A REVIEW OF THERAPIES FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

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Part 1: Overview and Clinical Evaluation of the Use of Methylphenidate for Attention-Deficit/Hyperactivity Disorder

Part 2: The Efficacy of Medical and Other Therapies for Attention-Deficit/Hyperactivity Disorder in Children and Youth: a Systematic Review and Meta-analysis of the Clinical Evidence

Part 3: Economic Evaluation of Pharmaceutical and Psychological/behavioural Therapies for Attention-Deficit/Hyperactivity Disorder
Project Overview

This is a report to the Canadian Coordinating Office of Health Technology Assessment which summarizes work completed between August 1997 and July 1998, funded by CCOHTA under RFP #ADHD-1196. The broad objectives were to (1) critically evaluate the clinical evidence regarding certain aspects of the use of methylphenidate in attention-deficit/hyperactivity disorder (ADHD) in pre-schoolers, school-aged children, adolescents and adults and (2) to conduct a systematic review of efficacy and an economic evaluation of the cost-effectiveness of methylphenidate, other stimulant drugs, and non-drug (psychological/behavioral) treatments for ADHD in children and youth.

One of the primary motivations underlying this request for evaluation was concern on the part of drug managers related to the increasing utilization of methylphenidate in both children and adults and the potential for abuse or illicit use of this drug. Concerns included whether the medication is prescribed appropriately from both a therapeutic and economic perspective, and the effectiveness of other modalities of therapy. We decided to structure this report as a three-part modular series with each section addressing a particular need or set of concerns.

Part 1, Overview and Clinical Evaluation of the Use of Methylphenidate for Attention-Deficit/Hyperactivity Disorder represents a comprehensive, synthetic and innovative review of published information and unpublished data to deal with the questions of utilization, efficacy, abuse/illicit use and appropriateness of prescription of methylphenidate. In it we:

1. document marked upward trends in prescription of methylphenidate in Canada and find that the increasing prevalence of use is largely (though not entirely) related to increased prescription to children and youth. Possible reasons for these increases are discussed;
2. describe the robust body of evidence for the efficacy of methylphenidate in ameliorating the behaviour problems of children and adolescents with ADHD in short-term studies. We also note, however, that its efficacy with pre-schoolers and adults is less clearly established, and that evidence of long-term effectiveness of stimulant therapy remains lacking;
3. find that abuse/illicit use of stimulant drugs appears to be limited, at least in relation to other drugs. However, data on methylphenidate specifically, and data from the last few years, are lacking. We acknowledge that the potential exists for significant abuse/illicit use; and finally
4. we conclude on the basis of a qualitative analysis of indirect evidence from various sources that management of ADHD is likely to be suboptimal in at least a sizeable minority of cases, and that in some of these cases, methylphenidate will likely have been prescribed inappropriately. We recognize, however, the difficulties in evaluating Appropriateness in a domain where a fundamental role for individual clinical judgment is widely acknowledged, and where the political and economic realities of service delivery in the education and health care sectors mitigate against optimal care for children with developmental and behavioral disorders. We also recognize the need to place the question of appropriateness within the context of current North American social-cultural attitudes and pressures.
Part 2, The Efficacy of Medical and Other Therapies for ADHD in Children and Youth: A Systematic Review and Meta-analysis of the Clinical Evidence involves a systematic search for and evaluation and meta-analysis of data to address the relative efficacy of the stimulant drugs (individually and collectively), psychological/behavioural therapies, and combinations of drugs and psychological/behavioural therapies. An important purpose of this process was to derive estimates of efficacy that could be incorporated into the subsequent cost-effectiveness analysis. In terms of improvements as teacher and parent ratings of behaviours that are likely to bring a child with ADHD to clinical attention, the stimulant drugs were consistently efficacious and no clear differences were detected between methylphenidate, dextroamphetamine and pemoline. The effect sizes (weighted mean difference) (WMD) found on the Conner Teacher Rating Scale for individual drugs vs. placebo were as follows: methylphenidate (8 studies, 421 subjects) WMD = - 6.73, 95% CI = - 7.57, - 5.89; dextroamphetamine (4 studies, 61 subjects) WMD = - 4.71, 95% CI = - 6.43, - 2.99; pemoline high dose (1 study, 28 subjects) WMD = - 7.8, 95% CI = - 11.2, - 4.36; pemoline low dose (1 study, 28 subjects) WMD = - 4.0, 95%, CI = - 7.8, - 0.2. Psychological/behavioural therapies were not consistently efficacious. Combinations of medications with psychological/behavioural therapies were no more efficacious than drug therapy alone, and showed an inconsistent pattern of efficacy when contrasted with no therapy/placebo or with psychological/behavioural therapies alone. A very cautious interpretation of these findings is advised, however, because serious methodological difficulties inherent in the treatment literature on ADHD necessitated a number of decisions to be taken regarding the design of our study that potentially compromise internal validity and external generalizability.

Part 3, Economic Evaluation of Medical and Psychological/Behavioural Therapies for ADHD used the estimates of efficacy derived from Part 2 and costs from published sources and expert panels in a decision analytic model to analyze incremental cost-effectiveness of drug therapy alone, psychological/behavioural therapy alone, and a combination of these two modalities. The economic analysis suggests that, when pemoline is excluded from consideration or included at the lower dosage found in the literature, methylphenidate is dominant over both the other pharmaceutical and the non-pharmaceutical or combined options. When pemoline is included at the higher dosage found in the literature, it becomes a viable option but has a cost-effectiveness ratio inferior to that of methylphenidate. The conclusions are generally robust in extensive sensitivity analyses. As was the case with Part 2, methodological limitations indicate the need for extreme caution in interpreting these findings and applying them to policy decisions.
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Part 1: Overview and Clinical Evaluation of the Use of Methylphenidate for Attention-Deficit/Hyperactivity Disorder

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1. Background

Methylphenidate hydrochloride (MPH), widely-known by the trade name Ritalin, is the most frequently used modality of treatment for children with attention-deficit/hyperactivity disorder (ADHD). ADHD is a syndromic diagnosis consisting of a combination of four core behavioural features: developmentally inappropriate levels of inattentiveness to task, distractibility, impulsiveness and motoric overactivity.\(^1,2\) It is strongly associated with academic underachievement, a pattern of conflictual and often unsatisfactory relations with peers, family members and teachers, and low self-esteem. These associated features probably account for much of the morbidity of the condition. In spite of the fact that ADHD is the most frequently diagnosed behaviour disorder in North American children\(^3\) and the most abundantly researched entity in child psychiatry, controversies continue about the definitional limits of the ADHD syndrome, its underlying pathogenesis, and the best ways to manage it.

Given the absence of objective biological markers of an underlying neurological disorder and the fact that the behaviours of a child with ADHD may differ from those of a normal child only in degree or intensity, it is understandable that some have questioned the validity of ADHD as a diagnosis and as a psychiatric disorder.\(^4,5\) Critics have also tried to discredit the validity of this disorder by pointing to the many changes in conceptualization, categorization and nomenclature that have arisen with successive versions of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM) which defines (by consensus among experts) diagnostic criteria for the disorder in North America. Adding to the controversy is the fact that in many countries (European countries, for example) the diagnosis is used only minimally whereas in North American studies, it has been estimated that 3\(^\text{B}5\%\) of school-aged children are diagnosed with ADHD (DSM- IV).\(^1\)

The controversies about the existence and definitional limits of ADHD understandably extend to issues of management of children with behaviours characteristic of ADHD. Psychostimulant drugs have been known for many years to be useful in the management of children with behavioural disorders including those previously labelled as hyperactive and having minimal brain dysfunction,\(^6\) many of whom would now be diagnosed with ADHD. More recently, there has been abundant evidence from short-term intervention studies of the clinical efficacy of MPH in controlling the core symptoms of ADHD and normalizing behaviour.\(^7,8\) Benefits have been found in home, classroom and laboratory contexts and these include reductions in off-task behaviour, motor restlessness and conflictual interactions, improved ability to restrain impulsive responding and improved performance on a variety of learning and academic tasks. However the dilemma for clinicians and often for parents has been whether and when to use psychoactive drugs with children with disordered or difficult-to-manage behaviours.

It has been estimated that between 50\% and 90\% of children diagnosed with ADHD in the U.S. will be treated with stimulant drugs at some point in time.\(^9,10\) of whom 70\% will receive methylphenidate,\(^10\) and further that between 2 and 4\% of American children between the ages of 5 and 14 years are receiving stimulant medication for management of ADHD.\(^9,11\) Critics of the use of medication point to the diagnostic difficulties mentioned above, the potential for as-yet undocumented risks in using psychoactive medication over long periods with children, and the fact that evidence for medium to long term effectiveness of medication remains
undemonstrated. An argument advanced to explain the discrepancy between short-term efficacy studies and long-term outcome studies is that medication alone cannot be expected to be effective over the long term for a disorder that pervades many or most aspects of daily functioning and which often co-exists with other conditions predisposing to adverse outcomes such as learning disabilities, conduct disorders and social disadvantage. A corollary to this argument is that longer term changes in outcome may perhaps be found when medical therapy is combined with other forms of intervention. Whereas short-term efficacy studies have shown that no single non-medication intervention when used alone produces superior effects to medical therapy alone, there is some evidence from medium-term follow-up studies that combinations of medical therapy with other modalities (parent counselling and training, behaviour modification approaches, social skills training and educational interventions) may selectively improve outcome.

Over the past few years concerns have been expressed in the popular media and the medical-scientific community about the increasing prevalence of MPH prescriptions and about possible over-diagnosis of ADHD and over-prescription of MPH. There are concerns about the safety of individual patients who take the drug (e.g. the possibility of adverse effects), the potential for illicit use and abuse of these drugs, the economic impact of increasing prescriptions and the relative effectiveness and safety of non-drug interventions.

2. Objectives
The aim of this section (Part 1) of the report is to evaluate critically the clinical evidence regarding the use of MPH for ADHD in pre-schoolers, school-aged children, adolescents and adults with reference to four particular areas of concern: (1) trends in utilization (particularly in Canada); (2) efficacy; (3) the extent of abuse/illicit use or risk thereof; and (4) the appropriateness of prescription of MPH. In subsequent sections we present the results of a systematic review of the literature on the efficacy of medical and non-medical modalities of therapy for ADHD and an economic evaluation to compare MPH to other stimulants as well as to psychological/behavioural forms of therapy.

3. Methodology
To address each of the four areas of concern, we sought to be as systematic and comprehensive as possible in locating, extracting and synthesizing available data within the constraints imposed by this section being only one of three to be reported, and limited resources. A particular set of data needs was drawn up for each question area. The search for data involved tapping multiple sources as described under the individual question areas below. The available sources were then carefully reviewed and the relevant data extracted and synthesized, presented as findings. Finally, the findings are critically reviewed and commented upon in the sections headed

Review of Therapies - Part 1
4. Results
4.1 Trends in MPH Utilization
4.1.1 Data needs
1. Amount of MPH consumed in Canada in recent years.
2. Number of prescriptions for MPH and prescriptees in Canada and its regions in recent years.
3. Number of prescriptions and prescriptees in other western countries in recent years.

4.1.2 Sources of data
4.1.2.1 Computerized databases
A search of the English language literature in the Medline (since 1990) and Current Contents (since 1995) electronic databases was conducted using keywords Attention deficit hyperactivity disorder, methylphenidate, central nervous system stimulants, and related terms cross-referenced against terms that included Epidemiology, prevalence, and utilization. Relevant article titles and abstracts were scrutinized to seek relevant information.

4.1.2.2 Handsearching
A list of key review articles for handsearching was identified consisting of publications in major psychiatric, psychological and pediatric journals, chapters in major psychiatric and pediatric textbooks and sections of books dealing with ADHD and published since 1995. The list appears in Appendix 1. These sources were scrutinized and relevant articles were retrieved and reviewed.

4.1.2.3 Other sources
B.C. Methylphenidate Survey (Miller AR, Armstrong RW, Lalonde CE, unpublished). The prescription of MPH is regulated in B.C. under the province’s Triplicate Prescription Program. This mandates central notification of all prescriptions of MPH to the B.C. College of Physicians and Surgeons. We have accessed the Triplicate Prescription Program file to create a database of the population of recipients of prescriptions of MPH (referred to in the remainder of this report as prescriptees) in the province of B.C. from 1990 to 1996. The Triplicate Prescription Program database includes a unique personal identifier for each prescriptee and prescribing physician (withheld from the investigators to ensure anonymity of prescriptees and prescribers), the prescriptees postal code and date of birth, and information about the formulation of MPH prescribed, tablet strength, number of tablets, date dispensed and a pharmacy identifier. Linkage procedures were applied to add further data about prescriptees and prescribers. Linkage was made with files managed by the B.C. Ministry of Health covering background information on all persons enrolled under the Province’s health insurance plan (the Medical Services Plan), as well as information on payment claims, hospital separations and other indicators of health services utilization, files managed by Vital Statistics that include reporting of deaths, and files that contain further particulars of B.C. physicians. The setup and analysis of this database is a joint venture between investigators in the Department of Pediatrics at the University of B.C. (Principal Investigator A. Miller) and the university’s Centre for Health Services and Policy Research.

Intercontinental Medical Statistics (IMS). The Montreal office of this international organization provides market research and consultation services to the Canadian pharmaceutical industry.
Using extensive and continuous surveys of pharmacists and prescribing physicians, IMS can be a valuable source of information on current patterns of drug prescription and utilization in Canada. Their Compuscript file comprises data reported by a sample of almost 2000 pharmacies designed to be representative of the kinds and distribution of pharmacies across Canada. The sample is stratified by province, store type (chain or independent) and store size (large or small).

4.1.3 Findings

Figure 1 depicts an overall net increase in consumption of MPH in Canada from 1982 to 1996 from data supplied by Health Canada. The trend appears irregular over the years, with a large apparent jump between 1993 and 1994. Consumption is defined as the difference between (stock on hand from the previous year plus imports for the current year) and (stock on hand at the end of the current year plus exports for the current year).

Figure 2 depicts a monotonic increase in prescriptions of MPH dispensed from a sample of retail Canadian pharmacies from 1991 to 1996.

Figure 3 depicts regional trends in increased numbers of prescriptions of MPH from the sample of Canadian pharmacies. All regions show major increases, though the extent varies from 3-to 5-fold net increases between 1992 and 1996.

Figure 4 depicts prescriptions of MPH to persons in B.C. between 1990 and 1996, differentiating children (≤ 19 years of age) and adults.

Figure 5 depicts prescriptions of MPH to children in B.C. 1990 to 1996 by gender and age subgroups.

Figure 6 depicts the prevalence of MPH use among children in B.C. from 1990 to 1996, in terms of all children receiving a prescription in each year per 1000 children.

Figure 7 depicts the incidence of MPH use among children in B.C. from 1990 to 1996 in terms of children receiving their first-ever prescription (recorded during the six-year study window) per 1000 children.

Figure 8 depicts the number of MPH 10 mg tablets prescribed to males in Saskatchewan by age group, from 1991 to 1995.

Figure 9 depicts the number of MPH 10 mg tablets prescribed to females in Saskatchewan by age group, from 1991 to 1995.

Figure 10 depicts the prevalence of MPH treatment among Baltimore County, U.S. public school students aged 5 to 17 years, from 1991 to 1995. The prevalence figures are based on a synthesis of data from various sources as reported by Safer et al.
Figure 11 depicts the prevalence of stimulant medication use among males in New South Wales, Australia from 1988 to 1993. The data are derived from information provided by health departments of that state, though the precise method of ascertainment is not reported.

4.1.4 Conclusions
There are clear upward trends in the consumption and prescription of MPH in Canada in recent years, with an accelerating trend seen in the period since 1993, roughly. Similar uptrends are seen in the U.S. and Australia. These upward trends are robust in the sense that they are independent of the method used to obtain prevalence figures. The trends seen using IMS survey data, which involve sampling of pharmacists, are also apparent in the B.C. MPH Survey which uses database analysis of all prescriptions dispensed in the province and the Saskatchewan data which draw on a similar source of information.

The prevalence of MPH prescriptions in 1995 in the U.S. (at least in Baltimore County) at about 37/1000 appears to be substantially higher than in B.C. at about 11/1000. However, the data sources are not equivalent. The Baltimore figures are for children aged 5-17 years while the B.C data are for all children under 19 years of age. Because there are few children under five years on MPH, the prevalence for B.C. would underestimate the number of school-aged children on MPH. However it is doubtful whether this mechanism alone would account for the magnitude of the difference. It might, on the other hand, account for the slightly higher prevalence of 6 to 12 year-old prescriptees in New South Wales, Australia in 1993 in comparison with B.C.

From B.C. and Saskatchewan data we see that the trend in increased prescription of MPH is accounted for largely by increased prescription to persons under 19 years of age, i.e. to children. Finally, among children, we see that the group most frequently prescribed for is school-aged children, ages 5 to 14 years. Data from the B.C. Methylphenidate Survey shows that adolescents 15 to 19 years account for 8.4 % of prescriptees and pre-schoolers under 5 years account for 4.6% of prescriptees.

This rising trend has been attributed by some to factors such as increasing use of medication for attention deficit disorder 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. However the Canadian data cited suggest that the prescription of MPH to older individuals is not the main factor driving increasing prevalence of use. A more cogent argument is an increased frequency of clinical recognition of ADHD resulting from heightened public awareness due to the emergence of effective parent advocacy groups and, in the U.S., changes in educational law and policy which obligate public schools to identify and serve students with ADHD. The Canadian situation likely reflects trends in U.S. practices, notwithstanding the fact that similar changes in law and policy have not occurred in Canada.

4.2 Efficacy of MPH
4.2.1 Data needs
1. Evidence of the efficacy of MPH in school-aged children.
2. Evidence of the efficacy of MPH in adolescents.

4.2.2 Sources of data
Original studies of the clinical efficacy of MPH in the non-adult population were sought in the course of an exhaustive and systematic search of the ADHD treatment literature, described in Part 2 of this report. The search included a variety of electronic databases, handsearching of key reference lists and bibliographies, and requests for data made to various agencies.

In addition, for this part of the present study we searched the same electronic database described in Section 4.1.2.1 for overviews and systematic reviews of the efficacy of MPH therapy for all the age groups listed above. We also ran a less exhaustive search for original studies of MPH efficacy in the pre-school and adult populations using Medline.

Finally, the reference lists in Appendix 1 were manually searched for publications relevant to the question of efficacy in all age groups.

The materials reviewed specific to this section are listed in Appendices 2, 3 and 4, organized by age group.

4.2.3 Findings
4.2.3.1 Efficacy of MPH in school-aged children
The evidence from a large number of individual studies and our own meta-analysis which is described in Part 2 of the present series of reports attest to the efficacy of MPH in reducing the symptoms of ADHD and improving function in various domains, at least over the short term. In addition the efficacy of stimulant drugs as a group in ADHD has been evaluated in three formal meta-analyses collectively involving hundreds of published studies and thousands of subjects, a review of reviews and a recent systematic review (which we however consider as a semi-systematic review because the search for eligible studies was fairly limited, there was minimal information about inclusion and exclusion criteria for potentially eligible studies and because no attempt was made to evaluate the scientific validity of included studies).

These overviews are consistent in finding significant effects of stimulant drugs in children with hyperactivity, ADD or ADHD. Though the reviews involve stimulant drugs, the findings largely reflect MPH since it is the agent most frequently used in studies across reviews. Furthermore, the meta-analyses found that MPH does not differ significantly in efficacy from other stimulants such as amphetamine and pemoline. Therefore in quoting from this literature, we have used MPH and stimulants interchangeably.

The previously published meta-analyses show significant effects in all major domains of child functioning examined. However the magnitude of these effects varies across domains. The most powerful effects are found on measures of observable social and classroom behaviour, with effect sizes (as defined by Kazis et al., namely the difference between the means before treatment and after treatment divided by the standard deviation of the same measure before treatment) ranging from .63 to .85. (average .81) and measures of attention, distractibility and impulsivity, ranging from .75 to .84 (average .78). Effects on intelligence and achievement tests are more modest.
however and range from .19 to .47 (average .34). According to Cohen, benchmarks for assessing the relative magnitude of treatment responsiveness are that an effect size of 0.2 represents a small change, 0.5, a moderate change, and 0.8, a large change. Another way of evaluating efficacy is by estimating the proportion of subjects who are judged to show a significant improvement attributable to MPH (responders). The 1996 review of Spencer et al. found an average response rate of 70% which is very close to the figure of about 75% found by Barkley in a review 20 years ago.

It should be noted however that while hundreds of studies have demonstrated short-term efficacy of MPH, stimulant treatment in childhood has not yet been demonstrated to have long-term therapeutic effects. Various hypotheses have been put forward to account for this discrepant finding, including the methodological challenges in long-term treatment studies of children with ADHD. In a formal review of extended treatment studies, defined as lasting 3 to 7 months, Schachar et al. found stimulants to be more effective than placebo, non-pharmacological therapy and no treatment in ameliorating core behavioural symptoms of ADHD. However, few children became symptom free and there was minimal evidence that stimulant therapy improved cognitive deficits or associated problems such as conduct disturbance, low self-esteem, poor peer relationships or academic underachievement.

4.2.3.2 Efficacy of MPH in adolescents
There are relatively few treatment studies targeting this particular population and no meta-analyses. The semi-systematic review of Spencer et al. examined the use of stimulant drugs in seven studies (four controlled and three open studies) of adolescents with hyperactivity/ADHD. They found the overall rate of response within controlled studies to be highly consistent with that observed in school-aged children.

4.2.3.3 Efficacy of MPH in pre-schoolers
There are few studies of drug treatment in this population, in part because MPH is not recommended for use with children less than 6 years of age. Spencer et al reviewed five controlled studies of stimulants with pre-schoolers and concluded that young children respond less well to stimulant therapy than school-aged children. The five studies show considerable variability across outcome measures and between subjects. A recent and carefully designed trial published subsequent to Spencer’s review found substantial improvement in ADHD core behaviours in their pre-school-aged subjects (effect size of approximately 0.8) but little improvement in compliance with parental instructions. Some studies have found negative effects on mood and social interactive behaviours with peers among young children on stimulants. These and a variety of other unwanted effects have led clinicians and reviewers to conclude that MPH is not as well tolerated by young children as older children and youth, and that these effects reduce the acceptability of this form of therapy for young children.

4.2.3.4 Efficacy of MPH in adults
There are relatively few treatment studies targeting this group. Although adult ADHD is a concept which has gained in recognition and popularity in recent years, as a discrete diagnostic entity and a legitimate focus for therapeutic efforts it remains contentious. The semi-systematic review of Spencer et al. and an earlier review of pharmacotherapy of adult ADHD by this same
found conflicting results concerning the efficacy of stimulants for adults with ADHD in nine studies (six controlled and three open). The controlled studies showed variable responsiveness with response rate varying from 25 to 78% and an overall response rate of 54%, lower than that found for children and youth. One problem with the Spencer review is that clear definitions of positive response are not provided, and it would appear that the reviewers simply adopted the definitions used in the individual primary studies. The higher figure of 78% is from a recent study which used well-defined diagnostic criteria and robust doses of MPH. Some studies have reported that side effects and other considerations result in few adults, even responders, maintaining themselves on MPH therapy.

