

# Summary of Current Evidence

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**CADTH** | Guidelines and Recommendations for  
October 2011 | ADHD in Children and Adolescents

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The information in this report is intended to help health care decision-makers, patients, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services.

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# EXECUTIVE SUMMARY

## Issue

Medications to treat attention-deficit/hyperactivity disorder (ADHD) in children and adolescents are available in short- and long-acting formulations. Short-acting formulations of methylphenidate (e.g., Ritalin) and dextroamphetamine (e.g., Dexedrine) are generally given two to three times daily.<sup>1</sup> They have been shown to be effective in reducing ADHD symptoms and provide dosing flexibility.<sup>2-4</sup> Compared with short-acting formulations, long-acting formulations are given less frequently, but are more expensive and are not covered in all insurance plans.<sup>5</sup> Recommendations about the use of long- or short-acting formulations are largely derived from expert opinion of best practices. Discourse on the use of long-acting formulations have centred on the following issues: compliance, social stigma, in-school dosing, and drug diversion.<sup>6,7</sup>

In 2010, publicly funded drug plans in Canada spent more than \$35 million on long-acting formulations, which represented 77% of total expenditures on ADHD medications. As expenditures on ADHD medications continue to rise, health care decision-makers require evidence-based information on the issue of selecting the most appropriate formulation for treating ADHD in children and adolescents.

## Objectives

The objective of this report was to summarize the current clinical evidence and findings of guidelines and recommendations. The report was also designed to explore the current utilization patterns and costs associated with the use of long- and short-acting ADHD medications.

The information in this report is intended to help health care decision-makers, patients, health care professionals, health systems leaders, and policy-makers make informed decisions.

## Methods

Information provided is based on a review of eight Canadian and major international guidelines addressing long-acting and short-acting medications for ADHD in children and adolescents. In addition, drug payment information (i.e., administrative claims data) was obtained from IMS Brogan Inc.

## Conclusions

Evidence-based recommendations support the use of stimulants as first-line therapy and the consideration of symptom profile in the use of long- or short-acting formulations when treating children and adolescents with severe ADHD.

The drug payment information presented in this summary report reveals substantial use of health care budgets to reimburse long-acting formulations. In 2010, expenditures on long-acting medications had exceeded \$35 million (or 77% of total expenditures on ADHD medications) by public drug plans in Canada.

## ABBREVIATIONS

AACAP	American Academy of Child & Adolescent Psychiatry
ADHD	attention-deficit/hyperactivity disorder
ADHD/HKD	attention-deficit and hyperkinetic disorders
AGREE	Appraisal of Guidelines for Research & Evaluation
AMP	amphetamines
CADDRA	Canadian ADHD Resource Alliance
CADTH	Canadian Agency for Drugs and Technologies in Health
CPP	clinical practice points
CPS	Canadian Paediatric Society
DEX	dextroamphetamine
DSM	Diagnostic and Statistical Manual of Mental Disorders
ER	extended release (also XR)
IR	immediate release
LA	long-acting
MPH	methylphenidate
MR	modified release
NCCMH	National Collaborating Centre for Mental Health
NHMRC	National Health and Medical Research Council
NICE	National Institute for Health and Clinical Excellence
NIHB	Non-Insured Health Benefits Program
RCT	randomized controlled trial
SA	short-acting
SIGN	Scottish Intercollegiate Guidelines Network
SR	sustained release
XR	extended release (also ER)

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# 1 INTRODUCTION

## 1.1 CONDITION

Attention-deficit/hyperactivity disorder (ADHD) is a developmental disorder that affects approximately one in 20 children.<sup>8</sup> Core symptoms include inattention, hyperactivity, and impulsivity. Some children with ADHD show symptoms of inattention and are not hyperactive or impulsive. Others show symptoms of hyperactivity-impulsivity only. In most cases, however, symptoms of both inattention and hyperactivity-impulsivity are present. The fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) identifies three subtypes of ADHD:

- ADHD, Combined Type
- ADHD, Predominantly Inattentive Type
- ADHD, Predominantly Hyperactive-Impulsive Type.

The core symptoms of ADHD will often persist throughout a person's lifetime, and approximately one-half to two-thirds of children with ADHD will continue to have significant problems as adults.<sup>9</sup> Management of ADHD may involve a combination of pharmacological treatments, behaviour modifications, lifestyle changes, and counselling.

## 1.2 PHARMACOLOGICAL TREATMENTS

Stimulants, including methylphenidate (MPH) and amphetamines (AMP) such as dextroamphetamine (DEX), have been used for more than 50 years to treat symptoms of ADHD and are considered the pharmacological treatment of choice.<sup>10</sup>

Medications to treat ADHD are available in short-acting (SA) and long-acting (LA) formulations. SA formulations of MPH (e.g., Ritalin) and DEX (e.g., Dexedrine) are generally given two to three times daily.<sup>1</sup> They have been shown to be effective in reducing ADHD symptoms and provide dosing flexibility.<sup>2-4</sup> Compared with SA formulations, LA formulations are given less frequently but are more expensive and are not covered in all insurance plans.<sup>5</sup> Recommendations to use LA or SA formulations have not been developed based on evidence. Discourse on the use of LA formulations has centred on the following issues: compliance, social stigma, in-school dosing, and drug diversion.<sup>6,7</sup>

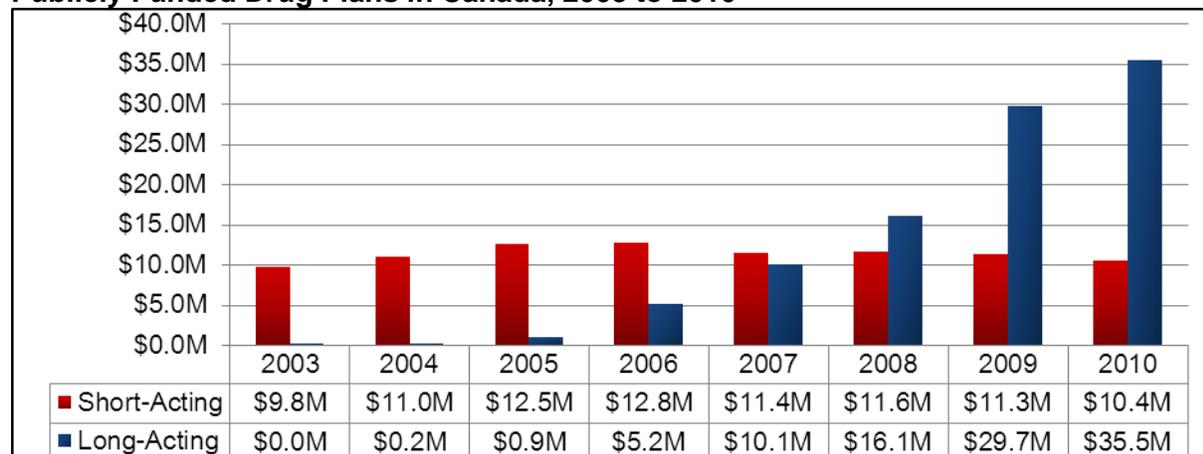
LA MPH stimulants include Concerta (extended-release MPH), generic extended-release MPH, and Biphentin (controlled-release MPH). LA AMP stimulants include Adderall XR (mixed salts AMP) and Vyvanse (lisdexamfetamine dimesylate). Strattera (atomoxetine) is a non-stimulant, LA medication indicated to treat ADHD. These medications are all indicated for the treatment of ADHD in patients aged six years and older.<sup>1</sup>

