**Title**

Long-term adverse effects of methylphenidate in children and adolescents with ADHD: Results of a two-year naturalistic pharmacovigilance study.

**Authors & Affiliations**

Kenneth K.C. Man\*, Alexander Häge\*, Tobias Banaschewski\*, Sarah Inglis,

Jan Buitelaar, Sara Carucci, Marina Danckaerts, R W Dittmann, Bruno Falissard, Peter Garas, Chris Hollis, Kerstin Konrad, Hanna Kovshoff, Elizabeth Liddle, Suzanne McCarthy, Antje Neubert, Peter Nagy, Eric Rosenthal, Edmund Sonuga-Barke, Alessandro Zuddas,

Ian C.K. Wong\*, David Coghill\* and the ADDUCE Consortium

\* equal contribution

Kenneth K.C. Man, PhD; Centre for Medicines Optimisation Research and Education, Research Department of Practice and Policy, School of Pharmacy, University College London, London, United Kingdom (email: kenneth.man@ucl.ac.uk)

Alexander Häge, MD; Department of Child & Adolescent Psychiatry and Psychotherapy, Medical Faculty Mannheim, Central Institute of Mental Health, University of Heidelberg, Mannheim, Germany; J5, 68159 Mannheim, Germany; (email: alexander.haege@zi-mannheim.de)

Ian C.K. Wong PhD; Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, L02-56, 2/F, Laboratory Block, Li Ka Shing Faculty of Medicine, The University of Hong Kong, 21 Sassoon Road, Pokfulam, Hong Kong SAR China and Centre for Medicines Optimisation Research and Education, Research Department of Practice and Policy, School of Pharmacy, University College London, London, United Kingdom (email: wongick@hku.hk)

**Abstract/summary:**

Background:

Methylphenidate is the most frequently prescribed medication for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children and adolescents. While many studies have described the short-term efficacy, tolerability, and safety of methylphenidate, data on long-term safety and tolerability are limited.

Methods:

As part of the European ADDUCE (Attention Deficit Hyperactivity Disorder Drugs Use Chronic Effects) research program, a two-year naturalistic, longitudinal study was conducted to assess adverse effects of methylphenidate on growth and development as well as psychiatric, neurological, and cardiovascular health. Three cohorts were recruited: medication-naive ADHD patients who intended to start methylphenidate treatment (ADHD-MPH), medication-naive ADHD patients who did not intend to start any ADHD medication (ADHD-noMPH), and participants without ADHD (noADHD).

Findings:

In total, n=1,410 participants were included (ADHD-MPH: n=756, ADHD-noMPH: n=391, noADHD: n=263). After controlling for baseline differences, the ADHD-MPH and ADHD-noMPH groups did not differ with respect to height velocity between baseline and any time point from six to 24 months. However, statistical analyses confirmed a greater increase in pulse rate and systolic and diastolic blood pressure in the ADHD-MPH group compared to the ADHD-noMPH group after 24 months. No adverse effects of methylphenidate treatment on psychiatric or neurological health were found.

Interpretation:

Overall, the results suggest that long-term treatment with methylphenidate for two years is well tolerated. The data do not support the hypothesis that long-term methylphenidate treatment leads to relevant impairments in growth. Pulse and blood pressure changes, although minor on average, require regular monitoring.

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**Research in context**

**Evidence before this study**

Although methylphenidate (MPH) is recommended as a first-line treatment in all current evidence-based clinical guidelines for attention-deficit/hyperactivity disorder (ADHD), it is not currently on the World Health Organization (WHO) model list of essential medicines, due in particular to the insufficient evidence on long-term tolerability. This lack of data was also highlighted by the European Commission's Committee for Medicinal Products for Human Use (CHMP), which specifically requested data on the long-term effects of MPH on growth and development, neurological and psychiatric health, and cardiovascular responses in children and adolescents.

As part of the European Union-funded ADDUCE (Attention-Deficit-Hyperactivity-Disorder-Drugs-Use-Chronic-Effects) project, we conducted and published two systematic reviews and meta-analyses of adverse effects of MPH/ADHD medication on growth and cardiovascular health, respectively, and a systematic review of long-term effects of MPH treatment on neurological and psychiatric symptoms.

