Title

The impact of methylphenidate on pubertal maturation and bone age in ADHD children and adolescents: results from the Attention Deficit Hyperactivity Disorder Drugs Use Chronic Effects (ADDUCE) project.

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Short running title

ADDUCE Pubertal Maturation and Bone Age

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Disclosures

SC reports collaboration on projects from the EU Seventh Framework Programme and on clinical trials sponsored by Lundbeck, Otsuka, Janssen-Cilag, Angelini and Acadia.

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Abstract

Objective: The short-term safety of methylphenidate (MPH) has been widely demonstrated; however the long-term safety is less clear. The aim of this study was to investigate the safety of MPH in relation to pubertal maturation and to explore the monitoring of bone age.

Method: Participants from ADDUCE, a two-year observational longitudinal study with three parallel cohorts (MPH group, no-MPH group and a non-ADHD control group), were compared with respect to Tanner staging. An Italian subsample of medicated-ADHD was further assessed by the monitoring of bone age.

Results: The medicated and unmedicated ADHD groups did not differ in Tanner stages indicating no higher risk of sexual maturational delay in the MPH-treated patients. The medicated subsample monitored for bone age showed a slight acceleration of the bone maturation after 24 months, however their predicted adult height remained stable.

Conclusion: Our results do not suggest safety concerns on long-term treatment with MPH in relation to pubertal maturation and growth.

Introduction

Methylphenidate (MPH) is recommended as a first-choice medication for the treatment of ADHD in children and adolescents (Cortese et al., 2018). Its mechanism of action is suggested to be via the enhancement of dopamine and norepinephrine neurotransmission, mediated by blocking their reuptake by the respective monoamine transporters (Arnsten & Pliszka, 2011; Volkow et al., 2002). The therapeutic effects on attention and behavior also appear to be related to the enhanced neurotransmission of these catecholamines, especially in the pre-frontal cortex (Arnsten, 2011). While the efficacy of MPH on ADHD core and related symptoms has been confirmed in many studies since the middle of last century (Cortese et al., 2018; Coghill et al., 2017), concerns have been raised about long-term safety (European Union 2007). Particularly, as ADHD is a neurodevelopmental disorder whose symptoms may not be self- limiting and persisting into adulthood, appropriate insights about the effects of long-term medication treatments have been considered a challenge in the field of drug development (EMA 2011).

Since stimulants increase the availability of synaptic dopamine and may potentially affect patients' endocrine system (Hysek et al., 2014; Lurie and O'Quinn, 1991), these processes could induce a decrease of the growth hormone secretion (Zegher et al., 1993), and determine a potential impact on pubertal and growth maturation. Previous research examining pubertal and bone maturation in ADHD subjects is quite limited and characterized by somewhat contrasting results. One study (Poulton et al., 2013) found that boys aged 14-15.99 years, with a mean treatment duration of stimulants of about 6.3 ± 1.9 years, had a delayed pubertal maturation, while other research did not confirm a significant association between medication use and delayed pubertal timing (Greenfield et al., 2014). A two-Year Open-Label Study of Lisdexamfetamine Dimesylate (LDX) in ADHD Children and Adolescents also confirmed that there was no evidence of a delayed onset of puberty after two years of continuous treatment (Banaschewski et al. 2018).

The mechanism by which stimulants can impact on growth on a bone level is possibly related to their indirect sympathomimetic action that activate peripheral β-adrenergic receptors leading to a decrease bone mass (Richards et al., 2015). However only a few studies examined the bone age and the bone age density changes in subjects treated with stimulant medications revealing conflicting results (Poulton et al.,2012; Lahat et al., 2014; Howard et al., 2015). A later study by Poulton et al. (2016) comparing 40 ADHD medicated subjects to 22 siblings serving as controls found a normal bone age progression notwithstanding a slower growth in the medicated population.

Against the background of these concerns, the European Commission, in June 2007, requested a community referral to its Committee for Medicinal Products for Human Use (CHMP) for all MPH-containing products. In January 2009, the CHMP concluded that overall, the benefit of MPH outweighed the risks (European Union 2009), however the Committee recommended that, to address the relative lack of data about the longer term clinical safety of ADHD medications, clinical trials and further research should assess (1) growth and sexual development, (2) neurological health, (3) psychiatric health, (4) sexual development and fertility and (5) cardiovascular effects (EMA 2011). To fill these gaps of knowledge, the Attention Deficit Hyperactivity Disorder Drugs Use Chronic Effects (ADDUCE) consortium was established and funded in 2012. The ADDUCE research program included empirical work packages (WPs; *ADDUCE consortium http://www.adhd-adduce.org/page/view/2/Home*) that together aimed to provide information about the long-term safety effects of MPH (Inglis et al., 2016).

