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Review Article

The Evidence of the Benefits and Harms of Methylphenidate in the Treatment of Attention Deficit/Hyperactivity Disorder is Inconclusive

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Abstract

Attention deficit/hyperactivity disorder (ADHD) is a frequent diagnosis in children and adolescents and is also diagnosed in adults. The ADHD core symptoms of inattention, hyperactivity and impulsivity frequently cause significant impairments in behavioral, social and academic functioning in children, adolescents and adults. The goals in ADHD therapy should consider the chronicity and long-term impact of the disorder. This review provides an overview of the current debate regarding benefits and harms of methylphenidate in ADHD. Short-term benefits of pharmacotherapy, including the use of psychostimulants such as methylphenidate, have consistently been demonstrated in many studies. However, the recommendation of methylphenidate as first-line treatment for children and adolescents with ADHD has been questioned on the basis of two recent Cochrane reviews, which have raised questions concerning the overall quality of the available methylphenidate trials. The extent of the efficacy of methylphenidate in the treatment of ADHD remains a matter of debate in view of low quality of outcome measures and of possible bias of research studies. Extended use of stimulant medication has been shown to offer no benefits in regard to reduction of symptom severity but to be associated with suppression of adult height. Other adverse effects of methylphenidate may include serious cardiovascular events. The findings of trials assessing efficacy and safety of methylphenidate over short time periods need to be interpreted with caution and cannot be extrapolated to long-term effects. The long-term administration of methylphenidate for ADHD has not been shown to have proven efficacy and may be associated with various adverse effects. Scant research has adequately evaluated the long-term safety of methylphenidate, especially in elderly adults. Given the limited or absent long-term benefits of methylphenidate, the therapeutic value of this compound may be outweighed by its adverse effects. In clinical practice, careful weighting of risks and benefits of methylphenidate is important.

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ABBREVIATIONS

ADHD: Attention Deficit/Hyperactivity Disorder; MPH: Methylphenidate; RCT: Randomized Controlled Trial

INTRODUCTION

ADHD is one of the most common psychiatric diagnoses in childhood and adolescence. ADHD is characterized by age-inappropriate and detrimental levels of inattention, hyperactivity and impulsivity, and is associated with long-term behavioral, academic, social, and mental health problems [1,2]. Symptoms of ADHD can also be found in adults [3]. Major impairments in children and adolescents with ADHD include social and educational problems, while adult individuals with ADHD are often affected by occupational problems, accidents, or substance abuse [4]. Since the symptoms of ADHD frequently persist into adulthood and may compromise an individual's functioning over years and even decades, the evaluation of treatments needs to adopt a lifespan perspective. Children with ADHD are at substantial risk of adverse outcomes in adolescence and adulthood, such as poor education [5], antisocial behavior including the need for police intervention, and substance misuse in adolescence and adulthood [6,7]. The treatment of ADHD should therefore improve long-term functioning and outcomes and diminish long-term adverse effects.

Approximately 6% of school-aged children in the United States receive medication for the treatment of ADHD [8]. The most common drugs prescribed for ADHD are psychostimulants, such as MPH [9], which have been the first-line medication for many decades. In view of the widespread administration of MPH, clear evidence of its efficacy, outcome and safety is needed.

MPH has been demonstrated to yield short-term symptom reduction and other beneficial outcomes [10-12]. MPH has been recommended as first-line pharmacotherapy for children and adolescents with ADHD [13,14]. However, the magnitude of the reported therapeutic benefits of MPH has been called into question, and the recommendation of MPH as first-line pharmacological treatment has also been questioned on the basis of two recent Cochrane reviews [15,16]. A concise summary of these reviews concerning benefits and harms of therapy for ADHD using MPH has recently been provided [17]. The first review included 185 RCTs estimating the benefits of MPH treatment [15]; the second review of 260 non-randomized trials estimated harms [16]. These reviews have raised questions concerning the overall quality of the available MPH trials.

