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Assessment of Attention Deficit/ Hyperactivity Disorder: A Canadian Perspective

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Assessment of Attention Deficit/ Hyperactivity Disorder Therapy: A Canadian Perspective

January 1999

This Overview is based on the study commissioned by CCOHTA:

Miller A, Lee SK, Raina P, et al.

A review of therapies for attention deficit/hyperactivity disorder.[1]

This Overview does not necessarily reflect the opinions of the original investigators, and was prepared by:

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ASSESSMENT OF ATTENTION DEFICIT/ HYPERACTIVITY DISORDER THERAPY

Executive Summary

The Issue

Attention-deficit hyperactivity disorder (ADHD) is the most commonly diagnosed neuropsychiatric disorder in children in North America. Psychostimulants, including methylphenidate (MPH), dextroamphetamine sulphate (DAS) and magnesium pemoline (PEM), are commonly used to treat ADHD. The use of MPH, the most commonly prescribed psychostimulant, has substantially increased in Canada and the U.S. in recent years. Concerns have been raised that this increase may be due to inappropriate prescribing and illicit use.

- Is the increased utilization of stimulant drugs appropriate or inappropriate?
- Is there sufficient evidence that stimulant drugs work in children with ADHD?
- Should drugs, psychological/behavioural therapy or some combination be recommended as general treatment for ADHD?

This Overview was reviewed by external reviewers and by members of CCOHTA's Scientific Advisory Panel. CCOHTA takes sole responsibility for the final form and content.

Study Objectives

This evaluation summarizes an analysis by Miller et al. commissioned by CCOHTA.[1] The primary purposes were:

a) To critically evaluate the clinical evidence regarding the use of MPH for ADHD in preschoolers, school-aged children, adolescents and adults. In particular four areas of concern were addressed:
   - utilization trends within Canada
   - efficacy
   - the extent of abuse/illicit use or risk thereof
   - the appropriateness of MPH prescribing

b) To conduct a systematic review of efficacy using published studies

c) To perform an economic evaluation of the cost-effectiveness of MPH, other stimulant drugs, and non-drug treatments (psychological/behavioral) for ADHD in children.

Limitations

- Due to the lack of objective criteria for the diagnosis of ADHD, it is difficult to determine the actual incidence of inappropriate prescription of MPH.
- Good quality studies on therapies other than MPH were lacking. Thus conclusions derived from the comparison of MPH to other drugs or psychological/behavioural therapy should be taken cautiously.
- The outcomes for published efficacy trials were usually based on the difference in behavioural rating scale scores. There is little work that has translated changes in scale results to clinically important changes. In published meta-analyses, one of the few clinically based outcomes (improvement in academic performance) failed to find significant changes with drug therapy.[2] Thus, conclusions based on significant changes in behavioural scales may or may not translate into clinically useful outcomes.

Conclusions

1 There are clear upward trends in consumption and prescription of MPH in Canada in recent years. Data from British Columbia and Saskatchewan indicate that this upward trend is primarily related to an increase in prescribing of MPH to children. Similar trends are found in United States and Australia.

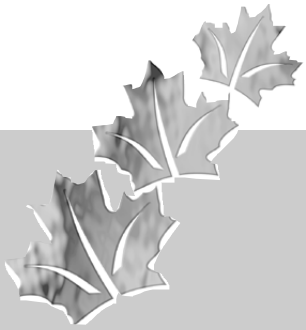
2 Abuse or misuse of stimulant drugs appears to be limited, at least in relation to other drugs. However, data specifically on MPH are lacking.

3 Evidence from a number of sources indicates indirectly that ADHD may be inadequately managed and MPH inappropriately prescribed in a proportion of cases that cannot be accurately estimated, but may range between 10 and 40 percent.

4 Sufficient evidence exists to demonstrate the efficacy of MPH in improving the behavioural problems of children and adolescent with ADHD in short term studies. The evidence of long term effectiveness of stimulant therapy is lacking. Similarly, the efficacy of stimulants in preschoolers and adults is less clearly established.

