 37.6/32.7 Male 47%/57% Ethnicity NR	Placebo/OROS MPH CGI Severity Mild 0/1 Moderate 56/40 Marked 29/38 Severe 3/1 P = 0.1 Lifetime Psychiatric Comorbidity 46% / 33% P = 0.1
Boonstra 2007 Netherlands (companion to Kooij 2004)	Sleep Activity log (completed twice a day: morning and evening), Questions about activities throughout the day (use of medication, alcohol, caffeine, cigarettes, bed/waking times) and 5-point Likert scale questions about subjective experience of different aspects of sleep (how well rested/ how well did one sleep). High scores = poor sleep.	Mean age 37.9 48% male 52% female ethnicity: NR	ADHD subtype 1 (3%) ADHD hyperactive / impulsive subtype 32 (97%) ADHD combined subtype None of the participants had been treated with MPH prior to the study.

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Number screened/ eligible/ enrolled N per drug	Number withdrawn/ lost to fu/ analyzed: N per drug
Wender, 1985 U.S. (Fair)	NR/NR/37 Same subjects exposed to both treatments	0% withdrawn; 0% lost to followup; 37 (100%) analyzed, N per drug not reported (phases were combined in analysis).
Wood, 1976 (Fair)	15/11 N per drug NR	0/0/11 analyzed: N NR
Methylphenidate SR		
Biederman 2006	204/276/149 - Placebo 77 OROS MPH 72	Placebo/MPH Withdrawn 11/18 Lost to F/U 4/7 Analyzed 74/67
Boonstra 2007 Netherlands (companion to Kooij 2004)	NR/NR/33 (total enrolled) enrolled per drug not reported	2/0/# analyzed per drug NR

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Results	Method of adverse effects assessment
Wender, 1985 U.S. (Fair)	Final physician and patient ratings, methylphenidate vs placebo: Physician's Global Rating scale 1.4 vs 0.16 (p<0.005) Global Assessment Scale 69.17 vs 61.26 (p<0.005) Physician's target symptom ratings (1=none, 4=marked): hyperactivity 2.33 vs 3.29 (p<0.005); short attention span 2.27 vs 3.35 (p<0.0005); mood problems 2.36 vs 3.14 (p<0.005); anger 2.35 vs 3.11 (p<0.01); disorganization 2.12 vs 3.03 (p<0.005); conduct disorder 1.42 vs 1.67 (ns) Patient's subjective experience (1=absent, 5=very much): nervous 2.56 vs 2.97 (ns); happy 3.16 vs 2.70 (p<0.05); energetic 3.27 vs 3.11 (ns); mind wandering 2.37 vs 2.97 (p<0.025); hot tempered 2.32 vs 2.43 (ns); calm 2.83 vs 2.35 (ns); sad 1.81 vs 2.10 (ns); tired/sleepy 1.88 vs 2.28 (ns); concentrating 2.86 vs 2.41 (ns); hungry 1.97 vs 2.51 (p<0.025); cool tempered 3.97 vs 2.44 (p<0.025); global 4.97 vs 4.31 (ns) Profile of mood states: tension-anxiety 49.06 vs 55.71 (p<0.001); depression-dejection 43.88 vs 50.50 (p<0.001); anger-hostility 50.34 vs 57.03 (p<0.01); vigor 70.40 vs 66.53 (ns); fatigue 48.00 vs 53.47 (p<0.05); confusion 51.53 vs 58.25 (p<0.001) BDI 8.94 vs 9.23 (ns)	Self-report
Wood, 1976 (Fair)	**Self-rating Responses of Double-Blind Trial (n=11) of Methylphenidate vs Placebo** Methylphenidate vs Placebo; p-Value Happy-Sad: 1.37 vs 2.66; pNS Calm-Nervous: 2.15 vs 3.60; p=.01 Energetic-Tired: 1.66 vs 3.25; p=.05 Concentrating Mind-Wandering Mind: 1.75 vs 3.28; p=.01 Cool-Tempered-Hot-Tempered: 1.65 vs 3.55; p=.01	self-report, results on questionnaire data
Methylphenidate SR		
Biederman 2006	Response of much or very much improved on the Clinical Global Impression–Improvement scale plus a >30% reduction in Adult ADHD Investigator System Report Scale score Placebo 39% vs. OROS MPH 66% P = NR	Spontaneous reports through open-ended questions at each visit. Weight and vital signs were obtained at each visit, and an ECG was performed at baseline and endpoint.
Boonstra 2007 Netherlands (companion to Kooij 2004)	Sleeping problems reported in 33% MPH compared to 22% placebo Mean scores (arbitrary units unless otherwise noted) Well-rested: 2.84 pla; 3.03 MPH (NS) Sleep onset latency (hours): 0:17 pla; 0:24 MPH (NS) Difficulty initiating sleep: 2.15 pla; 2.33 MPH (NS) Nocturnal awakenings: 0.99 pla; 0.82 MPH (P<0.01) Sleep quality: 2.47 pla; 2.67 MPH (NS) Rested at wake up: 3.01 pla; 3.12 MPH (NS)	NR

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Adverse Effects Reported	By treatment, total withdrawals; withdrawals due to adverse events
Wender, 1985 U.S. (Fair)	Mild anxiety, insomnia, jaw tension, tooth grinding, overstimulation, irritability, nose tingling	Methylphenidate vs placebo: Total withdrawals 0 vs 0 Withdrawals due to AEs 0 vs 0
Wood, 1976 (Fair)	No adverse effects reported, no response to meds: n=1	0/0
Methylphenidate SR		
Biederman 2006	OROS MPH / Placebo n(%) Decreased Appetite (Anorexia) 23 (34) / 2 (3) , P < .001 Dry Eyes, Nose, Mouth 23 (34) / 5 (7) P < .001 Headache 21 (31) / 22 (30) P = .8 Gastrointestinal 19 (28) / 10 (14) P = .03 Colds/Allergies/Infections 12 (18) / 18 (24) , P = .4 Tension/Jitteriness 12 (18) / 0 (0) , P < .001 Sleep Problems 12 (18) / 4 (5) , P = .02 Aches/Pains 9 (13) / 10 (14) , P = .9 Cardiovascular Complaints 6 (9) / 1 (1) , P = .04 Depression 5 (8) / 0 (0) , P = .02 Agitation 5 (7) / 6 (8) , P = .9 Dizziness 5 (7) / 0 (0) , P = .02 Menstrual Problems 2 (7) / 0 (0) , P = .1 Anxiety 4 (6) / 0 (0) , P = .03 Change in Systolic BP 3.5 vs. -1.1 P = 0.02 Diastolic BP 4.0 vs. -2.1 P < 0.001 Heart rate (bpm) 4.5 vs. -2.7 P < 0.001 QTC interval (msec) 1.9 vs. -1.2 P = 0.3	Placebo/MPH Total 11/18 Due to AEs (side effects) 3/9
Boonstra 2007 Netherlands (companion to Kooij 2004)	82% MPH compared to 69% for placebo. Individual adverse effects not reported. Sleeping problems were reported in 33% MPH compared to 22% placebo.	withdrawals due to AEs 0/33

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Comments
Wender, 1985 U.S. (Fair)	Data from the first phase was not reported separately. Outcomes were presented as combined data from phases of each drug.
Wood, 1976 (Fair)	
Methylphenidate SR	
Biederman 2006	
Boonstra 2007 Netherlands (companion to Kooij 2004)	

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, regimen, duration)	Run-in/ Washout period	Allowed other medications/ interventions
Chronis-Tuscano 2009 United States (Washington DC)		Mothers: Mothers with children (ages 6-12 yrs) were assessed using the CAARS-S:SV. T-scores and the ADHD Index had to fall a minimum of > 1.5 SD above the mean for the participant's age and gender to proceed to the diagnostic treatment. Met DSM-IV criteria (4 or 5 symptoms of ADHD currently present, with evidence that full ADHD criteria were met prior to age 12 years. And functional impairment in at least 1 setting with history of impairment in at least 2 settings during childhood. Children: ages 6-12 years who met DSM-IV criteria between age 6-12 with no prior diagnosis of pervasive developmental disorder or mental retardation.	Phase 1: MPH OROS and placebo titrated for 5 weeks to until the following criteria were met: 30% reduction in CAARS scores, CGSI-S scale indicated normal / not ill (score of 1) or borderline (score of 2), and medication was well tolerated. Maximum does 90 mg/day. Phase 2: placebo or MPH OROS at maximally effective dose (mean dose 83.7mg/day) x 2 weeks Outcome measure repeated again at end of phase 2	NR	NR
Levin 2002 U.S. (Fair)	DB RCT parallel design	Adults ages 19-56; all were positive for ADHD according to DSM-IV; all were nonsmokers verified by end tidal carbon monoxide measurements less than 8 ppm; an experienced clinical psychologist made the diagnoses of ADHD using the Wender Utah Rating Scale, the Conners/Wells Adolescent and Adult Self-Report, a modified version of Barkley's adult ADHD semistructured interview	Placebo Nicotine transdermal patches: Week 1=5 mg per day, Weeks 2-3=10 mg per day, Week 4: 5 mg per day Methylphenidate sustained release 20 mg per day Nicotine+methylphenidate sustained release Duration: 4 weeks	NR/NR	NR
Levin 2006 U.S.	DB RCT	Ages 18-60, meet DSM-IV criteria for opiate dependence and adult ADHD, on the same dose of methadone for at least 3 weeks	Placebo, sustained-release MPH, and sustained-release bupropion (BPR) 2-week placebo lead-in, 2-week dose titration period followed by 8 weeks at stable dose MPH titration phase standard formulation 2X/day starting at 10 mg/day increased by 10 mg/day, up to 40 mg/day, then standard formulation replaced by sustained-release formulation as two 20 mg doses, dose increased up to maximum of 80 mg/day. Patients discontinued if could not tolerate at least 40 mg/day MPH. BPR was started at 100 mg/day and increased by 100 mg by the end of the first week of the titration phase. Patients received 200 mg 2 X/day for the maximum dose of 400 mg/day by the end of the second week. Patients discontinued if could not tolerate at least 200 mg/day BPR.	Two week placebo lead-in	Medication and treatment at a methadone program, weekly individual cognitive behavioral therapy for drug use

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics
Chronis-Tuscano 2009 United States (Washington DC)	Primary outcome measures: Conner's Adult ADHD Rating Scale (CAARS) Alabama Parenting Questionnaire CGI-S weekly (1=normal; 7=severely ill) Secondary outcome measures: Side effects ratings: Pittsburgh Side Effect Rating Scale; The Beck Depression Inventory-II	Mothers: age: 39.8 White: 91.3% Asian: 4.3% Hispanic: 4.3% Children: male: 57%	Mothers: ADHD subtype: combined type: 56.5% inattentive type: 34.8% hyperactive/impulsive type 8.7% Children: inattentive ADHD subtype: 13% comorbid oppositional-defiant disorder 65% conduct disorder 13% received stable med. doses 61%
Levin 2002 U.S. (Fair)	CGI scale assessed by clinician on Treatment Days 1, 8 and 21 Individual questions from the Profile of Mood States (POMS) battery (tension, fatigue, vigor, depression, anger and difficulty concentrating: Treatment days 1, 8, 15 and 21 Conners CPT: Treatment days 1 and 21 Automated Neuropsychological Assessment Metrics (ANAM): simple reaction time, mental spatial rotation reaction time and delayed matching to sample administered on Treatment Days 1 and 21	Mean age=37 62.5% male race nr	NR
Levin 2006 U.S.	Weekly clinical assessments of ADHD symptoms using: AARS as primary measure Clinical Global Improvement Scale (CGI) Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS)	Mean age placebo/MPH/BPR 39/40/38, p=0.59 57% male 40% white 40% Hispanic 20% black	Currently employed at baseline placebo/MPH/BPR 43%, 58%, 89%, p=0.001 34% enrolled in methadone maintenance program for less than 12 weeks, 58% enrolled for more than 6 months

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Number screened/ eligible/ enrolled N per drug	Number withdrawn/ lost to fu/ analyzed: N per drug
Chronis-Tuscano 2009 United States (Washington DC)	71/28/23	1/2/20 total 11 placebo; 9 MPH OROS
Levin 2002 U.S. (Fair)	NR/NR/40 Placebo patch + placebo pill, n=10 Nicotine, n=10 Methylphenidate, n=10 Nicotine + methylphenidate, n=10	6 (15%) withdrawn/lost to fu nr/34 analyzed (placebo n=7, nicotine n=9, MPH n=9, combination n=9)
Levin 2006 U.S.	526/232/115 33 placebo 32 MPH 33 BPR	Placebo/MPH/BPR Withdrawn 8/11/10 Lost to F/U NR Analyzed 25/21/23

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Results	Method of adverse effects assessment
Chronis-Tuscano 2009 United States (Washington DC)	ADHD symptom scores: phase 2 -- week 7 CAARS self-report inattention: MPH OROS 57.78; pla 65.55 (-7.77) Cohen d (effect size) .48 hyperactivity/impulsitivity: MPH OROS 49.33; pla 48.27 (-1.06) Cohen d (effect size) .06 ADHD index: MPH OROS 54.44; pla 60.27 (-5.83) Cohen d (effect size) .38 CGI-S: MPH OROS 3.11; pla 3.3 (-.19) Cohen d (effect size) .15 Parenting scores: APQ: phase 2 -- week 7 Involvement: MPH OROS 40.67; pla 38.00 (-2.67) Cohen d (effect size) .52 Positive parenting: MPH OROS 24.22; pla 24.82 (-.6) Cohen d (effect size) .15 Poor monitoring/ supervision: MPH OROS 11.44; pla 13.27 (-1.83) Cohen d (effect size) .70 Inconsistent discipline: MPH OROS 12.00; pla 14.63 (-2.63) Cohen d (effect size) .71 Corporal punishment: MPH OROS 3.33; pla 3.64 (-.31) Cohen d (effect size) .42	Pittsburgh Side Effect Rating Scale; The Beck Depression Inventory-II
Levin 2002 U.S. (Fair)	MPH vs placebo (differences are NS unless otherwise noted) CGI Day 1 (acute): 5.0 vs 4.8 Days 15 and 28 (chronic): 5.4 vs 4.1 Change from baseline to day 28: -0.5 vs -0.6 POMS MPH vs placebo on day 21: F(1,26)=6.55, p=0.025; NS on days 1, 15 and withdrawal days (data nr) CPT Omission-- Acute: 2.4 vs 1.0; Chronic: 1.0 vs 1.3 Commission errors-- Acute: 16.6 vs 13.0; Chronic: 12.2 vs 13.1 Reaction time (ms)-- Acute: 324 vs 355; Chronic: 326 vs 329 Reaction time variability-- Acute: 7.8 vs 7.7; Chronic: 6.0 vs 6.0 Attention-- Acute: 2.7 vs 3.4; Chronic: 3.5 vs 3.0 ANAM Reaction time (ms): 280 vs 293 Spatial rotation (ms): 2,208 vs 2,198 Delayed matching (%): 91.9 vs 91.2	NR
Levin 2006 U.S.	AARS response >30% reduction placebo 46%, MPH 34%, BPR 49%, p=0.48 CGI response improvement rating <3 placebo 39%, PMH 19%, BPR 30%, p=0.19 No significant differences in any drug or cocaine use.	NR but rated on a 0 to 3 scale (none to severe)

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Adverse Effects Reported	By treatment, total withdrawals; withdrawals due to adverse events
Chronis-Tuscano 2009 United States (Washington DC)	Reported for titration phase only: tics, buccal, picking skin, worried, dull/listless, headache, stomachache, irritable, tearful, withdrawn, hallucinations, appetite loss, sleep trouble heart rate, beats/min NS systolic blood pressure NS diastolic blood pressure NS weight/ kg baseline: 74.49 kg vs. 73.39 (54 mg), 73.08 (72 mg), 73.39 (90 mg) significant at < .05.	3 during phase 1 (not randomized at that point) Withdrawals due to AE 1(MPH OROS)
Levin 2002 U.S. (Fair)	NR	Methylphenidate vs placebo, Total withdrawals: 1 (10%) vs 3 (30%); p=NS Withdrawals due to adverse events nr
Levin 2006 U.S.	Fatigue 9% placebo Increased sweating MPH 6%, BPR 9% Nosebleed placebo n=1 Psychomotor agitation MPH n=1	Placebo/MPH/BPR Total withdrawn 8/11/10 Withdrawn AEs (side effects) 2/1/0

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Comments
Chronis-Tuscano 2009 United States (Washington DC)	
Levin 2002 U.S. (Fair)	
Levin 2006 U.S.	

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, regimen, duration)	Run-in/ Washout period	Allowed other medications/ interventions
Levin 2007 U.S.	DB RCT	ages of 18–60 to meet DSM-IV criteria for cocaine dependence and persistent adult attention deficit hyperactivity disorder	Placebo and MPH dosing was initiated at 10 mg/day of standard formulation methylphenidate and increased up to 20 mg two times a day (40 mg/day) one week lead-in, two week titration and 11 weeks at stable dose	One week placebo lead-in	Not reported (NR)
Medori 2008 Europe	DB RCT Parallel-group	Ages 18-65, chronic symptomology from childhood to adulthood with some symptoms present before age 7. Diagnosis of ADHD (DSM IV criteria) and confirmed by Conners' Adult ADHD Diagnostic interview. CAARS total score of ≥ 24 at screening.	Four treatment groups: PR Methylphenidate 18 mg once daily X 5 weeks PR Methylphenidate 36 mg once daily X 5 weeks PR Methylphenidate 72 mg titrated from 36 mg/ day for 4 days, 54 mg/ day for 3 days, 72 mg day X 4 weeks placebo once daily X 5 weeks	up to 4 weeks washout period	Stable dosage of antidepressant therapy for patients on therapy for 3 mo ≤. MOIs not allowed.
Reimherr 2007	DB RCT crossover design	Adults (18-65 yrs) with current diagnosis of ADHD using DSM-IV with at least moderate symptoms	Osmotic release oral system methylphenidate (OROS MPH) vs. placebo, titrated up from 18 mg per day until response w/ maximum dose of 90 mg per day. 2 arms 4 weeks each	No	NR
Verster 2008 Netherlands	DB (see note) RCT Crossover design	Ages 21-55 with 6 ≤ of DSM-IV ADHD criteria of inattention and/or hyperactivity/impulsivity in childhood; 5 ≤criteria DSM-IV ADHD criteria of inattention and/or hyperactivity/impulsivity in adulthood; chronic persisting ADHD from childhood to adulthood; moderate to severe impairment due to ADHD. Driver's license 3 + years.	Prior to study participation participants were effectively treated with MPH. MPH regular dose (mean 14.7 mg) or placebo 1.5 hrs before driving test	3 days no treatment prior to 1st test day. 6 / 7 days washout during crossover.	NR

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics
Levin 2007 U.S.	AARS Clinical Global Improvement scale (CGI) Targeted Adult Attention Deficit Disorder Scale (TAADDS)	Mean age 37.0 83% male 60% white 20% black 14% Hispanic 6% other	Employed full-time 72% placebo 50% MPH Baseline AARS Placebo 33.47 MPH 30.40
Medori 2008 Europe	Conners' Adult ADHD Rating Scales (CAARS) Primary Efficacy measure: CAARS: O-SV (observer) compared with baseline Secondary endpoint: CAARS: S-S (self) Clinical Global Impression Severity of Illness subscale (CGI-S); Sheehan's Disability Scale (SDS)	Mean age 34.0 54.4% male 97.5% white 2.5% other	Mean age at diagnosis: 29.9 Adult ADHD subtype: combined type 70.8% predominantly inattentive 24.2% predominantly hyperactive-impulsive 4.0% Alcohol / substance use disorders currently active .7% history not active 13.5% Mood and anxiety disorders currently active: 12% history and not active: 29.9%
Reimherr 2007	Wender-Reimherradult ADD Scale ADHD-RS CGI-I Assessed weekly	Age 30.6 Male 66% Ethnicity NR	#(%) ADHD alone 8(17) ADHD + Emotional dysregulation 18(38) ADHD +ED+ODD 19(40)
Verster 2008 Netherlands	Primary outcome measurement: standard deviation of lateral psotiion (SDLP) was measured by a driving test mounted with a camera that measured the vehicle's lateral position to the road delineation and recorded. The test was performe during normal traffic on a 100km track. Seconary outcome measurement: SD of speed and pt reports of driving performance was obtained by calculating the SD of speed (km/h). Patient reports of driving peformance was assessed by having patients rate 6 dimension fof their driving style and comparing their driving style to average drivers.	Mean age 38.3 61% male Ethnicity: NR	Baseline CAARS: 64.7 Baseline DSM attention index: 13.8 Baseline DSM hyperactivity index: 15.2 Baseline DSM ADHD index: 28.9 Mean years driving: 16.8 (range 3-30)

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Number screened/ eligible/ enrolled N per drug	Number withdrawn/ lost to fu/ analyzed: N per drug
Levin 2007 U.S.	1125/580/124 Placebo 53 MPH 53	Placebo/MPH Withdrawn 29/30 Lost to F/U NR
Medori 2008 Europe	448/NR/402 96 placebo 101 MPH 18 mg 102 MPH 36 mg 102 MPH 72 mg (total 401)	total withdrawn: 7 loss to fu: NR Analyzed 95/99/101/99 Efficacy: N=394 Safety: N=401
Reimherr 2007	NR/NR/47	6/NR/43-safety 41-efficacy
Verster 2008 Netherlands	72/19/19 10 MPH; 9 placebo	1 /10 MPH /0/9 placebo Lost to FU 0/18 9 MPH/ 9 placebo

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Results	Method of adverse effects assessment
Levin 2007 U.S.	AARS response rate 30% reduction Placebo 55% MPH 47% P = 0.44 Clinical Global Improvement scale (CGI) Placebo 30% MPH 34% P = 0.68 Targeted Adult Attention Deficit Disorder Scale (TAADDS) response 30% reduction Placebo 40% MPH 28% P = 0.22 No significant differences in cocaine use	NR but rated on a 0 to 3 scale (none to severe)
Medori 2008 Europe	Mean change in CAARS:O-SV (compared with baseline) N=493 placebo -7.6 (CI -9.63; -5.59); MPH 18 mg -10.6 (P=.015); MPH 36 mg -11.5 (P=.013); MPH 72 mg -13.7 (P<.001) (no sig. between MPH groups) CAARS: O-SV >30% reduction Placebo 27.4%; MPH 18 mg 50.5%; MPH 36 mg 48.5%; MPH 72 mg 59.6% (P< .001) (no sig. between MPH groups) Mean change in CAARS:S-S (compared with baseline) Placebo -5.8 (CI -8.14; -3.45); MPH 18 mg -10.4 (P=.003); MPH 36 mg -11.3 (P=.003); MPH 72 mg -14.4 (P<.001) Mean change in CGI-S from baseline (N=388) placebo -.5 (CI -.69; -.32); MPH 18 mg -.9 (P=.003); MPH 36 mg -.9 (P=.005); MPH 72 mg -1.2 (P<.001) Mean change in SDS (N=304) placebo -2.2 (CI -3.08; -1.27); MPH 18 mg -4.8 (P=.008); MPH 36 mg -4.1 (P=.NS); MPH 72 mg -5.1 (P=.004)	NR
Reimherr 2007	Mean total WRAADS score decrease Placebo 13% vs 42% OROS MPH P < 0.001 Mean total ADHD-RS score decrease Placebo 14% vs 41% OROS MPH P = 0.003	Assessed at interviews and spontaneously reported
Verster 2008 Netherlands	SDLP (cm) (Weaving of car) mean scores: Placebo 21.1; MPH 18.8 (difference 2.3) P=0.004 Lateral position: NS SD speed (km/h): NS Mean speed (km/h): NS Self Reports of driving quality: Compared to placebo, MPH improved driving quality (P=0.023); mental effort while driving less for MPH (P=0.028) (data not available)	NR