To assess potential cardiovascular effects of MPH in children and adolescents, we performed a systematic review and meta-analysis of the effects of ADHD medications on diastolic and systolic blood pressure and heart rate. We searched MEDLINE, Embase, and PsychINFO from the beginning of the databases up to May 15th, 2015 for published studies on children with ADHD who were treated with MPH, amphetamines (AMPH), or atomoxetine (ATX), and in whom diastolic blood pressure (DBP) and systolic blood pressure (SBP) and/or heart rate (HR) were measured at baseline and at the end of study treatment. Eighteen clinical trials met the inclusion criteria (ten for MPH), with data from 5,837 participants (80-7% boys) and a mean duration of 28-7 weeks (range 4-96 weeks). Consistent with AMPH and ATX, MPH was associated with a small but statistically significant increase in SBP before and after treatment (MPH: standard mean difference [SMD] 0-25, 95% confidence interval [CI] 0-08-0-42, p = 0-01). In contrast to AMPH and ATX, MPH had no pre-post effect on DBP and HR.

To evaluate the effects of long-term MPH exposure on growth in children and adolescents with ADHD, we performed a systematic review and meta-analysis of the effects of MPH treatment (> six months) on height and weight. We first searched for the most relevant published reviews on the topic. In a second search, we considered individual trials published from the 1970s up to December 2018 and not included in the previous reviews, using PubMed, MEDLINE, Embase and PsychINFO. Eighteen studies, encompassing data on 4,868 children and adolescents with ADHD, were included in the meta-analysis. Adequate data on the impact of MPH on growth (and development) were available for 2,570 subjects (range = 24-410; mean = 142·77; SD = 128·19). MPH was associated with consistent statistically significant pre-post differences for both height (SMD = 0·27, 95% CI 0·16-0.38, p *<* 0·0001) and weight (SMD = 0·33, 95% CI 0·22-0.44, p *<* 0·0001) Z scores. However, effect sizes were small and the clinical impact potentially minimal.

To investigate neurological and psychiatric adverse effects of long-term MPH treatment in ADHD, we searched MEDLINE, Embase, and PsychINFO from initiation of the databases until February 19th, 2019 for studies that investigated any potential neurological, psychiatric or behavioural outcome of MPH treatment (outside the core symptoms of ADHD), irrespective of whether they were hypothesised to be positive or negative. As an inclusion criterion for this review, the mean, median or modal treatment duration had to be 12 months or more. Forty-six publications met the criteria for inclusion, consisting of 39 group studies, eight case series studies, and 17 single case studies. A number of different outcome measures were presented and discussed, including risk of depression, suicidality, psychotic symptoms, dyskinesia, and tics. We found several studies, including two well-powered comparative studies, suggesting that long-term MPH treatment may reduce depression in ADHD. Moreover, several studies, including three large comparative cohorts, suggested that long-term MPH treatment may reduce suicide in ADHD. Due to some inconsistencies in the study results regarding tics, dyskinesia, and psychosis-like symptoms as possible adverse consequences of long-term treatment, it was concluded that further research is needed in this regard.

**Added value of this study**

This is the first naturalistic, prospective, longitudinal study to investigate two-year long-term effects of MPH treatment on growth and development, psychiatric health, neurological health, and cardiovascular function in children and adolescents. Data from 1,410 children and adolescents were analyzed. We found no evidence for a relevant influence of long-term treatment with MPH on the height and weight development of children and adolescents after two years. The data suggest that MPH is effective in reducing core ADHD symptoms even after two years of treatment. Moreover, we found no evidence that long-term treatment with MPH increases the risk of other psychiatric and neurological symptoms. Rather, the evidence suggests that long-term MPH treatment may contribute to improvements (for example, in depressive symptoms). We also found that long-term MPH treatment contributed to significant, albeit only moderate on average, increases in systolic and diastolic blood pressure and pulse rate.