In various publications,<sup>2-8,11</sup> LA formulations are also referred to as extended release (ER or XR) or modified release (MR), while SA formulations are also referred to as immediate release (IR).

## 2 ISSUE

In 2010, publicly funded drug plans in Canada spent more than \$35 million on LA formulations (see Figure 1), which represented 77% of total expenditures on ADHD medications (see Figure 2). As expenditures on ADHD medications continue to rise, health care decision-makers require evidence-based information on the issue of selecting the most appropriate formulation for treating ADHD in children and adolescents.

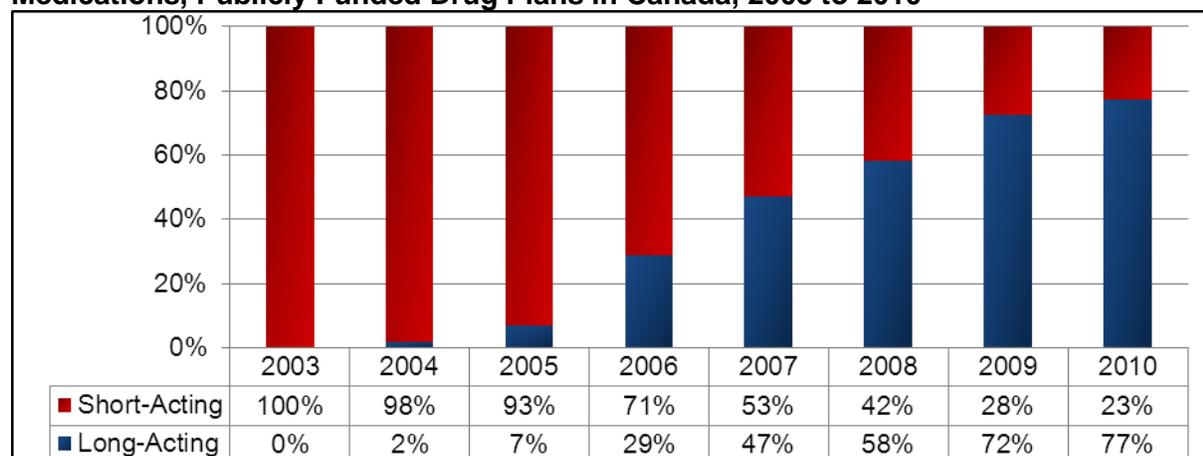
**Figure 1: Expenditures (\$) for Short-Acting and Long-Acting ADHD Medications, Publicly Funded Drug Plans in Canada, 2003 to 2010**



ADHD = attention-deficit/hyperactivity disorder; M = millions.

Figure 1 results were prepared using data from Brogan Inc., a unit of IMS, PharmaStat®, Public Drug Plan databases, 2003-2010, but the analyses, conclusions, opinions and statements expressed are those of CADTH and not of Brogan Inc., a unit of IMS.

**Figure 2: Share of Expenditures (%) by Short-Acting versus Long-Acting ADHD Medications, Publicly Funded Drug Plans in Canada, 2003 to 2010**



ADHD = attention-deficit/hyperactivity disorder.

Figure 2 results were prepared using data from Brogan Inc., a unit of IMS, PharmaStat®, Public Drug Plan databases, 2003-2010, but the analyses, conclusions, opinions and statements expressed are those of CADTH and not of Brogan Inc., a unit of IMS.

## 3 OBJECTIVES

The objective of this report is to summarize the current clinical evidence and findings of guidelines and recommendations. The report was also designed to explore the current utilization patterns and costs associated with the use of LA and SA ADHD medications.

The information in this report is intended to help health care decision-makers, patients, health care professionals, health systems leaders, and policy-makers make informed decisions.

## 4 METHODS

### 4.1 Guidelines and Recommendations

A limited literature search was conducted on key resources including PubMed, ECRI, and Canadian and major international guidelines, as well as a focused Internet search. Methodological filters were applied to limit retrieval to guidelines. The search was also limited to English language documents published between January 1, 2006 and May 19, 2011.

Guidelines were included in the review if they were major national ADHD guidelines or produced by a recognized national organization and systematically developed. Relevant to the local environment, two Canadian guidelines were included.<sup>5,8</sup> The relevant population consisted of children and adolescents (aged  $\leq 18$  years). Guidelines were excluded if they were not systematically developed or were representative of a smaller jurisdiction (i.e., a US state), or a specific health care organization or health plan.

The Appraisal of Guidelines for Research & Evaluation (AGREE) instrument was used to evaluate the quality of the guidelines identified in the literature search.<sup>12</sup> Domains considered included scope and purpose, stakeholder involvement, rigour of development, clarity and presentation, applicability, and editorial independence. Numeric domain scores were not calculated. Instead, narrative assessment of each guideline is provided.

### 4.2 Economic Data

*The following information refers to the economic data presented in Figures 1 and 2 of the Issues section of the report.*

Aggregate-level data were obtained from IMS Brogan Inc. The IMS Brogan Inc. database is the largest source of drug payment information (i.e., administrative claims data) in Canada. IMS Brogan Inc. databases comply with federal and provincial privacy legislation.<sup>13</sup>

Aggregate-level data from public drug plans in Canada were available for nine of the 10 provinces (i.e., British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Québec, New Brunswick, Nova Scotia, and Newfoundland) and the Non-Insured Health Benefits (NIHB) Program. Aggregate-level data were not available for publicly funded programs in Prince Edward Island, Northwest Territories, Yukon Territory, and Nunavut Territory, because data from these programs are not provided to IMS Brogan Inc.