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Adverse Effects Reported	By treatment, total withdrawals; withdrawals due to adverse events
Levin 2007 U.S.	Headache placebo 2% MPH 8% GI upset placebo 4% MPH 8% Diarrhea placebo 9% MPH 2% Insomnia placebo 2% MPH 9%	Placebo/MPH Total 29/30 Due to AEs (side effects) 1/1 Most withdrew because "Not interested" 22/19
Medori 2008 Europe	Adverse event > 3% total (top 10 events listed) placebo; MPH (18 mg, 36 mg, 72 mg) Decreased appetite: pla 7.3%; 18 mg 19.8%; 36 mg 21.6%; 72 mg 34.3% Headache: pla 17.7%; 18 mg 25.7%; 36 mg 20.6%; 72 mg 16.7% Insomnia: pla 7.3%; 18 mg 11.9%; 36 mg 11.8%; 72 mg 16.7% Nausea: pla 4.2%; 18 mg 7.9%; 36 mg 15.7%; 72 mg 14.7% Dry mouth: pla 2.1%; 18 mg 7.9%; 36 mg 6.9%; 72 mg 20.6% Dizziness; pla 7.3%; 18 mg 5.9%; 36 mg 9.8%; 72 mg 8.8% Weight decreased: pla 5.2%; 18 mg 3%; 36 mg 7.8%; 72 mg 10.8% Nasopharyngitis: pla 9.4%; 18 mg 6.9%; 36 mg 7.8%; 72 mg (3.9%) Tachycardia: pla 0; 18 mg 4%; 36 mg 4.9%; 72 mg 7.8% Irritability: pla 1%; 18 mg 4%; 36 mg 3.9%; 72 mg 8.8% Cardiac (placebo vs. PR methylphenidate 75 mg) Systolic BP ≥ 140 mm Hg: pla 15.8% baseline, 19.3% week 5; PR MPH 13.9% baseline, 21.2 week 5 Diastolic BP ≥ 90 mm Hg: pla 25.3% baseline, 15.9% week 5; PR MPH 18.8% baseline, 27.1% week 5 Pulse ≥90 bpm pla 3.2% baseline, 5.7% week 5; PR MPH 1% baseline, 14.1% week 5.	Total withdrawals NR Withdrawals due to AE (n=13 4.3%) pla 1%; 18 mg 1%; 36 mg 3.9%; 72 mg 7.8%
Reimherr 2007	Placebo/ OROS MPH Mean weight change lbs 1.3 / -2.5 Decreased appetite 0/5 Sleep/insomnia 3/9 Anxiety 0/4 Subjects w/ at least 1 AE 39% / 55% at moderate impairment 23% / 39%	By trmt NA Total withdrawals 6 due to AEs NR
Verster 2008 Netherlands	NR	Placebo/ MPH 0/9; 1/9 0/18 withdrawals due to AE

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Comments
Levin 2007 U.S.	
Medori 2008 Europe	Withdrawals, loss to follow up not reported.
Reimherr 2007	
Verster 2008 Netherlands	Blinding: 61.1% patients guessed which treatment they received at day 22 of 36 test days.

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, regimen, duration)	Run-in/ Washout period	Allowed other medications/ interventions
MPH ER					
Rosler 2009 Germany	DB, RCT parallel-design	Outpatients >18 years of age who met diagnosis of ADHD using DSM-IV-TR criteria established by psychiatric expert. German short version of the Wender Utah rating scale (WURS) was used to make sure that childhood ADHD symptoms were present by a retrospective self report of the patient. Subjects needed a WAARDS score of > 28 points to be included in the study.	MPH ER (50% MPH IR and MPH 50% ER) bid morning and afternoon dose. 10 mg/day titrated 5 weeks up to 60 mg/day depending on efficacy and tolerability. Mean daily dose .55 mg/ kg. X24 weeks total	NR	NR

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics
MPH ER			
Rosler 2009 Germany	Primary outcome measure: Wender-Reimherr adult attention deficit disorder scale (WRAADDS) Secondary outcome measures: Conners adult ADHD rating scale self report long form (CAARS-S:L) DSM-IV symptoms total subscale (DATS) Clinical global impression scale (CGI)	Mean age: MPH 35.2; Pla 33.8 50% male	ADHD-DC score inattention: 7.7% hyperactivity/impulsitivity: 7.1% other characteristics: WRAADS score at baseline: MPH ER 44.8; pla. 45.5 CAARS-S:L DSM-IV ADHD total score at baseline: MPH ER 119.2; pla. 117.9 CGI severity of illness at baseline: MPH ER 5.0; pla. 5.1 Age at ADHD diagnosis:5.75 yrs

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Number screened/ eligible/ enrolled N per drug	Number withdrawn/ lost to fu/ analyzed: N per drug
MPH ER		
Rosler 2009 Germany	NR/NR/363 randomized (total) 241 MPH ER; 118 placebo 4 excluded (protocol violations)	MPH ER 58(24%); pla 52(43%) lost to FU: MPH ER 12 (5%); pla 11(9%) analyzed per drug: MPH ER 241; pla 118

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Results	Method of adverse effects assessment
MPH ER		
Rosler 2009 Germany	WAARDDS total effect size on the primary outcome was 0.39. Paired Wilcoxon-Test, P=0.004 (maintenance phase week 6 - week 24). WAARDDS > 30% reduction by week 24: 61% MPH ER vs. 42% pla (P=0.001) CAARS-DATS: at week 24 difference was statistically significant (P=0.016) in favor of MPH ER (data not reported). Effect size=0.028 CGI ratings of vast and decided improvement regarding therapeutic effect MPH ER =60.1%; pla=38.1% (P=0.0003)	Free registration of complaints of the patients Use of 40 somatic item sheet of the AMDP-system

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Adverse Effects Reported	By treatment, total withdrawals; withdrawals due to adverse events
MPH ER		
Rosler 2009 Germany	Adverse events MPH > placebo decreased appetite 38 vs. 13% dry mouth 30 vs. 16% difficulties falling asleep 25 vs. 18% palpitations 23 vs. 19% excessive thirst 24 vs. 12% menstrual difficulties 11 vs. 0% reduced libido 11 vs. 3% hyperhidrosis 12 vs. 1% hot flashes 10 vs. 5% diarrhea 9 vs. 4% seborrhea 8 vs. 2% breathing difficulties 8 vs. 1% tremor 7 vs. 0% cardiac pain 7 vs. 1% blurred vision 5 vs. 1% paresthesia 4 vs. 0% nausea 9 vs. 3% Adverse events placebo > MPH ER drowsiness 47 vs. 30% shortened sleep 26 vs. 15% gastric discomfort 26 vs. 15% excessive appetite 16 vs. 10% chills 14 vs. 9% heaviness in legs 13 vs. 5% micturition difficulties 5 vs 1% vomiting 2.6 vs. .4%	MPH ER 58 (24%); pla 52 (43%) withdrawals due to AE MPH ER 31 (13%); pla 10 (8%)

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Comments
MPH ER	
Rosler 2009 Germany	

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, regimen, duration)	Run-in/ Washout period	Allowed other medications/ interventions
MPH OROS					
Adler 2009 U.S.	RCT, DB	Age 18-65 years with a minimum weight of 100 lbs (45.4 kg) at Screening. Diagnosis of ADHD as defined by the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria with symptomatology from childhood to adulthood, symptoms present before age seven years and continue to meet full DSM-IV criteria at time of assessment. Diagnosis of ADHD confirmed by the Adult ADHD Clinical Diagnostic Scale (ACDS) at Baseline and Adult ADHD Investigator Symptom Rating Scale (AISRS) score of 24 or greater as determined by the Investigator at Baseline. Global Assessment of Functioning (GAF) Scale score of 41 to 60, inclusive, at Baseline.	MPH OROS Starting dose was 36 mg/d (subjects unable to tolerate the initial dose of 36 mg were discontinued from the study) Incremental dose increases of 18 mg every 7 days (±2 days) were continued until a protocol-defined response was achieved (36mg, 54mg, 72mg, 90mg, or 108mg) or the highest dose was reached (108 mg/d). Placebo All subjects assigned to placebo followed the same dosing schedule and procedures as those for the subjects randomized to MPH OROS. Duration: 7 weeks.	7-14 days	No additional MPH or other ADHD medication
Mixed amphetamine salts extended release					
Goodman, 2005 (QU.E.S.T)	Open label Multi-center	outpatients >18 years of age who were referred by clinics and had a primary diagnosis of ADHD established by psychiatric evaluation using *DSM-IV-TR* criteria	Daily morning dose of placebo MAS XR 20 mg, 40 mg, or 60 mg for 4 weeks	One week washout	NR

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics
MPH OROS			
Adler 2009 U.S.	Primary Outcomes Change from Baseline in the Adult ADHD Investigator Symptom Rating Scale (AISRS) total score as assessed by the investigator at the Final Visit/Two Week Efficacy Assessment Visit (last observation carried forwarded; LOCF). Secondary Outcomes Clinical Global Impression-Improvement (CGI-I) rating at the final visit Percentage of Responder (defined as subjects with 30% improvement in AISRS Score and a CGI-I rating of much or very much improve) was assessed at each Titration Visits and at the Final Visit.	mean age: 39 years male: 56.8% Race: 86% Caucasian 6.1% African American 3.1% Asian 4.8% Other	ADHD subtype: combined 79.9% Baseline mean global assessment of functioning: MPH OROS 53.1; placebo 53
Mixed amphetamine salts extended release			
Goodman, 2005 (QU.E.S.T)	ADHD rating scale at clinic visits Conners' Adult ADHD Rating Scale-Short Version-Self-Report (CAARS-S-S) 4- and 12-hours postdose 3 days/week during the washout week and each of the 4 treatment weeks. CGI-S baseline and endpoint CGI-I baseline and weekly CGI-E weekly	Mean age (yrs): Placebo 39.3 20mg 38.8 40mg 38.9 60mg 39.9 Male (%) Placebo 68 20mg 64 40mg 59 60mg 48 Ethnicity (%) White: Placebo 90 20mg 87 40mg 91 60mg 88 African American: Placebo 5 20mg 5 40mg 3 60mg 0 Hispanic: Placebo 3 20mg 6 40mg 3 60mg 8 Other: Placebo 2 20mg 2 40mg 3 60mg 3	Years since diagnosis Placebo 5.0 20mg 4.6 40mg 4.9 60mg 7.1 ADHD-RS (baseline) Placebo 33.0 20mg 31.1 40mg 31.3 60mg 32.9

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Number screened/ eligible/ enrolled N per drug	Number withdrawn/ lost to fu/ analyzed: N per drug
MPH OROS		
Adler 2009 U.S.	348/NR/229 113 randomized to MPH OROS 116 randomized to placebo	MPH OROS 42/8/110 (3 patients randomized failed to meet inclusion criteria and did not receive study packets) placebo 26/4/116
Mixed amphetamine salts extended release		
Goodman, 2005 (QU.E.S.T)	339/259/255 Placebo-64 20mg-66 40mg-64 60mg-61	Number withdrawn Placebo 22 20mg 19 40mg 15 60mg 16 Lost to FU Placebo 2 20mg 4 40mg 1 60mg 3 Analyzed Placebo 60 20mg 64 40mg 64 60mg 60

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Results	Method of adverse effects assessment
MPH OROS		
Adler 2009 U.S.	Primary Endpoint Least squares mean (LSMean) change from baseline AISRS total score: MPH OROS (-10.6); placebo (-6.8), P=0.012. Secondary Endpoints Least squares mean final visit CGI-I score (lower values indicated improvement): MPH OROS (3.02); placebo (3.43) at the Final Visit (LOCF), p=0.008. Responders (subjects who had at least 30% improvement in the AISRS score and had a CGI-I score of 1 or 2 (very much improved or much improved). MPH OROS (36.9%) compared with the placebo group (20.9%) were responders at the Final Visit (LOCF), P=0.009.	Adverse events: throughout the course of the study Blood pressure and pulse: throughout the course of the study Triplicate blood pressure and pulse measurements were recorded at all study visits and were assessed after subjects had been seated for three minutes between each measurement. ECG: at screening, baseline, the visit subsequent to each upward dose titration, and the Final Visit. Weight was recorded at all study visits Laboratory tests: at screening and the Final Visit.
Mixed amphetamine salts extended release		
Goodman, 2005 (QU.E.S.T)	SF-36 (version 2) Change from baseline to endpoint N=702 Changes are presented in table format and are estimated here for the purpose of reporting results physical functioning: change aprox. 5 points; P< .001 role/physical: change aprox. 9 points; P< .001 bodily pain NS general health: change aprox. 5 points; P< .001 vitality: change aprox. 20 points; P<.001 social functioning: change aprox. 10 points; P< .001 role/ emotional: change aprox. 20 points; P< .001 mental health: change aprox. 12 points; P< .001	Physical examination, neurologic evaluation, vital sign measurements, and clinical laboratory test results. A 12-lead ECG, performed at baseline and 2-week intervals,

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Adverse Effects Reported	By treatment, total withdrawals; withdrawals due to adverse events
MPH OROS		
Adler 2009 U.S.	Total AE reported: MPH OROS 93 (84.5%); placebo 74 (63.8%) AE reported by at least 10% of MPH OROS subjects decreased appetite: MPH OROS 25.5%; pla 6% headache: MPH OROS 25.5%; pla 13.8% dry mouth: MPH OROS 20.0%; pla 5.2% anxiety: MPH OROS 16.4%; pla 3.4% nausea: MPH OROS 12.7%; pla 2.6% blood pressure increased: MPH OROS 10%; pla 5.2% Change in blood pressure and pulse Mean (SD) change in systolic blood pressure from baseline to the final visit was –1.2 (8.92) mm Hg for MPH OROS –0.5 (9.72) mm Hg for placebo. Mean (SD) change in diastolic blood pressure from baseline to the final visit was +1.1 (6.72) mm Hg for MPH OROS and +0.4 (7.43) mm Hg for placebo. Mean (SD) change in pulse was +3.6 (9.78) bpm for MPH OROS and –1.6 (8.33) bpm for placebo.	MPH OROS: 42 (due to AE n=16) placebo: 26 (due to AE n=6)
Mixed amphetamine salts extended release		
Goodman, 2005 (QU.E.S.T)	Placebo/20mg/40mg/60mg (%) Anorexia: 3/20/42/38 Insomnia: 13/21/30/26 Headache: 16% vs 4% (p=0.18)3/14/30/26 Nervousness: 13/11/16/12 Dry mouth: 5/24/44/38 Weight loss: 0/5/16/12 Nausea: 5/8/6/10 Agitation: 5/8/6/10 Anxiety: 3/6/6/10	Total withdrawals Placebo 22 20mg 19 40mg 15 60mg 16 Withdrawals due to Aes (%) Placebo 1 20mg 9 40mg 6 60mg 8

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Comments
MPH OROS	
Adler 2009 U.S.	
Mixed amphetamine salts extended release	
Goodman, 2005 (QU.E.S.T)	

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, regimen, duration)	Run-in/ Washout period	Allowed other medications/ interventions
Kay 2009 United States (see note in comments section)	RCT, DB, Crossover	Age 19-25 with the following criteria satisfied. DSM-IV diagnosis of ADHD Score of ≥ 24 (severity worse to moderate range) on ADHD-RS rating scale Normal intellectual functioning (score ≥ 89 on Wechsler abbreviated Scale of Intelligence) Demonstrated no greater than average performance on at least two standardized measures of executive function (Stroop Color and Word Test; Halstead-Reitan Category Test)	Mixed amphetamine salts extended release (MAS XR) titrated up to 50 mg/day x 3 weeks Placebo titrated up to 50 mg/ day x 3 weeks	Washout period for other drugs was 7-28 days. No washout between crossover.	NS
Modafinil					
Turner, 2004 U.K. (Fair)	DB RCT crossover design	DSM-IV diagnosis of ADHD; DSM-IV ratings from patient and/or informant of predominantly inattentive type and/or hyperactive-impulsive type during childhood and previous 6 months, and judgment by a consultant psychiatrist that patients' symptoms interfered with ability to function and were not explained by another disorder. Patients were also assessed by the GSI.	Modafinil single oral dose of 200 mg Lactose placebo, single oral dose 10 subjects were randomized to receive a single oral dose of lactose placebo first, followed by single dose of modafinil in the second session; the time of day that the dose was administered was not reported. 10 subjects were randomized to receive the drug first, followed by placebo. The single-dose treatment sessions were separated by one week. Duration: 1 week	Run-in NR; 1-week washout between single-dose treatment phases	NR

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics
Kay 2009 United States (see note in comments section)	Primary outcome measure: Driving Safety Score consisting of 8 variables (traffic tickets, total collisions, time to collision, driving out-of-lane incidents, percentage of time above excessive speed threshold, number of times over cornering, number of times tailgating). The eighth variable is the rating of the driver's response to crash-likely events. DSS test scores were standardized using population based z-scores. Subjects were tested at 2,7,and 12 hours after dose on test day (3 weeks after the start of drug treatment). The mean z-score for the three tests is reported for visits 3 and 4. Lower score=better driving Subjects returned 3 weeks later and were tested again (visit 4) this time either placebo or Atomoxetine (80 mg). Secondary Efficacy Assessments: Above mentioned measures ADHD symptom severity assessed by ADHD-RS and CGI scale (clinician's assessment of baseline condition severity and change in improvement)	Mean age: 22.3 Male: 89.5% Caucasian: 78.9% African American: 10.5% Asian 5.3%	Mean Weight (lbs): 173.8 Mean Height (inches): 69.2
Modafinil			
Turner, 2004 U.K. (Fair)	Patients were tested 2 hours post drug administration for approximately 2 hours. Testing sessions were separated by at least a week. Neuropsychological test battery, including CANTAB; Logan stop-signal task; PRM task; IDED; NTOL The order in which patients received the tasks differed for placebo and drug conditions and was randomized across patients.	Mean age 28 65% male Ethnicity NR	Mean NART score 108 Mean GSI score 1.6 Mean education 13.5 Subjects were matched for age, NART verbal IQ, education level, and GSI, previous use of stimulant medication, current use of stimulant medication

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Number screened/ eligible/ enrolled N per drug	Number withdrawn/ lost to fu/ analyzed: N per drug
Kay 2009 United States (see note in comments section)	NR/NR/19 9 MAS XR 10 placebo	4/0/MAS XR 8/pla 7
Modafinil		
Turner, 2004 U.K. (Fair)	NR/NR/20 Enrolled in 1st treatment phase: 10 in modafinil, 10 in placebo	Withdrawn NR Lost to followup NR 20 (100%) analyzed Analysis of 1st treatment phase included 10 in modafinil, 10 in placebo

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Results	Method of adverse effects assessment
Kay 2009 United States (see note in comments section)	**Mean Driving Scores (driving safety score = z score)** 2 hr. test: Pla 0.28; MAS XR -0.26 (0.54) P=NS 7 hr. test: Pla 0.33; MAS XR -0.31 (0.64) P=0.013 12 hr. test: Pla 0.31; MAS XR -0.29 (6) P=0.005 Mean total score: pla 0.3; MAS XR -0.29 P=0.014 ADHD-RS and CGI-I scores: ADHD-RS score: Improved ≥30% baseline: MAS XR 80%; pla 13.3% P=0.0004 CGI-I: subjects rated as very much/ much improved: MAS XR 66.7%; pla 0% P=NE	At each study visit and during a follow-up phone interview 30 days after study completion, "subjects could volunteer information" about AEs.
Modafinil		
Turner, 2004 U.K. (Fair)	Mean score among outcomes with significant drug x order interactions, on which a between-subjects analysis for the first session only was performed, modafinil vs placebo: Immediate PRM % correct 91.25 vs 91.25 (ns) DMTS % correct 87.50 vs 79.80 (p=0.016) SSP span length 6.50 vs 6.35 (ns); total errors 53.65 vs 55.10 (ns) NTOL latency (all moves) 19126 vs 15351 ms (p=0.004) RVIP target sensitivity (A') 0.937 vs 0.926 (ns) Mean scores on other tests, on which data from both sessions was combined, modafinil vs placebo: Digit span forwards score: 9.45 vs 8.00 (p<0.001); backwards score 8.35 vs 7.00 (p=0.017) Immediate PRM response latency 1889 vs 1714 ms (ns) Delayed PRM % correct 8735 vs 79.8 (p=0.016); response latency in ms 2340 vs 1769 (ns) PAL 1st trial memory score 16.7 vs 15.8 (ns); total errors 9.25 vs 9.95 (ns); total trials 8.1 vs 8.65 (ns) DMTS latency 5057 vs 4121 ms (ns) SWM strategy score 29.5 vs 30.1 (ns); between errors 17.35 vs 19.8 (ns); within errors 1.3 vs 1.35 (ns) NTOL mean attempts (all moves) 7.22 vs 7.86 (p=0.009) RVIP mean latency 439 vs 434 ms (ns); response bias (B") 0.83 vs 0.97 (ns) IDED total errors 24.4 vs 22.4 (ns); total reversal errors 12.2 vs 12.9 (ns); total EDS errors 7.7 vs 4.9 (ns) Gamble probability of choosing most likely outcome 0.92 vs 0.91 (ns); % bet (average) 58.7 vs 57.44 (ns); deliberation time 2473 vs 2244 ms (ns) STOP go reaction time 444 vs 420 ms (ns); go reaction time variability 137 vs 124 (ns); stop-signal reaction time 150.1 vs 172.7 (p=0.028); errors 5.7 vs 3.0 (ns)	Subjective measures were self-rated on 16 measures. Blood pressure and pulse were taken before drug administration and at 2, 3, and 4 hours after drug administration.