5 Meta-analysis of the clinical studies on pharmaceutical and non-pharmaceutical options for the treatment of ADHD in children and youth concluded: (a) Drug-only therapy was efficacious in ADHD and there was no difference found between MPH, DAS and PEM, (b) psychological/behavioural therapies consisting of various combinations of cognitive behavioural therapy (CBT) were not efficacious in ADHD, (c) the combination of medication and psychological/behavioural therapies were no more efficacious than medication given alone.

6 Economic analysis suggests that when PEM was excluded from consideration or included at a lower dosage (1.4 mg/kg), MPH was dominant over other pharmaceuticals, psychological/behavioural therapy, or combined drug and psychological/behavioural therapy. When results from a trial evaluated PEM at a higher dosage (2.8 mg/kg), it became a viable option but had a cost-effectiveness ratio inferior to that of MPH. Extensive sensitivity analyses including the use of a generic brand of MPH, worst case analysis, increased or decreased physician and psychologist fees, compliance, lower (16 kg) or higher (40 kg) body weight for drug dose calculation, failed to alter these conclusions.



Introduction

ADHD is the most frequently diagnosed psychiatric disorder in children in North America. Approximately 5% of school-aged children are estimated to meet the diagnostic criteria set out in the American Psychiatric Association's Diagnostic and Statistical Manual for Mental Disorders Version IV (DSM IV).[3,4]

Attention-deficit hyperactivity disorder (ADHD) is a neuropsychiatric disorder characterized by symptoms of inattentiveness and/or hyperactivity-impulsivity.[3,5] Two additional features, difficulty in following rules and excess variability of task or work performance, are also considered central to the disorder by some authorities.3 These last two features of ADHD are not diagnostic. Children affected by ADHD commonly exhibit disruptive behaviour in the classroom, underachieve academically, and tend to have conflictual relations with family members and peers. Diagnosis of ADHD is based on subjective assessments as there are no laboratory tests available for its diagnosis. Controversies continue about the definition of ADHD, its underlying pathogenesis and the best way to manage it.[3]

Management strategies and goals for ADHD broadly consist of:

- using pharmacological agents to reduce the frequency and intensity of problematic behaviours and to allow the child to achieve better self control and better regulation of attention to task;
- educating parents and teachers about the nature of ADHD thereby allowing them to have realistic expectations of the child, providing them with simple strategies to modify the child's environment to reduce behaviour problems, and training them to acquire effective behaviour management skills; and
- using psychological therapy with the child to teach him/her self-control and self-monitoring skills.

The stimulant class of drugs, MPH, DAS and PEM, are the most widely used agents for the medical management of ADHD. MPH is used in more than 90 percent of cases. Over the last five years the use of MPH has increased dramatically in Canada, United States and Australia. Concerns have been expressed in the popular media and in the medical-scientific community about this trend. Questions have been raised about the value of pharmacological therapy, possible illicit use of MPH and possible over diagnosis of ADHD. These concerns also raise the question about the cost-effectiveness of these agents compared to no treatment or other treatment modalities.

Objectives

To address the above issues the original study was undertaken with the following broad objectives:

- To critically evaluate the clinical evidence regarding the following aspects of the use of MPH in preschoolers, school aged children, adolescents and adults: (i) trends in utilization (particularly in Canada); (ii) efficacy; (iii) the extent of abuse/illicit use and (iv) the appropriateness of prescribing MPH.
- To conduct a systematic review and meta-analysis of evidence for the efficacy of three stimulant drugs, as well as three management strategies, that clinicians may adopt in managing a child with ADHD: (i) use of medication(s) alone; (ii) use of psychological/behavioural interventions alone or (iii) a combination of these two modalities.
- To conduct an economic evaluation of the cost-effectiveness of methylphenidate, other stimulant drugs, and non-drug (psychological/behavioral) treatments for ADHD in children and youth.

Clinical Review

Method

For the clinical evaluation of the use of MPH, studies reviewed were obtained by searching MEDLINE (1990- present), Current Contents (1995 to present) and hand searching of retrieved articles. The sources used to determine utilization patterns were the British Columbia Methylphenidate survey (BC MPH survey, Miller AR et al, unpublished), Health Canada Statistics and Canadian Retail Pharmacy Prescription data obtained from Intercontinental Medical Statistics (IMS). The available sources were then carefully reviewed and the relevant data extracted and synthesized.