ADHD medications that were identified in the IMS Brogan Inc. database for publicly funded drug plans are presented in Table 1.

**Table 1: Publicly Funded ADHD Medications in Canada (identified for the purpose of this report)**

Brand Name		
	Available Strengths (mg)*	Average Cost (\$)†
<b>Long-Acting Formulations</b>		
<b>Adderall XR</b> (amphetamine mixed salts)	5, 10, 15, 20, 25, 30	82.52
<b>Biphentin</b> (methylphenidate HCl)	10, 15, 20, 30, 40, 50, 60, 80	48.18
<b>Concerta</b> (methylphenidate HCl)	18, 27, 36, 54	73.58
<b>Strattera</b> (atomoxetine)	10, 18, 25, 40, 60, 80, 100	93.17
<b>Vyvanse</b> (lisdexamfetamine dimesylate)	20, 30, 40, 50, 60	79.86
<b>Short-Acting and Intermediate-Acting Formulations</b>		
<b>Adderall</b> (amphetamine mixed salts)	20	N/A
<b>Dexedrine</b> (dexamphetamine sulfate)	5	50.44
<b>Dexedrine Spansule</b> (dextroamphetamine sulphate)	10, 15	46.08
<b>Ritalin</b> (methylphenidate HCl)	5, 10, 20	9.35
<b>Ritalin SR</b> (methylphenidate HCl)	20	14.54

Table 1 results were prepared using data from Brogan Inc., a unit of IMS, PharmaStat®, Public Drug Plan databases, 2003-2010, but the analyses, conclusions, opinions and statements expressed are those of CADTH and not of Brogan Inc., a unit of IMS.

\* Strengths listed include available generic versions.

† Average cost (total cost divided by total claims) was calculated using 2010 data.

## 5 SUMMARY OF FINDINGS

### 5.1 Guidelines and Recommendations

Eight guidelines that addressed LA and SA medications for ADHD were identified. All guidelines were informed by evidence and include statements of consensus or best practice recommendations. The guidelines reviewed are found in Table 2.

Three national evidence-based guidelines were produced using rigorous scientific methods. These include guidelines by the Scottish Intercollegiate Guidelines Network (SIGN), the National Institute for Health and Clinical Excellence (NICE), and the Royal Australasian College of Physicians. Selected recommendations from these guidelines are found in Appendix 1.<sup>2-4</sup>

**Table 2: Evidence-based Guidelines for ADHD**

Organization	Year of Publication	Title of Publication
<i>Major National Guidelines</i>		
SIGN <sup>2</sup>	2009	<i>Management of Attention Deficit and Hyperkinetic Disorders in Children and Young People: A National Clinical Guideline</i>
NICE <sup>3</sup>	2009	<i>Attention Deficit Hyperactivity Disorder: Diagnosis and Management of ADHD in Children, Young People and Adults</i>
Royal Australasian College of Physicians <sup>4</sup>	2009	<i>Australian Guidelines on Attention Deficit Hyperactivity Disorder</i>
<i>Additional Guidelines</i>		
CADDRA <sup>5</sup>	2011	<i>Canadian ADHD Practice Guidelines (3<sup>rd</sup> Edition)</i>
CPS (Feldman et al) <sup>8</sup>	2009	<i>Extended-release Medications for Children and Adolescents with Attention-Deficit Hyperactivity Disorder</i>
AACAP <sup>11</sup>	2007	<i>Practice Parameter for the Assessment and Treatment of Children and Adolescents with Attention-Deficit/Hyperactivity Disorder</i>
AACAP (Gleason et al) <sup>6</sup>	2007	<i>Psychopharmacological Treatment for Very Young Children: Contexts and Guidelines</i>
European Society of Child and Adolescent Psychiatry (Banaschewski et al) <sup>7</sup>	2006	<i>Long-acting Medications for the Hyperkinetic Disorders: A Systematic Review and European Treatment Guideline</i>

AACAP = American Academy of Child & Adolescent Psychiatry; CADDRA = Canadian ADHD Resource Alliance; CPS = Canadian Paediatric Society; NICE = National Institute for Health and Clinical Excellence; SIGN = Scottish Intercollegiate Guidelines Network

### **SIGN (2009) National Clinical Guideline on ADHD**

In 2009, SIGN published a national clinical guideline on the management of attention-deficit and hyperkinetic disorders (ADHD/HKD) in children and young people, which is an update of a 2001 guideline.<sup>2</sup> This clinical guideline was developed using a standard methodology based on a systematic review of the evidence. The complete guideline development methodology is found on the SIGN website.<sup>14</sup>

The overall aim of the guideline was to provide a framework for the evidence-based assessment and management of ADHD/HKD from which multidisciplinary and multi-agency approaches could be developed locally. The Guideline Development Group was multidisciplinary, including practising clinicians and patient or caregiver representatives. In addition, SIGN provided support for guideline development, literature review, and facilitation.

There was a clear link between recommendations and the supporting evidence. The recommendations were specific and easily identifiable, and levels of supporting evidence and grades of recommendations were stated. A number of independent expert referees reviewed the guideline. NHS Quality Improvement Scotland funded the guideline. All members of the guideline development group made declarations of interest.

## Summary of recommendations from SIGN

### *Evidence-based:*

- a) SIGN recommends treatment of children with severe ADHD using stimulants as the first choice of medications. (Grade A.)
- b) Atomoxetine is recommended in children where psychostimulant medication is not appropriate, not tolerated, or is ineffective. (Grade A.)

*Grade A:* at least one meta-analysis, systematic review, or good quality randomized controlled trial (RCT), and directly applicable to the target population

### *Consensus-based (good practice):*

- a) LA medications should be considered if there is a likelihood of diversion.
- b) When selecting a formulation, clinicians should consider practical issues of convenience and applicability on an individual case basis.

## **Australian Guidelines on ADHD (2009)**

Since November 2009, the Royal Australasian College of Physicians has provided access to draft Australian guidelines on ADHD.<sup>4</sup> This is an extensive guideline that includes recommendations and a discussion of the supporting evidence for all aspects of the diagnosis and treatment of ADHD. The guidelines are available in draft because a formal conflict of interest investigation into a researcher has not been completed in the United States.