**Implications of all the available evidence**

**Available data on the long-term safety of MPH in the treatment of children and adolescents with ADHD indicate an overall good tolerability. Furthermore, long-term treatment with MPH appears to have beneficial effects not only on the core symptoms of ADHD but also on several symptoms commonly associated with ADHD. However, recommended follow-up examinations should be performed and, in particular, pulse and blood pressure levels should be monitored.**

**Manuscript**

**Introduction:**

Attention-deficit/hyperactivity disorder (ADHD) is a childhood-onset neurodevelopmental disorder characterised by the core symptoms of inattention, hyperactivity, and impulsivity, and is associated with a wide range of psychiatric comorbidities and adverse health-related, academic, and psychosocial outcomes 1,2. The worldwide prevalence is estimated to lie between 5-7% in children and adolescents and 2-3% in adults, and the disorder is more common in males than in females 3,4.

Methylphenidate (MPH), a central nervous system psychostimulant medication recommended as a first-line treatment option in clinical guidelines, is the most commonly prescribed medication for the treatment of ADHD in children and adolescents globally 5,6. MPH is known to inhibit the reuptake of dopamine and norepinephrine into presynaptic neurons 7. It is assumed that MPH increases the efficiency of prefrontal cortex activity and optimises executive and attentional functions in patients suffering from ADHD by improving dopaminergic and noradrenergic modulation of cortical and subcortical circuits 8.

In recent decades, the use of MPH has increased significantly in many European countries as well as the United States, Asia, and Australia 6. While MPH is recommended as a first-line treatment for ADHD in all current evidence-based ADHD clinical guidelines, it is not available in all countries worldwide and is not currently included in the World Health Organisation (WHO) model list of essential medicines 9,10. Indeed, two recent applications for inclusion in this list were rejected by the committee, who stated that in their opinion, the benefit to harm ratio of methylphenidate remains uncertain for long-term use 10. Moreover, the committee also commented that evidence for safety of at least 52 weeks duration would be informative for any future consideration for inclusion of methylphenidate in the model list 10.

We agree that while short- and medium-term efficacy and tolerability of MPH have been extensively studied 11, data regarding the long-term efficacy and safety of MPH are limited. This was also highlighted by the European Commission's Committee for Medicinal Products for Human Use (CHMP), which specifically called for data describing the long-term (> 52 weeks) effects of MPH on (1) growth and development, (2) neurological health, (3) psychiatric health, (4) sexual development and fertility, and (5) cardiovascular responses in children and adolescents 12. Here, we present data from the Attention Deficit Hyperactivity Disorder Drugs Use Chronic Effects (ADDUCE) research programme. The ADDUCE consortium has conducted a programme of research designed to fill the identified gaps in the current literature and to address the concerns of the CHMP 13. ADDUCE has previously published a series of systematic reviews and secondary analyses of existing datasets that describe the state of the art of the field 14-16. We identified that a major gap in the field has been the failure to compare individuals taking ADHD medications with individuals with ADHD who are not on medication. The present paper addresses this gap and describes the findings from a two-year prospective cohort study designed to provide new data on long-term MPH safety in children and adolescents with ADHD.

Methods

Study design

The ADDUCE study was a two-year naturalistic prospective pharmacovigilance multicentre study designed to investigate the long-term tolerability and safety of MPH in children and adolescents aged six to 17 years. The study was conducted in 27 European child and adolescent mental health centres in the United Kingdom, Germany, Italy, and Hungary. Ethical approval for the study was obtained from the East of Scotland Research Ethics Service. In addition, ethical approvals were obtained for the other countries and individual sites as necessary. During the two-year follow-up period, study participants were assessed five times regarding growth and development as well as psychiatric, neurological, and cardiovascular health (see figure 1). Three cohorts of children and adolescents were recruited:

ADHD-MPH group: comprised children and adolescents with ADHD not previously medicated with any ADHD medication who were about to start MPH treatment.

ADHD-noMPH group: comprised children and adolescents with ADHD not previously medicated with any ADHD medication and who did not intend to start any ADHD medication.

noADHD group: comprised children and adolescents without ADHD who screened negative for ADHD at study enrolment.

Details of the study and of the study protocol have been published elsewhere 17.

Participants

To ensure that the study captured individuals with ADHD who typically present to clinical services throughout the EU, the inclusion criteria were deliberately broad and the exclusion criteria minimal.

Eligible participants for the ADHD-MPH and ADHD-noMPH groups were children and adolescents aged six to 17 years with ADHD diagnosed by a qualified clinician according to the DSM-IV criteria. Participants eligible for the noADHD group were children and adolescents within the same age range who scored less than 1·5 on average on the Swanson, Nolan, and Pelham IV rating scale (SNAP-IV)18 for ADHD items, and whose hyperactivity score on the parent-rated Strengths and Difficulties Questionnaire (SDQ)19 was within the normal range (<6).