For meta-analysis of the clinical evidence regarding the efficacy of medical and other therapies for ADHD, the studies reviewed were obtained by searching MEDLINE (1981-present), Current Contents (1995-present), Healthstar (1981-present), Psychoinfo 1981-present), First Search (1990-present), Current Index to Journal in Education (1981-present), Embase (1988-Oct 1997) and hand searching for retrieved articles.

Data Extraction for Meta-analysis

To obtain estimates of treatment efficacy, a qualitative systematic review of the evidence from treatment studies of ADHD, followed by a meta-analysis of the treatment effects, were preformed. Commonly problematic ADHD behaviors as exemplified by the Hyperactivity Index (HI)/Abbreviated Symptom Questionnaire (ASQ) were used to evaluate the effect of treatment. HI/ASQ consists of ten items derived from the longer original and revised Conners Teacher Rating Scale (CTRS) and Conners Parent Rating Scales (CPRS). These scales are checked by teachers and parents, respectively. They have been found to be sensitive indicators of medication effects.[6,7] Five of the items relate to core ADHD symptoms (inattention/distractibility, hyperactivity and impulsivity). Another five items relate to common characteristics which contribute to the social and academic adjustment problems these children experience, including disruptive and destructive behaviour, inconsistency, low frustration tolerance and liability. Studies using other ADHD evaluation scales were also included if the outcome measure was functionally similar or equivalent to the HI/ASQ. Data were extracted from the studies for one teacher and one parent rating scale. Low scores indicate better functions. Difference in effect size was calculated by subtracting control and treatment group scores. Negative scores represent a better outcome.

Results

A. Trends in MPH Utilization

Statistics from Health Canada data demonstrate a net increase in MPH consumption from 1982 to 1996. The trend appears to be irregular, with a large jump (approximately a three fold increase) between 1993 and 1996. Analysis of the Canadian Retail Pharmacy prescription data demonstrates some regional variation in this increase ranging from a three fold, to as high as a six fold, increase from 1992 to 1996.

Data from British Columbia and Saskatchewan indicate that increased prescribing of MPH occurred primarily in those children less than 19 years of age. Among children, the group most frequently prescribed for is school-aged children, ages five to 14 years. In the BC MPH survey the children of this age group accounted for nearly 86% of the children population receiving MPH prescription. In the same survey, adolescents 15 to 19 years age and preschoolers (<five years of age) accounted for 8.4% and 4.6%, respectively, of the children population receiving MPH prescriptions.

Similar patterns of increased utilization of MPH have also been demonstrated in the U.S. and Australia. Other minor factors which are responsible for an increase in utilization of MPH include the increasing use of medication for ADHD without hyperactivity (reflecting an evolution in the conceptualization of this condition), the prolongation of stimulant therapy into the secondary school years and increasing use in adults.[8]

B. Efficacy of MPH

Several studies have demonstrated that MPH and other stimulants, including DAS and PEM, are effective in reducing the symptoms of hyperactivity, impulsivity, and inattentiveness at least over a short term. Based on different meta-analyses the efficacy of various stimulants including MPH, DAS and PEM are comparable.[9,10,11] The most powerful effect of these drugs is on measures of observable social and classroom behavior, as well as measures of attention, distractibility and impulsivity. However, few children become symptom free and there is minimal evidence that stimulant therapy improves cognitive deficits or associated problems such as conduct disturbances, low self esteem, poor peer relationships or academic under-achievements. Long term therapeutic effects of MPH and other stimulants have not yet been adequately demonstrated. Beneficial effects of stimulants in preschool age children and adults are less consistent, although few well-conducted studies are available.

C. Abuse and/or Illicit Use of MPH

MPH is not a major public health problem relative to other illicit drugs. Although some diversion can be demonstrated, little of the increased volume of use can be attributed to the illicit use of stimulants.