In May 2011, the conflict of interest allegations had not been resolved, so the National Health and Medical Research Council (NHMRC) decided to convene a working party to develop clinical practice points (CPPs) to ensure up-to-date clinical advice on ADHD. The website noted that “the final CPPs will be provided to the Minister for Mental Health and Ageing for his consideration and possible public consultation, by the end of September 2011.”<sup>15</sup>

In June 2011, the website stated, “while the work of this US-based researcher is referenced in the draft Guidelines, the researcher has not been involved in any way in the production of the Guidelines.”<sup>15</sup> NHMRC guideline development processes were followed. The complete guideline development process was available as a separate appendix.<sup>16</sup> Steps included a literature review, stakeholder consultation, public consultation, email, and face-to-face meetings. As a result, until an update to the guidelines is ready, NHMRC will continue to provide access to the 2009 draft guidelines as an information resource.<sup>15</sup>

The aim of these guidelines was to support and inform the care of individuals with ADHD by providing a series of recommendations to guide assessment, management, and care. The guidelines apply to the care of preschoolers, children, adolescents, and adults with ADHD. They are intended to provide a framework based on the best available evidence that can be adapted to local needs and resources, and individual circumstances. The guideline development group included experts from key professional disciplines, including pediatrics, child and adolescent psychiatry, adult psychiatry, psychology, general practice, and education, as well as consumers

and caregivers. These guidelines addressed social and economic considerations in the treatment of ADHD, including the economic burden of ADHD and the cost-effectiveness of treatment.

The method for formulating the recommendations was clearly described. In the document, the research question, summary evidence statements (with level of evidence), and resulting recommendations were provided, followed by the research evidence. For areas of practice not addressed by current research, recommendations were developed based on the consensus opinion of the clinicians, educators, and consumers from the reference group. Funding for these guidelines was provided by the Australian Government's Department of Health and Ageing. Conflicts of interest were recorded for each member of the development group.

### *Summary of recommendations from the Australian guidelines*

#### *Evidence-based:*

- a) Where severe, impairing ADHD is present, treatment with stimulants (MPH or DEX) should be considered as a first-line pharmacological treatment. (Grade A.)
- b) The choice of IR-MPH or ER-MPH depends on the symptom profile, as well as individual child and parent or caregiver preferences. (Grade A for children, grade B for adolescents.)
- c) Atomoxetine should be considered for children and adolescents with severe ADHD who do not respond to or are intolerant of stimulant medication, or in whom stimulant medication is contraindicated. (Grade B.)

*Grade A:* Body of evidence can be trusted to guide practice.

*Grade B:* Body of evidence can be trusted to guide practice in most situations.

#### *Consensus-based (best practice):*

- a) Not all people with ADHD require pharmacological management. Medications should only be used when symptoms are pervasive across settings and cause significant impairment in academic, social, or behavioural function.
- b) IR forms should be the initial treatment, to titrate to the optimal dose, and they may be the preferred maintenance therapy for various reasons; for example, flexibility of dosing. If starting on IR stimulants, consideration should be given to changing to an ER form once the optimal dose has been established. This can help to avoid the stigma and inconvenience of taking medication at school.
- c) Atomoxetine may be considered as the first-line medication if there is comorbid substance abuse, severe tic disorder, or anxiety disorder.

### **NICE (2009) Clinical Guideline on ADHD**

In 2009, NICE published a clinical practice guideline on the diagnosis and management of ADHD in children, young people, and adults.<sup>3</sup> A technology appraisal on “methylphenidate, atomoxetine and dexamfetamine for the treatment of ADHD in children and adolescents” informed the recommendations on drug treatment.<sup>17</sup> The clinical practice guideline is high quality and was developed based on methods outlined in the NICE Guideline Manual.<sup>18</sup> Steps in developing this guideline included a literature review, stakeholder consultation, public consultation, and face-to-face meetings.

The aim of the NICE guideline was to advise on the treatment and management of ADHD. It is considered a patient-centred, evidence-based guideline and is relevant for children (older than three years), young people, and adults with ADHD. The guideline development group consisted of health care professionals, lay representatives, and technical experts. Consulted stakeholders included service users and caregivers, professional groups, and manufacturers. Health economic evidence was assessed and incorporated into the recommendations.

The guideline review process is available in a flow chart in the guideline (p. 47). The method for formulating the recommendations was clearly described. The guideline was developed over a series of meetings, in which clinical questions and clinical evidence were reviewed and assessed and recommendations formulated and reviewed. Recommendations were evidence based, where possible, and if evidence was not available, informal consensus methods were used. Recommendations were specific and easily identifiable and an extensive evidence review for each topic was provided. Various stakeholders reviewed the guideline extensively prior to publication. This guideline was commissioned by NICE and developed within the National Collaborating Centre for Mental Health (NCCMH). Conflicts of interest for each member of the Guideline Development Group were recorded.

An extensive review of the evidence for drug treatment of ADHD is provided. The quality of evidence for each drug or topic was rated. Following the evidence review is a summary and a list of recommendations. Individual recommendations were not assigned a level for the supporting evidence on which they were based or a strength of recommendation. Therefore, it is not clear to what extent each recommendation is based on evidence or expert opinion.

### *Summary of recommendations from NICE*

- a) Drug treatment is not indicated as the first-line treatment for all school-aged children and young people with ADHD. It should be reserved for those with severe symptoms and impairment. Where drug treatment is considered appropriate, MPH, atomoxetine, and DEX are recommended.
- b) If there is a choice of more than one appropriate drug, the product with the lowest cost should be prescribed.
- c) To improve adherence to drug treatment, simple drug regimens (for example, once-daily MR doses) are recommended for people with ADHD.
- d) The decision regarding which product to use should be based on factors including:
  - specific issues regarding compliance; i.e., midday treatment dose at school
  - the potential for drug diversion and/or misuse
  - the preferences of the child or adolescent and/or his or her parent or guardian.
- e) When prescribing MPH for the treatment of children or young people, MR preparations should be considered for the following reasons:
  - convenience
  - improving adherence
  - reducing stigma (does not need to take medication at school)
  - reducing problems schools have in storing and administering controlled drugs
  - their pharmacokinetic profiles.
- f) Alternatively, IR preparations may be considered if more flexible dosing regimens are required, or during initial titration to determine correct dosing levels.

- g) Consider atomoxetine if MPH has been tried and has been ineffective at the maximum tolerated dose, or if intolerant to low or moderate doses of MPH.

### **Additional ADHD Guidelines**

Five additional ADHD guidelines were identified that included recommendations on LA versus SA drugs in children and adolescents. These guidelines varied with regard to their methodological quality. Recommendations on the use of LA versus SA drugs, along with relevant statements of evidence from each guideline, are found in Appendix 2.

