



Pharmacologic Treatments for ADHD

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The Health Resources Commission
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Health Resources Commission

The State of Oregon’s Health Resources Commission is a volunteer commission appointed by the Governor. The Health Resources Commission provides a public forum for discussion and development of consensus regarding significant emerging issues related to medical technology. Created by statute in 1991, it consists of four physicians experienced in health research and the evaluation of medical technologies and clinical outcomes; one representative of hospitals; one insurance industry representative; one business representative; one representative of labor organizations; one consumer representative; two pharmacists. All Health Resources Commissioners are selected with conflict of interest guidelines in mind. Any minor conflict of interest is disclosed.

The Commission is charged with conducting medical assessment of selected technologies, including prescription drugs. The commission may use advisory committees or subcommittees, the members to be appointed by the chairperson of the commission subject to approval by a majority of the commission. Subcommittee meetings and deliberations are public, where public testimony is encouraged. Subcommittee recommendations are presented to the Health Resources Commission in a public forum. The Commission gives strong consideration to the recommendations of the advisory subcommittee meetings and public testimony in developing its final reports.

Overview

The 2001 session of the Oregon Legislature passed Senate Bill 819, authorizing the creation of a Practitioner-managed Prescription Drug Plan (PMPDP). The statute specifically directs the Health Resources Commission (HRC) to advise the Oregon Medical Assistance (OMAP) Department of Human Services (DHS) on this Plan.

In the summer of 2007 the Oregon Health Resources Commission (HRC) appointed a Pharmaceutical subcommittee to perform an evidence-based reviews of the use of pharmaceutical agents. Membership of the subcommittee currently consists of three Physicians, a Nurse Practitioner, a PhD, RPh and a PharmD. The subcommittee had one meeting. All meetings are held in public with appropriate notice provided. The HRC

director worked with the Center for Evidence-based Policy (Center) and the Oregon Health and Science University's (OHSU) Evidence-based Practice Center (EPC) to develop and finalize key questions for this drug class review, specifying patient populations, medications to be studied and outcome measures for analysis, considering both effectiveness and safety. Evidence was specifically sought for subgroups of patients based on race, ethnicity and age, demographics, other medications and co-morbidities. Using standardized methods, the EPC reviewed systematic databases, the medical literature and dossiers submitted by pharmaceutical manufacturers. Inclusion and exclusion criteria were applied to titles and abstracts, and each study was assessed for quality according to predetermined criteria.

The EPC's report, "Pharmacologic Treatments for ADHD" was completed in May, 2006 and was circulated to subcommittee members and posted on the web. The subcommittee met to review the document and this report is the consensus result of those meetings. Time was allotted for public comment, questions and testimony.

This report does not recite or characterize all the evidence that was discussed by the OHSU EPC, the Subcommittee or the HRC. This report is not a substitute for any of the information provided during the subcommittee process, and readers are encouraged to review the source materials. This report is prepared to facilitate the HRC in providing recommendations to the Department of Human Services. The HRC, working together with the EPC, the Center for Evidence Based Policy, DMAP, and the Oregon State University College of Pharmacy, will monitor medical evidence for new developments in this drug class. Approximately once per year new pharmaceuticals will be reviewed and if appropriate, a recommendation for inclusion in the PMPDP will be made. For pharmaceuticals on the plan, significant new evidence will be assessed and Food and Drug Administration changes in indications and safety recommendations will be evaluated. The HRC reports will be updated if indicated. Substantive changes will be brought to the attention of the Health Resources Commission, who may choose to approve the report, or reconvene a subcommittee.

The full OHSU Evidence-based Practice Center's draft report, *Pharmacologic Treatments for ADHD* is available via the Office for Oregon Health Policy & Research, Practitioner-Managed Prescription Drug Plan website:

www.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml

Information regarding the Oregon Health Resources Commission and its subcommittee policy and process can be found on the Office for Oregon Health Policy & Research website: <http://www.oregon.gov/DAS/OHPPR/HRC/index.shtml>

You may request more information including copies of the draft report from:

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Information dossiers submitted by pharmaceutical manufacturers are available upon request from the OHSU Center for Evidence-based Policy by contacting:

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There will be a charge for copying and handling in providing documents from both the Office of Oregon Health Policy & Research and the Center for Evidence Based Policy.

Critical Policy

Senate Bill 819

– “The Department of Human Services shall adopt a Practitioner-managed Prescription Drug Plan for the Oregon Health Plan. The purpose of the plan is to ensure that enrollees of the Oregon Health Plan receive the most effective prescription drug available at the best possible price.”

Health Resources Commission

– “Clinical outcomes are the most important indicators of comparative effectiveness”

– “If evidence is insufficient to answer a question, neither a positive nor a negative association can be assumed.”

Clinical Overview

According to the most recent NIH Consensus Statement (1998), “attention deficit hyperactivity disorder (ADHD) is the most commonly diagnosed childhood behavioral disorder.”¹ Classification of hyperactivity and defects in attention emerged in the 1960’s as Minimal Brain Dysfunction (MBD) and Hyperkinetic Syndrome, and has continued to evolve over time.²

A number of community-based studies have reported ADHD prevalence rates that range from 1.7% to 16%.³ This is broader than the range of 3 to 5 percent that was estimated by the expert panelists that participated in the NIH Consensus Development Conference on Diagnosis and Treatment of Attention Deficit Hyperactivity Disorder (ADHD) in 1998.¹ The estimated prevalence cited in the most recent (1997) version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) is 3 to 7 percent. Differences in prevalence estimates may be due to variation in methods of ascertainment and diagnostic criteria. While no independent diagnostic test exists for ADHD, the DSM-IV provides standardized criteria that can be used as a foundation for clinical diagnosis. According to the DSM-IV, essential features of ADHD include persistent levels of inattention, impulsivity and/or hyperactivity that exceed usual developmental patterns. In order to qualify for a DSM-IV diagnosis of ADHD, symptoms must date back to before age 7, persist for at least six months, and cause impairment that interferes with functional capacity in at least two performance settings (social, academic, or employment). DSM-IV

specifies three distinct subtypes of ADHD that are characterized by predominantly inattentive, hyperactive-impulsive, or mixed symptoms.

ADHD is diagnosed more frequently in males than in females. 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. With regard to the course of ADHD, symptoms can persist into adolescence in 80 percent of cases and into adulthood in 65 percent of cases. Comorbid DSM-IV mood, anxiety, substance use, and/or impulse disorders also commonly occur in combination with ADHD in adults.

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

Included Drugs: Actions

The actions of each of the medications included in this review are briefly described below. We used the following drug name abbreviations throughout the report: dextroamphetamine=DEX, methylphenidate=MPH, and mixed amphetamine salts=MAS. **MAS (MAS):** Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. **Dextroamphetamine sulfate** is the dextro isomer of the compound *d,l*-amphetamine sulfate, a sympathomimetic amine of the amphetamine group.

Atomoxetine HCl : The precise mechanism by which atomoxetine produces its therapeutic effects in ADHD is unknown, but is thought to be related to selective inhibition of the pre-synaptic norepinephrine transporter, as determined in *ex vivo* uptake and neurotransmitter depletion studies.

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

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

Methylphenidate HCl 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, 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 activities of MAO-B or phosphodiesterases II-V. While only FDA-approved for narcolepsy treatment, modafinil is also being used to treat ADHD.

Quality of the Evidence

For quality of evidence the EPC and subcommittee took into account the number of studies, the total number of patients in each study, the length of the study period and the endpoints of the studies. Statistical significance was an important consideration. The subcommittee utilized the EPC's ratings of "good, fair or poor" for grading the body of evidence. Overall quality ratings for an individual study were based on the internal and external validity of the trial.

Internal validity of each trial was based on:

- 1) Methods used for randomization
- 2) Allocation concealment and blinding
- 3) Similarity of compared groups at baseline and maintenance of comparable groups
- 4) Adequate reporting of dropouts, attrition, and crossover
- 5) Loss to follow-up
- 6) Use of intention-to-treat analysis

External validity of trials was assessed based on:

- 1) Adequate description of the study population
- 2) Similarity of patients to other populations to whom the intervention would be applied
- 3) Control group receiving comparable treatment
- 4) Funding source that might affect publication bias.

For a complete discussion of quality assessment of the included studies please refer to Appendix C of the DERP report.

Effectiveness versus efficacy

Throughout this report, we highlight *effectiveness* studies conducted in primary care or office-based settings that use less stringent eligibility criteria, assess health outcomes, and have longer follow-up periods than most *efficacy* studies. *Effectiveness* studies conducted in primary care or office-based settings 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.

Weighing the Evidence

A particular randomized trial might receive two different ratings: one for efficacy and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the body of evidence relevant to that question.

Inclusion Criteria

Populations

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

Outcomes

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

Functional capacity (social, academic, and occupational productivity)

Caregiver satisfaction (parent, teacher)

Quality of life (child, parent, caregivers, teachers)

Overall adverse effect reports

Withdrawals due to adverse effects

Serious adverse events reported

Specific adverse events (hepatotoxicity, insomnia, anorexia, effects on growth, abuse potential)

Misuse/diversion (trading, selling, compliance, overdose, development of substance abuse disorders)

Time to onset of effectiveness

Duration of effectiveness

Scope and Key Questions

The subcommittee's task was 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

Key Questions

1. Evidence on Effectiveness and Efficacy

What is the comparative or noncomparative evidence that pharmacologic treatments for attention deficit disorders improve *effectiveness* outcomes?

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

2. Tolerability, Serious Adverse Events, Misuse and Diversion

a. What is the evidence of *comparative* tolerability of different pharmacologic treatments for attention deficit disorders?

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

c. What is the comparative or noncomparative evidence that pharmacologic treatments for attention deficit disorders increases the risk of misuse or illicit diversion in patients with no history of misuse or diversion?

stimulants vs. nonstimulants

immediate release vs. long-acting formulations

Any included pharmacologic treatment

3. Evidence in Subgroups of Patients

a. What is the evidence of benefits and harms of pharmacologic treatments for attention deficit disorders in subgroups of patients based on demographics (age, racial groups, gender), other medications or therapy, or co-morbidities (e.g. tics, anxiety, substance use disorders, disruptive behavior disorders)?

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

stimulants vs. nonstimulants

immediate release vs. long-acting formulations

Any included pharmacologic treatment

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

Table 1. ADHD drugs and doses

Generic Name	Trade Name*	FDA ADHD Approval	Year Introduced
Stimulants			
MAS**	Adderall®†	Children	1960
	Adderall XR®***	Children, adolescents, and adults	2001
Dextroamphetamine sulfate	Dexedrine®*	Children	1976
	Dextrostat®*†	Children	1975
Dexmethylphenidate HCl	Focalin®†	Children	2001
	Focalin XR®†	Children	2005
Lisdexamfetamine dimesylate	Vyvanse®	Children	2007
Methamphetamine hydrochloride	Desoxyn®†	Children	1943
Methylphenidate HCl	Biphentin®‡	N/A	N/A
	Concerta® (MPH OROS)	Children and adolescents	2000
	Daytrana† (Transdermal patch)	Children	2006
	Metadate CD®† (MPH CD)	Children	2001
	Metadate ER®† (MPH ER)	Children and adults	1999
	Methylin®†	Children and adults	2003
	Ritalin®*	Children and adults	1955
	Ritalin SR® (MPH SR)	Children and adults	1982
	Ritalin LA®† (MPH SODAS)	Children	2002
Modafinil	Provigil®	No	1998
Non-Stimulants			
Atomoxetine HCl	Strattera®	Children and adults	2002

*or generic equivalent

** (amphetamine aspartate; amphetamine sulfate; dextroamphetamine saccharate; dextroamphetamine sulfate)

***Notice of Compliance (NOC) suspended in February 2005 by Health Canada in response to case reports of sudden/cardiac death and/or stroke. NOC was reinstated in August 2005 and is again available for prescription in Canada

†Not available in Canada

‡Not available in the United States

Limitations of this study

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

Most of the studies were of short duration and many had small sample sizes.

Conclusions

KQ 1- Effectiveness and Efficacy

Young children (preschool age; three to five years)

1. Evidence on the long-term or comparative effectiveness of pharmacotherapy for ADHD in young children is seriously limited.
2. No comparative evidence was found.
3. MPH IR was superior to placebo in efficacy in two fair-quality PCTs that used validated assessment tools.