Participants were excluded if they had previously taken any ADHD medications, but remained eligible if they had previously taken or were currently taking other psychotropic drugs.

Participants in the ADHD-MPH and ADHD-noMPH groups were recruited from community-based child and adolescent mental health services at the four coordinating centres in the UK, Germany, Italy, and Hungary and additionally in 23 satellite sites (n=6 in the UK, n=4 in Italy, and n=13 in Germany and Switzerland). Children and adolescents in the noADHD group were recruited through advertisements in the communities local to the clinical sites.

In accordance with country-specific regulations, required written informed consent/assent was obtained from patients and their legal guardians prior to study participation.

Outcomes

The study outcomes were consistent with the categories highlighted by the European Medicines Agency (EMA) through CHMP as requiring research: growth, cardiovascular, psychiatric and neurological health, and MPH treatment effectiveness.

The primary outcome measure was height velocity, operationalised as height velocity standard deviation score (SDS). This was estimated from at least two consecutive height measurements, and normalized with reference to the mean and SD of a population of the same age and sex:

$$height velocity SDS=\frac{v- \overline{v}}{SD}$$

The mean and SD height velocities for each country represented in the study were obtained from the most recent standardized growth charts available for the respective countries.

Secondary growth outcome measures were weight and body mass index (BMI). Cardiovascular health was assessed through pulse rate and blood pressure, which were measured at each visit. Outcomes for psychiatric health included: the Mood and Feelings Questionnaire (MFQ)20 to assess symptoms of depression; a shortened version of the Psychosis-Like Symptoms semi-structured interview (PLiKSi)21 to assess delusions and hallucinations; and the Yale Global Tic Severity Scale (YGTSS)22 to assess motor and phonic tics. The Columbia - Suicide Severity Rating Scale (C-SSRS)23 and the Substance Use Questionnaire (SUQ)24 were used to assess suicidality and substance use, respectively. Neurological outcomes regarding dyskinesia were measured using the Abnormal Involuntary Movement Scale (AIMS)25. The effectiveness of MPH treatment on core ADHD and oppositional defiant disorder (ODD) symptoms was measured using the Swanson, Nolan, and Pelham IV rating scale (SNAP-IV)18. The study included further secondary assessment tools, the results of which are not presented here. Table S1 provides an overview of all outcome measures and Table S2 presents the schedule of visits and assessments.

Statistical analysis

Description at baseline

Characteristics of participants included in the study were presented for each group, and the groups were compared using statistical tests (t-test, ANOVA, chi-square tests where appropriate). The changes of time-varying factors throughout the study period were also presented.

Propensity score

We compared the outcome status between children in the ADHD-MPH group and the ADHD-noMPH group. As children with severe symptoms may have a higher likelihood of being treated with methylphenidate, propensity score (PS) adjustment was applied to address potential differences in patient characteristics between the treated and the untreated group. The PS denotes the probability that an individual will receive treatment given his/her characteristics26. It limits the biases relating to treatment allocation for the analysis of observational data. In the present study, PS was estimated as the predicted probability of receiving methylphenidate, conditional on the covariates measured, using a logistic regression model. 33 variables were included in the propensity score model: age, gender, type of family home, parents’ marital status, smoking status, alcohol consumption, marijuana consumption, underlying medical problems and physical conditions (febrile seizure, syncope, head injury, genetic disorders and others as listed in table 2), body mass index, fathers and mothers height, blood pressure and pulse rate, SNAP IV score, parent and child reported mood disorder, suicidality, psychotic symptoms, Tics, baseline values of all outcomes (listed in table 3), pubic hair and genital growth stage, and sleep score.

Analysis for each outcome variable

Logistic regression models were used for dichotomous outcomes and generalized mixed models were applied for continuous outcomes. The propensity scores were adjusted in all models. All continuous outcomes were log-transformed.

We did not adjust p-values for multiple comparisons, as the primary hypothesis concerned the effect of the ‘group’ variable. Moreover, in a pharmacovigilance study, statistical power is at least as important as type one error.

