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Title

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

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† We would like to dedicate this manuscript to our friend and colleague Alessandro Zuddas who contributed greatly to the ADDUCE Consortium and who sadly passed away in July 2022.

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Abstract/summary:

Background:

Methylphenidate is the most frequently prescribed medication for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children and adolescents in many countries. While many randomised controlled trials support short-term efficacy, tolerability, and safety, data on long-term safety and tolerability are limited. The aim of this study was to investigate the safety of MPH over a two-year period in relation to growth and development, psychiatric health, neurological health, and cardiovascular function in children and adolescents.

Methods:

As part of the European Attention-Deficit-Hyperactivity-Disorder-Drugs-Use-Chronic-Effects (ADDUCE) research program, a two-year naturalistic, longitudinal, controlled study was conducted to assess adverse effects of methylphenidate on growth and development, psychiatric, neurological, and cardiovascular health outcomes. 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 a control group without ADHD (noADHD).

Findings:

In total, n=1,410 participants were included (ADHD-MPH: n=756, ADHD-noMPH: n=391, noADHD: n=263). 1,070 (76.3%) participants were males, 332 (23.7%) were females and 8 with unknown gender. The average age for the cohort was 9.28 years (S.D.=2.78), interquartile range 7 to 11. 93.1% (n=1,312) of the participants were Caucasian. The ADHD-MPH and ADHD-noMPH groups differed in ADHD symptom severity and other characteristics. After controlling for the effects of these variables using propensity score, there was little evidence of impact on growth or increased risk of psychiatric/neurological adverse events in the ADHD-MPH compared to the ADHD-noMPH group. A statistically significant increase in pulse rate and systolic and diastolic blood pressure was observed in the ADHD-MPH group compared to the ADHD-noMPH group after 24 months of treatment.

Interpretation:

Overall, the results suggest that long-term treatment with methylphenidate for two years is safe. There was no evidence to support the hypothesis that methylphenidate treatment leads to

reductions in growth. Methylphenidate-related pulse and blood pressure changes, although relatively small do require regular monitoring.

Funding:

European Union's Seventh Framework Programme Grant agreement; ID:260576.

Research in context

Evidence before this study

As part of the European Union-funded Attention-Deficit-Hyperactivity-Disorder-Drugs-Use-Chronic-Effects (ADDUCE) project (ID: 260576) we conducted and published three systematic reviews of studies on long-term adverse effects of MPH/ADHD medication. These reviews highlighted the relative lack of long-term data for cardiovascular, growth, neurological and psychiatric effects. Of ten studies on cardiovascular safety only two were longer than one year. Neither of these reported significant changes in blood pressure or heart rate. We identified eighteen studies focussed on the long-term effects of MPH on growth. While MPH was associated with statistically significant pre-post reductions in both height and weight, effect sizes were small, inconsistent across studies, and the clinical impact judged to be minimal. Data on potential long-term effects of MPH on neurological and psychiatric outcomes were spread across forty-six publications of varying quality and design. While several studies suggested a reduction in depression and suicidality the findings for tics, dyskinesia, and psychosis-like symptoms were inconsistent. None of these studies across all outcome domains included a comparison with unmedicated ADHD.

Added value of this study

This is the first naturalistic, prospective, longitudinal, controlled study to investigate safety of MPH over a two-year period in relation to growth and development, psychiatric health, neurological health, and cardiovascular function in children and adolescents. Data from 1,410 children and adolescents were analysed. Over this period, save an effect on weight velocity at the six-month assessment, MPH was not associated with growth or psychiatric/neurological symptoms. Long-term MPH treatment was associated with significant, albeit moderate on average, increases in systolic and diastolic blood pressure and pulse rate.

Implications of all the available evidence

Long-term safety data suggest that MPH used for the treatment of child and adolescent ADHD is safe. 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 neurodevelopmental disorder characterised by the core symptoms of inattention, hyperactivity, and impulsivity, that is associated with a wide range of psychiatric comorbidities and adverse health, academic, and psychosocial outcomes [1,2]. The worldwide prevalence of ADHD is estimated to lie between 5-7% in children and adolescents and 2-3% in adults, and the disorder is apparently more common in males than in females [3,4].

MPH, a central nervous system psychostimulant medication recommended by clinical guidelines as a first-line treatment option for ADHD, 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 with ADHD by improving dopaminergic and noradrenergic modulation of cortical and subcortical circuits [8].

