

# Extended-release medications for children and adolescents with attention-deficit hyperactivity disorder



M Feldman, S Bélanger; Canadian Paediatric Society, Community Paediatrics Committee, Psychosocial Paediatrics Committee

Français en page 598

M Feldman, S Bélanger; Canadian Paediatric Society, Community Paediatrics Committee, Psychosocial Paediatrics Committee. Extended-release medications for children and adolescents with attention-deficit hyperactivity disorder. *Paediatr Child Health* 2009;14(9):593-597.

Attention-deficit hyperactivity disorder (ADHD) affects one in 20 Canadian children, and is associated with unfavourable academic and employment records, high rates of injury and substance abuse, poor interpersonal relationships, poor mental health outcomes and poor quality of life. Medications have been shown to be efficacious in treating ADHD symptoms in controlled trials, and are associated with better social and health outcomes in observational studies. Extended-release (XR) medications for ADHD are preferred over short-acting immediate-release medications by many families and their treating physicians. The XR preparations are often unaffordable for affected families who are disproportionately among the lower socioeconomic strata.

The objective of the present statement was to critically appraise the evidence for the relative effectiveness of XR versus immediate-release medications, and to make recommendations for their appropriate use in the treatment of ADHD.

When medication is indicated, XR preparations should be considered as first-line therapy for ADHD because they are more effective and less likely to be diverted. Future research and cost-benefit analyses should consider both efficacy and effectiveness, and the diversion and misuse potentials of these medications. Industry, insurance companies and government must work together to make these medications accessible to all children and youth with ADHD.

**Key Words:** *Atomoxetine; Attention-deficit hyperactivity disorder; Effectiveness; Extended-release; Immediate-release; Mixed amphetamine salt; OROS methylphenidate; Quality of life*

Extended-release (XR) medications are preferred over short-acting medications by many families affected with attention-deficit hyperactivity disorder (ADHD) and by prescribing physicians with expertise in treating ADHD (1-4). The XR preparations, however, are expensive and often unaffordable for affected families because ADHD is disproportionately diagnosed among children from disadvantaged populations (5) within advantaged countries (6). Not all Canadian public and private medication insurance plans cover XR medications for ADHD. The objective of the present statement was to examine the evidence for the relative effectiveness of XR versus immediate-release

## Les médicaments à libération prolongée pour les enfants et les adolescents ayant un trouble de déficit de l'attention avec hyperactivité

Le trouble de déficit de l'attention avec hyperactivité (TDAH) touche un enfant canadien sur 20 et s'associe à un dossier scolaire et à un registre d'emploi défavorables, à des taux élevés de blessures et de consommation de drogues ou d'alcool, à des relations interpersonnelles médiocres, à de mauvaises issues en santé mentale et à une qualité de vie insatisfaisante. Des essais contrôlés démontrent que les médicaments sont efficaces pour traiter les symptômes de TDAH tandis que des études d'observation indiquent qu'ils s'associent à de meilleures issues sociales et de santé. De nombreuses familles, ainsi que leur médecin traitant, préfèrent les médicaments à libération prolongée (LP) contre le TDAH aux médicaments à libération immédiate (LI) et à action brève. Toutefois, les préparations à LP sont souvent inabordables pour les familles, dont un nombre disproportionné fait partie de la strate à faible statut socioéconomique.

Le présent document de principes vise à proposer une évaluation critique des données probantes sur l'efficacité relative des médicaments à LP par rapport aux médicaments à LI ainsi que des recommandations au sujet de leur utilisation convenable dans le traitement du TDAH.

Lorsque les médicaments sont indiqués, il faut envisager d'utiliser des préparations à LP comme traitement de première intention contre le TDAH parce qu'elles sont plus efficaces et moins susceptibles d'être détournées. Les futures recherches et les analyses coûts-avantages doivent tenir compte à la fois de l'efficacité de médicaments dans des études contrôlées et de leur efficacité clinique en situation réelle ainsi que du potentiel de détournement et de mésusage de ces médicaments. L'industrie, les sociétés d'assurance et le gouvernement doivent collaborer pour rendre ces médicaments accessibles à tous les enfants et adolescents ayant un TDAH.

(IR) medications, and to make recommendations for their appropriate use in the treatment of ADHD.