Multiple imputation for missing data

Multiple imputations were conducted using a Gibbs sampler to address missing data. Both complete-case analyses and imputed analyses were conducted.

Role of funding

The project received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no. 324487. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between February 2012 and January 2016, n=756 participants were recruited into the ADHD-MPH group, n=391 into the ADHD-noMPH group, and n=263 into the noADHD group (see also Table S3). Due to the differences in clinical practice across the four participating countries, the proportions of participants in each group differed considerably between countries. As was to be expected, the majority of participants with ADHD were male (82·4% in the ADHD-MPH group and 85·0% in the ADHD-noMPH group), and the gender ratio in the noADHD group was much more balanced (45·6% male). The majority of subjects across all three groups were Caucasian. There were small but statistically significant differences in age between the three groups, with a mean age of 9·22 years in the ADHD-MPH group, 8·74 years in the ADHD-noMPH group, and 10·25 years in the noADHD group. Table 1 provides an overview of the baseline characteristics and Table 2 shows the corresponding group comparisons.

In accordance with the age differences between the groups, corresponding differences emerged with respect to height and weight at baseline, but not with respect to BMI. There were no differences between the groups with regard to diastolic blood pressure or pulse rate. However, mean systolic blood pressure was higher in the noADHD and the ADHD-MPH groups compared to the ADHD-noMPH group, and this difference remained statistically significant after adjusting for age and sex. In line with expectation, compared to the noADHD group, the two ADHD groups had higher scores on the SNAP-IV Total score, the Inattention and Hyperactivity/Impulsivity subscales, and the SNAP-IV ODD scale (all p<0·01). Moreover, the ADHD-MPH group had higher SNAP-IV scores (Total, Inattention and Hyperactivity/Impulsivity) than the ADHD-noMPH group (all p<0·01). Table 3 provides an overview of all baseline scores and the corresponding group differences.

Due to the different methods of recruitment for the groups with and without ADHD, it was not possible to conduct propensity score analyses to account for baseline differences for all three groups. For this reason, the longitudinal between-group analyses focus on comparisons between the ADHD-MPH and ADHD-noMPH groups (table 4 and table 5). All of the results presented have been adjusted for propensity score matching and multiple imputation of missing data.

After controlling for baseline differences, the ADHD-MPH group and the ADHD-noMPH group did not differ in terms of height velocity, the primary outcome measure for the study, between baseline and any time point from six to 24 months. Weight velocity between baseline and six months was lower in the ADHD-MPH group than in the ADHD-noMPH group (p<0·01). However, the findings revealed no between-group differences in weight velocity between baseline and 12, 18, or 24 months. Moreover, there were no group-level differences with respect to BMI between the medicated and unmedicated ADHD groups at six, 12, 18, or 24 months.

Systolic blood pressure increased significantly between baseline and 24 months in the ADHD-MPH (from 108 to 113 mmHg; p<0·01) and ADHD-noMPH (104 to 108 mmHg; p <0·01) groups but not in the noADHD group (109 to 111 mmHg; p =0·08). In the ADHD-MPH group, diastolic blood pressure (65 to 67 mmHg; p=0·02) and pulse rate (80 bpm to 83 bpm) increased over this period, while this was not the case for the other two groups (64 to 65 mmHg; 66 to 65 mmHg; 80 bpm to 79 bpm; 78 bpm to 79 bpm). Statistical analyses confirmed a greater increase in systolic and diastolic blood pressure in the ADHD-MPH group compared to the ADHD-noMPH group at 6, 12, and 24 (but not 18) months post-baseline. Moreover, pulse rate increased more in the ADHD-MPH group than in the ADHD-noMPH group at 12 and 24 months but not at six or 18 months.

From baseline to 24 months, both parent- and child-ratings of mood impairment improved significantly across all groups. Taking into account baseline differences, child self-rated mood improved significantly more in the ADHD-MPH group than in the ADHD-noMPH group after 24 months of treatment (p=0·01), with similar findings for parent-rated mood symptoms (p=0·02).

The prevalence of both broad and narrowly defined psychotic-like symptoms decreased in the ADHD-MPH group between baseline and 24 months. While absolute rates for the ADHD-noMPH and noADHD groups also decreased towards zero, the numbers at baseline were too small to allow for a meaningful statistical analysis. However, when adjusting for baseline differences, there were no significant differences between the changes for the ADHD-MPH and ADHD-noMPH groups between baseline and 24 months (p>0·1).