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Adverse Effects Reported	By treatment, total withdrawals; withdrawals due to adverse events
Kay 2009 United States (see note in comments section)	Total AE reported: MAS XR 12 (75%); pla 3 (16.7%) gastrointestinal: MAS XR 3 (18.8%); 1 (5.6%) dry mouth: MAS XR 3 (18.8%); pla 0 nausea: MAS XR 1 (6.3%); pla 1 (5.6%) general: MAS XR 1 (6.3%); pla 1 (5.6%) weight decrease: MAS XR 4 (25%); pla 1 (5.6%) metabolism/ nutrition: MAS XR 8 (50%); pla 0 anorexia: MAS XR 8 (50%); pla 0 nervous system: MAS XR 4 (25%); pla 1 (5.6%) headache: MAS XR 2 (12.5%); pla 1 (5.6%) Psychiatric: MAS XR 7 (43.8%); pla 0 Anger: MAS XR 2 (12.5%); pla 0 Anxiety: MAS XR 2 (12.5%); pla 0 Bruxism: MAS XR 3 (18.8%); pla 0 Insomnia: MAS XR 3 (18.8%); pla 0 Irritability: MAS XR 2 (12.5%); pla 0	MAS XR 1; Pla 3 Withdrawals due to AE 1 (MAS XR); 1 (placebo).
Modafinil		
Turner, 2004 U.K. (Fair)	NR	Modafinil vs placebo, Total withdrawals 0 vs 0 Withdrawals due to AEs 0 vs 0

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Comments
Kay 2009 United States (see note in comments section)	This study included two separate placebo controlled studies within a crossover study. Cohort 1: MAS XR vs. placebo Cohort 2: Atomoxetine vs. placebo (see Atomoxetine section)
Modafinil Turner, 2004 U.K. (Fair)	

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

	Internal Validity					
Author, Year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
Adler, 2009	Yes	Yes	Yes	Yes	NR	Yes
Adler, 2008 Atomoxetine	Method NR	Method NR	Yes	Yes	Not reported	NR
Adler, 2008 Lisdexamfetamine	Method NR	Method NR	Yes	Yes	Yes	NR
Barkley, 2007	Method NR	Yes	N/A (within group crossover design)	Yes	Yes	No
Biederman, 2006	Method NR	Method NR	No, SS difference in age and ADHD onset	Yes	NR	NR
Bouffard, 2003	No (numbers chosen from a hat)	No (see comment in Evidence Table)	Not reported by phase; same subjects exposed to both treatments	Yes	Yes but method not described	NR
Carpentier, 2005	Method NR	Method NR	NR	Yes	NR	NR
Chronis-Tuscano, 2009	NR	NR	Yes	Yes	NR	NR

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

		Internal Validity			
Author, Year	**Patient masked?**	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/ high**	**Intention-to-treat (ITT) analysis; If No: % analyzed**	**Post-randomization exclusions**
Adler, 2009	Yes	Yes NR Yes NR	No/ no	Yes	Yes, 3 patients randomized ot MPH OROS failed to meet inclusion criteria and did not receive study medication.
Adler, 2008 Atomoxetine	Not reported	Yes NR Yes NR	High: Yes, (58%) Differential: no	Unclear	No
Adler, 2008 Lisdexamfetamine	Yes	Yes No NR No	No/ no 7 (2%)	141 (98%)	No
Barkley, 2007	Yes	Yes no no no	No/ no	NR	No
Biederman, 2006	Yes	Yes NR NR NR	No/ no	No 141/149 (95%) analyzed	No
Bouffard, 2003	Yes but method not described	NR NR NR NR	No/ no	No: 79%	No
Carpentier, 2005	Yes	Yes NR NR NR	No/ no	No 19/25 (76%) analyzed	No
Chronis-Tuscano, 2009	stated blinding, but no details given	NR NR NR NR	No. 2/23	No: 87%	No

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

Author, Year	Quality rating
Adler, 2009	Fair
Adler, 2008 Atomoxetine	Fair
Adler, 2008 Lisdexamfetamine	Fair
Barkley, 2007	Fair
Biederman, 2006	Poor
Bouffard, 2003	Fair
Carpentier, 2005	Fair
Chronis-Tuscano, 2009	fair

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

	External Validity
Author, Year	**Number screened/ eligible/ enrolled**
Adler, 2009	348/NR/229
Adler, 2008 Atomoxetine	NR/NR/410
Adler, 2008 Lisdexamfetamine	NR/NR/420
Barkley, 2007	32/22/20
Biederman, 2006	204/178/149
Bouffard, 2003	93/NR/38 Same subjects exposed to both treatments
Carpentier, 2005	NR/NR/25
Chronis-Tuscano, 2009	71/28/23

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

Author, Year	Exclusion criteria
Adler, 2009	Excluded patients known to be non-responders to methylphenidate. History of allergy, sensitivity methylphenidate. Coexisting medical condition or taking concomitant medication that would interfere with safe administration of methylphenidate. Known or suspected structural cardiac abnormality. Diagnosis of or family history of Tourette's syndrome, or motor or verbal tics. History of seizures or a seizure disorder. Uncontrolled hyperthyroidism or hypothyroidism. Marked anxiety, tension or agitation, moderate severity of depression. Co-morbid psychiatric diagnosis of bipolar disorder, cyclothymic disorder, schizophrenia, schizoaffective disorder, pervasive developmental disorder or severe obsessive-compulsive disorder. History of drug or alcohol abuse within the past 6 months. Suicidal ideation or behavior over the past year.
Adler, 2008 Atomoxetine	Diagnosis of current major depression, an anxiety disorder, any current alcohol or substance abuse, lifetime history of bipolar illness or psychotic disorder. Also excluded if they had any medical illness that would contraindicate use of atomoxetine, current/ past hypertension, or organic brain disease.
Adler, 2008 Lisdexamfetamine	Comorbid psychiatric diagnosis with significant symptoms; history of seizures; taking medications that affect the central nervous system or blood pressure (excluding current ADHD meds); known cardiac abnormality; clinically significant ECG or laboratory abnormality at screening; history of hypertension; resting
Barkley, 2007	Diagnosis of bipolar disorder or any history of psychotic disorder; organic brain disease, traumatic brain injury; seizure disorder, history of adverse drug reactions; drug/ alcohol abuse; current use of psychotropic medication; pregnancy or breastfeeding; or use of any antipsychotic medication or mood stabilizers within 8 weeks of visit one.
Biederman, 2006	Clinically significant chronic medical conditions, abnormal baseline laboratory values, IQ <80, delirium, dementia, amnesic disorders, other clinically unstable psychiatric condition; drug or alcohol abuse or dependence w/in 6 mos; previous participation in MPH trial
Bouffard, 2003	Excluded psychiatric conditions that better accounted for their current symptoms or required other treatment; substance abuse in preceding 6 months; medical condition contraindicating stimulants (that is, hypertension or cardiac disease)
Carpentier, 2005	Psychiatric comorbidity that prevented study protocol compliance
Chronis-Tuscano, 2009	Mothers: any current Axis I disorder other than ADHD, Beck Depression Inventory-II scores above 16, severe tics or Tourette's syndrome, history of seizures or abnormal electroencephalogram, high BP, narrowing/ blockage of gastrointestinal tract, pregnancy, breast feeding, positive urine drug screen at intake, or concomitant psychotropic medication use.

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

	External Validity			
Author, Year	**Run-in/Washout**	**Class naïve patients only**	**Control group standard of care**	**Funding**
Adler, 2009	7-14 days	no	yes	Johnson & Johnson Pharmaceutical Research and Development
Adler, 2008 Atomoxetine	up to 28 days	NR	Yes	NR
Adler, 2008 Lisdexamfetamine	7-28 days	No	Yes	Shire Development Inc.
Barkley, 2007	NR/NR	NR	Yes	NR
Biederman, 2006	NR/NR	No	Yes	McNeil Consumer and Specialty Pharmaceuticals
Bouffard, 2003	3-day run-in of increasing dosages (15/30/45 mg/day); 5 to 7-day washout btw. active & placebo phases	No	Yes	FRSQ grant
Carpentier, 2005	Washout of psychotropic medication (duration NR)	NR	Yes	Novadic-Kentron Institute
Chronis-Tuscano, 2009	Run-in 5 weeks	NR	YES	McNeil Pediatrics

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

Author, Year	Relevance
Adler, 2009	Yes
Adler, 2008 Atomoxetine	Yes
Adler, 2008 Lisdexamfetamine	Yes
Barkley, 2007	Yes
Biederman, 2006	Yes
Bouffard, 2003	Yes
Carpentier, 2005	Inpatients
Chronis-Tuscano, 2009	Yes

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

	Internal Validity					
Author, Year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
Cox, 2000	Method NR	Method NR	Yes, except for history of moving violations and car crashes	Yes	Yes	Yes
Gualtieri, 1985	Method NR	Method NR	Not reported by phase; same subjects exposed to both treatments	Yes	Yes but method not described	NR
Kay, 2009	NR	NR	yes	yes	NR	NR
Kinsbourne, 2001	Method NR	Method NR	Not reported by phase; same subjects exposed to both treatments	Yes	Yes	NR
Levin, 2001	NR	NR	NR	Yes	Yes	Yes
Levin, 2006	Method NR	Method NR	Yes, except for employment status (significantly higher proportion of pts in bupropion group employed)	Yes	NR	NR
Levin, 2007	Method NR	Method NR	Yes	Yes	NR	NR

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

		Internal Validity			
Author, Year	**Patient masked?**	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/ high**	**Intention-to-treat (ITT) analysis; If No: % analyzed**	**Post-randomization exclusions**
Cox, 2000	Yes	Yes no no no	No/ no	Yes	No
Gualtieri, 1985	Yes but method not described	Yes NR NR NR	No/ no	Yes	No
Kay, 2009	pills the same	NR NR NR NR	No	No, 3 subjects taken out in cohort 1	No
Kinsbourne, 2001	Yes	No No No Yes	No/ no	Yes	No
Levin, 2001	Yes	Yes NR NR NR	NR	No	No
Levin, 2006	Yes	Yes NR NR NR	No/ no	Yes	No
Levin, 2007	Yes	NR NR NR NR	No/ no	Yes	No

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

Author, Year	Quality rating
Cox, 2000	Fair
Gualtieri, 1985	Fair
Kay, 2009	fair
Kinsbourne, 2001	Fair
Levin, 2001	Fair
Levin, 2006	Fair
Levin, 2007	Fair

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

	External Validity
Author, Year	**Number screened/ eligible/ enrolled**
Cox, 2000	NR/NR/13 Same subjects exposed to both treatments
Gualtieri, 1985	NR/NR/8 Same subjects exposed to both treatments
Kay, 2009	NR/NR35 (total)
Kinsbourne, 2001	NR/NR/17 Same subjects exposed to all treatments
Levin, 2001	NR/NR/40 Placebo patch + placebo pill, n=10 Nicotine, n=10 Methylphenidate, n=10 Nicotine + methylphenidate, n=10
Levin, 2006	526/232/98
Levin, 2007	1,125/580/106

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

Author, Year	Exclusion criteria
Cox, 2000	Excluded major psychiatric illness and Tourette's disease (screened using SCID), and active (past 12 month) substance abuse using the Michigan Alcoholism Screening Test and a urine drug screen.
Gualtieri, 1985	Not reported
Kay, 2009	Subjects that were naive to pharmacologic treatment of ADHD were excluded. Also, Women who were pregnant or lactating; recent history (6 mo) of drug dependence or substance abuse; alcohol use 24 hrs before test; any cardiac condition; current comorbid psychiatric diagnosis with significant Sx; documented failure to respond to amphetamines or atomoxetine; history of seizure; Tourette's syndrome, thyroid dysfunction; glaucoma.
Kinsbourne, 2001	Not reported
Levin, 2001	Participants with diagnoses of major depressive disorder or generalized anxiety disorder were excluded; medical exclusion criteria covered all relevant concerns for use of nicotine in a transdermal patch form: hypertension, cardiac disease, cerebrovascular disease, impaired renal function, history of seizure, skin disease, sensitivity to medical dressings or tapes, and history of skin allergies
Levin, 2006	DSM-IV criteria for current psychiatric disorders other than ADHD or substance abuse; physiologically dependent on sedatives or alcohol; suicidal or homicidal behavior within 2 yrs of study; use of prescription psychotropic medications other than methadone; unstable medical condition that would make participation hazardous; known sensitivity to methylphenidate or bupropion; nursing and/or pregnant; could not read or understand self-report assessment forms unaided or so severely impaired they could not comply with the requirements of the study
Levin, 2007	DSM-IV criteria for current psychiatric disorders other than ADHD or substance abuse; physiologically dependent on opioids, sedatives or alcohol; suicidal or homicidal behavior within 4 yrs of study; use of prescription psychotropic medications other than methadone; unstable medical condition that would make participation hazardous; known sensitivity to methylphenidate; nursing and/or pregnant; unable to give full and informed consent

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

	External Validity			
Author, Year	**Run-in/Washout**	**Class naïve patients only**	**Control group standard of care**	**Funding**
Cox, 2000	NR/NR	No	Yes	University of Virginia Health Sciences Center grant
Gualtieri, 1985	Run-in NR; 68-hr washout between treatment phases	No	Yes	USPHS Grant HD-10570
Kay, 2009	up to 28 days	NO	Yes	Shire Pharmaceuticals
Kinsbourne, 2001	NR/NR	No	Yes	Not reported
Levin, 2001	NR/NR	Unclear	Yes	NR
Levin, 2006	2 wk placebo run-in; washout NR	No	Yes	NIDA grants #R01 DA00144, K02 00465 and K02 DA 00288
Levin, 2007	1 wk placebo run-in, washout NR	No	Yes	NIDA grants # ROI DA11755 and K02 00465

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

Author, Year	Relevance
Cox, 2000	Yes
Gualtieri, 1985	Yes
Kay, 2009	Yes
Kinsbourne, 2001	Yes
Levin, 2001	Yes
Levin, 2006	Yes
Levin, 2007	Yes

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

	Internal Validity					
Author, Year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
Mattes, 1984	Method NR	Method NR	Not reported by phase; same subjects exposed to both treatments	Yes	Yes but method not described	NR
Medori, 2008	Yes	Yes	Yes	Yes	Described as double blind, but no details reported	NR
Michelson, 2003	Yes	Method NR	Yes	Yes	Yes	NR
Paterson, 1999	Method NR	Method NR	Yes	Yes	Yes but method not described	NR
Reimherr, 2007	Method NR	Method NR	Yes - there were some difference b/t groups but they did not reach statistical significance	Yes	NR	NR
Rosler, 2009	NR	NR	Yes	Yes	NR	NR
Schubiner, 2002	NR	NR	No; MPH>placebo in ASI psychiatric composite scores	Yes	Yes	Yes

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

		Internal Validity			
Author, Year	**Patient masked?**	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/ high**	**Intention-to-treat (ITT) analysis; If No: % analyzed**	**Post-randomization exclusions**
Mattes, 1984	Yes but method not described	NR NR NR NR	No/ no	No: 92%	No
Medori, 2008	Described as double blind, but no details reported	Yes NR NR NR	No/ no	No, excluded 7/401 (2%)	Yes
Michelson, 2003	Yes	Yes no no no	No/ no	No: 96%	No
Paterson, 1999	Yes	Yes NR NR NR	No/ no	Yes	No
Reimherr, 2007	Yes	Yes Yes Yes Yes	No/ no	No Efficacy analysis: 41/47 (87%) Safety analysis: 43/47 (91%)	No
Rosler, 2009	NR	NR NR NR NR	No. MPH ER 5%; pla 9%	Yes	No
Schubiner, 2002	Yes	Yes no no no	NR	Yes	No

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

Author, Year	Quality rating
Mattes, 1984	Fair
Medori, 2008	Fair
Michelson, 2003	Fair
Paterson, 1999	Fair
Reimherr, 2007	Fair
Rosler, 2009	Fair
Schubiner, 2002	Fair

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

	External Validity
Author, Year	**Number screened/ eligible/ enrolled**
Mattes, 1984	2829/116/66 Same subjects exposed to both treatments
Medori, 2008	448/402/402
Michelson, 2003	448/329/280 Atomoxetine n=141 Placebo n=139 388/325/256 Atomoxetine n=129 Placebo n=127
Paterson, 1999	68/51/45 24 dexamphetamine 21 placebo
Reimherr, 2007	NR/NR/41
Rosler, 2009	NR/NR/363
Schubiner, 2002	932/338/59 Methylphenidate n=24 Placebo n=24 Pemoline n=11 (dropped from analysis)

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

Author, Year	Exclusion criteria
Mattes, 1984	Excluded patients who met DSM-III criteria for schizophrenia, major affective disorder except a major depressive episode of mild severity, any other psychosis, mental retardation (mild or worse), organic brain syndrome, or current drug or alcohol dependence (drug or alcohol abuse was allowed).
Medori, 2008	Patients were excluded if the investigator judged they had a history of poor response or intolerance to methylphenidate; they had been diagnosed with any current clinically unstable psychiatric condition; diagnosed with substance use disorder within the last 6 months; family history of schizophrenia or affective psychosis; or serious illness.
Michelson, 2003	Excluded patients with current major depression or anxiety disorder; patients with current or past bipolar or psychotic disorders; patients with serious medical illness; patients who met DSM-IV criteria for alcohol dependence. Patients actively using recreational drugs at time of study entry were excluded. Urine screening for drugs of abuse was performed at the initial visit, and could be repeated during the trial at the investigator's discretion.
Paterson, 1999	Patients were excluded if they had an insufficient ADHD score, or comorbidity for other major psychiatric disorders, including a history of current substance abuse. Organic disorders that would contraindicate the use of dexamphetamine were also excluded.
Reimherr, 2007	DSM-IV current at time of study diagnosis of major depressive disorder, generalized anxiety disorder, panic disorder, OCD, PTSD, bipolar disorder, schizophrenia, other psychotic disorder; seizure disorder, hyper- or hypothyroidism; medical conditions likely to be destabilized with MPH treatment
Rosler, 2009	IQ < 85, schizophrenia, bipolar disorder, acute depressive episode, acute anxiety disorders and other unstable psychiatric conditions. Subjects with any serious medical illness or evidence of drug and alcohol dependence during prior 6 months. Pregnant or nursing women were also excluded, as were subjects who had participated in a drug trial during the past 30 days. Subjects treated with any psychopharmacological drug in addition to the study drug.
Schubiner, 2002	Less than an estimated IQ of 75 on the Shipley Institute of Living scale; schizophrenia, bipolar disorder, dementia, and delirium

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

	External Validity			
Author, Year	**Run-in/Washout**	**Class naïve patients only**	**Control group standard of care**	**Funding**
Mattes, 1984	NR/NR	No	Yes	Public Health Service grant
Medori, 2008	up to 4 weeks	No	Yes	Janssen Pharmaceutica N.V.; Belgium
Michelson, 2003	1-week washout, followed by 2-week placebo lead-in phase	No	Yes	Eli Lilly
Paterson, 1999	NR/NR	No	Yes	Health Department of Western Australia
Reimherr, 2007	Screening/baseline run-in (not further described)	NR	Yes	McNeil Pediatrics
Rosler, 2009	Wash out (≥2 weeks) of psychopharmacological drugs to be included in study.	NR	Yes	Medice
Schubiner, 2002	NR/NR	Unclear	Yes	National Institute on Drug Abuse Grant R01 DA 10271-03 and a Joe Young Srs. Research grant from the State of Michigan

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

Author, Year	Relevance
Mattes, 1984	This study included adults with ADD symptoms, with or without ADHD in childhood. Outcomes represent 26 patients with childhood ADHD; AEs reflect the experience of all study subjects.
Medori, 2008	Yes
Michelson, 2003	Yes
Paterson, 1999	Yes
Reimherr, 2007	Yes
Rosler, 2009	Yes
Schubiner, 2002	Yes

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

	Internal Validity					
Author, Year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
Spencer, 1995	Method NR	Method NR	Not reported by phase; same subjects exposed to both treatments	Yes	Yes	NR
Spencer, 2001	Method NR	Method NR	Not reported by phase; same subjects exposed to both treatments	Yes	Yes	NR
Spencer, 2005	Method NR	Method NR	No - MPH group younger	Yes	Yes	Yes
Spencer, 1998	Method NR	Method NR	Not reported by phase; same subjects exposed to both treatments	Yes	NR	NR
Tenenbaum, 2002	Method NR	Method NR	Not reported	Yes	Yes but method not described	NR

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

		Internal Validity			
Author, Year	**Patient masked?**	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/ high**	**Intention-to-treat (ITT) analysis; If No: % analyzed**	**Post-randomization exclusions**
Spencer, 1995	Yes	Yes NR NR NR	No/ no	No: 92%	No
Spencer, 2001	Yes	Yes NR NR NR	No/ no	No: 90%	No
Spencer, 2005	Yes	Yes NR NR NR	NR	No	No
Spencer, 1998	Yes	Yes NR NR NR	No/ no	No: 95.4%	No
Tenenbaum, 2002	Yes	Yes NR NR NR	No/ no	No: 72.7%	No

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

Author, Year	Quality rating
Spencer, 1995	Fair
Spencer, 2001	Fair
Spencer, 2005	Poor
Spencer, 1998	Fair
Tenenbaum, 2002	Fair

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

	External Validity
Author, Year	**Number screened/ eligible/ enrolled**
Spencer, 1995	85/25/25 N per drug during first phase not reported.
Spencer, 2001	103/41/30 Same subjects exposed to both treatments
Spencer, 2005	289/NR/146
Spencer, 1998	NR/NR/22
Tenenbaum, 2002	128/85/33 Same subjects exposed to all treatments.

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

Author, Year	Exclusion criteria
Spencer, 1995	Excluded prospective subjects if they had any clinically significant chronic medical conditions or abnormal baseline laboratory values or a history of tic disorders, mental retardation (IQ <75), organic brain disorders, clinically unstable psychiatric conditions (i.e., suicidal behaviors, psychosis, delinquency, criminality, or violence), or substance or alcohol abuse or dependence within the 6 months preceding the study or currently used psychotropics; also excluded pregnant or nursing women.
Spencer, 2001	Excluded clinically significant chronic medical conditions, abnormal baseline laboratory values, IQ less than 80, delirium, dementia, or amnestic disorders, any other clinically unstable psychiatric conditions (i.e., bipolar disorder, psychosis), drug or alcohol abuse or dependence within the 6 months preceding the study, previous adequate trial of Adderall, or current use of psychotropics; also excluded pregnant or nursing females.
Spencer, 2005	Subjects had clinically significant chronic medical conditions; abnormal baseline laboratory value; IQ<80; delirium, dementia, or amnestic disorders; other clinically unstable psychiatric conditions (i.e. bipolar disorder, psychosis, suicidality); drug or alcohol abuse or dependence within the 6 months preceding the study; previous adequate trial of stimulant (>0.5mg/kg/day of MPH or equivalent); or current use of other psychotropics. Pregnant or nursing women were also excluded.
Spencer, 1998	Exclusion criteria include clinically significant chronic medical conditions, abnormal baseline laboratory values, mental retardation (IQ<75), organic brain disorders, clinically unstable active psychiatric conditions, drug or alcohol abuse within the last 6 months, current use of psychotropics, and for women, pregnancy or nursing.
Tenenbaum, 2002	Potential participants were excluded if they had any clinically significant medical conditions such as heart condition, untreated thyroid condition, or tic disorder. Participants with active substance or alcohol abuse/dependence in the 6 months prior were also excluded. Other exclusions: pregnant or nursing females; neurological trauma or disorder (e.g.. concussion, epilepsy); chronic diseases; poor physical health; poor vision unless corrected. Individuals taking psychoactive medications (including methylphenidate) were excluded unless they discontinued such medications under the supervision of their prescribing physician for the duration of the study. Also excluded clients at the Attention Deficit Center, where all assessment and treatment sessions were conducted, due to potential conflict of interest. Excluded psychiatric disorders for which treatment with methylphenidate was contraindicated (e.g. panic disorder, major depression, moderate or more severe) or they were clinically unstable (e.g. suicidal behavior, psychosis, criminality/violence, bipolar disorder.