4.2.4 Conclusions
MPH as prototypic of the stimulant drugs has been found to be unequivocally efficacious in reducing symptoms associated with ADHD in school-aged children and youth over the short-term. The most powerful effects are on the core behaviours and associated behaviours such as disruptive behaviour. Improvements are also found on tests of intellectual functioning and academic achievement, but these effects are weaker. Efficacy has also been demonstrated for pre-school-aged children, and adults. However in these groups beneficial effects appear to be less consistent and adverse effects may render the treatment less acceptable. Long-term therapeutic effects of MPH have not yet been adequately demonstrated.

4.3 Abuse and/or Illicit Use of MPH

4.3.1 Data needs
1. Documentation of the prevalence of abuse or illicit use of MPH.
2. Estimation of the risk of abuse or illicit use of MPH
3. Documentation of the extent of diversion of MPH

4.3.2 Sources of data

4.3.2.1 Computerized Databases
A search of the Medline database (since 1990) and of Current Contents (since 1995) was conducted using keywords attention deficit hyperactivity disorder, methylphenidate, central nervous system stimulants, and cross-referenced with terms such as epidemiology, abuse, and illicit use. Relevant article titles and abstracts were scrutinized to seek relevant information.

4.3.2.2 Handsearching
The review articles described in Section 4.1.2.2 (see Appendix 1) were scrutinized and relevant articles were retrieved and reviewed.

4.3.2.3 Other sources
Data were sought through requests to the office of the Provincial Medical Health Officer of B.C., and the Canadian Centre on Substance Abuse.

A search of the World Wide Web was done in November 1997 and again in February 1998 using search terms Ritalin and methylphenidate.
4.3.3 Findings

It is widely appreciated that MPH tablets can be and are illicitly used for a stimulant or euphoric effect by either ingestion, injection (alone or combined with other drugs) or nasal inhalation. However the extent of abuse of MPH specifically is very difficult to define. No regional or large scale epidemiological studies have been performed to examine the prevalence or pervasiveness of the illicit use of MPH (personal communication, E. Single, President of the Canadian Centre on Substance Abuse; also Rappley M). A 1993 national survey of U.S. high school senior students reported that the illicit use of MPH, reported under the brand name Ritalin had remained stable over the previous five years at between 1% and 2% of students surveyed. This is significantly lower than the rate of alcohol and marijuana use in the same population.

Canadian data corroborate the finding that stimulant abuse is less prevalent than cannabis, LSD and cocaine. The percentage of grade 8 to 12 students in B.C reporting illicit use of one of these last three drugs over a 12-month period was 33.2%, 15%, and 3.7% respectively, compared to 2.6% for speed. Canadian data also corroborate that the proportion of Canadians who used LSD, speed or heroin was relatively stable between 1989 (0.4% of the population) and 1993 (0.3%). The incidence of hospital separations coded as nondependent abuse of drugs during the 1992-93 year was very low for Amphetamine Type drugs (4 cases) compared with Cannabis (71 cases), Hallucinogens (34 cases) Morphine Type (44 cases), Cocaine Type 167 (cases) and Other Abuse (351 cases).

In contrast to the above, material from the U.S. Justice Department’s Drug Enforcement Administration (DEA) Press Release on MPH dated October 20th, 1995, as obtained from the World Wide Web (www.usdoj.gov/dea/pubs/presrel/pr951020.html), refers to a significant (and increasing) number of children and adolescents diverting or abusing MPH medication intended for the treatment of ADHD and an increasing number of estimated emergency room mentions of MPH between 1990 and 1993. It states also that the number of mentions for MPH was significantly greater than mentions for Schedule III stimulants (such as amphetamine). The validity of these DEA assertions could not be verified for the purposes of the present report.

In terms of diversion of narcotics and controlled drugs in Canada, the following are noted: the largest thefts of narcotic drugs included in 1992 include codeine (915,014 tablets), meperidine (70,084 tablets), morphine (97,568 tablets) and oxycodone (307,248 tablets). The largest quantities of stolen controlled drugs for 1992 were MPH (51,356 tablets), phentermine capsules (17,162 capsules), barbiturate tablets (150,592) and steroid tablets (4,800 tabs). The U.S. DEA’s Press Release on MPH noted above, notes that MPH ranks in the top ten most frequently reported controlled pharmaceuticals stolen from licensed handlers.

4.3.4 Conclusions

Reports of 1-2% of senior students in the U.S. having used MPH illicitly is indicative of a large number of students in absolute terms. However, available published data suggest that abuse/illicit use of MPH is not a major public health problem relative to other illicit drugs. There are two caveats, however: (1) there are very limited published data on the extent of a problem with abuse/illicit use relating to MPH specifically; and (2) the absence of any published data from the last three years may camouflage a problem that may be growing as MPH becomes ever more...
widely prescribed. There is some indication of such a problem from anecdotal news reports from the U.S. about teens selling Ritalin tablets and the DEA data. Regarding a problem with diversion of MPH tablets through theft, there clearly is an illicit market for this drug but its extent and significance are difficult to evaluate from currently available data.

4.4 Appropriateness of MPH Prescription

4.4.1 Preamble
Any evaluation of appropriateness of a behaviour or practice requires the term appropriateness to be operationally defined. This task involves the application of a set of values which may be guided by scientific evidence or by more subjective individual or collective beliefs. Hence evaluating the appropriateness of prescription of MPH is a complex and difficult task and one which we felt could be best addressed by looking for answers to the following questions:

1. Is there consensus around how MPH should be prescribed and used?
2. How close is the fit between what practitioners currently do and what consensus suggests they should do? Are there features of current practice that might be readily construed as inappropriate or suspect?
3. What does expert opinion say about the appropriateness of current trends in MPH prescription?

4.4.2 Data needs
To address Question 1, we require information from various sources such as formal clinical practice guidelines and other authoritative sources about: (a) preconditions for the prescription of MPH and directives on when it should and should not be used; (b) practices consistent with safe and responsible prescribing; (c) who should prescribe MPH; and (d) the place of medication in the treatment regime of a child with ADHD.

To address Question 2, we require information from surveys, audits and other sources to examine physician practices in relation to prescription and follow-up of patients on MPH.

To address Question 3, we require the comments of experts in child mental health on the appropriateness or otherwise of recent trends in MPH prescription.

4.4.3 Sources of Data
Electronic databases. A search of the Medline database was performed using as key words ADD/ADHD, stimulant medication, methylphenidate and Ritalin. Among the citations obtained we focused on diagnosis and management, practice parameters, clinical practice guidelines, physician practice issues and surveys, epidemiology, reviews and commentaries. A search was also carried out with the help of University of British Columbia librarians to identify articles published in other countries and languages that may not have been indexed in Medline but that referred to practice patterns in those countries.

Handsearching of key review and chapter bibliographies (Appendix 1), of major textbooks on ADHD and of reference lists from available and retrieved papers to identify further relevant papers. An emphasis in searching for data was on publications since 1995 in leading psychiatric, pediatric or psychological journals.
B.C. Methylphenidate Survey (referenced above).

Review of other published and unpublished materials in the first authors possession.

Personal requests for data from investigators known to be working on surveys of physician management of ADHD.

4.4.4 Data analysis
Data describing frequencies and proportions were extracted from individual studies, and are presented below as raw counts and proportions. At other times, when multiple estimates were found for a certain variable across studies, these estimates were combined by calculating arithmetic means.

4.4.5 Findings

4.4.5.1 Consensus around how MPH should be prescribed and used

Database
A database of 15 sources was assembled and qualitatively analyzed to address this question of how MPH should be prescribed and used. These publications were written with a variety of purposes and audiences in mind. They did not all purport to be definitive guides on how to use medication in ADHD. Nevertheless they represent an authoritative body of directives and recommendations made by experts in four countries (U.S., Canada, U.K and Australia), that physicians seeking to learn about ADHD management and the use of MPH would likely refer to. These sources can be categorized as follows:

Guidelines, practice parameters or clinical practice guidelines published by responsible scientific or academic mental health-based groups. Represented here were the American Academy of Child and Adolescent Psychiatry, the Committee on Children with Disabilities and Committee on Drugs of the American Academy of Pediatrics, the Canadian Paediatric Society, and the New South Wales (Australia)Treatment Assessment Group (n = 5).

Book chapters from major texts in psychiatry, pediatrics or specific to ADHD (n = 4).

Recent reviews of ADHD and its treatment by leading clinicians and researchers in the field (n = 5).

A survey of attitudes toward treatment of ADHD among 24 leading academic psychiatrists in the U.K.

These sources are listed in detail in Appendix 5.

Results
Regarding when to use stimulant medication, the two themes referred to most frequently were (1) the importance of a complete and comprehensive assessment or careful appraisal before prescribing medication, and (2) the need to consider symptom severity and degree of functional
impairment in various settings in making decisions about medication (8 and 7 citations respectively). These sources note that a complete and comprehensive assessment should include information from multiple sources, aim to establish the diagnosis of ADHD, get a measure of baseline functioning and identify associated impairments or needs. Three additional citations mentioned the importance of the school system having properly evaluated the child, effected the most appropriate placement and ensured appropriate curricula and environmental accommodations prior to prescribing medication.

All the above sources were writing about MPH in the context of treatment of ADHD. A number of sources (n = 4) specifically emphasized the importance of making the diagnosis of ADHD. One author identified this as being of key importance, noting that ADHD is the only formal indication for the prescription of MPH with children, as per product guidelines. However several authors pointed out that the decision to use stimulants is not made on the diagnosis alone. Stimulants are not necessary for all children with ADHD and may be useful for others who have ADHD symptoms yet do not meet diagnostic criteria, the important factor being the presence of disabling symptoms that respond to stimulants rather than the presence of a diagnosis. Several experienced child psychiatrists consulted by the author concurred with this view and indicated that they would be willing to conduct a trial of MPH therapy for a child with significant problems of inattention, distractibility and impulsiveness even if other factors make it difficult or impossible to diagnose ADHD definitively (e.g. presence of associated learning, affective or behavioural disorders).

Weiss acknowledges the existence of a wide spectrum of opinion among child psychiatrists and psychologists on the use of stimulant medications. Four sources note that multiple factors need to be considered collectively, including severity of symptoms, preferences of the child and parents, ability of the child, parents and school to cope with the problem behaviours and success and failure of previous treatment as well as availability and accessibility of other treatments. Most authors acknowledge the centrality of clinical judgement in the decision to recommend medication and that there is no research to guide this decision.

Regarding the follow-up of a child on stimulant medication, most sources (n = 8) emphasized the importance of initial evaluation of stimulant efficacy using data from multiple sources and standardized rating scales. The point is made explicitly by many authorities that a prerequisite for ongoing stimulant therapy is the demonstration of significant benefit, defined variably as a reduction in behavioural rating scores from 25 - 50% of baseline. The sources quoted above also emphasize the need for periodic monitoring of the child's progress/status using parent and teacher ratings and academic assessments. Many sources also noted the need for a yearly re-evaluation for the need for medication by observing and assessing the child when off medication for several weeks. A number of sources noted the need for monitoring the height, weight and blood pressure of patients on MPH. A wide range of possible dosages in possible with most sources noting the dose, frequency and timing of administration depend on individual clinical needs. A number of authorities stated that doses of over 60 mg of MPH per day were rarely required, presumably following the manufacturer specifications.
Regarding contraindications and cautions, a few sources pointed out that mild impairment and reasonably good academic and behavioural adjustment indicated that MPH should not be used. Similarly if clear evidence was lacking that attentional disorders had led to the child’s social, behavioural and learning difficulties. Psychoses and thought disorder were noted to be contraindications to MPH therapy. In the NSW guidelines, stimulants were contraindicated in children under 4 years. Weiss notes that stimulants are rarely required under age 6 years and indeed the manufacturer does not recommend its use in this group. Caution is indicated when contemplating stimulant drugs with children with tic disorders, extreme anxiety and pervasive developmental disorders.

The question of who should prescribe MPH was largely untouched in the North American literature surveyed above. The Australian group mentions the assessment leading to initial prescription of stimulants is limited to consultant pediatricians, consultant child psychiatrists and other specially authorized medical practitioners. In Sayal’s U.K survey, about half of the respondents (themselves psychiatrists) felt that MPH should only be initiated by child psychiatrists and half felt that pediatricians should be able to initiate it. The vast majority agreed with general practitioners continuing the prescriptions until the next specialist review.

Finally, regarding the role of MPH vis a vis alternative treatment strategies, four sources specifically endorsed the view that medication should be used only as part of a more comprehensive treatment approach which includes behavioural and educational therapy strategies. About half of the U.K respondents felt it should only be used as an adjunct to psychological therapies. A number of additional authorities referred to the need to ensure that MPH not be used as a substitute for appropriate educational interventions and that school programmatic and environmental modifications and the involvement of the school psychologist are all in place.

### 4.4.5.2 Physician practices in relation to prescription and follow-up of patients on MPH

**Database**

Eight surveys of physician practices with regard to the management of children and youth with ADHD published or conducted in the past ten years were identified. Six of these surveys have been published in peer-reviewed journals. The two unpublished surveys have been conducted only recently, and in one of them, data have not yet been completely analyzed. However the investigator (R. Bergen, Department of Psychology, Geneva College, Pennsylvania) kindly agreed to share preliminary data. Finally, the BC Methylphenidate Survey database was searched for evidence of practices that might be construed as raising serious doubts about appropriateness. The eight studies can be briefly characterized as follows:

- A recent survey of 788 parents of children in New South Wales, Australia (NSW study) who had received prescriptions for stimulant drugs.
- A survey of B.C doctors who had prescribed MPH for children with ADHD.
Two studies of the practices of family practitioners in the U.S.\textsuperscript{55,56}

Two studies of the practices of pediatricians in the U.S.\textsuperscript{57,58}

A recent survey of 341 pediatric subspecialists in developmental-behavioural pediatrics (DBP\textsuperscript{=}s) and 209 general pediatricians in the U.S. (M. Reiff ADHD Diagnosis Survey, 1996, unpublished)

A recent survey of 646 physicians mainly in the U.S., including psychiatrists, child and adolescent psychiatrists, pediatricians, DBP\textsuperscript{=}s, family practitioners and others\textsuperscript{=} (M. Bergen ADHD Physician Prescription Practices Questionnaire, 1996, unpublished)

These sources are listed in detail in Appendix 6. The under-representation of surveys of psychiatrists\textsuperscript{=}s practice patterns is notable in view of the fact that many of the defining guidelines described above were produced by psychiatrists.

The completion rates and methodology of each of the eight surveys were different but there was sufficient commonality to be able to extract and synthesize data across surveys that related to the principal points of consensus on appropriate prescribing practices described earlier. It should be noted that an average of 53\% of subjects responded in seven surveys (range 38\% - 75\%). Therefore the results are likely to reflect practice patterns of more highly motivated physicians, who may also be more likely to be assiduous in their management of children with ADHD.

Results

Regarding the methods and comprehensiveness of assessment prior to prescribing medications, an average of 75\% of respondents (range 55\% - 95\%) reported communication with schools and teachers or reading of school records/reports (n = 5 studies).

Regarding the use of rating scales, an average of 51\% (range 20\% - 75\%) and 46\% (range 29\% - 62\%) of respondents respectively reported using parent and teacher scales (n = 3 studies). In Reiff\textsuperscript{=}s survey, however, subspecialist pediatricians (DBP\textsuperscript{=}s) reported using parent or teacher scales 84\% of the time. In Bergen\textsuperscript{=}s mixed sample of physician types, 75\% reported using rating scales\textsuperscript{=} (not further specified) frequently or almost always.

Regarding obtaining psychometric or psychoeducational testing, an average of 60\% of respondents reported getting this done (n = 3 studies) and an additional study reported 82\% of respondents obtained testing on more than 50\% of their patients\textsuperscript{=} (n = 3 studies). It should be noted that among these four sources, only a minority of respondents were primary care physicians.

Regarding making the diagnosis of ADHD and criteria used, two studies each reported that 43\% of physicians in those surveys referred patients out for diagnosis. Among physicians making the diagnosis themselves, there was a wide range in respondents who made specific use of DSM criteria, from 25\% among family practitioners\textsuperscript{56} and unspecified physicians\textsuperscript{54} to 58\% among general pediatricians and 76\% among DBP\textsuperscript{=}s (Reiff survey). In this latter survey, 76\% of DBP\textsuperscript{=}s found DSM criteria to be essential for the diagnosis compared with 58\% of general pediatricians surveyed. It is notable from this study also that 89\% and 74\% of DBP\textsuperscript{=}s and general pediatricians respectively reported using a consistent set of criteria\textsuperscript{=} to make the diagnosis, but that only in about 10\% of cases were the responses they provided in an open-ended question in the survey.
judged to be specific enough to be reproducible as criteria. In a similar vein, among Bergen respondents, 65% reported use of DSM - IV criteria: 18% DSM alone; 34.8% DSM plus clinical judgement; 10.5% DSM, clinical judgement and other method, and 1.4% DSM plus other method (Bergen survey).

Regarding evaluation of efficacy, only one study looked at the monitoring of initial response to medication. The most frequent methods were by parent report of changes in behaviour (78% of respondents) and teacher report of changes in behaviour (57%). Other studies reported in an informal way that continued monitoring relied largely on periodic re-evaluations using parent reports and use of teacher rating scales used in 34% B56% of cases (n = 2 studies). Periodic monitoring of height and weight was reported in three studies with an average of 76% of physicians performing these measurements.

**Drug holidays** or annual periods off medications were practised by an average of 67% respondents (n = 4 studies) though not apparently with the intent to evaluate an ongoing need for medication. In the NSW study, 34% did have annual drug-free periods to determine continued requirement, but in only 10% did this period take place during the school term.53

Regarding use of other modalities of therapy, 48% of family practitioners reported using behavioural therapy and 26% reported using it as a first line treatment, while 70% of pediatricians used it moderately frequently. By parent report, 38% received behavioural management advice in the New South Wales study, 30% received extra classroom support for behaviour, and 20% B34%, some form of psychological therapy.53

Regarding age limits for the use of stimulant drugs, 33% of pediatricians and 16% of family practitioners reported treating children under kindergarten age with stimulants.57,56

Across these surveys, interesting differences in the practice patterns of different specialties of physicians emerged. Some of these differences are covered above and other notable instances follow: (1) in terms of time devoted to an ADHD consultation, family practitioners spend the least time on average, general pediatricians an intermediate amount of time and specialists in developmental-behavioural pediatrics (DBP) the longest time; (2) DBP reported an average of 3.8 criteria or clinical indicators as critical to making the diagnosis of ADHD (including for example the use of DSM criteria, obtaining teacher information and consideration of comorbidity) while general pediatricians reported 1.8 such criteria or indicators (Reiff, unpublished); (3) consideration of comorbidity was considered essential in 91% of subspecialist DBP but only by 46% of general pediatricians (Reiff survey); (4) 84% of family practitioners feel that observed behaviour in the office is important diagnostically compared with 64% of pediatricians; and (5) child psychiatrists report using the highest doses of stimulants and family practitioners the lowest doses (R. Bergen, personal communication).

Bergen preliminary results also indicate differences in the exposure of physicians from different specialties to education about the management of ADHD. A significantly greater proportion of physicians affiliated with the American Academy of Child and Adolescent Psychiatry (94%) or the Society for Developmental-Behavioural Pediatrics (90%) reported receiving recent continuing
medical education on ADHD than physicians affiliated with the American Academy of Pediatrics (33.5%) or the American Academy of Family Practice (67%). Pediatricians affiliated with the Ambulatory Pediatric Association were intermediate (71% with recent exposure to continuing medical education in this area) (Bergen survey).

Finally, there was evidence of dubious practices patterns of MPH prescription to children (< 19 years) in the province of BC from analysis of the BC MPH Survey database in a number of areas. However the methodology used to identify these situations precludes the examination of individual circumstances, so this evidence can only be considered indirect. The dubious areas were as follows: (1) almost 0.7% of all prescriptions to children during the years 1990 to 1994 were written by physician specialties who would not customarily be expected to be involved in the management of ADHD in children and youth. These included general surgeons, medical microbiologists and casualty officers. Of course, some of these physicians may be registered in one specialty but also function in the role of a general practitioner; also, errors in database coding may account for some instances of prescribing attributed to unexpected sources; (2) the average prevalence of prescriptees per 1000 children across local health regions in the province of B.C. was 9.42, but the prevalence rates vary from a low of 6.51 to 22.74 per 1000. The prevalence of prescription between health regions thus varies by a factor of 3.5 and there is no readily apparent explanation for why this should be so. The low rate quoted above is for a large, mixed-income urban region (Vancouver) while the high rate is for prevalence in a smaller, more rural setting (the Thompson region); and (3) children under 5 years of age accounted for 3% of prescriptees, possibly an indicator of questionable practice in view of the manufacturers guidelines. In addition, we examined the frequency of children receiving just a single prescription of MPH during the seven-year study window. An early estimate of over 50% for this one-only phenomenon from the U.S. seemed to indicate highly questionable management practices. In B.C. on the other hand, this occurrence was found in only 19.1% of MPH prescriptees, which does not appear high given what is known from published studies of expected rates of positive and adverse responses.

**4.4.5.3 Expert opinion on the appropriateness of current trends in MPH prescription**

*Database*

This question has been addressed in passing in articles, editorials and letters in the medical and mental health literature as well as in the media. References to this question were sought through electronic database searching (Medline) and review of material collected over several years by the first author. It was impossible to be highly structured in pursuing this question in view of the range of settings in which assertions have been made and of opinions. Hence a sampling of comments and opinions from publications in the mainstream medical, psychiatric and psychological literature and from Reiff's unpublished survey is provided here to illustrate the themes used in arguing this question and the spectrum of opinion that exists.

Details of the sources cited are listed in Appendix 7.

*Results*

In Reiff's Survey (M. Reiff. ADHD Diagnosis Survey, 1996, unpublished) of 550 general and subspecialist pediatricians and psychologists, 70% felt that ADHD is over-diagnosed, 22% that it is not over-diagnosed, and 24% that it is under-diagnosed. In terms of factors believed to be
associated with overuse of stimulant medication, 78% endorsed lack of a thorough evaluation, 49% endorsed that the children may meet criteria for ADHD but actually have other disorders which appear to be ADHD, and 38% endorsed that children may not meet DSM criteria for ADHD.

