

Drug Class Review on Pharmacologic Treatments for ADHD

Final Report
Executive Summary
December 2007



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

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INTRODUCTION

According to the most recent NIH Consensus Statement (1998), “attention deficit hyperactivity disorder (ADHD) is the most commonly diagnosed childhood behavioral disorder.” 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.

A number of community-based studies have reported ADHD prevalence rates that range from 1.7% to 16%. 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. 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. 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.

Scope and Key Questions

The purpose of this review is to compare the benefits and harms of different pharmacologic treatments for ADHD. The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. Evidence on Effectiveness and Efficacy

- a. What is the comparative or noncomparative evidence that pharmacologic treatments for attention deficit disorders improve *effectiveness* outcomes?
 - b. What is the *comparative* efficacy of different pharmacologic treatments for attention deficit disorders?
2. Tolerability, Serious Adverse Events, Misuse and Diversion
- a. What is the evidence of *comparative* tolerability of different pharmacologic treatments for attention deficit disorders?
 - b. What is the evidence of serious adverse effects associated with use of pharmacologic treatments for attention deficit disorders?
 - c. What is the comparative or noncomparative evidence that pharmacologic treatments for attention deficit disorders increases the risk of misuse or illicit diversion in patients with no history of misuse or diversion?
 - i. stimulants vs. nonstimulants
 - ii. immediate release vs. long-acting formulations
 - iii. Any included pharmacologic treatment
3. Evidence in Subgroups of Patients
- a. What is the evidence of benefits and harms of pharmacologic treatments for attention deficit disorders in subgroups of patients based on demographics (age, racial groups, gender), other medications or therapy, or co-morbidities (e.g. tics, anxiety, substance use disorders, disruptive behavior disorders)?
 - b. What is the comparative or noncomparative evidence of misuse or illicit diversion of pharmacologic treatments for attention deficit disorders in patients with current or past substance use disorder comorbidities?
 - i. stimulants vs. nonstimulants
 - ii. immediate release vs. long-acting formulations
 - iii. Any included pharmacologic treatment

Inclusion Criteria

Populations

Pediatric, adolescent and adult outpatients with Attention Deficit Disorders

- Attention Deficit Disorder
- Attention Deficit Hyperactivity Disorder

Interventions

Table 1. ADHD drugs and indication

Generic Name	Trade Name*	Abbreviation in report	FDA ADHD Approval
Mixed amphetamine salts**	Adderall ^{®†}	MAS IR	Children
	Adderall XR ^{®***}	MAS XR	Children, adolescents, and adults
Atomoxetine HCl	Strattera [®]	none	Children and adults
Dextroamphetamine sulfate	Dexedrine ^{®*}	DEX IR	Children
	Dextrostat ^{®*†}	DEX ER	Children
Dexmethylphenidate HCl	Focalin ^{®*†}	d-MPH IR	Children
	Focalin XR ^{®†}	d-MPH XR	Children
Lisdexamfetamine dimesylate	Vyvanse [®]	none	Children
Methamphetamine hydrochloride	Desoxyn ^{®†}	none	Children
Methylphenidate HCl	Biphentin ^{®‡}	MPH ER	N/A
	Concerta [®]	MPH OROS	Children and adolescents
	Daytrana [†]	MPH transdermal	Children
	Metadate CD ^{®†}	MPH CD	Children
	Metadate ER ^{®†}	MPH ER	Children and adults
	Methylin ^{®†}	MPH ER	Children and adults
	Ritalin ^{®*}	MPH IR	Children and adults
	Ritalin SR [®]	MPH SR	Children and adults
	Ritalin LA ^{®†}	MPH SODAS	Children
Modafinil	Provigil [®]	none	Adults

*or generic equivalent

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

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

†Not available in Canada

‡Not available in the United States

Outcomes

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

Study Designs

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

METHODS

Literature Search

To identify relevant citations, we searched the Cochrane Central Register of Controlled Trials (1st Quarter 2007), Cochrane Database of Systematic Reviews (1st Quarter 1007), MEDLINE (1996 to March Week 3 2007), and PsycINFO (1985 to March Week 4 2007) using terms for included drugs, indications,

and study designs. We have attempted to identify additional studies through searches of reference lists of included studies and reviews, the FDA web site, as well as searching dossiers submitted by pharmaceutical companies for the current review.

