Drug Class Review

Pharmacologic Treatments for Attention Deficit Hyperactivity Disorder

Final Update 5 Report

Executive Summary

July 2015

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. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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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 A.

Table A. Attention deficit hyperactivity disorder drugs included in this review

Generic Name	Trade name	Forms
Mixed amphetamine salts	Adderall XR®	Extended-release oral capsule
Atomoxetine hydrochloride	Strattera®	Oral capsule
Clonidine hydrochloride	Catapres®, Catapres TTS	Oral tablet
	Kapvay™	Extended-release oral tablet
Dexmethylphenidate hydrochloride	Focalin®	Oral tablet
	Focalin XR®	Extended-release oral capsule
Dextroamphetamine sulfate	Dexedrine®	Oral tablet
	Dexedrine Spansule®	Sustained-release oral capsule
Guanfacine hydrochloride	Intuniv®	Extended-release oral tablet
	Tenex™	Oral tablet
Lisdexamfetamine dimesylate	Vyvanse®	Oral capsule
Methamphetamine hydrochloride	Desoxyn®	Oral tablet
Methylphenidate	Daytrana®	Extended-release transdermal film
Methylphenidate hydrochloride	Concerta®	Extended-release oral tablet
	Metadate CD®	Extended-release oral capsule
	Metadate ER®	Extended-release oral tablet
	Methylin®	Oral chewable tablet and solution
	Methylin ER®	Extended-release oral tablet
	Quillivant™ XR	Extended-release oral suspension
	Ritalin®	Oral tablet
	Ritalin LA®	Extended-release oral capsule
	Ritalin-SR®	Extended-release oral tablet
Modafinil	Provigil®	Oral tablet
Armodafinil	Nuvigil	Oral tablet

Abbreviations: CD, controlled delivery; ER or XR, extended release; LA, long acting; SR, sustained release; TTS, transdermal therapeutic system

The participating organizations of the Drug Effectiveness Review Project (DERP) approved the following key questions to guide this review:

1. What is the comparative evidence that pharmacologic treatments for attention deficit disorders differ in effectiveness or efficacy outcomes?
2. What is the comparative evidence that pharmacologic treatments for attention deficit disorders differ in harms (tolerability, serious adverse events, abuse/misuse/diversion) outcomes?
3. What is the comparative evidence that pharmacologic treatments for attention deficit disorders differ in effectiveness, efficacy or harms outcomes in subgroups of patients

based on demographics, socioeconomic status, other medications or therapy, or co-morbidities (e.g. tics, anxiety, substance use disorders, disruptive behavior disorders)?

METHODS

To identify relevant citations, we searched the Cochrane Central Register of Controlled Trials (February 2015), Cochrane Database of Systematic Reviews (2005 to February 2015), Ovid MEDLINE® and Ovid OLDMEDLINE® (1946 to March Week 5 2015), Ovid MEDLINE® In-Process & Other Non-Indexed Citations (April 01, 2015) and PsycINFO (1806 to March Week 5 2015) using terms for included drugs, indications, and study designs. We attempted to identify additional studies through searches of reference lists of included studies and reviews, including the U.S. Food and Drug Administration Center for Drug Evaluation and Research website for medical and statistical reviews of individual drug products. Finally, we requested dossiers of published and unpublished information from the relevant pharmaceutical companies for this review. All received dossiers were screened for studies or data not found through other searches.

We assessed the internal validity (quality) of trials based on predefined DERP criteria based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intent-to-treat analysis for trials, and similar aspects for observational studies.

RESULTS

Overall, we identified a total of 1,022 citations from searching electronic databases, pharmaceutical manufacturer dossier submissions, reviews of reference lists, and hand searches. By applying the eligibility and exclusion criteria to titles and abstracts of all identified citations, we obtained full-text copies of 121 citations. After re-applying the criteria for inclusion, we ultimately included 15 publications, including 8 head-to-head trials in 12 publications and 3 observational studies. A total of 126 publications are included in this review, reflecting studies identified in the current update and those identified in prior versions of this report. Dossiers were submitted by 2 pharmaceutical manufacturers for Update 5, Boehringer-Ingelheim (clonidine, Catapres® and Catapres TTS®) and Janssen (methylphenidate HCl, Concerta®).

Key Findings

Effectiveness

- No comparative evidence on effectiveness outcomes in direct head-to-head comparisons of drugs to treat ADHD was found.