Swanson et al., argue that the increasing rate of ADHD diagnosis and MPH prescription follows an increased frequency of its clinical recognition as a result of heightened public awareness secondary to the emergence of effective parent advocacy groups and changes in educational law and policy (in the U.S.) which obligate public schools to identify and serve students with ADHD.\textsuperscript{10}

Shaywitz and Shaywitz note that the increased use of stimulants might reflect a regressive step in which all behavioural and learning disorders are indiscriminately lumped together and treated in the same way. Conversely, the use of stimulant medication in newly recognized populations of affected children may reflect an increased awareness of newer concepts of behavioural and attention disorders in which the central role of inattention in the genesis of school problems is recognized.\textsuperscript{57}

Continuing this demographic trend of argument, Garber et al.,\textsuperscript{60} conclude that too many children are not being placed on medication for ADHD because population estimates of the prevalence of diagnosed ADHD in the U.S. are around over 2 million children, but a substantially lower number (750 000 to 1.6 million) are treated with MPH.

A pragmatic argument is that since stimulant medications are safe and often effective, this form of treatment is appropriate and useful for children with ADHD. Safer\textsuperscript{17} cites two studies which converge in showing that about 75% of children on stimulant medication clearly and measurably benefit from it. He also notes that parent satisfaction with the results of maintained stimulant treatment averages around 90%.\textsuperscript{17} On the other hand, Oberklaid and Jarman\textsuperscript{61} note that the fact that stimulants work so well creates a problem in that other components of a good management plan (classroom adaptation, remedial teaching, parent training, cognitive/behavioural therapy) are often not implemented, either because they are not readily available or because they are too expensive.

In a thoughtful paper, Diller\textsuperscript{62} notes that for many physicians, psychologists and educators the identification of potential ADHD and consequent stimulation medication are meeting an important need of the community. However he goes on to say that the ADHD/stimulant phenomenon may reflect how the demands on children and families have increased as the social network supporting them has declined and that the rise in stimulants is alarming and signals an urgent need for American society to re-evaluate its priorities. This theme is echoed by Vimpani from Australia\textsuperscript{16} who notes that the clinician’s desire to help the child and family by using stimulants may at times conflict with pediatricians’ collective advocacy role to promote a healthy society for children. Arguing that children in contemporary industrialized societies are exposed to many sources of social, familial and economic stress and that negative and disruptive behaviours in children may be manifestations of environmental distress, Vimpani argues that prescribing stimulants for such behaviour disorders may sometimes be against the best interests of the child.\textsuperscript{16}
Finally, an indirect comment on medication appropriateness is contained in the observations of Schachar et al. that in the U.S., as many as 75% of children with a clinical diagnosis of hyperactivity are treated with stimulants whereas medication is prescribed less frequently in Canada and is rarely used in Britain and Europe. “In these countries psychological interventions, particularly therapy aimed at altering parenting strategies, are the preferred therapy for hyperactive children. European clinicians seem to focus on the conduct disturbance and the emotional problems of hyperactive children and direct therapy toward mitigating deficient parenting practices, disturbance in family functioning and the psycho-educational deficits of the children”.

4.4.6 Conclusions
1. There is a wide-spectrum of opinion on many aspects of care of children with disorders of learning and behaviour who may have ADHD. There are no gold standards in their management and clinical judgement has an important role to play, as it presumably does in many aspects of clinical practice. However there is considerable consensus on the need for a thorough and detailed assessment that includes consideration of (a) the functional severity and impact of symptoms, (b) multiple factors in relation to the child (especially associated impairments or diagnoses), school and family, and (c) a range of possible foci of intervention.
2. There are important differences in the ways that physicians from different professional backgrounds evaluate and manage children with ADHD. The weight of consensus opinion favours the more thorough, detailed and careful procedures that are associated with specialist rather than primary care practice.
3. Synthesizing results across published surveys on a range of practices, we find that only rarely does physician practice accord with published guidelines more than 70% of the time. Hence it would not be unreasonable to suspect suboptimal management practices in at least 30% of cases of ADHD. Such practices would involve insufficient care and thoroughness at the levels of evaluation, monitoring and attention to other important management prerequisites. Considering that published surveys probably reflect the practices of more motivated and interested clinicians, it seems likely that the above figure represents an underestimate of the extent of deficiencies with regard to ADHD management and medication use. Furthermore when one considers what can realistically be accomplished in a 15- or even a 45-minute physician consultation and the time taken to contact teachers during initial evaluation of the child and for evaluation of medication efficacy, it is quite clear that the care of many children would be considered suboptimal, at least in relation to published guidelines which are the ideals.
4. While “suboptimal management” of ADHD is not synonymous with inappropriate prescription of stimulant drugs, it seems reasonable to conclude that in a significant minority of cases MPH may be prescribed to children inappropriately. The size of this minority can only be guessed at following the review above, and could range from 10% to 40% of treated cases. To estimate this proportion empirically would require a community-based audit of the management of a large number of cases of ADHD and the adoption of some kind of “gold standard” for management, which would be difficult to accomplish.
5. When noting “suboptimal management” of ADHD and inappropriate prescription of stimulant drugs it is important that the situation be viewed in the context of current North American social-cultural attitudes and pressures, as well as the political and economic realities of service delivery in the education and health care sectors.
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Appendix 1: Key Sources for Handsearching


Shaywitz BA, Fletcher JM, Shaywitz SE. Attention-deficit hyperactivity disorder. Advances in Pediatrics 1997; 44:331-367


Appendix 2: Sources of Information on Efficacy of Methylphenidate with Adolescents


Phillips S, Soffer SL. Recent advances regarding attention deficit-hyperactivity disorder in


Appendix 3: Sources of Information on Efficacy of Methylphenidate with Preschoolers


Appendix 4: Sources of Information on Efficacy of Methylphenidate with Adults


Appendix 5: ADHD Practice Parameters and Guidelines


Sayal K, Taylor E. Drug treatment in attention deficit disorder: a survey of professional


Appendix 6: Published Surveys of Physician Practices in Relation to ADHD


Appendix 7: Expert Opinion on Appropriateness of Methylphenidate Prescription


A REVIEW OF THERAPIES FOR ATTENTION DEFICIT/HYPERACTIVITY DISORDER

Part 2: The Efficacy of Medical and Other Therapies for Attention-Deficit/Hyperactivity Disorder in Children and Youth: a Systematic Review and Meta-analysis of the Clinical Evidence

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Parminder Raina, Ph.D.
Shoo K. Lee, MB.BS., Ph.D., FRCPC
Lise Olsen, BSN, MPH
**GLOSSARY OF ABBREVIATIONS**

<table>
<thead>
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<th>Description</th>
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<tr>
<td>ACPRS</td>
<td>Abbreviated Conners Parent Rating Scale</td>
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<td>ACTeRS</td>
<td>ADDH Comprehensive Teachers Rating Scale</td>
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<tr>
<td>ACTRS</td>
<td>Abbreviated Conners Teacher Rating Scale</td>
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<td>ADD</td>
<td>Attention Deficit Disorder</td>
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<td>ADDH</td>
<td>Attention Deficit Disorder with Hyperactivity</td>
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<td>ADHD</td>
<td>Attention-Deficit/Hyperactivity Disorder</td>
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<td>APA</td>
<td>American Psychiatric Association</td>
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<td>ASQ</td>
<td>Abbreviated Symptom Questionnaire</td>
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<td>CAP</td>
<td>Child Attention Profile Questionnaire</td>
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<tr>
<td>CBT</td>
<td>Cognitive-behavioural therapy</td>
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<td>CIJE</td>
<td>Current Index to Journals in Education</td>
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<td>CPRS</td>
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<td>Conners Teacher Rating Scales</td>
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<td>DAS</td>
<td>Dextroamphetamine sulfate</td>
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<td>DSM III</td>
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<tr>
<td>DSM IIIR</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, version 3, revised</td>
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<td>DSM IV</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, version 4</td>
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<td>HSQ</td>
<td>Home Situations Questionnaire</td>
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<td>MPH</td>
<td>Methylphenidate hydrochloride</td>
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<tr>
<td>RBPC</td>
<td>Revised Behaviour Problems Checklist</td>
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<td>SMD</td>
<td>Standardized mean difference</td>
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<td>SNAP</td>
<td>Swanson, Nolan and Pelham Rating Scale</td>
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<td>WMD</td>
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1. INTRODUCTION

1.1 Background

Attention-deficit/hyperactivity disorder (ADHD) is a frequently-made diagnosis among North American children. 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). The defining or core features of this syndrome relate to difficulties these children have in three domains: regulating attention to meet task demands (inattention/distractibility), inhibiting impulsive responding (behavioural disinhibition/impulsivity) and restraining task-inappropriate motor activity (hyperactivity). Russell Barkley, a leading figure in ADHD theory and research, describes two additional features which, while not diagnostic, are felt to be central to the disorder. These are deficient rule-governed behaviour and excessive variability of task or work performance over time. Limited research evidence points to a correlation between the ADHD symptom cluster and hypoperfusion of areas of the prefrontal cortex of the brain that are characteristically associated with executive functions, such as self-regulation, organization and judgment. Recent studies suggest a strong genetic component to ADHD.

Affected children commonly exhibit disruptive behaviour in the classroom, underachieve academically, and tend to have conflictual relations with family members and peers. ADHD is associated frequently with additional neurodevelopmental or psychiatric disturbances such as learning, anxiety and conduct disorders, but the symptoms of ADHD are likely to become the primary focus of the North American physician because they form a salient and readily recognizable cluster which has received considerable publicity in the medical, educational and lay media. Furthermore, they are amenable to a medical modality of therapy, namely the stimulant drugs, whose effectiveness at least over the short-term, is widely-reported in primary treatment studies, review articles and practice guidelines published in the medical literature.

Management strategies broadly consist of (a) medicating the child 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; (b) 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 (c) using psychological therapy with the child to teach him/her self-control and self-monitoring skills. Other modalities of therapy may also be applied depending on individual circumstances and needs, such as social skills training and academic tutoring.

The stimulant class of medications, comprising methylphenidate hydrochloride ("MPH", brand name Ritalin), dextroamphetamine sulphate ("DAS", brand name Dexedrine) and magnesium pemoline (brand name Cylert) are the most widely used form of medical management. These drugs act in the brain by increasing levels of catecholamines (dopamine, norepinephrine and serotonin) at the presynaptic cleft. MPH is the most frequently used agent. This drug is being prescribed to ever increasing numbers of children (described and discussed in Part 1 of this present series of reports) and there are concerns among provincial payers about whether it is...
being prescribed in an appropriate way both clinically and economically with reference to other stimulant drugs. There is also interest in whether alternatives to drug therapy are effective and being used appropriately. In this section of the report, we describe a systematic review and meta-analysis of the evidence for the efficacy of the three stimulant drugs, as well as the three main management strategies that clinicians may adopt in managing a child with ADHD: use of medication(s) alone, use of psychological/behavioural interventions alone, or a combination of these two modalities. An important purpose of the present review and meta-analysis was to obtain data that could be used in an economic evaluation of these various treatment strategies. Our cost-effectiveness analysis, based on a decision analysis model which considers the options of no therapy, medical therapy alone, psychological/behavioural interventions alone, or a combination of these two modalities, is reported in a subsequent section of the present series of reports (Part 3).

Children and youth with ADHD may present to health professionals with concerns about non-compliant or disruptive behaviour at home or school, aggressive or other socially deviant behaviours, academic underachievement or school failure, or social-emotional issues secondary to poor self-esteem. One thing they have in common is the combination of core ADHD symptoms that make up the syndrome. Ideally, a systematic review of treatment efficacy in ADHD would consider outcomes that relate to the whole array of problems with which these children present, including behavioural, academic and social-emotional. In the present study, however, the decision was made to focus on behavioural outcomes. The decision addressed a logistical need to keep the scope of the study manageable while recognizing the primacy of behavioural dysfunction in ADHD. A behavioural substrate, broadly defined to include attentional and self-regulatory functions, presumably underlies much of the impairment that children with ADHD experience across clinical presentations. Such a substrate presumably also accounts for a significant degree of the improvement that they might experience across outcome categories, as a result of treatment.

We looked therefore for a primary measure of treatment effect that would reflect behaviours that are observable in naturalistic contexts, that include the cluster of core ADHD symptoms, as well as associated behaviours such as deficient rule-governed behaviour and inconsistency in task performance over time. Behaviour rating scales and checklists completed by teachers and parents are widely-used and of established value both clinically to aid in diagnosis and monitor treatment effects, and in research applications with ADHD children.\textsuperscript{2,5,6} We reviewed the characteristics of the many behaviour rating scales in current use and scanned a sample of treatment studies in the investigators’ possession to get an idea of their relative frequency of use. We found that the Hyperactivity Index (HI) of the Conners Teacher Rating Scale (CTRS) and Conners Parent Rating Scale (CPRS), also known as the Abbreviated Symptom Questionnaire (ASQ)\textsuperscript{7} or Abbreviated Conners Teacher/Parent Rating Scales (ACTRS and ACPRS respectively) had been widely-used in treatment studies and came close to meeting our need for a measure which included both core and associated features of children with ADHD.

The HI/ASQ represents a good measure of overall psychopathology for children presenting with ADHD.\textsuperscript{7} It consists of ten items derived from factor analysis of the longer original and revised Conners Teacher and Conners Parent Rating Scales,\textsuperscript{8,9} that are most frequently checked by
parents and teachers as characteristic of hyperactive children and which have been found to be sensitive indicators of medication effects. Five of the items relate to core ADHD symptoms (inattention/distractibility, hyperactivity and impulsivity) and five to commonly (though not universally associated) characteristics which contribute to the social and academic adjustment problems these children experience, including disruptive and destructive behaviour, inconsistency, low frustration tolerance and emotional lability. The longer versions of Conners Rating Scales as well as the abbreviated versions have been thoroughly researched, validated and standardized, and very widely used to assess treatment effects in ADHD. Normative data are available. The HI/ASQ is loaded with the more disruptive symptoms of ADHD for which parents and teachers are likely to be seeking help.

Having decided to focus on a single outcome measure in the present study in the interests of parsimony and to reduce heterogeneity between, and increase comparability across, studies, the HI/ASQ was judged by the investigators to be the most relevant and appropriate single measure. Some primacy was given to the teacher-completed version for two reasons. First, a preliminary review of treatment studies showed the Teacher scale to be the more widely used. Second, in a significant proportion of cases, children with ADHD receive medical therapy for classroom-related behaviour problems, and they receive it only at school. In this situation, where effects on behaviour are predominantly occurring at school, we need teachers=observations of behaviour. However, we planned also to include the parent version, when it had been used in order to extend the range of analyses possible. Also, we created a short list of other behaviour rating scales that were similar in scope and psychometric properties to the HI/ASQ.

The decision to use behavioural rating scales as the sole category of outcome measure involved a restriction on what could be concluded about the efficacy of interventions for ADHD. The fact that the ASQ represents a mix of common, problematic ADHD behaviours is at once an advantage and disadvantage of this measure. Not all children with ADHD have all the characteristics covered in the ASQ, particularly those ADHD subgroups which were defined in the most recent fourth version of the DSM (DSM IV). Furthermore, the ASQ is most widely appreciated for its sensitivity to drug effects, and sensitivity to non-drug interventions is less well described. However, it seems reasonable to expect that teachers and parents would seek changes in the kinds of behaviours and characteristics covered by the ASQ, irrespective of treatment modality.

1.2 Objective
The objective of this 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 on commonly-used behavioural rating scales, such as the Conners Abbreviated Symptom Questionnaires or related measures. These estimates would then be used to conduct an economic analysis to compare the cost-effectiveness of these strategies. To obtain estimates of treatment efficacy, we aimed to conduct a qualitative systematic review of the evidence from treatment studies of ADHD, followed by a meta-analysis of treatment effects.

2. METHODS
2.1 Obtaining Clinical Evidence

2.1.1 Sources of clinical evidence
Evidence was sought among research studies published in peer reviewed journals, from drug manufacturers, the Cochrane library, and through handsearching of reference lists. Drug manufacturers were requested to provide published and unpublished studies available to them. Apart from this, no attempt was made to secure unpublished studies. Studies were limited to those produced in 1981 or later in order to coincide with the adoption of more detailed and stringent diagnostic criteria for children previously labeled as hyperactive or with hyperkinetic disorder, subsumed after 1980 into the category ADD and ADDH by the American Psychiatric Association's Diagnostic and Statistical Manual Edition 3, and subject to continued reformulations in subsequent versions. We also recognized the existence of three meta-analytic studies of drug treatment effectiveness for ADD/hyperactivity, published in the early 1980s, that had analyzed studies from the pre-1980 era. A formal appraisal of the quality of these meta-analytic reviews was carried out by two reviewers using the evaluative method described by Oxman and Guyatt. The reviews by Kavale and Ottenbacher were found by these stringent criteria to have major flaws and the review by Thurber to have major-to-extensive flaws. Nonetheless, all three showed a great deal of consistency in their main findings.

2.1.2 Published literature search strategy
Searches were conducted on the following electronic databases during August of 1997:
- Medline (1981 - present)
- Current Contents (1995 - present)
- Healthstar (1981 - present)
- PsycInfo (1981 - present)
- First Search (Article First) (1990-Present)
- CIJE (Current Index to Journals in Education) (1981 - present)
- Embase (1988 - 1997) (Search conducted October, 1997)

The overall search strategy was aimed at selecting all studies of drug and non-drug treatment efficacy for ADD/ADDH/ADHD across all age groups. The search strategy included controlled, uncontrolled, randomized and non-randomized studies. This initial search also identified background, review and meta-analytic articles regarding treatment effectiveness. Search terms included: Attention deficit disorder, Attention deficit disorder with hyperactivity, "attention-deficit/hyperactivity disorder", "hyperkinetic disorder" and "hyperkinesis". Search terms for drug treatment interventions included: "methylphenidate", "dextroamphetamine", "pemoline", "central nervous system stimulants", "psychostimulants", and the brand names "Ritalin", "Dexedrine" and "Cylert". Search terms for non-drug interventions included: "counseling", "psychotherapy", "cognitive therapy", "cognitive-behavioural therapy", "parent training", "family therapy", "family counseling", "behaviour therapy", "behaviour modification", "biofeedback", "neurofeedback" and "relaxation therapy".
2.1.3 Handsearching procedures

Additionally, ten bibliographic lists were identified as sources to be handsearched for additional references based on their position as up-to-date (1995 or more recent) and definitive chapters in textbooks of child and adolescent psychiatry, pediatrics and ADHD or reviews of ADHD and its treatment. These sources are listed in Appendix 1.

2.1.4 Accessing additional sources of evidence

Contact was made with the Coordinator of the Canadian Cochrane Centre in September 1997. We were informed that there were no completed reviews on the topic of effectiveness of treatment for attention deficit disorder in the Cochrane Database of Systematic Reviews, nor were any such reviews in progress. Requests for data were also made to the following drug manufacturers: Novartis (Ritalin), SmithKline Beecham (Dexedrine) and Abbott (Cylert). A number of articles published in the medical literature were supplied from their files.

2.2 Creation of Database of Intervention Effects

An important consideration in creating a database of intervention effects was the need for the database to be suitable for meta-analysis and subsequently for use in an economic evaluation of treatment options in ADHD. Because multiple sources of heterogeneity among patients, treatments and outcomes in published studies of ADHD pose significant challenges to interpreting research findings in this area,\textsuperscript{17,18} we adopted as a priority the need to minimize sources of heterogeneity between studies and subjects as far as possible. One of the ways to achieve this goal was to extract data derived from a single outcome measure. As previously described, the Abbreviated Conners Teacher and Parent Rating Scales were the instruments chosen. However, in order to avoid a potential situation of having too few data to analyze, data were also extracted on a limited number of other behavioural measures.

Steps involved in the creation of the database were: (1) identification of potentially relevant studies from initial search titles and abstracts based on their appearing to satisfy the eligibility criteria described in Section 2.2.1, and retrieval of articles using the following decision rule: if the paper definitely or possibly was eligible, it was retrieved; if it definitely was not eligible, such as a case report or review article, it was not retrieved. This step was conducted by a Masters-level research associate, who served as Project Coordinator (LO), in close collaboration around all doubtful items with the principal investigator of the overall project (AM); (2) detailed review of retrieved studies for eligibility using a predetermined set of criteria (see below); This step was performed twice - initially for the preparation of the first draft of this report, and a second time following external reviews of the first draft, in order to collect more detailed information on the ineligible studies. By the end of the second round, the vast majority of studies had been reviewed by two different
reviewers from a group of four who were Masters or Doctoral-level research associates, using protocols and forms developed for this study. Resolution of uncertainties was achieved through close consultation with the project principal investigator. For studies that met eligibility criteria, the reviewers proceeded to step (3) namely evaluation of study validity and step (4) data extraction. In order to assess the reliability of the quality evaluation and data extraction processes, ten studies (39%) were reviewed by more than one reviewer. Six were reviewed by two reviewers and four by all three reviewers. Intra-class correlation coefficients were computed to assess the interrater agreement for the validity scores. Kappa statistics were computed to assess agreement on certain descriptive categorical data.

2.2.1 Evaluation of eligibility
Retrieved studies were evaluated for eligibility against the criteria in Table 1. These eligibility criteria reflect the need to reduce heterogeneity described above, and the aim to make the treatment efficacy evaluation as ecologically relevant as possible. Hence the emphasis on studies of children who are broadly representative of the general population of children with ADHD (rather than diagnostic subgroups) and who are treated and monitored for effects in naturalistic settings, such as home and school rather than in laboratory-based settings. The rationale for restriction of eligible outcomes to rating scale measures of the common behavioural features of ADHD is presented in Section 1.1 above.

2.2.2 Study quality evaluation procedures
The methodological quality assessment scale developed by Detsky et al.\(^{19}\) was modified to meet the needs and objectives of the present review. The resulting 18-item form assessed how studies performed and reported in six key areas: randomization procedures; inclusion and exclusion of participants; descriptions of treatments provided; measurement of outcomes; methods of data analysis; and closeness of the aim of the study to the purposes of the current review. To provide the reviewers with operational definitions for the response categories of the validity form, but not to be used as an evaluative tool itself, a further form was developed based on Chalmers\(^{20}\) and tailored to reflect the quality criteria assessed in this study. (Forms available from the authors on request). The validity form provided a scoring system to generate a total quality score for each study that could range from 0 to either 34 or 36, depending on the response to one item, and that was then converted to a percentage. The quality score was used in this meta-analysis in two ways: (1) at the data analysis stage to examine whether findings of treatment efficacy were affected by quality of primary studies; and (2) to explore the relationship between quality of primary studies and variables such as study design, year of publication and treatment type.