### METHODS

XR medications for the treatment of ADHD came to market in the year 2000 or thereafter. PubMed and the Cochrane Central Register of Controlled Trials were searched for publications from 1998 to 2008 using the following search terms: ADHD, attention deficit disorder, compliance, OROS methylphenidate (MPH), extended-release, immediate-release, atomoxetine, Adderall XR, mixed amphetamine salt, quality of life and effectiveness. In

Correspondence: Canadian Paediatric Society, 2305 St Laurent Boulevard, Ottawa, Ontario K1G 4J8. Telephone 613-526-9397, fax 613-526-3332, Web sites [www.cps.ca](http://www.cps.ca), [www.caringforkids.cps.ca](http://www.caringforkids.cps.ca)

addition, a search was conducted for relevant systematic reviews from the Cochrane database and for relevant references from identified articles. The quality of the studies were appraised using the methods of Sackett et al (7), and systematic reviews were appraised using the method of Guyatt et al (8).

### BACKGROUND

ADHD affects approximately one in 20 children worldwide (6), and if suboptimally treated, ADHD is characterized by inattention, impulsivity and hyperactivity. Affected individuals report a reduced quality of life (9), and are at increased risk for injuries (10), behaviour problems and difficulty in school (both academically and socially) (11). Children diagnosed with ADHD have a higher risk of grave long-term outcomes (12-15).

The best available evidence from randomized controlled trials demonstrates that when compared with children with ADHD whose therapy does not include medication, children who are treated with medication do better academically (16-19) and socially (20). Furthermore, because learning, behavioural and emotional issues are frequently comorbid among children with ADHD, some who are treated with both stimulant medication and behavioural strategies have the best outcomes with respect to social skills, parent-child relationships and reading achievement (21).

Long-term observational studies comparing treated and untreated children with ADHD indicate that treatment with stimulant medication is associated with a reduced risk of poor social outcomes, such as developing drug or alcohol addiction (22,23).

Given both the potential benefit of stimulant medication for ADHD and the potential side effects of medication, it is important to determine which properties of the various available preparations for ADHD improve compliance, minimize side effects and maximize effectiveness.

### EFFECTIVENESS OF XR VERSUS IR MEDICATIONS FOR ADHD

The term 'efficacy' describes how well a treatment works under tightly controlled study conditions. The term 'effectiveness' describes how well a treatment works in a natural setting in real-world conditions.

A treatment may be efficacious but ineffective if the target population refuses to take it. Effective treatment for ADHD with short-acting IR medications requires the administration of repeated doses during the day. Adverse effects of repeated doses of IR medication, plus the stigma associated with taking these medications at school as well as the disruption to the school routine, may contribute to a child becoming disinclined to take medication, ultimately rendering the prescribed therapy ineffective.

Although there is little debate that efficacy during school hours is similar for XR and IR preparations of stimulant medications (24), there now exists a body of literature showing important differences in effectiveness between XR and IR medications for the treatment of ADHD.

Surveys (25-27) report that nearly one-half of the patients prescribed IR stimulant medication admit they are not taking the medication.

Upon study completion at 14 months, the landmark Multimodal Treatment Arm study (21) demonstrated considerable symptomatic relief among children with ADHD randomly assigned to receive carefully titrated IR MPH, compared with children in the nonmedicated arm and the routine community care group. The initial Multimodal Treatment Arm cohort that received medication was subsequently re-evaluated retrospectively and found to have more modest advantages in terms of core ADHD symptoms when observed at 24 months (28), and virtually no advantage by 36 months (29). The reduction in effectiveness can be explained, at least in part, by reduced compliance over time among the group initially assigned to medication (28,29).

It is difficult to determine exactly which characteristics of various ADHD medications affect compliance differently. Although adverse effects are commonly reported as reasons for discontinuing ADHD treatment, there is inadequate evidence from the published literature to determine whether the adverse effect profiles of XR medications and IR medications differ sufficiently to differentially affect compliance.

An important determinant of compliance with stimulant medication is the age of the child. Older children are more likely to discontinue treatment (27,30). It may be that older children are less likely to comply with IR medication because of the stigma associated with the administration of the medication by school staff.

