TITLE: Long versus Short Acting Drugs for Attention Deficit/Hyperactivity Disorder in Children and Adolescents: A Review of the Guidelines and Recommendations

DATE: 27 June 2011

CONTEXT AND POLICY ISSUES

Attention Deficit Hyperactivity Disorder (ADHD) affects approximately one in 20 children. Core symptoms include inattention, hyperactivity, and impulsivity. Stimulants, including methylphenidate (MPH) and amphetamines (AMP) such as dextroamphetamine (DEX) have been used for over 50 years to treat symptoms of ADHD and are considered the pharmacological treatment of choice.

Medications to treat ADHD are available in short and long acting formulations. Short acting formulations of MPH (Ritalin) and DEX (Dexedrine), are generally given two to three times daily. They have been shown to be effective in reducing ADHD symptoms and provide dosing flexibility. Long acting formulations have gained popularity in recent years. Potential advantages of a long acting formulation include improved compliance, reduced social stigma, lack of need for in-school dosing and reduced potential for drug diversion. However, long acting formulations are more expensive than immediate release alternatives and are not benefits in all insurance plans.

Long acting ADHD medications have been available in Canada since 2003. Long acting methylphenidate stimulants include Concerta (extended release MPH), generic MPH-extended release and Biphentin (controlled release MPH). Long acting amphetamine stimulants include Adderall XR (mixed salts amphetamine) and Vyvanse (lisdexamfetamine dimesylate). Strattera (atomoxetine) is a non-stimulant long acting medication indicated to treat ADHD. They are all indicated for the treatment of ADHD in patients aged six years and older.

In various publications long-acting (LA) formulations are also referred to as extended release (ER or XR) or modified release (MR) while short acting (SA) formulations are also referred to as immediate release (IR).

This report will review the evidence based guidelines and recommendations on long versus short acting medications used to treat ADHD. Recommendations for the place in therapy of
atomoxetine, when available, are stated separately from those recommendations on the use of long acting stimulants.

RESEARCH QUESTION

1) What are the evidence-based guidelines and recommendations on long versus short acting drugs for attention deficit/hyperactivity disorder in children?

KEY MESSAGE

Although evidence-based recommendations support the use of stimulants as first line therapy when treating children with ADHD, the recommendation to use long acting formulations over short acting is based on expert opinion. Considerations include patient preference, convenience, compliance, reducing stigma, and the potential for drug diversion.

METHODS

A limited literature search was conducted on key resources including PubMed, ECRI, 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. The relevant population was children and adolescents (aged ≤18 years). Guidelines were excluded if they were not systematically developed or were representative of a smaller jurisdiction (i.e. US State), or specific healthcare organization or health plan.

The AGREE (Appraisal of Guidelines for Research and Evaluation) instrument was used to evaluate the quality of the guidelines identified in the literature search.12 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.

SUMMARY OF FINDINGS: GUIDELINES AND RECOMMENDATIONS

Eight guidelines that addressed long acting and short acting 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 1.

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

<table>
<thead>
<tr>
<th>Organization</th>
<th>Year of Publication</th>
<th>Title of Publication</th>
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<tbody>
<tr>
<td>Major National Guidelines</td>
<td></td>
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<tr>
<td>SIGN (Scottish Intercollegiate Guidelines Network)</td>
<td>2009</td>
<td>Management of Attention Deficit and Hyperkinetic Disorders in children and young people: A national clinical guideline.</td>
</tr>
<tr>
<td>NICE (National Institute for Health and Clinical Excellence)</td>
<td>2009</td>
<td>Attention Deficit Hyperactivity Disorder: Diagnosis and Management of ADHD in children, young people and adults</td>
</tr>
<tr>
<td>Royal Australasian College of Physicians</td>
<td>2009</td>
<td>Australian Guidelines on Attention Deficit Hyperactivity Disorder</td>
</tr>
<tr>
<td>Additional Guidelines</td>
<td></td>
<td></td>
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<tr>
<td>Canadian ADHD Resource Alliance (CADDRA)</td>
<td>2011</td>
<td>Canadian ADHD Practice Guidelines 3rd edition</td>
</tr>
<tr>
<td>Canadian Paediatric Society (CPS) (Feldman et al)</td>
<td>2009</td>
<td>Extended-release medications for children and adolescents with ADHD</td>
</tr>
<tr>
<td>American Academy of Child and Adolescent Psychiatry</td>
<td>2007</td>
<td>Practice parameter for the Assessment and Treatment of Children and Adolescents with ADHD</td>
</tr>
<tr>
<td>American Academy of Child and Adolescent Psychiatry (Gleason et al)</td>
<td>2007</td>
<td>Psychopharmacological Treatment for Very Young Children: Contexts and Guidelines</td>
</tr>
<tr>
<td>European Society of Child and Adolescent Psychiatry (Banaschewski et al)</td>
<td>2006</td>
<td>Long-acting medications for hyperkinetic disorders: a systematic review and European treatment guideline</td>
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</table>