As a complementary component of the main 2-year ADDUCE naturalistic, longitudinal, pharmacovigilance multicenter study (Man et al., 2023), a specific exploratory sub-study was designed to investigate the long-term developmental effects of MPH on sexual maturation and onset of puberty and to explore whether the monitoring of bone age could improve the estimation of possible long-term growth adverse effects.

Based on this knowledge and according to the EMA requests, within the 2-year longitudinal pharmacovigilance ADDUCE study, we specifically aimed to compare:

1. *Puberty onset and sexual development* of MPH-medicated versus unmedicated ADHD subjects, using the Tanner scores (Marshall and Tanner, 1970). Puberty reflects the progression from the prepubertal to the mature final adult form.

2. The *bone age development in a medicated ADHD subsample*: Bone age assessment is regarded as the gold standard to evaluate the 'growing power' of an individual and represents a major tool to calculate the expected final height.

Method

The study was part of the Attention Deficit Hyperactivity Disorder Drugs Use Chronic Effects (ADDUCE) research program funded by the European Union's Seventh Framework Programme for research, technological development, and demonstration (grant agreement no. 260576). The full research protocol (Inglis et al., 2016) and the longitudinal 2-year controlled ADDUCE study were previously described in detail (Man et al., 2023).

At the heart of the ADDUCE program was a 2-year longitudinal, naturalistic, pharmacovigilance study, including 3 cohorts of children and adolescents (aged 6–17); "*MPH group*" n=756: ADHD medication- naive children and adolescents with a clinical diagnosis of ADHD about to start MPH treatment for the first time; "*No-MPH group*" n=391: children and adolescents with a clinical diagnosis of ADHD who have never been treated with ADHD medication and have no intention of beginning medication, and "*Non-ADHD control group"* n=263: children and adolescents without ADHD (Man et al., 2023).

Participants from the three cohorts completed an auxological assessment (including height and weight measurements) by Tanner ratings at baseline and at six months follow up visits (6, 12, 18 and 24

months after baseline). An Italian subsample of ADHD medicated children (n=39) was further assessed by the monitoring of bone age at baseline, and once a year thereafter, with the purpose of adding value to the routine auxological measures and calculating the predicted adult height.

Pubertal development

All the included 1410 participants were asked, after an explanation of the task, to independently complete the self-reported Tanner puberty scale (Tanner and Whitehouse 1976) and to indicate their genital development, axillary and pubic hair using staged ratings (from on a stage 1 [no evidence of breast, penis or pubic hair growth] to a stage 5 [fully mature]) rating with the help of pictures (Marshall and Tanner, 1970). Self-reported Tanner ratings are efficient and easy to use, they are a reliable method in research protocols with a moderate agreement and reliability between the self-assessment and the physician's assessment in children and adolescents (Desmangles et al. 2006; Schmitz et al. 2004; Jaruratanasirikul et al., 2014; Greenfield et al., 2014; Schlossberger et al., 1992).

The bone age sub-study

From September 2012 to July 2014, the ADHD medicated children, aged 6- to 12-year-old, who were enrolled at the Unit of Child and Adolescent Neuropsychiatry site in Cagliari, were invited to be assessed for sexual maturation by an expert paediatric endocrinologist who completed the Tanner ratings by direct observation and by the physical examination of testicle volume using Prader's orchidometer. Prader's orchidometer is the most used orchidometer, consisting of a series of ellipsoidal spheres and represents a gold standard approach to the measurement of the pubic stage in males (Karaman et al., 2005; Rollof & Elfving). When the orchidometer was not available, the estimate of the testicular volume was made through the measurement of the three axes and the application of the formula for an ellipsoid: Length (L) x Width (W) x Height (H) x 0.5233.

Visits for the assessment of possible adverse events on growth and pubertal development were conducted at baseline and subsequently every 6 months with a maximum number of 5 visits within 24 months. The same participants underwent an X-ray of the non-dominant hand and wrist for determination of bone age at baseline (V0), visit 2 (V2, 12 month) and at the final follow up (V4, 24th month). Bone age was determined by The Tanner & Whitehouse (TW2) method that it is based on a score given to the level of maturity for 20 bones regions of interest (ROI) of the wrist and the non-dominant hand (Khan et al., 2012). The sample size of 70 subjects was calculated for a pilot study to explore whether the monitoring of bone age could improve the estimation of possible long-term growth adverse effects.