In 2011, the Canadian ADHD Resource Alliance (CADDRA) published the third edition of its Canadian ADHD Practice Guidelines.<sup>5</sup> CADDRA is a national, independent, not-for-profit association with members from family practice, pediatrics, psychiatry, psychology, and other health professions. No objective or clinical question was specified for the guideline, but the authors included a list of core principles for the treatment of ADHD. The targeted users of the guideline are Canadian physicians who diagnose and treat ADHD, and the guideline applies to patients and their families living with ADHD.

Strengths of this guideline include the tools available for physicians and patients. Information, diagnostic instruments, forms, and scales that have been selected based on their validity, reliability and accessibility can be downloaded. These guidelines are considered an active document that will be revised online as new information comes available.

The major limitation is the lack of rigour used in the development of this guideline. For example, the methods used to search for evidence were not specified and no criteria were described for selecting the evidence. Specific recommendations were not identifiable and there was no link between recommendations and the supporting evidence. The authors state that evidence-based data were cited in the literature detailed in the reference section, and consensus-based statements were identified in the text. The introduction to the guideline states, “Consensus decisions have been made if there was no current evidence-based data available to deal with a specific clinical issue or where evidence-based data may have been impractical in the Canadian environment” (p. v).

CADDRA is an active advocacy group. Several statements were made in the document about the cost of many ER preparations, which are “beyond the reach” of many patients without extended health insurance: “CADDRA continues to advocate for a resolution of this problem at the government level” (p. 57). The Guidelines Committee “recommends that all medication approved for ADHD treatment should be accessible and covered by provincial drug plans” (p. 67). This advocacy, combined with a lack of supporting evidence for the group’s recommendations, creates significant bias that threatens the validity of the recommendations.

Individual recommendations are not assigned a level for the supporting evidence on which they were based, or a strength of recommendation. Therefore, it is not clear to what extent each recommendation is based on evidence or expert opinion.

### *Recommendations*

- a) LA preparations, including Adderall XR, Biphentin, Concerta, Strattera, and Vyvanse, are recommended as first-line treatment of ADHD.
- b) SA and intermediate-acting preparations are listed as second-line or adjunctive agents.

In 2009, the Canadian Paediatric Society published a statement on “extended-release medications for children and adolescents with attention-deficit disorder.”<sup>8</sup> The objective of the statement was to critically appraise the evidence for the relative effectiveness of XR versus IR medications and to make recommendations for their appropriate use in the treatment of ADHD. The statement was targeted at physicians prescribing medication for ADHD.

Strengths included a clearly described scope and purpose. Stakeholder involvement included physicians but not patients or their families. Key recommendations were specific, unambiguous, and easily identifiable. The authors of the paper indicated that they had no conflicts of interest to declare. The major limitation is the lack of rigour of development. Clinical questions were not provided, and although the search strategy was detailed, the criteria for selecting the evidence and the methods for formulating the recommendations were not provided. The statement indicates that the quality of the studies was appraised, although the details of the appraisal of individual studies or systematic reviews were not provided. References were provided throughout the statement. There was no link between the recommendations and the supporting evidence and no levels of evidence were assigned. Therefore, it is not clear to what extent each recommendation is based on evidence or expert opinion.

This statement made the distinction between “efficacy” and “effectiveness,” defining efficacy as how well a treatment works under tightly controlled study conditions, and effectiveness as how well a treatment works in a natural, real-world setting. The statement identified that cost is the major barrier to accessing XR preparations, and recommended that industry, private health insurance companies, and government work together to make these medications more accessible to all children with ADHD. No specific solutions were provided.

### *Recommendations*

- a) The authors acknowledge that the efficacy of IR and XR preparations are similar, as demonstrated through RCTs. Although not necessarily more efficacious than IR medication, the authors feel the XR preparations are more effective than IR and less likely to be diverted. Therefore, the authors recommend that XR preparations should be considered as first-line therapy.

In 2006, Banaschewski et al. published a supplement to European guidelines (2004) to provide recommendations about the use of LA medications for the hyperkinetic disorders.<sup>7</sup> The guideline was developed by a panel of experts from several European countries, including academic clinicians and clinical researchers. The author meetings were funded by several companies and authors’ expenses were also paid. Potential conflicts of interests were declared.

The authors identified the clinical questions. The guideline states that a systematic review of published and unpublished trials was completed. Details of the search were not provided,

although it was stated that the authors used recent systematic reviews by NICE and SIGN to identify papers. They also referred to recent meta-analyses. In addition, the manufacturers were asked to submit information (published and unpublished). A “quantitative review of data” was also conducted, including the calculation of effect sizes using standard methodology. The criteria for selecting the evidence were not described. The methods for formulating the recommendations were not specified, although the method of guideline development was described as “iterative.” Drafts of the paper were exchanged and discussed iteratively and all authors subscribed to the final document (and recommendations). There was a method for resolving disagreements, but in the end, all conclusions were unanimous. The paper included a narrative summary of each conclusion and a scientific examination of the data.

Strengths include the description of the guideline process and the clear presentation of the recommendations. Limitations include the lack of patient input. For each recommendation, there is a discussion of the supporting evidence and levels of evidence are assigned to certain, but not all, statements within the discussion.

### *Evidence statements*

- a) XR preparations are superior to placebo and some are equivalent to multiple doses of IR methylphenidate. (Grade A.)
- b) LA stimulants have similar effect sizes than IR stimulants (level 1a), while effect sizes for non-stimulants (atomoxetine) are somewhat smaller.
- c) SR medications may be less prone to abuse because they tend to have a slower rate of onset than IR. (Grade C.)
- d) Key advantages of IR: lower cost and flexibility of dosages. (Consensus.)
- e) Key advantages of LA: potential reduction of stigma at school, improved compliance, and possible reduced risk of misuse. (Consensus.)

*Level 1a:* the authors assigned a level of 1a; however, this does not match the grading systems described in the paper.

*Grade A:* at least one meta-analysis, systematic review, or good quality RCT, and directly applicable to the target population.

*Grade C:* well-conducted case control or cohort studies; directly applicable to target population.

### *Recommendations*

- a) LA preparations should be available and used.
- b) They should not replace SA drugs (which will be the initial treatment for many children, for reasons of cost and flexibility of dosing). Individual clinical choice will determine the choice of formulation used.