D. Appropriateness of MPH Prescription

The issue of inappropriateness of MPH prescription is difficult to address because the criteria for the diagnosis of ADHD is continuously evolving and the fundamental role of clinical judgement for the diagnosis of this condition is widely acknowledged. Different health care professionals have different approaches for the evaluation and management of ADHD. However, there is a considerable consensus on the need for a thorough and detailed assessment that includes consideration of (i) the functional severity and impact of symptoms; (ii) the presence of symptoms in more than one setting, e.g. school and home and (iii) the exclusion of other diagnoses with similar manifestations, e.g. visual or auditory impairments, anxiety, depression and learning disabilities. Results synthesized from published surveys on a range of practices, estimate that physicians follow published guidelines for management of ADHD in approximately 70% of cases, at best. In at least 30% of

cases, management practices are likely sub-optimal. Reasons for sub-optimal practices include insufficient care and thoroughness during evaluation of drug therapy, and insufficient monitoring and attention to other important management prerequisites.

Although sub-optimal management of ADHD is not necessarily synonymous with inappropriate prescribing of stimulant drugs, it seems reasonable to conclude that in some cases MPH may be prescribed inappropriately. Based on the data from published and unpublished surveys and studies, it was roughly estimated that in 10 to 40% of cases MPH may have been inappropriately prescribed. Instances of dubious practices were found from the analysis of the BC MPH Survey in the domains of (i) prescription by physicians not customarily expected to be prescribing MPH to children, e.g. general surgeons; (ii) large inter-regional variations in rates of prescription and (iii) the number of prescriptions to under 5-year-olds.

Meta-analysis of the Efficacy Studies

The aim of this part of study was to obtain estimates of the relative efficacy of various treatment strategies for ADHD in children (age <18 years) as demonstrated by differences in scores between treatment groups. The outcome measures were commonly used behavioral rating scales such as Conners Abbreviated Symptom Questionnaires or related measures. Weighted mean difference (WMD) was used when outcomes were the same. Standardized mean difference (SMD) was used when different scales were used to measure similar behaviour. Table 1 demonstrates that all of the stimulant drugs are significantly better than a placebo as measured by the Conners Teacher Rating Scale (CTRS).

Table 1. Efficacy of Different Drugs in Children with ADHD Using CTRS*

Intervention	# of Studies	# of Subjects		WMD+ (95% CI) of CTRS Scores*	Z Value
		Control	Treatment		
MPH vs. Placebo	8	422	421	-6.732 (-5.887 to -7.567)	15.63
DAS vs. Placebo	4	61	61	-4.711 (-2.992 to -6.431)	5.37
PEM vs. Placebo					
(a) high dose	1	28	28	-7.800 (-4.361 to -11.239)	4.45
(b) low dose				-4.00 (-0.20 to -7.80)	2.06

* Conners Teacher Rating Scale
+ WMD: Weighted mean difference between control and treatment group.

Combining all stimulant drug trials and using various teacher rating scales demonstrates that drug therapy significantly improves behaviour. On the other hand, psychological/behavioural therapy failed to significantly alter behaviour as assessed by these scales. (Table 2)

Combining studies using different parent rating scales as the outcome measure produces similar conclusions as using the teacher rating scales. (Table 3)

Table 2. Efficacy of Treatments in Children with ADHD Using Teacher Rating Scales (TRSs)

Intervention	# of Studies	# of Subjects Control	# of Subjects Treatment	SMD+ (95% CI) of TRS Scores	Z Value
Drug vs. Placebo*	18	655	662	-1.065 (-0.886 to -1.243)	11.72
Psychological/ Behavioural vs. Control	2	26	24	-0.398 (0.48 to -1.276)	0.89

* Only pemoline high dose efficacy data have been included for this presentation of meta-analysis. There is no significant difference in effect size between high and low dose pemoline.

+ SMD: Standardized mean difference between control and treatment group.

Table 3. Efficacy of Treatments in Children with ADHD Using Different Parent Rating Scales (PRSs)

Intervention	# of Studies	# of Subjects Control	# of Subjects Treatment	SMD+ (95% CI) of PRS Scores	Z Value
Drug vs. Placebo	13	564	571	-0.859 (-0.578 to -1.140)	5.99
Psychological/ Behavioural vs. Control	1	13	13	-0.488 (0.294 to -1.270)	1.22

+ SMD: Standardized mean difference between control and treatment group.

Using only the Conner's Teacher Rating Scale (CTRS) or Parent Rating Scale (PRS) demonstrates that stimulant drug therapy is significantly better than no treatment.