Measurements of bone age at baseline allowed calculation of the expected final height using the methods of Tanner (Tanner et al., 1975). Subsequent yearly measurements allowed calculation of the rate of bone maturation as gain or loss. The bone age/chronological age ratio is related to the growth potential of a child, with an increase of this ratio negatively related to the predicted final and adult height. A decrease in height velocity with no decrease in bone maturation rate will reduce the final expected height and may result in short stature; hence, representing an adverse growth outcome. We considered as potential clinically significant an increase in the difference (bone age−chronological age) ≥ ±6 months (+1 SD), representing a change in a child's growing potential.

The radiological risk related to X-ray of the hand is very low, equivalent to a 2-week stay at a mountain or seaside area (iaea.org). The children were not exposed to the risk of a cumulative effect of radiation because the time interval between two radiograms (1 year) was long enough.

The following measures were also considered:

- Z scores for height, weight, and BMI by the following formula:

$$Z = \frac{((X/M)^{**}L)-1}{LS}, L \neq 0 \text{ or } Z = \ln(X/M)/S, L = 0$$

where X = absolute value of height, weight, or BMI; M = median; S = generalized coefficient of variation and L = power in the Box-Cox transformation. M, S, and L were derived from the Italian infant growth charts (Cacciari et al., 2002).

- Z score for height corrected for bone age was calculated with the following formula:

$$\frac{\text{Measured value} - \text{Average Value (at bone age) in the reference population}}{\text{SD (at bone age) of the reference population}}$$

-Height velocity, was operationalised as height velocity SDS, defined as height velocity, v, estimated from at least two measurements setted v apart 6 months (cm/year), and normalized with reference to the mean and SD of a population of the same age and sex:

height velocity SDS = $v - \bar{v}/SD$ (see Inglis et al., 2016 for completion)

The mean and SD height velocities were obtained from the charts (Tanner and Whitehouse 1976).

-Target Height (TH) was calculated by the following formula: "TH = (Father height (cm) + Mother height (cm) + 13)/2 ± 6,5 cm" for male subjects and "TH = (Father height (cm) + Mother height (cm) - 13)/2 ± 6,5 cm" for female subjects.

-The Target Height Standard Deviation Score (TH-SDS) was calculated in order to obtain the Height Standard Deviation Score corrected for the genetic target (H- SDS corr) with the following formula "H-SDS corr = H-SDS – TH-SDS".

In order to exclude a possible impact of the pharmacological therapy on bone maturation, we were also able to calculate the Predicted Adult Height (PAH, Tanner 1975) at the last follow up point by the following formula: PAH= a*H + b*CA + c*BA +k where H= height, CA= Chronological Age, BA= Bone Age; a,b,c are coefficients associated to the chronological age and k is a constant.

This analysis was conducted only in male patients due to the small number of females and the growth dysmorphism between males and females.

Between May and June 2023, the subjects who completed the "*bone age sub-study*" have been telephonically contacted to have information about their current height. They were asked to visit their GP to have a height measurement or if they have been continuously followed-up at the research unit, measurements were taken during their last follow up visit within the same timeframe point.

Ethical approval for the prospective study was granted by the East of Scotland Research Ethics Service as the coordinating center and further ethical approvals were obtained for the other countries and individual sites as necessary. The complementary puberty and bone age trial was approved by the Ethical Committee of the Cagliari University Hospital (resolution n 3228.; date 24 May 2013). Participation in the study was on voluntary basis. Before any study procedure, parents or a legally authorized representative of the subject signed the informed consent. Children provided their written assent.

Analysis

As reported in the ADDUCE main paper (Man et al., 2023), in view of the substantial differences 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 conducted only for comparisons between the MPH and no-MPH groups. The propensity score (PS) adjustment is applied in this study to limit 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 MPH, conditional on the covariates measured, using a logistic regression model. In total, 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: asthma, diabetes, recurrent ear infection), 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, pubic hair and genital growth stage, and sleep score.

An ordinal logistic regression model was applied with the Tanner stage of the MPH and NO-MPH ADHD subjects as the outcome variable in 5 levels, representing the 5 stages. Odds ratios and the corresponding 95% confidence interval were estimated. Multiple imputations were conducted using a Gibbs sampler to address missing data. Missing data was only imputed for all covariates at baseline, neither the exposure nor the outcomes were imputed. Missing data that needed to be imputed were as following: Pubertal Hair 20 for the *MPH group*; 16 for *No-MPH group*; 5 for *Non-ADHD control group;* Genital Growth Stage: 17 for the *MPH group*; 14 for *No-MPH group*; 2 for *Non-ADHD control group.* Both complete-case analyses and imputed analyses were conducted. In the results we report the imputed analyses unless otherwise specified.