Children (elementary school age; six to twelve years)

1. No effectiveness trials were found.
2. Limited short duration studies on heterogeneous populations suggest higher efficacy vs. placebo for these agents.
3. Limited available evidence does not differentiate between these medications for efficacy.
4. Studies of modafinil consisted of PCT's and were inconclusive regarding efficacy in this age group.

Adolescents (ages 13 to 17)

1. No effectiveness trials were found.
2. No studies were found for modafinil in this age group.
3. Limited short duration studies on heterogeneous populations suggest higher efficacy vs. placebo for these agents.

Adults

1. There were no trials of adults with ADHD using d-MPH IR, lisdexamfetamine, methamphetamine, MPH transdermal, chewable tablet, or oral solution, MPH CD, MPH ER, or MPH SODAS.
2. Studies of other included agents were insufficient to determine comparative or long term efficacy.

3. Indirect comparisons from PCTs suggest that atomoxetine, DEX IR, d-MPH ER, MPH IR, MPH SR, MPH OROS, and MAS IR are all efficacious as *short-term treatments* for reducing ADHD symptoms.

KQ2- Adverse Effects, Safety and Tolerability

1. All of these agents can cause GI upset, transient weight loss and slowing of growth, appetite suppression, insomnia and irritability.
2. There is no *comparative* evidence on other long-term safety outcomes, including tics, seizures, cardiovascular adverse events, injury frequency, and hepatotoxicity.
3. Reports of hepatotoxicity with atomoxetine led to additional warnings in product label.
4. Evidence of Abuse/diversion from longitudinal studies with healthy or untreated ADHD controls is conflicting.

KQ3- Subgroups

Children

1. There is insufficient evidence to determine a comparative efficacy or safety in demographic subgroups of children
2. There is no consistent evidence that atomoxetine, DEX IR or MPH IR increased tic severity or frequency compared to placebo.

Adults

1. There is insufficient evidence to determine a comparative efficacy or safety in demographic subgroups of adults.

Supporting Evidence

Key Question 1. Evidence on Effectiveness and Efficacy

What is the comparative or noncomparative evidence that pharmacologic treatments for attention deficit disorders improve *effectiveness* outcomes?

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

Young Children (Preschool Age; 3-5 years)

Search results did not find any effectiveness trials or long-term observational studies assessing functional outcomes comparing drugs in young children with ADHD.

The evidence of any short-term benefit of stimulants in this age group comes from six placebo-controlled trials of MPH IR. Of these six placebo-controlled trials, four did not meet inclusion criteria based on trial quality and/or lack of a valid assessment tool.

One fair-quality trial used an assessment tool with good validity.³ 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 while on placebo at the end of 7 to 10 days of treatment. The high dose resulted in better final scores than the low dose on only the learning component of the CPRS-R with the low dose resulting in a mean of 8 points (10%) lower, and the high dose a mean of 14 points (18%) lower than the score while on placebo. The clinical importance of these differences is not known, and baseline scores are not reported or accounted for. Based on parental report, medication did not result in better compliance

with tasks compared to placebo, although reports of time on task were better with the higher dose (mean 52 seconds longer compared to placebo).

The Preschool ADHD Treatment Study (PATS), assessed the efficacy and safety of MPH IR relative to placebo.^{4,5} PATS was a multi-center, multi-phase trial that included, among others, a crossover titration phase (5 weeks; n=165), a parallel phase (4 weeks; n=114), and an open-label phase (10 months; n=140). In the publication describing the PATS design, Kollins, et al, described the primary outcome measure of the crossover phase of the trial as being a composite of scores from the Swanson, Conners, Milich, and Pelham and the Conners, Loney, and Milich Rating (CLAM) scales, while the primary outcome of the parallel phase was a derivative of the SNAP-IV scale.⁴ The results of the trial, which appear in a separate publication (Greenhill, et al) state that the *a priori* primary outcome of the crossover phase as a composite of CLAM and SKAMP scores, while the parallel phase primary outcome is based on the 'excellent responder' criteria of SNAP-IV. The reason for, or possible effect of, these discrepant outcome measures is unclear.

The crossover phase of PATS followed a 10-week parent-training phase and a 1-week, open-label run-in. The parent-training phase served to allow investigators to remove from the trial those children who were responders to non-pharmaceutical intervention; thus only children whose ADHD symptoms were not improved following parent training were randomized to the crossover phase of the trial. The crossover phase of PATS consisted of patients receiving MPH IR doses ranging from 1.25 to 7.5 mg tid and placebo. A dose of MPH IR 10 mg tid was also used when deemed necessary by investigators. The overall composite score of CLAM/SKAMP, based on parent and teacher scores, ranged from 0.91 (SD 0.48) for high-dose MPH IR to 1.19 (SD 0.59) for low dose MPH IR and 1.28 (SD 0.52) for placebo. Effect sizes of treatment relative to placebo during this phase ranged from 0.16 (MPH IR 1.25 mg tid) to 0.72 (MPH IR 7.5 mg tid).

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

Children (Elementary School Age; 6-12 years)

Generalizability Issues:

Studies of elementary school age children with ADHD were characterized by under-reporting of baseline subtype classifications, race or ethnicity, co-occurring disorders, and illness severity. This gap in the literature limits the generalizability of the findings to target populations. 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

Methylphenidate

Comparison of Immediate Release and Sustained Release Formulations

Of the 11 included trials of MPH IR versus SR formulations 4 were rated poor quality. The remaining studies compared MPH IR to 4 extended release formulations of MPH (Concerta®, Ritalin SR®, Medikinet®, or Metadate CD®). In addition, according to an FDA statistical review (http://www.fda.gov/cder/foi/nda/2000/21-121_Concerta_statr.pdf), MPH OROS (Concerta®) and MPH IR were compared in an additional trial of 64 children that has not yet been published.⁶

No trials comparing the other extended release formulations of MPH (Ritalin LA®, Methylin ER®, Metadate ER®, or Metadate CD®) to MPH IR were found.

MPH IR versus MPH OROS (Concerta®)

Four studies have compared MPH IR versus MPH OROS once daily enrolling a total of 561 children with ADHD. Two double-blind trials of MPH IR versus MPH OROS did not show overall differences in outcomes,^{7,8,9} while 2 open-label studies did find a significant difference favoring MPH OROS.^{10,11} While all of the studies suffer from design or conduct challenges and none were rated good quality, the 2 newer studies present more concerns of bias than the earlier studies. Importantly, across the studies, the weighted average daily dose of MPH OROS was 5 mg greater than the MPH IR daily dose. A second issue is the risk of selection bias in that none of the studies report the proportion of patients taking MPH IR or MPH OROS prior to enrollment.

In the largest, highest quality study there were no significant differences between the formulations on the primary outcome measure (IOWA Conners scale) or on 11 secondary measures in an RCT of 312 children.⁸ Similarly, a much smaller crossover trial (68 children), 7 days long, that included behavioral treatment found MPH OROS to have lower scores on the Abbreviated Conners Parents scale (total), and on the inattention/overactivity item (out of 16 items), however no differences were found based on assessments made by teachers and counselors.⁷

The study by Steele et al¹¹ was open-label, comparing usual care to switching to MPH OROS. Based on a definition of remission as a score of 0 or 1 (none or just a little) on the 18 items relating to ADHD symptoms only (excluding the items pertaining to ODD) of the parent assessed SNAP-IV scale, MPH OROS treatment resulted in more patients being classified as in remission at 8 weeks, with an NNT near 4. Similar results were found using other measures of parent assessment. This study does not include teacher ratings. Because the study was open to patients currently receiving treatment, including MPH IR, and was unblinded it is potentially biased against MPH IR. The EPC 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 studies. While the Wolraich and Pelham studies did not find significant differences in the mean change on this item, the pooled analysis with the Steele study does result in a statistically significant finding, favoring MPH OROS; weighted mean difference -1.19 (95% CI (-1.78; -0.60)). However, we do consider this an exploratory analysis because standard deviations were not provided in the Pelham⁷ and

Wolraich⁸ studies and we made an assumption that the baseline and final scores were moderately correlated ($r_2 = 0.25$).

A fourth study conducted in Taiwan found MPH OROS superior to MPH IR, assessing the change in CTRS-R-S score by either teacher or parent over 5 timepoints using a linear mixed model, P value <0.0001. The absolute difference in individual scores are not large, with the largest difference in teacher ratings being 1.12 for oppositional defiant behaviors (out of 5 possible), and 1.69 for hyperactivity/impulsivity (out of 7 possible) in the parent ratings. This study has the same potential for bias as the unblinded study by Steele, except that here all patients had previously been taking some form of MPH, but again the proportions taking MPH IR versus MPH OROS or other formulations prior to enrollment is not reported.

In contrast, findings from a retrospective study of 92 children from a “real-life clinical situation” in the UK suggest that 32% ($p < 0.001$) were considered treatment failures when switched to an extended release form of MPH (Concerta XL[®]) from MPH IR of an unknown duration.¹² The validity and generalizability of these findings are unclear, however, as the study was retrospective in nature, physicians’ use of personal case load to identify patients may have introduced a selection bias, treatment failure was not precisely defined, and it is unclear whether the UK formulation is comparable to MPH OROS as included in this review.

The FDA Statistical Review of the NDA for MPH OROS includes criticism of the 2 early trials^{7,8} and a similar unpublished trial, 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).⁶

MPH IR versus MPH SR (Ritalin SR[®])

In a small 2-week RCT (34 children) of MPH IR versus MPH SR found mixed results.¹³ 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” score favoring MPH IR. Parent questionnaires indicated a significant difference favoring MPH SR on the “Conduct Problem” item final score, and the physician scores showed no difference.

MPH IR vs MPH ER (Medikinet[®])

Results from a fair-quality, 2.5-week crossover trial of 79 pediatric patients did not suggest any differences between flexible dosages (≤ 1 mg/kg) of MPH IR BID and MPH ER in SKAMP Attention or Department subscale scores or in math problems attempted.¹⁴ Effect sizes were relatively similar regardless of time of day (9:30 am through 4:45 pm). This study was conducted in outpatient clinics in Germany and the formulation of MPH ER (Medikinet[®]) is not available in the U.S.

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

A 3-week study using over-encapsulation for blinding enrolled 327 children, comparing MPH IR to Equasym[®] (sold in the US as Metadate CD[®]). The study analyzed only 87% of patients in the main per-protocol analysis with unclear description of those excluded.¹⁵ The study included a non-inferiority analysis, assuming a difference of ≤ 1.5 points on the Conners I/O teachers rating scale to indicate equivalence (non-inferiority). At weeks

1, 2, and 3 MPH IR was found equivalent to Equasym®. Intention to treat analysis as well as subgroup analyses (country, dose, ADHD subtype) were reported in the discussion as supporting these results. Additional analysis examined the effects of the drugs in the morning and afternoon, but a direct comparison was made only to the placebo group as both MPH groups were found similarly superior to placebo at both timepoints throughout the study.

Other Measures of Comparative Effectiveness of IR vs SR formulations

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

Two observational database studies reported persistence outcomes for 12-month periods following index prescriptions of MPH IR and ER formulations.^{16,17} MPH ER formulations were associated with better persistence outcomes than MPH IR in both studies regardless of measurement methods. The findings of these studies should be interpreted with caution, however, until confirmed by a randomized controlled trial that would serve to rule out potential sources of bias, including between-group baseline differences in unmeasured clinical characteristics, physicians' prescribing preferences, and differences in reasons for discontinuation

In one study¹⁴ derived from the Integrated Health Care Information Services (IHCIS) National Managed Care Benchmark Database the proportion of 1,775 patients that persisted with their index prescription for 12 months *with no discontinuations exceeding 14 days* was greater for MPH OROS vs. MPH IR (12% vs. 1%, $p < 0.0001$). Ethnicity and comorbidity characteristics were not reported in this study.

California Medicaid claims files from a 3-year period were examined in the second study to identify youth prescribed MPH ($n = 11,537$)¹⁸. Total mean duration (days) of treatment without any 30-day gaps was greater for patients taking ER formulations (combined group of MPH OROS = 83%, MPH ER = 8.7%, MPH SODAS = 8.3%) than for those taking MPH IR (140.3 vs. 103.4; survival time ratio (STR) 1.37, 95% CI 1.32-1.42). Subgroup analysis results suggest that persistence duration was greatest for MPH OROS (147.2 days, 95% CI 142.6-151.7 days) compared to MPH SODAS (113 days; 95% CI 100.9-125.1 days) or MPH CD (101.1 days, 95% CI 91.2-111.0 days).