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

	External Validity			
Author, Year	**Run-in/Washout**	**Class naïve patients only**	**Control group standard of care**	**Funding**
Spencer, 1995	Run-in NR; 1-week washout between phases	No	Yes	Not reported
Spencer, 2001	Run-in NR; 1-week blinded placebo washout between phases	No	Yes	Shire Richwood Pharmaceuticals; NIMH grant
Spencer, 2005	NR/NR	Yes	Yes	NIMH and Novartis
Spencer, 1998	Run-in NR; 1-week washout between phases	NR	Yes	"Funded in part by Lilly Research Labs" and an NIMH grant
Tenenbaum, 2002	Run-in NR; 1-week washout between treatment phases	No, but excluded current use of MPH unless use was discontinued	Yes	Henkel Corporation

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

Author, Year	Relevance
Spencer, 1995	Yes
Spencer, 2001	Yes
Spencer, 2005	Yes
Spencer, 1998	Yes
Tenenbaum, 2002	Yes

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

	Internal Validity					
Author, Year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
Turner, 2004	Method NR	Method NR	Yes	Yes	Yes but method not described	Not reported
Verster, 2008	Yes	Method NR	Not reported	Yes	Not reported	NR
Weisler, 2006	Method NR	Yes	No; placebo group had significantly lower previous use of stimulants Also - Figure 2 (baseline characteristics) for the 'ITT' population only	Yes	NR	NR
Wender, 1981	Method NR	Method NR	Not reported	Yes	Yes but method not described	Not reported
Wender, 1985	Method NR	Method NR	Not reported by phase; same subjects exposed to both treatments	Yes	Yes	NR
Wernicke, 2004	Method NR	Method NR	Not reported	Yes	Yes	NR
Wilens, 1999	Method NR	Method NR	Not reported by phase; same subjects exposed to both treatments	Yes	Yes	Yes
Wilens, 2001	Method NR	Method NR	Yes	Yes	Yes	NR

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

		Internal Validity			
Author, Year	**Patient masked?**	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/ high**	**Intention-to-treat (ITT) analysis; If No: % analyzed**	**Post-randomization exclusions**
Turner, 2004	Yes but method not described	Yes NR Yes NR	No/ no	Yes	No
Verster, 2008	Yes	Yes NR NR NR	no/ no	No; 18/19 (94.7%) analyzed	No
Weisler, 2006	Yes	Yes NR NR NR	No/ no	No 183/255 (72%) analyzed	No
Wender, 1981	Yes but method not described	NR NR NR NR	No/ no	Unclear	No
Wender, 1985	Yes	Yes NR NR NR	No/ no	No	No
Wernicke, 2004	Yes but method not described	Attrition yes	No/ no	No: 99.2%	No
Wilens, 1999	Yes	Yes NR NR NR	No/ no	Yes	No
Wilens, 2001	Yes	Yes NR NR NR	No/ no	Yes	No

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

Author, Year	Quality rating
Turner, 2004	Fair
Verster, 2008	Fair
Weisler, 2006	Poor
Wender, 1981	Fair
Wender, 1985	Fair
Wernicke, 2004	Fair
Wilens, 1999	Fair
Wilens, 2001	Fair

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

	External Validity
Author, Year	**Number screened/ eligible/ enrolled**
Turner, 2004	NR/NR/20 Enrolled in 1st treatment phase: 10 in modafinil, 10 in placebo
Verster, 2008	75/19/19
Weisler, 2006	339/259/255
Wender, 1981	NR/60/48 Pemoline n=26 Placebo n=22
Wender, 1985	NR/NR/37 Same subjects exposed to both treatments
Wernicke, 2004	NR/NR/380; Atomoxetine with abrupt discontinuation n=90; Atomoxetine with tapered discontinuation n=94; Placebo n=196
Wilens, 1999	151/35/35 N per drug in 1st phase not reported
Wilens, 2001	154/NR/40 Bupropion n=21 Placebo n=19

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

Author, Year	Exclusion criteria
Turner, 2004	NART verbal IQ score <90, any significant visual or motor impairment, or the use of any medication contraindicated with modafinil. Patients were required to have no history of pervasive developmental disorders, neurologic disorders (including tic disorders), schizophrenia or psychotic disorders, bipolar disorder, or current major depressive disorder. Patients reported no substance abuse in the past 2 months. In addition, patients with a history of hypertension, cardiac disorder, or epilepsy. Patients were advised not to consume alcohol or caffeine for 12 hours before the study.
Verster, 2008	Insensitivity to MPH treatment; history, presence of alcohol dependence or substance abuse, positive alcohol breath test, use of medication known to affect driving performance, psychiatric disease, > 5 cups caffeine/ day and > 10 cigarettes / day.
Weisler, 2006	Incapable of following study instructions; IQ <80; comorbid diagnosis if psychosis, bipolar illness, pervasive developmental disorder, severe OCD, severe depressive or anxiety disorder; positive drug screen, substance abuse history or living with someone with substance abuse disorder; glaucoma; hyperthyroidism; seizure; tic disorder or Tourette syndrome; pregnancy or lactation; use of any anticonvulsant drug, clonidine, guanfacine, systemic steroids, medications that affect BP, heart or CNS, pemoline or investigational drugs w/in 30 days of study
Wender, 1981	Excluded DSM-III diagnoses of schizophrenia, schizoaffective disorder, primary affective disorder, schizotypal personality, or "borderline" personality; excluded organic brain syndrome and mental retardation. Excluded patients who reported that they had taken stimulant medication or "diet pills" in the past and that they had been stimulated, excited, or "wired" by such medication. Excluded gravid or lactating females. Excluded medical contraindications to stimulant drug therapy.
Wender, 1985	Excluded DSM-III diagnoses of schizophrenia or schizoaffective disorder, current major mood disorder, and any specific features of schizoid, schizotypal, or borderline personality disorder, such as unstable and intense interpersonal relationships with idealization and devaluation, identity disturbances, intolerance of being alone, and physically self-damaging acts, including self-mutilation and suicidal gestures.
Wernicke, 2004	Not reported
Wilens, 1999	Potential subjects were excluded if they had any clinically significant chronic medical conditions or clinically significant abnormal baseline laboratory liver function tests, mental retardation (IQ <75), organic brain disorders, clinically unstable psychiatric conditions, bipolar or psychotic disorders, drug or alcohol abuse or dependence within the 6 months preceding the study, previous exposure to pemoline, or current use of psychotropics. Also excluded pregnant or nursing women.
Wilens, 2001	Potential subjects were excluded if they had any clinically significant chronic medical conditions or clinically significant abnormal baseline laboratory liver function tests, mental retardation (IQ <75), organic brain disorders, clinically unstable psychiatric conditions, bipolar or psychotic disorders, drug or alcohol abuse or dependence within the 6 months preceding the study, or current use of psychotropics. Potential subjects with previous exposure to bupropion were also excluded.

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

	External Validity			
Author, Year	**Run-in/Washout**	**Class naïve patients only**	**Control group standard of care**	**Funding**
Turner, 2004	Run-in NR; 1-week washout between single-dose treatment phases	No	Yes	Wellcome Trust Program grant
Verster, 2008	6 to 7 days between treatments	No	Yes	Utrecht University
Weisler, 2006	1 wk washout (medications not specified)	NO	Yes	Shire Pharmaceuticals
Wender, 1981	NR/NR	No	Yes	Abbott Laboratories; NIMH grant
Wender, 1985	Run-in NR; 1-week washout between treatment phases	No	Yes	NIMH grant
Wernicke, 2004	NR/NR	No	Yes	Eli Lilly
Wilens, 1999	Run-in NR; 2-week washout between treatment phases	No, but excluded previous use of trial drug	Yes	Abbott Laboratories; NIH Scientist Development Award
Wilens, 2001	NR/NR	No, but excluded previous use of trial drug	Yes	Glaxo Wellcome Inc.; NIH; National Institute on Drug Abuse

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

Author, Year	Relevance
Turner, 2004	Yes
Verster, 2008	Yes
Weisler, 2006	Yes
Wender, 1981	Yes
Wender, 1985	Yes
Wernicke, 2004	Yes
Wilens, 1999	Yes
Wilens, 2001	Yes

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

	Internal Validity					
Author, Year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
Wood, 1976	Method NR	Method NR	Same 11 subjects in both drug groups	Yes	NR	NR

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

		Internal Validity			
Author, Year	**Patient masked?**	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/ high**	**Intention-to-treat (ITT) analysis; If No: % analyzed**	**Post-randomization exclusions**
Wood, 1976	Yes but method not described	Yes NR NR NR NR NR NR NR	No/ no	Yes	No

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

Author, Year	Quality rating
Wood, 1976	Fair

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

	External Validity
Author, Year	**Number screened/ eligible/ enrolled**
Wood, 1976	NR/25/15

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

Author, Year	Exclusion criteria
Wood, 1976	After first screening for inclusion, subjects who met the diagnosis of schizophrenia or primary affective disorders according to the Research Diagnostic Criteria of Spitzer were excluded.

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

	External Validity			
Author, Year	**Run-in/Washout**	**Class naïve patients only**	**Control group standard of care**	**Funding**
Wood, 1976	Run-in NR; no washout between phases of the crossover trial since MPH has "a short duration of action"	NR	Yes	NR

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

Author, Year	Relevance
Wood, 1976	Yes

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Design	Eligibility criteria	Duration	Interventions (mean dose)
Functional capacity				
Charles 1981 (Fair/poor)	Cross-sectional Setting: UCLA Department of Pediatrics	Children who had participated in a 16-week RCT of MPH vs placebo	4 years	Group 1: Stimulants < 6 months Group 2: Stimulants 6 mos to 2 years Group 3: Stimulants 2-3 years Group 4: Stimulants 3-4 years, but had discontinued ≥ 1 month prior to follow-up Group 5: Still on stimulants (MPH or pemoline)

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Concomitant medication	Assessment Techniques	Age Gender Ethnicity
Functional capacity			
Charles 1981 (Fair/poor)	NR	Teachers' responses to mail-based questionnaire	Mean age=12 years, 3 months 79% male 88.7% white 9.7% black 1.6% Hispanic

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Functional capacity		
Charles 1981 (Fair/poor)	98/70/62	n/a n/a Analyzed: Group1=13; Group2=10; Group3=14; Group4=13; Group5=12

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Outcomes
Functional capacity	
Charles 1981 (Fair/poor)	Group 1 vs 2 vs 3 vs 4 vs 5 <u>Teacher reports of below grade level work (% children):</u> Reading: 77 vs 75 vs 64 vs 73 vs 83 Spelling: 69 vs 75 vs 64 vs 55 vs 75 Mathematics: 69 vs 100 vs 56 vs 73 vs 58 Ability to sustain attention: 38 vs 75 vs 71 vs 73 vs 75 Unclear oral language: 15 vs 12 vs 14 vs 45 vs 50 <u>Other</u> Percentage of repeated grades (%): 46 vs 50 vs 36 vs 31 vs 8 Special education class placement: 31 vs 60 vs 36 vs 31 vs 58 Currently tutored: 15 vs 30 vs 14 vs 23 vs 41

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Design	Eligibility criteria	Duration	Interventions (mean dose)
Hechtman 1984 (Fair)	Retrospective Cohort study Setting: NR	6-12 years of age for sustained hyperactivity both at home and at school. Free of epilepsy, cerebral palsy, or psychosis	3 years between 6-12 years of age	MPH 20-50mg/day

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Concomitant medication	Assessment Techniques	Age Gender Ethnicity
Hechtman 1984 (Fair)	NR	NR	Mean age=21.8 years Gender: NR Ethnicity: NR

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Hechtman 1984 (Fair)	NR/NR/104	0/84/20

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Outcomes
Hechtman 1984 (Fair)	Stimulant-treated hyperactives (STH), non-STH, Matched controls (MC): Demographic data: residential moves: STH>MC, p<0.05 live with girlfriends/wives: STH>MC, p<0.02; STH>non-STH, p<0.01 future vacational plans or lower status plans: MC>STH, p<0.05 in debt: STH>MC, p<0.02 car accidents: non-STH>STH, p<0.004; STH vs MC, NS School: attending junior colleges and universities: MC>STH, p<0.05; STH>non-STH, p<0.03 fail grades in high school, STH>MC, p<0.1; STH vs non-STH, NS drop out school because of poor marks: STH>MC, p<0.08; STH vs non-STH, NS academic standing: MC>STH, p<0.05; STH vs non-STH, NS be expelled: STH>MC, p<0.07; STH vs non-STH, NS not in school because of lack of interests: non-STH>STH, p<0.05 Employer's Questionnaire get along with co-workers: STH>non-STH, no data reported being punctual, doing assigned work adequately, getting along with supervisors, completing tasks, and being rehired: all NS Work record: leave school earlier: STH>MC, p<0.028; STH vs non-STH, NS spend more time doing nothing: STH>MC, p<0.01; STH vs non-STH, NS have more job: STH>MC, p<0.01; STH vs non-STH, NS incomes: STH vs MC, NS; STH vs non-STH, NS greater debts: STH>MC, p<0.06; STH vs non-STH, NS longer period at last job: non-STH>STH, p<0.001 no problems with concentration: non-STH>STH, p<0.03 the percent of the work day: all NS full time jobs lasting less than 2 months, summer or part time jobs and reasons for leaving jobs: all NS

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Design	Eligibility criteria	Duration	Interventions (mean dose)
Lerer 1977 (Fair)	Before-After Setting: NR	Hyperactive children with IQ above 80 and marked academic underachievement	60 days - 6 months	MPH mean=43mg/day range=40-60mg/day
Paternite 1999 (Fair)	Descriptive study Setting: University of Iowa outpatient child psychiatry clinic	Patients with diagnoses of hyperkinetic reaction or a minimal braun dysfunction syndrome were treated with MPH between 1967-1972	Mean=30.4 months range=1-76 months	MPH mean=32mg/day range=8-80mg/day
Weiss 1975 (Fair)	Retrospective Cohort study Setting: the psychiatry department of the Montreal children's Hospital	Hyperactive children initially evaluated from 1962-1967 had been treated with methylphenidate, chlorpromazine, or none (group 1, 2 and 3).	Group 1: 51 months Group 2: 30 months	Group 1: MPH mean=30mg/day Group 2: chlorpromazine mean=75mg/day Group 3: none

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Concomitant medication	Assessment Techniques	Age Gender Ethnicity
Lerer 1977 (Fair)	NR	School grades (by teachers)	Mean age=15.5 years Gender: 92.6% male Ethnicity: 100% white
Paternite 1999 (Fair)	NR	General Interview structured interview by Loney Schedule of Affective Disorders and Schizophrenia (SADS-L) structured interview Interviewer: NR	Mean age=8.8 years Gender: 100% male Ethnicity: NR
Weiss 1975 (Fair)	NR	Academic performance (reported cards rated by teachers)	Mean age= 7.96, 8.15 and 8.21 years (group 1, 2 and 3) Gender: NR Ethnicity: NR

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Lerer 1977 (Fair)	55/27/27	0/0/0
Paternite 1999 (Fair)	219/121/97	NR/NR/97
Weiss 1975 (Fair)	NR/NR/150	NR/84/66

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Outcomes
Lerer 1977 (Fair)	15(55.6%) have shown impressive gains in behavior control and academic achievement during this period of time, as documented by improvement in school grades. After 7-12 months of follow-up, only 2 have shown improvement. 3 have been temporarily or permanently suspended from school.
Paternite 1999 (Fair)	Correlations with (a) "MPH dosage"; (b) "MPH response"; (c) "MPH duration" Psychiatric hospitalizations: none Suicide attempts: only (a) r= -0.23, p<0.05 Police contacts: none Emancipated living: only (b) r=0.31, p<0.05 Relationship commitment: only (b) r=0.25, p<0.05 High school graduation: only (b) r= -0.34, p<0.01 Post-secondary education: none Full employment: none Never fired from a job: none
Weiss 1975 (Fair)	Number of children in each group passing all grades or failing one or more grades: *Had never failed/ Had failed* Group 1: 13(54%)/11 Group 2: 9(41%)/12 Group 3: 6(30%)/14

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Design	Eligibility criteria	Duration	Interventions (mean dose)
Persistence				
Gau, 2006	Cross sectional, recruited from outpatient clinic of the dept of child psychiatry of natioan medical center in north Taiwan, private medical center south Taiwan and recruited through ADHD educational foundation.	Children 6-17 years of age, diagnosed with ADHD, treated with IR MPH for at least 6 months, mothers being main caregivers and capable of completing thequestionnaires	NR	MPH IR BID or TID or QID
Kemner 2006	Retrospective Cohort Data source: Integrated Health Care Information Services National Managed Care Benchmark Database Data collection period: 2/1/00-12/31/02	ICD-9 code 314.00 or 314.01 for diagnosis of ADHD; newly initiated on ER or IR MPH (no ER or IR MPH use in preceding 6 months); ≥ 6 years of age; continuous insurance coverage with same plan during the study periods	12 months	MPH IR 30 mg vs MPH ER 36 mg

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Concomitant medication	Assessment Techniques	Age Gender Ethnicity
Persistence			
Gau, 2006	NR	1) Demographic information 2) subject judgment on adherence 3)Chinese health questionnaiire (CHQ) 4)Chinese version of the Parental Bonding Instrument (PBI-C) 5)Chinese version of the social adjustment inventory for children and adolescents (SAICA-C) 6)Chinese version of the family adoptation and partnership, Growth, Affection and Resolve (Family APGAR-C) 7) Poor adherence defined as maternal report of child mising > 14 days of any dose of MPH IR on a daily basis for the past one month.	Mean (SD)age: 10.7 (2..7)yrs Male: 88.3% Ethnicity: Asian 100%
Kemner 2006	NR	**Medication usage patterns:** 1) Gaps in therapy of ≥ 15 days 2) Switches to alternative ADHD medications 3) Number of days on therapy 4) Adherence: percentage of patients receiving ER and IR MPH for 75%, 80%, and 90% of post-initiation period **Treatment patterns:** emergency room visit	Mean age=15 years 77% male Race NR

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Persistence		
Gau, 2006	NR/375/307	68/NR/307
Kemner 2006	NR/NR/5939	NR/NR/5939

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Outcomes
Persistence	
Gau, 2006	Poor adherents: 25.7%, good adherents: 74.3% Age (increment by 1 year)and its corelation to adherence: OR 1.24, CI 1.10-1.39, p<0.001 Gender (male vs female): OR 1.77, CI 0.60-5.43 Dosing Frequency and its corelation to Adherence: BID vs. QD: OR 2.12, CI 0.93-4.83 TID vs QD: OR 2.58, CI 1.10-6.08, p<0.05 QID vs QD:OR 2.28, CI 0.23-22.64 Scale sores: mean(SD) good adherence vs bad adherence CHQ score: 1.95 (2.23) vs 3.62 (3.17),p<0.0001 Family APGAR 7.98 (2.65) vs 9.16 (3.25), p<0.01 Parenting style by PBI Affection care: 26.15 (4.68) vs 24.61(5.11), p<0.05 Protection: 14.34 (4.59) vs 16.33 (4.91), p<0.01 SAICA score: Interaction with mother: 1.68 (0.55) vs 1.93 (0.70), p<0.01 Interaction with father: 1.92 (0.64) vs 2.16 (0.78), p<0.05 Problems with parents: 1.54 (0.53) vs 1.76(0.61), p<0.01
Kemner 2006	stimulant-treated hyperactives (STH), non-STH, Matched controls (MC): Demographic data: residential moves: STH>MC, p<0.05 live with girlfriends/wives: STH>MC, p<0.02; STH>non-STH, p<0.01 future vacational plans or lower status plans: MC>STH, p<0.05 in deb

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Design	Eligibility criteria	Duration	Interventions (mean dose)
Kemner 2006b (OROS MPH vs. TID IR MPH)	Retrospective Cohort Data source: Integrated Health Care Information Services National Managed Care Benchmark Database Data collection period: 2/1/00-12/31/02	ICD-9 code 314.00 or 314.01 for diagnosis of ADHD; newly initiated on OROS or IR MPH (no OROS or IR MPH use in preceding 6 months); ≥ 6 years of age; continuous insurance coverage with same plan during the study periods	12 months	TID IR MPH: dose not reported OROS MPH: dose not reported 81% of the sample initiated therapy on OROS MPH

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Concomitant medication	Assessment Techniques	Age Gender Ethnicity
Kemner 2006b (OROS MPH vs. TID IR MPH)	NR	**Medication usage patterns:** 1) Gaps in therapy of ≥ 15 days 2) Switches to alternative ADHD medications 3) Number of days on therapy 4) Adherence: percentage of patients receiving ER and IR MPH for 75%, 80%, and 90% of post-initiation period **Variables used in analysis:** GAP 15=15 day or greater gap between the end of one ADHD medication prescription and the start of the next ADHD medication. GAP 30= 30 day or greater gap between the end of one ADHD medication prescription and the start of the next ADHD medication. SWITCH=cessation of treatment on the initial ADHD medication and initiation of treatment with an alternative ADHD medication. SWITCHITT= cessation of treatment with OROS MPH and initiation of treatment with TID MPH, or vise versa. Adherence90, adherence80, adherence75= number of days the individual received the ITT medication over the 365 day post-period (90%, 80%, 75%, respectively). **Treatment patterns:** emergency room visit	Mean age=15 77% male Race NR

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Kemner 2006b (OROS MPH vs. TID IR MPH)	NR/NR/5939	NR/NR/5939

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Outcomes
Kemner 2006b (OROS MPH vs. TID IR MPH)	OROS MPH vs. TID IR MPH GAP 15: 85% vs. 97%, P<0.0001 GAP 30: 77% vs. 95%, P<0.0001 SWITCH: 27% vs. 68%, P<0.0001 SWITCHITT: 1% vs. 33%, P<0.0001 DAYS on ITT medication: 90% compliant: 24% vs. 5%, P<0.0001 80% compliant: 29% vs. 7%, P<0.0001 75% compliant: 30% vs. 5%, P<0.0001 Hospitalizations -- OROS MPH : OR=0.668, P=0.045 (Individuals who received OROS MPH were 33% less likely to be hospitalized compared to individuals who received TID IR MPH)

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Design	Eligibility criteria	Duration	Interventions (mean dose)
Lage 2004	Retrospective Cohort study Setting: NR Data resource: the Integrated Health Care information Services (IHCIS) National Managed Care Benchmark Database	1) Age 6-12 years at date of first prescription for XR MPH or TID IR MPH (index date); 2) patient-level data files containing information for at least 6 months before and 12 months after the index date; 3) no ADHD medications (i.e. amphetamine, dextroamphetamine, methylphenidate, imipramine, desipramine, clonidine, and bupropion) in the 6 months before the index date; and 4) no XR MPH use by the IR MPH group in the 12-month follow-up period.	NR	XR MPH TID IR MPH
Marcus 2005	Retrospective Cohort study Setting: California Medicaid	Patients aged 6 to 17 years who were prescribed MPH and were eligible for California Medicaid benefits for at least 6 months preceding and 12 months following an index MPH prescription. Patients should not have a prescription claim for an ADHD medication during the 6 months preceding the index MPH prescription and did not have any inpatient claims during the follow-up period.	12 months	ER-MPH IR-MPH

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Concomitant medication	Assessment Techniques	Age Gender Ethnicity
Lage 2004	NR	NR	Mean age=9.73 years 75% male Ethnicity: NR
Marcus 2005	NR	sequentially counting the unduplicated continuous prescriptions using the date of the prescription and the number of days of medications supplied	Mean age: NR 70% 6-12 years 29% 13-17 years 78% male 45.3% White; 22.9% Black; 26.0% Hispanic; 5.7% Other

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Lage 2004	NR/NR/NR	NR/NR/1775
Marcus 2005	NR/NR/NR	NR/NR/11427