Within the "*bone age sub-study*" the characteristics of the ADHD medicated participants included in the study are described and the changes of time-varying factors throughout the study period are also presented. Repeated-measures data were analyzed using a generalized mixed model with sex, age, auxological parameters and medication dose (MPH mg/kg/day) as covariates.

All analyses were two-tailed, and statistical significance was taken as P value less than 0.05. All analyses were conducted with SAS (version 9.4).

Results

Puberty

Demographic and clinical characteristics of participants are reported in Table 1 and in more detail elsewhere (Man et al., 2023).

At baseline self-reported Tanner ratings were available for 736/756 MPH, 375/391 NO-MPH and 258/263 non-ADHD subjects, missing data were counted for 41 subjects. At 12 months follow up missing data increased to 620 and pubertal staging were available for 403 MPH, 202 NO-MPH and 185 non-ADHD participants. At the final 24 months follow up assessment reported pubertal outcomes were available respectively for 364 MPH, 195 NO-MPH and 176 control subjects.

Between-group statistical analyses revealed no significant impact of MPH on pubertal maturation with no delayed maturation or significant differences on stage of puberty: The medicated versus the unmedicated groups, in fact, did not significantly differ for any of the self-reported Tanner items during the 24 month follow up assesments (pubic hair stage odds ratio 1.28; p=0.16; Gential Growth Stage in Males odds ratio 1.35; p=0.08; Gential Growth Stage in Females odds ratio 0.89; p=0.82). (Tables II, IIIa and IIIb).

Bone age

Parents of 44 children consented to participate in "*the bone-age sub-study*" and 39 participants had a complete baseline assessment. Children aged 8.75±1.77 years (range: 6.4–12.1 years), 89.7% were males (n=35), while 10.3% were females (n=4). Almost all participants were in a prepubertal status with a clinician rated Tanner staging <3 (n=29 were on a stage 1, n=8 stage 2 and n=2 stage 3); 2 male subjects had a testicular volume <10 mL while 2 other subjects had >12 mL. Most children were diagnosed with ADHD combined type (89.7%); oppositional defiant disorder (ODD) and specific learning disorders (SLD) were the most frequent coexisting conditions (ODD 61.5 %, SLD 53.8%), 2 subjects suffered from diabetes and 2 from epilepsy (Table IV).

All participants were started on MPH immediate release formulation following enrolment at a mean initial dosage of 0.25 ± 0.07 mg/kg/day (range 0.13 – 0.54 mg/kg). Dosage was later gradually titrated to the most beneficial amount of 22.96±11.07 mg/day (range 7.5 – 50.0 mg/day) equal to 0.71 ± 0.32 mg/kg/day. During the first 12 month, 15 subjects switched to a sustained release formulation, introduced into the Italian market in 2013 (Table V).

X-rays were repeated after 12 months in n= 23/39 of the enrolled subjects, and n= 25/39 participants completed the study with a third radiograph at the final 24-month visit. The 14 children who prematurely terminated the study were comparable to the completers in age (8.58±1.64 vs 8.85±1.54 years, respectively, p=0.33.), sex ratio (100% males vs 84%, p=0.15) and baseline ADHD symptom scores on the SNAP (to be calculated).

Auxologic characteristics and bone age: 24 months of follow up.

According to the Italian growth norms the 39 medicated ADHD enrolled in the sub-study presented with a normal growth pattern at the baseline visit: height Z-score was -0.02±1.11, weight Z-score 0.07±1.24, BMI Z-score 0.15±1.25 and the SDS Target Height for the male population was -0.34±0.87 (due to the small number of female subjects the mean SDS Target Height was calculated only for males). Three subjects had a baseline height Z-score < 2 SD (-2.44±0.22).

At baseline, the bone age calculated by the Tanner and Whitehouse II method was 8.07±2.10, years, resulted in a bone age slightly behind the chronological age of 8.75±1.77 ($p<0.01$), which is however considered not clinically significant and thus not requiring any further clinical investigation (conventionally, constitutional delay of growth is defined by delayed bone age, at least 2 SD, i.e. approximatively 2 years, compared to chronological age associated with short stature and a delay in both pubertal maturation, compared to peers; Cavallo et al., 2021). No clinically significant differences were found also when considering separately the carpal (8.45 ± 2.04) and the radius, ulna, and short (RUS) bones (RUS 7.67 ± 2.23) (Table VI).