On the other hand, while long-acting XR medications for ADHD obviate the need for the interruptions and the stigma associated with multiple daily dosing during school hours, other factors related to XR medications may deter compliance. Empirically, there are reported differences in compliance when researchers compare IR stimulants with XR stimulants for ADHD.

In a randomized, unblinded, controlled trial (2) comparing XR MPH with IR MPH, the authors reported better adherence in the XR arm of the study, even under strict study conditions (which tend to improve compliance in both arms).

In a comparison of prescriptions written with prescriptions filled from a Texas Medicaid database, Sanchez et al (31) showed a significantly higher 'medication possession ratio' for XR MPH than for IR MPH. Similarly, using a California Medicaid database, Marcus et al (32) showed that children treated with XR MPH used their prescribed medication for a 37% longer duration than those prescribed IR MPH.

Using data from the United States Integrated Health Care Information Services administrative database, Lage and Hwang (33) showed that children who were initially treated with XR stimulant medications were less likely to switch, discontinue or have gaps in their treatment, than children prescribed IR stimulant medications.

The inattention and impulsivity among children with ADHD places them at higher risk for injuries. Using a large insurance claims database in the United States, Kemner and Lage (34,35) showed that children with ADHD prescribed XR stimulant medication were less likely to visit an emergency department and less likely to be hospitalized than those initially prescribed IR stimulant medications. Moreover, if hospitalized, children prescribed XR stimulant medications stayed in hospital for a shorter period of time than children with ADHD prescribed IR stimulant medications. What makes these latter observational studies more compelling is that the authors controlled for demographic characteristics, patient general health status and comorbid diagnoses.

It is difficult to know whether the favourable risk for emergency department visits and hospitalizations associated with XR preparations is due to enhanced effectiveness of XR preparations (due to enhanced compliance) or enhanced efficacy of XR preparations because of their prolonged therapeutic effect with a reduction in inattentive or impulsive (risk-taking) behaviours in the evening.

In summary, the best available evidence indicates that although XR medications are not necessarily more efficacious than IR medications, they are more effective than IR medications for the treatment of ADHD. Recently, the United Kingdom's National Institute for Clinical Excellence published an evidence-based guideline (36) with recommendations concerning the appropriate use of pharmacotherapy for children and adults with ADHD. In this guideline, the authors concluded that when children or young people are prescribed MPH, modified-release preparations should be considered. The reasons for this included:

- improving adherence,
- reducing stigma (because the child or young person does not need to take medication at school),
- reducing problems schools have in storing and administering controlled drugs, and
- their pharmacokinetic profiles.

#### MISUSE AND DIVERSION OF XR VERSUS IR MEDICATIONS FOR ADHD

'Diversion' of medication may be defined as the transfer of medication from one patient for whom it is prescribed to another patient for whom it is not prescribed. 'Misuse' refers to the use of nonprescribed medications or the use of prescribed medications at doses, times or in combinations other than for which they were prescribed.

Compared to those without ADHD, children with ADHD have a higher risk of substance abuse. However, children with ADHD who are treated with medication have a lower risk of substance abuse than children with ADHD who are not treated (22,23).

A minority of treated adolescents with ADHD, however, will misuse or divert their medication. Eleven per cent of middle-class adolescents and young adults surveyed from a large United States health maintenance organization reported that they sold their stimulant medication

and that 22% misused it. The subgroup with comorbid conduct disorder was at greatest risk (37). In Canada, a survey (38) of high school children from the Atlantic provinces revealed that 26% of adolescents report having diverted their ADHD medications at one time or more. These surveys studied children who were, for the most part, prescribed IR MPH.

In a three-arm, double-blind, crossover comparison (39) of XR MPH, IR MPH and placebo among recreational drug users in Toronto, Ontario, study subjects were asked for their opinion regarding which preparation would have the most potential to be misused. Respondents subjectively reported IR MPH to have significantly higher misuse potential than that of the XR MPH.

A recently published, well-designed Internet-based survey (40) regarding the nonmedical use of MPH among college students was conducted. Significantly more students reported having used IR MPH than XR MPH for 'partying' and the route of choice was intranasal. Misuse of XR MPH in this study was reported at a much lower rate and was more likely to be used for 'studying' as opposed to 'partying'.