Comparisons of SR Formulations

MPH OROS (Concerta®) vs MPH CD (Metadate CD®)

Results from the fair-quality COMACS crossover study of 184 children suggest that relative improvements in SKAMP deportment and attention scale scores differed for the comparison of MPH OROS 18-54 mg and MPH CD 20-60 mg (both given once daily) depending on time of assessment.^{19,20} This study examined the pharmacodynamic

differences of these products resulting from differences in pharmacokinetic profiles. The children were mostly male (73.8%), with a mean age of 9.6 years and they were randomized to low, medium or high dosage treatment group sequences based on their previous dosages of MPH IR. The study suggests that MPH CD was associated with significantly larger effect sizes than MPH OROS in the morning, treatment effects were similar in the afternoon, and MPH OROS was superior in the evening. This study presents several problems, however, in that the SKAMP scale has been criticized for lack of sensitivity to change in symptoms, and that ANOVA analysis found the interaction of site x treatment x sequence (the order to randomization within patients) was found to be statistically significant. This finding resulted in the authors conducting additional analyses; however the effect of sequence was not included in these subsequent analyses. Therefore, these findings should be interpreted with caution.

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

A small 1-week crossover study of MPH SODAS 20mg versus MPH OROS 18mg and 36mg²¹ found MPH SODAS superior on the attention or deportment subscores of the Swanson, Kotlin, Agler, M-Flynn and Pelham (SKAMP) scale depending on the time-point and dose comparison. Secondary outcome assessment also found MPH SODAS superior on one measure (proportion correct on math test). These limited differences are mitigated by concerns over the assessment tool (SKAMP) sensitivity, use of a simulated classroom, involvement of study sponsor in authorship, and differences in groups at baseline. A similar second crossover study of MPH OROS (18 and 36 mg) and MPH SODAS (20 and 40 mg) also assessed children in a simulated classroom setting after a single dose of the study medication using the SKAMP.²² Here MPH SODAS 40 mg was found superior to MPH OROS 36 mg at all timepoints (0-4, 0-8 and 0-12 hours) based on the SKAMP attention subscale score area under the curve (AUC) analyses, while MPH SODAS 20 mg was not significantly different to either dose of MPH OROS. Here, concerns over the clinical importance of the difference in AUC, involvement of study sponsor in authorship, and the impact of sequence of randomized treatment (analysis of treatment sequence was stated to be planned but results not reported) are present.

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

Methylphenidate ER (Metadate®) vs Placebo

A 3-week trial of Metadate® versus placebo enrolled 314 children out of 507 screened.²³ 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 CGI ratings combined, in the morning and afternoon, were significantly lower (better) in the Metadate® group. Secondary measures also favored Metadate®.

Immediate Release Formulations: Efficacy Outcomes

Dextroamphetamine versus Methylphenidate

We included nine fair quality studies (reported in 11 publications) of DEX versus MPH IR. All nine fair quality studies were randomized, blinded crossover trials with durations from 2-8 weeks. The two largest studies (n=125 and n=102)^{24,25} did not provide details on the efficacy results, other than summary statements that there were no differences between the two drugs based on children's self-assessment³⁴ and based on parent and teacher ratings.²⁵ Of the 7 small studies (n = 12 to 48), only one found a difference between the drugs.²⁶ 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. The text of the paper reports that in a post-hoc analysis, DEX was the most effective drug *in instances where a positive effect was seen*. Because this study did not use a standardized tool for diagnosis, and ADHD subtypes, co-morbidities or ethnicity are not reported, it must be assumed that significant heterogeneity in the population may have lead to the discordant results.

Response rates

Very few studies attempted to make a comparison of the rate of response (defined a priori) between 2 drugs. Overall, no differences in response rates, as defined by each study, were found between the comparisons of MPH OROS, DEX IR, or MAS to MPH IR. Additionally, the majority of these response rates are lower than those reported and quoted from placebo controlled trials (rates of approximately 75%).

Immediate Release Formulations: Effectiveness Outcomes

We found extremely limited information on effectiveness outcomes from the clinical trials. Therefore, we included observational studies of ≥ 6 months duration that reported effectiveness outcomes

MPH IR versus MPH OROS (Concerta®)

IHCIS managed care claims data suggest that MPH OROS was associated with fewer outpatient visits/hospitalization for accidents/injury than MPH IR over a 12-month follow-up period (odds ratio 0.58, 95% CI 0.353 to 0.945)¹⁶ Patient population was not well defined other than that the study population was 75% male, with a mean age of 9.7 years.

MPH IR

In a 4-year follow-up study of 62 children treated with MPH, the effect of duration of treatment on academic performance was assessed.²⁷ 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.

Adherence rates as proxy measures of duration of effectiveness and caregiver satisfaction were reported for 307 Chinese children with ADHD taking MPH IR who were followed for 6 months of treatment.²⁸ Parents of 100 children (32.6%) were unsatisfied with their children's adherence to MPH IR and cited the following reasons for missing doses: forgetting to take MPH IR at school (72.9%), the medication having no effect (20%), forgetting to bring MPH IR to school (19.1%), refusing to take MPH IR (12.7%), bitterness (11.4%), side effect (11.4%) and teacher's objection (7.7%). Compared to

families with children demonstrating good adherence, poor adherence was associated with increased risk of impairments in maternal psychological status and perceived family support.

Maintenance of short-term symptom response effects

MPH or DEX versus placebo or non-drug therapy

All of the trials reported above are very short-term trials (range 1 to 9 weeks). Because of this serious limitation, the evidence does not provide information on the long-term benefits of these drugs in treating ADHD. To provide further evidence on duration of effect and longer-term outcomes, placebo- or non-drug therapy controlled trials of ADHD drugs with duration ≥ 6 months are reported here.

Overall, the MPH IR studies provide a mixed picture of the consistency of efficacy of MPH over 6 months to 2 years. The only study reporting that the short-term effects were maintained over the follow-up period was the Multimodal Treatment Study of Children with Attention Deficit/Hyperactivity Disorder (MTA) study²⁹.

The Multimodal Treatment Study of Children with Attention Deficit/Hyperactivity Disorder (MTA) was a relatively large study (n = 579) funded by the NIMH assessing medication management, behavioral treatments, standard community care, and combined medication management and behavioral treatments over a 14-month period. Outcomes are available for 540 children that were followed an additional 10 months subsequent to trial discontinuation.⁴³ Medication management could involve any stimulant medication, but started with MPH titration. At study end, 73% of those in one of the medication management groups were on MPH, and 10% on DEX, with small numbers of patients taking no medication, pemoline, imipramine, bupropion or haloperidol, and 6% refusing to be in the medication arm assigned. All participants met DSM-IV criteria for ADHD combined type, had a mean age of 8.5 years, and 80% were males. The sample population was ethnically diverse and included several comorbidities.

Medication management alone resulted in better scores compared to behavioral therapy for the symptoms of inattention (both parents and teachers) and hyperactive-impulsive symptoms (parent ratings). Medication alone resulted in better scores on all ADHD symptoms than community care, except as measured by a classroom observer.

Aggression-ODD symptoms scores were better with medication alone compared to community care in teacher ratings only. Combined therapy (medication and behavioral therapy) was not different to medication alone on any scale. Important to this review of ADHD medications, the effect of medication management was maintained over the 14 month period. However, the outcome measures were not effectiveness outcomes, so the trial must still be viewed as an efficacy trial that indicates that with careful monitoring of dose and drug regimen, ADHD stimulant medications can reduce symptoms of ADHD over a 14-month period. Families were contacted 10 months after the end of the 14-month study (24 months post-randomization) to assess longer-term persistence of treatment effects.³⁰ At 24 months post-randomization, medication alone resulted in better scores on ADHD and ODD symptoms than behavioral therapy and community care. Despite this, analyses of combined outcomes from the medication management alone and combined therapy groups compared to those of the behavioral therapy and community care groups suggest a reduction in the improvement magnitude by half from the 14-month to 24-month timepoints; effect size changes for ADHD symptoms=0.60 vs. 0.30 and ODD symptoms=0.39 vs. 0.21.

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

Remission rates: MPH IR

One study³¹ included a group of 21 boys who had been treated with MPH for a mean of 1.75 years and randomized to 3 weeks of placebo or MPH. Using the CTRS, this study found that on the Subscale items of hyperactivity and defiance the scores during the placebo period were significantly worse than during the MPH period. No baseline assessments were presented, and the analyses are based on scores at week 3 of each condition only so there is no information about the effectiveness of their pre-existing MPH regimen at baseline. In addition, the effect of order of drug/placebo was not analyzed in this crossover study, so the results must be interpreted with caution.

Other stimulants

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

Fifty-one children were enrolled in a randomized crossover study of extended release Adderall® at 10, 20 and 30mg, Adderall® 10mg, and placebo given once daily for seven days. Study assessments were taken during a single 12-hour day with assessments every 1.5 hours in a simulated classroom setting.³² The study used a run-in period where children were given Adderall XR® 20mg after which 4% (2 of 51) dropped out after this session for “withdrawal of consent”. Based on the SKAMP scale deorientation and attention variables and a math test (PERMP), the extended release formulation had statistically significantly better scores compared to placebo on all time points for the 30mg dose. However, the 10 and 20mg doses showed more variable benefits early (at 1.5 hours) and late (10.5 and 12 hours). Immediate release Adderall® showed a benefit over placebo early in the day, and more variable results as the day progressed. Direct comparisons were not undertaken.

MAS versus Methylphenidate Immediate Release

Three small, fair-quality studies of MAS versus MPH IR were found. One was a parallel group RCT while the other two were randomized cross-over trials.

The parallel group RCT³³ enrolled 58 children with ADHD and randomized to 3 weeks of MAS, MPH IR, or placebo. The mean doses at the end of study were MAS 12.5 mg/day and MPH IR 25.2 mg/day (divided into morning +/- noon doses for both drugs). No differences were found in the mean IOWA CTRS scores (Inattention/Overactivity and Aggression/Defiance subscales) rated by teachers 4 mornings and afternoons a week, but MAS was significantly better on both subscales when morning and afternoon scores were combined. No differences were found in parent ratings. The mean CGI-Improvement score (rated by a blinded psychiatrist) was also significantly lower (better) in the MAS group than the MPH IR (final score 1.6 vs. 2.35, $p < 0.05$), but the difference in the proportions of responders (90% vs. 65%, respectively) did not reach statistical significance. No differences were found on the Conners Global Index or final weight.

The two crossover studies were conducted in the same manner by the same authors and were conducted in a summer treatment program.^{34,35,36} These short-term studies (6 – 8 weeks) enrolled 21 and 25 children with a higher prevalence of comorbid oppositional defiant disorder (67% and 52%) than the general population of children with ADHD. The first study found MAS to be superior to MPH IR given once daily, while few or no differences were found when comparing to MPH IR given twice daily, based on

counselor and teacher ratings. Parent ratings of after school behavior indicated that the addition of a third 0.3mg/kg dose of MPH IR or the MAS 0.3 mg/kg once daily dose lead to the best results based on combinations of parent ratings and child task completion. The results of the second study indicate that on a few measures the low dose (10mg twice daily) of MPH IR was not as effective as the higher dose (17.5 mg twice daily) or either dose of MAS (7.5 or 12.5 mg twice daily). Measures where this difference was seen were interruption, conduct problems, negative verbalizations, the daily report card score, and counselor ratings of oppositional defiant scores. No difference in response was seen between the two doses of MAS and the higher dose of MPH IR.

MAS versus Dextroamphetamine

There was a single poor quality study. No conclusions could be drawn.

Dexmethylphenidate (d-MPH) Immediate Release

Only one of two placebo-controlled studies of d-MPH referred to in the most recent FDA Medical Review (http://www.fda.gov/cder/foi/nda/2001/21-278_Focalin_medr_P1.pdf) has been published.³⁷ d-MPH was associated with significantly greater mean reductions in Teacher SNAP rating score than placebo ($p=0.004$) after four weeks in a fair-quality trial of 132 children (88% male; mean age = 9.8 years) with ADHD of mostly the combined type (64%).³⁷ No conclusions can be drawn about the comparative efficacy of d-MPH.