Efficacy and Tolerability

Young children (preschool age; 3-5 years)

Comparative evidence in young children was not found. Placebo-controlled evidence was mixed on efficacy outcomes. Adverse events occurred significantly more often with methylphenidate than with placebo. Over longer-term treatment, some resolved but others did not.

Children (elementary school age; 6-12 years)

Stimulants

Immediate-release compared with extended-release formulations. The evidence regarding immediate-release methylphenidate compared with methylphenidate OROS was conflicting, with 2 double-blind trials unable to identify differences, while 2 open-label studies found that methylphenidate osmotic-release oral system (OROS) resulted in greater improvements on some but not all assessments.

Limited evidence was available for the comparisons of immediate-release methylphenidate to other extended-release formulations. Overall, the studies were unable to identify differences between methylphenidate sustained-release (SR) and immediate-release methylphenidate, and methylphenidate controlled-delivery (CD) was found to be noninferior to immediate-release methylphenidate. Significantly more children taking lisdexamfetamine achieved response (18% more) and had greater improvement in ADHD Rating Scale (ADHD-RS) scores at 7 weeks than those taking methylphenidate OROS (difference -5.6 points). Parent ratings found lisdexamfetamine had better scores in the morning, afternoon, and evening. Overall adverse event rates did not differ, but there were slightly more discontinuations with lisdexamfetamine. More children had anorexia, decreased appetite, decreased weight, insomnia, and nausea with lisdexamfetamine, and headaches and nasopharyngitis with methylphenidate OROS.

Sustained-release compared with sustained-release formulations. Limited evidence from 2 small crossover studies suggested that methylphenidate long-acting (LA) was superior to methylphenidate OROS on some, but not all efficacy outcomes. However, these results should be interpreted with caution until higher quality evidence is available. Methylphenidate CD was better than methylphenidate OROS in the morning, similar in the afternoon, and methylphenidate OROS was superior in the evening. Methylphenidate OROS had statistically significantly higher rates of insomnia and decreased appetite than methylphenidate CD. Limited evidence from 2 similar trials indicated that dexmethylphenidate extended-release (ER) resulted in better response from 0.5 to up to 6 hours post dose compared with methylphenidate OROS (primary outcome measure). Methylphenidate OROS resulted in better scores later in the day; from 10 to 12 hours post dose. Math scores followed a similar pattern. Limited evidence of no difference in response rates or symptom improvement was found between dexmethylphenidate ER and mixed amphetamine salts extended-release (XR) after 8 weeks. There was no evidence of a difference in adverse events between immediate-release and sustained-release formulations. Differences were not found between lisdexamfetamine and mixed amphetamine salts XR using the Swanson, Kotkin, Agler, M-Flynn, and Pelham Deportment Scale (SKAMP-DS) scores in a simulated classroom setting, or using the Clinical Global Impressions – Improvement (CGI-I) response rates after 1 week. Adverse events were reported to not be different, but data were not reported.

Immediate-release compared with immediate-release formulations. For dextroamphetamine compared with methylphenidate, the body of evidence clearly indicated no difference in efficacy between immediate-release dextroamphetamine and immediate-release methylphenidate. Evidence from short-term trials and observational studies suggested that weight loss was greater with immediate-release dextroamphetamine than immediate-release methylphenidate. For mixed amphetamine salts compared with methylphenidate, immediate-release mixed amphetamine salts were superior to immediate-release methylphenidate on a few efficacy outcome measures in 2 trials, but clear evidence of superiority was lacking. For modafinil compared with methylphenidate, differences were not found between modafinil and immediate-release methylphenidate over 6 weeks. For dextroamphetamine compared with mixed amphetamine salts, limited evidence suggested that immediate-release dextroamphetamine was superior to dextroamphetamine SR in the morning, and that dextroamphetamine SR was superior to mixed amphetamine salts in the afternoon. Transient weight loss was greater with mixed amphetamine salts and dextroamphetamine SR than with immediate-release dextroamphetamine. For transdermal methylphenidate compared with methylphenidate OROS, methylphenidate transdermal system was found to have similar efficacy to methylphenidate OROS (over 7 weeks starting 4 hours after administration) and immediate-release methylphenidate (over 12 hours in a simulated classroom setting, starting 30 minutes after dosing). Differences in adverse events were not found between methylphenidate transdermal system and immediate-release methylphenidate.