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Outcomes
Lage 2004	Treatment pattern- XR MPH vsTID IR MPH, p value Days supplied: 186 vs 127, p<0.0001 Discontinue, stopped receiving all ADJD medications prior to t+1 year-28days: 47% vs 72%, p<0.0001 Switch, stopped prescription for one ADHD medication and started prescription another: 37% vs 59%, p<0.0001 Persist, no discontinuations or gap (>14days): 12% vs 1%, p<0.0001 Covariates of Accident/Injury- Coefficient, Odds ratio(95% CI) XR MPH: -0.5486, 0.578(0.353-0.945) Age(years): 0.1156, 1.123(0.994-1.267) Female: -0.9015, 0.406(0.225-0.734) Preferred provider: -0.5671, 0.567(0.365-0.882) Prior accidents present: 1.0576, 2.879(0.928-8.937) Prior total cost: -0.00024, 1.000(1.000-1.000) Number of chronic medications: -0.1480, 0.862(0.758-0.982) Number of diagnosis: 0.2286, 1.257(1.195-1.321) Intercept: -4.2703
Marcus 2005	Mean treatment duration- ER-MPH vs IR MPH, STR(95% CI) total: 140.3 vs 103.4, 1.37(1.32-1.42) Age 6-12y: 149.5 vs 107.5, 1.38(1.32-1.45) 13-17y: 125.1 vs 91.3, 1.35(1.27-1.43) Gender Male: 140.9 vs 101.8, 1.40(1.34-1.46) Female: 138.4 vs 109.1, 1.27(1.18-1.38) Race White: 154.9 vs 116.8, 1.43(1.35-1.52) Black: 125.7 vs 90.8, 1.37(1.27-1.48) Hispanic: 126.2 vs 94.9, 1.28(1.19-1.38) Other: 130.4 vs 93.9, 1.29(1.10-1.53)

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Design	Eligibility criteria	Duration	Interventions (mean dose)
Sanchez 2005	Retrospective Cohort Texas Medicaid prescription claims database	Texas Medicaid recipients aged 5-18 years with continuous paid prescription claims from June 1, 2001-May 31, 2002; new to stimulant therapy (no stimulants dispensed for at least 60 days prior to index prescription); and at least one dispensed prescription for MPH IR, MPH SR, MPH ER, MPH OROS, MAS IR, DEX IR, DEX ER	6 months	MPH IR, MPH SR, MPH ER, MPH OROS, MAS IR, DEX IR, DEX ER
Thomson, 2006	Retrospective study, patients identified from computer database and personal case load records	NR	Unclear. Study population consisted of patients taking IR psychostimulant any time between Feb 2002-Feb 2004 2 year period	IR psychostimulant SR MPH

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Concomitant medication	Assessment Techniques	Age Gender Ethnicity
Sanchez 2005	NR	**Persistence:** number of days from date of the first prescription to the end of the treatment period of the last prescription for each stimulant divided by the defined treatment window of 6 months; breaks in treatment of longer than 15 days constituted end of treatment period **Medication Possession Ratio (MPR):** actual number of days of therapy divided by the optimum number of days of therapy	Mean age=9.93 years 75.7% male Ethnicity NR
Thomson, 2006	NR	A standardized pro forma	12 years 9 months (range 6-17 years) 83.5% male NR

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Sanchez 2005	NR/NR/9,549	N/A
Thomson, 2006	NR/NR/103	6/NR/92

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Outcomes
Sanchez 2005	Comparisons among stimulant groups (MAS IR vs MPH IR vs MPH OROS) Persistence: 0.42 vs 0.37 vs 0.50 (F=159, df=2, p<0.0001) MPR: 0.73 vs 0.69 vs 0.76 (F=32, df=2, p<0.001) 150-180 day treatment duration (% pts): 19% vs 14% vs 30% (χ^2=327, df=10, p<0.00) Comparisons among age groups for all drugs combined (5-9 yrs vs 10-14 yrs vs 15-18 yrs) Persistence: 0.45 vs 0.41 vs 0.41 (F=21.6, df=2, p<0.001) MPR: 0.73 vs 0.73 vs 0.67 (F=11.8, df=2, p<0.001)
Thomson, 2006	Good response on IR psychostimulant: 88.6% Good response on switching to SR MPH: 64.9%, difference between both response significant p<0.001 % of people switiching back to IR psychostimulant from SR MPH=27%, p<0.0001

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Design	Eligibility criteria	Duration	Interventions (mean dose)
Race				
Barbaresi 2007	Retrospective, population-based cohort	All children who were ever enrolled at any of the district's public, private, or parochial schools in ISD#535, as well as children who were home-schooled.	Followed from age 5 until emigration, death, school graduation, or dropout. Median age at last follow-up was 18.4 years	Any stimulants

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Concomitant medication	Assessment Techniques	Age Gender Ethnicity Race
Barbaresi 2007	NR	**Primary:** California Achievement Test Modifiers were: Stimulant use, average daily dose, duration of treatment with stimulants, age at onset of treatment, DSM-IV diagnosis subtype, comorbid conditions, type of educational intervention, maternal education at birth	Median age at last follow-up: 18.4 years 74.9% male Ethnicity NR

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Race		
Barbaresi 2007	5,718/NR/370	NR/NR/370

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Outcomes
Race	
Barbaresi 2007	**Academic achievement** Stimulant yes/no: P = 0.75 Average daily dose: P = .058 Duration of treatment with stimulants, yr: P= 0.32 Age at onset of treatment with stimulants, yr: P = 0 .66 Type of educational intervention: P < 0.001 Maternal education at birth: P < 0.001 **Percentage of days absent by grade level** Stimulant yes/no: P=0.012 Average daily dose: P=0.71 Duration of treatment with stimulants, yr: P=0.041 Age at onset of treatment with stimulants, yr: P=0.34 Comorbid conditions: P=0.006 Type of educational intervention: P<0.001 Maternal education at birth: P=0.005 **Grade retention** Type of educational intervention: P<0.001 Maternal education at birth: P<0.001 **Dropping out of school** Stimulant yes/no: P=0.54 Average daily dose: P=0.35 Duration of treatment with stimulants, yr: P=0.52 Age at onset of treatment with stimulants, yr: P=0.54 Comorbid conditions: P=0.003 Type of educational intervention: P<0.001 Maternal education at birth: p<0.001

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Design	Eligibility criteria	Duration	Interventions (mean dose)
Olfson 2007	Retrospective, claims data review	Patients 18-64 years on the date of the first or index pharmacy claim for ER-MPH or IR-MPH, who were continuously enrolled in the health plan for 6 months before and 12 months after the index MPH prescription.	4 year period of claims data	ER-MPH IR-MPH

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Concomitant medication	Assessment Techniques	Age Gender Ethnicity
Olfson 2007	NR	**Primary:** mean and median duration of MPH treatment.	ER-MPH Mean age: 31.2 years 60.3% male Ethnicity NR IR-MPH Mean age: 33.3 years 55.8% male Ethnicity NR

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Olfson 2007	54,961/NR/5,122	None withdrawn 5,122 analyzed

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Outcomes
Olfson 2007	ER-MPH vs IR-MPH Overall median days on treatment: 68.0 vs 39.0 2 or more stimulant pharmacy claims: 61.4% vs 50.5% (p<0.001) Median days on treatment for those with 2 ore more stimulant pharmacy claims: 138 vs 121

Evidence Table 14. Quality assessment of observational studies - functional outcomes

Author	Non-biased selection?	For studies with ≥ 2 groups: Similar at baseline?	Eligibility criteria specified?	Attrition specified?	Loss to follow-up specified? If yes, low overall loss to follow-up?
Barabesi 2007	Yes	Yes	Yes.	Yes	Yes. 16.8% moved; 1.9% had unknown graduation drop out status Yes
Charles 1981	No: excluded 36 (36.7%)	n/a	No	n/a	n/a
Gau 2006	Yes; 88% or target recruited	NA (cross sectional study)	Yes	Yes; 18.1%	NR; attrition due to 'not currently treated with" ADHD drug
Hechtman 1984	Yes	No	Yes	Yes	Yes No
Kemner 2006/Lage 2004	Yes	No; ER group was significantly younger and had a significantly higher total number of diagnoses in the 6-month preinitiation period	Yes	Hospitalization data was analyzed for 100% of patients; unclear if all other data points were available for all patients	NR

Evidence Table 14. Quality assessment of observational studies - functional outcomes

Author	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Barabesi 2007	Yes	Yes	Yes	No. Controlled for age and grade.	Yes	Fair
Charles 1981	No	No	No	No	Yes	Fair-Poor
Gau 2006	Yes	Yes	Yes; questionnaires administer to patients and families	Yes; regression model of predictors for drug adherence; poor and good adherence groups compared; controlled for age, sex, education	Yes, 1 month	Fair
Hechtman 1984	Yes	No	Unclear	No	Yes	Fair
Kemner 2006/Lage 2004	Yes	Yes	Yes	Yes; controlled for demographic characteristics, general health status, comorbid diagnoses associated with diagnosis of ADHD and use of ADHD medications	Yes	Fair

Evidence Table 14. Quality assessment of observational studies - functional outcomes

Author	Non-biased selection?	For studies with ≥ 2 groups: Similar at baseline?	Eligibility criteria specified?	Attrition specified?	Loss to follow-up specified? If yes, low overall loss to follow-up?
Kemner 2006b (OROS MPH vs. TID IR MPH)	Yes	No, Mean age higher for TID IR MPH group, Higher % live on East Coast, fewer live on West Coast for OROS MPH group, higher percentage of diagnoses during the 6-month pre-period.	Yes	Unclear	NR
Lage 2004	Yes	No; XR group older, more HMO use, more chronic medications and diagnoses, and higher prior total medical costs	Yes	n/a	n/a
Lee 2007	Unclear as to how many were eligible compared to how many were enrolled	N/A	Yes	Yes	Yes/Yes
Lerer 1977	No: excluded 11 (41%) nonresponders	n/a	Yes	Yes	No
Marcus 2005	Unclear	No; ER group patients received treatment for a mental disorder other than ADHD during the 6 months preceding the index prescription and more likely to have been prescribed antidepressants, antipsychotic medications, and mood stabilizers during the follow-up period	Yes	n/a	n/a

Evidence Table 14. Quality assessment of observational studies - functional outcomes

Author	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Kemner 2006b (OROS MPH vs. TID IR MPH)	Yes	Yes	Yes	Yes, controlled for demographics, health status, comorbid diagnosis, and use of ADHD medicatons.	Yes	Fair
Lage 2004	Yes	Yes	Yes	Yes	Yes	Fair
Lee 2007	Yes	Yes	Yes	N/A	Yes	Fair
Lerer 1977	Yes	No	Unclear	NR	Yes	Fair
Marcus 2005	Yes	Yes	Yes	Yes	Yes	Fair

Evidence Table 14. Quality assessment of observational studies - functional outcomes

Author	Non-biased selection?	For studies with ≥ 2 groups: Similar at baseline?	Eligibility criteria specified?	Attrition specified?	Loss to follow-up specified? If yes, low overall loss to follow-up?
Olfson 2007	Yes	No. ER MPH patients were primarily young adults, male, treated by a doctor who was not a psychiatrist, and treated for hyperactive subtype of ADHD.significantly larger % of patients treated with MPH-IR received treatment with anxiolytic and antidepressant medications 6 months preceding the index MPH prescription.	Yes	No attition	No loss to follow-up
Paternite 1999	No: excluded 24 (19.8%)	n/a	Yes	Yes	NR
Perwein 2006	Unclear; no data on recruitment	NA (pre vs post study)	Yes	Yes	Yes; Yes: 65% completed acute phase (10w); long-term 34% (24 m); most withdrawals due to discontinuation of drug
Sanchez 2005	Yes	NR	Yes	N/A	N/A
Thompson 2006	Unclear; no data on recruitment	NA	No	Yes; 5%	Yes; 5% data unavailable
Weiss 1975	No	NR	Yes	No	No

Evidence Table 14. Quality assessment of observational studies - functional outcomes

Author	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Olfson 2007	Yes	Yes	Yes	Yes. Statistical analysis was done controlling for age, gender, treating specialist, other treated mental disorders, claims for other prescribed psychotropic medications, claims for ER and inpatient services in which the first listed diagnosis is mental disorder.	Yes	Fair
Paternite 1999	Yes	Yes	Yes	Yes	Yes	Fair
Perwein 2006	Yes	Yes	Yes	NA (single-group study)	Yes, 24m	Poor; high attrition rate
Sanchez 2005	Yes	Yes	Yes	No	Yes	Fair
Thompson 2006	Unclear; had standardized form	No	Unclear; no information on the form or data collection techniques	NA (single-group study)	Unclear	Poor
Weiss 1975	Yes	No	Unclear	NR	Yes	Fair

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Design	Eligibility criteria	Duration
Elementary School Children - Atomoxetine (tomoxetine)			
Kratochvil 2001 U.S. (Fair)	Before-after, prospective Setting: 1 of 24 clinical research sites involved in an ongoing multicenter study	DSM-IV criteria for ADHD	10 weeks
Elementary School Children - Methylphenidate			
Batterson 2005	Cross-sectional study Setting: NR	MPH IR group: Children who had taken MPH IR for a minimum of 2 years at a minimum dose of 20 mg/day; no missing permanent mandibular teeth (with the exception of third molars); excellent diagnostic quality of panoramic radiograph; no prior comprehensive orthodontic treatment; absence of any disorder affecting growth and/or tooth development; no history of ingesting any medication affecting growth and/or tooth development Healthy control group: Matched for gender and age within 1 month; inclusion criteria identical to MPH IR group, with exception of having no history of any MPH IR use and no history of any long-term medication use	N/A

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Interventions (mean dose)	Concomitant medication	Safety Assessment
Elementary School Children - Atomoxetine (tomoxetine)			
Kratochvil 2001 U.S. (Fair)	Tomoxetine mean dose nr	NR	Weight measured at weekly clinic visits
Elementary School Children - Methylphenidate			
Batterson 2005	MPH IR at a minimum dose of 20 mg/day	NR	Assessment of dental age using panoramic radiograph

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Elementary School Children - Atomoxetine (tomoxetine)			
Kratochvil 2001 U.S. (Fair)	Mean age NR 100% male 90% White 10% Hispanic	NR/NR/100	2 (20%) withdrawn 0 lost to fu 10 analyzed
Elementary School Children - Methylphenidate			
Batterson 2005	Mean age: 11.6 years 71% male Race NR	NR/NR/84	N/A

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Safety outcomes
Elementary School Children - Atomoxetine (tomoxetine)	
Kratochvil 2001 U.S. (Fair)	Weight change (mean change): -0.15 kg, p=NS
Elementary School Children - Methylphenidate	
Batterson 2005	MPH IR vs control Dental age (years): 12.20 vs 12.58, NS

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Comments
Elementary School Children - Atomoxetine (tomoxetine)	
Kratochvil 2001 U.S. (Fair)	
Elementary School Children - Methylphenidate	
Batterson 2005	

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Design	Eligibility criteria	Duration
Brehaut 2003 Canada (Fair)	British Columbia Linked Health Dataset (BCLHD)	January 1, 1990 and December 31, 1996	NR

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Interventions (mean dose)	Concomitant medication	Safety Assessment
Brehaut 2003 Canada (Fair)	Methylphenidate (mean dose NR)	Any individual who was <19 years of age on December 31, 1996. Children were included in the childhood behavior disorder (CBD) group if they were listed as having been prescribed MPH at least once between January 1, 1990 and December 31, 1996. All other children and youth were included in the no CBD group.	51.4% male <4 y=18.2% 4-8, 11 mo=27.2% 9-13 y, 11 mo=27.4% 14-18 y, 11 mo=27.1% Ethnicity NR

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Brehaut 2003 Canada (Fair)	1,028,028 exposed Eligible NR Selected=1,026,873	1,028,028/ 1,026,873/ 1,026,873	NR/ NR/ 1026873

Evidence Table 15. Observational studies - long-term safety

Author
Year
Country **Safety outcomes**

Brehaut
2003
Canada
(Fair)

Injury	No CBD Frequencies (n=1,010,067)	CBD Frequencies (n=16,806)	Odds Ratios 99% CI	Logistic Regression Odds Ratios 99% CI
Nature of injury				
Fractures	20,025 (2.0%)	723 (4.3%)	2.22 2.01-2.46	1.42 1.27-1.58
Open wounds	4858 (0.5%)	224 (1.3%)	2.80 2.34-3.34	1.89 1.56-2.29
Poisoning/toxic effect	3882 (0.4%)	184 (1.1%)	2.87 2.36-3.49	2.67 2.16-3.30
Intracranial	2675 (0.3%)	107 (0.6%)	2.41 1.87-3.11	1.66 1.27-2.19
Concussion	2667 (0.3%)	127 (0.8%)	2.88 2.27-3.64	1.82 1.42-2.35
Burns	1301 (0.1%)	45 (0.3%)	2.08 1.41-3.08	1.99 1.31-3.02
Total	32,242 (3.2%)	1,257 (7.5%)	2.45 2.27-2.65	1.67 1.54-1.81
Cause of injury				
Falls	16426 (1.6%)	573 (3.4%)	2.14 1.91-2.39	1.46 1.29-1.64
Postoperative complications	6166 (0.6%)	168 (1.0%)	1.64 1.34-2.01	1.37 1.10-1.71
Struck by object	4146 (0.4%)	157 (0.9%)	2.29 1.85-2.82	1.35 1.07-1.69
Motor vehicle accident	3333 (0.3%)	136 (0.8%)	2.46 1.97-3.09	1.56 1.23-1.99
Adverse effects	2370 (0.2%)	87 (0.5%)	2.21 1.67-2.93	2.12 1.58-2.85
Nonmotor vehicle pedal	2360 (0.2%)	118 (0.7%)	3.02 2.37-3.85	1.71 1.33-2.22
Suffocation	813 (0.1%)	23 (0.1%)	1.70 0.99-2.93	2.02 1.13-3.60
Drowning	185 (<0.1%)	6 (<0.1%)	1.95 0.67-5.68	1.75 0.59-5.17
Total	33855 (3.4%)	1180 (7.0%)	2.18 2.01-2.36	1.52 1.40-1.66

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Comments
Brehaut 2003 Canada (Fair)	

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Design	Eligibility criteria	Duration
Charach 2006	Open-label extension study Participants drawn from referrals to an assessment and treatment program for ADHD	Confirmed DSM-III-R diagnosis of ADHD based on parent and teacher interviews; aged 6-12 years; completion of a 12-month RCT of combined MPH IR and parent-treatment	5 years
Forrester 2006	Cross-sectional study Data source: Texas Poison Control Network (TPCN)	Cases were all calls involving MPH IR received during 1998-2004	Annual

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Interventions (mean dose)	Concomitant medication	Safety Assessment
Charach 2006	Psychostimulants (% patients): 43 (54%) DEX IR: 19% MPH IR: 81% Dosages NR	NR	Standing height: measured in centimeters without shoes from floor to vertex of head Weight: in indoor clothing, without shoes, measured in kilograms Both measured annually using an Accustat Genentec stadiometer
Forrester 2006	MPH IR dosage NR	NR	Medical outcome rated as no effect (no symptoms due to exposure), minor effect (some minimally troublesome symptoms), moderate effect (more pronounced, prolonged symptoms), major effect (symptoms that are life-threatening or produce significant disability or disfigurement) or death

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Charach 2006	Demographics NR	91/91/79	14% withdrawn/LTFU NR/height=45 (49%) and weight=45 (49%)
Forrester 2006	Age (years): < 13: 20.3% 13-19: 54.7% > 19: 25% 61.9% male Race NR	Calls: 6798 total/eligible NR/enrolled=322	Withdrawn N/A/Medical outcome unknown for 133 MPH IR abuse calls (41%)

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Safety outcomes
Charach 2006	Association between increased dose and height (controlled for time since initiation of treatment): ß coefficient = -0.11, p<0.001 Association between increased dose and weight (controlled for time since initiation of treatment): ß coefficient = -0.29, p<0.001
Forrester 2006	Medical outcomes: All MPH IR exposures vs **MPH IR abuse exposures** vs MPH IR nonabuse exposures: No effect: 49.9% vs **28.6%** vs 52.1% Minor effect: 28.5% vs **36.5%** vs 27.7% Moderate effect: 19.2% vs **29.1%** vs 18.2% Major effect: 2.4% vs **5.8%** vs 2.0% Death: 0 vs **0** vs 0 Proportion of annual human abuse calls relating to MPH IR: 1998: 10.6% 1999: 11.4% 2000: 7.2% 2001: 5.9% 2002: 7.4% 2003: 9.8% 2004: 7.3% Total: 8.5%

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Comments
Charach 2006	
Forrester 2006	

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Design	Eligibility criteria	Duration
Gadow 1999 U.S. (Fair)	Long-term follow-up to participation in an 8-233k controlled trial of methylphenidate and placebo Setting: NR Noncomparative	DSM-III-R diagnostic criteria for ADHD and either chronic motor tic disorder and, in general, were above cutoff on 2 of 3 parent-completed and 2 of 3 teacher-completed	2 years

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Interventions (mean dose)	Concomitant medication	Safety Assessment
Gadow 1999 U.S. (Fair)	Methylphenidate Short-term dose trial mean dose: 8.3 mg Long-term follow-up mean dosages: 6 months=13.3 mg 12 months=16.2 mg 18 months=29.2 mg 24 months=34.5 mg	NR	Height Weight Tics

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Gadow 1999 U.S. (Fair)	Short-term dose trial (n=34) Mean age=8.8 91.2% male Race NR	NR/NR/34	Number of subjects at each follow-up visit/number receiving stimulants: 6 months=28/27 12 months=33/30 18 months=29/26 24 months=29/26 (1 switched to dextroamphetamine)

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Safety outcomes
Gadow 1999 U.S. (Fair)	Weight in kg (mean expected/actual/difference/p-value): 41.95/41.23/0.72/p=0.59 Height in cm (mean expected/actual/difference/p-value): 147.48/146.81/0.67/p=0.57 Tic measurements (diagnostic/placebo/6 month/12 month/18 month/24 month) YGTSS Total Motor Tics: 13.9/11.4/12.1/12.2/13.0/12.6 Total Phonic Tics: 11.2/7.9/7.6/8.1/8.3/8.0 Overall Improvement Rating: 19.5/7.6/9.7/9.4/10.2/8.5 Global Severity Scale: 42.9/26.5/27.1/30.0/31.3/29.9 STESS: 2.9/1.6/1.8/2.0/1.9/1.9 TS-CGI: 2.6/3.1/3.1/2.3/2.4/2.3 TS unified Rating Scale: Shapiro Symptom Checklist No of Motor Tics: 13.2/11.7/12.0/12.8/14.0/13.4 No. of Vocal Tics: 5.0/3.1/2.5/2.9/2.8/2.5 2-Minute Tic Count Motor Tic Count: 10.0/9.5/13.8/14.4/18.1/17.2 Vocal Tic Count: 1.1/0.6/0.4/1.1/1.3/1.5 GTRS Motor Tic Index: 4.8/4.9/5.0/5.0/4.8/4.8 Vocal Tic Index: 1.9/1.0/1.1/1.1/1.4/1.4 Tic Severity Index: 3.2/1.4/1.8/2.2/2.5/2.6 LeWitt Disability Scale: 61.9/68.6/72.9/72.4/70.7/73.1 CGI-OC: 2.7/1.6/1.8/1.7/1.9/1.8 Parent Ratings GTRS Motor Tic Index: 3.7/2.2/2.4/3.2/2.5/2.4 Vocal Tic Index: 1.8/0.9/0.9/1.2/0.8/0.6 Tic Severity Index: 3.3/1.6/1.8/2.4/1.9/2.1 Classroom observations: Motor Tic Frequency: 18.6/18.6/23.8/21.0/21.0/19.5/18.9

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Comments
Gadow 1999 U.S. (Fair)	Only 2 comparisons indicated that tics were worse on medication than placebo (data nr)

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Design	Eligibility criteria	Duration
Gross 1976 U.S. (Fair)	Retrospective analysis of height and weight data among 100 children treated for at least 2 years for ADHD, and with mean follow-up of 6 years. Setting: NR Comparative	Eligible subjects were children and adolescents diagnosed with hyperkinetic syndrome or minimal brain dysfunction within the investigator's clinical practice. To be included in the study required that a measurement of weight and height be available within 1 year prior to the onset of pharmacotherapy; 91% of measurements were within 6 months of treatment.	Subjects received at least 2 (mean=5) years of treatment. Mean follow-up time: 5.8 years for MPH, 6.8 years for dextroamphetamine.

