Drug Class Review

Pharmacologic Treatments for Attention Deficit Hyperactivity Disorder

Final Update 4 Report
Executive Summary

December 2011

The purpose of the Executive Summary is to summarize key information contained in the Drug Effectiveness Review Project report "Pharmacologic Treatments for Attention Deficit Hyperactivity Disorder", dated December 2011. The full report can be accessed at the following web address: http://derp.ohsu.edu/about/final-document-display.cfm. Readers are advised to review the full report. The purpose of Drug Effectiveness Review Project reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. They are not intended to provide any legal or business advice. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Update 3: October 2009
Update 2: November 2007
Update 1: May 2006
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The literature on this topic is scanned periodically.

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INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) affects children and adults and is treated with both pharmacologic and nonpharmacologic interventions. Multiple drugs are used to treat ADHD. This review evaluates the evidence on how these drugs compare to each other in benefits and harms.

Scope and Key Questions

The purpose of this review is to compare the benefits and harms of different pharmacologic treatments for ADHD. Included drugs are shown in Table 1.

Table 1. Attention deficit hyperactivity disorder drugs and indication

Active ingredient(s)	Referred to in this report as	Trade name	Forms
Amphetamine mixture (amphetamine aspartate; amphetamine sulfate; dextroamphetamine saccharate; dextroamphetamine sulfate)	Mixed amphetamine salts XR	Adderall XR®[a]	Extended-release oral capsule
Atomoxetine hydrochloride	Atomoxetine	Strattera®[b]	Oral capsule
Clonidine hydrochloride	Immediate-release clonidine	Catapres®[b]	Oral tablet
	Extended-release clonidine	Kapvay™[c]	Extended-release oral tablet
Dexmethylphenidate hydrochloride	Immediate-release dexmethylphenidate	Focalin®[b,c]	Oral tablet
	Extended-release dexmethylphenidate	Focalin XR®[c]	Extended-release oral capsule
Dextroamphetamine sulfate	Immediate-release dextroamphetamine	Dexedrine®[b]	Oral tablet[d]
	Sustained-release dextroamphetamine	Dexedrine Spansule®	Sustained-release oral capsule
Guanfacine hydrochloride	Immediate-release guanfacine	Tenex™[b, c]	Oral tablet
	Extended-release guanfacine	Intuniv®[c]	Extended-release oral tablet
Lisdexamfetamine dimesylate	Lisdexamfetamine	Vyvanse®	Oral capsule
Methamphetamine hydrochloride	Methamphetamine	Desoxyn®[b,c]	Oral tablet
Methylphenidate	Methylphenidate transdermal	Daytrana®[c]	Extended-release transdermal film
Methylphenidate hydrochloride	Methylphenidate osmotic-release oral system	Concerta®	Extended-release oral tablet

Active ingredient(s)	Referred to in this report as	Trade name	Forms
	Methylphenidate CD	Metadate CD®c, e	Extended-release oral capsule
	Methylphenidate ER	Metadate ER®c	Extended-release oral tablet
	Methylphenidate chewable Methylphenidate solution	Methylin®b,c	Oral chewable tablet and Oral solution
	Immediate-release methylphenidate	Ritalin®b	Oral tablet
	Methylphenidate long acting	Ritalin LA®c	Extended-release oral capsule
	Multilayer-release methylphenidate	Biphentin®d	Extended-release oral capsule
	Methylphenidate sustained-release	Ritalin SR®b	Extended-release oral tablet
Modafinil	Modafinil	Provigil®c	Oral tablet
		Alertec®d	Oral tablet

Abbreviations: ER, extended release; LA, long acting; SR, sustained release; XR, extended release.
[a] The active ingredient for Adderall XR in Canada is amphetamine aspartate monohydrate.
[b] Or generic equivalent.
[c] Not available in Canada.
[d] Not available in the United States.
[e] Metadate CD® is marketed as Equasym XL® in some countries outside the United States and Canada.

The participating organizations of the Drug Effectiveness Review Project approved the following key questions to guide the review for this report:

1. Evidence on Effectiveness and Efficacy
    a. What is the comparative or noncomparative evidence that pharmacologic treatments for attention deficit disorders improve *effectiveness* outcomes?
        i. Comparisons include individual drugs, as well as between stimulants and nonstimulants, and immediate-release compared with intermediate-release compared with long-acting formulations.
        ii. Noncomparative evidence will be considered for drugs with no comparative evidence.
    b. What is the *comparative* efficacy between any included pharmacologic treatment, between stimulants and nonstimulants, and between immediate-release compared with intermediate-release compared with long-acting formulations, for attention deficit disorders?