Tic prevalence decreased in both ADHD groups between baseline and 24 months (p<0·01 for both groups) and in the noADHD group (p=0·02). After adjusting for baseline differences, the two ADHD groups did not significantly differ regarding tic reduction at six months. However, at 12 months, the tic reduction was significantly greater in the ADHD-noMPH group than in the ADHD-MPH group (odds ratio 4·71; p=0·041). At 24 months, the prevalence of tics in the ADHD-MPH group was still 2·4% but it was not possible to calculate an odds ratio between the two groups at this time point as the prevalence in the ADHD-noMPH group was zero.

The incidence of suicidal ideation and behaviour decreased steadily across all groups over the 24 months of the study. At 24 months, the incidence lay at 3·2% in the ADHD-MPH group, 0·77% in the ADHD-noMPH group, and 0·76% in the noADHD group. After adjusting for baseline differences, there were no significant group differences between the ADHD-MPH and ADHD-noMPH groups at the six-, 12-, and 24-month follow-ups. The results were unchanged when considering suicidal ideation and suicidal behaviour separately.

Prevalence rates for reported smoking were low at baseline in all groups (ADHD-MPH: 4·9%, ADHD-noMPH: 2·8%, noADHD: 3·0%), remained low in all three groups over the entire 24-month observation period with rates at 24 months of 2·1%, 1·5% and 2·7% respectively, and decreased over this period in the ADHD-MPH group. Alcohol use was significantly less prevalent in both ADHD groups than in the noADHD group at baseline (0·5% in both ADHD groups vs. 2·3% in the controls) and remained below the level of the control group during the observation period (ADHD-MPH: 0·9%, ADHD-noMPH: 0%, noADHD: 4·9%). Marijuana use was also uncommon at baseline in all groups and remained low throughout the observation period (always less than 1% in all groups). After adjusting for baseline differences, we found no evidence for negative effects of MPH on smoking, alcohol use, or marijuana use.

Scores on the AIMS, indicating abnormal movements, decreased (with lower scores reflecting greater improvement) for all three groups during the 24-month period. After adjusting for baseline differences, we found a larger AIMS score reduction during treatment in the ADHD-MPH group than in the ADHD-noMPH group at six (p<0·01) and 12 (p<0·01) but not 24 (p>0·05) months.

Total ADHD symptoms as well as inattentive and hyperactive/impulsive symptoms measured by the SNAP-IV decreased from baseline to 24 months for both ADHD groups. Total ADHD symptoms on the SNAP-IV decreased significantly more (all p < ·01) and mean SNAP-IV Total symptom and Inattention and Hyperactive/Impulsive subscale scores were lower at 24 months (1·2 vs 1·5; 1·3 vs 1·5; 1·1 vs 1·4 respectively) for the ADHD-MPH group compared to the ADHD-noMPH group. ODD symptoms likewise decreased in both ADHD groups from baseline through to 24 months. The extent of this decrease from baseline only differed between the two ADHD groups at the 12-month follow-up, with a greater reduction in the ADHD-MPH group than in the ADHD-noMPH group (p = 0·02). The two groups did not differ in ODD symptoms at the six- or 24-month follow-ups.

Discussion

Using a naturalistic, prospective, longitudinal design, the ADDUCE study was the first to collect comprehensive data on the two-year, long-term effects of MPH treatment on growth and development, psychiatric health, neurological health, and cardiovascular function in children and adolescents.

Due to concerns that a reduction in growth may be a particularly common adverse effect of long-term administration of MPH for ADHD, we chose height velocity as the primary outcome measure for this study. Our findings did not reveal any differences in height velocity between the groups with and without MPH treatment at any of the follow-up time points. These findings conflict to a certain degree with the conclusions of our recent systematic review and meta-analysis on the impact of long-term stimulant treatment on growth by Carucci and colleagues14. Specifically, their data suggested that MPH might be associated with a slight growth deficit, especially with respect to height, but that these reductions were judged to have a minimal clinical impact and to generally remit in adulthood. The pre-post standardized mean difference for the effects of 24-month treatment with either MPH or amphetamine was small (SMD 0·27, 95% confidence intervals 0·22-0·31), and interestingly, only half (6/12) of the included studies reported pre-post differences in height14.

