Title

Methylphenidate and sleep difficulties in children and adolescents with ADHD – results from the two-year naturalistic pharmacovigilance ADDUCE study

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Abstract:

Objective

Short-term RCTs have demonstrated that MPH (MPH) treatment significantly reduces ADHD symptoms, but is also associated with adverse events, including sleep problems. However, data on long-term effects of MPH on sleep remain limited.

Methods

To investigate long-term effects of MPH we performed a two-year naturalistic prospective pharmacovigilance multicentre study. Participants were recruited into three groups: ADHD patients who intended to start MPH-treatment (MPH-group), those who did not intend to use ADHD-medication (no-MPH-group), and a non-ADHD control group. Sleep problems were assessed with the Children's-Sleep-Habits-Questionnaire (CSHQ).

Results

In total, 1410 participants were enrolled. Baseline mean CSHQ-total-sleep-scores could be considered clinically significant for the MPH-group and the no-MPH-group, but not for controls. The only group to show a statistically significant increase in any aspect of sleep from baseline to 24 months was the control group. Comparing the MPH to the no-MPH group and adjusting for baseline differences, no differences in total sleep score changes were found.

Conclusion

Our findings support that sleep problems are common in ADHD, but do not suggest significant negative long-term effects of MPH on sleep.

Introduction:

ADHD, characterized by symptoms of inattention, impulsivity and hyperactivity, is one of the most prevalent neurodevelopmental disorders and often coexists with various other symptoms and comorbidities, including oppositional defiant behavior, conduct disorder, anxiety and mood disorders, sleep problems and learning disabilities[1]. Especially for severe cases of ADHD, several evidence-based clinical guidelines recommend pharmacotherapy as first-line treatment[2]. Currently, there are various stimulants and non-stimulants approved for the treatment of ADHD, with methylphenidate (MPH) being the most commonly prescribed worldwide[3,4]. MPH treatment is associated with reduction in ADHD core symptoms, reduction in functional impairment, and improved quality of life in patients with ADHD [5-7]. Moreover, MPH treatment is associated with an alleviation of morbidity related to coexisting disorders such as oppositional defiant disorder and conduct disorder[6]. However, it may also lead to adverse events like reduced appetite, insomnia and mood changes, which might outweigh the benefits of treatment in some cases, potentially leading to discontinuation of pharmacotherapy[5,6,8].

Sleep disturbances are a common issue among individuals with ADHD, and patients with ADHD frequently experience various types of sleep problems[1,9-14]. These sleep disturbances often have a significant impact on the quality of life of patients and may furthermore exacerbate the ADHD core symptomatology[9,15].

While adequate pharmacological treatment of ADHD can sometimes lead to improvements in sleep, sleep disturbances may also occur or worsen as a side effect of ADHD pharmacotherapy[16,17]. Despite this, several aspects concerning the relationship of ADHD, sleep problems and pharmacological treatments remain inadequately understood[10,18]. Specifically, most studies have focused on the short-term or immediate effects of ADHD medication on sleep behavior and sleep problems in patients with ADHD, leaving a gap in our understanding of long-term outcomes in this context. In this study, we aim to bridge this gap by presenting data on sleep patterns and sleep issues in children and adolescents with ADHD treated with MPH compared to children and adolescents with ADHD not treated with MPH and controls without ADHD as part of a 2-year naturalistic prospective pharmacovigilance study.

Methods:

Study design:

Data were collected as part of a two-year naturalistic prospective pharmacovigilance multicentre study designed to investigate the long-term safety of MPH in children and adolescents aged 6 to 17 years. The study was part of the Attention Deficit Hyperactivity Disorder Drugs Use Chronic Effects (ADDUCE) research programme funded by the European Union's Seventh Framework Programme for research, technological development and demonstration (grant agreement no. 324487).

The study was conducted in 27 European child and adolescent mental health centres in the United Kingdom, Germany, Switzerland, Italy, and Hungary. The overall goal of the study was to investigate long-term effects of the drug on growth and development, neurological health, psychiatric health, sexual development and fertility, and cardiovascular responses in children and adolescents. Ethical approval for the study was obtained from the East of Scotland Research Ethics Service as the coordinating centre, and in addition for the other countries and individual sites as required. Study participants were assessed five times at six-month intervals over a two-year follow-up period (see Figure 1). Three cohorts of children and adolescents were recruited:

(1) children and adolescents with ADHD not previously medicated with any ADHD medication who were about to start MPH treatment (= MPH group).
(2) children and adolescents with ADHD not previously medicated with any ADHD medication, and who did not intend to start any ADHD medication (= no-MPH group).
(3) children and adolescents without ADHD who screened negative for ADHD at study enrolment (= control group).

Details of the study and of the study protocol as well as the main outcomes have been published elsewhere [19,20].

(Figure 1)

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 MPH group and the no-MPH group 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 control 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)[21] for ADHD

items, and whose hyperactivity score on the parent-rated Strengths and Difficulties Questionnaire (SDQ)[22] was within the normal range (<6). Participants could not be included if they had previously taken any ADHD medications. Participants were recruited 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). In accordance with country-specific regulations, required written informed consent/assent was obtained from participants and their legal guardians prior to study participation.

Assessment - Children's Sleep Habits Questionnaire:

The primary outcome and main results of the study have been published elsewhere[20]. Here, as a secondary outcome of the ADDUCE study, we present data regarding participants` sleep difficulties at baseline and changes over the two-year observation period.