The 25 subjects retained in the study at the 24 month follow up and assessed for bone age at baseline, presented with an adequate pattern of growth in terms of height (baseline Z score = 0.23±1.03 vs T24 Z score = 0.42±1.09). Height velocity and height velocity SDS after 12 months were 5.79±2.8 cm and 0.84±0.42 respectively, after 24 months height velocity was 7.02±2.77 cm while height velocity SDS was 0.99±0.39. BMI was slightly reduced after 24 months of treatment (baseline Z score = 0.40±1.32 vs T24 Z score = 0.05±1.27; p= 0.006). Almost all patients, apart from two subjects that discontinued medication without specific reasons, were continuously medicated for 2 years; 17 subjects, according to local practice, had drug holidays during summertime.

The bone age at the 24-month follow-up (11.03±2.21 years) was correctly aligned with the chronological age (10.96±1.83). The difference in bone age after 24 months was 2.74 years (baseline bone age 8.29±2.33) slightly higher than the 2.11 years difference in chronological age (baseline age 8.85±1.86) evidencing a possible acceleration of bone maturation. This data is confirmed by the reduction of the height Z score corrected by bone age, which reduced from 0.80±0.92 to 0.50±1.09 over the 24 months (p=0.125) (Table VII)

The Height Z score and the Height Z score corrected for by bone age at 24 months were comparable (respectively 0.42±1.09 vs 0.50±1.09).

Same results have been found when excluding the 4 participants who had already started pubertal maturation at baseline. Medication dosage and age did not influence the results.

Only one of the three subjects with a baseline Height Z score <2 SD completed the study: The Height Z score after 24 months was comparable to the baseline Z score (baseline -2.19 vs T24 -2.10), as well as the Z score for height velocity (T12 =0.47 vs T24 = 0.88) while the difference between chronological age and bone age at 24 months was 2.12 y, reduced from the difference calculated at baseline equal to 2.84 y. Comparable results were found for the other two subjects who interrupted the study after 12 months.

Predicted adult height

There was no evidence of a decrease in the stature prognosis values at either of the two follow-up times. After 12 months of treatment, the difference in expected adult height was only 0.7 cm less, and at the 24-month follow-up assessment, the stature prognosis is even higher compared to baseline (baseline= 176.08±8.32 cm; T12 =175.67±10.37 cm; T24=176.74±8.74 cm), thus indicating that the possible acceleration in bone maturation could be correlated to a specific individual growth pattern rather than to the impact of drug treatment.

About 7 years after their last follow up, we were finally able to contact n = 15 of the 25 subjects who had completed the study, at a mean age of 19.02±2.04. Participants have been asked to report their final height (mean±DS =175.06±10.47 cm), that resulted comparable to the predicted adult height calculated at the 24 month follow up. About half of the patients continued their ADHD medication treatment until the age of 18, however data about doses and compliance are not available. The only subject with a Height Z score <2 SD at baseline (age 8.04), at the age of 17.8 years was 161 cm tall, while his predicted adult height was 165.7 cm at baseline and 163.8 cm at 24 months.

Discussion

Methylphenidate is recommended by clinical guidelines as a first-line treatment option for ADHD and it is the most prescribed medication in children and adolescents (Raman et al., 2018). Its short-term beneficial effects on ADHD core symptoms have been replicated in several trials (Cortese et al., 2018) as well as its benefits on several long-term outcomes measures including academic, antisocial behavior, driving, non-medicinal drug use/addictive behavior, obesity, occupation, services use, self-esteem, and social function (Fredriksen et al., 2013; Shaw et al., 2012), while tolerability and safety concerns have been a matter of debate during the last decade (EMA 2007). The prospective,

longitudinal, pharmacovigilance ADDUCE study is the first study designed to acquire precise information on the long-term safety of methylphenidate (MPH) in response to the requests from the European Medicine Agency (EMA). The current study aimed to answer the still open questions about whether MPH has negative effects on pubertal growth and maturation in children and adolescents with ADHD who are treated with stimulants. We also aimed to investigate whether the monitoring of bone age could improve the estimation of possible long-term stimulant-related growth adverse effects.