Dexmethylphenidate (d-MPH) Extended Release (ER)

According to the Center for Drug Evaluation and Research (CDER) Medical Review, data from two short-term, randomized, placebo-controlled, double-blind efficacy trials were submitted to the FDA in the NDA for d-MPH ER, both of which have been published. Both were fair-quality. Study 2301 was a 7-week, parallel-group, flexible-dosing trial of 103 children.³⁸ Study US08 was a 2-week, fixed-dose, crossover trial of 54 children.³⁹ d-MPH ER was significantly superior to placebo for both primary outcomes of change from baseline to final visit in Conners ADHD/DSM-IV Scale-Teacher version in Study 2301 (-16.3 vs. -5.7 points; $p<0.001$) and of mean change in SKAMP-Combined scores from predose to 1-hour post-dose in Study US08 (-10.014 vs. 0.078, $p<0.001$).

Methamphetamine

The only evidence we identified for methamphetamine is in the form of a dissertation report published in 1973 and is characterized by measures of cognitive impulsivity, planning, new learning, IQ, and social behavior.⁴⁰ In this trial, 32 boys with hyperkinesia were randomized to 4 week treatment periods of either methamphetamine or placebo. Methamphetamine was started at 5 mg/day for first 2 weeks and then the dose was increased to 10 mg/day for the following 2 weeks. The main findings were that methamphetamine was superior to placebo in improving scores on measures of impulsivity, social behavior, and on one of two measure of new learning. There were no between-group differences on measures of general intelligence.

Methylphenidate transdermal system (Daytrana®)

According to the product label, the efficacy of methylphenidate transdermal system (MTS) was established in two controlled trials in children, only one of which has been fully published.⁴¹ The fully published trial was a 1-week, randomized, placebo-controlled, crossover trial conducted in a laboratory classroom setting enrolling 80 children. Findings from a mixed linear model ANOVA showed that MTS was significantly superior to placebo on the SKAMP Deportment and Attention scales and in

the number of math problems attempted and number of math problems correct on the Permanent Product Measure of Performance (PERMP).

Lisdexamfetamine dimesylate

We identified two fair-quality, randomized controlled trials of lisdexamfetamine, both of which were included as pivotal efficacy trials in the NDA submitted to the FDA. Study 201 was a 3-way crossover trial that compared 1-week treatment periods of lisdexamfetamine, MAS XR, and placebo in 52 children. Complete details of Study 201 have not yet been fully published, but are available in the Center for Drug Evaluation and Research Medical Review (CDER).⁴² Study 301 was a placebo-controlled, 4-week, parallel-group trial of three different dosages of lisdexamfetamine (30mg, 50mg or 70mg) in 290 children.⁴³ Both trial populations are notable for reflecting more racial diversity than in other randomized controlled trials. Primary efficacy analyses were performed using the average of SKAMP-DS scores across the treatment assessment day in study 201 and the change in mean ADHD-RS-IV total score in study 301. Scores in all lisdexamfetamine groups were significantly superior to placebo group scores across both trials.⁴² In study 201, there were no significant differences between lisdexamfetamine and MAS XR in average SKAMP-DS scores.

Modafinil

Efficacy findings for modafinil are inconsistent across the five placebo-controlled trials included in this review. It appears that dosing regimen may play an important role in the efficacy of this product.

The first study randomized involved 24 patients who were followed for mean durations of 5 or 6 weeks (placebo and modafinil, respectively). The mean age of patients was 8 years and 58% were male. In this study, less than 1/3 had oppositional defiant disorder or conduct disorder (27% combined), and the ADHD subtype was primarily Mixed (73%). When dosed at 200-300mg in this study, modafinil was not found to be better than placebo in improving ADHD-RS.⁴⁴

Among the later trials, there were three that used very similar designs and involved very similar patient populations. In these trials, a total of 638 children with ADHD were randomized to either modafinil (mean dosage range 361mg to 395mg) or placebo for treatment periods that were 7-9 weeks in duration.^{44,45,46} Patient mean age was 10 years and 71% were male. Change in the ADHD-RS was identified as the primary outcome in all three trials. In these trials, using a higher dosage level than in the earlier trial, modafinil was found to be consistently superior to placebo on ADHD-RS score change from baseline and also in the proportion of patients that were rated as “much improved” or “very much improved” on the CGI-I.

In the final and most recent placebo-controlled trial of modafinil, the objective was to compare the efficacy and safety of several different BID and QD dosing regimens.⁴⁷ In this trial, 248 children with ADHD were randomized to 4-week treatment periods of either 300mg QD or divided (morning/mid-day) dosages of 200/100mg, 100/200mg, or 200/200mg. The majority of patients were male, with a mean age of 9 years. With regard to mean change from baseline in ADHD-RS, only the groups assigned to 300mg QD or 200/100mg divided dosages had significantly greater score reductions

than those in the placebo group. However, none of the groups were superior to placebo for the proportions of patients rated as “much improved” or “very much improved” on the CGI-I.

Atomoxetine

Atomoxetine versus Methylphenidate

Atomoxetine, the first nonstimulant introduced specifically for ADHD, was compared to MPH IR in 3 RCT’s. However, 2 of these studies were really comparisons to placebo, with only few patients enrolled in the MPH arms. Therefore, these are considered placebo-controlled trials, below. The single study comparing atomoxetine and MPH IR found no differences between the drugs based on changes in the ADHD-RS, the CPRS-R hyperactivity item, and the CGI-S.⁴⁸ Concerns over the study quality indicating potential bias suggest caution in interpreting these findings

A second poor quality study comparing MPH IR and atomoxetine primarily assessed the impact of each drug on sleep, using a crossover design and sleep labs.

Atomoxetine versus MPH OROS

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

Atomoxetine versus MAS XR (Adderall SR®)

The extended release form of MAS (Adderall SR®) 10-30 mg was superior to atomoxetine 0.5-1.2 mg/kg/day on most efficacy outcomes after three weeks in a fair-quality trial of 215 children (mean age = 8.7 years).⁴⁹ This trial, also known as StART (Strattera®/Adderall XR® Randomized Trial), was conducted in a simulated classroom setting which involved 12 hours of observation per day. Participants were mostly male (71.9%) who were diagnosed with ADHD of either the hyperactive/impulsive or combined subtypes. Adderall XR® was associated with significantly greater reductions in the mean SKAMP department scale scores, which was prespecified as the primary outcome (-0.56 vs. -0.13; $p < 0.0001$). Adderall 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” ($\geq 25\%$ improvement on Department and/or Attention scales), and numbers of math problems attempted and/or completed correctly. One caution regarding the interpretation of these findings is that the SKAMP scale has been criticized for lack of sensitivity to change in symptoms.

Atomoxetine versus Standard Therapy

A British study of atomoxetine compared to standard treatment assessed the child’s function and health status using the final score on the Child Health and Illness Profile – Child Edition (which the EPC considered an unvalidated tool) as the primary outcome measure. This study was rated poor quality

Atomoxetine versus Placebo

Six placebo-controlled studies of atomoxetine in children and adolescents with ADHD found atomoxetine to be superior based on ADHD-RS as the primary outcome measure and various scales as secondary measures. Results of two of the six trials were described as identically-designed and were reported in one publication⁵⁰. The mean

change on ADHD-RS in these 6 to 9 week studies ranged from -12.8 to -16.7 with atomoxetine compared to -5.0 to -7.0 for placebo. A study of once daily dosing reported response rates (defined as $\geq 25\%$ reduction in ADHD-RS score) in the atomoxetine group of 59.5% versus 31.3% in the placebo group ($p < 0.001$).⁵¹ Remission rates (defined as an endpoint CGI-S score of 1 or 2) were 28.6% and 9.6%, respectively ($p = 0.003$). All 5 studies were funded and co-authored by representatives of the manufacturer of atomoxetine, and 4 were part of the NDA submitted to the FDA. There are also some concerns about population heterogeneity between groups.

A significantly greater proportion of patients taking once daily dosages of atomoxetine (≤ 1.8 mg/kg/day) responded to atomoxetine rather than placebo (69% vs. 43.1%; $p = 0.003$) in a more recent fair-quality trial ($n = 153$).⁵² “Response” was defined as a 20% or greater mean reduction in total scores from the ADHD-RS-IV-Teacher Version. This trial differs from the previous five in that it was designed with a primary measure of response that was based on teacher reports in the school setting rather than on parent ratings. Children in this trial were predominantly male (80.4%) with ADHD of the Combined type (72.5%) and had a mean age of 9.9 years.

Atomoxetine was associated with less rapid times to relapse than placebo under double-blind conditions (218 days vs. 146 days; $p < 0.001$) in a randomized subgroup of 416 children (out of 603) that were classified as “responders” following an initial 12-week, open-label period of treatment with atomoxetine.⁵¹ The primary outcome measure was the number of days to relapse and relapse was defined as return to 90% of baseline ADHD-RS score and CGI-S score increase of at least 2 points. Similarly, fewer patients on atomoxetine relapsed than on placebo (22% versus 38%, $p < 0.002$).

Atomoxetine: Effectiveness outcomes

A few noncomparative observational studies evaluated duration of effectiveness for atomoxetine. In one study, 229 children who had a $\geq 40\%$ reduction in ADHD-RS total score after a 7 to 9-week trial of atomoxetine (51% of original sample) were randomly assigned to continue treatment for 8 months at the same or lower dosages.⁵³ 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).⁵⁴ Both studies were consistent in finding that improvements in ADHD symptoms and in aspects of health-related quality of life were maintained during longer-term treatment periods, even with reduced dosages of atomoxetine. Although encouraging, findings from these studies must be interpreted with caution, mainly due to the extremely high attrition rates.

Functional outcomes: MPH IR

We found extremely limited information on functional capacity outcomes from the clinical trials. Therefore, we included observational studies of ≥ 6 months 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. Due to various methodological limitations, these studies do not provide good evidence for long-term effectiveness, even for MPH.

In a cross-sectional follow-up study of young men diagnosed with ‘persistent hyperactivity’ at ages 6 to 12 years, those who had not received medication were compared to a group that had received MPH for at least 3 years during childhood.⁵⁵ The

groups were initially seen in different time-periods, separated by 5 to 15 years. Because the groups were from different periods, a third group of normal children who were contemporaneous to the MPH group was added. The sizes of the groups also differed, with 64 in the non-treated hyperactive group, 20 in the MPH treated group, and 20 in the normal controls, and data were not available for all subjects on all questions. Mean follow-up of the hyperactive groups was 10 to 12 years. No information on baseline characteristics from childhood is given. No consistent differences in functional outcomes were found between the MPH and untreated groups. 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. The MPH group in this study was previously reported after 5 years of follow-up (as adolescents), with comparison groups of boys treated with chlorpromazine or untreated boys.⁵⁶ 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. We did not find any effectiveness trials or long-term observational studies (assessing functional or safety outcomes) in adolescents with ADHD. Adolescents were studied in one head-to-head trial of MPH IR and SR (OROS) and in 9 placebo-controlled trials of MPH.

Direct comparisons

MPH IR vs. MPH OROS (Concerta®)

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

MPH OROS versus MAS

A 17-day, small ($n=35$) crossover study compared the effect of stimulant use on the driving ability of adolescents with ADHD.⁵⁷ There was no significant difference between MPH OROS 72 mg qd and MAS 30 mg qd in self-reported symptom improvement among participants ($p=0.55$) although both interventions appeared to improve symptoms compared to baseline (no further data provided). MPH OROS was associated with significantly better overall driving performance relative to MAS based on testing in a driving simulator ($p=0.03$). However, subjective ratings of driving performance by participants failed to detect a difference between the two study drugs.

Indirect comparisons

MAS

A 4-week, placebo-controlled study of extended-release MAS (Adderall XR®) using a forced-dose titration schedule (up to 40 mg qd) assessed efficacy in 287 patients using the ADHD-RS-IV and CGI-I scale scores. All doses of extended-release MAS were associated with significant improvement in ADHD-RS-IV scores compared to placebo. Mean change in ADHD-RS-IV score from baseline was -17.8 for active treatment (all doses) and -9.4 for placebo ($p < 0.001$ for all doses except 10 mg dose, for which $p < 0.005$) with significant score improvement for all doses of extended-release MAS ($p \leq 0.005$). Based on CGI-I scale scores, the proportion of patients who were improved follow treatment with extended-release MAS (range 51.9%-70.7%, dose dependent) was significantly higher than placebo (26.9%; $p \leq 0.01$).