2. Tolerability, Serious Adverse Events, Misuse, and Diversion
    a. What is the evidence of *comparative* tolerability of different pharmacologic treatments, between stimulants and nonstimulants, and between immediate-release compared with intermediate-release compared with long-acting formulations, for attention deficit disorders?
    b. What is the evidence of serious adverse events or long-term adverse events associated with use of pharmacologic treatments for attention deficit disorders?
    c. What is the comparative or noncomparative evidence that pharmacologic treatments for attention deficit disorders impact the risk of misuse or illicit diversion in patients with no history of misuse or diversion?
        i. Comparisons include individual drugs, as well as between stimulants and nonstimulants, and immediate-release compared with intermediate-release compared with long-acting formulations.
        ii. Noncomparative evidence will be considered for drugs with no comparative evidence.

3. Evidence in Subgroups of Patients
    a. What is the evidence of benefits and harms of pharmacologic treatments, between stimulants and nonstimulants, and between immediate-release compared with intermediate-release compared with long-acting formulations, for attention deficit disorders in subgroups of patients based on demographics (age, racial groups, gender), socioeconomic status, other medications or therapy, or comorbidities (e.g. tics, anxiety, substance use disorders, disruptive behavior disorders)?
    b. What is the comparative or noncomparative evidence of misuse or illicit diversion of pharmacologic treatments for attention deficit disorders in patients with current or past substance use disorder comorbidities?
        i. Comparisons include individual drugs, as well as between stimulants and nonstimulants, and immediate-release compared with intermediate-release compared with long-acting formulations.
        ii. Noncomparative evidence will be considered for drugs with no comparative evidence.

METHODS

Literature Search

To identify relevant citations, we searched the Cochrane Central Register of Controlled Trials (2nd Quarter 2011), Cochrane Database of Systematic Reviews (2005 to June 2011), MEDLINE (1996 to June l Week 4 20011), and PsycINFO (1806 to June Week 4 2011) using terms for included drugs, indications, and study designs. We also searched reference lists of included studies and reviews, and the US Food and Drug Administration Center for Drug Evaluation and

Research website. Finally, we requested published and unpublished information from the relevant pharmaceutical companies for this review.

Validity Assessment

We assessed the internal validity (quality) of all studies using predefined criteria based on study design (see www.ohsu.edu/drugeffectiveness). We also determined the quality of studies to be *good, fair, or poor* based on predefined criteria. Trials that had a fatal flaw were rated poor quality; trials that met all criteria were rated good quality; the remainder were rated fair quality.

RESULTS AND SUMMARY

We included 404 studies and of these, 60 were identified in the most recent update. Dossiers were submitted by 4 pharmaceutical manufacturers for Update 4: Shire US, Inc (guanfacine and lisdexamfetamine); UCB, Inc, (methylphenidate CD); Shionogi Inc (clonidine); and Ortho-McNeil Janssen Scientific Affairs, LLC (methylphenidate OROS).

There were no *trials* of comparative effectiveness of these drugs for treatment of ADHD. The evidence for comparative efficacy of drugs for treating ADHD was severely limited by small sample sizes, very short durations, and the lack of studies measuring functional or long-term outcomes. Methods of measuring or reporting symptom control varied significantly across studies.

Characterization of ADHD symptomatology across studies was limited due to use of varied or indeterminate diagnostic processes. Minorities and the most seriously ill patients were underrepresented and the small sample sizes of these trials did not allow for statistical analyses of potential effects of these factors. The evidence in preschool-age children is most applicable to white boys, ages 4 to 5, with moderately severe symptoms, and evidence in school-aged children applies best to white boys age 8 to 9 years, with the combined subtype of ADHD, often with comorbid oppositional defiant disorder, conduct disorder, or anxiety. The evidence in adolescents is more diverse; while many studies reflect populations that are mainly white boys (mean age 14) with moderate to severe symptoms, a few studies included populations with close to 50% girls and 50% boys, and higher percentages of non-white teens. Evidence in adults applies best to white men or women in their mid-thirties, but other characteristics were too poorly reported to assess.

The results of this review are summarized in Table 2 below.