The coating mechanism of XR preparations for ADHD may make the active stimulant more difficult to extract and less likely to produce euphoria. If this is true, XR preparations should be less likely to be diverted or misused than IR preparations. Intranasal use of XR MPH to achieve a 'high' has been reported to be unsuccessful in case series (41).

A recent systematic review of the literature by Wilens et al (42) examined the diversion and misuse of ADHD medications. They concluded that IR stimulants are more likely than XR stimulants to be associated with diversion and misuse.

#### RECOMMENDATIONS

- 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.
- Future research and cost-benefit analyses should take into consideration both efficacy and effectiveness, and the diversion and misuse potential of these medications.
- Industry, private health insurance companies and government must work together to make these medications more accessible to all children with ADHD.

---

**CONFLICT OF INTEREST:** The authors of this paper receive no payment or benefit, directly or indirectly, from pharmaceutical companies, distributors, sellers or resellers of medication.

---

#### REFERENCES

1. Pelham WH, Gnagy EM, Burrows-Maclean L, et al. Once-a-day Concerta methylphenidate versus three-times-daily methylphenidate in laboratory and natural settings. *Pediatrics* 2001;107:E105.

2. Steele M, Weiss M, Swanson J, Wang J, Prinzo RS, Binder CE. A randomized, controlled, effectiveness trial of OROS-methylphenidate compared to usual care with immediate-release methylphenidate in attention deficit-hyperactivity disorder. *Can J Clin Pharmacol* 2006;13:E50-62.
3. Canadian ADHD Resource Alliance. Canadian ADHD Practice Guidelines: CADDRA 2007/2008. <[http://www.caddra.ca/english/phys\\_guide.html](http://www.caddra.ca/english/phys_guide.html)> (Version current at April 8, 2009).
4. Kutcher S, Aman M, Brooks SJ, et al. International consensus statement on attention-deficit/hyperactivity disorder (ADHD) and disruptive behaviour disorders (DBDS): Clinical implications and treatment practice suggestions. *Eur Neuropsychopharmacol* 2004;14:11-28.
5. Froehlich TE, Epstein JN, Barbaresi WJ, Kahn RS. Prevalence, recognition, and treatment of attention-deficit/hyperactivity disorder in a national sample of US children. *Arch Pediatr Adolesc Med* 2007;161:857-64.
6. Faraone SV, Sergeant J, Gillberg C, Biederman J. The worldwide prevalence of ADHD: Is it an American condition? *World Psychiatry* 2003;2:104-13.
7. Sackett DL, Haynes BR, Tugwell P. *Clinical Epidemiology – A Basic Science For Clinical Medicine*. Michigan: Little, Brown, and Company, 1985:171-97.
8. Oxman AD, Cook DJ, Guyatt GH. Users' guides to the medical literature. VI. How to use an overview. Evidence-Based Medicine Working Group. *JAMA* 1994;272:1367-71.
9. Escobar R, Soutella CA, Hervas A, Gastaminza X, Polavieja P, Gilaberte I. Worse quality of life for children with newly diagnosed attention-deficit/hyperactivity disorder, compared with asthmatic and healthy children. *Pediatrics* 2005;116:E364-9.
10. DiScala C, Lescobier I, Barthel M, Guohua L. Injuries to children with attention deficit hyperactivity disorder. *Pediatrics* 1998;102:1415-21.
11. Klassen AF, Miller A, Fine S. Health-related quality of life in children and adolescents who have a diagnosis of attention-deficit/hyperactivity disorder. *Pediatrics* 2004;114:E541-7.
12. Barkley RA, Fisher M, Smallish L, Fletcher K. Young adult outcome of hyperactive children: Adaptive functioning in major life activities. *J Am Acad Child Adolesc Psychiatry* 2006;45:192-202.
13. Biederman J, Faraone SV, Spencer TJ, Mick E, Monuteaux MC, Aleardi M. Functional impairments in adults with self-reports of diagnosed ADHD: A controlled study of 1001 adults in the community. *J Clin Psychiatry* 2006;67:524-40.
14. Wilens TE, Biederman J, Mick E. Does ADHD affect the course of substance abuse? Findings from a sample of adults with and without ADHD. *Am J Addict* 1998;7:156-63.
15. Biederman J, Petty CR, Fried R, et al. Educational and occupational underattainment in adults with attention-deficit/hyperactivity disorder: A controlled study. *J Clin Psychiatry* 2008;69:1217-22.
16. Brams M, Muniz R, Childress A, et al. A randomized, double-blind, crossover study of once-daily dexamethylphenidate in children with attention-deficit hyperactivity disorder: Rapid onset of effect. *CNS Drugs* 2008;22:693-704.
17. Carlson CL, Pelham WR Jr, Swanson JM, Wagner JL. A divided attention analysis of the effects of methylphenidate on the arithmetic performance of children with attention-deficit hyperactivity disorder. *J Child Psychol Psychiatry* 1991;32:463-71.
18. Firestone P, Kelly MJ, Goodman JT, Davey J. Differential effects of parent training and stimulant medication with hyperactives: A progress report. *J Am Acad Child Psychiatry* 1981;20:135-47.