MPH OROS

One trial compared the efficacy MPH OROS to placebo in adolescents. Of 220 enrolled subjects, 177 were randomized to a two-week double-blind phase following an open-label titration phase lasting up to 4 weeks. There was a significantly higher mean change in investigator assessed ADHD-RS scores (the primary outcome) with MPH OROS compared to placebo (MPH OROS -14.93 [SD 10.72] versus placebo -9.58 [SD 9.73]; $p = 0.001$). Parent-assessed scores were similar, and also favored MPH OROS over placebo ($p = 0.008$).

MPH IR

Seven placebo-controlled crossover trials of MPH IR enrolled a total of 171 adolescents. Patients were diagnosed primarily using the DSM III-R or DSM-IV criteria. Only one trial clearly described the distributions of the different ADHD subtypes and in this trial there were 87.5% patients with the Combined subtype.⁵⁸ MPH IR generally was superior to placebo in improving core ADHD symptoms, but was associated with greater frequency of appetite and sleep problems. MPH mean dosages ranged from 8.8⁵⁹ to 75 mg.⁶⁰ The trials reported a variety of outcome measures. All but one were consistent in using various forms of the highly valid Conners' rating scales (long- and abbreviated forms).⁵⁸ However, inconsistency in the way results are reported make estimation of an overall magnitude of effect impossible.

Functional outcomes: MPH IR

We found extremely limited information on functional capacity outcomes from the clinical trials. Therefore, we included observational studies of ≥ 6 months duration that reported outcomes that reflect functional capacity, for example academic achievement in terms of progression through grades, suicide attempts, police contacts, etc. We found only 2 studies reporting outcomes in adolescents. In an uncontrolled study, a simple follow-up of 16 of 27 (59%) adolescents who had responded to MPH in an uncontrolled study,⁶¹ after 6 to 14 months of follow-up the authors simply report that 15 of the 16 had "improved grades". In a study using interviews and data from patient charts, 97 young adult males who had taken MPH as children and teens (mean age at discontinuation of MPH was 17 years) were studied.⁶² There is no comparison group in this descriptive study. The authors conducted a hierarchical analysis to assess the effect of various factors. Significant findings relating to use of MPH were: fewer suicide attempts positively associated with higher dose of MPH and emancipated living situation,

and level of relationship commitment were positively associated with response to MPH. Early response to MPH was however, negatively associated with high school graduation.

Adults

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

There were few studies of only DEX, MPH IR, and pemoline in adults available at the time of the Jadad review (1999).⁶³ Jadad et al. criticized these studies for their small sample sizes, short durations (≤ 6 weeks), and for incomplete reporting methods. The review included one study of DEX and MPH and placebo-controlled studies of MPH, pemoline, and other drugs not included in our review. No direct comparisons of DEX and MPH were reported in the study in Jadad only changes from baseline. Jadad et al. also reported that MPH's efficacy in reducing core ADHD symptoms was inconsistent across placebo-controlled trials and that pemoline was not associated with overall symptom improvement.

Studies have been published since the Jadad review that expand the evidence base for DEX, MPH, MAS, atomoxetine, and modafinil. All of these studies were rated fair quality except for the newest MPH study which was rated poor quality and not included. The fair quality studies are discussed below.

Direct comparisons

One head-to-head trial with identical proportions of adults (n=22) with ADHD responding to modafinil 206.8 mg and DEX IR 21.8 mg (48% vs. 48%; p=NS). Response was defined as a 30% or greater mean improvement in ADHD Rating Scale total scores. Patients in this trial were mostly male (59%) and had a mean age of 40.8 years.⁶⁴ 154

Indirect comparisons

Numerous (26 meeting inclusion criteria) placebo-controlled trials have been conducted to evaluate whether adults with ADHD benefit from the same treatments that are used in children. All but three were rated fair quality and are discussed below.

There was significant heterogeneity in the composition of populations with respect to ADHD subtype, comorbidities, outcome measures, and duration. Regardless of approach, atomoxetine, DEX, d-MPH ER, MPH IR, MPH SR, MPH OROS, MAS IR, and MAS XR were generally all found to be effective short-term treatments for ADHD symptoms in adults. The only exceptions were that the effects of low-dose MPH IR (45 mg/day TID)⁶⁵ and 60-90 mg/day of MPH SR BID^{66,67} were notably limited in patients with comorbid substance abuse disorders. Findings from placebo-controlled trials of MPH in adults with ADHD and comorbid substance abuse disorders will be discussed in more detail in Key Question 3. It should also be noted that uncertainty remains regarding the efficacy of modafinil in reducing core ADHD symptoms, as the only trial of modafinil we identified focused only on cognitive outcomes.

Indirect comparisons between competing drugs in ADHD symptom improvement outcomes are difficult to interpret across these adult trials due to the heterogeneity in outcome assessment methods. Therefore, we also considered whether any of the various ADHD drugs could be differentiated from the others by any other elements of their respective treatment profiles. Other treatment outcomes considered included improvements in ADHD-associated depressive and anxiety symptoms, cognitive deficits,

driving performance, and quality of life. Overall, evidence did not provide overwhelming support of the efficacy of these drugs in these areas and evidence regarding the effects of these drugs on quality of life was extremely limited.

MPH IR

A substantially higher number of adults with ADHD (N=542) have been randomized to MPH IR than any other drug in placebo-controlled trials. It appears that MPH IR may be distinguished as more consistently providing an advantage over placebo in reducing ADHD-associated anxiety symptoms and cognitive deficits relative to other trials of competing drugs.

MPH IR is the only drug that has evidence, albeit limited, of having any advantage over placebo for improving driving safety. Simulator driving performance was assessed in adults with ADHD in two small, single-dose, placebo-controlled trials and results found that MPH IR 10mg significantly improved an Impaired Driving Score ($p=0.05$),⁶⁸ MPH IR 40mg significantly reduced steering variability,⁶⁹ and MPH IR 20mg significantly improved appropriate use of turn signals.⁶⁹ Although promising, results from driving performance trials should be considered preliminary and would be strengthened by further confirmation based on assessment of effects in patients driving their own vehicles in every-day traffic settings, across multiple occasions.

Atomoxetine

Although we did not find any evidence of the effects of any included ADHD drug on quality of life in any placebo-controlled trials of adult patients, findings from a 6-week trial of atomoxetine that lacked a control group appear somewhat promising.⁷⁰ In this trial, 218 adults with ADHD were randomized to double-blind treatment with atomoxetine 80mg, dosed either QD or BID. Based on changes from baseline in SF-36 scores (+4.78 points on Mental Component Summary (MCS) score; $p<0.001$), the authors concluded that atomoxetine had improved patients' perceived quality of life. The MCS score was noted to be a sum of subscores from the Vitality, Social Function, Role Emotion, and Mental Health domains.

MAS XR

The only other reports of quality of life outcomes we identified was from a 10-week interim analysis of patients taking open MAS XR (10-60mg) as part of the 30-week Quality of life, Effectiveness, Safety, and Tolerability (Q.U.E.S.T) trial.⁷¹ Again, the SF-36 was used to assess quality of life and results suggested significant improvements from baseline on all individual domains except bodily pain.

Key Question 2: Safety

A. What is the comparative tolerability and safety of different pharmacologic treatments for attention deficit disorders?

B. What is the evidence of serious adverse effects associated with use of pharmacologic treatments for attention deficit disorders?

C. Evidence on the Risk of misuse or diversion of drugs used to treat ADHD in patients with no previous history of misuse/diversion

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 MPH IR reported results of adverse event assessments.⁵⁴ MPH IR was clearly associated with higher rates of increased sadness, decreased appetite, and sociability impairments than placebo after 7-10 days in 31 preschoolers.

PATS provides some limited evidence on the short-term safety of MPH.^{5,72} Overall, 21/183 (11%) of PATS patients taking MPH withdrew due to adverse events, although there is no data on withdrawals among placebo patients during the phases of the trial that included placebo arms. One serious adverse event, a suspected seizure, was potentially linked to MPH use. Rates of moderate to severe adverse events ranged from 16%-30% in MPH groups and 16%-21% in placebo groups. While numerous severe adverse events are listed in the Wigal publication⁷², 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. Parent-rated rates of several specific adverse events were significantly higher with MPH use compared to placebo during the crossover titration phase of the study. These include trouble sleeping ($p \leq 0.005$), appetite loss ($p \leq 0.003$), stomachache ($p \leq 0.03$), dull/tired/listless behavior ($p \leq 0.02$), social withdrawal ($p \leq 0.03$), and buccal-lingual movements ($p \leq 0.01$). Data from the 10-month open-label phase of the study, in which all patients who had previously improved with active treatment received MPH, show that rates of some adverse events significantly decreased ($p \leq 0.03$: irritability, crying, sadness/depression, listless/tired behavior) while others remained stable (appetite loss, picking, trouble sleeping, anxiety, social withdrawal, stomachache, headache, abnormal movements, and buccal-lingual movements).

Growth Effects

An analysis of growth data from PATS found that ADHD patients ($n=140$; mean age 4.4 yrs) enrolled in the study were in general larger than average at baseline, based on CDC growth charts (73.1% for height; 79.7% for weight). Use of MPH (mean 337 days) was associated with a reduction in growth rate based on a mixed-effect regression analysis, with a mean loss of -6.35 percentiles in height and -14.42 percentiles in weight. 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 which are discussed below.

Direct evidence

Stimulants

Four of six trials of DEX versus MPH IR reported no differences between the drugs in adverse events.^{36, 77-79} However, 2 short-term crossover trials found DEX to cause greater weight loss than MPH IR with mean weight change differences of 0.7 kg to 0.97 kg.^{73,74}

One of 3 trials of MAS versus MPH IR found no difference in adverse event rates,⁹⁷ The other two did find some differences but study weaknesses make these two studies less reliable.

All 3 studies of MPH IR versus extended release formulations (MPH OROS, MPH SODAS, and MPH SR) that reported no significant differences in the incidence of side effects^{7,8,13}.

Atomoxetine

Atomoxetine caused significantly more vomiting and somnolence than both MPH IR⁴⁸ and Adderall XR[®]⁴⁹ in two trials. Atomoxetine was associated with lower rates of 'abnormal thinking'⁴⁸ than MPH IR and lower rates of insomnia than Adderall XR[®].⁴⁹

Indirect evidence

Dexmethylphenidate (d-MPH) Extended Release (ER)

Rates of overall adverse events were comparable for d-MPH ER compared to placebo in both the 2-week (28.3% vs. 22.2%)³⁹ and 7-week³⁸ (75.5% vs. 57.4%) trials. The most frequently reported adverse events were typical of stimulant products and were generally comparable between d-MPH ER and placebo. The only occasion for which rates of a specific adverse event were statistically significantly higher in patients taking d-MPH ER compared to placebo was for decreased appetite in the 7-week trial (30.2% vs. 8.5%; $p < 0.0068$).

Lisdexamfetamine dimesylate

Adverse event rates were reported for study 301.⁴³ Overall adverse event rates were significantly greater ($p \leq 0.05$) for patients taking lisdexamfetamine 30mg (71.8%), 50mg (67.6%), or 70mg (83.6%) compared to placebo (47.2%). Also, when compared to placebo, all dosages of lisdexamfetamine were associated with significantly greater rates ($p \leq 0.05$) of decreased appetite (39% vs. 4.2%), insomnia (18.8% vs. 2.8%), and irritability (9.6% vs. 0). Weight loss incidence was only greater for patients in the 70mg group compared to placebo (9.2% vs. 1.4%; $p \leq 0.05$). Withdrawals due to any of these adverse events only occurred in $< 1\%$ of patients, however.⁴²

Methylphenidate transdermal system (Daytrana[®])

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

Modafinil

Overall, modafinil appeared to be well-tolerated. Rates of withdrawal due to adverse events did not exceed 5% for modafinil, and were generally comparable to rates in the placebo groups. The one exception to this comes from the trial with the highest mean dosage of modafinil (395mg).⁴⁴ In this trial, 10% of patients taking modafinil withdrew due to adverse events, compared to 0 in the placebo group ($p = 0.0058$).

Otherwise, the only adverse event that consistently occurred in more patients taking modafinil (range 12% to 29%) than placebo was insomnia. Decreased appetite also occurred in more patients taking modafinil than placebo. One patient (0.6%) was diagnosed with Stevens-Johnson syndrome.⁴⁶

Growth effects

A study of withdrawing MPH IR during summer months versus not withdrawing assessed the effect on weight and height.⁷⁵ The serious limitations of this study, in design and conduct, limit the likelihood that the findings are valid.