Table 2. Summary of the evidence

	Comparison: Overall strength of the evidence	Conclusion
Key Question 1. Benefits		
General: Effectiveness		
	No trials found: Insufficient	No conclusions about comparative effectiveness of different pharmacotherapies for ADHD could be made.
Young children: Efficacy		
	MPH IR: Low	The evidence on efficacy of MPH IR compared with placebo in the short term was inconsistent.
	Atomoxetine: Insufficient	One placebo-controlled trial.

	Comparison: Overall strength of the evidence	Conclusion
Children: Efficacy		
Stimulants		
IR vs. SR formulations	MPH IR vs. MPH SR: Moderate	Studies of MPH IR vs. extended-release formulations in children generally were unable to identify significant differences in symptom improvement. Studies of MPH IR and MPH OROS were conflicting; a difference was not found in double-blind studies while open-label studies indicated greater improvement with MPH OROS on some measures.
SR vs. SR formulations	MPH SR vs. MPH SR formulations: Low	Limited evidence from 2 small crossover studies suggested that MPH LA was superior to MPH OROS on some, but not all efficacy outcomes. Limited evidence suggested that MPH CD was superior to MPH OROS on outcomes in the morning; they had similar effects in the afternoon; and MPH OROS was superior in the evening. d-MPH ER was superior to MPH OROS at 2 to 6 hours post-dose and MPH OROS was superior at 10 to 12 hours in 1 trial.
IR vs. IR	DEX IR vs. MPH IR: High	The body of evidence clearly indicated no difference in efficacy between DEX and MPH IR.
	MAS IR vs. MPH IR: Moderate	MAS IR was superior to MPH IR on a few efficacy outcome measures in 2 trials but clear evidence of superiority was lacking.
	DEX IR vs. DEX ER vs. MAS: Low	Evidence on the comparison of DEX IR vs. DEX SR vs. MAS may suggest that measures made in the morning show DEX IR superior to DEX SR, and afternoon measures show DEX SR superior to MAS.
	Modafinil vs. MPH IR: Moderate	Based on 1 trial, modafinil was similar to MPH IR in efficacy
	Dexmethylphenidate: Insufficient	Only placebo-controlled evidence was found.
Transdermal MPH	MTS vs. MPH OROS: Moderate MTS vs. MPH IR: Low	Based on 1 trial each, MTS had similar efficacy compared with MPH OROS or MPH IR.
Lisdexamfetamine	Moderate	Lisdexamfetamine was comparable to MAS XR on average SKAMP-DS scores and superior to placebo on same, as well as on ADHD rating scale IV mean changes.
Atomoxetine	Atomoxetine vs. MPH IR: Low	Limited evidence suggested a lack of a difference in efficacy compared with MPH IR.
	Atomoxetine vs. MAS XR: Low	Limited evidence suggested that MAS XR is superior to atomoxetine on most efficacy measures.
	Atomoxetine vs. MPH OROS: Moderate	MPH OROS was superior to atomoxetine in response rates.
Clonidine	Clonidine IR vs. MPH IR: Moderate	Clonidine IR was found to be similar to MPH IR on teacher assessment of ADHD symptoms, but other findings were inconsistent.
	Clonidine ER: Insufficient	No head-to-head evidence. Placebo-controlled trials indicated modest benefit as add-on or monotherapy.
Guanfacine	Guanfacine IR: Low	No head-to-head evidence. Indirect evidence was insufficient to make conclusions.
	Guanfacine XR: Insufficient	No head-to-head evidence. Placebo-controlled trials indicated modest benefit up to 8 hours post-dose.
Adolescents: Efficacy		
	MPH OROS vs. MAS IR: Moderate	Effectiveness outcomes: NR Short-term improvements in core ADHD symptoms: No