Quality Assessment

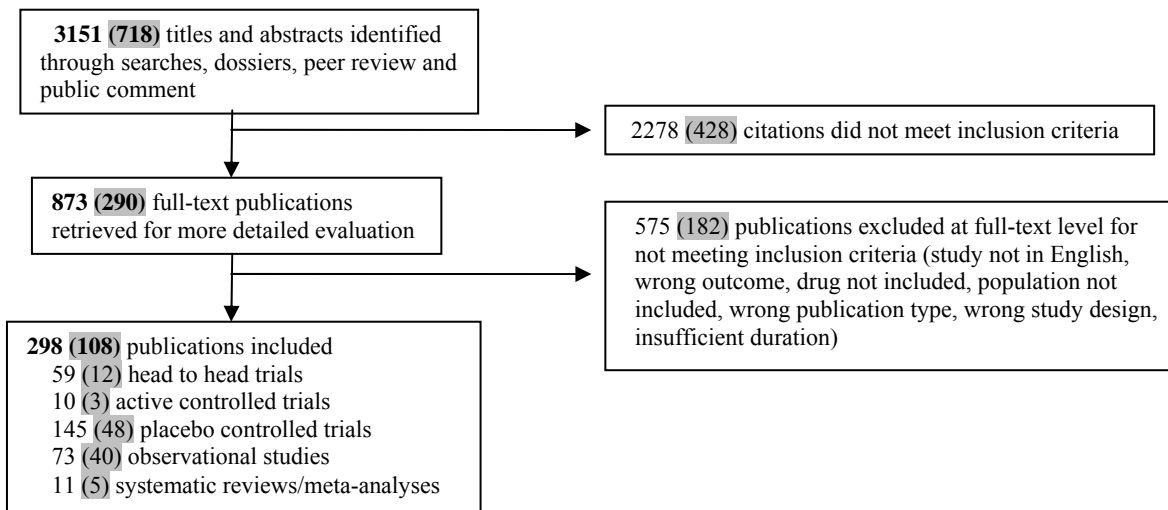
We assessed the internal validity (quality) of trials based on the predefined criteria. These criteria are based on the U.S. Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (U.K.) criteria. Trials that had a fatal flaw in multiple categories were rated “poor-quality”; trials that met all criteria were rated “good-quality”; the remainder were rated “fair-quality.” A fatal flaw occurs when there is evidence of bias or confounding in the trial, for example when randomization and concealment of allocation of random order are not reported and baseline characteristics differ significantly between the groups. In this case, randomization has apparently failed and for one reason or another bias has been introduced.

RESULTS

Overview

Figure 1 details the results of our literature searches. Overall, we identified a total of 3151 citations from searching electronic databases, reviews of reference lists, pharmaceutical manufacturer dossier submissions, and public comment. Of these, 718 were identified in the most recent update. After applying the eligibility and exclusion criteria to the titles and abstracts, we obtained full-paper copies of 873 publications (290 specific to update #2). After re-applying the criteria for inclusion, we ultimately included 298 publications (108 new in Update #2). A list of excluded studies is reported in Appendix E.

Figure 1. Results of Literature Search



*Shaded totals in parentheses reflect results of literature search specific to Update #2

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

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

	MPH IR	MPH ER	DEX	d-MPH	MAS	MAS XR	Modafinil	Atomoxetine	LisDex
MPH IR									
MPH ER	C: 11 T: 1	C: 3							
DEX	C: 11 A: 1	--							
d-MPH	--	--	--						
MAS IR [®]	C: 5	--	C: 1	--					
MAS XR	--	T:1	--	--	C: 1				
Modafinil	--	--	A: 1	--	--				
Atomoxetine	C: 5*	C: 1	--	--	C: 1	--	--		
LisDex	--	--	--	--	C:1	--	--	--	

Abbreviations: C= children, T=adolescents, A=adults *1 trial vs. standard care

Previous systematic review findings

While there are a large number of reviews of pharmacotherapy for symptoms of ADHD, we found a limited number of good quality systematic reviews, including one in the U.S., one in Canada, and one in the U.K. These reviews consistently found a lack of evidence of a difference between the drugs studied in efficacy or adverse events. In some part, the reason for not finding a difference was thought to be due to small sample sizes lacking power to find a difference, and some studies were given less weight due to poor quality. Differences in adverse events were thought to be minor, although the assessment and reporting of adverse events was criticized. These reviewers also commented on the lack of good quality studies assessing long-term outcomes, both of effectiveness and serious adverse events.