Adolescents

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

Trials of other stimulants provide no long-term evidence on safety. One 17-day study comparing MPH OROS and MAS reports a single adverse event – urinary difficulty – in a patient receiving MPH OROS.⁵⁷ Another multi-phase, placebo-controlled study of MPH OROS reported no serious adverse events during the two-week double-blind phase, although one serious adverse event (suicidal ideation) was reported during a run-in, open-label dose titration phase. Other adverse events commonly reported during the open-label dose titration phase were headache (25% of patients), decreased appetite (21%), insomnia (15%), and abdominal pain (18%). However, adverse event rates during the double-blind phase were similar for MPH OROS and for placebo and the only withdrawal due to adverse events was reported in a placebo patient.⁷⁶ Results from a four-week trial found that when compared to placebo, extended-release MAS were associated with higher rates of anorexia/decreased appetite (35.6% versus 1.9% for placebo), insomnia (12.0% versus 3.7%), abdominal pain (10.7% versus 1.9%), and weight loss (9.4% versus 0%). Five patients taking extended-release MAS withdrew from the study due to adverse events. No placebo patients discontinued due to adverse events and no serious adverse events were reported in either group.

Adults

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

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

Direct comparisons of stimulants versus nonstimulants

Modafinil and DEX IR were associated with similar rates of insomnia (38% vs. 19%, NS), muscle tension (24% vs. 19%, NS) and appetite suppression (24% vs. 19%; NS) in the only included head-to-head trial.⁶⁴ There were no withdrawals due to adverse effects.

Indirect comparisons

Adverse event reporting was limited in placebo-controlled trials of adults with ADHD. Indirect comparisons between competing drugs in tolerability and adverse event rates are difficult to interpret across these adult trials due to incomplete reporting and heterogeneity in adverse event definitions, as evidenced by variation in placebo group rates. We noted that atomoxetine was the only drug to be associated with significantly higher rates of adverse event-related withdrawals relative to placebo, however this may

be due to shorter follow-up durations and the smaller sample sizes used in the stimulant trials.

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.

We are aware of an ongoing open-label, one-year safety study of lisdexamfetamine (Study 302),⁴² but not enough detail about study methodology is yet available for quality assessment and inclusion in this review. All but two studies were 1 to 5 years in duration.^{77,78} All but one study involved elementary school-aged children. The exception was one before-after study of MAS in adults with ADHD.⁷⁹ 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.

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

Height and weight effects

A frequently cited nonsystematic review concluded that effects on weight and height associated with MPH IR vary across short-term clinical trials and long-term observational studies and are mostly transient.⁸⁰ We reached similar conclusions based on our analysis of a larger number of primarily long-term observational studies that compared MPH IR to DEX IR, imipramine, or unmedicated hyperactive control groups.

Height and weight changes associated with MPH IR and OROS were also observed in long-term noncomparative studies. A noncomparative study of MAS (Adderall XR®) found a low overall rate of withdrawal due to weight loss (4.8%), however weight loss was the most common reason for withdrawal from this 24-month extension of placebo-controlled trials.⁸¹

Comparative studies

Height

These studies do not answer the question of whether any one stimulant suppresses growth in height any more than any other, nor do they clearly support a relationship between MPH and suppression of height. The only comparative evidence comes from two studies of DEX and MPH.^{82,83} Results are mixed across these studies. It is impossible to determine if heterogeneity is responsible for this as one of the studies did not report mean age, dosage, or duration.⁸³

Weight

Results from three comparative studies suggest that DEX is associated with significantly greater suppression of weight gain than MPH, at least in the first 1 to 2 years. DEX was associated with a significantly lower mean weight gain (kg) than MPH after nine months in one study,⁸⁴ significantly greater declines in weight percentiles after the first of 5 years another study,⁸² and at end of treatment (≥ 2 years) in yet another.⁸³

In the 5-year, partly retrospective and partly prospective study that involved 84 children differences in decreased weight percentiles between DEX and MPH resolved by

the second year and resulted in significantly greater than expected mean increases in weight percentiles at final follow-up (+10.9, $p < 0.01$ and +12.8, $p < 0.001$, respectively).⁸²

The 9-month study also reported a few subgroup analyses.¹⁹⁶ The first suggests that comparison of mean weight gain between DEX and MPH may have been confounded by dosage disparities. Apparently, the difference between DEX and MPH resolved when four patients taking lower-dose MPH (20 mg/day) were removed from the analysis (0.13 vs. 0.12 kg per month). In patients taking DEX, medication continuation of medication over the summer was associated with significantly lower mean weight gain than in children who discontinued medication (0.14 vs. 0.47 kg per month, $p < 0.01$). Medication continuation status did not have an effect on weight gain in the group of patients taking MPH.

MPH was associated with decreases in weight percentiles similar to imipramine after one year⁸⁵ and absolute weight changes that were similar those in unmedicated healthy controls in another 2-year study.⁸⁶ Results were mixed across two studies that compared children taking MPH to unmedicated hyperactives, however.^{85,87}

Noncomparative studies

Multiple noncomparative study findings provide inconclusive evidence regarding MPH IR effects on children's height and weight. A pooled analysis of data from open-label extensions of 13 trials of atomoxetine assessed the effect on height and weight.⁸⁸

Height

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

A before-after study followed 407 children with ADHD taking MPH OROS 40 mg/day for 12 months.⁸⁹ 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 2.3 cm less than expected.

Based on the PATS trial, preschool-aged children treated with MPH IR were found to be taller at baseline than age-based norms (+2.04 cm).⁹⁰ Children who remained on MPH had reduced growth, a mean of 1.38 cm/year.

Weight

MPH IR. Noncomparative studies provide mixed evidence about the association between MPH IR and suppression of weight gain in school-aged children. Based on data from the PATS study, preschool-aged children were heavier than age-based norms by 1.78 Kg.⁹⁰ After a year of treatment, those who stayed on MPH IR experienced less weight gain than those who did not complete by 1.32 Kg/year.

MPH OROS. In the before-after study of 407 children (above), absolute weight increased a mean of 6.0 kg during 21 months, with the baseline weight being slightly above expected and the final weight being slightly below expected for age. The final weight was 1.23 Kg (2.64 lbs) less than expected for age.⁸⁹

MAS XR. Twenty-seven of 568 (4.7%) children withdrew due to weight loss in a 24-month before-after study of MAS XR.^{81,91} Eligibility for this study was restricted to patients that completed either of two placebo-controlled trials without any clinically relevant adverse events or withdrew for any other reasons. Overall, the children had a

mean weight deficit at endpoint (change in age-adjusted weight quartile -15.15). The deficit was greatest among those in the highest quartiles at baseline, and among those who were stimulant naïve. Weight change was greatest during the first year, with change in the second year not statistically significant. A second open-label study of MAS XR treated adolescents (mean age 14 yrs; n = 138) reports that 25% (34/138) experienced weight loss as an adverse event, 2 of whom discontinued drug for this reason.⁹² The mean weight decreased by 2.4 Kg (5.2 lbs), with approximately 9.2 lb weight loss being the mean among MAS XR-naïve patients. The study also found that those in the 75th percentile for weight lost more weight (mean 4.2 Kg) compared to those in the 25th-75th percentile (1.5 Kg), while those below the 25th percentile gained 0.5 Kg (mean).

Atomoxetine. Based on 412 patients (children and adolescents) who had received atomoxetine for at least 2 years and had at least one post-baseline height and weight measurement, atomoxetine resulted in a mean decrease in expected weight of 0.87 kg, and decrease in expected height of 0.44 cm.⁸⁸ Results from another before-after study of 10 boys (mean age NR) suggested that tomoxetine (same as atomoxetine) was associated with a weight loss of 1.15 kg after 10 weeks.⁹³

Tics

Four studies reported tic-related outcomes. One of these is a long-term placebo-controlled trial⁹⁴ of MPH IR. Although the 1-year study started out with similar numbers assigned to placebo and MPH, by the study end 72 were on MPH and only 18 on placebo. Development of new tics or worsening of pre-existing tics was not different between the two groups. These studies do not provide any information about how different pharmacologic treatments for ADHD compare in safety with regard to tic-related outcomes. In addition, a meta-analysis of data from 3 short-term PCT's found similar rates of tics reported as an adverse event among the groups (MPH OROS 4%, MPH IR 2.3%, placebo 3.7%, P=0.5249).⁹⁵

Seizures

One study evaluated seizures as an adverse event.⁸⁵ None of the 70 males with hyperactivity experienced a seizure over the one-year study period.

Injuries

A retrospective database study analyzed an association between childhood behavioral disorders and common childhood injuries by using the British Columbia Linked Health Data Set to identify injuries. Children with behavioral disorders were identified using MPH prescriptions as a proxy for diagnosis using data in a Triplicate Prescription Program.⁷⁸ Injury frequencies in children prescribed MPH at least once between 1/1/1990 and 12/31/1996 (n=16,806) were compared to those in children not taking MPH (n=1,010,067). Odds of any injury (fractures, open wounds, poisoning/toxic effect, intracranial, concussion, and burns) were significantly higher in children taking MPH than for those not taking MPH (OR 1.67, 95% CI 1.54 to 1.81), even after adjusting for baseline age, sex, socioeconomic status, and region. Since MPH was used simply as a proxy for behavioral disorders, the relationship between the drug and the increase in injuries is not necessarily clear.

Suicide

One before-after study followed 8 adult males (mean age of 27.2 years) that continued on open MPH for three to six months subsequent to participation in short-term

clinical trials.⁷⁷ One participant (12.5%) attempted to commit suicide by consuming a month's supply of MPH.

In September 2005, FDA issued a public health advisory and a directive to update the product label with a black boxed warning regarding a potential association of atomoxetine and risk of suicidality in children and adolescents (<http://www.fda.gov/bbs/topics/news/2005/new01237.html>). This came after an FDA review of results from an unpublished meta-analysis of 12 placebo-controlled trials of children in which atomoxetine was associated with significantly higher risk of suicidal ideation than placebo: 0.37% (5/1357) vs. 0% (0/851); Maentel-Haenzel Incidence Difference 0.46, 95% CI 0.09, 0.83; $p=0.016$. Suicide attempts were slightly higher with atomoxetine; 0.07% (1/1357) vs. 0% (0/851).⁹⁶

Cardiovascular adverse events

MAS XR. Four open-label extension studies of MAS XR, one each in children, adolescents, and adults examined the cardiovascular effects over periods of 6 to 24 months. In each of these studies the subjects were populations of patients who were highly selected and are described as being healthy other than the diagnosis of ADHD. The studies in children and adolescents also included a short-term placebo-controlled phase. While no statistically significant differences compared to placebo in any ECG measure were found in children in the short-term trial, 2% (11/568) had DBP > 90 mmHg, and 9% (50/568) had a SBP > 130 mmHg at some point during follow-up. Overall, 0.7% (4/586) withdrew from the study due to a cardiovascular adverse event; 1 due to tachycardia (max 121 bpm compared to 108 bpm at baseline), 2 due to chest pain (both had sinus bradycardia at baseline), and 1 due to elevated blood pressure (130/90 mmHg with resolved to 115/80 after 1 month without drug). In a shorter duration open-label study, 2968 children were given MAS XR for a period of up to 15 weeks. The absolute numbers of patients with cardiovascular adverse events are not clearly reported. It is reported that 0.2% (7/2968) discontinued MAS XR due to cardiovascular adverse events. Nine patients had treatment for emergent cardiovascular adverse events that were moderate or serious in intensity, 5 of which were deemed probably related to MAS XR. Thirteen of 79 adolescent patients (16%) experienced adverse events during a 4-week study of MAS XR versus placebo that included cardiovascular symptoms such as syncope, tachycardia, and ECG abnormality.⁹⁷ 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.⁹⁸ Statistically significant, but not considered clinically meaningful, increases in SBP and DBP were seen at various points throughout the study (mean increase SBP 2.3 mmHg, DBP 1.3 mmHg at endpoint). While a statistically significant increase in QTcB (7.2 msec; $P<0.001$) was found, no patient had a QTcB >480 msec. Three percent withdrew due to cardiovascular events (2 due to palpitations or tachycardia with the extent not reported, and 5 due to hypertension).