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Interventions (mean dose)	Concomitant medication	Safety Assessment
Gross 1976 U.S. (Fair)	Methylphenidate mean dose 34 mg/day, n=60 Dextroamphetamine mean dose 16.5 mg/day, n=24 (Imipramine/desipramine, n=16)	NR	Changes in weight and height percentiles, compared with Iowa city norms

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Gross 1976 U.S. (Fair)	Mean age at onset of treatment: 9 Gender 82% Ethnicity NR At final measurement, 45% were aged 1 6+ 17% were aged 18+	NR/NR/100	NR/NR/100

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Safety outcomes
Gross 1976 U.S. (Fair)	Average in percentile of weight, MPH vs dextroamphetamine: Time after onset: 1 year, -5.2 (p<0.05) vs -5.9 (NS); 2 year, -4.3 (NS) vs -6.0 (NS); 3 year: -3.0 (NS) vs

Methylphenidate group: changes in percentiles of weight and height				
Time after onset (yrs)	N on medication	Mean daily dose	Average change in percentile (p-value)	
			Weight	Height
1	60	24.4	-5.2 (p<0.05)	-0.1 (ns)
2	60	31.7	-4.3 (ns)	+0.4 (ns)
3	54	38.5	-3.0 (ns)	-1.9 (ns)
4	44	43.3	+7.5 (ns)	+7.0 (ns)
5	35	47.2	+7.2 (ns)	+7.1 (ns)
6	24	51.2	+10.4 (ns)	+8.9 (ns)
7	15	40.0	+24.4 (p<0.05)	+14.9 (p<0.05)
8	6	40.0	+19.1 (p<0.05)	+12.2 (p<0.05)
At final f/u (mean 5.8y)	30	43.8	+11.4 (p<0.001)	+12.8 (p<0.001)
Dextroamphetamine group: changes in percentiles of weight and height				
1	24	12.2	-5.9 (p<0.05)	-1.8 (ns)
2	24	14.5	-6.0 (ns)	+0.8 (ns)
3	24	17.7	-3.4 (ns)	+1.9 (ns)
4	22	18.9	+2.2 (ns)	+5.2 (ns)
5	15	20.1	+3.2 (ns)	+6.2 (ns)
6	12	16.7	+9.3 (ns)	+9.8 (ns)
7	6	18.0	+18.1 (ns)	+13.4 (ns)
8	4	20.0	+10.5 (ns)	+13.2 (ns)
9	2	25.0	+41.0 (ns)	+17.3 (ns)
At final f/u (mean 6.8y)	12	19.6	+16.0 (p<0.02)	+10.9 (p<0.01)

Patients who had discontinued medication at final follow-up had larger increments in percentiles for both height and weight compared with patients still taking medication, but differences were not significant.
Analysis by age at treatment onset found that older children made greater gains in weight and height percentiles than younger children, but the difference was not statistically significant.
Correlations between mean dose during treatment vs. change in percentile from onset to final follow-up, and between age at onset of treatment vs. change in percentile from onset to final follow-up, were low in magnitude (0.03 to –0.22 for *r*) and not significant.

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Comments
Gross 1976 U.S. (Fair)	Loss of weight compared with expected norms occurs during the first 3 years with MPH and dextroamphetamine, but there is a statistically significant increase in weight and height percentiles at final measurement in both treatment groups. Compliance was assessed by checking prescription records.

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Design	Eligibility criteria	Duration
Gualtieri 1985 U.S. (Fair)	Open-label 3-6 month followup of MPH responders.	Subjects (n=8) who appeared to respond favorably to MPH in either a short-term efficacy study or in open clinical trials. All subjects (n=8) had initially responded with improvement in attention span, greater work efficiency, decreased feelings of restlessness and impatience, improved interpersonal relationships, and diminished temper outbursts. Two of these subjects were also narcoleptics, and in both cases MPH also led to control of sleep attacks.	3-6 months

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Interventions (mean dose)	Concomitant medication	Safety Assessment
Gualtieri 1985 U.S. (Fair)	MPH was administered in doses ranging from 0.1 to 2.0 mg/kg, bid or tid. Most subjects received doses below 0.5 mg/kg and only the 2 narcoleptic subjects received doses in excess of that level.	Not reported	Monthly clinic visits, NOS.

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Gualtieri 1985 U.S. (Fair)	Mean age 27.2 100% male Ethnicity NR (represents n=22, of which 8 were included in the long-term followup study)	NR/NR/8	3 withdrew Lost to fu NR 0 analyzed (results described per individual)

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Safety outcomes
Gualtieri 1985 U.S. (Fair)	One subject consumed a month's supply of MPH in "an abortive suicide attempt".

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Comments
Gualtieri 1985 U.S. (Fair)	

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Design	Eligibility criteria	Duration
Mattes 1983 U.S. (Fair)	Before-after (open trial of methylphenidate) Setting: NR Noncomparative	Children had to be considered hyperactive both in school and at either home or the clinic; furthermore, a high level of disruptive behavior was required	Up to 4 years Duration of treatment (weeks): Up to 1 year: 20.7 1-2 yr: 59.4 2-3 yr: 99.1 3-4 yr: 130.0

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Interventions (mean dose)	Concomitant medication	Safety Assessment
Mattes 1983 U.S. (Fair)	Methylphenidate mean dosages (mg): Up to 1 year: 39.9 1-2 year: 41.3 2-3 year: 41.0 3-4 year: 41.4	Thioridazine hydrochloride received by 34 (39.5%) at some time during the study	Changes in weight and height percentiles

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Mattes 1983 U.S. (Fair)	Mean age NR Gender NR Race NR	NR/NR/86	44 (51.2%) withdrawn by end of year 4

Evidence Table 15. Observational studies - long-term safety

Author Year Country | **Safety outcomes**

Mattes 1983 U.S. (Fair)

Year	N	Pretreatment	End of year	t	p	Correlation with treatment duration (Pearson's r, p-value)	Correlation with mean daily dose (Pearson's r, p-value)	Correlation with total cumulative dose (Pearson's r, p-value)
Height								
1	51	51.1	49.7	1.56	NS	-.20, NS	0.04, NS	-0.17, NS
2	56	51.7	43.6	7.10	<0.001	0.18, NS	0.09, NS	0.16, NS
3	37	60.5	47.1	8.13	<0.001	0.04, NS	0.29, NS	0.24, NS
4	19	66.6	48.5	6.50	<0.001	0.33, NS	0.15, NS	0.28, NS
Weight								
1	69	59.2	49.5	6.81	<0.001	0.17, NS	0.17, NS	0.26, p<0.05
2	69	57.4	41.5	9.24	<0.001	0.31, p<0.01	0.12, NS	0.29, p<0.05
3	44	62.1	43.5	10.18	<0.001	0.05, NS	0.05, NS	0.09, NS
4	26	62.5	41.9	5.82	<0.001	0.39, p<0.05	-0.01, NS	0.018, NS

Multiple regression analysis of relationship of dosage and final height (n=42, includes 6 children who were off MPH at 3 years)

Step	Factors	Multiple correlation	Total explained variance (%)	Unique variance contribution of each factor (%)
1	Baseline height	0.94	87.8	87.8 (Pearson's r)
2	Baseline weight	0.94	88.2	0.4
3	Age at final height measurement	0.94	88.3	0.0
4	Baseline age	0.94	88.5	0.2
5	Total cumulative dosage of MPH	0.95	90.5	2.0 (p<0.01)

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Comments
Mattes 1983 U.S. (Fair)	Once a year the methylphenidate regimen was replaced by a single-blind placebo trial. Only children whose behavior clearly deteriorated while they received placebo were returned to active treatment. Many of the children discontinued the medication regimen during the summer; methylphenidate therapy was reinstated in the fall only if behavioral complaints from school were received.

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Design	Eligibility criteria	Duration
McGough 2005 U.S.	Multicenter Long-term follow-up of two different placebo-controlled trials of Adderall (Biederman 2002 and McCracken 2003).	Boys and girls aged 6-12 years, mostly with combined subtype, with vital signs in the normal range, who satisfied DSM-IV criteria for a primary diagnosis of ADHD. Patients had to complete their previous trial without any clinical relevant adverse events (AEs) or withdrew from the previous trials for reasons other than AEs.	24 months

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Interventions (mean dose)	Concomitant medication	Safety Assessment
McGough 2005 U.S.	Adderall XR (Mixed Amphetamine Salts) Starting dose was 10 mg/d and could be uptitrated by 10 mg increments to 20 or 30 mg/d.	Prohibited concomitant medications included: alpha-2 agonists, anticonvulsant drugs, and medications that affect blood pressure, heart rate, or central nervous system performance.	Safety was assessed by analysis of AEs and vital signs recorded at each study visit, height and weight at baseline and months 12-24, lab tests conducted at baseline and 6-month intervals, physical examinations performed at baseline and months 12, 18, and 24. AEs were collected by spontaneous report and by investigator queries of subject and caregiver at each visit.

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
McGough 2005 U.S.	Mean age: 8.7 years 78% male 73% white 12% Black 9% Hispanic 1% Asian/ Pacific Islander 3% Other	NR / 635 / 568	284 total (87 of these formally "withdrew consent") 74 273 (48%) completed study

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Safety outcomes
McGough 2005 U.S.	92% (n=525) of patients had ≥ 1 AE during the study. Of patients reporting AEs, 84% (n=440) experienced at least 1 AE deemed by the investigator to be "possibly" treatment related. Most frequently reported AEs: headache (15% of all AEs), anorexia (15% of all AEs), and insomnia (11% of all AEs). 21 serious AEs (SAEs) were reported by 18 patients (3%); only 2 (both convulsions) were thought to be related to Adderall; both were discontinued from the study. 12 SAEs were severe, but none were thought to be related to Adderall. 84 patients (15%) withdrew due to AEs; the most frequently reported AEs associated with treatment withdrawal included weight loss (n=27), anorexia/decreased appetite (n=22), insomnia (n=11), depression (n=7), and emotional lability (n=4). Overall medication compliance was 94%. Mean systolic blood pressure increased by 3.5 mmHg, diastolic blood pressure increased by 2.6 mmHg, and mean pulse increased by 3.4 beats/min. 134 reports of weight loss occurred over the 24 months. The decrease in the expected weight gain was -7.8 kg for the patients above the 75th percentile on the CDC weight charts at baseline, and was -2.1kg for patients below the 25th percentile at baseline.

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Comments
McGough 2005 U.S.	635 patients were enrolled in the original PCTs; 568 enrolled from those studies into this long-term extension.

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Design	Eligibility criteria	Duration
McNutt 1976a (preliminary report) McNutt 1976b U.S. (Fair)	Long-term follow-up anterospective study of subjects in short-term studies on the effects of different doses of methylphenidate Setting: Physical Fitness Research Laboratory at Institute for Child Behavior and Development, University of Illinois at Urbana-Champaign	Hyperactive children on methylphenidate that had been subjects in short-term studies	≥ 8 months of medication during a 12-month period ≥ 16 months of medication during a 24-month period
Millichap 1977 U.S. (Fair)	Before-after Setting: Children's Memorial Hospital (Chicago)	Boys, 5 to 10 years of age, referred for pediatric neurology evaluation because of hyperactive behavior and failure to achieve the level of academic potential expected in school. Signs of minimal brain dysfunction were recognized on examination and tests of perception revealed deficits in visual and/or auditory channels despite normal intelligence.	6-26 months (mean=16 months)

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Interventions (mean dose)	Concomitant medication	Safety Assessment
McNutt 1976a (preliminary report) McNutt 1976b U.S. (Fair)	Methylphenidate mean daily doses: 12-month cohort: 24.1 mg 24-month cohort: 29.1 mg Dosing schedule NR	NR	Height: measured with a stadiometer and recorded in cm to the nearest mm; taken while the subject was standing with heels together with the body help in a maximally erect position and hands on the hips with a maximal inspiration of air Weight: after urine was voided, measured with the subject standing on a platform scale (Howe-Richardson) attired in standard lightweight gym shorts and barefooted; determined to the nearest grams Body composition: subcutaneous fat, body girth, and skeletal width were all made on the right side of the body; body fat and lean body mass were estimated from body weight and upper arm and back skinfold thicknesses according to regression equations established by Lohman; two thicknesses of skin and subcutaneous fat were included; reading from the calipers were recorded to the nearest mm and the mean of 3 readings at each site was rounded to the nearest 0.1 mm and used as the representative reading
Millichap 1977 U.S. (Fair)	MPH was prescribed as an adjunct to remedial education, beginning with a dose of 5 mg, morning and noon on school days only and increasing the dose to a maximum of 20 mg daily when necessary	NR	Measurements of height and weight were made by the author at the times of initial neurologic examination and at re-examination during treatment

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
McNutt 1976a (preliminary report) McNutt 1976b U.S. (Fair)	Medicated (n=28) vs nonmedicated (n=24) vs control (n=47) vs overall <u>12-month</u> Mean age: 10.5 vs 10.7 vs 9.71 vs 10.2 % male: 85.7% vs 87.5% vs 68% vs 77.8% Race nr <u>24-month</u> Mean age: 10.1 vs 9.7 vs 9.87 vs 9.9 % male: 84.6% vs 90% vs 85.7% vs 86.5% Race nr	NR NR NR	NR NR 12 months: medicated n=28, nonmedicated n=24, control n=47 24 months: medication n=13, nonmedicated n=10, control n-14
Millichap 1977 U.S. (Fair)	Mean age nr 100% male Race NR	NR/NR/36	NR NR NR

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Safety outcomes
McNutt 1976a (preliminary report) McNutt 1976b U.S. (Fair)	12 months Growth (age, height, and weight): medicated=controls (data nr); Analysis of covariance (with age as covariate): medicated=controls (data nr); medicated=nonmedicated Lean body mass, percent body fat, body girth: medicated=controls; Analysis of covariance (with age as covariate): medicated=controls (data nr); medicated=nonmedicated Skeletal width: hyperactives>controls, F(1.73)=4.75, p<0.03; Analysis of covariance (with age as covariate): hyperactives=controls 24 months Growth: medicated=controls; medicated=nonmedicated Body composition: medicated=controls, but group-by-time interaction on percent body fat (hyperactives increased, controls decreased); medicated=nonmedicated
Millichap 1977 U.S. (Fair)	Patients that lost weight: 2/36 (5.5%) Heights (% patients at baseline/after therapy) (difference NS) Above 50th percentile: 14 (38.9%) / 13 (36%) Below the 50th percentile: 22 (61.1%) / 23 (64%) Below the 5th percentile: 4 (11.1%) / 0 Decrease rate of growth: 2 (5.5%)

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Comments
McNutt 1976a (preliminary report) McNutt 1976b U.S. (Fair)	Significant difference in age between medicated and controls, F(1,73)=5.83, p<0.02
Millichap 1977 U.S. (Fair)	

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Design	Eligibility criteria	Duration
Pliszka 2006	Cohort, retrospective Data source: University-based child and adolescent psychiatry/psychopharmacology clinical database	Diagnosis of ADHD; ≥ 1 years of continuous treatment with a single class of stimulants medication (MPH or MAS) and not switched from one stimulant to another at any point during the treatment period; no treatment with any other psychotropic medication	Mean=2.6 years
Quinn 1975 U.S. (Fair)	Unblinded follow-up of samples that continued their original randomly assigned medication (6-week, randomized, DB study: Rapoport, 1974) Setting: Hyperactivity Clinic Noncomparative	NR	1 year

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Interventions (mean dose)	Concomitant medication	Safety Assessment
Pliszka 2006	MPH (any form) vs MAS (any form) Highest daily dosages: 34.8 mg vs 22.7 mg	NR	Height and weight measured at least 3 times per year using the same scale throughout the study period; always recorded within 4 months of the last medication refill; Growth Plus 3.1 program (Applied Micro Solutions) calculated Z scores according to the child's age and gender using normative data from the national Center for Health Statistics
Quinn 1975 U.S. (Fair)	Methylphenidate mean daily dose of 20.56 mg Imipramine mean daily dose of 65.4 mg	NR	Height Weight Seizures

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Pliszka 2006	Mean age=8.7 years 81.0% male Race NR	NR/NR/179	NR/NR/63 (35%) included in 3-year analysis
Quinn 1975 U.S. (Fair)	Mean age nr 100% male Race NR	NR/NR/75	28 (37.3%) withdrawn overall/lost to fu=0

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Safety outcomes
Pliszka 2006	Final Z scores for MAS vs MPH: Height: 0.0 vs -0.2 Weight: 0.4 vs 0.6 BMI: 20.1 vs 20.9 No main effects for either stimulant type on height, weight or BMI
Quinn 1975 U.S. (Fair)	Safety compared only for children initially assigned to the active drug group and continued on the same medication for one year (methylphenidate n=23; imipramine n=13) Anorexia: 9 (47%) vs 5 (39%) Seizures: none reported Condition 1=Imipramine Condition 2=methylphenidate all doses (n=23) Condition 3=methylphenidate > 20 mg a day (n=5) Condition 4=methylphenidate 20 mg a day or less (n=18) Condition 5=no treatment (n=12) Weight change (percentile scores): -7.54 vs -8.81 vs -15.40 vs -6.88 vs +1.61 t-scores, p-values for comparisons of condition 5 with 1; 2; 3; 4: 2.45, p<0.01; 3.42, p<0.005; 4.18, p<0.005; 3.44, p<0.005 t-scores, p-values for comparisons of condition 1 with 2; 3; 4: .37, p=NS; 1.27, p=NS; 0.19, p=NS Height changes (percentile scores): -2.20 vs +3.19 vs -3.0 vs +5.12 vs -1.46 t-scores for comparisons of condition 5 with 1; 2; 3; 4 (p-values all NS): 0.23; 1.05; 0.22; 1.59 t-scores, p-values for comparisons of condition 1 with 2, 3, and 4: 1.25, p=NS; 0.12, p=NS; 1.90, p<0.05

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Comments
Pliszka 2006	
Quinn 1975 U.S. (Fair)	

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Design	Eligibility criteria	Duration
Safer 1972 U.S. (Fair)	Retrospective analysis of height and weight data among 2 groups: 1) hyperactive children who had been on stimulant medication for 9 months and had been either kept on or taken off treatment during the 3-month summer period; 2) hyperactive children, some who received continuous medication for 2+ years, and some who received no medication. Setting: NR Comparative	Group 1: 20 hyperactive children in an elementary school who were known by the school nurse to be regularly taking either methylphenidate or dextroamphetamine for hyperactivity. Group 2: 9 hyperactive children who had been on medication continuously for 2 or more years, and 7 children who although referred for stimulants were not given any owing to parental objection.	Group 1: 1 year Group 2: 2+ years
Safer 1973 U.S. (Fair)	Retrospective cohort (student health records) Setting: six elementary schools in Baltimore, Maryland	Hyperactive children who received stimulant medication for >/= 2 years	≥ 2 years

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Interventions (mean dose)	Concomitant medication	Safety Assessment
Safer 1972 U.S. (Fair)	Group 1: Methylphenidate 28.7 mg/day Dextroamphetamine 11.8 mg/day Group 2: Methylphenidate continuous treatment for 2+ years (dose not reported; 7 of 9 subjects were also in group 1 above) Control group: no medication	NR	Group 1: Height and weight were recorded in September, 1970 at the beginning of the school year, June 1971 before summer vacation, and again in September 1971. Group 2: The nurse obtained past height and weight measurements from school admission information at the age of five or six.
Safer 1973 U.S. (Fair)	DEX MPH Unmedicated controls Mean dosages NR	NR	School nurses completed a form based on review of school health records

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Safer 1972 U.S. (Fair)	Group 1: Mean age 9.8 Gender NR 100% white Group 2: Mean age NR Gender NR Ethnicity NR	NR/NR/29: 20 in Group 1, 16 in Group 2, with 7 occurring in both groups	NR/NR/29
Safer 1973 U.S. (Fair)	Mean age nr 89.8% male in children on medication; 100% male in unmedicated control group 100% white	NR/NR/44 on medication, 14 unmedicated controls	NR NR 44 on medication (DEX=29, MPH=20), 14 unmedicated controls

Evidence Table 15. Observational studies - long-term safety

Author
Year
Country **Safety outcomes**

Safer
1972
U.S.
(Fair)

Group 1	N	Dose of MPH mg/day	Dose of DAMP mg/day	Weight gain in school year (Sept-June), kg/mo		Weight gain in summer (June-July-Aug), kg/mo		
				All patients	All on MPH vs all on DAMP	All patients	Patients on MPH	Patients on DAMP
Continued meds. in summer	7	37.5	11.7	0.15	0.23 vs 0.12 (p<0.05)	0.22 (60% of expected gain)	0.29	0.14
Discontinued meds. in summer	13	24.0	11.8	0.17		0.45 (130% of expected gain)	0.41	0.47
P-value, Continued vs Discontinued		p<0.05	ns	ns		p<0.05	ns	p<0.01

Group 2	N	Average percentile changes in growth over 2 or more years		
		Weight	Height	
Medication 2+ years	9	-17.5	-16.3	Mean yearly weight gain of children on stimulants for 2 years was 1.8kg, compared with expected gain of 3.1 kg. Mean percentile for weight decreased from 62nd to 40th.
No medication	7	+1.3	+4.0	
P-value, Medicated vs. Not		p<0.05	p<0.05	

DAMP's effects on weight gain did not differ between doses of 10 and 15 mg/day.
MPH 20 mg/day showed significantly greater weight gains than 30 and 40 mg/day.