Nonstimulants

Atomoxetine. Evidence from 2 trials suggested that atomoxetine was associated with efficacy outcomes similar to immediate-release methylphenidate. Methylphenidate OROS had higher response rates than atomoxetine (56% methylphenidate OROS and 45% atomoxetine; P=0.02) and greater reduction in ADHD-RS scale score after 4 to 6 weeks. Lisdexamfetamine resulted in clinical improvement 9 days earlier and more patients had achieved clinical response (82% versus 64%), and had greater change in the ADHD-RS score (difference -6.5) at 9 weeks than atomoxetine. Mixed amphetamine salts XR was found superior to atomoxetine on most measures of efficacy in a simulated classroom study.

Atomoxetine was associated with significantly higher rates of vomiting, somnolence, nausea, and anorexia than stimulants, depending on the specific drug comparison. Incidence of vomiting (12% to 13%) was approximately 3 times greater than immediate-release methylphenidate or mixed amphetamine salts XR. Incidence of somnolence (6% to 26%) was 3 to 4 times greater than methylphenidate OROS and mixed amphetamine salts XR. Methylphenidate OROS and mixed amphetamine salts XR caused higher rates of insomnia than atomoxetine in 2 trials (7% atomoxetine, 13% methylphenidate OROS, 28% mixed amphetamine salts XR).

Clonidine. Current evidence did not clearly identify a difference in improvement of ADHD symptoms between immediate-release clonidine and immediate-release methylphenidate in children with ADHD (both with comorbid Tourette's disorder and without). Caution is suggested in interpreting these results due to inconsistency in some outcomes. Immediate-release clonidine resulted in higher rates of sedation (42%) than immediate-release methylphenidate (14%), with 28% reporting the sedation to be moderate or severe. Evidence indicates that somnolence may improve with time. No head-to-head evidence was available on extended-release clonidine

Guanfacine. No head-to-head evidence was available on immediate-release guanfacine. Extended-release guanfacine had superior reduction in ADHD-RS scores at 6 weeks, compared with atomoxetine (difference -5.1), but no difference in the proportion clinically improved (RR 1.15; 95% CI, 0.93 to 1.43) based on a single study. Adverse event rates did not differ between the drugs.

Adolescents

Methylphenidate OROS resulted in better simulated driving scores than immediate-release methylphenidate (only in the late evening or nighttime) and immediate-release mixed amphetamine salts.

Adults

Four small short-term trials provided low-strength evidence of similar effects on ADHD symptoms after 2 to 6 weeks for the comparisons between immediate-release dextroamphetamine and either modafinil or guanfacine, between continuing with immediate-release methylphenidate or switching to methylphenidate OROS, or between immediate-release compared with extended-release mixed amphetamine salts. Those same four trials provided low-strength evidence of no difference in harms, except for the comparison of immediate-release and extended-release mixed amphetamine salts, for which evidence was insufficient to draw conclusions on harms because there were no comparisons between drugs.

Long-Term Safety

Cardiovascular deaths and events

For children, 2 retrospective cohort studies (in 3 publications) provided low-strength evidence of no significant differences between methylphenidate or amphetamine products in the rate of emergency department visits for cardiac reasons or between methylphenidate, amphetamines or atomoxetine in sudden death or ventricular arrhythmia. For adults, 2 retrospective cohort studies provided low-strength evidence of similar risk of stroke or transient ischemic attack (TIA) for atomoxetine compared with stimulants and 1 retrospective cohort provided low-strength evidence of similar risk of sudden cardiac death for atomoxetine compared with stimulants.

Growth

There was moderate-strength evidence that immediate-release dextroamphetamine led to greater height and weight suppression than immediate-release methylphenidate within the first few years, but the differences resolve in later years. There was moderate-strength evidence that immediate-release methylphenidate and mixed amphetamine salts had similar effects on height and weight at 3 years.

Other long-term safety outcomes

Evidence on longer-term insomnia, appetite suppression and headaches was low strength. Insomnia and decreased appetite were not statistically significantly different among immediate-

release methylphenidate, methylphenidate OROS, mixed amphetamine salts, mixed amphetamine salts XR, and atomoxetine. Atomoxetine had lower rates of headache compared with mixed amphetamine salts XR (0% and 12%; *P*=0.001), immediate-release mixed amphetamine salts (0% and 11%; *P*=0.001), or methylphenidate OROS (0% and 10%; *P*=0.002). There was no comparative evidence on other long-term safety outcomes, including tics, seizures, cardiovascular adverse events, injury frequency, and hepatotoxicity.