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. 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.

The overall aim of the guideline was to provide a framework for the evidence based assessment and management of ADHD/HKD from which multi-disciplinary and multi-agency approaches could be developed locally. The Guideline Development Group was multidisciplinary, including practicing clinicians and patient / care giver representatives. In addition, there was support provided by SIGN 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. The guideline was reviewed by a number of independent expert referees. This guideline was funded by NHS Quality Improvement Scotland. 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 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 MA, SR or good quality RCT and directly applicable to the target population

Consensus Based (Good Practice):

a) Long acting 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)

In 2009 the Royal Australasian College of Physicians published the Australian Guidelines on ADHD. This is an extensive guideline including recommendations and a discussion of the supporting evidence for all aspects of the diagnosis and treatment of ADHD. These guidelines are currently considered draft until a formal Conflict of Interest investigation into a researcher is completed in the United States. The website notes that “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.” National Health and Medical Research Council (NHMRC) guideline development processes were followed. The complete guideline development process was available as a separate appendix. Steps included a literature review, stakeholder consultation, public consultation, email and face to face meetings.

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 guideline applies to the care of preschoolers, children, adolescents and adults with ADHD. It is 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, education as well as consumers and care givers. This guideline 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 on the basis of the consensus opinion of the clinicians, educators and consumers from the reference group. Funding for these guidelines was provided by the Australian Government 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/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 causing 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. A technology appraisal on “methylphenidate, atomoxetine and dexamfetamine for the treatment of ADHD in children and adolescents” informed the recommendations on drug treatment. The clinical practice guideline is high quality and was developed based on methods outlined in the NICE Guideline Manual. 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-centered, evidence based guideline and is relevant for children (over the age of 3 years), young people and adults with ADHD. The guideline development group consisted of healthcare 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 where 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. The guideline was extensively reviewed by various stakeholders prior to publications. 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 was provided. The quality of evidence for each drug or topic was rated. Following the evidence review, there is 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 age 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 modified-release 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. mid-day treatment dose at school
   • the potential for drug diversion and/or misuse
   • the preferences of the child/adolescent and/or his or her parent or guardian.

e) When prescribing MPH for the treatment of children or young people, modified release 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 long versus short acting drugs in children and adolescents. These guidelines varied in their methodological quality. Recommendations on the use of long versus short acting 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 their Canadian ADHD Practice Guidelines. CADDRA is a national, independent, not-for-profit association with members from family practice, pediatrics, psychiatry, psychology and other health professions. There was no objective or clinical question 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 of development. 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 that “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 through 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 their recommendations, creates significant bias which threatens the validity of the recommendations.

Individual recommendations are 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.

**Recommendations:**

a) Long acting preparations, including Adderall XR, Biphentin, Concerta, Strattera and Vyvanse are recommended as first line treatment of ADHD.

b) Short-acting and intermediate acting preparations are listed as second line / adjunctive agents.

In 2009, the Canadian Paediatric Society published a statement on “extended-release medications for children and adolescents with attention-deficit disorder”.¹ 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 to 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: The authors acknowledge that the efficacy of IR and XR preparations are similar, as demonstrated through randomized controlled trials. Although not necessarily more efficacious than immediate release medication, the authors feel the XR preparations are more effective than immediate release 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 long acting medications for the hyperkinetic disorders. 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.