Psychological/behavioural therapy, either alone or as an adjunct to pharmacological therapy, does not improve outcomes. (Tables 4 and 5)

Table 4: Efficacy of Treatments in Children with ADHD Using CTRS

Intervention	# of Studies	# of Subjects Control	# of Subjects Treatment	WMD+ (95% CI) of CTRS Scores	Z Value
Drug vs. Placebo	13	511	510	-6.447 (-5.604 to -7.290)	14.99
Psychological/ Behavioural vs. Control	1	13	11	0.300 (5.069 to -4.469)	0.12
Combination* vs. Placebo/Comparison	2	17	19	-3.777 (0.510 to -8.064)	1.73
Combination vs. Drug	3	41	35	1.285 (3.286 to -0.717)	1.26
Combination vs. Psychological/ Behavioural	3	33	35	-2.006 (0.163 to -4.174)	1.81

* Combination: Drug and psychological/behavioural.
+ WMD: Weighted mean difference between control and treatment group.

Table 5: Efficacy of Treatments in Children with ADHD Using CPRS

Intervention	# of Studies	# of Subjects Control	# of Subjects Treatment	WMD+ (95% CI) of CTRS Scores	Z Value
Drug vs. Placebo	9	404	403	-4.515 (-3.241 to -5.790)	6.95
Psychological/ Behavioural vs. Control	0				
Combination* vs. Placebo/Comparison	2	17	19	-7.345 (2.401 to -12.289)	2.91
Combination vs. Drug	2	19	19	-0.460 (2.942 to -3.861)	0.26
Combination vs. Psychological/ Behavioural	2	20	19	-5.911 (-3.190 to -8.631)	4.26

* Combination: Drug and psychological/behavioural.

Cost-effectiveness Analysis

Decision Model

The analysis was structured around a decision tree that characterized five different alternatives available to a health care professional for the treatment of a child with ADHD. These alternatives included three drug therapies (MPH, DAS and PEM), one psychological/behavioural (PSY/BEH) therapy and one combination (COMB) of PSY/BEH and MPH therapy. The model follows patients over a one year period and determines cost in terms of a one point and a six-point reduction in mean Conners Teacher Rating Scale. A six-point reduction in CTRS is considered as a valid and reliable indicator of a clinical response to treatments for ADHD.[12] The analysis assumed that untreated children had four additional visits to the general practitioner per year relative to their unaffected peers. This assumption was based on the data indicating higher incidences of accidents and injuries in children with ADHD.

Treatment Comparator

The alternatives specified above represent all of the standard modes of therapy for ADHD. In addition, the do-nothing alternative was used as an initial treatment comparator.

Results

Table 6 summarizes the cost effectiveness of different alternatives available for the treatment of ADHD in children compared to no treatment using base case estimates.

These results indicate that MPH is the most cost-effective alternative for the management of ADHD. High dose pemoline appears to be the next best choice, but its effectiveness data was obtained from one small study in 28 patients and the analysis did not consider the risk of hepatotoxicity. Although DAS does not show a six-point reduction in CTRS, such an outcome lies within the confidence interval of effectiveness data. PSY/BEH and COMB are not effective in producing clinically significant outcomes. PSY/BEH and COMB outcome data are based on the analysis of one and two small studies, respectively.

Sensitivity analyses

A number of one-way sensitivity analyses were carried out to determine the effect of altering the estimates of the variables for which reliable figures do not exist, or which are known to have a high degree of variability.

- The wide confidence intervals give uncertainty to the effectiveness data of PEM, therefore the upper limit of the 95% CI was used in a sensitivity analysis. Using this extreme, PEM became almost two times more effective and more cost-effective (C/E= $74/CTRS point) than MPH. Hence MPH dominance is sensitive to the assumed effectiveness of PEM within the boundary of the 95% CI.

Table 6: Cost-effectiveness of Alternatives

Strategy	Cost (C) ($)	Incremental Cost (>C) ($)	Effectiveness (E) (CTRS Points)	Incremental Effectiveness (>E) with 95% CI (CTRS Points)	Cost Effectiveness ($ per CTRS Point) C/E	>C/>E
Do Nothing	128	-	0	-	-	-
MPH	559	431	-6.7	-6.7	83	64
DAS	566	438	-4.7	-4.7	120	93
PEM	829	701	-7.8	-7.8	106	89
PSY/BEH	1946	1818	0.3 (no effect)	-	-	-
COMB*	2505	2377	-3.8	-3.8	659	625

* Combination: Psychological/behavioural therapy + MPH.