Inter-reviewer reliability for the validity form was expressed by an intraclass correlation coefficient (rho) of 0.43 for 10 studies where ratings were made by two reviewers, and 0.79 for four studies where ratings were made by three different reviewers. There was a high degree of agreement on most but not all items. There was perfect agreement between the
two reviewers who evaluated the 10 studies on five items, one instance of disagreement on five items, two instances of disagreement on three items, three instances of disagreement on four items and eight instances of disagreement on one item. This latter item asked

Description of randomization -- adequate, partial or inadequate. However, deleting this item from the analysis did not appreciably change the intraclass correlation coefficient.

2.2.3 Data extraction procedures
A data extraction form (available from author) was created to describe background information on the characteristics of individual studies, and to capture data on the effects of various treatments. The data extraction form consisted of 6 key areas: (1) study characteristics, such as design; (2) subject characteristics, such as age and gender studied and diagnostic characteristics; (3) intervention characteristics, such as details of the type of the treatment used; (4) study findings, in terms of the results reported on main behaviour rating scales; (5) subject attrition from the study, with reasons; and (6) adverse reactions to treatment.

Reliability of data extraction between reviewers was ascertained by finding high degrees of concordance (k = 0.8 to 1.0) on most items and moderate concordance (down to k = .5) on a few items, such as coding of specific diagnostic groups (i.e. disagreements about whether subjects should be coded as ADDH (DSM III) vs. ADD/ADDH/ADHD not further specified and the number of comorbidities present in a study sample. In cases of disagreement between data extracted by the two reviewers, a further reviewer went back to the original article to resolve the difference. In addition, as a quality control measure, all extracted data for the principal dependent variable (i.e. scores from rating scales) were checked against the original study at the time of their entry to the database.

Treatment studies in ADHD employ varied and often multiple outcome measures, but we had predetermined to evaluate the effects of treatment on the commonly problematic ADHD behaviours as exemplified by the HI/ASQ. Because we did not want to exclude studies that used an outcome measure that may have been functionally similar or even equivalent to the HI/ASQ, the commonly-used teacher and parent-completed behaviour rating scales were organized hierarchically into an algorithmic chart. The hierarchical listing was established by the investigators, based on scanning the individual instruments and determining their closeness in content and purpose to the HI/ASQ. The algorithmic chart is reproduced in Appendix 2. If the study had not used the Abbreviated Conners Scales (or Hyperactivity Index), reviewers were guided to extract data from the IOWA Conners Teacher or Parent Rating Scales (IOWA CTRS and IOWA CPRS, respectively), followed by the Attentional Problems subscale on the Achenbach Child Behaviour Checklist Teacher Report Form (CBCL-TRF), the Child Attention Profile Questionnaire (CAP), Revised Behaviour Problems Checklist (RBPC), ADD-H Comprehensive Teacher Rating Scale (ACTeRS), the Home Situations Questionnaire (HSQ), and various other instruments that were not finally used.

The utility, standardization, psychometric properties, and validity of these instruments have been reported and reviewed. The Conners Scales, HSQ, CAP Questionnaire, and...
ACTeRS have all been found to be sensitive to treatment effects.\textsuperscript{2} The RBPC shows convergent validity with other instruments.\textsuperscript{6} The Abbreviated Conners Scales, IOWA Conners Scales and RBPC include a mixed group of core ADHD symptoms along with aggressive and disruptive behaviours, emotional lability, etc. The ACTeRS (Attention and Hyperactivity subscales), CAP Questionnaire and HSQ have a somewhat narrower focus on core symptoms.

2.3 Data Management and Analysis
SPSS for Windows was used to enter and analyze the validity data and the background characteristics. Meta-analytic procedures were conducted using RevMan software. RevMan software was developed by the Cochrane Collaboration for the synthesis of study data in systematic reviews.

The studies to be analyzed varied on: (1) specific stimulant drug used; (2) whether dosage was expressed in absolute terms i.e. total mg. of drug, or alternatively in relation to body weight i.e. in mg/kg; and (3) whether a single or alternatively multiple dose levels had been used and reported. To be able to utilize as much available data as possible, three decisions were made. First, that stimulant drugs would be analyzed both as individual agents (i.e. MPH, DAS and pemoline separately) as well as collectively under the heading of stimulant drugs.\textsuperscript{12,13} This approach seemed reasonable given that (a) many authoritative reviews of pharmacotherapy of ADHD consider these three drugs as a common class of medication with very similar effects; (b) previous overviews/meta-analyses of stimulant effects have examined the stimulants in this way, and have not found major differences in effects, and (c) it was the most appropriate way to compare one class of treatment (stimulant drugs) with another class of treatment (psychological/behavioural therapies). Second, to adopt mg/kg as the standardized unit of expressing dose levels. When the primary study had not used this unit of measurement, it had to be calculated from the absolute doses that were used. This was done using the average weight of children in the study, when provided. When not provided, we estimated the average weight from information on the average age of children in the study and the proportion of males, based on normative information on weights of boys and girls of various ages supplied by the National Center for Health Statistics. Third, to keep the scope of the analyses manageable, that we would analyze drug effects for a single dose level only from each study. This necessitated selecting a particular dose level in studies that reported effects of multiple dose levels. We acknowledge that this decision precludes examination of dose-response relationships, which may be important if the effect of stimulants are not linear with dose level. However, the dose-response relationships reported among groups of ADHD children treated with stimulants most frequently have been linear in nature.\textsuperscript{29} Furthermore, by adopting a strategy to select the most commonly-used dose, we would analyze effects that have the most real-world relevance. To achieve this, we examined the dose levels used in the single dose studies and computed the average dose level used across these studies. This value was then used as a guide for choosing outcome data from the multiple dose studies. Outcome data were extracted for the medication condition closest to the average drug dose from the single dose studies.
Data were extracted from studies for one teacher and one parent rating scale. If outcome data for more than one scale were given in the report, only one of each was extracted using the algorithmic guidelines described above. Before combining the data, we ensured that the data presented in the individual studies were in comparable units of measurement. With one exception, all the instruments used to assess outcome are scored on scales where low scores indicate better function. For this instrument, negative signs were added to the scores on the ACTeRS measure to make them consistent with those scored in the reverse direction, enabling us to include these data in the meta-analysis.

Although the Parent/Teacher ASQ and the Hyperactivity Index of the CTRS and CPRS are functionally identical, scores may sometimes be expressed as total scores or as average scores per item, thereby differing by a factor of ten. Prior to data combining, these inconsistencies were corrected by multiplying by ten when indicated. One study required the ACPRS scores to be analyzed in terms of T-scores.

Four instruments, the IOWA Conners Teacher Rating Scale (IOWA CTRS), IOWA Conners Parent Rating Scale (IOWA CPRS), Child Attention Profile (CAP) and the ADDH Comprehensive Teacher's Rating Scale (ACTeRS) provide separate scores for different subscales. The IOWA CTRS and CPRS are composed of two subscales, Inattentive/Overactive and Aggressive. The CAP is composed of two subscales, Inattention and Overactivity. The ACTeRS is composed of four subscales, Attention, Hyperactivity, Social Skills and Oppositional Behaviour. The subscale scores for the IOWA Scales and the CAP can be summed to produce a total overall score since the items that compose each scale do not overlap. Where studies presented results as subscale scores rather than total scores on these instruments, we summed the mean score for each subscale and pooled the standard deviations for purposes of the meta-analysis. It is not appropriate however to produce a total score from the subscale scores of the ACTeRS, so where subscale scores were reported for this instrument, we elected to use the Attention subscale score in the analysis.

In situations where results were presented by mutually exclusive subgroups (such as low, average, and high-weight subjects) rather than for the sample as a whole, it seemed reasonable to pool the data and report an overall sample mean and standard deviation.

Since some studies reported on outcomes from more than one point of time, the decision was made to analyze data from the first post-treatment assessment, and to perform a sensitivity analysis on the follow-up data to assess any change in efficacy over time.

Since the data extracted from the studies were continuous and different outcome instruments were used, weighted mean differences (WMD) and standardized mean differences (SMD) were the summary statistics used for the meta-analysis. The WMD were used for combining results across studies that used the same outcome measure. The SMD were used when different outcome measures had been employed across studies, since data for these were in different units.
The SMD, also called the effect size, is obtained by dividing the difference between the mean in the treatment group and the mean in the control group by the standard deviation in the control group.

RevMan can be used to test the heterogeneity of study results for each table of comparisons, to assess whether the results of different studies are similar (homogeneous). However, since tests of heterogeneity are highly conservative, and heterogeneity can exist even when a hypothesis for heterogeneity is rejected,\textsuperscript{31} and the trials included in this review differed across a range of variables e.g. intervention, drug dose, timing of follow-up, outcome measures, sample size etc., we assumed that there was heterogeneity of treatment effect across the studies in each meta-analysis and chose the random effects model.

The meta-analysis method used was that of DerSimonian and Laird.\textsuperscript{32} Since only studies that supplied outcome data were included in the analyses, there were no missing data in the review. Our intention was to combine data from cross-over trials with data from parallel group studies in these analyses, if necessary. Meta-analyses were performed separately for the teacher and parent rating scales.
3. RESULTS

3.1 Search Findings
The initial search of the electronic databases yielded over 1000 citations. Table 2 shows the total number of citations identified through the various electronic databases. Since there was some duplication of studies across databases, the total number of discrete studies to be reviewed was lower than the sum of the individual database totals. No unpublished studies data were obtained.

Citations and abstracts were examined and potentially eligible articles were retrieved. These were reviewed along with studies identified through handsearching (n = 25), papers made available by pharmaceutical companies and other contacts, and papers already in the investigator's possession. A total of 195 treatment studies were examined in detail according to the two-stage procedure described in Section 2.2. These studies are listed in Appendix 3. Of these, 26 studies (listed in Appendix 4) met the inclusion criteria set out in Table 1. The findings from these studies formed the database of intervention effects. Details about the studies deemed ineligible under individual criterion categories are presented in Table 3. Forty-six studies were excluded because they were not designed as randomized clinical trials. No further checking for eligibility was done with these. Of the remaining 123, it will be noted in Table 3 that fairly frequently individual studies failed to meet more than one eligibility criterion.\(^\text{1}\)

3.2 Characteristics of Studies in the Database of Intervention Effects

3.2.1 General
The salient characteristics of each of the 26 treatment studies including their methodological quality scores are given in Table 4. Further details about the intervention(s) in the 21 drug studies are provided in Table 5, for the two psychological/behavioural studies in Table 6 and for the three combination studies in Table 7. There are a number of important observations to be made about the database of intervention effects. First, these 26 studies represent only a small proportion of all studies reviewed, and include very few studies of psychological/behavioural and combined treatment modalities. Second, among the small group of five studies (Tables 6 and 7) there was considerable diversity in the specific interventions used and in the selection and management of control groups. A "package" of therapeutic interventions (apart from drug therapy) could, however, be discerned, consisting of: (1) individual psychological therapy with the child, usually cognitive or cognitive-behavioural therapy (CBT); (2) some parent training in application of CBT principles at home as well as in behaviour management; and (3) provision of a teacher-training component in some cases as well. Though this "package" was not applied uniformly across studies analyzed, it provided the basis for calculations to be used in the subsequent section of the paper to do with economic evaluation. Third, across studies there was only limited uniformity among outcome measures used. This further limited the number of studies where effects could be directly compared. Below we describe in some detail the characteristics of the individual studies.

3.2.2 Quality scores
Expressed as a percentage of maximum quality, these ranged from 38 to 94, with a mean score of 75 and s.d. of 14, indicating that while methodological quality of studies in the efficacy database

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\(^{1}\) Details about the exclusion of individual studies may be obtained from the authors on request.
was reasonably high, it was variable. Quality scores of individual studies are presented in Table 4. To investigate the possible impact of quality differences on study results (i.e. the overall likelihood of a study finding of treatment efficacy), the six studies of highest quality were compared with the six studies with the lowest quality scores. No overall differences in efficacy were found (details reported under section 3.3.1.1). To investigate whether the quality of a randomized controlled trial was related to other factors, comparisons were made between validity score and a number of variables. There was no difference in the mean validity score and study design (parallel vs. within study design); type of study (drug vs. psychological/behavioural and combination study) nor was there any correlation with sample size. There was a strong correlation ($r = .53, p = .005$) between validity score and year of publication, with quality improving steadily over time.

### 3.2.3 Study characteristics

A within-subject crossover design was used in 19 studies, all of them drug treatment studies. A between-subjects parallel design was used in seven studies (two drug studies and five non-drug or combination type). We decided to combine data from the two parallel group design studies with the other drug studies that employed a crossover design in view of the following: (1) excluding them had very little impact on the results; and (2) there is no consensus on the legitimacy or otherwise on combining data from these two kinds of study designs.

### 3.2.4 Subject characteristics

In the majority of cases (20 out of 23 studies reporting this aspect) subject recruitment was from children referred to a clinic or clinic-based research program. Twenty-four of 26 samples consisted of school-aged children, and, as seen in Table 4, subjects were mostly males. In all 26 studies, subjects were described as having ADD, ADDH or ADHD. In 22 studies, it was explicit that they fulfilled DSM III ($n = 14$) or DSM-IIIR ($n = 8$) criteria for one of these diagnoses. In a further four studies, the diagnosis appeared to have been made using a combination of clinical evaluation and other criteria, such as exceeding cutoff scores on various behaviour rating instruments. Twenty-two studies used more than one standardized criterion for diagnosing subjects as ADD/ADHD. Sample sizes (defined by subjects completing the study) varied from 9 to 161. The mean sample size was 38 (s.d = 31) and the total sample size was 999. Eleven studies reported the presence of comorbidities in their subjects. The most frequent of these were Conduct Disorder (nine studies) and Oppositional Defiant Disorder (seven studies).

A reason for attrition from the study was mentioned in ten of the 26 studies. The percentage of participants reported as lost from these studies ranged from 4% to 78%, with a mean of 21.7% calculated from the percentage reported in individual studies. A variety of reasons were given for attrition.

### 3.2.5 Intervention characteristics

Certain studies (1, 7 and 24) reported on efficacy of DAS relative to placebo and to other agents. We extracted only those data relevant to contrast of DAS against placebo. In addition, one study (study 14) measured the efficacy of sustained release MPH, standard MPH and a combination of MPH sustained release and standard MPH. We chose to focus on the standard rather than
sustained release MPH treatment. In one study (study 10), one of nine subjects in the study sample was administered pemoline because he had previously been non-responsive to MPH; the rest of the sample were given MPH. This study was analyzed as a study of the efficacy of MPH. In total, 24 studies involved the use of medication: one studied the efficacy of pemoline, four studied Dextroamphetamine, and 19 studied MPH.

Thirteen studies measured the efficacy of a single dose of stimulant drug (nine MPH and four DAS), while the remaining 11 (ten MPH and one pemoline) examined the effects of different doses. The mean daily MPH dose from single dose studies was calculated to be .7 mg/kg, and the results from the MPH dose-response studies closest to this dosing level were used. In the pemoline dose-response study, data were reported for doses of 18.75 mg, 37.5 mg, 75 mg and 112.5 mg of pemoline. It has been reported that 10 mg of MPH given b.i.d produces equivalent behavioural effects to a dose of pemoline of about 58 mg.\textsuperscript{33,34,35} Since 10 mg of MPH given twice a day to a nine year-old, 28-kg child is roughly equivalent to .7 mg/kg/day, the closest equivalent dose for pemoline is 58 mg. The most equivalent dose for pemoline to the MPH dose we were studying was therefore intermediate between the 75 mg and 37.5 mg dosing levels reported in the study of pemoline effects. Hence analyses for pemoline effects were run using dosing levels both at one level above and one below the ideal equivalent dose of 58 mg.

In five studies, dosages were specified in mg. and these had to be converted to mg/kg dose levels. The doses specified in Tables 5 and 7 are the daily dose levels extracted from each study which involved administration of medication and outcomes data corresponding to these levels were used in the meta-analysis.

The occurrence of adverse reactions to MPH that resulted in subjects dropping out of the study was reported in two studies. In one (study 21), these side effects were cited as the reason for five subjects discontinuing MPH. In the other study (study 22) adverse effects led to one child terminating the study prematurely.

3.2.6 Outcome characteristics

Data were extracted for both a teacher and parent scale from 13 studies, for a teacher rating scale alone in ten, and for a parent rating scale alone in three studies. Twenty-three studies reported results from teachers scales, and five different teacher instruments were used. Fifteen studies reported results from parents scales, and four different parent rating scales were used. The most commonly used teacher and parent measures were the respective versions of the Abbreviated Conners Rating Scale (ACPRS/ACTRS/ASQ/HI). Tables 8 and 9 list the teacher and parent instruments used in the 26 studies broken down by type of study and number of times each instrument was used.

Four drug studies (8, 15, 16 and 19) presented outcome data for subgroups of children in those samples individually. The data from these subgroups were combined in the manner described in Section 2.3.

For the drug studies the post-treatment assessment took place at 7 to 25 days following the onset
of the intervention. Overall, the time to follow-up was less than two weeks after commencement of intervention. This would be considered a short period of time compared with most clinical trials, but given the rapid action of the stimulant drugs, it is adequate to observe important and consistent changes in behaviour. One drug study (study 21) conducted a post-treatment and follow-up assessment. The five psychological/behavioural and combination studies conducted both a post-treatment and follow-up assessment. The post-treatment follow-up took place on average 91 days after treatment had commenced (range 70 - 120), and the follow-up averaged 195 days after treatment (range 112 - 365). One study (study 12) included further follow-up, 24 month after treatment. Tables 5 to 7 contain information about the length of time from baseline to follow-up for the 26 studies.

3.3 Estimation of Treatment Efficacy
3.3.1 Efficacy of drug treatment alone
3.3.1.1 Drug vs. placebo contrasts
Significant treatment effects attributable to drugs were found across drugs and outcome measures.

Teacher rating scales. Eighteen trials provided data about the efficacy of drug treatment measured in terms of a teacher rating scale. In the first analysis, the low dose level for pemoline was used (see Section 3.2.5). In three trials, the treatment was no more effective than placebo. However, when the data from all studies were combined using a random effects model, the point estimate and 95% confidence intervals for a standardized mean difference, revealed that drug treatment was more effective than placebo (SMD = -1.028; 95% CI = -1.212, -0.843 Z = 10.92) (Fig 1). Subsequent analysis showed these effects to be independent of the methodological quality of the studies analyzed. When the six studies with the highest quality scores (mean quality score 89.5) were compared with the six lowest scoring studies (mean quality score 65), the effect sizes were SMD = -1.02 (95% CI = -1.385, -0.654) and -1.122 (95% CI = -1.357, -0.887) respectively.

In the second analysis, the high dose level for pemoline was used. Under these conditions, treatment was found to be no more effective than placebo in two studies and after combing data from all studies, a significant effect for drug over placebo was found (SMD = -1.065; 95% CI = -1.243, -0.886, Z = 11.72) (Fig 2).

Conners Teacher Rating Scale. Thirteen trials from the above analysis used the ACTRS to compare drug treatment with placebo. In the first analysis, the low dose level for pemoline was used. A weighted mean difference statistic was used, and the results indicate that drug treatment was more effective than placebo (WMD = -6.265; 95% CI = -7.140, -5.390; Z = 14.03). (Fig 3).

In the analysis using the high dose level for pemoline, not surprisingly a similar effect was found (WMD = -6.447; 95% CI = -7.290, -5.604, Z = 14.99) (Fig 4).

Parent rating scales. Thirteen trials provided parent rating scale data which could be pooled using a standardized mean difference. Two trials produced negative results. The combined effect size and 95% confidence intervals indicate that treatment was more effective than placebo (SMD
Conners Parent Rating Scale. Nine studies provided data for the ACPRS in the same units and could be combined to produce a combined effect size using a weighted mean difference statistic (one trial, which presented the ACPRS results in T-scores, was not included in this analysis). The results indicate that drug therapy was more effective than placebo (WMD = -4.515; 95% CI = -5.790, -3.241; Z = 6.95). (Fig 6).

### 3.3.1.2 Specific drug vs. placebo contrasts

Because the pemoline and four Dextroamphetamine studies used the ACTRS, as did eight of the MPH trials, the analyses in this section have been limited to the ACTRS to increase comparability. The results are summarized in Table 10 with details below. It was not possible to analyze results using parent rating scales because although 12 MPH studies included a parent outcome measure, only one trial of Dextroamphetamine did so.

**MPH vs. placebo.** The results for eight trials of MPH were combined. The weighted mean difference and 95% confidence intervals resulted in the following point estimate (WMD = -6.732; 95% CI = -7.576, -5.887; Z = 15.63). (Fig 7)

**Dextroamphetamine vs. placebo.** The results of four trials of DAS were combined. The weighted mean difference for the three studies of DAS was WMD = -4.771 (95% CI = -6.431, -2.992; Z = 5.37). (Fig 8)

**Pemoline vs. placebo.** The effect size for the single pemoline trial using the low dose condition was WMD = -4.00; 95% CI = -7.80, -2.0; Z = 2.06)(Fig 9). For the high dose condition, the effect size was markedly larger at WMD = -7.8 (95% CI = -11.239 -4.361 Z = 4.45) (Fig 10). The confidence intervals were broad for both these analyses.

### 3.3.2 Efficacy of psychological/behavioural treatments

Two studies provided data about the efficacy of psychological/behavioural treatments used alone. Significant effects were not found for such treatments analyzed as a combined "package" in relation to controls or the comparison group.

**Teacher rating scales.** The pooled effect size was SMD = -0.398 (95% CI = -1.276, 0.48; Z = .89) (Fig. 11). One study (study 11) used the parent Revised Behaviour Problems Checklist (RBPC) and showed a significant result for the treatment arm. The other study (study 3) using the ACTRS, showed a non-significant effect size of WMD = 0.30 (95% CI = -4.469, 5.069; Z = .12) (Fig 12).

**Parent rating scale.** One study used the parent RBPC. The effect was not significant (WMD = -3.800; 95% CI = -9.599, 1.999; Z = 1.28 ) (Fig 13).

### 3.3.3 Efficacy of combined medical and psychological/behavioural treatments

Three studies provided data about combined modalities of treatment. The way that results were presented in these studies permitted three kinds of comparisons to be made, which are described in detail below but can be summarized as follows: (1) combination therapy was more efficacious than placebo/no treatment based on parent but not teacher ratings; (2) combination therapy was not more efficacious than drug therapy alone; (3) combination therapy was more efficacious than psychological/behavioural treatments alone based on parent but not teacher ratings.
3.3.3.1 Combination therapy vs. placebo/no-treatment contrasts

Conners Teacher Rating Scale. Two trials measured the benefit of combination therapy versus a control condition group with discrepant results and no overall effect (WMD = -3.777; 95% CI = -8.064, 0.510; Z = 1.73) (Fig. 14).

Conners Parent Rating Scale. In the above two trials (Studies 5 and 6), outcomes were also measured with the ACPRS. As with the teacher rating scales, the two studies showed discrepant results, but the overall effect here was statistically significant favoring combination therapy (WMD = -7.345; 95% CI = -12.289, -2.401; Z = 2.91) (Fig. 15).