In recent decades, the use of MPH has increased considerably in many European countries as well as in 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 has not yet been 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 MPH remains uncertain for long-term use [10]. Moreover, the committee also specifically recommended that evidence on tolerability and safety of at least 52 weeks duration would be informative for any future consideration for inclusion of MPH in the model list [10].

While short- and medium-term safety and tolerability of MPH have been extensively studied [11], we agree that long-term data are limited. This gap in knowledge 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

178 fertility, and (5) cardiovascular responses in children and adolescents [12]. Here, we present data
179 from the Attention Deficit Hyperactivity Disorder Drugs Use Chronic Effects (ADDUCE)
180 research programme (ID: 260576). The ADDUCE consortium has conducted a programme of
181 research designed to fill the identified gaps in the current literature and to address the concerns
182 of the CHMP [13]. ADDUCE has previously published a series of systematic reviews and
183 secondary analyses of existing datasets that describe the state of the art of the field [14-16]. These
184 identified that a major gap in the field has been the failure to compare individuals routinely
185 taking ADHD medications in general clinical practice with individuals with ADHD who are
186 not on medication. The present paper addresses this gap and describes the findings from a two-
187 year (104 week) prospective cohort study designed to provide new data on long-term MPH
188 safety in children and adolescents with ADHD.

Methods

Study design

The ADDUCE study was a two-year (104 week) naturalistic prospective pharmacovigilance multicentre study designed to investigate the long-term 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, Switzerland, Italy, and Hungary. Ethical approval for the study was obtained from the East of Scotland Research Ethics Service as the coordinating centre. In addition, ethical approvals were obtained for the other countries and individual sites as necessary. Study participants were assessed five times over a two-year follow-up period (see Figure 1). Three cohorts of children and adolescents were recruited:

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

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

noADHD group: an index group of 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 results could be generalised to typical ADHD populations in 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 those highlighted by the European Medicines Agency (EMA) through CHMP as needing additional research: growth, cardiovascular, psychiatric and neurological health.

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:

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

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 outcomes 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 also measured. Table S1 provides an overview of all outcome measures, and Table S2 presents the schedule of visits and assessments.

Statistical analyses

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 are also presented.

Within group changes over time were calculated using the crude scores for all three groups. Due to the substantial difference between the groups with and without ADHD, it was not possible to conduct propensity score analyses to account for baseline differences for all three groups. Therefore, the longitudinal between-group analyses using adjusted estimates were only conducted for comparisons between the ADHD-MPH and ADHD-noMPH groups (Table 2 and Table 3).

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 MPH, propensity score (PS) adjustment was applied to address potential differences in patient characteristics between the medicated and the not medicated group[26]. (Appendix 1)

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 as a continuous variable in all models. All continuous outcomes were log-transformed to ensure the model assumptions are met for robust analyses[27,28].

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. Only the 33 baseline factors that were included in the propensity score model were were included in the imputation. Both complete-case analyses and imputed analyses were conducted.

All analyses were conducted with SAS version 9.4.

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. However, the team worked with the European Medicines Agency to ensure that the objectives of ADDUCE programme are addressing the public health concerns raised by the CHMP.

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 (male: 82·4%, n=622; female: 17·6%, n=133; unknown: n=1 in the ADHD-MPH group and male: 85·0%, n=329; female: 14·8%, n=58; unknown: n=4 in the ADHD-noMPH group), and the sex ratio in the noADHD group was much more balanced (45·6%, n=119 male, 53·6%, n=141 female). The majority of subjects across all three groups were Caucasian (ADHD-MPH group: 696, ADHD-noMPH group: 373, noADHD group: 243). There were 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, shows the corresponding group comparisons. As this was a non interventional observational study not all participants attended every visit (see Table S3) reasons for non-attendance were not captured. There was no substantial difference in baseline characteristics between the complete sample (Table 1) and those participants included in the 24 month follow-up assessments (Table S4). Few participants in the ADHD-MPH group who attended visit reported discontinuing MPH since previous visit (Table S5).

Baseline differences

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, baseline mean systolic blood pressure was higher in the noADHD and the ADHD-MPH groups compared to the ADHD-noMPH group, and these differences 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 $p<0·0001$). Moreover, the ADHD-MPH group had higher SNAP-IV scores (Total, Inattention and Hyperactivity/Impulsivity) than the ADHD-noMPH group (all $p<0·0001$). Table 1 provides an overview of all baseline scores and the corresponding group differences.

Adverse events

No serious adverse events were reported during the study. The results of the between group analyses (ADHD-MPH and ADHD-noMPH) are detailed in Tables 2 and 3 (imputed analyses) and Tables S7 and S8 (complete case analyses).