Abuse/Misuse/Diversion

Survey data suggested that lifetime nonmedical use was more frequent with immediate-release methylphenidate or dextroamphetamine compared with mixed amphetamine salts and that amphetamine/dextroamphetamine had the highest rate of diversion.

Subgroups

No head-to-head evidence was found for demographic, socioeconomic, or co-intervention subgroups. Differences in the rate of anxiety as an adverse event did not differ statistically significantly between immediate-release methylphenidate and immediate-release dextroamphetamine, mixed amphetamine salts, methylphenidate SR, methylphenidate OROS, or atomoxetine. In children with Tourette's disorder, immediate-release methylphenidate and immediate-release clonidine had similar effects on ADHD symptoms.

SUMMARY

Table B. Summary of the evidence

Key Question Category	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 and Atomoxetine	Insufficient	Only placebo-controlled trials found. No comparative evidence.
Children: Efficacy		
Stimulants		
IR vs. SR formulations	MPH IR vs. MPH SR: Low	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. Lisdexamfetamine was comparable to MAS XR on average SKAMP-DS scores in simulated classroom, and clinician perception of improvement. Lisdexamfetamine superior to MPH-OROS in response and change in symptom scores and parent scores (morning, afternoon, evening).

Table B. Summary of the evidence

Key Question Category	Comparison: Overall strength of the evidence	Conclusion
SR vs. SR formulations	MPH SR vs. MPH SR formulations: Low	Limited evidence that MPH LA was superior to MPH OROS on some, but not all efficacy outcomes. Limited evidence that MPH CD was superior to MPH OROS on outcomes in the morning; similar effects in the afternoon; and MPH OROS was superior in the evening. d-MPH ER was superior to MPH OROS at 0.5 to 6 hours post dose and MPH OROS was superior at 10 to 12 hours (2 small trials). d-MPH-ER was no found different to MAS XR in efficacy at 8 weeks.
IR vs. IR	DEX IR vs. MPH IR: Moderate	The body of evidence clearly indicated no difference in efficacy between DEX and MPH IR.
	MAS IR vs. MPH IR: Low	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: Low	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: Low MTS vs. MPH IR: Low	Based on 1 trial each, MTS had similar efficacy compared with MPH OROS or MPH IR.
Nonstimulants		
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 was superior to atomoxetine on most efficacy measures.
	Atomoxetine vs. MPH OROS: Moderate	MPH OROS was superior to atomoxetine in response rates.
	Atomoxetine vs. lisdexamfetamine: Low	Lisdexamfetamine resulted in clinical improvement 9 days earlier; more patients had achieved response at 9 weeks (82% versus 64%), and had greater change in the ADHD-RS score (difference -6.5) than atomoxetine.
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.
Guanfacine	Guanfacine IR: Insufficient	No head-to-head evidence.
	Guanfacine XR: Low	Guanfacine had superior reduction in ADHD-RS scores at 6 weeks, compared with atomoxetine (difference -5.1), but no difference in the proportion clinically improved (RR 1.15; 95% CI, 0.93 to 1.43).
Adolescents: Efficacy		
	MPH OROS vs. MAS IR: Moderate	Effectiveness outcomes: NR Short-term improvements in core ADHD symptoms: No differences. Other: MPH OROS > MAS IR on overall simulator driving performance.
	MPH IR vs. MPH OROS: Low	Short-term improvements of core ADHD symptoms: NR. Driving performance: MPH OROS > MPH IR in evening and at night.