With respect to weight, the only differences between medicated and unmedicated individuals with ADHD in our sample were identified six months after starting medication, and there were no between-group differences at 12, 18, or 24 months. These findings are in line with the results of the meta-analysis by Carucci and colleagues, who reported small but significant reductions in weight gain associated with MPH as a monotherapy (SMD 0·24, 95% CI 0·14-0·35), which is equivalent to a reduction in weight gain of around 1.43 kg over a 2-year period for a ten-year-old boy14. Similar to the findings of our study, several authors have reported that the effects of psychostimulants on weight are time-limited and subsequently normalize27-29.

The finding of an increased systolic blood pressure in our sample is consistent with a recent systematic review and meta-analysis by Hennissen and colleagues, who reported a small but statistically significant increase associated with MPH treatment (standard mean difference 0·25, 95% confidence interval [CI] 0·08–0·42, p<0·01) when pooling the results of 10 trials 15. However, unlike the latter review, we also found significant increases in both diastolic blood pressure and pulse rate in the medicated vs. unmedicated ADHD group. To date, it is unclear whether these modest but significant increases have negative long-term clinical consequences. Further studies in this regard would be necessary.

Depression scores in our sample, as measured by the MFQ, were higher at baseline in patients with ADHD than in controls, but decreased in the ADHD-MPH group over the 24 months of the study. This corresponds to findings from several other studies providing evidence that long-term MPH treatment is associated with a favourable outcome regarding mood and depression 16,30,31. A nationwide longitudinal cohort study using the Swedish national registers found that ADHD medication was associated with a reduced long-term risk (i.e., three years later) for depression, and this risk was lower for longer duration of ADHD medication32. Moreover, a within-individual analysis suggested that depression was 20% less common during periods when patients received ADHD medication compared with periods when they did not receive medication32.

We found no evidence that initiation of MPH treatment increased the risk of psychosis-like symptoms. This finding is consistent with several previous studies. An analysis of population-based electronic medical records in Hong Kong, based on Clinical Data Analysis and Reporting System (CDARS) data from 2001 to 2014, found no increased risk of psychosis during MPH-exposed compared with non-exposed periods 33. Furthermore, a Swedish cohort study using population-based observational data from three population-based registries likewise found no increase in psychotic events during MPH treatment 34. Two other comparative studies also provided evidence that MPH reduces the risk of psychosis-like symptoms 35,36 and one study found that MPH treatment reduces the risk of hospitalization for psychosis31. However, as we pointed out in our own review by Krinzinger and colleagues, there is also some, albeit limited, evidence that psychosis may result from MPH treatment in individual cases16.

Our findings suggest that long-term MPH use is generally safe in patients with ADHD and comorbid tics. This is in line with several studies showing that in most cases, stimulants do not worsen tics in patients with ADHD and coexisting tic disorder37. However, clinicians should continue to exercise caution when using MPH in individuals prone to tics, as it may still exacerbate existing tics in individual cases.

The higher reported rates of suicidal behavior and/or suicidal ideation in the ADHD-MPH group before treatment may reflect the severity of the psychiatric symptoms that prompt the decision to assess for ADHD in the first place. Similarly, the higher rates in the ADHD-MPH group compared to the ADHD-noMPH group may also be reflected in the clinical decision to initiate medication treatment due to greater severity. Our finding that MPH treatment was not associated with an increased incidence of suicidal ideation, and may in fact be associated with a reduction in risk, is in line with several other studies16. Chen and colleagues reported a 20% within-patient reduction in the rate of suicide-related events during periods on stimulant medication38. Using a self-controlled case series design based on data from the Hong Kong CDARS registry, Man and colleagues reported that the incidence of suicide attempts was higher in the 90-day period immediately before the start of MPH treatment and returned to baseline levels during continuation of MPH treatment39. In a Taiwanese nationwide population-based cohort study, Liang and colleagues observed a 72% risk reduction in those prescribed more than 180 days of MPH40. Moreover, in a large cohort of patients with ADHD, within-individual analyses demonstrated that stimulant medication was associated with a 28% reduced risk of suicide attempts41.