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

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

There are no *trials* of comparative effectiveness of these drugs for treatment of ADHD. Good quality evidence on the use of drugs to affect outcomes relating to global academic performance, consequences of risky behaviors, social achievements, etc. is lacking. The evidence for comparative efficacy and adverse events of drugs for treating ADHD is severely limited by small sample sizes, very short durations, and the lack of studies measuring functional or long-term outcomes. Methods of measuring symptom control vary significantly across studies. The crossover design was frequently used, with few analyzing the effect of order of administration of drugs, and those that did found a significant effect. No head-to-head efficacy trial was good quality. The small numbers of patients in these trials limits the ability to show a difference between drugs if one exists. Limitations to the generalizability of these trials include the following: Characterization of ADHD symptomatology across studies is limited due to use of varied or indeterminate diagnostic processes, minorities and the most seriously ill patients

were underrepresented, the small sample sizes of these trials did not allow for statistical analyses of potential effects of these factors.

Overall, the rate of response to stimulants appears to be in the range of 60 to 80%, however the definitions of response rate varied and may not be comparable. Depending on the definition used, there is lack of clarity on the relationship of response rate to clinical significance. Response rates of non stimulants vary, but the range in placebo-controlled trials is similar to that found with stimulants. Significant variation in the method of assessment and definition of response are most likely the reason for the wide variation.

Young children (preschool age; 3-5 years)

No comparative evidence in young children was found. MPH IR was superior to placebo in efficacy in 2 fair-quality placebo-controlled trials that used validated assessment tools; but was also associated with higher rates of adverse events. Evidence from one trial of MPH IR showed reduced growth rates based on a mixed-effects regression analysis.

Children (elementary school age; 6-12 years)

Effectiveness

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

Efficacy and tolerability

Immediate Release versus Extended Release formulations of MPH

The evidence regarding the comparisons of MPH IR versus MPH OROS is conflicting; with 2 double-blind trials unable to identify differences, while 2 open-label studies found that MPH OROS resulted in greater improvements on some but not all assessments. Exploratory pooled analysis of the inattention/overactivity scores of the IOWA Conners' scale indicate MPH OROS may result in greater improvement [weighted mean difference -1.19, 95% CI (-1.78; -0.60)]. Database studies using intermediate outcomes report greater persistence with MPH OROS and MPH SODAS compared to MPH IR. Methodologic concerns indicate caution in interpreting this evidence.

Limited evidence is available for the comparisons of MPH IR to MPH ER, MPH SR, or MPH CD, with 1 small trial each. Overall, the studies of MPH ER and MPH SR were unable to identify differences compared to MPH IR, while the 3rd study found MPH CD to be noninferior to MPH IR.

Sustained Release versus Sustained Release formulations of MPH

Limited evidence from 2 small crossover studies suggests that MPH SODAS was superior to MPH OROS on some, but not all efficacy outcomes. However, these results should be interpreted with caution until higher quality evidence is available. The COMACS study results suggest that MPH CD was associated with significantly larger effect sizes than MPH OROS in the morning, treatment effects were similar in the afternoon, and MPH OROS was superior in the evening. Methodologic concerns indicate caution in interpreting these findings.

Dextroamphetamine versus methylphenidate

The body of evidence clearly indicates no difference in efficacy between DEX IR and MPH IR. Evidence from short-term trials and observational studies suggests that short-term weight loss is greater with DEX IR than MPH IR.

Mixed amphetamine salts versus methylphenidate

MAS IR was superior to MPH IR on a few efficacy outcome measures in two trials, but clear evidence of superiority is lacking. Very limited evidence suggests that twice daily dosing of MAS IR led to higher rates of loss of appetite and sleep trouble than once daily dosing or MAS IR.

Dextroamphetamine versus Mixed amphetamine salts

Evidence on the comparison of DEX IR versus SR versus MAS IR is limited and conflicting, but may suggest that measures made in the morning show DEX IR superior to DEX SR, and afternoon measures show DEX SR superior to MAS IR. Transient weight loss was greater with MAS IR and DEX SR than with DEX IR. However, this evidence should be interpreted with caution.

Lisdexamfetamine versus Mixed amphetamine salts extended release

Evidence from CDER medical review and manufacturer-submitted data dossier suggests that mean SKAMP-DS scores were similar in children following one-week of lisdexamfetamine or MAS XR. Adverse event data were not available for the individual treatment groups, but the data dossier did not specify any differences between them.

Atomoxetine

Limited evidence suggests that atomoxetine was associated with efficacy outcomes similar to MPH IR in one trial, but was associated with less significant efficacy outcomes than MAS XR in another trial. Two additional studies of atomoxetine compared to MPH IR or standard therapies assessed impact on sleep or functional status but were found to be poor quality. Atomoxetine was associated with significantly higher rates of vomiting and somnolence than both MPH IR and MAS XR, while MPH IR caused more 'abnormal thinking' and MAS XR caused more insomnia.