3.3.3.2 Combination therapy vs. drug-only therapy contrasts

Conners Teacher Rating Scale. Three studies contributed data. There was no significant difference between combination and drug-only therapy. The pooled effect size was WMD = 1.285 (95% CI = -0.717, 3.286; Z = 1.26) (Fig 16).

Conners Parent Rating Scale. Two trials used the ACPRS to measure outcome. There was no significant difference between combination and drug-only therapy. The pooled WMD was -0.460 (95% CI = -3.861, 2.942; Z = 0.26)(Fig. 17).

3.3.3.3 Combination therapy vs. psychological/behavioural treatments

Conners Teacher Rating Scale. Three studies provided data for this comparison. No significant differences were found between combinations of psychological/behavioural treatments with medication (MPH) and psychological/behavioural treatments either given alone or combined with a medication placebo. The combined WMD was -2.006 (95% CI = -4.174, 0.163; Z = 1.81)(Fig 18).

Conners Parent Rating Scales. Two studies provided data for this comparison, both using the ACPRS. A significant effect was found favoring Combination therapy, with overall WMD = -5.911 (95% CI = -8.631, -3.190; Z = 4.26)(Fig 19).

3.3.4 Relative efficacy of drug, psychological/behavioural and combined therapies

Tables 11 and 12 summarize the main contrasts described above by teacher and parent measures respectively. Tables 13 and 14 summarize these findings by ACTRS and ACPRS respectively. Discrepancies between the statistics in these tables and those found in the individual figures above are because all effect sizes in these tables are expressed in the units of SMD's for consistency.

4. CONCLUSIONS

4.1 Summary of Main Findings

The results of this review and meta-analysis can be summarized as follows:

- Findings for drug therapy (as a category of intervention) were consistent.
- Drug-only therapy is efficacious in ADHD.
- No clear differences in efficacy were found between the agents MPH, DAS and pemoline.
- Findings for psychological/behavioural therapies and combinations of medication with psychological/behavioural therapies were inconsistent.
- Psychological/behavioural therapies used alone appeared not to be efficacious in ADHD.
Combinations of medication with psychological/behavioural therapies were more efficacious than various control/placebo conditions for parent but not teacher ratings of ADHD.

Combinations of medication with psychological/behavioural therapies were no more efficacious than medication given alone. In other words, the addition of various psychological/behavioural therapies to a regimen of MPH added nothing over-and-above the effects of MPH alone.

Combinations of medication with psychological/behavioural therapies were more efficacious than psychological/behavioural therapies used alone for parent but not teacher ratings of ADHD.

The above findings need to be interpreted with caution for three main reasons:

1. there is a paucity of good quality experimental studies, resulting in wide confidence intervals for the estimates of efficacy of certain treatments;
2. there is extreme heterogeneity in the literature on treatment of ADHD. Even after taking steps to reduce this as much as possible, there remains considerable heterogeneity among the studies analyzed with respect to study quality, design, subject characteristics, interventions, outcome measures and follow up. There are risks in interpreting results from analyses which combine data from studies that are as heterogeneous as these; and
3. the findings are limited to the effects of treatments on a particular class of outcome (i.e. observable behaviours) as captured by a narrow selection of behaviour rating scales.

4.2 Expansion and Interpretation of Main Findings

4.2.1 Drug-only studies

The statement that drug-only therapy is efficacious in ADHD is more accurately informative when framed in the particular context and constraints of the present review. This would then state that medication therapy is efficacious in reducing elevated levels of behaviours ("symptoms"), such as overactivity, disruptive and immature behaviours, emotional lability, distractibility, impulsiveness, lack of perseverance with tasks and difficulty following directions, as measured by changes within individual subjects within weeks of treatment onset, and while continuing to take medication.

Our ability to make accurate comparisons of relative efficacy was limited by the paucity of data available on DAS and in particular, pemoline. Analyzed pemoline effects varied widely with the dose level selected, and irrespective of dose level, confidence intervals were wide. In spite of this, however, and based on our estimation of efficacy from differences in scores on the Conners Abbreviated Teacher Rating Scale, we can say that there appeared not to be any major differences between MPH, DAS and pemoline. Previous studies comparing MPH and DAS similarly found that neither drug was superior to the other, and that non-responders to one of the drugs are likely to respond to the other. Similarly, while their side-effect profiles are similar, some patients tolerate one agent better than the other. Hence it has been recommended that children who fail to respond or tolerate the one stimulant should be tried on the other. pemoline offers the advantage that dosing is once daily, so the inconvenience of a noon dose at school is avoided. Single daily dosing also presumably improves adherence. However the use of pemoline is limited by fears of...
liver damage and the need to check liver enzymes periodically. Though the evidence for a causal relationship has been challenged,\textsuperscript{37} the HPB approved product monograph states that because of its association with life-threatening hepatic failure, it should not ordinarily be considered as first-line therapy for ADHD.

### 4.2.2 Psychological/behavioural therapies

The statement that psychological/behavioural therapies used alone appeared not to be efficacious in ADHD also needs to be framed within the context and constraints of the present review. This would make explicit that psychological/behavioural therapies consisting of various combinations of CBT administered to individual children and groups and parents as individual dyads and groups, as well as education sessions with parents and teachers when applied in parallel group designs, failed to produce significant differences in ADHD symptomatology on teacher or parent measures between these groups. It would also emphasize that there were only two studies analyzed in this category, each with very small samples (n < 13 in all experimental arms), and that these two studies differed in their findings in that one found a significant effect of treatment while the other did not (Fig. 11). The two studies also differed in terms of interventions provided, the selection and management of controls and follow-up arrangements (as outlined in Table 6), as well as in the outcome measures used.

These results need to be viewed alongside others in the published literature, which were not included in the efficacy database of the present study. This literature also provides mixed or conflicting evidence of the efficacy of psychological/behavioural therapies used alone. For example, some studies report absent or weak/variable effects due to therapies such as behavioural therapy, cognitive training or social skills training,\textsuperscript{38,39,40} while others have found parent management training\textsuperscript{41} and comprehensive behaviour modification classrooms to be helpful.\textsuperscript{42} A recent meta-analysis found that school-based interventions are effective in enhancing the classroom behaviour of elementary school-aged students with ADHD, and further, as discussed below, that certain types of interventions were more effective than others.\textsuperscript{43}

### 4.2.3 Combinations of drug with psychological/behavioural therapies

It should be emphasized here that although a number of analyses were done to contrast various treatment conditions (e.g. Combined therapy vs. no active treatment; Combined therapy vs. Drug-only), the data used were derived from a limited pool of just three studies, all of which used small samples averaging about 15 subjects, and differed in terms of treatments provided, comparison/control groups used, and follow-up arrangements (summarized in Table 7). Furthermore, for many of the contrasts performed, results were discrepant between studies in that contrast category. When combination therapy was compared with no treatment/placebo on the Conners Teacher measure, one of the studies showed a statistically significant effect and one did not. Study 6, which showed a significant benefit to Combination therapy, used for comparison a no-treatment group recruited (non-randomly) from children previously on a waiting list at the authors clinic. Study 5, which did not detect a difference between the treatment and control arm, used a control group which was randomly assigned and obtained a placebo drug and a placebo psychosocial therapy - the same amount of exposure to material and a therapist but no instructions in problem-solving strategies. Sometimes when individual studies were discrepant, an
overall significant effect was found (e.g. for parent measures of Combination therapy vs. no therapy/placebo), and sometimes an effect was not found (e.g. teacher measures of Combination therapy vs. no therapy/placebo).

Since drug therapy alone was found to be efficacious, we might expect the combination of drug therapy plus another modality of therapy also to be efficacious compared with either no therapy/placebo or psychological/behavioural therapies used alone. However, present results offer only partial support for this expectation. There is discrepant evidence for Combination therapy's efficacy vs. no therapy/placebo, and only on parent measures did Combination therapy appear to be more efficacious than psychological/behavioural therapies. Methodological factors to do with study design (within subject designs for drug studies and parallel group designs for combination therapies), diversity in interventions applied and control conditions used, likely account for this situation, which is discussed further below. Such factors may also explain the discrepancies to be found in the broader published literature (including studies not included in our intervention effects database) examining the efficacy of combined modalities of therapy. Some have demonstrated a relative benefit to combining psychological/behavioural therapies with medication, \(^{44,45,46}\) while others have found no added benefit. \(^{40,47}\) Several experimental studies point to the major effect in combined interventions arising from the medical rather than the psychological/behavioural component. \(^{46,48,49}\)

### 4.3 Interpretation of Results: Caveats and Limitations

We encountered serious difficulties in trying to compare the relative efficacy of medical, psychological/behavioural and combined forms of therapy for children and youth with ADHD using the methods of systematic review of published evidence and meta-analysis. The considerable methodological challenges that face investigators in this area have been reviewed by others. \(^{17,18}\) The most serious problem we encountered was a lack of studies providing data of adequate quality that could be used in the review and meta-analysis. This lack of data was attributable to two main factors: (1) a relative paucity of treatment studies other than drug treatment studies. Many studies have been published on the management of hyperactive and ADHD children in the past 25 years, but the vast majority have been studies of medication effects. Furthermore, while the effects of stimulant medications lend themselves well to highly controlled experimental studies, behavioural treatments are harder to evaluate in this way, leading to a further scarcity of methodologically rigorous data; and (2) heterogeneity of various kinds that exist in relation to ADHD and its treatment. In attempting to reconcile the needs of the present study with the realities imposed by the co-existence of these two factors, we strove continually for a sense of balance in the restrictiveness of eligibility criteria around study designs and methods. A less restrictive approach would have compromised standards of quality and perhaps prevented meaningful combination of data, while a more restrictive approach would have left very little material to combine and analyze.

In the absence of specific biological markers, ADHD remains a descriptive, syndromic behavioural diagnosis, comprising behaviours which may be seen in many normal children and also in children with a wide variety of other social, emotional, developmental and neuropsychological problems. Hence there is great heterogeneity among the population of children diagnosed with ADHD.
over-and-above the heterogeneity associated with the specific labels of ADD vs. ADDH vs. ADHD). We attempted to reduce diagnostic heterogeneity by limiting our search to studies of children who were described as having ADD or ADHD in accordance with the more stringent criteria for diagnosing these conditions that came into effect with the publication of DSM III and subsequent versions. Prior to DSM III, the criteria for diagnosis of hyperactivity in children were more broadly defined, increasing the likelihood that early studies (prior to 1980) tended to consist of a mixed group of children with various sorts of behavioural problems. Our stringent search strategy limited the number of studies (and therefore subjects) available for analysis. Notwithstanding the stringency of our eligibility criteria, the heterogeneity among subjects in the eligible studies was large, as evidenced, for example, by the variability in comorbidity across studies in those that chose to report this important variable. One way of dealing with subject heterogeneity is to analyze the data by subgroups defined by various characteristics. This strategy is now recognized as a major research need, but too few instances of this kind of study were found to allow us to apply it in the present project.

Children with ADHD are heterogeneous with respect to the problems they present to clinicians (and teachers, parents and peers) as well as in their needs. Appropriate needs for one "group" of patients may not be appropriate for another group. This has led to the suggestion that each ADHD child requires a detailed assessment of his particular needs and an intervention program tailored accordingly. The research literature however has tended to assemble cohorts of ADHD cases by convenience, and provide a predetermined package of therapy or therapies without regard for individual needs and differences. In such situations we would expect to find that within-subject research designs, which control for individual differences show larger effects, and indeed this tendency has been described. In the present study, this mechanism could explain at least in part the strong evidence of efficacy for drug-only studies and the weak and inconsistent findings for other kinds of interventions. The drug studies largely used within-subject designs, whereas the others all used between-subject comparisons within parallel group designs.

Besides heterogeneity in subject and study designs, other pitfalls in attempting to make comparisons across modalities of therapy include heterogeneity in treatments and outcome measurements. While different dosage levels were used in studies of stimulant drug efficacy, we were able to analyze the effects of comparable dosage levels, particularly with MPH where plenty of data were available. When we find a lack of efficacy of other therapeutic modalities however, it is important to note the variety of specific interventions that were employed across studies. Some studies evaluated the effects of individual cognitive-behavioural therapy or parent training, and others evaluated the effects of group-based interventions. A recent meta-analysis of the school-based interventions for ADHD found contingency management and academic interventions to be more effective than cognitive-behavioural procedures in terms of improving classroom behaviours. On the other hand, cognitive-behavioural procedures were more effective in enhancing academic performance. It is noted that in our database of intervention effects, the studies used largely cognitive-behavioural procedures, but behavioural outcomes had been designated as the target for assessing efficacy. A mismatch of this type between specifics of the intervention and outcome would tend to conceal a potential benefit of psychological/behavioural therapies in the present study.
Studies also varied in the dosage level or intensity of such interventions. It is questionable whether combining such data will result in valid and interpretable data. We elected to combine data from studies that differed in their interventions in view of the broad commonalities across these studies and in order to increase cumulative numbers of treated and control subjects, a prime purpose of meta-analysis. Even then, however, sample sizes remain small so that failure to find significant results may reflect a Type II statistical error, while discrepancies between studies may reflect the discrepant treatments, outcome measures and control conditions they used. We believe that differences in how control groups were assembled and treated are an important source of heterogeneity and a threat to the validity of the results.

The use of different outcome measures across studies is another such factor. Our strategy in this study was to select one particular type of outcome measure that is widely-used, standardized and relevant to the broad sweep of behaviour and learning problems that bring parents to seek help in the first place. We reasoned that to make valid comparisons of treatment efficacy, we would have to use a common outcome measure across treatment modalities. Furthermore, this would reduce heterogeneity between studies. The ACTRS fulfills most of these specifications, and its longer parent forms have been widely used to monitor drug effects as well as the effects of psychological interventions. However we found that many published studies (rejected for present purposes) had not used checklist-type outcome measures at all, and among those that did, not all of them used the Conners. In this instance, we elected to extend the range of eligible outcome measures to include behaviour rating scales, which were, in our judgment, broadly comparable with the Conners scales, rather than risk an overly restricted database of intervention effects. So while most studies in the database used the ASQ of Conners, the inclusion of a number of different outcome measures raises concerns when analyzing effects combined across studies.

A further significant caveat in interpreting the results from this study is a theoretical question of whether it is appropriate to look to the same outcome measure to show effects of drug and non-medical interventions. Whereas parents and teachers want to see improvements in behavioural symptoms such as those covered in the Conners scale, it is possible that medication may be most efficacious at reducing the primary or core symptoms of ADHD, while psychological/behavioural therapies involving parents and/or teachers may be most efficacious at reducing associated features, such as conflicted peers relations and academic underachievement secondary to social skill and academic skills deficits. The latter kinds of effects would be expected to show up less on a checklist of core symptom behaviours and more on other kinds of measures, such as direct observations of the student, global improvement ratings by parents and teachers, peer ratings and measures of individual achievement. Hence this study’s exclusive focus on behaviour rating scales may introduce a bias in favor of medication over psychological/behavioural therapies. We did not estimate efficacy in all these domains because only some studies included them, and because of the wide range of measures it would have necessitated combining. It has also been questioned whether it is justified to seek effects of home-based parent training in teacher reports from the classroom. Unfortunately these issues remain unresolved in ADHD research. Our use of parent as well as teacher measures was an attempt to address these concerns. The finding of instances of differential effects on parent vs. teacher rating scales goes some way towards...
validating this strategy, although there is no clear explanation for the specific differences that were found.

A criticism that could be raised about our analytic approach is that drug effects were generally evaluated a few weeks after the onset of therapy while psychological/behavioural therapies were evaluated over a longer time frame, and how do we know that the effects due to drugs persist. One study in our database of intervention effects (study 21) followed up children at 120 days post-initiation of therapy and found that improvements in teacher-rated core behaviours of hyperactivity-inattentiveness and associated aggressive behaviours at the end of the titration phase persisted over the 4-month follow-up. A recent paper by Gillberg et al, studying the effects of dextroamphetamine in ADHD, similarly showed persistence of beneficial effects at 15 months after initiation of therapy.\textsuperscript{51} Finally, it has been pointed out that there has been no convincing empirical demonstration of attenuation of stimulant effects over time.\textsuperscript{4,29}

Our results suggest that medical therapy is efficacious in management of children with ADHD, that non-medical interventions used alone are not, and that combinations of medical and non-medical therapies may be efficacious in some situations. We have discussed above the main reasons why these results should not be taken at face value. These include a paucity of research to evaluate non-medical modalities of therapy with ADD/ADHD children, a lack of good quality experimental research and a great deal of heterogeneity between studies in choice of subjects, interventions, controls and outcome measures which made the combining of results across studies difficult to interpret. These and other pitfalls have led previous reviewers to conclude that any attempt to identify the best treatment becomes an empty and futile exercise.\textsuperscript{17} While this may be an overstatement, we believe these factors limit the applicability of our results towards making health policy decisions, particularly as regards psychological/behavioural and combined forms of therapy. We recommend that caution be exercised in this regard. The relative benefits of different modalities of therapy for ADHD in children may need to be revisited at such time as the deficits identified in the published literature have been addressed. We also await with interest the findings of a large, U.S National Institutes on Mental Health-funded multicentre experimental trial currently in progress. This study, known as the Collaborative Multisite Multimodal Treatment Study of Children with ADHD (the "MTA Study") was set up specifically to evaluate different modalities of therapy for ADHD.\textsuperscript{52}
References


Review of Therapies - Part 3


25. Quay HC, Peterson DR. Appendix 1 to the interim manual for the revised Behavior Problems Checklist. Unpublished manuscript, University of Miami, 1983


32. DerSimonian R, Laird N. Meta-analysis and clinical trials. Controlled Clinical Trials 1986; 7:177-188


38. Abikoff H, Gittelman R. Does behaviour therapy normalize the classroom behaviour of hyperactive children? Arch Gen Psychiatry 1984; 41:449-454


Review of Therapies - Part 3


Table 1. Study Eligibility Criteria

<table>
<thead>
<tr>
<th>AREA</th>
<th>CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Date of Publication</td>
<td>1981 or later</td>
</tr>
<tr>
<td>2. Study design</td>
<td>Prospective studies of an intervention or interventions which had to be either parallel-group designs with random assignment of subjects to treatment conditions or within-subject crossover designs with random assignment of subjects to treatment order. Observational (cohort) and single subject studies were ineligible.</td>
</tr>
<tr>
<td>3. Target population</td>
<td>Children 0-18 years with a diagnosis of ADD, ADDH or ADHD made in an explicit and reproducible way.</td>
</tr>
<tr>
<td>4. Co-morbidity</td>
<td>Studies involved subjects unselected as to the presence of specific associated or co-existing diagnoses such as Tourette or other tic disorder, mental retardation, autism, learning disability or conduct disorder. However the presence of these and other comorbidities such as anxiety, depression and aggression was acceptable provided that the focus of the study was not the effect of an intervention on a specific ADHD sub-population as defined by the presence of such comorbid diagnoses.</td>
</tr>
<tr>
<td>5. Intervention</td>
<td>Effects of at least 1 week of stimulant medication (MPH, DAS, pemoline) administered on consecutive days. Effects of a course of psychosocial intervention which may include: -contingency management methods (behaviour modification, parent-or teacher-mediated) -cognitive-behavioural therapy -individual psychotherapy -parent training and education -teacher training and education -parent or family counseling/therapy -social skills training -EEG biofeedback or relaxation therapy</td>
</tr>
<tr>
<td>6. Outcome measures</td>
<td>The focus was on effects of intervention on aspects of behaviour that are discernible to teachers, and/or parent, and/or clinicians in everyday life. Outcomes were measured with standardized behaviour rating scale-type of instruments which measure in a broad-based way core ADHD behaviours (inattention, distractibility, impulsiveness and hyperactivity) as well as the disruptive behaviours that are the most salient associated feature of ADHD. Excluded were outcome measures specific to academic performance, cognitive function, neurological/physiological measures and other laboratory-based measures.</td>
</tr>
<tr>
<td>7. Data presentation</td>
<td>Outcome data to be presented in a form that is complete and suitable to be extracted for meta-analysis.</td>
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Table 2. Total Number of Citations Identified Through Electronic Database Searches

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</tr>
<tr>
<td>PyscInfo (1980 - present)</td>
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<tr>
<td>CIJE</td>
<td>70</td>
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<td>First Search</td>
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<tr>
<td>Embase</td>
<td>167</td>
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Table 3. Details of Ineligible Studies

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<tr>
<th>CATEGORY/SUBCATEGORY/DESCRIPTION</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total ineligible treatment studies</strong></td>
<td>169 (46%)</td>
</tr>
</tbody>
</table>

Ineligible by Design criterion (no further evaluation of eligibility status)
Not a randomized clinical trial (e.g. observational study, single subject experiment).
Randomization procedure found to be faulty by investigators

<table>
<thead>
<tr>
<th>Treatment studies remaining for further evaluation of eligibility</th>
<th>123</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ineligible by Subject criterion</td>
<td>33 (27%)</td>
</tr>
</tbody>
</table>

- Subjects older than 18 years
- Not clear if subjects had diagnosis of ADD/ADHD and/or how diagnosis ascertained
- Subjects all carried a particular comorbid diagnosis
- Other (e.g. some subjects had ADD/ADHD, others had different behavioural disorders)

<table>
<thead>
<tr>
<th>Ineligible by Intervention criterion</th>
<th>38 (31%)</th>
</tr>
</thead>
</table>

- Drug therapy lasted less than 7 days
- Drug used but data not reported
- Type of intervention was not on eligible list (e.g. dietary)
- Other (e.g. comparison of two types of psychological/behavioural therapies)

<table>
<thead>
<tr>
<th>Ineligible by Outcomes criterion</th>
<th>71 (58%)</th>
</tr>
</thead>
</table>

- Behaviour rating scale was not used
- Behaviour rating scale used but was not a predetermined eligible measure (see Appendix 2)

<table>
<thead>
<tr>
<th>Ineligible by Data criterion</th>
<th>27 (22%)</th>
</tr>
</thead>
</table>

- Data not presented in a form usable for meta-analysis (e.g. means and s.d. not reported)

<table>
<thead>
<tr>
<th>Ineligible by Other criteria</th>
<th>4 (3%)</th>
</tr>
</thead>
</table>

- Data already reported in another publication
- Eligible behaviour rating scale used but data not reported (not a focus of study)

Note: of 123 studies not eliminated by Design criterion:
- 76 (62%) were ineligible by a further *single* criterion
- 44 (36%) were ineligible by *two* further criteria
- 3 (2%) were ineligible by *three or more* criteria
Table 4. Characteristics of Studies in Database of Intervention Effects