Safer
1973
U.S.
(Fair)

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

Height: -13.45; -9.40, -5.20, -1.00; +1.29
DEX > MPH all-dosage, low-dosage and control groups, but DEX=MPH high-dosage group; MPH high-dosage > controls; MPH all-dosage and low-dosage=controls

All differences remained significant following a covariance analysis that controlled for differences in initial values of weight and height percentiles

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Comments
Safer 1972 U.S. (Fair)	The school nurse determined the use of medication during summer based on the children's self-report. At the start of the following school year, the nurse would ascertain if their parents had kept them on medication during the summer.
Safer 1973 U.S. (Fair)	Initial weight/height percentile values were initially larger for DEX group

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Design	Eligibility criteria	Duration
Safer 1975 (Poor)	Prospective cohort study setting: NR	only children who remained in the school for one calendar year were included in the evaluation. Those children whose therapy was changed from one stimulant medication to another during the calendar year, or was discontinued during the school year, were also excluded	I year
Satterfield 1979 U.S. (Good)	Prospective study of weight and height in boys treated for two years with methylphenidate. Setting: clinic, single-site Noncomparative	Subjects were all children who were referred to Gateways Hospital Hyperkinetic Children's Clinic, Los Angeles, from September 1973 thru December 1974, and met the following criteria: boys aged 6-12, attending school, having normal vision and hearing, of normal intelligence on the Wechsler Intelligence Scale for Children (80+); hyperactive by behavioral criteria that required evidence of chronic symptoms of hyperexcitability, impulsivity, and poor attention span, as reported by parents and teachers; nonpsychotic, non-brain-damaged. 20% of subjects had received stimulant drugs prior to entering the study.	2 years

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Interventions (mean dose)	Concomitant medication	Safety Assessment
Safer 1975 (Poor)	MPH: 27mg/day, range 10-60mg dextroamphetamine 12mg/day, range 5-20mg	NR	the height and the weight were recorded by two independent examiners
Satterfield 1979 U.S. (Good)	Methylphenidate, taken bid (morning and noon) on 5 weekdays; some patients required a third dose midafternoon, and others required medication 7 days/week. Some children took the medication only during the school year; others continued medication during the summer but at a lower dosage. Mean dose, year 1: 24.2 mg/day, 0.47 mg/kg/day Mean dose, year 2: 0.59 mg/kg/day	NR	Initial height and weight measures were converted to percentile rank based on the Iowa growth tables for normal children. Using these tables, this percentile rank predicted height and weight at years 1 and 2 for each subject. Expected gains for years 1 and 2 were computed based on initial and predicted percentiles. Growth deficits were computed from predicted vs observed growth. Monthly weight and height measurements were obtained by research staff on a pediatric scale, with child's shoes removed and pockets emptied. All measurements were used to determine growth rates and total year's growth.

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Safer 1975 (Poor)	Mean age: 10.3 years, range 8-13 years Gender: 80% male 100% Caucasian	66/NR/NR	NR/NR/26
Satterfield 1979 U.S. (Good)	Age range 6-12, mean age NR 100% male Ethnicity NR	NR/NR/72	NR/NR/72 72 analyzed in year 1 48 analyzed in year 2

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Safety outcomes
Safer 1975 (Poor)	Compare growth rate in school year and summer Continued group (CG): growth rate of the height and weight, NS Discontinued group (DG): dextroamphetamine, weight- school year<summer, p<0.005 dextroamphetamine, height- school year< summer, p<0.05 MPH, weight- school year<summer, p<0.005 MPH, height- school year< summer, p<0.05

Satterfield
1979
U.S.
(Good)

Patient group	N	Mean dosage mg/kg/day	Growth difference in % of expected growth (p-value); mean difference	
			Weight	Height
Year 1				
Total	72	0.47	-29% (p<0.01) 0.85 kg less	-19% (p<0.001) 1.03 cm less
Received summer med.	31	0.627	-35% (p<0.05)	-17% (p<0.05)
No summer medication	41	0.37	-24.5% (p<0.05)	-19.5% (p<0.05)
Year 2				
Total	48	0.59	-10% (ns) 0.31 kg less	+8% (ns) 0.42 cm more
Received summer med.	24	0.81	-20% (p<0.05) 0.67 kg less	+7.5% (ns) 0.36 cm more
No summer medication	24	0.37	+2.5% (ns) 0.25 kg more	+10% (ns) 0.49cm more
Accumulated growth: Year 1 plus Year 2				
Total	48	0.56	-13% (ns)	+2% (ns)
Height and weight deficits in year 1 and in year 2 were not significantly correlated with average daily dosage, age, or before-treatment height or weight. Height and weight deficits in the first year were not significantly correlated with similar deficits in the second year of treatment.				

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Comments
Safer 1975 (Poor)	
Satterfield 1979 U.S. (Good)	Adherence in 93% of patients was confirmed by monthly urinalysis. Significant deficits in growth were observed in the 1st year. Greater-than-expected gains in height and weight occurred in the 2nd year of treatment, though these increases were not statistically significant.

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Design	Eligibility criteria	Duration
Wernicke 2003 U.S. (Fair)	Pooled analyses of (1) 3 short-term trials in children/adolescents (Spencer 2002, Michelson 2001); (2) 2 short-term trials in adults (Michelson 2003); and (3) long-term, open-label extensions or a blinded continuation following the three short-term treatment trials The short-term QTc-interval and cardiovascular adverse events data were not reported in the original publications	Children and adolescents with ADHD	At least 1 year

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Interventions (mean dose)	Concomitant medication	Safety Assessment
Wernicke 2003 U.S. (Fair)	Atomoxetine maximum dosage of 2 mg/kg/day administered in two divided doses (mean dose nr)	NR	QT interval prolongation using Bazett (exponent of 0.5) and Fridericia (exponent of 0.33) corrections. Categorical changes (increases of at least 30, 60, or to at least 500 msec) are those proposed by the European CPMP

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Wernicke 2003 U.S. (Fair)	Children/adolescents (n=550) Mean age=10.5 75.1% male 78.5% white Adults Mean age=41.1 64.9% male 90.8% white Long-term population data nr	NR/NR/NR	NR/NR

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Safety outcomes
Wernicke 2003 U.S. (Fair)	Baseline change in corrected (Friderida formulate) QT intervals: short-term treatment atomoxetine vs placebo, p-value Children (n=325 vs n=202): QTcD, mean change at endpoint: -3.1 vs -4.4, NS QTcD, increase > 30msec: 2.2% vs 4.5%, NS QTcD, increase > 60 msec or > 500 msec: NR QTcB, mean change at endpoint: 1.5 vs -4.5, p=0.004 QTcB, increase > 30 msec: 6.2% vs 7.4%, NS QTcB, increase > 60 msec: 0.3% vs 1.0%, NS QTcB, increase > 500 msec: NR QTcF, mean change at endpoint: -5.3 vs -4.4, NS QTcF, increase > 30 msec: 1.8% vs 2.5%, NS QTcF, increase > 60 msec or > 500 msec: NR Adults (n=257 vs n=257) QTcD, mean change at endpoint: 0.6 vs 0.8, NS QTcD, increase > 30msec: 2.3% vs 3.5%, NS QTcD, increase > 60 msec or > 500 msec: NR QTcB, mean change at endpoint: 5.7 vs 0.6, p<0.001 QTcB, increase > 30 msec: 6.2% vs 4.7%, NS QTcB, increase > 60 msec: 0.0% vs 0.0%, NS QTcB, increase > 500 msec: NR QTcF, mean change at endpoint: -2.7 vs 0.9, p=0.008 QTcF, increase > 30 msec: 1.2% vs 2.7%, NS QTcF, increase > 60 msec or > 500 msec: NR Long-term treatment group: "There is no evidence of an increase in QTc with increasing dosage of atomoxetine as indicated by lack of a dose effect (p=0.792)" Data NR. Number of patients with treatment-emergent cardiovascular adverse events, atomoxetine vs placebo, p-value: Children (n=340 vs n=207): Palpitation:0.3% vs 0%, NS Tachycardia:0.9% vs 0%, NS Cardiac murmur: 0.6% vs 0%, NS Extrasystoles: 0% vs 0%, NA

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Comments
Wernicke 2003 U.S. (Fair)	

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Design	Eligibility criteria	Duration
Wilens 2003; 2004; 2005 U.S. (Fair)	Open-label trial of OROS MPH, non-randomized, 12-month study in children who had used OROS MPH in previous trials and were found to be responders. Setting: 14 sites Non-comparative	All subjects except one had participated in a previous trial of OROS MPH. Eligible for inclusion were children with ADHD, aged 6-13, with normal urinalysis, hematology, and blood chemistry. Subjects who were already receiving specific behavioral interventions for ADHD on an ongoing basis were permitted to enter the study, but new behavioral interventions could not be initiated during the study. Children with mild or moderate vocal or motor tics, but not a diagnosis of Tourette's syndrome, were included. Exclusions: children with Tourette's syndrome; an ongoing seizure disorder; a psychotic disorder; clinically significant GI problems: a history of hypertension; known hypersensitivity to MPH; a coexisting condition or concurrent medication likely to interfere with MPH; females who had reached menarche.	12 months

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Interventions (mean dose)	Concomitant medication	Safety Assessment
Wilens 2003; 2004; 2005 U.S. (Fair)	Methylphenidate in a once-daily, osmotic controlled-release formulation (OROS MPH) Subjects were assigned to one of 3 dosing levels of OROS MPH (18 mg, 36 mg, or 54 mg qd) based on previous treatment. Dose could be adjusted up or down in 18 mg increments during the monthly clinic visits. Doses could be reduced or discontinued on weekends or nonschool days, or on other medication holidays. Mean dose at study entry: 35 mg/day Mean dose at 12 months: 41 mg/day	Allowed, but not specified	Urinalysis, hematology, serum chemistry were performed at baseline, at 6 and 12 months. Height, weight, blood pressure, and pulse were recorded at monthly clinic visits. Adverse events were elicited by the investigator and by spontaneous report by the subjects or their parents caregivers, and assessed as to severity and possible relationship to study medication. At monthly visits, parents were asked about their child's sleep quality; whether their child had experienced tics, or whether tics had changed in severity or specificity in the previous month.

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Wilens 2003; 2004; 2005 U.S. (Fair)	Mean age 9.2 83% male 86% white 5.7% black 0.7% Asian 4.4% Hispanic	NR/NR/436	143 (32.8%) withdrawn, 25 because data from one site was found to be unreliable 16 (3.7%) lost to fu 407 (93.3%) analyzed 28 (6.4%) withdrew due to AEs

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Safety outcomes
	Sinus tachycardia: 0.6% vs 0%, NS Ventricular extrasystole: 0.3% vs 0%, NS Atrial hypertrophy: 0% vs 0%, NA Sinus bradycardia: 0% vs 0%, NA Adults (n=269 vs n=263): Palpitation: 3.7% vs 0.8%, p=0.037 Tachycardia: 1.5% vs 0.8%, NS

Wilens
2003; 2004; 2005
U.S.
(Fair)

Adverse event	N (%)	Withdrawals due to AE	Specific adverse events
Headache	102 (25.1)	1	Tics: New onset occurred in 23 (6.4%) of 359 subjects with no known history of tics.
Insomnia	60 (14.7)	5	
Appetite suppression	55 (13.5)	7	
Abdominal pain	31 (7.6)	1	
Twitching	31 (7.6)	7	Sleep: sleep quality was rated good/excellent for 71% of subjects (282/398) in month 1, and for 74% of remaining subjects (134/182) in month 12. LOCF analysis showed that 69% of subjects received a good/excellent sleep quality rating at end of study.
Aggravation reaction	10 (2.5)		
Somnolence	10 (2.5)	1	
Reaction unevaluable	9 (2.2)		
Anxiety	9 (2.2)		
Weight loss	8 (2.0)	1	
Emotional lability	8 (2.0)	1	
Hostility	8 (2.0)	2	
Nausea	7 (1.7)		
Dizziness	7 (1.7)		Vital signs: 5 developed hypertension. 1 withdrew; elevated systolic readings resolved with discontinuation.
Vomiting	6 (1.5)		
Nervousness	6 (1.5)		
Depression	6 (1.5)		
Asthenia	5 (1.2)		
Hypertension	5 (1.2)	1	Growth: Mean weight decreased by 0.1 kg over the first 3 months then increased over the remainder of the study. See table below.
Apathy	4 (1.0)		
Worsening of ADHD	NR	3	
Compulsive skin picking	NR	1	
Hallucinations	NR	1	

Growth	Baseline	Month 3	Month 6	Month 9	Month 12
Weight (kg)	34.2	34.1	34.5	35.6	36.8
Rate of change (kg/mo)	---	**-0.033**	+0.133	+0.366	+0.400
Height (cm)	137.1	138.4	139.6	140.8	142.3
Rate of change (cm/mo)	---	+0.43	+0.40	+0.40	+0.50

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Comments
Wilens 2003; 2004; 2005 U.S. (Fair)	Most children were already MPH responders prior to entry into the study, and patients with known hypersensitivity to MPH were excluded.

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Design	Eligibility criteria	Duration
Wilens 2005/Spencer 2006 U.S.	Open-label extension study Setting: Multicenter, 14 sites	Children with ADHD who all (except one) participated in one of several previous efficacy or pharmacokinetic studies	24 months
Zeiner 1995 Norway (Fair)	Prospective cohort study Setting: Child psychiatric outpatient unit	Boys, between the ages of 7-12 years, DSM-III diagnosis of ADHD	Mean=634 days

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Interventions (mean dose)	Concomitant medication	Safety Assessment
Wilens 2005/Spencer 2006 U.S.	MPH; OROS® (for growth analysis: mean daily dose increased from 34.3 mg at baseline to 43.7 mg at month 21)	NR	Height and weight measured monthly during the first year and every 3 months thereafter at clinic visits
Zeiner 1995 Norway (Fair)	Medicated (MPH 23 mg) vs unmedicated	Medicated: no cc meds Unmedicated: 3 (13%) on imipramine x 6 weeks; 1 (4%) on imipramine x 6 months	measurements for height, weight, heart rate and blood pressure.

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Wilens 2005/Spencer 2006 U.S.	Growth analysis only: Mean age 9.4 years (6-13) 83.7% male 87.1% White 5.6% Black 0.6% Asian 2.8% Hispanic 3.9% other	NR/NR/407	178 (43.7%) total withdrawn 31 (7.6%) withdrawn AE 29 lost to fu 178 analyzed (had height and weight measured at both baseline and 21 months)
Zeiner 1995 Norway (Fair)	mean age 9.0 yrs 100% male Ethnicity NR	36/25/23	0/0/23 analyzed

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Safety outcomes
Wilens 2005/Spencer 2006 U.S.	Height was on average 0.23 cm less than expected at 21 months Weight was on average 1.23 kg less than expected at month 21, weight did not increase and BMI decreased slightly in the first 4 months Drug holidays did not significantly affect growth
Zeiner 1995 Norway (Fair)	Measurements at end of treatment: Medicated (n=23) vs unmedicated (n=23) Weight: 42.0 vs 40.3; p=NS Height: 150.4 vs 148.3; p=NS

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Comments
Wilens 2005/Spencer 2006 U.S.	Growth analyzed in a subgroup of study subjects
Zeiner 1995 Norway (Fair)	

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Design	Eligibility criteria	Duration
Elementary School Children - Stimulants (combined therapy)			
Rao 1998 U.S./Canada (Fair)	Cohort, retrospective Setting: National Cooperative Growth Study (NCGS) Database	1) diagnosis of IGHD or ISS (max stimulated GH level < 10 µg/L for IGHD and ≥ 10 µg/L for ISS); 2) no GH therapy before enrollment; 3) prepubertal at enrollment; 4) between 3 and 20 years of age at enrollment; 5) height below the 5th percentile for age and sex; 6) no other significant medical conditions that affect growth; and 7) height reported after at least 180 of GH therapy. Patients who met the criteria and who also were treated for ADHD with MPH or pemoline	NR

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Interventions (mean dose)	Concomitant medication	Safety Assessment
Elementary School Children - Stimulants (combined therapy)			
Rao 1998 U.S./Canada (Fair)	MPH or pemoline Mean dosages NR	NR	Information from case report forms

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Elementary School Children - Stimulants (combined therapy)			
Rao 1998 U.S./Canada (Fair)	Mean age=9.3 years 74.8% male Race NR	NR NR 3897 enrolled	n/a n/a Analyzed: IGHD-ADHD=184; IGHD=2313; ISS-ADHD=117; ISS=1283

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Safety outcomes
Elementary School Children - Stimulants (combined therapy)	
Rao 1998 U.S./Canada (Fair)	Factors w/significant effect on GH-therapy response (stepwise multiple regression): MPH/pemoline-treatment: Regression-coefficient= -0.17; contribution to R2= 0.002; p=0.001

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Comments
Elementary School Children - Stimulants (combined therapy)	
Rao 1998 U.S./Canada (Fair)	

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Design	Eligibility criteria	Duration
Weizman 1987 Israel (Fair)	Before-after, prospective Setting: NR	**Patients:** ADDH and (1) regular attendance at school, (2) cooperative parents and teacher willing to fill out the Conners rating scale, (3) IQ > 80; (4) absence of significant medical or neurological disease; (5) all patients were drug free for at least 3 months **Controls:** No psychopathology was observed in the subjects or their parents. All subjects were free of lifetime psychiatric disorder	9 weeks
Elementary School Children - Mixed amphetamine salts			
Donner 2007	Open-label, noncomparative, community-based study Setting: NR	To be eligible for enrollment, children had to be in good medical health with normal BP and pulse, and have clinically normal results on a 12-lead ECG. Subjects were not negligible for this study if their physical condition would preclude the use of MAS XR, compromise their safety or confound interpretation of any study measurement or results. Furthermore, subjects taking any medication with known effects on BP or the hearth within 30 days before the screening visit were excluded. Informed consent was obtained from the subject, as well as the subject's parent or legally authorized guardian.	Initial tx: 7 wks Extension tx: initial tx and 4 wks ± 3 days more

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Interventions (mean dose)	Concomitant medication	Safety Assessment
Weizman 1987 Israel (Fair)	MPH 10.3 mg	NR	Blood samples for GH were obtained at 8:00-9:00 am after an overnight fast as follows: (1) morning before treatment initiation; (2) 2 hours after first dose; (3) after 4 weeks; (4) 2 hours after repeated challenge with MPH 5 mg Plasma GH levels were determined by double antibody RIA using materials provided by SORIN S.P.A. (France)
Elementary School Children - Mixed amphetamine salts			
Donner 2007	Once daily dose of MAS XR of 10, 20 or 30 mg/d according to medication-conversion algorithm mean dose NR	NR	Any diagnostic or lab finding considered to be abnormal by investigator for individual subject and a clinically significant change from a previous finding was designated an adverse event. A 12-lead ECG performed at screening and at the end of extension phase or early termination; abnormal ECG findings were reported as AEs SBP, DBP, pulse measured at each study visit after sitting at rest for 5 minutes. spontaneously reported AEs also recorded at each visit.

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Weizman 1987 Israel (Fair)	Mean age=8.8 years 81% male Race NR	NR NR 16 patients/16 controls	NR NR 16 patients/16 controls
Elementary School Children - Mixed amphetamine salts			
Donner 2007	Average age: 9.5 yrs ± 1.8 Male: 76.1% White: 88% African American: 6.7% Asian/Pacific Islander: 0.3% Hispanic: 3.5% Native American: 0.1% Other: 1.4%	3428 / 2968/ 2280 for initial phase, 441 for extension phase	293 discontinued and 673 had participation terminated by sponsor Analyzed: 1407 for extension phase and 441 for extension phase

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Safety outcomes
Weizman 1987 Israel (Fair)	GH (ng/ml) in ADDH patients Pre-treatment: 0': 2.6, p=NS 120': 5.9, p=NS Post-treatment: 0': 2.1; p=NS 120': 7.8; p=p<0.05 GH in controls: NR
Elementary School Children - Mixed amphetamine salts	
Donner 2007	<u>MAS XR 10mg/d vs MAS XR 20 mg/d vs MAS XR 30 mg/d vs MAS XR 40 mg/d</u> Mean SBP(mm Hg) change from baseline to final visit: 0.4 vs 1 vs 0.2 vs 0.7 Mean DBP (mm Hg) change from baseline to final visit: 0.5 vs 0.8 vs 0.6 vs 0.5 Pulse (bom) from baseline to final visit: 1.2 vs 1.6 vs 1.8 vs 1.3 <u>New abnormalities (total pts)</u> Atrial premature complex: 2 Ventricular premature complex: 6 Incomplete right bundle-branch block: 6 Increased QT interval: 2 Left anterior hemi-block: 9 Right bundle-branch block: 5 Low voltage morphology: 2 right ventriculat hypertrophy morphology: 1 Ectopic atrial rhythm: 27 Sinua tachycardia: 2 T-wave: 9 U-wave abnormality: 1

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Comments
Weizman 1987 Israel (Fair)	
Elementary School Children - Mixed amphetamine salts	
Donner 2007	

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Design	Eligibility criteria	Duration
Faraone 2005 U.S.	Open-label extension study Setting: multicenter	DSM-IV criteria for ADHD, children exposed to double-blind study medication or not due to enrollment termination from one of two previous studies, children who discontinued previous study completed at least 1 week of double-blind treatment and had no clinically significant adverse medical experiences	6-30 months
Findling 2005 U.S.	Open-label extension study Setting: multicenter	DSM-IV criteria for ADHD, children who were part of one of two previous studies, no clinically relevant AEs from prior study	2 years

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Interventions (mean dose)	Concomitant medication	Safety Assessment
Faraone 2005 U.S.	MAS XR 10-30 mg/day (mean dose NR)	NR	Weekly visits for the first 4 weeks then monthly thereafter Baseline value was the value immediately prior to any MAS XR dose in a treatment study Endpoint was the last height value recorded
Findling 2005 U.S.	MAS XR; Adderall XR® (mean dose ranged from 20 mg/day at 3 months to 22 mg/day at 24 months)	Prohibited concomitant medications included: anticonvulsant drugs, clonidine, guanfacine, and any medications that may have affected blood pressure, pulse, or central nervous system performance	Resting sitting blood pressure and pulse at baseline, weekly for first month, then monthly up to 24 months clinic visits; ECG measurements at baseline, 12, 18, and 24 months clinic visits

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Faraone 2005 U.S.	Mean age 8.7 years (6-12) 78% male 73% White 12% Black 9% Hispanic 19% Asian/Pacific Islander 3% other	NR/638/568	Height >24-30 months, 203 analyzed Weight >24-30 months, 199 analyzed BMI >24-30 months, 198 analyzed
Findling 2005 U.S.	Mean age 8.7 years (6-12) 78% male 73% White 12% Black 9% Hispanic 4% other	NR/NR/568	291 (51%) withdrawn by 24 months 277 analyzed at 24 months

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Safety outcomes
Faraone 2005 U.S.	Growth was less than expected based on CDC norms Losses in expected weight and BMI were greatest for heaviest children, losses in expected height were greatest for tallest children Nearly all growth deficits occurred in year one; loss in expected growth NS in year 2 Those previously treated with stimulants showed smaller weight and height deficits for the first year
Findling 2005 U.S.	4 (0.7%) cardiovascular AEs: 1 (0.2%) tachycardia (108 bpm at baseline, 101 to 121 bpm long-term treatment), moderate in severity, MAS XR 20 mg/day 2 (0.4%) intermittent chest pain that resolved, mild in severity, MAS XR 20 mg/day (1 at 9 months, 1 at 12 months) 1 (0.2%) hypertension, 130/90 mm Hg after 12 months, moderate severity, MAS XR 10 mg/day Change in group mean QTcB values NS Most common ECG abnormalities, none clinically significant, at MAS XR 20 mg/day, were: 25 (4.4%) sinus arrhythmia 5 (0.9%) ST-T wave abnormalities 4 (0.7%) poor anterior R-wave progression

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Comments
Faraone 2005 U.S.	
Findling 2005 U.S.	