The present narrative mini review provides a concise summary of the current evidence of short-term efficacy and adverse effects of MPH in the treatment of ADHD, the ongoing controversy concerning the effect size of MPH in ADHD, and the problems regarding the investigation of long-term benefits and harms of MPH administration.

SHORT-TERM EFFECTS OF MPH IN ADHD

Many clinical trials of ADHD medications have used symptom reduction as the primary outcome measure for treatment response [18-20]. However, beyond short-term response and improvement of symptoms, long-term goals of pharmacotherapy for ADHD should be defined. These goals should address optimal treatment outcomes extending beyond statistically significant but functionally modest reductions of ADHD symptoms, and should include syndromatic, symptomatic, and functional remission [21].

RCTs are at the highest level in the hierarchy of evidence in regard to therapeutic problems and are the best means of evaluating the efficacy of an intervention [22,23]. Numerous RCTs have established short-term benefits of MPH in regard to the symptoms and behavioral problems related to ADHD. Randomized, placebo-controlled trials of MPH have demonstrated marked short-term effects on ADHD symptoms in children and adolescents [24].

However, evidence of benefits of MPH on major outcome parameters associated with ADHD, particularly school performance, is sparse. ADHD in children and adolescents has a profound negative impact on school performance, and a retrospective descriptive study has assessed differences in school performance among children using methylphenidate at the end of primary school [25]. The school performance of children with an earlier onset of MPH therapy was shown to be worse than that of children starting treatment later [25]. This could indicate a limited effect of long-term therapy or a more severely affected group of children who needed treatment early. Furthermore, children with ADHD receiving MPH performed worse at school compared to their peers [25]. In conclusion, there is no conclusive evidence that MPH has beneficial effects on school performance of children with ADHD.

A systematic review of MPH for children and adolescents with ADHD using Cochrane methodology and pre-publication of a peer reviewed protocol raised several concerns regarding the therapeutic efficacy of MPH in ADHD [26]. The findings of meta-analyses were based on the ratings of ADHD symptoms and general behavior by teachers, parents and observers. The results of the Cochrane systematic review were as follows: MPH may improve teacher reported ADHD symptoms, teacher reported general behavioral problems, and parent reported quality of life [15]. MPH was associated with an increased risk of non-serious adverse events, particularly decreased appetite and insomnia, but no evidence of an increase in the risk of serious adverse events (short follow-up periods of the included trials: median treatment duration of 49 days in 38 parallel group trials, 14 days in 147 crossover trials). The vast majority of trials (96.8%) were considered to be at high risk of bias according to the Cochrane guidelines [15]. The consistent bias and the low quality of outcomes [27] led to a less favorable judgement of the available studies than in previously published meta-analyses, and to the conclusion that the exact therapeutic benefit of MPH is uncertain [15,17]. This conclusion sparked a vigorous debate [28]. Major criticisms of the Cochrane study include the assertions that the inclusion and exclusion criteria for qualifying trials may be flawed, that the comparison of trials with short-term versus long-term intervention may be compromised, that the assumption in the review of unblinding by common non-serious adverse events may not be warranted for the primary outcome, that vested interest was added as a domain of risk-of-bias, and that the conclusion that quality-of-evidence was very low is not consistent with other appraisals in the available literature [28]. Potential conflict of interest among investigators was the most common single source of bias in the Cochrane review on MPH for ADHD in children and adolescents [15,17]. The majority of studies evaluating the efficacy of ADHD medications were funded by manufacturers of these drugs. Sponsorship and conflicts of interest have been shown to be able to influence intervention effects on outcomes, i.e. they may lead to overestimation of benefit and underestimation of harm [29]. Virtually the same criticisms of the Cochrane review were published in several papers [30-33]. Most of the critiques were from investigators with possible conflicts of interest; some of these authors disclosed this [30,31], while others did not [33].

A Cochrane systematic review on MPH for adults with ADHD [34] was recently withdrawn [35], following serious criticism of quality-of-evidence, flawed conclusions, and vested interest bias. A summary of the criticism leading to the withdrawal can be found elsewhere [36]. The retraction of the Cochrane systematic review recognizes previous unreliable clinical ADHD research and suggests that clinical trials of MPH in adults with ADHD are of very low quality. Well-conducted long-term trials assessing the benefits and harms of MPH in adult ADHD are urgently needed.