Growth

There was no difference between the ADHD-MPH and ADHD-noMPH groups on height velocity, the primary outcome, at any time point. Weight velocity showed an initial slowing at six months in the ADHD-MPH group ($p<0{\cdot}0001$), but no differences were seen after this point. There were no group differences with respect to BMI at any time point (see Table 3).

We further investigated the percentage changes in the height and weight velocity for the 3 groups detailed in figures S1-4. There were few differences between the three groups on the percentage changes in the height and weight velocity (figure S1 and S2). We looked in more detail at the subgroup of participants who had a decreased weight velocity at 6-months (n=366 in the ADHD-MPH group, n=116 in the ADHD-noMPH group and n=109 in the noADHD group). While no major difference is observed for this group on height velocity in this subgroup, there was a trend for increasing weight velocity throughout the follow-up period (figure S3 and S4). Although we cannot conduct further analyses due to the limited sample size, these results do not suggest that, at a group level, the reduction in weight velocity seen at 6 months continued and that there was no subsequent loss of height velocity for this group, but instead their weight velocity improved throughout the follow-up period.

Cardiovascular

Within group analyses identified that mean systolic blood pressure increased significantly between baseline and 24 months in the ADHD-MPH (from 108 to 113 mmHg, $p<0{\cdot}0001$) and ADHD-noMPH (104 to 108 mmHg, $p <0{\cdot}0001$) groups but not in the noADHD group (109 to 111 mmHg, $p =0{\cdot}08$). In the ADHD-MPH group, diastolic blood pressure (65 to 67 mmHg, $p=0{\cdot}02$) and pulse rate (80 to 83 bpm) also increased over this period, while this was not the case for the other two groups (64 to 65 mmHg, 66 to 65 mmHg, 80 to 79 bpm, 78 to 79 bpm). Between group statistical analyses confirmed a greater increase in systolic and diastolic blood pressure in the ADHD-MPH group compared to the ADHD-noMPH group at six, 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 (see Table 3).

Psychiatric and Neurological Symptoms

Parent- and child-ratings of mood improved significantly across all three groups during the study. Child self-rated and parent-rated mood improved significantly more in the ADHD-MPH group than in the ADHD-noMPH group after 24 months of treatment (p=0·01, p=0·02) (see Table 3).

The prevalence of both broad and narrowly defined psychotic-like symptoms decreased for all three groups. 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 (see Table 2).

Tic prevalence decreased in all three groups (p<0·0001 for both ADHD groups and p=0·02 in the noADHD group). 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 because the prevalence in the ADHD-noMPH group was zero (see Table 2).

The prevalence of suicidal ideation and behaviour decreased steadily for all three groups across the study. At 24 months, the prevalence lay at 3·17% 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 suicidal ideation and suicidal behaviour were considered separately (see Table 2).

Prevalence rates for reported smoking were low at baseline in all three groups (ADHD-MPH: 4·9%, ADHD-noMPH: 2·8%, noADHD: 3·0%), remained low in all 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 three 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 (see Table 2).

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 ($p<0·0001$) and 12 ($p<0·0016$) but not 24 ($p=0·09$) months (see Table 3).

Results on ADHD core symptoms are summarised in Table 3 and Appendix 2.

Discussion

Using a naturalistic, prospective, longitudinal, controlled design, the ADDUCE study was the first to collect comprehensive data on the safety of MPH in previously stimulant naïve children and adolescents with ADHD over a two-year period in terms of growth, cardiovascular function, and psychiatric and neurological health and compared these with participants with ADHD not treated with MPH and a non-ADHD comparison group.

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 with the conclusions of our recent systematic review and meta-analysis on the impact of long-term stimulant treatment on growth by Carucci and colleagues[14]. There we reported 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. In that review the pre-post standardized mean difference for the effects of 24-month treatment with a stimulant medication (either MPH or amphetamine) was small (SMD 0·27, 95% CI 0·22-0·31), and interestingly, only half (6/12) of the included studies reported pre-post differences in height[14].

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[14] , 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 boy. Similar to the findings of our current study, several authors have reported that the effects of psychostimulants on weight are time-limited and subsequently normalize[29-31].

