

Methylphenidate in the treatment of children with attention-deficit hyperactivity disorder

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The reports in this issue by Howard Schachter and colleagues¹ and by Anton Miller and associates² attest to the interest and controversy that stimulant medications continue to raise despite more than 50 years of clinical use of these drugs in the treatment of attention-deficit hyperactivity disorder (ADHD). Schachter and colleagues conducted a meta-analysis to determine the evidence for the efficacy and safety of methylphenidate in the treatment of children with ADHD. This meta-analysis was restricted to placebo-controlled studies published between 1981 and 1999 that tested short-acting (i.e., immediate release) methylphenidate in patients less than 18 years of age. Based on the 62 studies that were considered in the meta-analysis, the authors concluded that there is evidence for the short-term efficacy of methylphenidate in alleviating the symptoms of ADHD in children, but several limitations were found in the existing literature. Many studies had a small sample size and short duration (usually a few days or weeks) and failed to report methodological details such as the randomization process, preservation of blinding and the possible presence of carryover effects in crossover designs. In addition, the plot of effect size versus sample size from published studies was suggestive of substantial publication bias (i.e., a number of studies with results that would not support the efficacy of methylphenidate may not have been published).

The scientific literature concerning the treatment effects of stimulant medications is the largest in child psychiatry and one of the largest in general psychiatry. By 1996, 155 controlled studies involving more than 5000 children had been reported.³ Over the years, a number of reviews have concluded that the administration of methylphenidate dramatically decreases the core symptoms of ADHD, which include hyperactivity, impulsiveness and inattention.⁴ The data also consistently indicate that methylphenidate is more efficacious than nonpharmacological interventions.^{5,6} The pharmacological effect is clinically detectable minutes after administration and lasts only a few hours, thus requiring twice or thrice daily dosing. This short duration of action is the reason for the recent development of extended-release formulations that obviate the need for multiple daily dosing. Side effects are common and dose related, most notably being a decrease in appetite, but also stomach ache, headache, irritable mood and sleep difficulties.⁷ These side effects, however, are usually mild and responsive to dose adjustment and often abate with continuous use. Serious adverse events, such as hallucinations, are rare. Continuous use has been associated with slowing of physical growth,

which is slight, transient and of unclear cause.^{8,9} In both the United States and Europe, methylphenidate is a controlled prescription medication that is approved for children aged 6 years and older as an integral part of a comprehensive treatment approach to ADHD. This use is endorsed by various practice parameters and treatment algorithms.¹⁰⁻¹²

Statistically, the effect of methylphenidate is considered "large," that is, the difference between methylphenidate and placebo on rating scales of ADHD symptoms is about 0.8 standard deviation or greater. Clinically, this can mean the difference between a child who has major problems concentrating, and is viewed as problem by teachers and parents alike, and a child who is very close to normal for the age group. The rate of improvement approaches 80% on methylphenidate and is less than 15% on placebo. These figures translate into a number needed to treat with methylphenidate in order to add one patient to those who would improve on placebo of about 1.5. This number needed to treat compares very favourably with other treatments. For instance, the number needed to treat with antidepressant medication for adult depression is about 7.

The large effect size of methylphenidate can be found to be statistically significant with a relatively small number of patients. In addition, because the pharmacological effects emerge minutes after the first dose and wane in a matter of a few hours, carryover effects to the next day are not expected and the crossover design can be used for experimental purposes. Some studies tested for the possible presence of carryover effects and did not find any.^{13,14} Indeed, even if carryover effects were present, these would favour the placebo arm and make it more difficult to show efficacy for methylphenidate. Many studies have employed very small sample sizes (fewer than 40 subjects). Under these conditions, the risk of not finding a statistically significant difference is high even in the presence of a large effect size, thus explaining the possible publication bias that Schachter and colleagues have reported. I am not, however, aware of any studies with a sample size that was moderately large (at least 40 subjects) that could not find a difference between methylphenidate and placebo in ADHD symptoms. The largest placebo-controlled study thus far conducted is the titration trial of the Multimodal Treatment Study of Children with Attention Deficit Hyperactivity Disorder (MTA),⁶ which was not included in the meta-analysis by Schachter and colleagues because it was published after 1999.¹⁴ In this double-blind, controlled trial, 289 children aged 7-9 years received methylphenidate at 3 different dosages and placebo in a 4-week crossover study.

Methylphenidate was superior to placebo on all measures of behaviour in school and at home ($p < 0.0001$). Based on teacher ratings, the effect size was 0.75 on measures of inattention and overactivity, and 1.31 on measures of aggression and defiance. Methylphenidate was effective and superior to placebo for 77% of these children, whereas the response to placebo was 12.5%. This 4-week study was followed by a 13-month open-label maintenance phase. Of the 198 children for whom an optimal dose of methylphenidate was identified during the 4-week study, 174 (88%) were still on methylphenidate at the end of the 13-month maintenance phase.¹⁵ These data indicate that most children with ADHD improve on methylphenidate in the short term and maintain their improvement without intolerable adverse events for at least 13 months. Likewise, amphetamine, which is another stimulant medication similar to methylphenidate in therapeutic activity, was found to have long-term efficacy in a placebo-controlled discontinuation trial.¹⁶

Thus, the efficacy of methylphenidate in decreasing the symptoms of ADHD is well documented. In spite of the methodological limitations of many reports, there are enough well-designed trials to conclude that this drug has a clear-cut effect in reducing hyperactive, impulsive and inattentive behaviours. The rapid emergence of treatment effects and side effects makes it difficult to maintain double-blind conditions in the long term. The feasibility of an extended placebo-controlled trial of methylphenidate is also questionable, because families may object to withholding active treatment for longer than a few weeks in the face of persisting behavioural and academic difficulties.

However, a number of important questions about methylphenidate, and the whole treatment of ADHD, remain to be addressed and call for more research. Arguably, the most critical question is whether the reduction of the ADHD symptoms, achieved through pharmacological or behavioural intervention, will ultimately translate into a better prognosis with respect to improved educational and occupational achievement and decreased risk of accidental trauma, anti-social behaviours and substance abuse. Until this issue is settled, the treatment of ADHD will continue to find critics arguing that we are just controlling symptoms but not necessarily improving long-term outcomes. Another critical issue is the safety of stimulant use in special patient populations, such as children of preschool age or those at increased risk for bipolar disorder or schizophrenia. It is extremely important for families and physicians to make sure that these children do not get exposed to potentially harmful treatments, while still being helped with their behavioural and learning difficulties. Finally, pharmacoepidemiological studies are needed to provide information about the extent of drug use in the community and about patient, family, physician and health care characteristics that moderate this use. The report by Miller and colleagues adds new information by showing that the dramatic increase in the use of methylphenidate in the 1990s was not limited to the United States. The finding of greater use of methylphenidate among lower socioeco-

omic classes is also interesting, because it contrasts with reports of the opposite situation in the United States¹⁶ and calls for further investigation of the paths to drug prescribing for ADHD.

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