LONG-TERM ADMINISTRATION OF MPH

While short-term effects of MPH on the core symptoms of ADHD have consistently been shown in many individuals

with ADHD, it is unclear whether or not this drug improves the outcome over an extended time period, and concerns have been raised in regard to the long-term safety of MPH [37].

Improvements of functioning in children with ADHD have been shown following MPH treatment, while long-term outcomes failed to be normalized. In the RCTs included in the Cochrane analysis of benefits and harms of methylphenidate in children and adolescents with ADHD, the median duration of drug therapy was less than two months. The largest RCT so far conducted, the Multimodal Treatment Study of children with ADHD, demonstrated that the administration of medication over 14 months resulted in substantial improvements in symptoms, severity of associated disorders, and multiple aspects of functional impairments [38]. While symptoms and several domains of impairment were improved at the end of the active treatment period, these improvements had been lost within two years post-treatment [39]. At long-term post-treatment assessment six and eight years after baseline, some of the treatment gains were still present. However, individuals treated with medication showed substantial impairment in comparison to their classmates without ADHD [40].

Evidence from randomized controlled trials of longer term benefits of medication is largely absent. A systematic review identified five RCTs and 10 open-label extension studies of initial short-term RCTs, with a minimum total follow-up of 24 weeks [41]. The available RCTs showed that medication was significantly more efficacious than placebo in adults with ADHD, and the positive effect was maintained during the open-label follow-up period [41]. The maximum duration of these trials was four years. Observational studies suggested a positive correlation between stimulant treatment during childhood and favorable long-term outcome in adult individuals with ADHD [41]. However, in light of the fact that measures of efficacy focus on ADHD symptoms rather than on the functional consequences of MPH treatment, firm conclusions based on the currently available long-term studies cannot be drawn. Moreover, the wide variety of study designs and outcome measures used in these studies preclude a meta-analytic evaluation.

In a long-term observational continuation of the randomized controlled Multimodal Treatment Study, children who had received stimulant medication for ADHD into adulthood showed no ongoing symptom reduction, i.e. benefits in regard to symptom severity could not be found when these individuals were compared to those who had discontinued pharmacological treatment or who had never received stimulants [42].

Pharmaco-epidemiological studies from Sweden have compared periods when individuals with ADHD were on versus off ADHD medications. The findings of these observational studies have suggested potential long-term benefits of pharmacotherapy on serious co-occurring problems, including substance abuse [43], suicidal behavior [44], transport accidents [45], and criminal convictions [37,46]. These population-based register studies are vulnerable to many threats to validity (e.g. selection effects), and cannot account for the confounding variables related to the selection of patients for therapy [47]. Differences in the indications for pharmacotherapy are the biggest threat, since some patients might receive drugs for more severe or more numerous symptoms and comorbid conditions. In Sweden, prescription of ADHD medication is indeed likely to indicate a greater severity of ADHD symptomatology [46]. Furthermore, the effects of confounding variables that varied during follow-up (e.g. cyclic nature of the disorder, crime, or substance use) cannot be excluded, and RCTs need to be performed. In conclusion, the Swedish population data [43-46] cannot readily be generalized, since various factors, such as prevalence of ADHD diagnosis, rate of pharmacotherapy, other kinds of treatment, or substance abuse may vary between different countries.

ADVERSE EVENTS, HARMS AND SAFETY OF MPH THERAPY

The most commonly reported adverse effects of treatment with MPH are decreased appetite, growth retardation, and insomnia; other side effects include cardiovascular problems and gastrointestinal symptoms [48,49]. Compared to no intervention, MPH was shown to significantly increase the risk of serious adverse events including psychotic disorders, arrhythmia, hypertension, and seizures [16]. Furthermore, more than 7% of participants withdrew from MPH therapy because of adverse events of "unknown seriousness" [17].