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[15], who found a small but statistically significant increase associated with MPH treatment (SMD 0·25, 95% CI 0·08–0·42, p<0·01) when pooling the results of ten trials. However, unlike the latter review, we here also found statistically significant increases in both diastolic blood pressure and pulse rate in the

medicated vs. unmedicated ADHD group. Results of another study of the ADDUCE consortium showed that long-term use of MPH in adolescents and young adults with ADHD (aged 12 to 25 years) was associated with a small but statistically significant increase in systolic blood pressure and heart rate compared to controls (=ADHD patients without MPH treatment), whereas diastolic blood pressure did not differ between the two groups[32]. Overall, current data suggest that long-term treatment with MPH affects cardiovascular parameters, although these effects appear to be mostly without clinical significance.

Depression scores in our sample, as measured by the MFQ, were higher (worse) 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 [16,33,34]. 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 medication[35]. Moreover, a within-individual analysis suggested that depression was 20% less common during periods when patients received ADHD medication compared to periods when they did not receive medication[35].

We found no evidence that long-term treatment with MPH 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 evidence for increased risk of psychosis during MPH-exposed compared with non-exposed periods [36]. Furthermore, a Swedish cohort study using population-based observational data from three population-based registries also found no increase in psychotic events during MPH treatment [37]. Two other comparative studies also provided evidence that MPH reduces the risk of psychosis-like symptoms [38,39] and one study found that MPH treatment reduced the risk of hospitalization for psychosis [34]. However, as we pointed out in our own review, there is also some, albeit limited, evidence that psychosis may result from MPH treatment in individual cases [16].

Our findings also 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 disorder[40]. 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 behaviour and/or suicidal ideation in the ADHD-MPH group before treatment may reflect the severity of the psychiatric symptoms that prompted 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 studies[16]. Chen and colleagues reported a 20% within-patient reduction in the rate of suicide-related events during periods on stimulant medication[41]. 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 treatment[42]. In a Taiwanese nationwide population-based cohort study, Liang and colleagues observed a 72% risk reduction in those prescribed MPH for more than 180 days[43]. 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 attempts[44].

Potentially due to the relatively young age of our sample, we found a very low prevalence of reported substance use in the two ADHD groups, which were even lower than those 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, 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 types[45]. Likewise, Chang and colleagues found no increased risk of substance abuse among individuals prescribed with stimulant ADHD medication[46]. 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 psychopathology[47].

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 as measured by the AIMS. This may be mediated by reduced hyperactivity and improved motor control.

The present findings need to be interpreted in the context of some limitations. First, the study focussed on long-term safety rather than tolerability so we cannot comment on long-term tolerability. Second, in common with all long-term observational studies and clinical trials, we experienced a high loss-to-follow up over the 2 years follow-up period with 53·5% (n=755) attended the visit at 24-month. Our participants were all stimulant naive at entry into the study and it is likely that tolerability estimates are going to be lower in this type of sample than seen in industry-sponsored studies that almost include those previously treated. While it is important to highlight this limitation and note that the interpretations of our findings should be with caution it is also important to recognise that longer term safety outcomes are only relevant to those individuals that continue a treatment. Third, the observation period of the study was two years, but, in routine care, many children and adolescents with ADHD will be treated with MPH for a longer period. Fourth, 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 adverse events; however, previous retrospective studies with very large samples have not yielded significant safety concern[35-37,41,42,44,46,48-51]. Fifth, of relevance for the interpretation of the results, a lack of mean change 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 remain indicated even if there were no changes on average for the study population as a whole. Sixth, as most of the participants are males and Caucasian, we are not able to perform gender-specific or ethnicity-specific analyses due to the limited diversity in the study cohort. Seventh, this is an observational study, we allowed the clinicians to choose the most appropriate treatment for the individual patient in their own clinic and therefore did not restrict the treatment form in any preparation, formulation, and dose. In addition, dose was recorded using a free-text entry and adherence to treatment was not assessed. Eighth, similar to all observational studies, we could not exclude the possibility of unmeasured confounding due to the naturalistic and observational nature of this study. Additionally, the application of propensity score adjustment is one of the few propensity-score-based analytic methods where the extent to which covariates were successfully balanced between treated and comparator groups is difficult to investigate and to demonstrate empirically[26]. Ninth, as participants were recruited from 27 sites across four countries it was not possible to compare findings across the different sites as the sample size

517 will not allow meaningful comparison. Finally, the study investigated long-term effects of MPH
518 only. To compare the safety profile of MPH with other approved ADHD medications, further
519 comparable prospective studies would be desirable.

520 In summary, the results of this study suggest that safety profile of long-term treatment with
521 MPH for two years is acceptable. The data do not support the hypothesis that long-term MPH
522 treatment is associated with impairments in growth. Pulse and blood pressure changes, although
523 minor on average, require regular monitoring. Moreover, long-term MPH treatment in children
524 with ADHD appears to have rather beneficial effects on some co-existing psychiatric
525 symptoms.