Clinical questions were identified by the authors. 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 the final document (and recommendations) was subscribed to by all authors. 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) Long acting stimulants have similar effect sizes to IR stimulants (level 1a) while effect sizes for non-stimulants (atomoxetine) are somewhat smaller.

c) Sustained release 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 long acting: 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 MA, SR 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) Long acting preparations should be available and used.
b) They should not replace short-acting 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 and Adolescent Psychiatry (AACAP) published two guidelines on the treatment of ADHD. A Practice Parameter for the Assessment and Treatment of Children and Adolescents with ADHD was published in July 2007 and Contexts and Guidelines for the Psychopharmacological Treatment for Very Young Children was published in December 2007.7,11

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.11 The Work Group consisted of academic clinicians and researchers. The parameter was targeted to clinicians who treat children and adolescents with ADHD. Clinical questions were not defined, although areas of discussion included clinical evaluation, co-morbid 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 American Academy of Child and Adolescent Psychiatry. 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 2 to 3 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 long acting 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 equally efficacious as the IR forms and have been shown to be efficacious in adolescents as well as children (reference cited)
b) Advantages of long acting: 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 short acting MPH (reference cited; RCT)
e) Short acting stimulants often used as initial treatment in small children (<16kg) for whom there are no long acting forms in sufficiently low dose (no references cited)

Although there were references 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. 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. Conflicts of interest for all members of the panel were recorded. The target population of this guideline was preschool age children (3 to 6 years). In Canada, ADHD medication is indicated in children aged six and over.

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 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 practicing 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 labeled 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 / 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 three times a day dosing.

**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, MA 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

**Limitations**

Three national evidence based guidelines were identified that were produced using rigorous scientific methods.⁴⁻⁶ 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 long versus short acting formulations.¹⁻⁷⁻⁹,¹¹ 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. Since 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 2009.¹⁰ It is not included in the guidelines reviewed, with the exception of the 2011 CADDRA guideline.

**CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:**

Three national evidence based guidelines were identified that were produced using rigorous scientific methods.¹⁻⁶ Five additional guidelines were identified that varied in their methodological quality.¹⁻⁷⁻⁹,¹¹ All guidelines reviewed were informed by evidence and developed by consensus.

Evidence-based recommendations support the use of stimulants as first line therapy when treatment is indicated for children with ADHD. These recommendations do not specify to use long or short acting formulations. Atomoxetine is a long acting non-stimulant treatment alternative that is generally considered a third line treatment alternative after methylphenidate and amphetamine stimulants, except in the presence of certain co-morbidities.
Discussions of evidence within the guidelines reviewed state that long acting formulations are equally efficacious to short acting, but not superior. Recommendations to use long acting medications in ADHD are based on expert opinion of best practice. Guideline developers acknowledge the need for more research into the benefits of long acting agents over short acting. In the guidelines, long acting stimulants are referred to as a group, without specifying individual formulations or brands; advantages of one formulation over another cannot be determined.

Advantages of short acting agents include lower cost and flexibility of dosing. Potential advantages of long acting agents include improved convenience and compliance, reduced stigma, and reduced potential for drug diversion. Expert opinion suggests that individualized treatment for each patient is best practice. Cost and the ability to pay is one consideration in selecting a treatment.

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REFERENCES:


Long versus Short Acting Drugs for Attention Deficit/Hyperactivity Disorder in Children and Adolescents