	Comparison: Overall strength of the evidence	Conclusion
		differences. Other: MPH OROS > MAS IR on overall simulator driving performance.
	MPH IR vs. MPH OROS: Moderate	Functional capacity: NR Short-term improvements of core ADHD symptoms: NR. Driving performance: MPH OROS > MPH IR in evening and at night.
	Placebo-controlled studies of MPH IR and Lisdexamfetamine: Insufficient	Functional capacity: NR Short-term improvements of core ADHD symptoms.
Adults: Efficacy		
	Switch to MPH OROS vs. continuing on MPH IR: Low	No significant difference in maintenance of response at 6 weeks.
	IR guanfacine vs. DEX IR: Low	No significant difference in mean total symptom score of the DSM-IV ADHD Behavior Checklist for Adults.
	Modafinil vs. DEX IR: Low	No significant difference in response rates.
	Placebo-controlled evidence of atomoxetine, DEX IR, d-MPH XR, lisdexamfetamine, MPH ER, MPH IR, MPH OROS, MAS IR, MAS XR: Insufficient	Compared with placebo, response rates were significantly greater for all. *Other efficacy outcomes:* Atomoxetine: Not consistently significantly superior to placebo in improving quality of life and driving performance outcomes. MPH IR: Consistently superior to placebo in improving driving performance outcomes; not significantly superior to placebo on 5 of 6 sleep outcomes in 1 trial. MAS XR: Superior to placebo in improving overall simulated driving performance outcomes in 1 trial. MPH OROS: Superior to placebo in improvements on some parenting skill measures in 1 trial.
	Methylphenidate transdermal system: Insufficient	No conclusions could be drawn based on the single included poor-quality, placebo-controlled trial.
Key Question 2. Safety		
2b. Short-term trial evidence		Very few studies reported methods for assessing adverse events a priori.
Young children		
	1 placebo-controlled trial of MPH: Insufficient	Indirect comparisons cannot be made; MPH associated with higher rates of adverse events than placebo.
Children		
	Moderate	Very few studies reported methods for assessing adverse events a priori.
	MPH IR vs. MPH SR	There is no evidence of a difference in adverse events between IR and SR formulations.
	MPH SR vs. MPH SR formulations	No differences in adverse events were found, except that MPH OROS had higher rates of insomnia and decreased appetite than MPH CD.
	MTS vs.MPH IR or OROS	No differences found in overall adverse events.
	DEX vs. MPH IR	Limited evidence from short-term trials suggested that weight loss is greater with DEX than MPH IR.
	MAS vs. MPH IR	Very limited evidence suggested that twice daily dosing of MAS led to higher rates of loss of appetite and sleep trouble.
	DEX IR vs. DEX ER vs. MAS	Transient weight loss was greater with MAS and DEX SR than with DEX IR.
	Lisdexamfetamine	No differences in adverse event rates between lisdexamfetamine vs. MAS XR.

	Comparison: Overall strength of the evidence	Conclusion
	Atomoxetine vs. MPH IR, MPH OROS, MAS XR	Vomiting: atomoxetine rates 12% to 13%, approximately 3 times greater than rates for MPH IR or MAS XR. Somnolence: atomoxetine rates 6% to 26%, which was 3 to 4 times greater than MPH OROS and MPH XR; 7 times greater than MPH IR. Nausea and anorexia: greater with atomoxetine than MPH IR in 1 trial. Insomnia: 13% MPH OROS, 28% MAS XR vs. 7% atomoxetine.
	Clonidine IR vs. MPH IR: Moderate	Sedation: 42% with clonidine, 14% MPH IR. 28% reported as moderate to severe, may improve over time.
	Clonidine ER: Insufficient	No head-to-head evidence. In placebo-controlled trials somnolence and fatigue were the most common adverse events with clonidine ER and peaked at 2 weeks. Dose-response in withdrawal due to adverse events, flexible dosing improved discontinuation rate.
	Guanfacine XR: Insufficient	No head-to-head evidence. Placebo-controlled trials indicated somnolence, fatigue, and headache most common adverse events with guanfacine XR, dose-response in withdrawals due to adverse events; flexible dosing did not resolve the difference compared with placebo.
Adults		
	Switch to MPH OROS vs. continuing on MPH IR: Insufficient	Difference in proportions of patients with no adverse events was unclear due to serious methodological limitations of the trial.
	IR guanfacine vs. DEX IR: Low	No significant difference in number of adverse events. Withdrawals due to adverse events were not reported.
	Modafinil vs. DEX IR: Low	No withdrawals due to adverse events. No significant differences in insomnia or appetite suppression.
	Placebo-controlled evidence on atomoxetine, DEX IR, d-MPH XR, lisdexamfetamine, MPH ER, MPH IR, MPH OROS, MAS IR, MAS XR: Insufficient	Indirect meta-analysis of harms was not undertaken due to concerns about sparse data and heterogeneity in outcome measurement methods and trial duration. Conclusions about comparisons to placebo were also limited by a scarcity of statistical analyses.
	Methylphenidate transdermal system: Insufficient	No conclusions could be drawn based on the single included poor-quality, placebo-controlled trial.
2b. Long-term safety: Observational studies		
Mixed populations, primarily children		
	Suicidal behavior/suicide: Low	Increased risk with atomoxetine compared with placebo (risk difference, 0.52; 95% CI, 0.12 to 0.91) based on meta-analysis. Time to onset of behavior 9 to 32 days. Overall rate of suicidal behavior and ideation was 0.44% in this study compared with 1.7% in another meta-analysis of longer-term duration.
	Sudden cardiac death: Low	Evidence was inconsistent. Stimulant medications, particularly MPH IR, may have increased risk compared with nonuse, but comparative evidence was insufficient to make conclusions.