526

Contributors

ICKW, DC and TB were responsible for the study concept. All authors were responsible for the study design. DC, AH, TB, SI, JB, SC, RWD, PG, and PN responsible for subject recruitment. DC, TB, KM and ICKW verified the underlying data, BF and KM did the statistical analyses. 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.

TB served in an advisory or consultancy role for Eyelevel, Infectopharm, Lundbeck, Medice, Neurim Pharmaceuticals, Oberberg GmbH, Roche and Takeda. He received conference support or speaker's fee by Jansen, Medice, and Takeda. He received royalities from Hogrefe, Kohlhammer, CIP Medien, Oxford University Press; the present work is unrelated to these relationships.

SI has no conflict of interest.

JB has been in the past 3 years a consultant to / member of advisory board of / and/or speaker for Takeda/Shire, Roche, Medice, Angelini, Janssen, and Servier. He is not an employee of any of these companies, and not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, royalties.

SC had collaborations within projects from the European Union (7th Framework Program) and in sponsored clinical trials by Shire Pharmaceutical Company, Lundbeck, Otsuka, Janssen-Cilag and Angelini.

MD has received research funding outside this study from Takeda/Shire.

RWD has received compensation for serving as consultant or speaker, or he or the institution he works for have received research support or royalties from the organizations or companies indicated: EU (FP7 Programme), US National Institute of Mental Health (NIMH), German Federal Ministry of Health/Regulatory Agency (BMG/BfArM), German Federal Ministry of Education and Research (BMBF), German Research Foundation (DFG), Volkswagen Foundation; Boehringer Ingelheim, Ferring, Janssen-Cilag, Lilly, Lundbeck, Otsuka, Servier, Shire, Sunovion/Takeda and Theravance. He was a former employee in clinical CNS research of Eli Lilly until Aug 2008, and owns Eli Lilly stock (small part of the respective annual salary). Since then, he has fully been affiliated with the Department of CAP, CIMH, Med Faculty Mannheim, University of Heidelberg, Germany.

BF has been a consultant to and/o speaker for Abbvie, Actelion, Allergan, Almirall, Alnylam, Amgen, Astellas, Astrazeneca, Bayer, Biogen, Biopecs, Bioproject, Biotronik, BMS, Boehringer, Celgène, Daiichi-Sankyio, Ethypharm, Forestlab, Genevrier, Genzyme, Gilead, Grünenthal, GSK, Idorsia, IMS, Indivior, IQVIA, JNJ, Léo, Lilly, Lundbeck, Menarini, MSD, Novartis, Novonordisk, Otsuka, Pfizer, Pierre-Frabre, Recordati, Roche, SANOFI, Servier, Takeda, UCB, ViiV and Wellmera.

PG has no conflict of interest.

CH recieves research funding from the National Institute of Health Research (NIHR) including the Health Technology Assessment (HTA) SATURN trial (Grant ref: NIHR128472) comparing methylpheidate with guanfacine for children and young people with ADHD and tics. CH was chair of the NICE Guideline (CG155) for psychosis and schizophrenia in children and young people; member of the NICE ADHD Guideline Update committee (NG87) and is a member of Eunethydis and the Europhean ADHD Guideline Group.

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HK has no conflict of interest.

EL has no conflict of interest.

SM has received speaker's fee, travel support and research support from Shire outside the submitted work.

AN received research funding from the European Commission, the German Ministry of Health and the German Federal Joint Committee outside the submitted work.

PN has been a consultant to and/or speaker for Medice, Servier, and Egis Pharmaceuticals for work that is unrelated to the present paper.

ER received speaker's fee and travel support support from Shire outside the submitted work.

ESB has received in the last 3 years speakers fees from Takeda and Medice and research support from QBTech.

AZ served in an advisory or consultancy role for Angelini, EduPharma, Servier. He received conference support or speaker's fee by Angelini and Janssen. He has been involved in clinical trials conducted by Angelini, Janssen, Lundbeck, Otsuka, Roche, Sevier, and Shire. He received royalties from Giunti OS, Oxford University Press.

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DC has been in the past 3 years a consultant to / member of advisory board of / and/or speaker for Takeda/Shire, Medice, Novartis, and Servier. He has received royalties from Oxford University press and Cambridge University press. He is not an employee of any of these companies, and not a stock shareholder of any of these companies. He has received research support during this period from the Australian National Health and Medical Research Council and the Royal Children's Hospital Foundation and funding for the current study from the European Commission

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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