The American Academy of Child & Adolescent Psychiatry (AACAP) published two guidelines on the treatment of ADHD. The *Practice Parameter for the Assessment and Treatment of Children and Adolescents with Attention-Deficit/Hyperactivity Disorder* was published in July 2007 and *Psychopharmacological Treatment for Very Young Children: Contexts and Guidelines* was published in December 2007.<sup>6,11</sup>

The objective of the practice parameter was to describe the assessment and treatment of children and adolescents with ADHD, based on the current scientific evidence and clinical consensus of experts in the field.<sup>11</sup> The Working Group consisted of academic clinicians and researchers. The parameter was targeted at clinicians who treat children and adolescents with ADHD. Clinical questions were not defined, although areas of discussion included clinical evaluation, comorbid conditions, research on the etiology, and interventions. The funding body for this Working Group and development of the practice parameter was not clear, although it was sponsored by the AACAP. Conflicts of interest for all members of the panel were recorded.

Details of the systematic literature search were provided, including databases searched from 1996 to 2006. In addition, bibliographies were reviewed and references were included from the previous version of the parameter. Articles were included if they “appeared to inform the field on the diagnosis and/or treatment of ADHD.” Priority was given to recent authoritative reviews of literature and recent treatment studies within the previous two to three years. Treatment recommendations were based on empirical evidence and clinical consensus and were graded according to the strength of the underlying empirical and/or clinical support. The methods for formulating the recommendations were not described. The overall recommendations on best treatment practices were stated with a strength of underlying evidence, followed by a discussion of the supporting evidence. Specific recommendation statements about the use of LA agents were found within the text, and referenced. Individual references were not assigned a level of evidence and therefore it not clear to what extent each recommendation is based on evidence or expert opinion. Additional limitations included the lack of patient or family involvement.

#### *Evidence statements*

- a) LA formulations are as efficacious as the IR forms and have been shown to be efficacious in adolescents as well as children (reference cited).
- b) Advantages of LA: greater convenience for patient and family; enhanced confidentiality at school (no dose given at school); greater compliance (no references cited).
- c) Disadvantages of LA: may have greater problematic effects on evening appetite and sleep (no references cited).
- d) LA MPH may improve driving performance in adolescents relative to SA MPH (reference cited; RCT).
- e) SA stimulants are often used as initial treatment in small children (< 16 kg) for whom there are no LA forms in sufficiently low dose (no references cited).

*Although references were cited for some statements, the level of evidence was assigned for only one statement (see above statement (d)).*

#### *Recommendations (found within the body of the text)*

- a) Stimulants are recommended first-line treatment for ADHD. No specific formulation is recommended; it is the sole choice of the family and the clinician as to which agent should be used; each patient’s treatment must be individualized.
- b) Atomoxetine may be considered as the first-line agent for ADHD in individuals with an active substance abuse problem, comorbid anxiety, or tics.

The aim of the AACAP Working Group on Medication Treatment in Very Young Children was to develop best-practice algorithms for the use of psychopharmacological agents in preschool

children, based upon literature review, clinical experience, and expert consensus.<sup>6</sup> The Working Group included professionals with expertise in early childhood psychiatric disorders, psychopharmacology, pediatrics, psychology, and neurodevelopmental processes. The development of this algorithm was supported by a grant from the AACAP, which is the same organization that was responsible for editing and publishing the guideline. Conflicts of interest for all members of the panel were recorded. The target population of this guideline was preschool-aged children (three to six years). In Canada, ADHD medication is indicated in children aged six and older.

Systematic methods were used to search for evidence, and included a defined search period (1990 to 2007), a list of databases searched (limited to PubMed and PsycINFO), and defined search terms. Criteria for selecting the evidence were described as those publications that were “relevant,” including evidence in preschool-aged children as well as the highest level of evidence in older children. Although specific methods for developing the algorithm were not described, input included a systematic literature review, survey responses from practising clinicians, and the research and clinical expertise of the Working Group.

Steps in the algorithm were specific and clearly identifiable. Each step of the algorithm was labelled with the level of supporting evidence and included different options for treatment. There was a discussion of the available evidence within the text of the document. Limitations included the lack of patient and/or family involvement. Clinical questions were not described.

#### *Statements about the evidence*

- a) No data exist to support ER stimulants in preschoolers.
- b) Clinical experience highlights the challenges of dosing three times a day.

#### *Recommendations for preschoolers (steps of the algorithm)*

- a) First-line: MPH (level A); second-line: AMP (level C); third-line option: atomoxetine (level C); no formulations are specified.
- b) ER formulations can be used to address compliance considerations. ER formulations limit dosing flexibility in the lowest dose ranges and therefore may be contraindicated in children whose optimal tolerated dose is lower than the ER dose.

*Level A:* well-controlled, randomized trials, large meta-analysis, or overwhelming clinical consensus.

*Level B:* empirical evidence, open trials, case series, or strong clinical consensus.

*Level C:* single case reports or no published reports, recommendation based on clinical and research experiences.

## **5.2 Limitations**

Three national evidence-based guidelines were identified that were produced using rigorous scientific methods.<sup>2-4</sup> No major limitations were identified for the SIGN and Australia guidelines. Although the development process was rigorous in the NICE guideline, individual recommendations were not assigned a level for the supporting evidence on which it was based, or a strength of recommendation. Therefore, it is not clear to what extent each recommendation is based on evidence or expert opinion.

Five additional ADHD guidelines were identified that made recommendations for LA versus SA formulations.<sup>5-8,11</sup> These guidelines varied in their methodological quality. In general, guidelines were lacking in their rigour of development. In many cases, there was no link between recommendations and the supporting evidence. As there was no level of supporting evidence or grade provided for recommendations, it was not clear if they were based on evidence or expert opinion.

Vyvanse (lisdexamfetamine dimesylate) has been available in Canada since 2009.<sup>19</sup> It is not included in the guidelines reviewed, with the exception of the 2011 CADDRA guideline.

## **6 CONCLUSIONS AND IMPLICATIONS FOR DECISION- OR POLICY-MAKING**

Three national evidence-based guidelines were identified that were produced using rigorous scientific methods.<sup>2-4</sup> Five additional guidelines were identified that varied with regard to methodological quality.<sup>5-8,11</sup> All guidelines reviewed were informed by evidence and developed by consensus.

Evidence-based recommendations support the use of stimulants as first-line therapy when treating children and adolescents with severe ADHD. Atomoxetine is an LA non-stimulant treatment alternative that is generally considered a third-line treatment alternative after methylphenidate and amphetamine stimulants, except in the presence of certain comorbidities.

Evidence-based recommendations support the consideration of symptom profile in the use of LA or SA formulations. Discussions of evidence within the guidelines reviewed also state that LA formulations are as efficacious as SA, but not superior. Other recommendations about the use of LA or SA formulations are largely derived from expert opinion of best practice. Advantages of one formulation over another cannot be determined and guideline developers acknowledge the need for more research comparing LA and SA medications.