Atomoxetine. Open-label extension studies of atomoxetine have reported on cardiovascular adverse events in children or teens⁹⁹ and in adults.¹⁰⁰ Linear regression

analysis of the report concerning children or adolescents (n=169) suggests that there is no evidence of an increase in QTc with increasing dosage of atomoxetine. 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.

Post-marketing Surveillance Evidence.

An analysis conducted by the Office of Drug Safety (ODS) in April 2004 evaluated reports of sudden death or serious cardiovascular events associated with use of amphetamine and methylphenidate products at usual dosages received by the FDA Adverse Event Reporting System (AERS). ODS recently updated this analysis to include a broader reporting period and which also included atomoxetine (http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4210b_06_01_Gelperin.pdf). The more recent findings were presented in meetings on February 9, 2006 for the Drug Safety and Risk Management Advisory Committee (DSaRM) and on March 22, 2006 for the Pediatric Advisory Committee. In both meetings there was consensus that it is not yet possible to determine causality, impact of pre-existing heart disease, and magnitude of risk due to limitations in the reliability of spontaneous report data. Reports indicate that the DSaRM called for adding a black box warning to ADHD drug product labels. The Pediatric Advisory Committee agreed there was a need to supplement the labels with information about potential cardiovascular risks, but concluded that the available evidence does not yet warrant the seriousness level of a black box warning.

Hepatotoxicity

Atomoxetine. Two case reports (via the FDA MedWatch system) of hepatotoxicity in patients taking atomoxetine (one adult, one child) have resulted in the addition of a warning in the product labeling: “Postmarketing reports indicate that STRATTERA can cause severe liver injury in rare cases. Although no evidence of liver injury was detected in clinical trials of about 6000 patients, there have been two reported cases of markedly elevated hepatic enzymes and bilirubin, in the absence of other obvious explanatory factors, out of more than 2 million patients during the first two years of postmarketing experience. Such reactions may occur several months after therapy is started, but laboratory abnormalities may continue to worsen for several weeks after drug is stopped. Because of probable under reporting, it is impossible to provide an accurate estimate of the true incidence of these events. The patients described above recovered from their liver injury and did not require a liver transplant.

However, in a small percentage of patients, severe drug-related liver injury may progress to acute liver failure resulting in death or the need for a liver transplant. STRATTERA should be discontinued in patients with jaundice or laboratory evidence of liver injury, and should not be restarted. Laboratory testing to determine liver enzyme levels should be done upon the first symptom or sign of liver dysfunction (e.g., pruritus, dark urine, jaundice, right upper quadrant tenderness, or unexplained “flu-like” symptoms).”¹⁰¹

Key Question 2C. Evidence on the Risk of misuse or diversion of drugs used to treat ADHD in patients with no previous history of misuse/diversion

Because the potential for misuse and/or diversion crosses the lines of childhood to adulthood, the evidence is considered as one body here. Also, because development of

abuse and diversion are longer-term issues, we did not examine short-term trial evidence regarding apparent misuse based on tablet counts.

Direct evidence

No evidence involving direct comparisons of stimulants vs. nonstimulants or immediate release vs. long-acting formulations was found for children or adults.

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, but a clear conclusion has not yet been reached. In general these studies suffer from methodologic flaws that hinder clear conclusions from being drawn. 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. We have rated all of these studies as fair quality and suggest caution in interpreting the results of any one study as conclusive.

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.^{102,103} Due to small size and study design issues these studies are not conclusive.

Diversion

We found a single study of the misuse or diversion of prescription stimulants.¹⁰⁴ This study used data collected as part of the National Survey on Drug Use and Health from 2000, 2001, and 2002. This study found that 34.7% had ever misused a prescription stimulant intended or use to treat ADHD. The most commonly misused stimulants in this survey were methylphenidate and dexamphetamine, with smaller numbers reporting use of other drugs, including MAS and MPH OROS. Similarly, 30% had misused an ADHD stimulant in the past year, with significantly higher rates among those aged 12- 25 years compared to older participants, and among whites compared to other races. Using combined data from 2000 and 2001 (due to low numbers in each survey), 4.7% were determined to be dependent or abusing a prescription ADHD stimulant drug, with rates highest again among those 12 -25 years old. Rates of dependence were higher among women, whereas rates of abuse were higher among men. This study indicates a serious problem with dependence and abuse of ADHD stimulant drugs, but does not provide insight into the course of development of abuse or dependence, or the medical history of those found to be abusing or dependent on stimulants.

Key Question 3: Subgroups

- A. Are there subgroups of patients based on demographics (age, racial groups, gender, and ethnicity), other medications, or co-morbidities for which one pharmacologic treatment is more effective or associated with fewer adverse events?**
- 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**

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

ADHD subtypes, comorbidities, and race or ethnicity were not recorded in most randomized controlled trials and observational studies. For example, only one-quarter of all studies of school-aged children reported ADHD subtype prevalence rates. Importantly, of those that did record demographic information, only one poor-quality trial reported results of a subgroup analysis of Black children with ADHD.¹⁰⁵ 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

A subgroup analysis of the poor quality FOCUS study conducted specifically to evaluate the comparative efficacy and safety of *open-label* methylphenidate OROS and atomoxetine in 183 Black children with ADHD (out of 1,323 children that participated in the overall trial) found treatment outcomes to be similar to those for the overall study population.¹⁰⁶

MPH IR

MPH IR 0.15, 0.30 and 0.50 mg/kg was studied in a placebo-controlled, crossover trial (2 weeks in each arm) of 11 Black male adolescents (mean age=13.6 years)^{59,106}. MPH IR had a positive effect on 75% of efficacy measures. This response rate is similar to that seen in other placebo-controlled trials of MPH IR. MPH IR was associated with significant linear elevations diastolic blood pressure among these patients.

An analysis of California Medicaid claims data suggests that mean persistence (days of treatment without any 30-day gaps) was longer for children taking MPH ER formulations (OROS and SODAS) than for those taking MPH IR regardless of ethnicity (White, Black, Hispanic).⁴² This same data indicates that mean treatment durations overall (MPH OROS, SODAS, and IR) were significantly shorter for children of Black (survival time ratio (STR) 0.77; 95% CI 0.73-0.80), Hispanic (STR 0.81; 95% CI 0.78-0.84), and other ethnicities (STR 0.81; 95% CI 0.75-0.87) than for White children.

Lisdexamfetamine

Subgroup analyses of ethnic origin (Caucasian vs. Non-Caucasian) were performed using data from two double-blind, randomized controlled trials of lisdexamfetamine and results were reported in the CDER Medical Review.⁴² In the one-week, crossover study (#201), average SKAMP-DS scores for lisdexamfetamine were similar to MAS XR and superior to placebo, regardless of ethnic origin. In the 4-week, parallel-group study (#301), mean changes in ADHD-RS-IV for lisdexamfetamine 30mg versus placebo appeared less robust for the subgroup of non-Caucasians (-18.5 vs. -10.1; p=0.0754) compared to the population overall (-21.8 vs. -6.2 points; p<0.0001). Treatment effects for the lisdexamfetamine 50mg and 70mg dosage groups also appeared less robust in non-Caucasians, but mean changes in the ADHD-RS-IV scores remained statistically significantly greater than placebo.

Gender

A study designed to assess differences between the response in boys and girls when taking MPH IR enrolled 24 children.¹⁰⁷ Children were randomly assigned to placebo or MPH IR, and then crossed over to the other treatment. The randomization was done daily, with 5 to 9 days of data recorded for each condition. A number of outcome measures were used. The MANOVA analysis of results indicated a significant effect of MPH IR, but found no interaction between drug and gender.

In a study of 42 girls,¹⁰⁸ analyses were primarily conducted combining data for MPH IR and DEX IR and making an *indirect* comparison to a study of boys conducted by the same group of researchers earlier¹⁰⁹. This report concludes that there are no striking differences between boys and girls in response to these 2 stimulants, and that both can be effective in either group.

Subgroup analyses based on gender were also performed based on data from two double-blind, randomized controlled trials of lisdexamfetamine.⁴² Again, average SKAMP-DS scores for lisdexamfetamine were similar to MAS XR and superior to placebo regardless of gender in the one-week, crossover study (#201). In the 4-week, parallel-group trial, treatment effects appeared less robust in subgroups of girls for all dosage groups of lisdexamfetamine compared to placebo, but changes in ADHD-RS-IV lost statistical significance only in the 30mg treatment group (-19 vs. -8.1, $p=0.0537$). Results from the subgroups of girls in study #301 must be interpreted with caution, however, due the small sample sizes ($n=88$).

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.²⁵³ This analysis of 52 girls reported similar efficacy to that reported for the whole trial group (atomoxetine superior to placebo on most measures) but did not make a comparison of the effects in boys versus girls.

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

ADHD subtypes

The potentially moderating effects of ADHD subtypes (inattentive, hyperactive/impulsive, or combined) in children have been examined in short-term placebo-controlled trials of atomoxetine,⁵¹ MPH IR, and MPH OROS. Results from all trials suggest that these drugs have superior efficacy relative to placebo in children with ADHD, regardless of diagnostic subtype.

One trial each of MPH IR ($n=40$)¹¹⁰ or MPH OROS ($n=47$)¹¹¹ also examined the potential relationship between stimulant dose and ADHD subtype. Although very preliminary, there were findings in both trials suggesting that the greatest symptom improvements may occur at higher dosages of MPH IR or OROS ($\geq 30\text{mg/day}$) in children diagnosed with ADHD of the combined subtype or ADD with hyperactivity, whereas greater symptom improvements may occur at lower dosages ($\leq 18\text{ mg/day}$) in children with ADHD of the inattentive type or ADD without hyperactivity.

In the trial of MPH IR, conclusions about the dose-response relationship were based entirely on clinical judgment.¹¹¹

In the trial of MPH OROS, analyses were based on linear and higher-order dose-response curves.¹¹² In this trial, significant relationships between ADHD subtype and MPH OROS were detected for some, but not all, efficacy outcomes. It was noted that

children with the combined type of ADHD had the greatest decreases in symptoms between the 36mg and 54mg dosages of MPH OROS, whereas children with the inattentive type of ADHD had the greatest decreases in symptoms (based on the the ADHD-RS-IV Scale) between placebo and the 18mg dosages of MPH OROS. Caution must be used in interpreting these results as differences in appearance between placebo and MPH OROS capsules may have increased parents' awareness of medication condition and could have affected efficacy ratings. Also, a similar pattern in subtype differences based on dosage was not observed when CGI scale-related ratings were considered.

Co-morbidity

Rates of comorbidities were only reported in around half of all studies. With the exception of depression, the ranges of comorbidities reported in these trials encompass the American Academy of Pediatrics estimates on prevalence of common comorbidities: Oppositional defiant disorder=35.2 (27.2, 43.8), conduct disorder=25.7 (12.8, 41.3), anxiety disorder=25.8 (17.6, 35.3), and depressive disorder=18.2(11.1, 26.6).¹¹²

One placebo-controlled trial of atomoxetine 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.¹¹³ This trial does not provide evidence of comparative efficacy among subgroups of patients with comorbidities.

Efficacy of ADHD drugs have also been evaluated in adults with ADHD and comorbid "emotional dysregulation" symptoms. "Emotional dysregulation" (ED) is a classification term recently coined by a group of researchers¹¹⁵ used to describe a set of "nonspecific emotional symptoms" that can accompany ADHD including mood lability, mild periods of depression, irritability, problems with temper control, overreaction to stress, and frequent feelings of frustration.

In two placebo-controlled trials, treatment effects of either atomoxetine or MPH OROS were considered in patients with and without comorbid ED. Among an original population of 536 patients, atomoxetine had superior efficacy compared to placebo on all measures of ADHD symptom improvement regardless of the presence of ED.¹¹⁴ In contrast, in the trial of MPH OROS, the presence of ED appeared to have a moderating effect on patient outcome.¹¹⁵ In this trial, improvements in mean total WRAADDS scores were significantly greater for MPH OROS compared to placebo for the overall patient population (-42% vs. -13%, $p < 0.001$, $n = 47$), but not for the subgroup of 16 patients with ADHD+ED (-25% vs. -15%, $p = \text{NS}$).

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. The majority of these trials were only 2-3 weeks in duration and involved very small numbers of children. Children participating in these trials were mostly male ($\geq 85\%$), with a mean age of 10.5 years. Overall, there was very little evidence across these trials to indicate that MPH IR, DEX IR, or atomoxetine were associated with any tic exacerbation effects.