The precise mechanism of action of MPH on growth and pubertal maturation remains unclear; preclinical studies have demonstrated that the increase in dopamine levels determined by MPH (Volkow et al., 2001) may alter the gonadotropin-releasing hormone (GnRH) release due to inhibitory effects of dopamine on the excitability of GnRH neurons (Liu et al., 2013; Novaira et al. 2011). And previous studies on MPH administration in rats evidenced that also short treatment with MPH could have an impact on hormone levels (Adriani et al., 2006) and spermatogenesis (Cansu et al., 2011). A recent study examining the impact of MPH on the onset of puberty and reproductive organ development in rats demonstrated that MPH administered in a prepubertal phase (from Post Natal Day 21) could affect the reproductive functions in both males and females, however, effects appeared to be transient and remitted after 30 days of drug cessation (Khoubbieh et al., 2023).

A potential role for prolactin (PRL) has also been discussed (Shaywitz et al., 1990). PRL is mainly secreted by the lactotroph cells of the anterior pituitary, and its secretion, spontaneously elevated, is mainly controlled by the hypothalamus inhibitory factors, the most important of which is dopamine, acting through the D2 receptors in the lactotroph cells. Since prolactin interferes, by slowing or blocking sexual development (Lasaga & Debeljuk 2011), treatment with MPH could therefore interfere with the onset of puberty. Lurie and O'Quinn (1991) reviewed 13 studies on the prolactin response to stimulants treatment (amphetamines and methylphenidate) in children and adults and reported that neither MPH nor d-amphetamine had a consistent effect on PRL secretion and

hypothesised that acute MPH administration could decrease PRL secretion but, chronically, there could be an adaptation of the system with PRL secretion normalization.

One of the major strengths of this work is the inclusion of the Tanner's staging in addition to the auxological parameters. In fact, although it is well known that height velocity dramatically increases at the onset of puberty, most studies have not included data on pubertal development thus limiting the possibility of identifying negative effects of psychostimulants on the interplay between sexual maturation and physical growth during adolescence.

Zhang et al., when examining the effect of stimulants on growth, included only subjects under Tanner stage II (Zhang et al., 2010) identifying a small but significant deceleration of height velocity, while Gadow et al. (1999) generically described a sample of prepubertal subjects evidencing no effect of MPH on growth. Spencer (Spencer et al., 1996) divided the sample into two subgroups based on Tanner's stage ($\leq$ 2-3 or $\geq$ 3-4) and showed a significant difference in height z scores only for children in an early pubertal phase, with Tanner staging equal or less than 2-3. The results of these studies could therefore allow for a more precise standardization of the population.

In our study, when compared to the ADHD unmedicated group, medicated ADHD children and adolescents did not experience delayed pubertal development according to the self-reported Tanner scale, supporting previous findings that stimulant medication had no impact on sexual maturation during adolescence (Greenfield et al., 2014). The cross-sectional analyses from the follow up MTA study, further add to this evidence that stimulants do not impact the timing of puberty. Within the MTA 342 ADHD subjects and a non-ADHD control group (n = 159) completed the self-report Tanner staging at the 36-month follow-up assessment. No statistically significant differences in Tanner stages were found between the ADHD and non-ADHD groups at the age of assessment (between 10 and 14 years of age). Further comparisons were made according to the medication status comparing 61 ADHD *medicated* participants with other ADHD subjects who were *never* (n = 56), *newly* (n = 74)

and *inconsistently* (n = 116) medicated with stimulants. No differences on pubertal maturation were found among these four ADHD medication sub-groups (Greenfield et al., 2014). A recent work replicates the MTA findings in an all-female sample where no significant difference for Tanner staging were found between stimulant users vs. non-users, although girls with ADHD with no premenarcheal stimulant use had an earlier menarche onset than those with a history of stimulant use, potentially related to BMI differences (Rosenthal & Hinshaw, 2023). A 12-month prospective study in children with ADHD undergoing 12-month MPH treatment (n= 146; mean age: 8.9 years, 76.7% males) suggests that MPH at usual doses does not significantly alter gonadal function and pubescent development compared to healthy control subjects (n=70; mean age: 9.2 years, 65.7% males) (Wang et al. 2021).

Previous data on the impact of MPH on timing of puberty are limited and present contrasting findings. Spencer et al. (1996), in their study examining 124 ADHD male children and adolescents and a matched control group, did not detect any obvious influence of MPH using a self-staging questionnaire for pubertal maturation. The same result was found in a similar study performed on 124 ADHD girls (Biederman et al., 2003). However, Poulton et al. (2013) reported a delay in pubertal maturation in the long term (after 3 years of continuous treatment with stimulants) in adolescents aged 14 to 16 years. No significant difference in the stage of puberty was found for the sample of boys aged 12.0–13.9 years, suggesting that medication may delay the rate of maturation during puberty without influencing the onset of puberty (Poulton et al. 2013). Contrasting results should be interpreted considering possible different medications regimen in terms of age and length of treatment although all the three studies examined subjects aged 12 to 18 and considered the early and late pubertal stages separately.