Long-term safety

Although the observational studies provide some estimate of the prevalence of serious longer-term adverse events with MAS IR, atomoxetine, DEX IR, and MPH (IR and SR), few studies directly compared different pharmacologic treatments for ADHD for any one adverse event.

For outcomes where only uncontrolled evidence is available, it is not possible to draw conclusions about comparative long-term safety through indirect comparisons across observational studies due to large differences in study characteristics. The overall body of evidence is poor quality due to a variety of flaws in design and analysis and should be interpreted with caution.

Height change in children:

Evidence on DEX IR versus MPH IR is inconsistent. Evidence suggests that MPH IR and MPH OROS adversely impact expected height gain at least during the first 12 months of treatment. Limited evidence suggests that height changes resulting from atomoxetine are similar to those reported with MPH IR, and are also transient.

Weight in children:

DEX IR versus MPH IR: Results from comparative observational studies suggest that DEX IR is associated with significantly greater suppression of weight gain than MPH IR in the first 1-2 years. However, the difference between DEX IR and MPH IR appears to resolve by the second year and the difference found in years 1-2 may have been exaggerated by higher relative DEX dosages. Ultimately, these data should be interpreted with caution, due to methodological flaws in the measurement of weight. The remaining comparative and noncomparative observational studies suggest a small reduction in expected weight gain, especially among those with greater weight at baseline for MPH IR, MPH OROS, and MAS XR for at least the first year of treatment. Effects after 1 year are not clear, but may be less evident.

Limited evidence suggests that weight changes resulting from atomoxetine are similar to those reported with MPH IR, and are also transient.

Other Adverse Events

There is no *comparative* evidence on other long-term safety outcomes, including tics, seizures, cardiovascular adverse events, injury frequency, and hepatotoxicity.

Abuse/diversion

Evidence from longitudinal studies with healthy controls, or untreated ADHD controls, is conflicting. Several studies have found no adverse relationship between stimulant therapy (primarily MPH IR) during childhood or adolescence and later use or abuse of substances, and some studies even find a protective effect. However, other studies have found increased risk of later tobacco use and dependence and cocaine use or dependence. Variations in populations studied, control groups, age at follow-up, extent and type of analysis controlling for potential confounding, and approach to statistical analysis of data may all contribute to these contradictory findings.

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

Adolescents

Adolescents were studied in a small number of short-term trials that involved MPH IR or MPH OROS. Studies of atomoxetine included adolescents and are discussed above.

MPH OROS versus MPH IR: A single, very small, *single blinded* study showed MPH OROS superior to MPH IR on some measures of simulated driving skills during tests administered in the late evening or nighttime. No difference was found during other test times. Placebo-controlled trials of MPH IR do not provide indirect evidence of comparative efficacy or tolerability due to heterogeneity in outcome reporting. MPH IR generally was superior to placebo in improving core ADHD symptoms, but was associated with more frequent reports of appetite and sleep disturbances.

MPH OROS versus MAS IR:

One small, crossover study found no significant difference between MPH OROS and MAS IR in self-reported symptom improvement or subjective ratings of driving performance, although MPH OROS was associated with significantly better overall driving performance relative to MAS IR based on testing in a driving simulator.

Observational studies of MPH IR that report functional outcomes found mixed results. In an uncontrolled study of young adult males who had taken MPH as children (mean age at discontinuation of MPH 17 years), fewer suicide attempts were associated with higher dosages of MPH. Emancipated living

situation and level of relationship commitment was associated with response to MPH. Early response to MPH was negatively associated with high school graduation, however. Another uncontrolled follow-up of MPH IR responders reported “improved grades” after 6 – 14 months. Methodological limitations of these studies severely limit the interpretation of these findings.

Long-term safety

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

Adults

Pharmacological treatment of ADHD in adults has not been widely studied. There were no trials of adults with ADHD using DEX IR, lisdexamfetamine, methamphetamine, MPH transdermal, MPH chewable tablet, or oral solution, and some extended release forms of MPH (MPH CD, MPH ER, and MPH SODAS). Direct comparative evidence was limited to one trial of DEX IR versus modafinil. Equivalent rates of patients (48%) responded to both treatments.

Indirect comparisons from placebo-controlled trials suggest that atomoxetine, DEX IR, d-MPH ER, MPH IR, MPH SR, MPH OROS, and MAS IR are all effective as short-term treatments for reducing ADHD symptoms, with response rates ranging from 38% to 78%. One poor-quality trial of MAS XR provided inconclusive evidence of benefit for ADHD symptoms and tolerability. Short-term, randomized controlled trials do not provide clear evidence that any one stimulant is more tolerable than another or that atomoxetine offers an advantageous tolerability profile over stimulants.