Paradoxically, in one 2-week trial of 34 children, only the lowest dose of MPH IR (0.1 mg/kg/day) was associated with any tic worsening, characterized by an increase in motor tics only in the classroom setting.^{116,117} In another 3-week trial of 12 children, only the higher dosages of MPH IR (0.67 mg/kg/day or 1.20 mg/kg/day) were associated with tic exacerbations.¹¹⁰ Otherwise, compared to placebo, MPH IR, DEX IR, and atomoxetine were all consistently associated with improved tic severity in these trials. Furthermore, children also showed greater improvements in ADHD symptoms with MPH IR, DEX IR, and atomoxetine compared to placebo.

Mental retardation

Seven randomized crossover trials of MPH IR versus placebo in children with mental retardation and ADHD (five conducted by the same group of researchers) were found. All children enrolled had mild to borderline mental retardation, as described by the eligibility criteria in each study. All of these studies had a 7 day treatment phase, and assigned patients to 0.3 and 0.6 mg/kg doses given twice daily. One crossover trial also included exposure to a low-dosage of 0.15 mg/kg.¹¹⁸ Taken together, these studies indicate that MPH IR is effective in improving some measures of ADHD symptoms. Adverse events were common, with increased staring and social withdrawal being prominent with MPH IR. Unfortunately, these do not provide comparative evidence with other drugs.

Pervasive Developmental Disorders/Autism Spectrum Disorders (PDD/ASD)

Few, short-term placebo-controlled trials of either MPH IR¹¹⁹ or atomoxetine¹²⁰ have explored treatment of ADHD symptoms in children with PDD/ASD. Collectively, findings from these trials suggest that atomoxetine and MPH IR are both feasible options for ADHD symptom control in children with PDD/ASD. Compared to placebo, atomoxetine and MPH IR significantly improved scores on the Hyperactivity subscale of the Aberrant Behavior Checklist (ABC-H), which was the primary efficacy measure in the most recent trials. Although encouraging, compared to effects in typically developing children, atomoxetine and MPH IR may be less efficacious in reducing ADHD symptoms and associated with more frequent adverse in children with PDD/ASD. Due to heterogeneity in methods and patient populations, these trials provided inconclusive evidence regarding the indirect comparative efficacy and adverse effects of atomoxetine and MPH IR.

Learning disabilities

We identified one study that examined whether children with and without learning disabilities benefit from MPH IR to the same extent when treated for ADHD.¹²¹ This study was based on outcome data from 95 children with ADHD (85% male, mean age=9.2 years) who participated in a two-week, placebo-controlled, crossover trial of MPH IR BID 0.5 mg/kg. Ultimately, children were assigned consensus clinical response (CCR) scores (0=nonresponder, 1=mild response, 2=moderate response, 3=large response) to reflect overall degree of ADHD symptom control while taking MPH IR. Children with CCR scores of 0-1 were categorized as “nonresponders” and children with CCR scores of 2-3 were categorized as “responders.” When compared to children without learning disabilities, the number of “responders” to MPH IR were significantly fewer in children with learning disabilities overall (75% vs. 55%; p=0.034) and when the disability was specific to mathematics (72% vs. 50%; p=0.034), but not when the disability was specific to reading (68% vs. 59%; p=NS).

Epilepsy

A small (n= 30) randomized crossover study of children (mean age 10 years) with ADHD and epilepsy studied the effect of adding placebo or MPH IR to the child's current anti-epilepsy regimen.¹²² MPH IR was shown superior to placebo on the CPT based on speed of response and more "time on task" during the 45-minute test. The data presented on adverse events relates primarily to an observational period, although is not presented clearly. Loss of appetite was reported as an adverse event related to MPH IR that was not persistent. All others were assessed as being transient.

Oppositional Defiant Disorder (ODD)

The impact of comorbid oppositional defiant disorder on treatment of ADHD in children has been most widely studied for atomoxetine. Meta-analyses of data from two earlier¹²³ and three more recent¹²⁴ placebo-controlled trials of atomoxetine were respectively designed to evaluate the efficacy and adverse effects of atomoxetine in children with ADHD and comorbid ODD. Additionally, findings are available from post-hoc analyses of data from single placebo-controlled trials evaluating this same issue.^{125,126} Collectively, these studies consistently found that the presence of ODD does not impact the effectiveness of atomoxetine in treating children with ADHD.

In the meta-analyses that pooled outcomes from different subsets of children with coexisting ADHD and ODD, atomoxetine was consistently associated with significantly greater reductions in ADHD-RS Total Scores across two earlier (-17.0 vs. -7.5; p<0.001; n=98)¹²⁴ and three more recent placebo-controlled trials (-15.8 vs. -4.2; p<0.001; n=99).¹²⁵ Additionally, in the most recent meta-analysis (2007), children with ADHD and ODD taking atomoxetine demonstrated similar or greater improvements than placebo on all quality-of-life-related subscales of the Child Health Questionnaire (CHQ), except 'parental impact-emotional', 'parental impact-time', and 'self-esteem'.¹²⁵

A few additional aspects of atomoxetine treatment in children with ADHD and ODD were evaluated in the post-hoc analyses of single placebo-controlled trials.

In the first of these post-hoc analyses, the main findings suggest that response to treatment of ADHD in children with comorbid ODD (n=113) may be related to dose.¹²⁶ Improvements in ADHD symptom and QOL measures after 8 weeks were significantly greater for atomoxetine than placebo for the group of children with ODD taking 1.8 mg/kg, but not for the 1.2 mg/kg or 0.5 mg/kg groups.

The second post-hoc study involved data from a longer-term, 9-month, placebo-controlled trial.¹²⁷ This study had an unusual design. The primary trial analyses focused on *between-treatment group* comparisons and the main result was that staying on atomoxetine significantly reduced the risk of relapse when compared to switching to placebo (RR 0.59; 95% CI 0.43, 0.80). Subsequently, findings from post-hoc, *within-groups* analyses suggested that risk of relapse in ADHD symptoms were not significantly altered in the presence of comorbid ODD either in children taking atomoxetine (RR 0.67; 95% CI 0.42, 1.06) or in children taking placebo (RR 1.27; 95% CI 0.81, 1.99). However, no subgroup analyses based on presence of ODD were reported for the comparisons between atomoxetine and placebo. (Please see the DERP report page 71 for further comments)

The efficacy and adverse effects of MAS XR 10-40mg (Adderall® XR) has also been studied in 235 children with ADHD and ODD.¹²⁷ This was a 4-week, parallel-design, randomized, placebo-controlled trial that focused on ODD as the primary

diagnosis, with only 79.2% of the original 308 children having comorbid ADHD. In the ODD+ADHD subgroup ITT population, improvements in ADHD symptoms were significantly greater for MAS XR compared to placebo on the parent- and teacher-rated ADHD subscale of the SNAP-IV for the 10mg, 30mg, and 40mg groups and on the clinician-rated CGI-I for ADHD for the 20mg, 30mg, and 40mg groups. Adverse event outcomes were not reported separately for the ODD+ADHD subgroup, but were typically higher for MAS XR compared to placebo for anorexia/decreased appetite, insomnia, headache, abdominal pain, and weight loss. Limitations of this study include: mean change from baseline on the ADHD subscale of the SNAP-IV was included as a secondary outcome measure and it is unclear if the analysis was adequately powered to measure between-group differences. Although between-groups baseline characteristics were reportedly comparable at baseline for all 308 patients (mean age=10.6 years; 79.2% male), it is unclear if baseline characteristics were similar among the subgroup of 235 children with ODD and ADHD.

Bipolar Disorder

When added to divalproex, MAS(Adderall®) was associated with significantly greater improvements in ADHD symptoms than placebo after 4 weeks, but had no effect on bipolar disorder symptoms in 30 pediatric patients with comorbid ADHD and bipolar disorder (mean age 9.8 years).¹²⁸ 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.

Fetal Alcohol Syndrome

A very small double-blind crossover study (n = 4) examined the effects of MPH IR in Native American Children with FAS and found hyperactivity scores to be improved based on both parent and teacher Connors scale scores over a 5-day period compared to placebo.¹²⁹ The authors note that Daydreaming-attention scores were not improved on the teacher's ratings.

Symptoms of Anxiety

Children

While several trials included patients with comorbid anxiety disorders, we did not find any that conducted subgroup analysis of these patients. Overall, 6 head-to-head trials and 10 PCT's reported symptoms of anxiety or nervousness as an adverse event and 1 head-to-head comparison and 1 PCT reported it as a symptom of ADHD. In the head-to-head comparisons (MPH IR vs. DEX, MAS, MPH SR, MPH OROS or atomoxetine), no statistically significant differences were found. Placebo-controlled trial evidence is conflicting; with some studies showing higher rates of anxiety or nervousness with MPH, showing a dose-dependent effect, while others showing no increase over placebo rates. Reports of anxiety were similar between placebo and atomoxetine in 2 studies,^{50,130} and modafinil in 2 others.^{45,46}

Because most of these studies are reporting these as spontaneously reported adverse events, we do not believe that the quality of the data warrants a conclusion. The 2 trials that assessed anxiety symptoms as part of ADHD did not find a difference between MPH IR and MPH SR in children with minimal brain dysfunction¹³ or between MPH IR and placebo in children with ADHD and mental retardation.¹³¹

Adults

As in children, we found no trials that examined whether or not the presence of comorbid anxiety symptoms affects clinical outcomes of treatment for ADHD in adults. Alternatively, numerous placebo-controlled trials examined whether treatment with ADHD drugs improves comorbid anxiety symptoms. However, only MPH IR was consistently associated with improvements in anxiety symptoms in adults with ADHD.^{132,133,134} Finally, in terms of adverse effects, only MPH OROS has been associated with significantly greater adverse anxiety effects in adults than placebo across two trials.^{116,135}

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 1993-1999 examined the prevalence of abuse of MPH or DEX.¹³⁶ Twenty-three percent had ever used, and 6% were currently using MPH or DEX, most often reported to be used as crushed tablets taken intranasally. Further assessment of covariates indicated that higher rates of abuse of MPH/DEX were associated with the teen being out of school or having an eating disorder ($p < 0.01$), but not with a diagnosis of ADHD; 36% of abusers had a diagnosis of ADHD, compared to 24% of non abusers (not statistically significant). An assessment of correlation of abuse of MPH/DEX with abuse of other substances did not reveal any statistically significant results. The authors note that this population had a higher psychiatric comorbidity rate than the general adolescent population, which may have affected the results.

Adults

Two trials each of MPH IR and MPH SR focused only on patients with ADHD and comorbid substance abuse disorders. One trial of MPH IR involved a broader population of patients with any alcohol or drug dependence,¹³⁷ while the others focused on either patients with cocaine dependence^{67,138} or methadone-maintained patients.⁶⁶ None reported results of direct assessment of misuse or illicit diversion outcomes. As a potential proxy measure of abuse/diversion, three trials reported medication compliance. Patient self-reported compliance rates were similar in treatment and placebo groups across all three trials (88.5% to 95%). Additionally, no differences were found between MPH and placebo in the proportions of riboflavin positive fluorescence (range 0.77 to 0.84).^{66,67}

The primary objectives of these trials were to investigate (1) whether use of MPH IR or SR in adult substance abusers with ADHD reduces ADHD symptoms to a similar extent as in non-substance abusers and with ADHD, and (2) what kind of impact MPH IR or SR use may have on the course of the substance abuse disorder. Overall, although use of MPH IR or SR in adult substance abusers with ADHD did not appear to negatively influence the course of the substance abuse disorder recovery process (cravings, abstinence duration, proportion of days of substance use, amount of money spent on substances, or number of days until first negative urine sample),^{66,67,139} MPH IR or SR also did not appear to offer much of a benefit in the reduction of these patients' ADHD

symptoms. In all but one of these trials, not only were there less robust treatment response rates in substance abusers with ADHD compared to non-substance abusers (34% - 47% vs. 38% - 78%), but the placebo response rates in the substance abuser trials were also substantially greater (ranges 21% to 55% vs. 4% to 16%).⁶⁵⁻⁶⁷ Trial authors noted several possible factors that may have led to these abnormally negative findings, including that MPH treatment-resistance may be characteristic of substance abusers in general and/or that patients in substance abuse treatment may be more eager to please research staff and have a tendency to over-endorse improvements in any areas of functioning.

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