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

<table>
<thead>
<tr>
<th>Organization</th>
<th>Overall Recommendations (excerpts)</th>
</tr>
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<tbody>
<tr>
<td>SIGN (2009)</td>
<td>For school aged children and young people with hyperkinetic disorder (severe ADHD) medication is recommended (Grade A)</td>
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<tr>
<td></td>
<td>Psychostimulants are recommended as the first choice medication for the core symptoms of ADHD/HKD in children. (Grade A)</td>
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<td></td>
<td>IR vs ER</td>
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<td></td>
<td>Use of modified release formulations or ATX should be considered where there is likelihood of diversion (good practice point)</td>
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<td></td>
<td>Clinicians should familiarise themselves with the release patterns of the different methylphenidate formulations. It may be necessary to combine IR and MR preparations to provide medications cover throughout the day. (good practice point)</td>
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<td></td>
<td>When selecting a formulation, clinicians should consider practical issues of convenience and applicability on an individual case basis. (good practice point)</td>
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<tr>
<td>Place in therapy: atomoxetine</td>
<td>Atomoxetine is recommended as treatment for the core symptoms of ADHD/HKD in children where psychostimulant medications is not appropriate, not tolerated, or is ineffective. (Grade A)</td>
</tr>
<tr>
<td>Grade A</td>
<td>at least one MA, SR or good quality RCT and directly applicable to the target population</td>
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<tr>
<td>Good Practice Point</td>
<td>recommended best practice based on the clinical experience of the guideline development group</td>
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<thead>
<tr>
<th>NICE (2009)</th>
<th>Overall Recommendations (excerpts)</th>
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<tbody>
<tr>
<td></td>
<td>Drug treatment is not indicated as the first-line treatment for all school age children and young people with ADHD. It should be reserved for those with severe symptoms and impairment</td>
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<td>Where drug treatment is considered appropriate, MPH, ATX and DEX are recommended,</td>
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<td>If there is a choice of more than one appropriate drug, the product with the lowest cost should be prescribed.</td>
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<td></td>
<td>To improve adherence to drug treatment, simple drug regimens (for example, once-daily modified-release doses) are recommended for people with ADHD.</td>
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<tr>
<td>IR vs ER</td>
<td>The decision regarding which product to use should be based on factors including</td>
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<td>specific issues regarding compliance, i.e. mid-day treatment dose at school</td>
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<td>the potential for drug diversion and/or misuse</td>
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<td></td>
<td>the preferences of the child/adolescent and/or his or her parent or guardian.</td>
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<td></td>
<td>When prescribing MPH for the treatment of children or young people, MR preparations should be considered for the following reasons:</td>
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<td></td>
<td>convenience</td>
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<td></td>
<td>improving adherence</td>
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<td></td>
<td>reducing stigma (does not need to take medication at school)</td>
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<td></td>
<td>reducing problems schools have in storing and administering controlled drugs</td>
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<td>their pharmacokinetic profiles.</td>
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<td>Alternatively, IR preparations may be considered if more flexible dosing regimens are required, or during initial titration to determine correct dosing levels.</td>
</tr>
</tbody>
</table>

| Place in therapy: atomoxetine | 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. |

**No Grades** were provided for each recommendation. No link between the recommendation and supporting evidence was provided.
### Organization Recommendations

<table>
<thead>
<tr>
<th>Royal Australasian College of Physicians(^6) (2009)</th>
<th>Overall recommendations (excerpts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>· Not all people with ADHD require pharmacological management. (Recommended best practice)</td>
<td></td>
</tr>
<tr>
<td>· 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)</td>
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</tr>
<tr>
<td>· Where severe, impairing ADHD is present, treatment with MPH or DEX should be considered as a first-line pharmacological treatment. (Grade A)</td>
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</table>

**IR vs ER**

- The choice of IR-MPH or ER-MPH depends on the symptom profile, as well as individual child and parent/caregiver preferences. (Grade A for children, grade B for adolescents)
- 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)
- 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)
- 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 extended-release form. (Recommended best practice)
- ER forms of stimulants should not be routinely used in preschool-aged children. (Recommended best practice)

**Place in therapy: atomoxetine**

- 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)
- ATX may be considered as the first-line medication if there is comorbid substance abuse, severe tic disorder or anxiety disorder. (Recommended best practice)

**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  
**Best practice points:** Recommended best practice based on clinical experience and expert opinion

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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; RCT=randomized controlled trial; SR=systematic review;
### APPENDIX 2: SUMMARY OF EVIDENCE AND RECOMMENDATIONS FROM GUIDELINES ON ADHD