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Design	Eligibility criteria	Duration
Spencer 2005 U.S.	Open-label extension study Setting: multicenter	DSM-IV criteria for ADHD, adolescents who participated and completed the previous study and those who discontinued early so long as treatment was not interrupted, excluded patients from previous study who discontinued due to noncompliance or safety concerns	6 months
Wilens 2005 U.S.	Open-label extension study Setting: Multicenter	DSM-IV criteria for ADHD, adolescents who were part of the previous study	6 months
Adults			
Adler 2005 U.S./Canada	Interim analysis of open-label extension study Setting: multicenter, 31 sites	DSM-IV criteria for ADHD, adults who were part of one of two previous studies, no selection based on completion of previous study or responders	97 weeks
Horrigan 2000 U.S. (Fair)	Before-after, retrospective Setting: University-based neuropsychiatric clinic	Adult outpatients with ADHD (DSM-IV 314.01, combined type)	12 months

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Interventions (mean dose)	Concomitant medication	Safety Assessment
Spencer 2005 U.S.	MAS XR, flexible dosing 10-60 mg/day, most patients (>80%) received 20-40 mg/day throughout the study	Prohibited medications (not including ADHD medications) that could affect blood pressure or heart rate	Weekly study visits for the first 4 weeks, then visits 30 days apart up to 6 months, followup telephone contact at ~ 30 days post discontinuation or after study completion to collect AE information Body weight measured at each study visit
Wilens 2005 U.S.	MAS XR flexible dosing 10-60 mg/day (mean dose ranged 29 mg/day at 1 month to 32 mg/day at 4 months, >80% subjects received 20-40 mg/day for the study duration)	Prohibited medications (not including ADHD medications) that could affect blood pressure or heart rate	Sitting blood pressure and pulse at baseline, weekly during the first month, then monthly for up to 6 months clinic visits ECG measurements at baseline, month 3, and month 6 or the final clinic visit; central lab used to evaluate all ECG readings
Adults			
Adler 2005 U.S./Canada	Atomoxetine, maximum total daily dose did not exceed 160 mg/day (mean final dose=98.6 mg/day, median final dose=120 mg/day)	NR	Every other week for the 1st 4 visits, monthly for 4 visits, then every 3 months for duration of study Adverse events assessed by open-ended questioning at each visit and lab tests ECG completed w/in 30 days of 1st visit - baseline measurement
Horrigan 2000 U.S. (Fair)	Adderall (modal dose 10 mg - bid dosing)	SSRI (sertraline or venlafaxine) in 4 patients	Motor tic

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Spencer 2005 U.S.	Mean age 14.4 years (13-17) 71.0% male 71.7% White 15.2% Black 10.1% Hispanic 2.8% other	NR/NR/138	33 (23.9%) total withdrawn 6 (4.3%) withdrawn AE 19 (13.8%) withdrawn due to protocol violations and lost to fu 105 analyzed at 6 months
Wilens 2005 U.S.	Mean age 14.4 years (13-17) 71.0% male 72.0% White	NR/NR/138	28 (20%) withdrawn by 6 months 110 analyzed at 6 months
Adults			
Adler 2005 U.S./Canada	Mean age=42.4 years 64.1% male 92.2% White 3.6 % Hispanic 2.1 % African American 1.0% Eastern Asian 0.5% Western Asian 0.5% other	NR/536/385	260 (67.5%) total withdrawn 42 (10.9%) withdrawn AE 110 lost to fu 125 continued after 97 weeks
Horrigan 2000 U.S. (Fair)	Mean age=33 50% male Ethnicity NR	NR/NR/24	NR NR 24

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Safety outcomes
Spencer 2005 U.S.	34 (24.6%) anorexia, MAS XR dose 10 mg n=8, 20mg n=10, 30 mg n=13, 40 mg n=3, 50 mg n=1, 60 mg n=2 34 (24.6%) weight loss, 2 patients discontinued treatment, MAS XR dose 10 mg n=3, 20 mg n=12, 30 mg n=15, 40 mg n=3, 50 mg n=2, 60 mg n=0 Mean body weight decreased by 2.4 kg (5.2 lbs) from baseline to endpoint, p<.0001 Decrease in body weight among MAS XR-naïve patients (-9.2 lbs, p<.0001) was greater than among MAS XR-continuous patients (-3.3 lbs, p=.0004) Magnitude of weight loss related to baseline weight, those >75th percentile at baseline lost the most weight (4.2 kg [9.2 lbs], p<.0001)
Wilens 2005 U.S.	1 (0.7%) tachycardia (124 bpm), MAS XR dose NR 1 (0.7%) pulse 115 bpm at 5 months, MAS XR 30 mg/day 2 (1.4%) postural hypotension, MAS XR dose NR 2 (1.4%) syncope, MAS XR dose NR Decrease in QTcB interval from baseline (-4.6±19.9 msec) was statistically (p=.009), but not clinically, significant at 6 months
Adults	
Adler 2005 U.S./Canada	Mean decrease in weight of 1.3 kg, p<.001 Increases in heart rate, mean change 5.1 bpm, p<.001 Increases in blood pressure, mean change for systolic and diastolic <2.0 mm Hg, p<.05 No clinically relevant changes in QTc (Fridericia) No clinically significant changes in lab measures
Horrigan 2000 U.S. (Fair)	Motor tic: 1/24 (4%)

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Comments
Spencer 2005 U.S.	
Wilens 2005 U.S.	
Adults	
Adler 2005 U.S./Canada	35 (9.1%) of patients rolled into the open-label trial w/out entering the discontinuation period of the previous studies
Horrigan 2000 U.S. (Fair)	

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Design	Eligibility criteria	Duration
Weisler 2005 U.S.	Open-label extension study Setting: multicenter	DSM-IV criteria for ADHD, healthy adults at short-term study entry who completed at least 1 week of treatment without experiencing any clinically important AEs in the short-term study, excluded those with blood pressure consistently >139/89 mm Hg, heart rate consistently <50 or >120 bpm	24 months

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Interventions (mean dose)	Concomitant medication	Safety Assessment
Weisler 2005 U.S.	MAS XR; Adderall XR®, 20-60 mg/day, after 1 month 179 (80.3%) = dose of 40 or 60 mg/day (mean dose NR)	Prohibited medications that could affect heart rate, blood pressure, or CNS	Resting sitting blood pressure and pulse at baseline, weekly for the 1st 4 weeks, then monthly up to 24 months ECG at baseline, at months 3, 6, 12, 18, and 24 or upon early termination Central lab used to evaluate ECGs

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Weisler 2005 U.S.	Mean age=39.8 years (18-76) 59.3% male 90.5% White 5.0% Hispanic 2.7% Black 1.8% other	NR/NR/223	147 (66%) total withdrawn 48 (22%) withdrawn AE 23 lost to fu 76 analyzed at 24 months

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Safety outcomes
Weisler 2005 U.S.	7 (3.1%) discontinued due to a cardiovascular AE: 5 (2.2%) hypertension; MAS XR 20 mg/day, n=1; 40 mg/day, n=1; 60 mg/day, n=3 2 (0.9%) palpitations and/or tachycardia, MAS XR 40 mg/day, which resolved upon discontinuation Clinically insignificant increases in mean QTcB (corrected by Bazett's formula) (7.2 msec, p<.001) and QTcF intervals (2.9 msec, p=.009) at 24 months No subject exhibited QTcB interval >480 msec (QTcF [corrected by Fridericia's formula] >454 msec) 2 (0.9%) clinically significant abnormal ECGs; n=1 at baseline, abnormal T-wave and lengthened QT interval that resolved, n=1 left anterior hemiblock at month 3 and ongoing at month 24; neither subject withdrawn

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Comments
Weisler 2005 U.S.	Rollover from short-term study divided into 3 groups for analysis: MAS XR naïve, MAS XR continuous, and MAS XR interrupted

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Design	Eligibility criteria	Duration
Preschool children			
Swanson 2006 (PATS) U.S.	Before-after, prospective Setting: multicenter	Stimulant-naïve preschool-age children with diagnoses of ADHD who entered the PATS protocol	~ 1 year
Goldman 2008 U.S.	Case control Setting: Akron Children's Hospital and Medical Center	All patients seen in the pediatric rheumatology clinic who had signs and symptoms of Raynaud's Syndrome (RS) and met pulse volume recording diagnostic criteria	5 years
Miller-Horn 2008 U.S.	Retrospective cohort (database analysis) Setting: St. Christopher's Hospital for Children in Philadelphia	Children who met DSM-IV criteria for one of the subtypes of ADHD and treated with any of the 5 medications (listed in interventions).	24 months

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Interventions (mean dose)	Concomitant medication	Safety Assessment
Preschool children			
Swanson 2006 (PATS) U.S.	MPH, titrated doses (average 14.2 mg/day) 3 times daily, 7 days/week	NR	Height and weight measurements at 29 potential visits ranging from -117 average days from baseline to 378 average days from baseline Weekly visits early on after baseline then monthly during maintenance phase CDC growth charts utilized
Goldman 2008 U.S.	Methylphenidate Dextroamphetamine Combined dextroamphetamine and amphetamine	NR	Chart reviews for the presence or absence of antinuclear antibody, anti-Sm, anti-RNP, anticentromere antibody, anti-SSA, anti-SSB, anti-Scl-70 and rheumatoid factor, for the erythrocyte sedimentation rate, and for levels of C-reactive protein, cryoglobulin, von Willebrand factor antigen, and factor VIII, as well as for findings of EKG, echo, and pulmonary function testing.
Miller-Horn 2008 U.S.	(i) Amphetamine/dextroamphetamine extended release (Adderall XR) (ii) Amphetamine/dextroamphetamine (Adderall) (iii) osmotic controlled-released formulation of methylphenidate (OROS) (iv) atomoxetine (Strattera) (v) methylphenidate standard release (MPH)	NR	Subjective global clinical impression

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Preschool children			
Swanson 2006 (PATS) U.S.	Mean age=4.4 years 74% male	NR/NR/140	Subgroups of children who completed the maintenance phase of the PATS (n=95) and those who did not (n=45) were compared
Goldman 2008 U.S.	Mean age cases: 15.9 years controls: 16.1 years 28.2% males Ethnicity: NR	NR/NR/64	NR NR 64
Miller-Horn 2008 U.S.	Mean age males: 9.9 years females: 10.9 years 79.6% male Ethnicity: NR	516/150/137	NR NR 137

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Safety outcomes
Preschool children	
Swanson 2006 (PATS) U.S.	Mean growth rate slowed with treatment (p<.0001) For children who remained on medication (n=95) annual gain was 20.3% less than expected for height and 55.2% less than expected for weight
Goldman 2008 U.S.	McNemar's test showed a significant association between past or current use of ADHD stimulants and the presence of RS (x^2=5.00, P=0.01) Controls had significantly higher CRP levels compared to cases (P=0.03) Controls had significantly higher ESR levels compared to cases (P<0.001)
Miller-Horn 2008 U.S.	35 of 137 reported side effects (25%) Adderall XR vs Adderall vs OROS vs Strattera vs MPH Insomnia: 3.8% vs 22.2% vs 12.5% vs 6.7% vs 8.7% Tics: 0% vs 5.5% vs 2.5% vs 3.3% vs 8.7% Decreased appetite: 15.4% vs 22.2% vs 17.5% vs 10% vs 8.7% Headaches: 11.5% vs 11.3% vs 10% 0% vs 4.3% (P=0.035)

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Comments
Preschool children	
Swanson 2006 (PATS) U.S.	Greater than expected height and weight observed at baseline (p<.0001)
Goldman 2008 U.S.	
Miller-Horn 2008 U.S.	

Evidence Table 16. Quality of observational studies of long-term safety

Author	Non-biased selection?	Low overall loss to follow-up?	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Batterson 2005	Unclear	N/A - cross-sectional	Yes	Yes	Yes
Brehaut 2003	Yes	Yes	Yes	Yes	Yes
Charach 2006	No - only 87% of children who completed 12-month RCT were enrolled	LTFU NR; overall withdrawal rate of 25% at year 5	Yes	Yes	Unclear who collected measurements and whether they were blinded to medication status
Coleman 2005	No	No follow up - cross-sectional	unclear	No - limited	Unclear
Donner 2007	No (select group of known responders and tolerant to drug)	No; 441/2968 completed (15%)	Yes	Yes	Unclear
Faraone 2005	Unclear	No (48% attrition)	Yes	Yes	Yes
Findling 2005	No	No 4-w study: completion I 90%, C 82% 2-y study: overall 40%	Yes	Yes	Unclear; ECGs were read at central office
Forrester 2006	No - medical outcome only known for 53% of all human exposures	N/A - cross-sectional	Yes	Yes	Unclear who classified medical exposure
Gadow 1999	Yes	Yes	No	Yes	Yes
Goldman 2008	Unclear, all subjects w/ RS eligible.	Yes	Only RS	Yes	Yes
Gross 1976	No	Yes	Yes	Yes	Yes

Evidence Table 16. Quality of observational studies of long-term safety

Author	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall adverse event assessment quality	Notes
Batterson 2005	No	None	Poor	
Brehaut 2003	Yes	Yes	Fair	
Charach 2006	Yes	Yes	Poor	
Coleman 2005	None	None	Poor	
Donner 2007	NR	Yes; 15w	Poor	Large single-group cohort study; low follow-up rate
Faraone 2005	NR	Yes (generally 6+m)	Poor	Open-label extension of RCT; high attrition and attrition related to weight deficit
Findling 2005	NR	Yes, 2 years	Poor	Open-label extension of RCT; no comparison group and high attrition
Forrester 2006	None	Yes	Poor	
Gadow 1999	Yes	Yes	Fair	
Goldman 2008	Unclear, used case control sample based on demographics.	N/A retrospective study of patients w/in a 5 year period.	Fair/ poor	Retrospective case control study looked at RS only. Limited description of case control sample.
Gross 1976	NR	Yes	Fair	Study included only patients within the investigator's clinical practice, for whom pre-treatment weight and height data were available.

Evidence Table 16. Quality of observational studies of long-term safety

Author	Non-biased selection?	Low overall loss to follow-up?	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Gualtieri 1985	No	Yes	No	No	Unclear
Horrigan 2000	Yes	Yes	No	No	Unclear
Kratochvil 2001	Yes	Yes	No	No	Yes
Mattes 1983	No	No	Yes	No	Yes
McGough 2005	No, only subjects with no prior clinically relevant AE in previous study were eligible.	Yes	Yes	Yes	Yes
McNutt 1976a (preliminary report) McNutt 1976b	Unclear; # of children in short-term studies NR	Unclear	Yes	Yes	Yes
Miller-Horn 2008	No, first 150 entered into the database were included.	N/A	Yes	Yes	Yes
Millichap 1977	Yes	NR	Yes	No	Yes

Evidence Table 16. Quality of observational studies of long-term safety

Author	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall adverse event assessment quality	Notes
Gualtieri 1985	NR	Yes	Fair	
Horrigan 2000	NR	Yes	Fair	
Kratochvil 2001	Yes	No	Fair	
Mattes 1983	Yes	Yes	Fair	
McGough 2005	NR	Yes, 24 months	Fair	Open-label extension of RCT
McNutt 1976a (preliminary report) McNutt 1976b	Yes	Yes	Fair	
Miller-Horn 2008	NR	N/A retrospective study of patients over a 24 mo. period.	Fair	Open-label retrospective study
Millichap 1977	No	Yes	Fair	

Evidence Table 16. Quality of observational studies of long-term safety

Author	Non-biased selection?	Low overall loss to follow-up?	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Pliszka 2006	Yes	No - 3-year analysis excluded 65% of patients	Yes	Yes	Yes
Quinn 1975	No	Yes	No	No	Yes
Rao 1998	Yes	n/a	Yes	No	Yes
Safer 1973	Yes	Yes	No	Yes	No
Safer 1975	Yes	Yes	Yes	No	Unclear
Safer 1972	No	Yes	Yes	No	No
Satterfield 1979	Yes	Yes	Yes	Yes	Yes
Spencer 2005	No (select group of compliant subjects known to be tolerant to the drug)	No (completion 76%)	Yes	Yes	No (spontaneously-reported Aes, reported to unblinded provider)
Swanson 2006	Unclear	No; 67% completed	Yes	Yes	Yes

Evidence Table 16. Quality of observational studies of long-term safety

Author	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall adverse event assessment quality	Notes
Pliszka 2006	Adjusted for age and time	Yes	Poor	
Quinn 1975	NR	Yes	Fair	
Rao 1998	Yes	Unclear	Fair	
Safer 1973	Yes	Yes	Fair	
Safer 1975	No	Yes	Poor	
Safer 1972	NR	Yes	Fair	Main outcome (percentile change) uses two time points (single baseline measurement taken at school admission at age 5-6, to end of 2+ year treatment) rather than construction of individual growth curves. Classification of treatment during summer based on child's self-report, rather than prescription records
Satterfield 1979	NR	Yes	Good	Adherence was assessed by monthly urinalysis.
Spencer 2005	NR	Yes, 6m	Fair	Open-label extension of RCT
Swanson 2006	Yes; completers and study site	Yes, 4.4y	Fair	Open-label extension of RCT

Evidence Table 16. Quality of observational studies of long-term safety

Author	Non-biased selection?	Low overall loss to follow-up?	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Weisler 2005	No, only subjects with no prior clinically relevant AE in previous study were eligible.	Yes, 44% completed	Yes, cardiac only	Yes	Yes
Weizman 1987	Unclear	Unclear	Yes	Yes	Yes
Wernicke 2003	No	Yes	Yes	Yes	Yes for ECG; unclear for adverse events
Wilens 2003; 2004; 2005	No	Yes	Yes	Yes	Yes
Wilens 2005	No (low rate of inclusion into 6-m extension study)	No (80% completed 6m study)	Yes	Yes	Unclear; ECGs were read at central office
Wilens 2005/Spencer 2006	Unclear	No, 71% completed 12m (Aes measurement); 44% completed 21+ months for growth measures	Yes	Yes	Yes
Zeiner 1995	No	Yes	Yes	No	Unclear

Evidence Table 16. Quality of observational studies of long-term safety

Author	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall adverse event assessment quality	Notes
Weisler 2005	NR	Yes, 24 months	Fair	Analysis was from a 4-weel RCT and a 24-month open-label extension study.
Weizman 1987	No	No	Fair	
Wernicke 2003	Unclear	Yes	Fair	
Wilens 2003; 2004; 2005	NR	Yes	Fair	Study selected for MPH responders, decreasing likelihood of AEs.
Wilens 2005	NR	Yes, 6m	Fair	Open-label extension of RCT
Wilens 2005/Spencer 2006	NR	Yes, 21+ m	Poor	Open-label extension of RCT; no comparison group and high attrition
Zeiner 1995	Yes	Yes	Fair	

Evidence Table 17. Abuse and diversion studies

Author Year (Quality)	Study Design Setting	Eligibility criteria
Fredericks 2005	Observational	Children 10-14 years with established ADHD taking methylphenidate
Oesterheld 1998	RCT cross-over in residential school	Native American child 5 to 12 years with full or partial fetal alcohol syndrome with ADHD

Evidence Table 17. Abuse and diversion studies

Author Year (Quality)	Comorbidity
Fredericks 2005	No
Oesterheld 1998	Fetal alcohol syndrome (full or partial) with ADHD

Evidence Table 17. Abuse and diversion studies

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions
Fredericks 2005	Maintenance doses were encapsulated for each participant (three participants with 10 mg, one with 20 mg and one with 30 mg) Total 3 weeks Participants were given MPH or placebo and were to take that except for the six sampling sessions where participants had a chance to experience both drugs and six choice sessions where participants had the opportunity to choose their preference (Methylphenidate or placebo or neither)	NR	NR
Oesterheld 1998	Methylphenidate 0.6 mg /kg 5 days- lactose placebo 5 days and vitamin C placebo 2 days off in between Total 3 weeks	NR	None

Evidence Table 17. Abuse and diversion studies

Author Year (Quality)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Fredericks 2005	Reinforcing effects were assessed using a double-blind choice procedure, with six sampling sessions and six choice sessions. Participant-rated effects were measured using self-report questionnaires. Clinical effects were measured using direct observations and behavior ratings.	Mean age=12 yrs Gender: 80% male Ethnicity: NR
Oesterheld 1998	Conners Parent Rating Scale (CPRS-48), and the Conners Teacher Rating Scale (CTRS-39) daily during active treatment	Mean age=8.25 yrs Gender: 50% male Ethnicity: 100% Native American

Evidence Table 17. Abuse and diversion studies

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Fredericks 2005	All participants had current prescription for MPH for tx of ADHD symptoms and have been taking immediate-release MPH tx for at least 1 yr prior to the study	Screened: 14 Eligible: 5 Enrolled: 5	0/ 0/ 5
Oesterheld 1998	2 boys full FAS 2 girls partial FAS	Screened: 30 Eligible: 7 Enrolled: 4	NA

Evidence Table 17. Abuse and diversion studies

Author Year (Quality)	Results
Fredericks 2005	Differences between the number of MPH, Placebo, and Neither choices across participants were significant ($X^2 = 9.6$; $p < 0.01$). Three of five participants reliably chose MPH more often than placebo. MPH produced idiosyncratic patterns of participant-rated effects but failed to produce significant clinical effects.
Oesterheld 1998	CPRS-48 Hyperactivity-Impulsivity scale (HI) F= 4.34 df 4 P< 0.05 the daydreaming attention scale was NS CTRS-39 HI F= 6.42 df 4 P < 0.02

Evidence Table 17. Abuse and diversion studies

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Fredericks 2005	NR	NR	NR	
Oesterheld 1998	NR	During active treatment- **Decreased appetite** 75% **Stomach ache** 50% **Headache** 50%	Total 0 Due to AEs 0	

Evidence Table 18. Quality of abuse - diversion

	Internal Validity							
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**	**Reporting of attrition, crossovers, adherence, and contamination**
Fredericks 2005	Y; The order in which placebo and MPH were scheduled in the sampling sessions was counterbalanced across subjects and within-subjects across weeks.	Y	Y; only 5 participants	Y	Y	Y; medication dispensers blinded	Y	n/a
Oesterheld 1998	NR	Unclear	Y; only 4 participants	Y	Y	Y	Y	n/a

Evidence Table 18. Quality of abuse - diversion

					External Validity
Author, Year Country	**Loss to follow-up: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**
Fredericks 2005	N/N	NR	N	Poor; not sure how to rate this study	14/5/5
Oesterheld 1998	N/N	NR	N	Poor; not sure how to rate this study	30/7/4

Evidence Table 18. Quality of abuse - diversion

Author, Year Country	Exclusion criteria	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Fredericks 2005	Taking any other type of psychoactive medication, exhibited any gross neurological, sensory, or motor impairment, had a history of other significant learning or psychiatric problems, and/or had a known family history of diabetes.	n/a	N; All participants were taking their maintenance dose of MPH at noon on experimental days.	n/a	NR	Limited; small N, simulated class room environment
Oesterheld 1998	Pregnant, evidence of lactose intolerance, prior psychotropic medication use, or acute and chronic medical or neurologic disorders (including current history of seizures or lead levels of more than 9 mcg/dL). Height and weight at or below the 3rd percentile. IQ < 60.	NR/Y Study drug given M-F/no drug given Sat/Sun; no tx drugs given for 2 days between tx trials. [Methylphenidate half-life 2.6 h]	Y	n/a	U of South Dakota: USF-Minigrant 94 202-4590-005	limited; small N; lack of standardized tests