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<tr>
<th>Study identifier</th>
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<th>Quality score (%)</th>
<th>Description of comorbidity provided</th>
<th>Teacher scale</th>
<th>Parent scale</th>
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<td>DAS</td>
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<td>100</td>
<td>38</td>
<td>No</td>
<td>ACTRS</td>
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<td>2</td>
<td>Barkley et al. 1985 within MPH 60</td>
<td>within</td>
<td>MPH</td>
<td>60</td>
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For abbreviations: see text or Glossary of Abbreviations
Table 4 continued

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<th>Intervention</th>
<th>Sample size</th>
<th>Age range (yr)</th>
<th>% male</th>
<th>Quality score (%)</th>
<th>Description of comorbidity provided</th>
<th>Teacher scale</th>
<th>Parent scale</th>
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For abbreviations: see text or Glossary of Abbreviations
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<th>Drug type</th>
<th>No. dosage levels given in study</th>
<th>Dose level (mg/kg/day) used in meta-analysis</th>
<th>Period for follow-up (days)</th>
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* Analyses were performed using two dose levels for pemoline (see text).
Table 6. Studies of Psychological/Behavioural Treatments

<table>
<thead>
<tr>
<th>Study identifier</th>
<th>Author and year of publication</th>
<th>Interventions and number of subjects in each group</th>
<th>Sample and methods</th>
<th>Duration of intervention</th>
<th>Trainers</th>
<th>Follow-up (from baseline)</th>
</tr>
</thead>
</table>
| 3                | Bloomquist et al. 1991         | i. multicomponent CBT - child, parent and teacher (n=11)  
ii. teacher component (n=12)  
iii. no treatment control group (assignment random) (n=13) | Children with ADHD were identified at 3 schools. Two schools were selected at random to be the sites for the treatment arms. Subjects in these schools were randomly assigned to either multicomponent or teacher only intervention. The third school provided control subjects. | child component - 20x1-hr group (6-8 children) sessions over 10 weeks  
teacher component - 1x120 min inservice and 6x45-60 min group sessions over 10 weeks  
parent component - 7x90 min group sessions educating on ADHD | school psychologists at the two schools were trained to function as primary therapists; undergrad psychology students were cotherapists | Pre-test  
10 week post-test  
16 week follow-up |
| 11               | Fehlings et al. 1991           | i. CBT (n=13)  
ii. control group (assignment random) (n=13) | Children were referred to Child Development Clinic at one hospital. Subjects were randomized to the treatment or control group. | child component -12x60min individual sessions, met twice weekly  
parent component - sessions 8x120min sessions in parents home, met once every two weeks  
control - (child) same exposure to therapists, tasks and rewards but no instruction in CBT strategies; (parent) same education about ADHD, time and exposure to therapists but CBT replaced with supportive listening | behavioural therapist | pre-test  
4 month post-test  
5 month follow-up |
Table 7. Studies of Combination Treatments

<table>
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<th>Study identifier</th>
<th>Author and year of publication</th>
<th>Interventions and number of subjects in each group</th>
<th>Sample and methods</th>
<th>Duration</th>
<th>Trainers</th>
<th>Follow-up (from baseline)</th>
</tr>
</thead>
</table>
| 5                | Brown et al. 1986              | i. medication (0.6 mg/kg MPH) and attention control (n=7)  
  ii. cognitive therapy and placebo drug (n=10)  
  iii. medication (0.6 mg/kg MPH) and cognitive therapy (n=9)  
  iv. attention control and placebo drug (n=7) | Children were referred to the project and were assigned randomly to one of four treatment groups. | treatment - 22x1hr individual CBT sessions over 3 months  
  control - equivalent exposure to training materials and therapist but no instructions in problem-solving strategies | had master's degrees in psychology or special education | Pre-test 3 month post-test 6 month follow-up |
| 6                | Brown et al. 1985              | i. medication (0.6 mg/kg MPH) (n=10)  
  ii. cognitive training (n=10)  
  iii. medication (0.6 mg/kg MPH) and cognitive training (n=10)  
  iv no treatment comparison group (n=10) | Children were referred to the project and were randomly assigned to one of three treatment groups. Assignment to comparison group not random as subjects recruited from past waiting list at authors' clinic. | children - 24x60 min individual sessions over 3 months  
  parent and teacher given consultation sessions on applying training strategies (amount not described); mothers observed several training sessions of their children from behind one-way mirror and instructed on how training procedures could be applied at home | not described | pre-test 3 month post-test 6 month follow-up |
| Firestone et al. 1986 | i. parent training and medication (0.93 mg/kg MPH) (n=16)  
ii. parent training and placebo drug (n=13)  
iii. medication (0.93 mg/kg MPH) (n=22) | Children were recruited from referrals to learning, psychiatry or psychology outpatient services at one hospital. Subjects were randomly assigned to one of three groups.  
parent - in 3 initial consultation sessions, asked to read a book and understand the behavioural principles; asked to join a parent group and attend 6 sessions to learn child behaviour management programs and how to deal with school personnel.  
teacher - 2 consultations were provided to teachers involved in study | senior doctoral-level interns in clinical psychology supervised by registered psychologists | pre-test  
3 month  
10-12 month  
22-24 month  
follow-up |
### Table 8. Outcome Measures Completed by Teachers

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<th>Instrument</th>
<th>Drug</th>
<th>Psych/behavioural</th>
<th>Combination</th>
<th>Total</th>
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<td>Child Attention Profile (CAP)</td>
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<td>Revised Behaviour Problem Checklist (RBPC)</td>
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### Table 9. Outcome Measures Completed by Parents

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<th>Combination</th>
<th>Total</th>
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### Table 10. Differences in Effect Size: Drug Studies

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<th>No. subjects treated</th>
<th>No. subjects control</th>
<th>WMD</th>
<th>95% CI</th>
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<td>high dose</td>
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### Table 11. Differences in Effect Size: Teacher Rating Scales

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<thead>
<tr>
<th>Teacher rating scales</th>
<th>No. of studies</th>
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<td></td>
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### Table 12. Differences in Effect Size: Parent Rating Scales

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<th>SMD</th>
<th>95% CI</th>
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### Table 13. Differences in Effect Size: Conner Teacher Rating Scale

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<th>Teacher rating scales</th>
<th>No. of studies</th>
<th>No. subjects treated</th>
<th>No. subjects control</th>
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### Table 14. Differences in Effect Size: Conner Parent Rating Scale

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*Note: CI = Confidence Interval, CI Width = Difference between the upper and lower limits of the confidence interval.*

**Figure 1:** Performance low dose condition.
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<th>Favour Control</th>
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**Figure 2**

**Pemoline high dose condition**

- **Study:** Teacher rating scores
- **Comprehension:** Drug therapy vs. placebo
- **Objective:** Teacher rating scores

**Note:** Teacher rating scores in brackets.
<table>
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<tr>
<th>Year</th>
<th>Faunus Treatment</th>
<th>Faunus Control</th>
<th>CHr-Sgene 25% 9d (412) Z=2.99</th>
<th>571</th>
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<td>1996</td>
<td>7.6</td>
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Study outcome: Drug therapy vs. placebo
<table>
<thead>
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<th>0.75% (~7.57%, 6.88%)</th>
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<td>26.400</td>
<td>34.100 (34.71%, 28.54%)</td>
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<tr>
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<td>34.100</td>
<td>43.200 (43.69%, 37.79%)</td>
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<tr>
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<td>53.900 (54.39%, 48.58%)</td>
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Figure 7
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<tr>
<th>Year</th>
<th>Outcome</th>
<th>95% CI (Random)</th>
<th>% Weigh</th>
<th>95% CI (Fixed)</th>
<th>% Fixed</th>
<th>Posterior Probability</th>
<th>95% CI (Fixed)</th>
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**Figure 8**
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<th>Weight SMD</th>
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Chisquare 2.37 (df=1) Z=0.39

Total (85%) (84)

Figure 11

Outcome: Psychological/behavioral therapy vs. control group
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<th>(95% CI Random)</th>
<th>Weight (WMD)</th>
<th>(95% CI Random)</th>
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</thead>
<tbody>
<tr>
<td>1985</td>
<td>6.17</td>
<td>[-3.27, 4.34]</td>
<td>10.00</td>
<td>[3.03, 11.87]</td>
</tr>
<tr>
<td>1986</td>
<td>3.63</td>
<td>[-0.52, 4.79]</td>
<td>0.00</td>
<td>[-0.52, 0.52]</td>
</tr>
</tbody>
</table>

Chi-square 1.96 (df=1) Z=1.73
Total (95% CI) 19

Study

Conclusion: Combination therapy vs. control or comparison group

FIGURE 1A
<table>
<thead>
<tr>
<th>Year</th>
<th>Favour Treatment</th>
<th>Favour Control</th>
<th>Total (55%)</th>
<th>CTR (95%)</th>
<th>1.63 (df=1)</th>
<th>Z=2.91</th>
</tr>
</thead>
<tbody>
<tr>
<td>1986</td>
<td>30.1 (11.73, 41.17)</td>
<td>20.0 (12.48, 33.72)</td>
<td>7.70 (5.40)</td>
<td>7.70 (5.40)</td>
<td>0.95 (2.65)</td>
<td>0.95 (2.65)</td>
</tr>
<tr>
<td>1985</td>
<td>69.9 (95.43)</td>
<td>40.9 (65.42)</td>
<td>10.70 (2.85)</td>
<td>10.70 (2.85)</td>
<td>0.95 (2.65)</td>
<td>0.95 (2.65)</td>
</tr>
</tbody>
</table>

**Figure 15**
<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
<th>Outcome</th>
<th>Combined Treatment vs. Drug Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1986</td>
<td>9</td>
<td>G5 Down</td>
<td>0.100 - 0.325 (4.20)</td>
</tr>
<tr>
<td>1986</td>
<td>16</td>
<td>G5 Down</td>
<td>0.100 - 0.325 (4.20)</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>G5 Down</td>
<td>0.100 - 0.325 (4.20)</td>
</tr>
</tbody>
</table>

Chi-square: 1.15 (df=2) Z=1.25
Tour (95%CI): 35

Figure 16
<table>
<thead>
<tr>
<th>Year</th>
<th>Treatment</th>
<th>Control</th>
<th>df</th>
<th>Mean (SEM)</th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
<th>95% CI</th>
<th>T-Test</th>
<th>P-Value</th>
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</thead>
<tbody>
<tr>
<td>1996</td>
<td>4.064</td>
<td>4.9</td>
<td>6</td>
<td>15.7 (2.9)</td>
<td>15.9 (2.9)</td>
<td>15.7 (2.9)</td>
<td></td>
<td>1.33</td>
<td>0.19</td>
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<tr>
<td>1995</td>
<td>2.330</td>
<td>1.8</td>
<td>6</td>
<td>18.0 (5.1)</td>
<td>18.0 (5.1)</td>
<td>18.0 (5.1)</td>
<td></td>
<td>0.57</td>
<td>0.57</td>
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<tr>
<td>1994</td>
<td>2.980</td>
<td>2.4</td>
<td>6</td>
<td>16.5 (3.5)</td>
<td>16.5 (3.5)</td>
<td>16.5 (3.5)</td>
<td></td>
<td>1.25</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Conclusion: Combination therapy vs. psychological/behavioral therapy.
Appendix 1: Key Sources for Handsearching


Shaywitz BA, Fletcher JM, Shaywitz SE. Attention-deficit hyperactivity disorder. Advances in Pediatrics 1997; 44:331-367


Appendix 2: Algorithmic Chart for Selection of Behaviour Rating Scales

Method:
1. From each paper, extract data from the first measure on the list and specify measure used.
2. If Teacher & Parent Measures were used: record data from first measure on each list. Otherwise, just record Teacher or Parent measure.

A. TEACHER MEASURES

1. Conners Teacher Rating Scale
   - abbreviated Symptom Questionnaire (CASQ/Hyperactivity Index)

2. IOWA Conners Teacher Rating Scale
   - Total ADHD behaviours score
   - If not given, use: Inattention/overactivity score and Oppositional/defiant scores

3. Achenbach Child Behaviour Checklist - Teacher Report Form (TRF)
   - Attentional Problems score
   - If not given, use: Externalizing behaviours score (if neither of above reported, set aside for Anton to check)

4. Child Attention Profile (CAP) (Barkley, 1988)
   - use Total Score
   - If not given, use: subscale scores

5. School Situations Questionnaire - Original or Revised Version (SSQ or SSQ-R)
   - use Total Severity score

6. Revised Behaviour Problem Checklist (RBPC) (Quay, 1983/4)
   - use Attention problems - Immaturity score

7. ADD-H Comprehensive Teacher Rating Scale (ACTeRS)
   - use Attention and Hyperactivity scores

8. Attention-Deficit Disorder Evaluation Scale (ADDES)
   - use Total score
   - If not given, use: Inattentive, Impulsive and Hyperactive scores


10. ADHD Rating Scale (DuPaul, 1990)
    - use Total score
    - If not given, use: subscale scores
11. Swanson, Nolan & Pelman (SNAP)
B. PARENT MEASURES

1. Conners Parent Rating Scale
   - Abbreviated Symptom Questionnaire (CASQ/Hyperactivity Index)

2. Conners, Loney & Milich Questionnaire (CLAM) (Swanson, 1989)
   - use Conners Hyperactivity Index Score
   - If not given, use: IOWA Conners mixed Inattention/overactivity score and
     Oppositional/defiant factor scores

3. Achenbach Child Behaviour Checklist
   - Attentional Problems score
   - If not given, use: Externalizing Behaviours score
   (if neither of above reported, set aside for Anton to check)

4. Home Situations Questionnaire - Original or Revised version (HSQ or HSQ-R)
   - use Total Severity score

5. Revised Behaviour Problem Checklist (RBPC) (Quay, 1983/4)
   - use Attention problems - Immaturity score

6. Attention-Deficit Disorder Evaluation Scale (ADDES)
   - use Total score
   - If not given, use: Inattentive, Impulsive and Hyperactive scores

7. Children's Attention & Adjustment Survey (CAAS) (Lambert, 1990)

8. ADHD Rating Scale (DuPaul, 1990)
   - use Total score
   - If not given, use: subscale scores

9. Swanson, Nolan & Pelham (SNAP)
Appendix 3: Reviewed Treatment Studies


Arnold LE, Sheridan K, Estreicher D. Multifamily parent-child group therapy for behavior and


Borcherding BG, Keysor CS, Cooper TB, Rapoport JL. Differential effects of methylphenidate...


Denkowski KM, Denkowski GC. Is group progressive relaxation training as effective as effective with hyperactive children as individual EMG biofeedback treatment?. Biofeedback Self Regul 1984;9(3):353-64.


Garfinkel BD, Wender PH, Sloman L, et al. Tricyclic antidepressant and methylphenidate


Horn WF, Ialongo NS et al. Additive effects of behavioral parent training and self-control


Klorman R, Brumaghim JT, Fitzpatrick PA, Borgstedt AD. Clinical effects of a controlled trial of


Martin CA, Vore M, Potts BD, Kryscio RJ, Norton JC, Madigan JM, Welsh RJ, Heffron WM,


Pelham WE, Bender ME, Caddell J, Booth S, Moorer SH. Methylphenidate and children with attention deficit disorder: dose effects on classroom academic and social behavior. Arch Gen Psychiatry 1985;42(10):948-52.


Resnick RJ, Hamer RM, Goldberg SC. Attention deficit disorder without hyperactivity: a


Solanto MV, Conners CK. A dose-response and time-action analysis of autonomic and behavioral


Ullman RK, Sleator EK. Attention deficit disorder children with or without hyperactivity: which behaviors are helped by stimulants? Clinical Pediatr (Phila) 1985;24:547-551.


Appendix 4: Studies in Database of Intervention Effects


Part 3: Economic evaluation of pharmaceutical and psychological/behavioural therapies for attention-deficit/hyperactivity disorder

John A. F. Zupancic, MD, MS, FRCPC
Anton Miller, MB.ChB., FRCPC
Parminder Raina, PhD.
Shoo K. Lee, MB.BS., PhD., FRCPC
Anne Klassen, D Phil
Lise Olsen, BSN, MPH
1. Introduction

1.1 Attention Deficit Disorder

Attention deficit hyperactivity disorder (ADHD) is estimated to affect 3% - 5% of school-age children.\(^1\) Clinical manifestations of the diagnosis include impulsive behavior, increased task-inappropriate motor activity, and difficulties in regulating attention to meet task demands. Children commonly exhibit disruptive behavior in the classroom, academic underachievement and conflictual peer and family relations. ADHD is also frequently associated with neurodevelopmental and psychiatric disturbances such as learning, anxiety and conduct disorders.

Management strategies broadly consist of (a) medicating the child to reduce the frequency and intensity of problematic behaviors and to allow the child to achieve better self-control and better regulation of attention to task; (b) 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 behavior problems, and training them to acquire effective behavior management skills; and (c) psychological therapy with the child to teach him/her self-control and self-monitoring skills. Other modalities of therapy may also be applied depending on individual circumstances and needs, such as social skills training and academic tutoring.

The high prevalence and educational impact of the disorder is reflected in the high rates of prescription of the three most commonly used medications. However, there has been concern among provincial payers that these patterns of prescription may not be clinically and economically appropriate. Moreover, there is interest in whether alternatives to drug therapy are effective and being used appropriately. The techniques of economic evaluation, partnered with the methodologies of systematic literature review and meta-analysis, provide an approach to evaluating and balancing effective care with the realities of economic constraint.

1.2 Product Description

The stimulant class of medications, comprising methylphenidate hydrochloride (brand name Ritalin), dextroamphetamine sulfate (brand name Dexedrine) and magnesium pemoline (brand name Cylert) are the most widely-used form of medical management. All three act by increasing levels of biogenic amines (norepinephrine, dopamine and serotonin) at the presynaptic cleft by mechanisms which include release of certain of these catecholamines and reuptake blockade of others. In North America, methylphenidate has been adopted by physicians as the most frequently-used first-line drug, and is available in both proprietary (Ritalin, manufacturer Novartis) and generic form (manufacturer Pharmascience). Dexedrine (manufacturer SmithKline Beecham) and Cylert (manufacturer Abbott) are not available generically.

Canadian prescription sales of these products for the year 1996 are 178 000, 400 000, 84 000 and 43 000 prescriptions for methylphenidate generic, Ritalin, Dexedrine and Cylert, respectively,\(^2\) and the vast majority (at least 80%) are for children and youth under 20 years of age\(^3\) (see also Part 1 of this present series of reports) for whom ADHD is the principal indication.
All three medications are associated with nuisance adverse effects such as appetite suppression, insomnia and anxiety, which may decrease compliance or necessitate discontinuation.\textsuperscript{4,13} Pemoline may be associated with a chemical hepatitis in up to 3\% of cases\textsuperscript{5} but which is benign and reversible. A number of cases of pemoline-associated potentially fatal fulminant hepatic failure have been reported.\textsuperscript{5,6,7} This seems to be a rare occurrence, and no data are available on its incidence in the population. Some have questioned the causal nature of this association.\textsuperscript{8} Nevertheless, this phenomenon has not been reported for the other stimulant drugs, and the risk of its occurrence has led the manufacturer of pemoline to recommend against its use as a first-line treatment for children and youth with ADHD.\textsuperscript{9} Serious adverse effects such as the emergence of permanent movement and tic disorders may be seen with all the stimulants and psychotic reactions with dextroamphetamine and methylphenidate, but these are again very rare occurrences.

### 1.3 Study Objective

The objective of the study was to compare the costs and clinical outcomes of five alternative modes of treatment for ADHD, including three medication strategies, one non-medication strategy and one alternative combining medication and non-medication therapies. Outcomes were derived from the meta-analysis of published clinical trials described in Part 2 of the present series of reports and quantified in terms of differences in scores on behavioral rating scales. Decision analytic methodology was used to structure the problem and to estimate expected costs and outcomes for each alternative. Incremental cost-effectiveness analysis was performed on the resulting estimates.

### 1.4 Disclosure of Relationships

The study was completed under a contract with the Canadian Coordinating Office for Health Technology Assessment. The authors have no financial or contractual relationships with the pharmaceutical manufacturers of the drugs assessed.

### 2. Methods

#### 2.1 Type of Analyses

The analysis was a retrospective assessment using data from the meta-analysis of published clinical trials described in Part 2 of the present series of reports, and panels representing experts and community-based service providers who were consulted to provide information about current patterns, standards and costs of care in a number of communities across Canada (refer to the Appendix for details).

The problem was structured using the decision analytic tree shown in Figure 1. Five alternative strategies, shown in the tree diagram (Figure 1) and detailed in Table 1, were compared. These included three drug therapies (pemoline, PEM; dextroamphetamine, DAS; methylphenidate, MPH) as well as one psychological/behavioural therapy (PSYCH/BEHAV) and one combination therapy (COMB) which included both methylphenidate and psychological/behavioural treatment. For each alternative, separate costs and effectiveness were estimated for full compliance or partial compliance with therapy. Where appropriate, the costs and outcomes associated with severe adverse reactions to therapy were also estimated.
In light of the potentially fatal consequences of pemoline use in this population, the analysis was also performed after excluding pemoline from consideration. This was thought to reflect more closely the practice of many clinicians, for whom the drug may not currently be considered a therapeutic alternative (see also Section 1.2 above).

Two levels of analysis were undertaken. First, a cost-consequence analysis derived individual direct medical costs associated with the therapeutic alternatives, and the consequences in terms of differences in mean scores on the behavioural rating scales (see Section 3.7).

These results were then aggregated in a cost-effectiveness analysis, in which each alternative was compared to the next best strategy, and to the reference strategy of no treatment. Strategies for which the cost was higher for lower effect were eliminated by dominance, and the results reported in terms of the incremental cost-effectiveness of each of the remaining strategies.

All analyses were performed using DATA 3.0.16 decision analysis software (TreeAge Software: Williamstown, Massachusetts; 1997).

2.2 Target Audience
The target audience for this report is the Department of Health and private third-party payer. Although societal costs could not be estimated for the reasons outlined in Section 3.3, secondary target audiences will include educators, clinicians interested in economically prudent prescribing, and parents of the patients involved, who in many cases bear at least some portion of the direct medical costs of therapy.

2.3 Viewpoint
Costs were assessed from the perspective of a third party payer for health care and pharmaceuticals, specifically, the provincial and territorial ministries of health and their associated drug benefit plans. Such a perspective considered all direct medical costs, including medication, physician visits and hospitalisation, but excluded spillover costs to the educational sector and costs accruing to the family. It should be noted that costs for psychological therapies do accrue to families, except where such services are obtained in the public sector setting; however, in the interest of consistency, this analysis made the simplifying assumption that these costs are borne by the ministry.
In light of the impact on the educational system of the large numbers of children with ADHD, an ideal analysis would take a higher-level perspective. However, a provincial inter-ministry analysis would have required data on educational costs associated with the treatment alternatives, and these were unavailable either from the literature or from an informal survey of educators. Further, analysis from the societal viewpoint would have required data on indirect costs borne by parents (for example, time lost from work), which were also unavailable.