19. Döpfner M, Gerber WD, Banaschewski T, et al. Comparative efficacy of once-a-day extended-release methylphenidate, two-times-daily immediate-release methylphenidate, and placebo in a laboratory school setting. *Eur Child Adolesc Psychiatry* 2004;13(Suppl 1):I93-I101.
20. Whalen CK, Henker B, Buhrmester D, Hinshaw SP, Huber A, Laski K. Does stimulant medication improve the peer status of hyperactive children? *J Consult Clin Psychol* 1989;57:545-9.
21. The MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. Multimodal Treatment Study of Children with ADHD. *Arch Gen Psychiatry* 1999;56:1073-86.
22. Katusic SK, Barbaresi WJ, Colligan RC, Weaver AL, Leibson CL, Jacobsen SJ. Psychostimulant treatment and risk for substance abuse among young adults with a history of attention-deficit/hyperactivity disorder: A population-based, birth cohort study. *J Child Adolesc Psychopharmacol* 2005;15:764-76.
23. Wilens TE, Faraone SV, Biederman J, Gunawardene S. Does stimulant therapy of attention-deficit/hyperactivity disorder beget later substance abuse? A meta-analytic review of the literature. *Pediatrics* 2003;111:179-85.
24. National Institute for Health and Clinical Excellence. Methylphenidate, atomoxetine and dexamfetamine for the treatment of attention deficit hyperactivity disorder in children and adolescents (including a review of guidance TA13). <<http://www.nice.org.uk/Guidance/TA98>> (Version current at April 8, 2009).
25. Hack S, Chow B. Pediatric psychotropic medication compliance: A literature review and research-based suggestions for improving treatment compliance. *J Child Adolesc Psychopharmacol* 2001;11:59-67.
26. Firestone P. Factors associated with children's adherence to stimulant medication. *Am J Orthopsychiatry* 1982;52:447-57.
27. Thiruchelvam D, Charach A, Schachar RJ. Moderators and mediators of long-term adherence to stimulant treatment in children with ADHD. *J Am Acad Child Adolesc Psychiatry* 2001;40:922-8.
28. MTA Cooperative Group. National Institute of Mental Health Multimodal Treatment Study of ADHD follow-up: 24-month outcomes of treatment strategies for attention-deficit/hyperactivity disorder. *Pediatrics* 2004;113:754-61.
29. Jensen PS, Arnold LE, Swanson JM, et al. 3-year follow-up of the NIMH MTA study. *J Am Acad Child Adolesc Psychiatry* 2007;46:989-1002.
30. Gau SS, Chen S, Chou WJ, et al. National survey of adherence, efficacy, and side effects of methylphenidate in children with attention-deficit/hyperactivity disorder in Taiwan. *J Clin Psychiatry* 2008;69:131-40.
31. Sanchez RJ, Crimmon ML, Barner JC, Bettinger T, Wilson JP. Assessment of adherence measures with different stimulants among children and adolescents. *Pharmacotherapy* 2005;25:909-17.
32. Marcus SC, Wan GJ, Kemner JE, Olfson M. Continuity of methylphenidate treatment for attention-deficit/hyperactivity disorder. *Arch Pediatr Adolesc Med* 2005;159:572-8.
33. Lage M, Hwang P. Effect of methylphenidate formulation for attention deficit hyperactivity disorder on patterns and outcomes of treatment. *J Child Adolesc Psychopharmacol* 2004;14:575-81.
34. Kemner JE, Lage MJ. Effect of methylphenidate formulation on treatment patterns and use of emergency room services. *Am J Health Syst Pharm* 2006;63:317-322.
35. Kemner JE, Lage MJ. Impact of methylphenidate formulation on treatment patterns and hospitalizations: A retrospective analysis. *Ann Gen Psychiatry* 2006;5:5.
36. National Institute for Health and Clinical Excellence. Attention deficit hyperactivity disorder: Diagnosis and management of ADHD in children, young people and adults. <<http://www.nice.org.uk/Guidance/CG72#documents>> (Version current at April 8, 2009).
37. Wilens TE, Gignac M, Swezey A, Monuteaux MC, Biederman J. Characteristics of adolescents and young adults with ADHD who divert or misuse their prescribed medications. *J Am Acad Child Adolesc Psychiatry* 2006;45:408-14.
38. Poulin C. From attention-deficit/hyperactivity disorder to medical stimulant use to the diversion of prescribed stimulants to nonmedical stimulant use: Connecting the dots. *Addiction* 2007;102:740-51.
39. Parasurampuria DA, Schoedel KA, Schuller R, et al. Do formulation differences alter abuse liability of methylphenidate? A placebo-controlled, randomized, double-blind, crossover study in recreational drug users. *J Clin Psychopharmacol* 2007;27:459-67.
40. Dupont RL, Coleman JJ, Bucher RH, Wilford BB. Characteristics and motives of college students who engage in nonmedical use of methylphenidate. *Am J Addict* 2008;17:167-71.
41. Jaffe SL. Failed attempts at intranasal abuse of Concerta. *J Am Acad Child Adolesc Psychiatry* 2002;41:5.
42. Wilens TE, Adler LA, Adams J, et al. Misuse and diversion of stimulants prescribed for ADHD: A systematic review of the literature. *J Am Acad Child Adolesc Psychiatry* 2008;47:21-31.