	Comparison: Overall strength of the evidence	Conclusion
	Cardiac events: Low	Emergency room visits for cardiac causes were not found statistically significantly different between current users of methylphenidate products and amphetamine products. Former use of these products also resulted in a nonsignificant finding. In adults, risk of stroke or TIA not found different between atomoxetine and stimulants.
	Height: Moderate	Evidence on DEX IR compared with MPH IR was inconsistent. Evidence suggested that MPH IR and MPH OROS adversely impacts expected height gain at least during the first 12 months of treatment. Limited evidence suggested that height changes resulting from atomoxetine were similar to those reported with MPH IR and were also transient, with peak impact at 18 months, but the difference resolved by 2 years.
	Weight: Moderate	DEX IR was associated with significantly greater suppression of weight gain than MPH IR in the first 1-2 years, but the difference resolved by the second year. Higher relative doses of DEX IR may have influenced findings. Noncomparative evidence indicated 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. Limited evidence suggested that weight changes resulting from atomoxetine were similar to those reported with MPH IR, and were also transient, but longer lasting - resolving by 5 years of treatment.
	Tics, seizures, cardiovascular adverse events, injuries, and suicidal behavior	No comparative evidence.
2c. Abuse/misuse/diversion		
Abuse	Low	Stimulant use during childhood was not associated with alcohol abuse later. May be protective against or delay nicotine dependence, but comorbid conduct disorder may be a significant confounder. Stimulant use may protect against later substance abuse, but again comorbid conduct disorder may be a confounder. Evidence on misuse and diversion reported wide ranges of prevalence with no comparative data.
Misuse	Low	Children and adolescents: 5% to 8% College students: 5% to 35% (26% to 63% for enhancement of academic performance) Adults: 29% Misuse of methylphenidate associated with illicit use of cocaine or amphetamines

	Comparison: Overall strength of the evidence	Conclusion
Diversion	Low	Children and adolescents: 15% to 24% gave them away 7% to 19% sold them 4% to 6% had them stolen College students: 26% reported selling or giving medication away. Of these: 70.5% Amphetamine/dextroamphetamine 37% Methylphenidate 39.1% methylphenidate OROS Adults: 44% reported diversion 97% gave it away 17% sold it 14% both Diversion is associated with younger age both at the time of the survey and at the time methylphenidate was first prescribed.
Key Question 3. Subgroups		
Children	Low	
	ADHD subtypes or severity	Atomoxetine, MPH IR, and MPH OROS had superior efficacy relative to placebo in children with ADHD, regardless of diagnostic subtype. There was inconsistency in evidence that response may be better in those with combined or inattentive subtype.
	Race/ethnicity	Children: Most trials were conducted in primarily White populations. Ethnicity/race was only reported in one half of studies. No analyses based on race. Very limited evidence suggested MPH IR in African American boys results in response rates similar to other populations studied. Evidence from subgroup analysis of a placebo-controlled trial suggested that effects of lisdexamfetamine may be less robust in non-Caucasian children. Adults: Significantly greater reduction of ADHD Rating Scale scores with methylphenidate OROS vs. placebo subgroups of white and non-white patients
	Gender	Subgroup analyses based on gender were limited. Evidence from subgroup analysis of a placebo-controlled trial suggested that lisdexamfetamine may be less efficacious in girls. Exploratory analysis indicated atomoxetine may have better response on emotional regulation items in women than men.
Common comorbidities	Low	Head-to-head trials provided no evidence in subgroups of interest.