2.4 Treatment Comparator
The alternatives specified represent all of the standard modes of therapy for ADHD. Since non-treatment is also undertaken in many instances, and since the effectiveness data were derived from studies involving comparison to a placebo, the do-nothing alternative was used as the initial treatment comparator. Data on the natural history of health care use by children with ADHD are lacking. There are data to suggest that affected children have more accidents and injuries than other children, but none to demonstrate that treatment of the condition reduces these untoward events. In the absence of such data, this analysis assumes that untreated children have 4 additional visits to the general practitioner per year relative to their unaffected peers (to maintain comparability with drug strategies), with sensitivity analysis varying this number between 0 and 4.

2.5 Time Horizon
There are varying estimates of the average duration of treatment in ADHD. Data from the B.C. Methylphenidate Survey (Miller AR, Armstrong RW, Lalonde CE, unpublished) suggest that the cumulative duration for a school-aged child, allowing for breaks in medication use of several months or more, and disregarding the significant minority of children who receive a single prescription only, is approximately 18 months. However, when all prescriptees are considered, only about 35% of school-aged children continue to receive prescriptions for MPH six months after commencing therapy. In the face of these considerations, we adopted a 1-year time horizon as a convenient compromise for the typical length of time that children remain on drug treatment. Adverse drug reactions, beneficial effects and costs are all assumed to cease with discontinuation of therapy. There is also no proven decrease in drug effectiveness over time. This implies that any change in length of drug therapy should result in proportional changes to both costs and effects, so that the results may be generalised to any time horizon. This may not apply equally to non-medical therapy, where the skills learned in early counselling sessions might be forgotten; in this case, longer time horizons than we presented would result in decreased effectiveness but constant costs.

2.6 Related Studies and Background
A complete systematic review of the literature related to the effectiveness of treatment strategies for ADHD, with a meta-analysis of clinical trials, is provided in Part 2 of the present series of reports. There have been no studies of the economic ramifications of the disorder or its treatment.

2.7 Outcome Measurement
The meta-analysis in Part 2 of the present series of reports expressed treatment outcomes in terms
of differences in mean scores on various behavioural rating scales completed by parents or teachers. Effectiveness outcomes of this economic evaluation are expressed as the mean difference between treatment and placebo groups/conditions for one such scale, the Abbreviated Conners Teacher Rating Scale (ACTRS). These values, along with the number of studies and aggregate sample size on which they are based, are summarised in Table 4.

The choice of this scale over the others is related to the fact that it is common to studies for all five alternatives assessed. In cases where these scales were similar across studies compared, the results could be expressed as mean differences in scale score between treatment and control groups, weighted by the inverse variance of the sample. However, where different scales were used, it was necessary to express efficacy as an effect size, or standardised mean difference. As this result is more difficult to understand intuitively as part of the cost-effectiveness ratio, it was avoided, despite the fact that including it would have allowed the expression of the effectiveness from the parents' viewpoint. A second reason is that, in a significant proportion of cases, children with ADHD receive medical therapy for classroom-related behaviour problems, and they receive it only at school. In this situation, where effects on behaviour are predominantly occurring at school, teachers' observations of behaviour are most relevant. A detailed presentation of the rationale behind the selection of the ACTRS as the primary outcome measure in this study, as well as further description of this measure and its advantages and disadvantages, can be found in Part 2 of the present series of reports, under Section 1.1, pages 3 - 4.

More important is the issue of expressing outcome using a continuous behaviour rating scale, which is in fact a surrogate outcome that must then be translated to a more clinically meaningful measure. Unfortunately, the data presentation in the analysed studies precluded any other format. In an effort to make the results more intuitive, the cost-effectiveness ratios are presented not only as cost per point difference in mean Conner Teacher Rating Scale, but also as the cost for a six point reduction. This corresponds to approximately one standard deviation in the distribution of CTRS in the studies analysed, an effect size cited by other respected clinical investigators as representing a valid and reliable indicator of changes (used to distinguish clinical response to treatments for ADHD). The use of a continuous rating scale as the denominator for the cost-effectiveness ratio requires two assumptions. First, the cost and desirability of achieving a small gain in CTRS score for many children is assumed to be the same as the cost and desirability of achieving a large gain for few children. Secondly, it is assumed that the baseline severity does not affect the cost-effectiveness, so that a one-point decrease for a severely affected child has the same associated costs as a one-point decrease for a mildly affected child. Cost-utility analysis was not performed, as there are no available data on health-related quality of life for children with ADHD.

2.8 Effectiveness and Therapeutic Compliance

Available data on compliance with therapy are poor. The data available from Part 2 of this report indicate only that, averaged across trials, 21% of subjects dropped out of medication therapy prematurely, but give no time course of patients discontinuing medication therapy. The average estimate by members of the main Expert Panel for children commenced on stimulant medication still to be taking it 6 and 12 months later was 86% and 75% respectively. On the other hand, extrapolation to six and twelve months from the four and ten month figures for subjects...
continuing on medication in a clinical trial context as reported by Firestone\textsuperscript{11} yields compliance estimates of 70% and 50% respectively. Finally, as mentioned in Section 2.5 above, analyses from the B.C Methylphenidate Survey for children receiving a prescription for MPH in a population context within the province during the years 1990–1996 (including those who only receive a single prescription) indicate that only 35% and 15% of school-aged children respectively, continue to have prescriptions filled six and twelve months following initial prescription. We felt that the BC data comes closest to reflecting what is happening with attrition in the \textit{real world} and felt that a six month frame was a relevant time to model attrition. It was assumed for the purposes of the study that such children continued to attend follow-up appointments, but that drug costs and effects became zero after the point of non-compliance. The percentage of children discontinuing medication was varied over the full range of 0 to 100% in sensitivity analyses.

2.9 Cost Measurement and Valuation

In order to measure costs, it was necessary to have information about clinical practice patterns and typical resource utilisation. As much of this information was not available in the literature, three expert panels, described in the Appendix were convened. The panels provided information regarding therapeutic strategies, compliance and dosage regimens typically used in management of the index case, a 9 year old, 28-kg boy. They also provided information about the costs that would be involved in treating such a child (and family) in their particular communities.

Frequencies of physician visits were estimated from the time between prescriptions, based on the average of 90 tablets per prescription reported in survey and prescription data\textsuperscript{2} (also Miller AR, Armstrong RW and Lalonde CE: B.C. Methylphenidate Survey, unpublished). Frequency and type of laboratory testing was based on published guidelines with the assumption that physicians do these tests according to those guidelines\textsuperscript{7,9,12,13}.

Unit drug prices are shown in Table 2. Drug prices were obtained from Intercontinental Medical Statistics (IMS)\textsuperscript{2} and represent national averages including dispensing fees and mark-ups. For drugs with generic equivalents, the baseline analysis was performed using the price for the proprietary product, and the generic price was introduced in sensitivity analysis.

Costs for physician services are shown in Table 3. These costs are for follow-up visits averaged across the provincial fee schedules for British Columbia, Ontario and Quebec. Only follow-up visits were considered, as it was assumed that the initial diagnostic consultation had already taken place at the time that a therapeutic decision was made, and that this diagnostic consultation was constant across all alternatives.

As discussed in more detail under Section 2.4 above, data on the health care utilisation of children with untreated ADHD are lacking. For the purposes of this analysis, it was assumed that untreated children visited their family physicians four more times per year than their unaffected peers. This is the same number of visits per year assumed for drug therapy in this model. Costs of psychological/behavioural therapies, also given in Table 3, were averages of: (1) estimates given by members of the expert panel for the time of professionals who would be likely to provide the services in their respective communities (including private practice or salaried psychologists and behavioural consultants); (2) figures obtained from provincial Psychological...
Associations for psychologist consultation; and (3) figures published in research reports of psychological/behavioural interventions in Canada.\textsuperscript{14}

The cost of toxic hepatitis (Table 3) was generalised from recent data in the literature on the direct medical costs of acute hepatitis B infection, converted to Canadian currency.\textsuperscript{15,16}

Laboratory costs for complete blood count and liver function tests (Table 3) were obtained from the fee schedule for British Columbia Children's Hospital.

Table 5 shows the calculation of the annual costs of treatment for each of the five alternatives, as well as for the no-treatment comparator, under the base case assumptions.

All costs were expressed in 1997 Canadian dollars. Because both costs and effects of therapy occurred in a continuous, monotonic stream, and because the time horizon was only one year, discounting was not applied.

2.10 Uncertainty
The impact of uncertainty was assessed using a series of sensitivity analyses for both costs and outcomes. These included the following:

1. Generic formulation for methylphenidate.
2. 95\% confidence intervals for weighted mean difference in Conner Teacher Rating Scale.
4. Costs of physician and psychologist visits, by 20\% in either direction, as this was assumed to represent a maximum of the interprovincial variation in physician fees and of market variation in fees for private practice psychologists.
5. Medication during school days only.
6. Compliance, expressed as the percent of patients who discontinue therapy because of adverse effects without notifying their physicians
7. A worst case analysis (with respect to pharmaceutical therapies) in which the upper confidence intervals and lower costs for psychological/behavioral therapies are used, and the lower confidence intervals and higher costs for pharmaceutical therapies are used.
8. Weight of child.

2.11 Subgroup Analyses
No subgroup analyses were performed.

2.12 Summary of Assumptions

\begin{itemize}
\item Model:
\item Toxicity and non-compliance develop at 0.5 year.
\item Both costs of ADHD therapy and beneficial outcomes cease with onset of toxicity.
\item Serious adverse effects with incidence less than that of toxic hepatitis are not modeled.
\item With non-compliance, costs of monitoring continue but drug costs and beneficial effects cease.
\end{itemize}
Nuisance side effects such as insomnia and appetite suppression are not modeled; we are therefore implicitly assuming that there are no direct medical costs associated with them.

The one-year time horizon does not introduce bias in the comparison of pharmaceutical and psychological/behavioral strategies, through waning of the skills learned in counseling.

It is equally desirable to provide a small gain in Conner Teacher Rating Scale to many children or a large gain to a few.

Clinical:
- Improvement in scores on the Conner teacher rating scale is a good surrogate for clinically significant improvement
- Improvement in scores on the Conner Teacher Rating Scale is independent of the pre-treatment score.
- The outcome data from pooled clinical trials accurately reflects the results that would be obtained in head-to-head comparison of the five treatment strategies.

Economic:
- The estimates of resource utilization and psychological/behavioral therapy costs provided by the expert panel accurately reflect the true values.
- Alternative strategies exhibit perfect divisibility.
- Costs of alternative strategies exhibit constant returns to scale.

3. Results
3.1 Pemoline Excluded
3.1.1 Base case analysis
Estimates of the expected costs and expected outcomes of alternatives under the base case assumptions, not including pemoline, are presented in Table 6 and graphically in Figure 6. DAS, PSYCH/BEHAV and COMB showed higher costs and smaller differences in CTRS scores than the other strategies: these were eliminated from further consideration by strict dominance.

Table 7 shows the incremental costs and effectiveness relative to the no-treatment comparator, as well as the summary incremental cost-effectiveness, for the remaining strategies. As shown, methylphenidate therapy costs $83 for each point difference in the Conner Teacher Rating Scale score sustained for one year.

Placing these values in terms of the clinically significant outcomes discussed earlier, a significant (6-point, or one standard deviation) improvement in outcome costs $498 with methylphenidate, when compared to the non-treatment alternative.

3.1.2 Sensitivity analysis
The basic finding, that methylphenidate therapy dominates other dextroamphetamine and the non-drug treatment strategies, generally remained robust through extensive sensitivity analyses. Table 8 summarises the findings of one-way sensitivity analyses.
Increased or decreased physician and psychologist fees had no effect on the preference for MPH and minimal effects on its absolute cost-effectiveness ratio.

Similarly, varying the efficacy for each therapy individually to the limits of its 95% confidence interval had little effect. Most significantly, there was no change in dominance of pharmaceutical over non-pharmaceutical therapies even when the upper confidence limit for psychological/behavioural therapy (PSYCH/BEHAV) was used. Although COMB therapy ceased to be dominated under its high confidence limit, it remained an inferior option to MPH.

Compliance was modelled as discontinuation of therapy without notification of the physician at 6 months of therapy. It is assumed, then, that costs of monitoring continue while effects and drug costs do not. Expected cost-effectiveness as a function of compliance with methylphenidate therapy is shown in Figure 2. The threshold value is a compliance of 0.10, at which point DAS becomes the preferred option, with a cost-effectiveness of $120. Given the similar common side-effect profiles for three medications considered in this study, such a discrepancy in compliance is unlikely to occur.

As we had assumed a weight of 28 kg for the baseline analysis, it was possible that psychological/behavioural therapies would become more attractive as patient size increased, since the costs of counselling remain constant. However, the preference for MPH was unchanged in analyses for a 16 kg or 40 kg child.

The expert panel also noted that most patients who are prescribed psychological/behavioral therapies do not receive as frequent counseling as those in research protocols. To test the impact of this less costly program, we decreased the number of therapy hours to the expert panel estimates of real-world practices (5, 9.5 and 1.3 hours for child, parent and teacher counseling respectively), but made the assumption that the efficacy was undiminished. Under this liberal assumption, MPH remained the more cost-effective option.

Finally, a strong test of the dominance of MPH was undertaken in a worst-case analysis. In this scenario, inputs were used that minimised efficacy and maximised costs for the pharmaceutical strategies, and the converse for the psychological/behavioural strategies. Although COMB then became a non-dominated option, it remained less attractive than MPH.

3.2 Pemoline Included
3.2.1 Base case analysis
Pemoline was included at two dosage levels, corresponding to the two regimens used in the trial that entered the meta-analysis. As shown in Tables 9 and 10, and graphically in Figure 7, inclusion of pemoline at the lower dose (37.5 mg daily or 1.4 mg/kg/day for the index 28 kg child) resulted in strict dominance of the PEM strategy by MPH. Results were otherwise identical to those for the analysis that excluded pemoline.

The results for the analysis including pemoline at the higher dose (75 mg daily or 2.8 mg/kg/day
for the index 28 kg child) are shown in Tables 12 and 13 and in Figure 8. At this dose, PEM is no
longer dominated, but remains an inferior option compared to MPH, with a cost of $106 for each
point difference in the Conner Teacher Rating Scale score sustained for one year (compared to
$83 for MPH), or $246 for each additional point difference in CTRS beyond that achieved by
MPH. In terms of the clinically significant 6-point (one standard deviation) difference discussed
earlier, PEM thus costs $636 for a clinically significant improvement or $1476 for each clinically
significant improvement beyond that which could be achieved by MPH.

3.2.2 Sensitivity analysis
Sensitivity analyses for the low dose pemoline strategy are shown in Table 11. The dominance of
MPH over the other strategies was maintained in almost all cases. The most notable exception
occurred when the effectiveness of pemoline was taken at its upper 95% confidence interval from
the meta-analysis, in which case it dominated dextroamphetamine, combination and non-
pharmaceutical therapies, and a weighted average of pemoline and no-treatment exhibited
extended dominance over methylphenidate. As before, the combination strategy became a viable
(non-dominated) option for the analyses using school days only, the upper 95% confidence limit
for COMB or the worst-case scenario favouring non-pharmaceutical therapies; however, in each
of these cases it remained less cost-effective than methylphenidate.

Similar sensitivity analyses for the high dose pemoline strategy are presented in Table 14. The
finding that pemoline at this dose is not dominated by methylphenidate but is less cost-effective
was robust to all of the sensitivity analyses described with three exceptions. Pemoline became
dominant over other strategies when its effectiveness is taken at the upper 95% confidence limit
from the meta-analysis. Pemoline also became more cost-effective than methylphenidate when the
compliance with methylphenidate therapy drops below 30%, while pemoline compliance remains
100%, as shown in Figure 3. Conversely, it was dominated in the worst case scenario,
presumably because of the very low 95% confidence limit resulting from the small sample size in
the meta-analysis.

Of note, results for the analysis including pemoline were also maintained when the risk of hepatic
failure was increased to a very high level of 1/1000.

4. Discussion
4.1 Interpretation
This study used incremental cost-effectiveness analysis to evaluate alternative approaches to the
therapy of attention deficit hyperactivity disorder. Three global approaches were examined in
relation to non-treatment: pharmaceutical therapy, psychological/behavioural therapy, and
combination drug and psychological/behavioural therapy. Within the pharmaceutical therapy
group, three individual medications Bmethylphenidate, dextroamphetamine and pemoline Bwere
considered. Because pemoline is associated with rare but potentially fatal hepatic failure, and is
therefore not considered a therapeutic option by many clinicians, the analysis was also performed
after excluding this strategy.

The results of the pemoline-exclusive analysis show that, relative to the no treatment comparator,
one drug therapy \textbf{B}methylphenidate \textbf{B}dominates both dextroamphetamine and the non-pharmaceutical strategies. Methylphenidate costs $83 for each point difference in the Conner Teacher Rating Scale, or approximately $498 for a clinically significant response.

The results were generally robust in sensitivity analysis, with the exception that substitution of the 95\% upper confidence boundary for efficacy of combination therapy caused that option to be non-dominated; however, it continued to have an inferior cost-effectiveness ratio compared to methylphenidate. Similarly, when medications were given only on school days, combination therapy becomes viable, if less cost-effective, and dextroamphetamine is no longer strictly dominated; rather, a weighted average of no-treatment and methylphenidate exhibits extended dominance over the DAS strategy.

When pemoline is included in the analysis at the lower dose used in the literature, the results are similar to those for the pemoline-exclusive analysis. Pemoline at the higher dose in the literature becomes a viable option, although it remains less cost-effective than methylphenidate, with a cost of $106 per one-point improvement in Conner Teacher Rating Scale of $636 per clinically significant improvement. These results are also robust in sensitivity analysis, with the exception of the dominance of pemoline at its upper 95\% confidence limit or at extremes of compliance, both unlikely scenarios.

More importantly, pharmaceutical therapies were more attractive than psychological/behavioral therapies under all conditions, including the use of the upper confidence limit of efficacy from published studies. Thus, even if future studies were undertaken and the interval was narrowed to the point of significance, it is unlikely that a package of psychological/behavioral therapy consisting largely of cognitive-behavior therapy for the child and training for the parents on how to implement the principles of cognitive-behavioral change, without adjunctive medical treatment, would become an economically attractive option.

Comparison of cost-effectiveness ratios across studies can be misleading because of differing methodologies and outcome measures. Despite this caveat, the above values for cost-effectiveness of methylphenidate therapy do appear to compare favorably with those from other accepted health care interventions in the pediatric population. For example, the cost-effectiveness of inhaled corticosteroid treatment of childhood asthma was estimated at $9.45 per symptom-free day, corresponding to approximately $3449 per year of clinically significant reduction in symptoms. Similarly, the pharmaceutical treatment of bulimia nervosa has been estimated to have a cost-effectiveness of $3117 for a one-year period of abstinence, and combination pharmaceutical and cognitive-behavioral therapies in the same study yielded a cost-effectiveness of $4830 per year of clinical resolution.

4.2 Study Limitations
Prior to applying the findings above to policy considerations, several limitations must be recognized. The most significant of these concerns the validity and stability of the estimates of efficacy derived from the meta-analysis of published trials. The limitations of the literature on
which efficacy inputs are based are detailed in Part 2 of the present series of reports and are briefly reviewed here. With the exception of the methylphenidate alternative, the number of acceptable trials (and thus the aggregate sample size) for each strategy was small, resulting in wide associated 95% confidence intervals. This problem was most marked for the psychological/behavioral and the combination strategies, for which the estimates were based on fewer than 20 patients each, but even the pemoline strategy included only one acceptable study. It is possible that our rankings of cost-effectiveness are biased by the decreased power of the studies to show an effect. Although sensitivity analysis on the extremes of the confidence bounds provides some reassurance that psychological/behavioral therapy does not represent an economically sound option, this cannot be said about other options, which tended to become viable, although not preferred, as the confidence limits for efficacy from published trials were reached. Moreover, sensitivity analysis using meta-analytic credible intervals accounts only for sample size and not for study quality. Thus, if the smaller studies were not as methodologically rigorous as those found on the more popular topic of methylphenidate, it is possible that a systematic bias would be introduced.

The preference of pemoline over dextroamphetamine and non-pharmaceutical therapies (although not over methylphenidate), and the dominance of pemoline in one sensitivity analysis, is of potential concern for a second reason. As noted earlier, the medication has significant non-behavioural health effects that are not captured in our measure of effect; specifically, life years lost from hepatic failure are not included in the analysis. Because no more inclusive health status measure exists for this population, we have approached the problem by repeating the analysis after excluding pemoline from consideration. The rationale here is that, although the drug features prominently in the literature (and this in fact was the reason that it was included in the economic analysis initially), the HPB approved product monograph states that because of its association with life-threatening hepatic failure, it should not ordinarily be considered as first-line therapy for ADHD, and it appears that a majority of clinicians would no longer consider it as part of their therapeutic arsenal. In both cases, methylphenidate appears to be an appropriate first-line choice on economic grounds.

A more general problem stems from the marked heterogeneity in treatments and in outcome measures across published trials. Although drug dosages and regimens are fairly comparable in the literature, there is wide variability in the type and intensity of treatments studied as psychological/behavioral alternatives. As noted in Part 2, the validity of pooling across such heterogeneous therapies is questionable. Furthermore, it is possible that the types of checklist outcome measures chosen, while providing a familiar and easily analyzable numeric outcome, may be biased towards drug treatments by virtue of their reliance on symptoms such as hyperactivity. That these outcome measures may underestimate the usefulness of cognitive-behavioral therapy is supported to some extent by recent evidence that cognitive-behavioral procedures are more effective in enhancing academic performance but less effective in improving classroom behavior than certain other behavior modification therapies. Conversely, it is possible that medication may be most efficacious at reducing the primary or core symptoms of ADHD, while psychological/behavioral therapies involving parents and/or teachers may be most efficacious at reducing associated features such as conflicted peers relations and academic underachievement.
which are secondary to social skill and academic skills deficits.  

A further limitation is the fact that the outcome for published efficacy trials is usually difference in behavioral rating scales, rather than a dichotomous outcome indicating a clinically significant improvement. The interpretation of the results of the cost-effectiveness analysis then becomes less intuitive, unless the results are bundled, as they were here, into a several-point difference. This process requires the assumption that many small improvements may be equivalent to a few large improvements, an assumption that may not be tenable. In addition to these concerns regarding the efficacy data, some assumptions of our model itself may not hold. As discussed earlier, the one-year time horizon may bias the results against combination and psychological/behavioral therapies if they are extrapolated into the future, since the skills learned may be forgotten while the drugs retain their effect. Moreover, some of the efficacy data are derived from studies in which the follow-up period was in fact less than one year; the direction of any resulting bias in this case is unclear.