As was shown in the Multimodal Treatment Study, extended use of stimulants was associated with suppression of adult height. The average height of individuals who had continued stimulant therapy into adulthood was more than 2 cm shorter than in those who had discontinued therapy [42]. Effects on growth in children with ADHD treated with MPH have been of longstanding concern [50]. While some studies found no such effects [51,32], others demonstrated that pharmacotherapy with stimulants in childhood modestly reduced expected height [53], and identified a small but significant deceleration of height velocity as a long-term side effect of MPH, the extent of which was related to the duration of therapy [54]. While the effects of stimulants on height may not affect quality of life, other potential metabolic long-term effects as yet unknown might be of more serious consequence and should be investigated.

Conflicting evidence regarding the cardiovascular safety of MPH has emerged over time [55]. Case reports of myocardial infarction and stroke following psychostimulant treatment in children and adolescents led to public and regulatory concern, and the marketing of ADHD medications was consequently temporarily suspended in Canada [56]. Public health concerns have been amplified through the increasing administration of stimulants in adults with ADHD. Evidence of an association of the use of psychostimulants with an increase in heart attacks, strokes and sudden deaths was not found in large retrospective population based cohort studies [57-60]. A methodological problem of these observational studies could be the under-reporting of adverse effects.

A systematic review of published studies reported that prescription stimulant use was not associated with adverse cardiovascular outcomes in six of seven studies in children and adolescents, while two out of three studies in adults found an association [61]. Case reports of adverse cardiovascular events and life threatening heart failure associated with MPH continue to be published [62,63]. The relative risk of arrhythmias and

myocardial infarction has been reported to be increased in the early period following the onset of MPH therapy in children and adolescents with ADHD [64]. Although the absolute risk of these cardiac adverse effects is likely to be low, the balance between benefits and risks of MPH therapy need to be considered carefully. In addition, psychostimulants have been shown to slightly accelerate the heart rate and raise blood pressure [55,65,66]. Minor increases in heart rate and blood pressure over extended periods of time may have a cumulative adverse effect on cardiovascular health. They may be risk factors for cardiovascular morbidity and mortality, especially in subgroups of patients experiencing larger increases. Both heart rate and blood pressure should therefore be monitored regularly in patients receiving MPH.

In Denmark, the longest prospective follow-up study so far conducted assessed the association between the use of stimulants in children with ADHD and the risk of cardiovascular events [67]. Cardiovascular events, including arrhythmias, hypertension, ischemic heart disease, heart failure, and cerebrovascular disease were rare but twice as likely in stimulant users as in non-users, both in the total national population and in a population-based sample of children and adolescents with ADHD [67]. These findings suggest an increase in the risk of cardiovascular disease related to stimulant therapy in children and adolescents.

While the increase in the risk of serious cardiovascular events following MPH administration might be small in children and adolescents, the risk following long-term medication and in adults has not been sufficiently investigated and could be higher. Since the use of MPH is increasing in adults with ADHD, cardiovascular adverse reactions need to be assessed for all relevant age groups over extended periods of time. In the available studies, elderly patients are under-represented and the findings on cardiovascular effects of MPH cannot be generalized to this population.

Scant research has been performed concerning the long-term safety of ADHD medications including MPH. The median length of time that drugs used for ADHD were evaluated prior to their market authorization by the US Food and Drug Administration was four weeks [68]. This indicates that the clinical trials conducted for approval were not designed to assess long-term safety and efficacy or rare adverse events. The enforcement of completion of post-marketing surveillance studies is needed [68].

The potential adverse influence of MPH on the developing brain is of concern in the treatment of children and adolescents with ADHD [69,70]. The results of investigations in young non-human primates suggest that chronic administration of MPH initiated in adolescence at clinically relevant doses has no significant effects on dopamine markers in the brain [71,72]. However, these findings in healthy animals may not apply to individuals with ADHD.