The impact of stimulants on height also continues to be discussed. A normal caloric and protein intake is deemed to be essential for correct secretion and homeostasis of growth hormone (Hartman et al., 1993). One of the most common side effects of ADHD medications is appetite loss, with consequent

reduction in caloric intake and perhaps protein intake that may be associated with reductions in weight and height gain after extended use (Cortese et al., 2013b; Storebø et al., 2018; Vitiello, 2008). Other possible mechanisms include medication effects on hepatic and/or CNS growth factors and direct effects on cartilage (Faraone et al., 2008), as well as a possible suppression of growth hormone (GH) secretion consequent to the dopaminergic effect of stimulants (Muller et al., 2011).

Lurie and O'Quinn (1991) reviewed 21 studies examining GH response to acute stimulant challenge. Most of these studies evidenced an increase in GH secretion after the administration of stimulants in both ADHD subjects and controls, while the studies conducted in male ADHD subjects chronically treated with stimulants treatment did not appear to affect the 24-hour pattern of GH secretion.

Likely the effects of stimulants on growth are mediated by the effects of GH on the cartilage tissue. GH stimulates the production of somatomedin-C (insulin-like growth factor-1 [IGF-1]) by the liver, which in turn stimulates the growth of cartilage in bone tissues. Direct effects of GH on cartilage are also known, however IGF-1 levels largely reflect the adequacy of GH production. Somatomedin C levels, examined in 4 studies, were not altered in patients chronically treated with stimulants (REF).

Kilgore et al. (1979) also found that pemoline, methylphenidate and methamphetamine can inhibit, *in vitro*, the sulphate uptake by cartilage, thus suggesting the change on cartilage metabolism as a possible mechanism of growth retardation.

In a human study, MPH determined a slight transient decrease in serum IGF-1 and IGF-binding protein-3 concentrations during the first 4 months of treatment with subsequent normalization and no sustained effect after 16 months (Bereket et al., 2005).

The present work is one of the very few studies where subjects treated with MPH were followed up longitudinally and had a bone age examination using X-rays of the non-dominant hand and wrist according to the Tanner and Whitehouse II method.

The study of bone age in our sample showed, a slight delay in maturation compared to the chronological age in male subjects at baseline, evidenced by the significant difference between the height SDS and the height SDS corrected for bone age ($p<0.01$). After 24th month we found a slight acceleration of the bone maturation with bone age parameters perfectly in line with the chronological age and a height Z score and a height Z score corrected for bone age exactly comparable.

Two studies (Poulton et al., 2012; Lahat et al., 2014) investigated the bone age and the bone age density changes in subjects treated with methylphenidate or dexamfetamine. Poulton et al., examined 34 initially drug-naive subjects aged between 4.7 and 9.1 years over 36 months and found a significant impact of stimulants on the long-term bone metabolism with a substantially reduced bone growth. Lahat et al. compared 10 ADHD patients treated with medication with 10 control subjects with a follow-up of 12 or 24 months and did not observe a significant impact on bone mineral density. A later study by Poulton et al. (2016) compared 40 ADHD medicated subjects to 22 siblings serving as controls and found a normal bone age progression despite a slower growth in the medicated population.

It is however essential to highlight that growth data should always be confirmed upon reaching the final height to allow fuller understanding of the effects seen in subjects who are still growing. The key question is whether children treated with medication obtain their expected height as adults, or not (Swanson et al., 2017). In our sample, the analysis of the predicted adult height further confirmed a low impact of MPH on height, since after two years of treatment the stature prognosis remained substantially unchanged, and even after 7 years, the predicted adult height resulted substantially confirmed.

Other data from adults treated with psychostimulants as children, suggest that final height may not be significantly impaired (Kramer et al., 2000; Safer et al., 1975; Klein et al., 1988; Satterfield et al., 1979). Hechtman et al. compared 20 MPH-treated males with 68 drug-naive subjects and 20 controls

(mean age 21.1 years, 21.8 years, and 19.6 years, respectively) and found no significant differences between the three groups (Hechtman et al.1984). Biederman et al., (2010) in their 10-year follow-up case-control study (mean age 21 years), found no evidence that stimulant treatment had an impact on growth.