There is less evidence that any ADHD drugs improve quality of life, other ADHD-related symptoms (depressed mood, anxiety, and cognition), or driving safety in adults. Improvements in quality of life were found in one uncontrolled trial for each of atomoxetine and MAS XR. MPH IR showed some benefit in reducing ADHD-associated anxiety symptoms and cognitive deficits and in improving driving safety.

We found no studies in adults with ADHD that compared any included ADHD drug to any other or placebo on risk of abuse or illicit diversion outcomes. One study used “preference” as a proxy measure of abuse/diversion and concluded that higher preference of MPH IR over placebo more likely reflected efficacy rather than abuse potential in 10 adults with ADHD.

Subgroups

Race/Ethnicity

Only half of studies reported race or ethnicity data. Studies were primarily conducted in White populations. In a study of lisdexamfetamine, the difference in ADHD-RS-IV mean change score compared to placebo remained statistically significant at the 50mg and 70mg doses, but not the 30mg dose, in a subpopulation of non-Caucasians.

Gender

There is limited evidence of difference in efficacy between boys and girls. In a study of lisdexamfetamine, the difference in ADHD-RS-IV mean change score compared to placebo remained statistically significant at the 50mg and 70mg doses, but not the 30mg dose, in a subpopulation of girls, but this analysis may have been under-powered by a small sample size.

ADHD subtypes

Results from short-term trials suggest that atomoxetine, MPH IR, and MPH OROS all have superior efficacy relative to placebo in children with ADHD, regardless of diagnostic subtype. Findings from 2 placebo controlled trials suggest 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.

Commonly occurring comorbidities

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

Prevalence in studies	AAP estimated prevalence % (range)
Oppositional defiant disorder: 19-66.7%	35.2% (27.2, 43.8)
Conduct disorder: 9-38.5%	25.7% (12.8, 41.3)
Anxiety: 1.4-42%	25.8% (17.6, 35.3)
Depression: 0.7-6.6%	18.2% (11.1, 26.6)

Oppositional defiant disorder: Very limited evidence indicates that atomoxetine was associated with significantly greater improvements in ADHD outcomes than placebo.

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

Learning disabilities: Very limited evidence that response to MPH IR may be moderated in children with mathematics learning disabilities.

Anxiety: No study conducted subgroup analyses of those with comorbid anxiety disorders. In children no differences found in incidence in treatment emergent anxiety with MPH IR compared to DEX IR, MAS IR, MPH SR, MPH OROS, or Atomoxetine. Evidence on development of anxiety with MPH IR vs Placebo is conflicting. No differences in rates of anxiety were found with atomoxetine or modafinil compared to placebo. In adults MPH IR improved anxiety symptoms more than placebo, and MPH OROS resulted in higher rates of anxiety than placebo.

Depression: In adolescents with ADHD and Major Depression, atomoxetine resulted in greater improvement in ADHD symptoms compared to placebo with no statistically significant differences in depression scale scores. In post-hoc analyses of 2 trials in adults, atomoxetine resulted in greater improvements on ADHD symptoms in those with comorbid Major Depression compared to those with no comorbidities.

Bipolar Disorder: MAS IR was found beneficial in improving most ADHD symptoms when added to divalproex in children with bipolar disorders.

Tic disorders: Overall, there was very little evidence across these trials to indicate that MPH IR, DEX IR, or atomoxetine were associated with any tic exacerbation effects. Rather, compared to placebo, MPH IR, DEX IR, and atomoxetine were all consistently associated with improved tic severity and ADHD symptoms.

Substance abuse: In adults placebo-controlled trials of MPH IR or SR focused on adults with ADHD and comorbid cocaine dependence, methadone-maintenance, or general alcohol or drug dependence do not provide clear support for the use of MPH IR or SR in substance abusers with ADHD. Only cross-sectional data are available to compare MPH OROS and other formulations of MPH. These data are inadequate to make conclusions of a comparative nature. In general, less robust treatment response rates were seen in substance abusers with ADHD compared to non-substance abusers (ranges 34% to 47% vs. 38% to 78%), but the placebo response rates in the substance abuser trials were also substantially greater (ranges 21% to 55% vs. 4% to 16%). Neither MPH IR nor SR had any negative effects on substance use outcomes such as cravings, abstinence duration, proportion of days of substance use, amount of money spent on substances, or number of days until first negative urine sample.