The drug payment information presented in this summary report reveals substantial use of health care budgets to reimburse LA formulations. In 2010, expenditures on LA formulations had exceeded \$35 million (or 77% of total expenditures on ADHD medications) by public drug plans in Canada.

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# APPENDIX 1: RECOMMENDATIONS FROM NATIONAL EVIDENCE-BASED GUIDELINES DEVELOPED USING RIGOROUS SCIENTIFIC METHODS

Organization	Recommendations
SIGN <sup>2</sup> (2009)	<p>Overall recommendations (excerpts)</p> <ul style="list-style-type: none"> <li>For school-aged children and young people with HKD (severe ADHD), medication is recommended (Grade A)</li> <li>Psychostimulants are recommended as the first choice of medication for the core symptoms of ADHD/HKD in children (Grade A).</li> </ul> <p>IR versus ER</p> <ul style="list-style-type: none"> <li>Use of MR formulations or ATX should be considered where there is likelihood of diversion (good practice point)</li> <li>Clinicians should familiarize themselves with the release patterns of the different MPH formulations. It may be necessary to combine IR and MR preparations to provide medications cover throughout the day (good practice point)</li> <li>When selecting a formulation, clinicians should consider practical issues of convenience and applicability on an individual case basis (good practice point).</li> </ul> <p>Place in therapy: ATX</p> <ul style="list-style-type: none"> <li>ATX is recommended as treatment for the core symptoms of ADHD/HKD in children where psychostimulant medication is not appropriate, not tolerated, or is ineffective (Grade A).</li> </ul> <p><b>Grade A:</b> at least one MA, SR, or good quality RCT, and directly applicable to the target population.  <b>Good practice point:</b> recommended best practice based on the clinical experience of the guideline development group.</p>
NICE <sup>3</sup> (2009)	<p>Overall recommendations (excerpts)</p> <ul style="list-style-type: none"> <li>Drug treatment is not indicated as the first-line treatment for all school-aged children and young people with ADHD. It should be reserved for those with severe symptoms and impairment.</li> <li>Where drug treatment is considered appropriate, MPH, ATX, and DEX are recommended.</li> <li>If there is a choice of more than one appropriate drug, the product with the lowest cost should be prescribed.</li> <li>To improve adherence to drug treatment, simple drug regimens (e.g., once-daily MR doses) are recommended for people with ADHD.</li> </ul> <p>IR versus ER</p> <ul style="list-style-type: none"> <li>The decision regarding which product to use should be based on factors including: <ul style="list-style-type: none"> <li>specific issues regarding compliance; i.e., midday treatment dose at school</li> <li>the potential for drug diversion and/or misuse</li> <li>the preferences of the child or adolescent and/or his or her parent or guardian.</li> </ul> </li> <li>When prescribing MPH for the treatment of children or young people, MR preparations should be considered for the following reasons: <ul style="list-style-type: none"> <li>convenience</li> <li>improving adherence</li> <li>reducing stigma (does not need to take medication at school)</li> <li>reducing problems schools have in storing and administering controlled drugs</li> <li>their pharmacokinetic profiles.</li> </ul> </li> <li>Alternatively, IR preparations may be considered if more flexible dosing regimens are required, or during initial titration to determine correct dosing levels.</li> </ul> <p>Place in therapy: ATX</p> <ul style="list-style-type: none"> <li>Consider ATX if MPH has been tried and has been ineffective at the maximum tolerated dose, or if the child or young person is intolerant to low or moderate doses of MPH.</li> </ul> <p><b>No grades</b> were provided for each recommendation. No link between the recommendation and supporting evidence was provided.</p>

Organization	Recommendations
Royal Australasian College of Physicians <sup>4</sup>  (2009)	<p>Overall recommendations (excerpts)</p> <ul style="list-style-type: none"> <li>• Not all people with ADHD require pharmacological management (recommended best practice).</li> <li>• Medications should only be used when symptoms are pervasive across settings (e.g., school and home) and causing significant impairment in academic, social, or behavioural function, and after careful consideration of non-pharmacological approaches (recommended best practice).</li> <li>• Where severe, impairing ADHD is present, treatment with MPH or DEX should be considered as a first-line pharmacological treatment (grade A).</li> </ul> <p>IR versus ER</p> <ul style="list-style-type: none"> <li>• The choice of IR-MPH or ER-MPH depends on the symptom profile, as well as individual child and parent or caregiver preferences (grade A for children, grade B for adolescents).</li> <li>• IR forms should be the initial treatment, to titrate to the optimal dose, and they may be the preferred maintenance therapy for various reasons; for example, flexibility of dosing (recommended best practice).</li> <li>• If starting on IR stimulants, consideration should be given to changing to an ER form once the optimal dose has been established. This can help to avoid the stigma and inconvenience of taking medication at school (recommended best practice).</li> <li>• In some cases, the combined use of IR and ER forms is required. This should only be considered if there is inadequate symptom control with the ER form (recommended best practice).</li> <li>• ER forms of stimulants should not be routinely used in preschool-aged children (recommended best practice).</li> </ul> <p>Place in therapy: ATX</p> <ul style="list-style-type: none"> <li>• ATX should be considered for children and adolescents with severe ADHD who do not respond to or are intolerant of stimulant medication, or in whom stimulant medication is contraindicated (grade B).</li> <li>• ATX may be considered as the first-line medication if there is comorbid substance abuse, severe tic disorder, or anxiety disorder (recommended best practice).</li> </ul> <p><b>Grade A:</b> Body of evidence can be trusted to guide practice.  <b>Grade B:</b> Body of evidence can be trusted to guide practice in most situations.  <b>Best practice points:</b> Recommended best practice based on clinical experience and expert opinion.</p>

ADHD = attention-deficit/hyperactivity disorder; ATX = atomoxetine; DEX = dextroamphetamine / dexamphetamine; ER = extended release; HKD = hyperkinetic disorder; IR = immediate release; MA = meta-analysis; MPH = methylphenidate; MR = modified release; NICE = National Institute for Health and Clinical Excellence; RCT = randomized controlled trial; SIGN = Scottish Intercollegiate Guidelines Network; SR = systematic review.