A recent study using 2004-05 data from the NESARC study (National Epidemiologic survey on Alcohol and Related Conditions, Peyre et al., 2013) also showed the absence of significant differences of adult height in ADHD subjects previously treated with ADHD medications during childhood (n = 216), compared to ADHD subjects who were never treated with stimulants (n = 591) and a control group (n = 34,652). These results were further confirmed in a population-based study showing no significant deficits in height into adulthood between stimulant-treated and stimulant-naive ADHD subjects (Harstad et al., 2014).

However, Swanson and the MTA Cooperative Group (Swanson et al., 2017) re-examined children's physical growth and revealed that the "*New medicated subgroup*" was, at the 36 months follow-up point, 3.04 cm shorter and 2.71 kg lighter than the "*Not medicated group*". During the follow-up observation into adulthood, the prolonged use of MPH in the ADHD group resulted in an average height of 1.29 ± 0.55 cm shorter than the control group ($p < 0.01$, $d = 0.21$). Within the treated sample, adherence to drug treatment was defined as *consistent*, *inconsistent*, or *negligible*: participants belonging to the *consistent* or *inconsistent* pattern were 2.55 ± 0.73 cm shorter than the subgroup with the *negligible* pattern ($p < 0.0005$, $d=0.42$) (Swanson et al., 2017).

Our previous meta-analysis on the effect of MPH on height found a small but statistically significant negative impact of methylphenidate on height (SMD = 0.27, 95% CI 0.16-0.38; $I^2 = 52\%$), an effect that may have low clinical significance (Carucci et al., 2021). Similar results (SMD = – 0.40; 95% CI = – 0.54, – 0.27; $I^2 = 91\%$) have been recently replicated in a recent systematic review and meta-analysis concluding that although minimal, the negative impact of MPH on growth should not be

neglected with the need of well- designed longitudinal studies to quantify the long-term treatment impacts on height (Duong et al., 2023).

Some recent publications confirm the safety of stimulants regarding this matter of discussion. A recent analysis of Growth Velocity in ADHD Children medicated with Serdexmethylphenidate/Dexmethylphenidate for 12 months confirm that the effects of medication on height were minimal and not clinically significant (Childress et al., 2023) while our previously reported findings from the full ADDUCE prospective study found no evidence of an MPH effect on height in the medicated population compared to the No-MPH group in the long-term (24 months). Only for weight velocity there was an initial slowing at 6 months in the MPH group with no group differences for BMI at any time point (Man et al., 2023).

Limitations

In addition to the aforementioned strengths this work had some limitations.

The prospective study is multicenter, including multiple sites in five different countries. This allowed the enrolment of a large number of subjects; however, it also involved a large number of different raters, with consequent possible precision biases, despite a common and highly specific training at the beginning of the study.

There was a relatively high drop-out rate over time especially for the non-pharmacological subjects (53.5% of participants attended the 24-month visit).

Because this was an observational study the clinicians were allowed to choose the most appropriate treatment for the individual patient in their own clinic and did not restrict the treatment form in any

preparation, formulation, and dose. Dose was recorded using a free-text entry while adherence to treatment was not assessed for all participants.

We examined only MPH and no other stimulant medications; therefore, the results are difficult to generalize to all stimulant treatments.

The bone age sample is very limited in size due to a combination of ethical and cost reasons, that prevented the procedure being extended to the entire sample. The number of 70 was considered sufficient for a pilot study to provide general information in order to evaluate the validity of this tool, however, the targeted sample was not reached for logistic reasons.

Finally, the observation period of the study was 2 years, but, in routine care, many children and adolescents with ADHD will be treated with MPH for a longer period. A lack of mean change in pubertal and bone maturation does not mean that clinically relevant changes cannot occur in individual cases.

Conclusion and clinical implications

ADHD is a chronic condition that in many cases persists into adolescence and adulthood (Kooij et al., 2010; Franke et al., 2018), therefore patients may receive long-term treatment for several years and this can be accompanied by concerns about possible long-term effects.

The results of this study confirm a good safety profile of MPH regarding pubertal growth and maturation, in line with recently published results (Man et al., 2023). The data currently available do not support the hypothesis that long-term MPH treatment is associated with impairments on pubertal maturation in ADHD medicated subjects.

The effects of MPH on physical and sexual maturation appear to be minimal and of little clinical concern for most individuals with ADHD and the significance of a deficit should always be considered in the context of the benefits of the treatment.

Accordingly, regular monitoring for physical growth, as recommended by clinical guidelines, remain indicated (Graham et al., 2011) including the monitoring of sexual development. The study of bone age, currently, remains beyond the clinical practice and indicated in children needing a referral for short stature (Gharib et al., 2003).

Ethics

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.

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