	Comparison: Overall strength of the evidence	Conclusion
	Anxiety	Children: The rate of anxiety being reported as an adverse event did not differ statistically significantly in head-to-head comparisons of: MPH IR compared with IR DEX, MAS, MPH SR, MPH OROS, or atomoxetine. Limited evidence suggested that MPH IR is somewhat less effective in reducing ADHD symptoms in children with baseline anxiety symptoms compared with those without these symptoms. Atomoxetine was superior to placebo in improving ADHD and anxiety symptoms in children with anxiety at baseline. Adults: In adults with ADHD and comorbid social anxiety disorder, there was significantly greater improvement in ADHD and anxiety symptoms for atomoxetine vs. placebo. MPH IR was generally significantly more effective than placebo in improving ADHD and anxiety symptoms in patients with ADHD but no diagnosis of anxiety disorder.
	Tic disorders	No consistent evidence that atomoxetine, DEX IR, or MPH IR increased tic severity or frequency compared with placebo. MPH IR showed a benefit on ADHD symptoms compared with placebo. MPH IR and IR clonidine both improved ADHD symptom scores and were not found to significantly differ from each other in children with Tourette's disorder. Guanfacine resulted in improvement in tic severity relative to placebo in children with tic disorders (58.8% = Tourette's disorder).
	Oppositional defiant disorder	Very limited evidence suggested that atomoxetine is beneficial on most ADHD outcomes compared with placebo. Guanfacine XR was superior to placebo in improving both ADHD and oppositional defiant symptoms compared with placebo.
	Bipolar disorder	Very limited evidence suggested that MAS IR or MPH IR have benefit on most ADHD outcomes compared with placebo. MPH IR did not improve ADHD symptoms when added to aripiprazole in children with comorbid ADHD and bipolar disorder.
	Substance abuse/substance use disorder	Adolescents: MPH SODAS was superior to placebo in reducing ADHD symptoms in teens with SUD. No significant treatment effect on drug use. Atomoxetine was not superior to placebo in improving ADHD symptoms in teens with SUD; number of days with abuse also was not affected. Adults: Substance use disorder: Atomoxetine and lisdexamfetamine both had limited evidence of significantly improving ADHD symptoms vs. placebo in adults, whereas no significant benefits were found with IR MPH and SR MPH vs. placebo.

Abbreviations: ADHD, attention deficit hyperactivity disorder; d-MPH, dexmethylphenidate; DEX, dextroamphetamine; ER, extended release; IR, immediate release; LA, long acting; MAS, mixed amphetamine salts; MPH, methylphenidate; NR, not reported; SR, sustained release; SUD, substance abuse disorder; TIA, transient ischemic attack.

CONCLUSION

Evidence on the comparative effectiveness of drugs to treat ADHD was insufficient. Evidence on the comparative efficacy in children and adolescents was moderate to low strength and indicated very few differences among the drugs in improving symptoms or in adverse event rates. Sustained-release formulations of stimulants showed benefit over comparators at specific times of day depending on the pharmacokinetics of the specific formulation, but overall differences were not found. Atomoxetine (a nonstimulant) was not found superior to some extended-release stimulant products. Atomoxetine resulted in higher rates of vomiting and somnolence, similar rates of nausea and anorexia, and lower rates of insomnia than stimulants. Extended-release formulations of other nonstimulant drugs (clonidine, guanfacine) have no comparative evidence to date. Immediate-release clonidine was similar to immediate-release methylphenidate.

Comparative evidence in adults provided low-strength evidence of no significant differences in efficacy between switching to methylphenidate OROS compared with continuing with immediate-release methylphenidate or between immediate-release guanfacine or modafinil compared with immediate-release dextroamphetamine. Low-strength evidence found no significant differences between immediate-release guanfacine or modafinil compared with immediate-release dextroamphetamine.

Evidence on the risk of serious harms was primarily indirect, and indicated atomoxetine has increased risk of suicidal behavior compared with placebo. Differences in risk for sudden death was unclear, cardiac adverse events were not different between stimulants, and cerebrovascular adverse events in adults did not differ between stimulants and atomoxetine. Dextroamphetamine immediate-release caused more inhibition of growth than other stimulants, but the difference was influenced by dose and resolved after 2 years of treatment. Atomoxetine caused similar inhibition of weight gain that lasted up to 5 years. Evidence on abuse, misuse, and diversion was limited, but indicated that stimulant use during childhood is not associated with increased risk of substance use later. Misuse and diversion rates varied by age and were highest among college students, and rates of diversion were highest with amphetamine-based products but similar among methylphenidate products. Evidence of effects in important subgroups of patients with ADHD (e.g. comorbid anxiety) was not comparative.