Possibly due to the young age of our sample, we found a very low prevalence of reported substance use in the two ADHD groups, which was even lower than in the noADHD control group. Notwithstanding the low prevalence of reported substance use at baseline, there was no indication that MPH treatment increased the risk for smoking or alcohol or marijuana use. This is in line with findings from previous studies. For instance, Humphreys and colleagues found comparable outcomes between children with ADHD with and without a history of medication treatment for any substance use as well as for abuse or dependence outcomes across all substance types42. Likewise, Chang and colleagues found no increased risk of substance abuse among individuals prescribed with stimulant ADHD medication43. Furthermore, Schoenfelder and colleagues reported that consistent stimulant treatment of ADHD may reduce smoking risk and that this effect was larger in samples with more severe psychopathology44.

In the present study, we found no evidence of an increased risk of MPH-induced dyskinesia. Rather, the results suggest that treatment with stimulants may, at least initially, reduce the abnormal involuntary movements measured with the AIMS. This may be mediated by reduced hyperactivity and improved motor control.

Although the effectiveness of MPH treatment was not the focus of this study, it is nevertheless important for further interpretation of the data in terms of weighing the benefits and risks of long-term MPH treatment. The results for clinical effectiveness in our sample support previous observations that MPH is an effective medication even after a treatment period of two years45. Our findings also suggest that MPH is equally effective over this time frame on symptoms of inattention and hyperactivity/impulsivity, although outcomes may be less strong than those generally reported in randomized controlled trials investigating short-term effects of MPH.

The present findings need to be interpreted in the context of some limitations. First, the observation period of the study was two years, but many children and adolescents with ADHD are treated with MPH for a longer period. Within the scope of this study, it is not possible to answer whether other safety aspects may arise over periods longer than two years. Second, despite the large sample size for a prospective study, the sample size is still too small to rule out the possibility that long-term MPH treatment might result in extremely rare but serious side effects. Third, of relevance for the interpretation of the results, a lack of mean changes in growth (and in other aspects) does not mean that clinically relevant changes cannot occur in individual cases. Accordingly, control examinations for height and weight progression, as recommended by clinical guidelines, may be indicated even if there are no changes on average for the population as a whole. Finally, the study investigated long-term effects of MPH only. To compare the safety profile of MPH with other approved ADHD medications, further comparable prospective studies would be desirable.

Overall, the results of the study suggest that safety profile of long-term treatment with MPH for two years is acceptable and treatment is well tolerated. The data clearly do not support the hypothesis that long-term MPH treatment leads to relevant impairments in growth. Moreover, long-term MPH treatment in children with ADHD appears to have a rather beneficial effect on some co-existing psychiatric symptoms. Pulse and blood pressure changes, although minor on average, require regular monitoring.

Contributors

ICKW, DC and TB were responsible for the study concept. All authors were responsible for the study design. AH, TB, SI, JB, SC RD, PG, and PN responsible for subject recruitment. BF and KM did the statistical analysis. All authors were involved in the interpretation of data. KKCM, AH, DC, TB and ICKW drafted the manuscript. All authors critically revised the manuscript for important intellectual content. DC and ICKW were responsible for resource acquisition.

All authors had full access to all the data in the study, contributed to drafting the report, and all take final responsibility for its content and for the decision to submit for publication.

Declaration of interests

KKCM reports grants from the CW Maplethorpe Fellowship, the National Institute for Health Research, United Kingdom; the European Union Horizon 2020 Framework, Hong Kong Research Grant Council and personal fees from IQVIA Holdings, Inc., unrelated to this work.

AH has received compensation for serving as consultant or speaker for Shire/Takeda and Medice. The present work is unrelated to the above grants and relationships.

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Data sharing

 The anonymised datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request subjected to IRB approval of the requestor’s institution and review of investigators of ADDUCE Consortium .

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TO BE ADDED:

Author statement (signed by each author)

<https://www.thelancet.com/for-authors/forms?section=tlp-author-sig>

if available: add study protocol; registration (?)/ clinical.trials.gov?

TO BE ADDED AFTER PEER REVIEW:

Contribution statement (signed by each author, same as above?!)

COI statement (by each author)

<https://www.thelancet.com/for-authors/forms?section=icmje-coi>

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