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Relevant statements about the available evidence</th>
<th>Relevant Recommendations on long acting versus short-acting drugs</th>
<th>Major Strengths / Limitations of Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>CADDRA²  (2011)</td>
<td>• The evidence for treating ADHD is not discussed. The evidence comparing long-acting and short-acting agents is not discussed. • Central philosophy: treat each patient as a unique being; 13 principles for medication selection in the treatment of ADHD are provided (p. 55)</td>
<td>Medical Treatment for uncomplicated ADHD for children and adolescents: • Long acting preparation, including Adderall XR, Biphentin, Concerta, Straterra, and Vyvanse are recommended as first line Short-acting and intermediate acting preparations are listed as second line / adjunctive agents</td>
<td>Major Limitation: Rigour of development No discussion of evidence supporting its practice guideline. No levels of evidence provided or strength of recommendations</td>
</tr>
<tr>
<td>CPS Statement¹  (2009)</td>
<td>• The authors acknowledge that the efficacy of IR and XR preparations are similar, as demonstrated through randomized controlled trials. • Although not necessarily more efficacious than immediate release medication, the authors feel the XR preparations are more effective than immediate release.</td>
<td>• When stimulant medications for ADHD are indicated, XR preparations should be considered as first line therapy because these preparations are more effective and less likely to be diverted. • XR medications are more likely than IR medications to be used by the children and teenagers with ADHD for whom they have been prescribed.</td>
<td>Strength: identified scope and purpose and stakeholder involvement Major Limitation: Rigour of development No link between the recommendation and supporting evidence, no levels of evidence provided or strength of recommendations</td>
</tr>
<tr>
<td>European : long acting medications for the hyperkinetic disorders⁸  (2006)</td>
<td>• XR preparations are superior to placebo and some are equivalent to multiple doses of IR methylphenidate (grade A) • XR stimulants have similar effect sizes to IR stimulants (level 1a) while effect sizes for non-stimulants (ATX) are somewhat smaller. • SR medications may be less prone to abuse because they tend to have a slower rate of onset than IR (grade C) • Key advantages of IR: lower cost and flexibility of dosages (consensus) • Key advantages of LA: potential reduction of stigma at school, improved compliance and possible reduced risk of misuse (consensus)</td>
<td>• Long acting preparations should be available and used. • They should not replace short-acting 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.</td>
<td>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 Limitations: Recommendations are not assigned a level of evidence on which they are based.</td>
</tr>
<tr>
<td>Guideline</td>
<td>Relevant statements about the available evidence</td>
<td>Relevant Recommendations on long acting versus short-acting drugs</td>
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</table>
| AACAP Practice Parameter<sup>11</sup> (2007) | • LA formulations are equally efficacious as the IR forms and have been shown to be efficacious in adolescents as well as children (reference cited)  
• Advantages of long acting: greater convenience for patient and family; enhanced confidentiality at school (no dose given at school); greater compliance (no references cited)  
• Disadvantages of LA: may have greater problematic effects on evening appetite and sleep (no references cited)  
• LA MPH may improve driving performance in adolescents relative to short acting MPH (reference cited; RCT)  
• Short acting stimulants often used as initial treatment in small children (<16kg) for whom there are no long acting forms in sufficiently low dose (no references cited) | • 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)  
• Stimulants are recommended first line. (references cited)  
• 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.  
Place in therapy: atomoxetine  
• May be considered as the first line agent for ADHD in individuals with an active substance abuse problem, comorbid anxiety or tics. (references cited)  
• Preferred if the patients experiences severe side effects of stimulants such as mood lability, tics. (references cited) | Strength: major recommendations are easily identifiable, followed by a discussion of the relevant evidence  
Limitation: rigour of development – methods for formulating the recommendations are not described. |
| AACAP Treatment for the very young<sup>7</sup> (2007) | • No data exist to support ER stimulants in preschoolers.  
• Clinical experience highlights the challenges of three times a day dosing. | Steps of the algorithm  
• First line: MPH (level A)  
• Second line: AMP (level C)  
• Third line option: atomoxetine (level C)  
No formulations are specified.  
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. | Strength: identified scope and purpose and stakeholder involvement; levels of evidence assigned to each step of the algorithm  
Limitation: Specific criteria for selecting evidence were not described. |

ADHD=attention deficit hyperactivity disorder; AMP=amphetamine; ATX=atomoxetine; DEX=dextroamphetamine / dexamphetamine; ER=extended release; IR=immediate release; LA=long acting; MD=medical doctor; MPH=methylphenidate; XR=extended release