**COMMUNITY PAEDIATRICS COMMITTEE**

**Members:** *Drs Minoli Amit, St Martha's Regional Hospital, Antigonish, Nova Scotia; Carl Cummings, Montreal, Quebec; Barbara Grueger, Whitehorse General Hospital, Whitehorse, Yukon; Mark Feldman, Toronto, Ontario (Chair); Mia Lang, Royal Alexandra Hospital, Edmonton, Alberta; Janet Grabowski, Winnipeg, Manitoba (Board representative)*

**Consultants:** *Drs Anita Greig, Mount Sinai Hospital, Toronto, Ontario; Hema Patel, The Montreal Children's Hospital, Montreal, Quebec*

**Liaison:** *Dr David Wong, Summerside, Prince Edward Island (Canadian Paediatric Society, Community Paediatrics Section)*

**Principal author:** *Dr Mark Feldman, Toronto, Ontario*

**PSYCHOSOCIAL PAEDIATRICS COMMITTEE**

**Members:** *Drs Stacey Bélanger, Saint-Justine Hospital, Montreal, Quebec; John C Leblanc, IWK Health Centre, Halifax, Nova Scotia (Chair); Brenda Miles, Mississauga, Ontario; Clare Mitchell, London, Ontario; Alan Murdock, University of Alberta, St. Albert, Alberta*

**Liaisons:** *Clare Gray, Children's Hospital of Eastern Ontario, Ottawa, Ontario (Canadian Paediatric Society, Mental Health Section); Christine Ann Looch, Sunny Hill Health Centre for Children, Vancouver, British Columbia (Canadian Paediatric Society, Developmental Section)*

**Principal author:** *Dr Stacey Bélanger, Montreal, Quebec*

The recommendations in this statement do not indicate an exclusive course of treatment or procedure to be followed.

Variations, taking into account individual circumstances, may be appropriate.

All Canadian Paediatric Society position statements are reviewed, revised or retired as needed on a regular basis.

For the most current version, please consult the "Position Statements" section of the CPS Web site ([www.cps.ca/english/publications/statementsindex.htm](http://www.cps.ca/english/publications/statementsindex.htm)).