## APPENDIX 2: SUMMARY OF EVIDENCE AND RECOMMENDATIONS FROM GUIDELINES ON ADHD

Guideline	Relevant Statements about the Available Evidence	Relevant Recommendations on Long-acting versus Short-acting Drugs	Major Strengths/Limitations of Guideline
CADDRA <sup>5</sup> (2011)	<ul style="list-style-type: none"> <li>The evidence for treating ADHD is not discussed. The evidence comparing LA and SA agents is not discussed.</li> <li>Central philosophy: treat each patient as a unique being; 13 principles for medication selection in the treatment of ADHD are provided (p. 55).</li> </ul>	<p>Medical treatment for uncomplicated ADHD for children and adolescents:</p> <ul style="list-style-type: none"> <li>LA preparation, including Adderall XR, Biphentin, Concerta, Strattera, and Vyvanse are recommended as first-line</li> <li>SA and intermediate-acting preparations are listed as second-line/adjunctive agents</li> </ul>	<p>Major limitation: rigour of development.</p> <p>No discussion of evidence supporting its practice guideline; no levels of evidence provided or strength of recommendations.</p>
CPS: Statement <sup>8</sup> (2009)	<ul style="list-style-type: none"> <li>The authors acknowledge that the efficacy of IR and XR preparations are similar, as demonstrated through RCTs.</li> <li>Although not necessarily more <i>efficacious</i> than IR medication, the authors feel the XR preparations are more <i>effective</i> than IR.</li> </ul>	<ul style="list-style-type: none"> <li>When stimulant medications for ADHD are indicated, XR preparations should be considered as first-line therapy because these preparations are more <i>effective</i> and less likely to be diverted.</li> <li>XR medications are more likely than IR medications to be used by the children and teenagers with ADHD for whom they have been prescribed.</li> </ul>	<p>Strength: identified scope and purpose and stakeholder involvement.</p> <p>Major limitation: rigour of development.</p> <p>No link between the recommendation and supporting evidence; no levels of evidence provided or strength of recommendations.</p>
European: <i>Long-acting Medications for the Hyperkinetic Disorders</i> <sup>7</sup> (2006)	<ul style="list-style-type: none"> <li>XR preparations are superior to placebo and some are equivalent to multiple doses of IR MPH (grade A).</li> <li>XR stimulants have similar effect sizes to IR stimulants (level 1a) while effect sizes for non-stimulants (ATX) are somewhat smaller.</li> <li>SR medications may be less prone to abuse because they tend to have a slower rate of onset than IR (grade C).</li> <li>Key advantages of IR: lower cost and flexibility of dosages (consensus).</li> <li>Key advantages of LA: potential reduction of stigma at school, improved compliance, and possible reduced risk of misuse (consensus).</li> </ul>	<ul style="list-style-type: none"> <li>LA preparations should be available and used.</li> <li>They should not replace SA drugs (which will be the initial treatment for many children, for reasons of cost and flexibility of dosing). Individual clinical choice will determine the choice of formulation used.</li> </ul>	<p>Strength: clinical questions defined, as well as method of guideline development (iterative); link between supporting evidence and recommendation; levels of evidence are provided for some, but not all; statement of supporting evidence</p> <p>Limitations: recommendations are not assigned a level of evidence on which they are based.</p>

Guideline	Relevant Statements about the Available Evidence	Relevant Recommendations on Long-acting versus Short-acting Drugs	Major Strengths/Limitations of Guideline
AACAP: Practice Parameter <sup>11</sup> (2007)	<ul style="list-style-type: none"> <li>LA formulations are as efficacious as the IR forms and have been shown to be efficacious in adolescents as well as children (reference cited).</li> <li>Advantages of LA: greater convenience for patient and family; enhanced confidentiality at school (no dose given at school); greater compliance (no references cited).</li> <li>Disadvantages of LA: may have greater problematic effects on evening appetite and sleep (no references cited).</li> <li>LA MPH may improve driving performance in adolescents relative to SA MPH (reference cited; RCT).</li> <li>SA stimulants often used as initial treatment in small children (&lt; 16 kg) for whom there are no LA forms in sufficiently low dose (no references cited).</li> </ul>	<ul style="list-style-type: none"> <li>Overall recommendation for treatment: The initial psychopharmacological treatment of ADHD should be a trial with an agent approved by the FDA for the treatment of ADHD (minimal standard).</li> <li>Stimulants are recommended first line (references cited).</li> <li>No specific formulation is recommended; it is the sole choice of the family and the clinician as to which agent should be used; each patient's treatment must be individualized.</li> </ul> <p>Place in therapy: ATX</p> <ul style="list-style-type: none"> <li>May be considered as the first-line agent for ADHD in individuals with an active substance abuse problem, comorbid anxiety, or tics (references cited).</li> <li>Preferred if the patient experiences severe side effects of stimulants, such as mood lability, tics (references cited).</li> </ul>	<p>Strength: major recommendations are easily identifiable, followed by a discussion of the relevant evidence.</p> <p>Limitation: rigour of development — methods for formulating the recommendations are not described.</p>
AACAP: Treatment for the Very Young <sup>6</sup> (2007)	<ul style="list-style-type: none"> <li>No data exist to support ER stimulants in preschoolers.</li> <li>Clinical experience highlights the challenges of dosing three times a day.</li> </ul>	<p>Steps of the algorithm:</p> <ul style="list-style-type: none"> <li>First-line: MPH (level A)</li> <li>Second-line: AMP (level C)</li> <li>Third-line option: ATX (level C)</li> </ul> <p>No formulations are specified.</p> <p>ER formulations can be used to address compliance considerations. ER formulations limit dosing flexibility in the lowest dose ranges and therefore may be contraindicated in children whose optimal tolerated dose is lower than the ER dose.</p> <p><b>Level A:</b> Well-controlled, randomized trials, large meta-analysis, or overwhelming clinical consensus.</p> <p><b>Level B:</b> Empirical evidence, open trials, case series, or strong clinical consensus.</p> <p><b>Level C:</b> Single case reports or no published reports, recommendation based on clinical and research experiences.</p>	<p>Strength: identified scope and purpose and stakeholder involvement; levels of evidence assigned to each step of the algorithm.</p> <p>Limitation: specific criteria for selecting evidence were not described.</p>

AACAP = American Academy of Child and Adolescent Psychiatry; ADHD = attention-deficit/hyperactivity disorder; AMP = amphetamine; ATX = atomoxetine; CADDRA = Canadian ADHD Resource Alliance; DEX = dextroamphetamine / dexamphetamine; CPS = Canadian Paediatric Society; ER = extended release; FDA = Food and Drug Administration; IR = immediate release; LA = long-acting; MD = medical doctor; MPH = methylphenidate; RCT = randomized controlled trial; SA = short-acting; XR = extended release.