Table B. Summary of the evidence

Key Question Category	Comparison: Overall strength of the evidence	Conclusion
Adults: Efficacy		
	Immediate-release dextroamphetamine vs. either modafinil or guanfacine; continuing with immediate-release methylphenidate or switching to methylphenidate OROS; immediate-release compared with extended-release mixed amphetamine salts: Low	Similar effects on ADHD symptoms after 2 to 6 weeks.
Key Question 2. Harms		
Young children		
	MPH: Insufficient	No head-to-head evidence.
Children		
	MPH IR vs. MPH SR	There was no evidence of a difference in adverse events between IR and SR formulations for any comparison.
	MPH SR vs. MPH SR formulations	No differences in adverse events, 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 was greater with DEX than MPH IR.
	MAS vs. MPH IR	Limited evidence 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 greater with MAS and DEX SR.
	Lisdexamfetamine vs. MPH OROS	More discontinuations due to adverse events with lisdexamfetamine (4.5% vs. 1.8%) than with methylphenidate OROS. More insomnia, nausea and decreased appetite and weight with lisdexamfetamine; more headaches and nasopharyngitis with MPH OROS.
	Atomoxetine vs. MPH IR, MPH OROS, MAS XR, lisdexamfetamine	Vomiting: atomoxetine rates 12% to 13%, approximately 3 times > MPH IR or MAS XR. Somnolence: atomoxetine rates 6% to 26%, 3 to 4 times > lisdexamfetamine, MPH OROS and MPH XR. Nausea and anorexia: > atomoxetine than MPH IR in 1 trial. Insomnia: 13% MPH OROS, 28% MAS XR, 12% lisdexamfetamine vs. 6-7% 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.
	Guanfacine ER vs. atomoxetine: Low	No differences in overall, serious or discontinuations due to adverse events. One case of syncope with guanfacine ER.
Adults		

Table B. Summary of the evidence

Key Question Category	Comparison: Overall strength of the evidence	Conclusion
	Immediate-release dextroamphetamine vs. modafinil or guanfacine; methylphenidate or switching to methylphenidate OROS: Low Immediate-release compared with extended-release mixed amphetamine salts: Insufficient (no direct comparison)	Similar effects on AE outcomes after 2 to 6 weeks.
Long-term safety: Observational studies		
Mixed populations, primarily children		
	Sudden cardiac death: Low	In children, similar risk of sudden death or ventricular arrhythmia for atomoxetine and stimulants. In adults, similar risk of sudden cardiac death for atomoxetine compared with stimulants
	Cardiac events: Low	Emergency room visits for cardiac causes were similar in current users of methylphenidate products and amphetamine products. Former use of these products also resulted in a nonsignificant finding. In adults, similar risk of stroke or TIA for atomoxetine and stimulants
	Height: Moderate	Evidence on DEX IR compared with MPH IR was inconsistent. Evidence suggested that MPH IR and MPH OROS adversely impacted expected height gain at least during the first 12 months of treatment.
	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.
	Tics, seizures, injuries, and suicidal behavior	No comparative evidence.
Abuse/Misuse/Diversion		
Abuse, misuse, diversion	Low	Survey data suggested that lifetime nonmedical use was more frequent with immediate-release methylphenidate or dextroamphetamine compared with mixed amphetamine salts and that amphetamine/dextroamphetamine had the highest rate of diversion
Key Question 3. Subgroups		
	ADHD subtypes or severity: insufficient	No head-to-head evidence
	Demographics: insufficient	No head-to-head evidence
Common comorbidities	Anxiety: Low	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.
	Tic disorders: Low	Children: 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.

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.

CONCLUSIONS

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 with few differences among the drugs in improving symptoms or in adverse event rates in the short-term. Comparisons of immediate-release and extended release stimulants found few differences; low-strength evidence suggested that lisdexamfetamine may be superior to methylphenidate OROS. Comparisons of sustained-release stimulant formulations showed differences at specific times of day depending on the pharmacokinetics, but overall differences were not found. Atomoxetine was not found superior to immediate-release methylphenidate, had lower efficacy than methylphenidate OROS, mixed amphetamine salts XR, lisdexamfetamine, and extended-release guanfacine, but resulted in higher rates of vomiting and somnolence, similar rates of nausea and anorexia, and lower rates of insomnia than stimulants. Immediate-release clonidine was similar to immediate-release methylphenidate. In adults, low-strength comparative evidence found similar efficacy for: immediate-release dextroamphetamine and modafinil or guanfacine; continuing immediate-release methylphenidate or switching to methylphenidate OROS; and immediate- versus extended-release mixed amphetamine salts. Differences in risk for sudden death and other cardiac events were not found among stimulants or between atomoxetine and stimulants. Dextroamphetamine immediate-release caused more inhibition of growth than other stimulants, with a dose-response, that resolved after 2 years. Comparative evidence on abuse, misuse, and diversion was limited and reported only on older stimulant drugs. Evidence of effects in subgroups of patients with anxiety or tic disorders indicated no differences among the stimulants.