- Additional sensitivity analysis showed that the base case analysis was not sensitive to the upper confidence interval of effectiveness data determined for DAS, PSY/BEH and COMB.
- The outcome of different treatments is sensitive to compliance. Compliance depends upon a number of factors including dosing schedule, adverse effects and ease of administration. PEM and MPH are administered orally on a once and twice daily dosing schedule, respectively. Available data on compliance with these drugs and other agents are poor. PEM was more cost-effective than MPH when compliance with MPH therapy dropped below 30% when PEM compliance was set at 100%. However there is no evidence to suggest that PEM would result in better compliance than MPH.

Limitations

- MPH utilization data provided in the report, in terms of prescription/1000 and prescriptees (population of recipients of prescription)/1000, do not reflect the true picture of utilization because of the wide dose range used in children with ADHD. This may be due to the limitation of the availability of data regarding average maintenance dose or defined daily dose (DDD) of MPH used in children with ADHD. In addition, drug utilization data provided in the report did not distinguish between utilization of MPH for chronic maintenance therapy and intermittent therapy.
- There is as yet no confirmatory objective test available for the diagnosis of ADHD. The interpretation of standard sets of diagnostic criteria are based on subjective assessment. This may lead to inconsistency in the diagnosis of ADHD from physician to physician and thus makes it difficult to determine the actual incidence of ADHD and inappropriate prescribing of MPH.
- With the exception of studies assessing MPH for the treatment of ADHD in children, the number of acceptable trials (and thus the aggregate sample size) for each treatment strategy was small, resulting in wide 95% confidence interval for the estimates of efficacy. This problem was most marked for the psychological/behavioral and combination therapy, for which the estimates were based on fewer than 20 patients each. The evaluation of pemoline strategy included only one acceptable study.
- Behavioural therapies such as parent management training and comprehensive behaviour modification in classrooms were found to be useful for children with ADHD.[13,14] The present results regarding inefficacy of psychological/behavioural therapies are based on studies using various combinations of cognitive behavioural therapy.
- Studies included in the meta-analysis have considerable heterogeneity among themselves with respect to study quality, design, subject characteristics, interventions, outcome measures and follow up, even after taking steps to reduce it. Thus one should use caution in interpreting the results of this meta-analysis.
- The findings of the meta-analysis in the present report are limited to the effects of treatments on a particular type of outcome (i.e. observable behaviours) as captured by a narrow selection of behaviour rating scales.
- There is a high probability of systematic bias in the ranking of cost-effectiveness. This bias is due to the decreased power and relatively poor quality of effectiveness studies on certain treatment strategies, such as psychological/behavioural and combination therapy.
- In the economic evaluation of pemoline strategy, life years lost from the hepatic failure due to pemoline therapy is not included in the analysis.
- The published outcome was usually the difference in behavioural rating scale scores, rather than an outcome indicating a clinically significant improvement. The interpretation of the results of cost-effectiveness analysis then becomes less intuitive, unless the results are bundled, as they were here, into a several-point difference. This process requires an assumption that many small improvements may be equivalent to a few large improvements, an assumption that may not be tenable.
- According to the model used in the report, assumptions were made that drug therapy and psychological/behavioural therapies were provided daily and 16 hours in a year, respectively. This one-year time horizon in the model may bias the results against combination and psychological/behavioural therapies. If the results are extrapolated into the future, the skills learned may be forgotten, while the drugs may retain their effect.

The model also assumed that the efficacy is constant across baseline levels of ADHD severity. However, some literature suggests that efficacy of stimulants depends upon the quality and severity of symptoms. This obviously would affect the generalizability of the findings, but again the direction of bias in ranking of cost-effectiveness is difficult to predict without data on whether the effects are constant across treatment alternatives. The clinical trials examined in the meta-analysis, however, did not stratify according to symptom severity, and a definitive answer to the question is therefore not available.

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