The model also assumed that efficacy is constant across baseline levels of ADHD severity. However, some literature suggests that state-contingent effects occur with stimulant drugs across a range of behavioral and other measures in children with ADHD. Accordingly, their responses to these drugs vary inversely with their level of symptomatology in the drug-free state. This obviously would affect the generalizability of the findings, but again the direction of bias in rankings 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.

Finally, our study has necessarily synthesized data from several retrospective and secondary sources, including compliance, resource utilization and practice pattern information from an expert panel. As this panel was a small sample of the population of clinicians treating ADHD, and by definition distinct in its familiarity with the disorder, its estimates may be not be representative of Canadian physicians in general.

4.3 Future Research Possibilities

Future research should endeavor to correct the deficiencies in the data described. Specifically, the conduct of an economic analysis alongside randomized trials of treatment should be encouraged. This would provide prospective and bias-free estimates of resource utilization and costs.

In light of the profound impact of ADHD on a child’s educational achievement, and the high prevalence of the disorder, it is likely that the spillover effects of treatment on the educational system would be at least as significant as those on the health sector, and potentially more so. Priority should be given to costing of these effects, and repetition of the above analysis with incorporation of those costs.

Finally, it is likely that the academic under-achievement, altered relations with peers and anxiety or emotional disorders associated with ADHD place a significant psychosocial burden on the child and family. This is not captured by an analysis that focuses exclusively on behavioral changes.
Assessment of health-related quality of life of the child and her family would add an important dimension to both the clinical and economic literature on ADHD.
References


Review of Therapies - Part 3


<table>
<thead>
<tr>
<th>Category of Therapy</th>
<th>Specific Alternatives Considered</th>
</tr>
</thead>
</table>
| **Pharmaceutical Therapies**     | MPH: Methylphenidate  
Treat with methylphenidate 10 mg/dose BID every day.  
DAS: Dextroamphetamine  
Treat with dextroamphetamine 15mg/day given 10 mg in the morning and 5 mg at lunch, every day.  
PEM: pemoline  
Treat with pemoline 37.5 or 75 mg/day once daily, every day. |
| **Psychological/Behavioral**     | PSYCH/BEHAV: Non-Medical Package  
Provide 16 hours of individual cognitive–behavioral (CBT) therapy to child by psychologist in private practice, 8 hours of parent training (application of CBT principles; some training in child behavior modification), and 2 hours teacher training. |
| **Combination Therapies**        | COMB: Combination Therapy  
Provide methylphenidate as for MPH and psychological/behavioral therapy as for PSYCH/BEHAV.                                                                                                                                 |
| **No Treatment Comparator**      | NORX:  
Provide four additional visits to general practitioner but no other interventions.                                                                                                                                                  |
Table 2: Unit Costs of Pharmaceuticals

<table>
<thead>
<tr>
<th>Drug</th>
<th>Unit</th>
<th>Cost Per Unit ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate</td>
<td>10 mg tablet</td>
<td>0.29</td>
</tr>
<tr>
<td>(Generic)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ritalin</td>
<td>10 mg tablet</td>
<td>0.37</td>
</tr>
<tr>
<td>(Methylphenidate proprietary)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexedrine</td>
<td>5 mg tablet</td>
<td>0.36</td>
</tr>
<tr>
<td>(Dextroamphetamine proprietary)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexedrine</td>
<td>10 mg tablet</td>
<td>0.56</td>
</tr>
<tr>
<td>(Dextroamphetamine proprietary)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cylert</td>
<td>37.5 mg tablet</td>
<td>0.87</td>
</tr>
<tr>
<td>(pemoline proprietary)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cylert</td>
<td>75 mg tablet</td>
<td>1.53</td>
</tr>
<tr>
<td>(pemoline proprietary)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abstracted from data supplied by IMS Canada (Compuscript file, 1996). Costs are based on national averages and include dispensing fees and markups.
Table 3: Psychological/behavioral Costs

<table>
<thead>
<tr>
<th>Item</th>
<th>Cost ($/per visit/hour)</th>
<th>Range for Sensitivity Analysis ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Blood Count</td>
<td>13.50</td>
<td></td>
</tr>
<tr>
<td>Liver Function Tests (AST, ALT)</td>
<td>11.70</td>
<td></td>
</tr>
<tr>
<td>Toxic Hepatitis</td>
<td>1860</td>
<td>508, 38064</td>
</tr>
<tr>
<td>Pediatric</td>
<td>67 per visit</td>
<td>54,80</td>
</tr>
<tr>
<td>General Practitioner</td>
<td>32 per visit</td>
<td>26,38</td>
</tr>
<tr>
<td>Psychiatrist</td>
<td>72 per visit</td>
<td>58,86</td>
</tr>
<tr>
<td>Psychologist</td>
<td>72 per hour</td>
<td>58,86</td>
</tr>
<tr>
<td>Parent training</td>
<td>78 per hour</td>
<td>62,94</td>
</tr>
<tr>
<td>Teacher training</td>
<td>85 per hour</td>
<td>68,102</td>
</tr>
<tr>
<td>Alternative Sample</td>
<td>Weighted Mean Difference * Mean</td>
<td>95% C.I.</td>
</tr>
<tr>
<td>--------------------</td>
<td>---------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>MPH</td>
<td>6.70</td>
<td>5.89, 7.58</td>
</tr>
<tr>
<td>DAS</td>
<td>4.71</td>
<td>2.99, 6.43</td>
</tr>
<tr>
<td>PEM (2.8 mg/kg dose)</td>
<td>7.80</td>
<td>4.36, 11.24</td>
</tr>
<tr>
<td>PEM (1.4 mg/kg dose)</td>
<td>4.00</td>
<td>0.20, 7.80</td>
</tr>
<tr>
<td>PSYCH/BEHAV</td>
<td>0.30</td>
<td>-5.07, 4.47</td>
</tr>
<tr>
<td>COMB</td>
<td>3.78</td>
<td>0.51, 8.06</td>
</tr>
</tbody>
</table>

* Expressed as reduction in Conners Teacher Rating Scale in intervention arm
<table>
<thead>
<tr>
<th>Alternative</th>
<th>Item Cost ($)</th>
<th>Subtotal ($)</th>
<th>Total ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPH</td>
<td>10mg tablet BID X 365 days 270.10 Medical Visits 2 specialist 139.00 4 GP 128.00 CBC (baseline and q12mo) 27.00</td>
<td>564.10</td>
<td></td>
</tr>
<tr>
<td>DAS</td>
<td>1 X 10mg tablet OD and 1 X 5mg tablet OD X 365 days 204.40 Medical Visits 2 specialist 139.00 3 GP 96.00</td>
<td>570.80</td>
<td></td>
</tr>
<tr>
<td>PEM (1.4 mg/kg)</td>
<td>37.5 mg tablet OD X 365 days 317.55 Medical Visits 2 specialist 139.00 2 GP 64.00 AST, ALT (baseline and q 6 mo) 35.10</td>
<td>555.65</td>
<td></td>
</tr>
<tr>
<td>PEM (2.8 mg/kg)</td>
<td>75 mg tablet OD X 365 days 558.45 Medical Visits 2 specialist 139.00 2 GP 64.00 AST, ALT (baseline and q 6 mo) 35.10</td>
<td>796.55</td>
<td></td>
</tr>
<tr>
<td>PSYCH/BEHAV</td>
<td>Child counseling X 16hr 1152.00 Parent training X 8hr 624.00 Teacher training X 2hr 170.00</td>
<td>1946.00</td>
<td></td>
</tr>
<tr>
<td>COMB</td>
<td>10mg tablet BID X 365 days 270.10 Medical Visits 2 specialist 139.00 4 GP 128.00 CBC (baseline and q12mo) 27.00 Child counseling X 16hr 1152.00 Parent training X 8hr 624.00 Teacher training X 2hr 170.00</td>
<td>2510.10</td>
<td></td>
</tr>
<tr>
<td>Strategy</td>
<td>Cost</td>
<td>Incremental Cost</td>
<td>Effectiveness</td>
</tr>
<tr>
<td>---------------</td>
<td>------</td>
<td>------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Do Nothing</td>
<td>128</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MPH</td>
<td>559</td>
<td>431</td>
<td>6.7</td>
</tr>
<tr>
<td>DAS</td>
<td>566</td>
<td>7</td>
<td>4.7</td>
</tr>
<tr>
<td>PSYCH/BEHAV</td>
<td>1946</td>
<td>1380</td>
<td>0.3</td>
</tr>
<tr>
<td>COMB</td>
<td>2505</td>
<td>559</td>
<td>3.8</td>
</tr>
</tbody>
</table>
Table 7: Cost-Effectiveness of Alternative Strategies Using Base Case Estimates Following Elimination of Dominated Strategies (Pemoline Excluded)

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost (C) ($)</th>
<th>Incremental Cost (∆C) ($)</th>
<th>Effectiveness (E) (CTRS points)</th>
<th>Incremental Effectiveness (∆E) (CTRS points)</th>
<th>Cost-Effectiveness C/E</th>
<th>∆C/∆E ($ per CTRS point)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do Nothing</td>
<td>128</td>
<td></td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>559</td>
<td>431</td>
<td>6.7</td>
<td>6.7</td>
<td>83</td>
<td>64</td>
</tr>
</tbody>
</table>
Table 8: Sensitivity Analyses (Pemoline Excluded)

<table>
<thead>
<tr>
<th>Variable Analyzed</th>
<th>Cost-Effectiveness (C/E) with reference to Non-treatment Comparator ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MPH</td>
</tr>
<tr>
<td>Base Case</td>
<td>83</td>
</tr>
<tr>
<td>Generic MPH</td>
<td>75</td>
</tr>
<tr>
<td>School Days Only</td>
<td>119</td>
</tr>
<tr>
<td>120% clinician fee</td>
<td>91</td>
</tr>
<tr>
<td>80% clinician fee</td>
<td>76</td>
</tr>
<tr>
<td>Fewer Counseling Hours but Same Effect</td>
<td>83</td>
</tr>
</tbody>
</table>

Confidence Limits:

| MPH low  | 95  | D   | D | D | D |
| MPH high | 74  | D   | D | D | D |
| DAS low  | 83  | D   | D | D | D |
| DAS high | 83  | D   | D | D | D |
| NON low  | 83  | D   | D | D | D |
| NON high | 83  | D   | D | D | D |
| COMB low | 83  | D   | D | D | D |
| COMB high| 83  | D   | D | 311|   |

Worst Case Scenario (Favor PSYCH/BEHAV)

| Weight 16kg | 66  | ED  | D | D | D |
| Weight 40kg | 101 | D   | D | D | D |

Legend
D: Dominated (Strict)
ED: Dominated (Extended, in weighted average with no-treatment comparator)
Table 9: Expected Costs and Effects of Alternative Strategies
Using Base Case Estimates (Pemoline 1.4 mg/kg Included)

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost (C) ($)</th>
<th>Incremental Cost (ΔC) ($)</th>
<th>Effectiveness (E) CTRS points</th>
<th>Incremental Effectiveness (ΔE) CTRS points</th>
<th>Cost-Effectiveness C/E</th>
<th>ΔC/ΔE ($ per CTRS point)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do Nothing</td>
<td>128</td>
<td></td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPH</td>
<td>559</td>
<td>431</td>
<td>6.7</td>
<td>6.7</td>
<td>83</td>
<td>64</td>
</tr>
<tr>
<td>DAS</td>
<td>566</td>
<td>7</td>
<td>4.7</td>
<td>-2.0</td>
<td>120</td>
<td>DOM</td>
</tr>
<tr>
<td>PEM</td>
<td>588</td>
<td>23</td>
<td>4.0</td>
<td>-0.7</td>
<td>147</td>
<td>DOM</td>
</tr>
<tr>
<td>PSYCH/BEHAV</td>
<td>1946</td>
<td>1358</td>
<td>0.3</td>
<td>-3.7</td>
<td>6487</td>
<td>DOM</td>
</tr>
<tr>
<td>COMB</td>
<td>2505</td>
<td>559</td>
<td>3.8</td>
<td>3.5</td>
<td>663</td>
<td>DOM</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost</th>
<th>Incremental Cost</th>
<th>Incremental Effectiveness</th>
<th>Incremental Effectiveness</th>
<th>Cost-Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(C) ($)</td>
<td>(ΔC) ($)</td>
<td>(E) (CTRS points)</td>
<td>(ΔE) (CTRS points)</td>
<td>C/E  ΔC/ΔE ($/ per CTRS point)</td>
</tr>
<tr>
<td>Do Nothing</td>
<td>128</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>559</td>
<td>431</td>
<td>6.7</td>
<td>6.7</td>
<td>83  64</td>
</tr>
</tbody>
</table>

Table 10: Cost-Effectiveness of Alternative Strategies Using Base Case Estimates Following Elimination of Dominated Strategies (Pemoline 1.4 mg/kg Included)
### Table 11: Sensitivity Analyses (Pemoline 1.4 mg/kg Included)

<table>
<thead>
<tr>
<th>Variable Analyzed</th>
<th>Cost-Effectiveness (C/E) with reference to Non-treatment Comparator ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MPH</td>
</tr>
<tr>
<td>Base Case</td>
<td>83</td>
</tr>
<tr>
<td>Generic MPH</td>
<td>75</td>
</tr>
<tr>
<td>School Days Only</td>
<td>119</td>
</tr>
<tr>
<td>120% clinician fee</td>
<td>91</td>
</tr>
<tr>
<td>80% clinician fee</td>
<td>76</td>
</tr>
<tr>
<td>Fewer Counseling Hours but Same Effect</td>
<td>83</td>
</tr>
<tr>
<td>Confidence Limits:</td>
<td></td>
</tr>
<tr>
<td>MPH low</td>
<td>95</td>
</tr>
<tr>
<td>MPH high</td>
<td>74</td>
</tr>
<tr>
<td>DAS low</td>
<td>83</td>
</tr>
<tr>
<td>DAS high</td>
<td>83</td>
</tr>
<tr>
<td>PEM low</td>
<td>83</td>
</tr>
<tr>
<td>PEM high</td>
<td>ED</td>
</tr>
<tr>
<td>NON low</td>
<td>83</td>
</tr>
<tr>
<td>NON high</td>
<td>83</td>
</tr>
<tr>
<td>COMB low</td>
<td>83</td>
</tr>
<tr>
<td>COMB high</td>
<td>83</td>
</tr>
<tr>
<td>Worst Case Scenario (Favor PSYCH/BEHAV)</td>
<td>103</td>
</tr>
<tr>
<td>Weight</td>
<td></td>
</tr>
<tr>
<td>16 kg</td>
<td>66</td>
</tr>
<tr>
<td>40 kg</td>
<td>71</td>
</tr>
</tbody>
</table>

Legend
D: Dominated (Strict)
ED: Dominated (Extended, in weighted average with no-treatment comparator)
### Table 12: Expected Costs and Effects of Alternative Strategies
Using Base Case Estimates (Pemoline 2.8 mg/kg Included)

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost (C) ($)</th>
<th>Incremental Cost (ΔC) ($)</th>
<th>Effectiveness (ΔE) CTRS points</th>
<th>Incremental Effectiveness (ΔE) CTRS points</th>
<th>Cost-Effectiveness (C/E)</th>
<th>ΔC/ΔE ($ per CTRS point)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do Nothing</td>
<td>128</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>83</td>
<td>64</td>
</tr>
<tr>
<td>MPH</td>
<td>559</td>
<td>431</td>
<td>6.7</td>
<td>6.7</td>
<td>83</td>
<td>64</td>
</tr>
<tr>
<td>DAS</td>
<td>566</td>
<td>7</td>
<td>4.7</td>
<td>-2.0</td>
<td>120</td>
<td>DOM</td>
</tr>
<tr>
<td>PEM</td>
<td>829</td>
<td>263</td>
<td>7.8</td>
<td>3.1</td>
<td>106</td>
<td>85</td>
</tr>
<tr>
<td>PSYCH/BEHAV</td>
<td>1946</td>
<td>1117</td>
<td>0.3</td>
<td>-7.5</td>
<td>6487</td>
<td>DOM</td>
</tr>
<tr>
<td>COMB</td>
<td>2505</td>
<td>559</td>
<td>3.8</td>
<td>3.5</td>
<td>663</td>
<td>DOM</td>
</tr>
</tbody>
</table>
Table 13: Cost-Effectiveness of Alternative Strategies Using Base Case Estimates Following Elimination of Dominated Strategies (Pemoline 2.8 mg/kg Included)

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost (C) ($)</th>
<th>Marginal Cost (ΔC) ($)</th>
<th>Effectiveness (E) (CTRS points)</th>
<th>Marginal Effectiveness (ΔE) (CTRS points)</th>
<th>Cost-Effectiveness C/E</th>
<th>ΔC/ΔE ($ per CTRS point)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do Nothing</td>
<td>128</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>559</td>
<td>431</td>
<td>6.7</td>
<td>6.7</td>
<td>83</td>
<td>64</td>
</tr>
<tr>
<td>Pemoline</td>
<td>829</td>
<td>270</td>
<td>7.8</td>
<td>1.1</td>
<td>106</td>
<td>246</td>
</tr>
</tbody>
</table>
### Table 14: Sensitivity Analyses (Pemoline 2.8 mg/kg Included)

<table>
<thead>
<tr>
<th>Variable Analyzed</th>
<th>Cost-Effectiveness (C/E) with reference to Non-treatment Comparator ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MPH</td>
</tr>
<tr>
<td>Base Case</td>
<td>83</td>
</tr>
<tr>
<td>Generic MPH</td>
<td>75</td>
</tr>
<tr>
<td>School Days Only</td>
<td>119</td>
</tr>
<tr>
<td>120% clinician fee</td>
<td>91</td>
</tr>
<tr>
<td>80% clinician fee</td>
<td>76</td>
</tr>
<tr>
<td>Fewer Counseling Hours but Same Effect</td>
<td>83</td>
</tr>
<tr>
<td>Confidence Limits:</td>
<td></td>
</tr>
<tr>
<td>MPH low</td>
<td>95</td>
</tr>
<tr>
<td>MPH high</td>
<td>74</td>
</tr>
<tr>
<td>DAS low</td>
<td>83</td>
</tr>
<tr>
<td>DAS high</td>
<td>83</td>
</tr>
<tr>
<td>PEM low</td>
<td>83</td>
</tr>
<tr>
<td>PEM high</td>
<td>ED</td>
</tr>
<tr>
<td>NON low</td>
<td>83</td>
</tr>
<tr>
<td>NON high</td>
<td>83</td>
</tr>
<tr>
<td>COMB low</td>
<td>83</td>
</tr>
<tr>
<td>COMB high</td>
<td>83</td>
</tr>
<tr>
<td>Worst Case Scenario (Favor PSYCH/BEHAV)</td>
<td>103</td>
</tr>
<tr>
<td>Weight</td>
<td></td>
</tr>
<tr>
<td>16 kg</td>
<td>66</td>
</tr>
<tr>
<td>40 kg</td>
<td>71</td>
</tr>
</tbody>
</table>

Legend
- D: Dominated (Strict)
- ED: Dominated (Extended, in weighted average with no-treatment comparator)
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Figure 6. Incremental Cost and Effectiveness of Therapies for ADHD, pemoline Excluded
Figure 7. Incremental Cost and Effectiveness of Therapies for ADHD, Including pemoline at Low Dose
Figure 8. Incremental Cost and Effectiveness of Therapies for ADHD, Including pemoline at High Dose
Appendix  Advisory and Expert Panels

A six-person panel provided information on the provision and costs of psychological/behavioural therapy in their communities. Two members, a Montreal paediatrician with special interest in developmental-behavioural paediatrics and the B.C psychologist active in a community-based clinic for children and youth with learning and behavioural problems, also served on a larger, 11-person panel whose composition and function are described below. Other members of the six-person panel were: a child psychiatrist from Montreal, a family and behavioural consultant who runs a community-based clinic for children and youth with learning and behavioural problems in Saskatoon, the director of a community-based organisation providing services to children and families with a variety of behavioural and social difficulties in lower mainland area of B.C., and an administrator of a program for ADHD intervention run by the Greater Vancouver Mental Health Service in B.C. Each of these panelists provided information about the provision, availability and costs of psychological/behavioral therapies in their respective communities. Average dollar values for various forms of therapies provided in different settings were calculated from the individual estimates provided.

The larger 11-person panel consisted of four academically-based child and family psychiatrists, three general paediatricians (one with special interest and training in developmental-behavioural paediatrics), two subspecialist developmental-behavioural paediatricians, a family practitioner with an interest in ADHD and a clinical psychologist active in assessment and management of ADHD in the community, and supplied information on their experience and management of ADHD in children. In particular, they documented their expectations of: (1) spontaneous resolution of ADHD symptoms over time; (2) uptake of treatment recommendations by patients; and (3) rates of dropping out from various forms of treatment. Six of the eleven reside in B.C., one in Saskatchewan, two in Ontario, one in Quebec and one in the U.S.

A seven-person subgroup of this main panel provided information about their perceptions of the likelihood of a child/family receiving various forms of therapy and the amount of therapy they were likely to receive. This subgroup consisted of two child and family psychiatrists, two general paediatricians, a developmental-behavioural paediatrician and the family practitioner and psychologist.
Figure 1: Decision Analysis Tree Diagram (Pemoline included)
Figure 2: Decision Analysis Tree Diagram (Pemoline excluded)
Figure 3: Sensitivity Analysis: Effect of Compliance Rate with Methylphenidate Therapy on Cost-Effectiveness of Pharmaceutical Strategies, Pemoline Excluded

Expected Cost / Effect

Compliance Rate

MPH
DEX
Figure 4: Sensitivity Analysis: Effect of Compliance Rate with Methylphenidate Therapy on Cost-Effectiveness of Pharmaceutical Strategies, Including Pemoline at Low Dose.
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Figure 6: Cost-Effectiveness of Therapies for ADHD Excluding Pemoline

Cost-Effectiveness Table:

<table>
<thead>
<tr>
<th>Cost</th>
<th>Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>$100</td>
<td>7.2</td>
</tr>
<tr>
<td>$700</td>
<td>6.4</td>
</tr>
<tr>
<td>$1300</td>
<td>5.6</td>
</tr>
<tr>
<td>$1900</td>
<td>4.8</td>
</tr>
<tr>
<td>$2500</td>
<td>4.0</td>
</tr>
</tbody>
</table>

- Do-Nothing
- Methylphenidate
- Dextroamphetamine
- Non-Drug Therapy
- Combined Therapy
Figure 7: Cost-Effectiveness of Therapies for ADHD With Pemoline Included at Low Dose

Cost

Eff
ecti
ven
ess

$100

$700

$1300

$1900

$2500

Do-Nothing
Methylphenidate
Dextroamphetamine
Pemoline
Non-Drug Therapy
Combined Therapy
Figure 8: Cost-Effectiveness of ADHD Therapies With Pemoline Included at High Dose