Central dopamine dysfunction in patients with ADHD could explain why stimulants, which increase dopamine signaling, produce therapeutic benefits. MPH enhances dopamine signaling by blocking the dopamine transporter [73]. Using positron emission tomography, the dopamine transporter availability was measured in the brains of never-medicated adult patients with ADHD before and after 12 months of MPH therapy and in controls who were also examined twice without stimulant medication [74]. The administration of MPH over 12 months increased the availability of the striatal dopamine transporter by 24% in the caudate, putamen and ventral striatum of patients with ADHD, while no alterations were found in control subjects retested following a 12-month period. Upregulation of dopamine transporter availability during long-term use of MPH may decrease treatment efficacy and exacerbate symptoms when medication is discontinued [74]. These findings might explain why long-term treatment with MPH was not efficacious in the follow-up of the Multimodal Treatment Study into adulthood [42].

The long-term safety of MPH remains an open question. Although the scientific evidence base is small, short-to-mid-term use of MPH over a period of up to two years has been suggested to be relatively safe, while much less is known about the longer-term safety [75]. However, both rates and severity of adverse events remain unclear, given inconclusive evidence and poor documentation of harms. The most pressing concern in regard to the long-term safety of MPH is the under-reporting of harms. The Cochrane studies showed that only 9 of 185 RCTs provided data that could be used to evaluate serious adverse events [15], and only two (of the comparative) and 50 (of the non-comparative studies) of a total of 260 non-randomized trials provided data for meta-analyses of serious adverse events [16]. These figures are unsatisfactory, considering the importance of harm measures for evidence-based practice. The under-reporting of harms is common in randomized trials [76]. Adverse effects may not be reported appropriately, partly because reporting is subject to influence by sponsors [77,78]. Under-reporting of harm may lead to a false perception of the risk-benefit ratio of medications.

In summary, MPH might cause substantially more harm in individuals with ADHD than is suggested by the available studies. Researchers should be required to always assess and report possible harms.

CONCLUSION

Conclusive evidence of long-term benefits of MPH remains elusive, since long-term RCTs, which represent the highest standard for measuring treatment effects, are largely absent. The view that MPH treatment has long-term beneficial effects and is well tolerated in patients with ADHD is based on a small number of RCTs and open-label extension studies with follow-up periods of as little as 24 weeks [41]. If ADHD is considered a life-long condition, effects of therapy should be investigated over decades rather than months. Comprehensive investigations of the long-term effects of MPH need to incorporate meaningful measures of functional impairment and to evaluate the degree of optimization of patients' behavior. Future studies should also include effects and outcomes of MPH treatment in regard to subgroups and comorbidities of ADHD under real life conditions.

Few studies have investigated the long-term safety of MPH in the treatment of ADHD. Short-term follow-up may not detect potentially serious, long-term adverse reactions. If ADHD can be a lifelong condition in some individuals, requiring medication over years or even decades, it is clear that possible adverse effects

must be assessed across the lifespan. The relatively low incidence of adverse events in young patients is probably not predictive for elderly individuals. The Multimodal Treatment Study of ADHD appears to be the only meaningful study for evaluating the effects of long-term MPH therapy. More long-term treatment studies are urgently needed. In view of the insufficient number of MPH trials providing data for the evaluation of serious adverse events [15,16], a major focus of future studies needs to be the consistent assessment and reporting of harms. Such studies may need to be conducted by investigators without vested interests.

Since the evidence of the benefits and harms of MPH in the treatment of ADHD is less clear than previously thought, other potentially promising treatment approaches should be investigated more thoroughly. These include lifestyle factors such as nutrition, dietary patterns or physical activity [79-82]. Large-scale, well-designed studies are needed in order to assess the effectiveness of these approaches as sole treatment or in combination with pharmacotherapy.

THE BOTTOM LINE

While numerous RCTs have demonstrated the efficacy of MPH in alleviating the core symptoms of ADHD, the size of these effects and potential harms are still unclear. In particular, the available data regarding effectiveness and adverse reactions of long-term administration of MPH is insufficient. Therefore, "the jury is still out on the benefits and harms of MPH for children and adolescents [and adults] with ADHD" [17].

CONFLICT OF INTERESTS

The author declares no competing interests regarding this paper.

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