To assess sleep difficulties we used the Children's Sleep Habits Questionnaire (CSHQ)[23], a parent-reported retrospective, questionnaire. The CSHQ has been designed to screen for the most common sleep problems in children and adolescents. The CSHQ focuses on sleep disorders in three domains: dyssomnias (difficulty getting to sleep or staying asleep), parasomnias (sleepwalking/talking, night terrors, bedwetting, restless legs syndrome, etc.), and sleep-disordered breathing. Thirty-three individual items contribute to a total score and different subscale scores including a bedtime resistance score, a parasomnia score, a sleep-onset delay score, and a sleep duration score. The total sleep disturbances score has a range of 33 to 99. A score exceeding 41 suggests clinically significant sleep problems[23]. For sub-score cut-offs we followed Marcovich et al., considering sub-scores clinically significant if they were >1 SD above the mean score of the Owens et al. norms[23,24]. The questionnaire was provided to the parents of the participants of all three groups at baseline (= visit 1), as well as after 6 months (= visit 2), 12 months (= visit 3) and 24 months (= visit 5). Parents were asked to recall sleep behaviors occurring over a typical recent week. Items were rated on a three-point scale: “usually” if the sleep behavior occurred five to seven times/week; “sometimes” for two to four times / week; and “rarely” for zero to one time/week.

Statistical analyses:

Characteristics of participants included in the ADDUCE study had been presented for each group in a previously published paper (for details see Man et al.[20]). The groups were compared using statistical tests (t test, ANOVA, and χ^2 tests where appropriate) and the changes of time-varying factors throughout the study period were also presented[20]. Within-group changes over time were calculated using the crude scores for all three groups. Owing to 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. As children with severe symptoms can have a higher likelihood of being treated with MPH, propensity score adjustment was applied to address potential differences in participant characteristics between the MPH and the no-MPH group[21]. Generalized mixed models were applied to evaluate the association between MPH and the outcomes. The propensity scores were adjusted as a continuous variable in all models. All outcomes were log-transformed to ensure the model assumptions were met for robust

analyses. 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 1 error. 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 included in the imputation. Both complete-case analyses and imputed analyses were conducted. All analyses were conducted with SAS (version 9.4).

Results

Between February 1st 2012 and January 31st 2016, a total of n = 1.410 participants were recruited for the ADDUCE study: n = 756 participants into the MPH group, n = 391 into the no-MPH group, and n = 263 into the control group. Owing to the differences in clinical practice across the four participating countries, the proportions of participants in each group differed considerably between countries. In the MPH group 82.4% (n=622) of the participants were male, compared to 85.0% (n=329) in the no-MPH group and 45.6% (n=119) in the control group. There were statistically significant differences in age between the three groups, with a mean age of 9.22 years in the MPH group, 8.74 years in the no-MPH group, and 10.25 years in the control group. As this was an observational study, not all participants attended every visit. Reasons for non-attendance were not captured. The loss-to-follow-up over the 2 year observation period was high with 53.5% (n=755) of participants attending the final visit at 24 months. More details on the sample as well as primary and different secondary outcomes were published elsewhere[20].

Table 1 gives an overview on data on sleeping difficulties measured by the CSHQ in the three groups at baseline and after 6, 12 and 24 months. At baseline the mean CSHQ total sleep scores was 47.3 for the MPH group and 45.3 for the no-MPH group. The scores for both groups were above the cut off score for clinical significance of 41 as determined by Owens et al 2000[23]. By contrast the CSHQ mean total sleep score for the control group was 39.7 and therefor below the cut off. For sleep duration only the MPH group (4.66) was above the cut off (3.87) and for sleep delay the MPH group (1.77) was equal to the clinical cut off (1.78) while the other two groups were below the cut off. For bedtime resistance, parasomnias and sleep duration all three groups were below the clinically significant cut off at baseline.

(Table 1)

The only group to show a statistically significant negative change in any aspect of sleep from baseline to 24 months was the control group for whom the sleep duration score increased from 3.68 to 3.99 ($p=0.03$) but remained below the clinically significant cut off (4.34). Both the MPH and the no-MPH group reported improved total sleep score ($p<0.01$), bedtime resistance ($p<0.01$) and parasomnia ($p<0.01$) scores and no statistically significant changes in sleep onset delay or sleep duration. The parasomnia score was the only improvement in the control group ($p<0.01$).

Comparing the MPH to the no-MPH group and adjusting for baseline differences, there were no differences between the two groups in change in total sleep score, bedtime resistance, or parasomnias between baseline and 6, 12 and 24 months. However, there were between group differences at 6, 12 and 24 months in change of sleep delay (all $p < 0.01$) and sleep duration (all $p < 0.01$) subscales with greater improvements in both subscales for the MPH group compared to the no-MPH group.

Discussion

Using a naturalistic, prospective, longitudinal, controlled design the ADDUCE study collected comprehensive data on adverse effects of MPH in previously psychostimulant-naive children and adolescents with ADHD. The final dataset comprised data from more than 1400 participants of three distinct groups (MPH group, no-MPH group, control group), followed up for a 2-year observation period.

The primary outcomes of the ADDUCE study were published elsewhere[20]. Here, we conducted secondary outcome analyses specifically focused on sleep difficulties as measured by the parent-reported Children´s Sleep Habits Questionnaire (CSHQ). At baseline, we found CSHQ total scores above the clinical cutoff in both ADHD groups (= the MPH group and the no-MPH group), but not in the control group, supporting the hypothesis and clinical observation that sleep difficulties are a prevalent coexisting issue in individuals with ADHD, warranting particular attention. Notably, the CSHQ-sub-scores sleep duration and sleep onset delay reached or exceeded the cutoffs in the MPH group at baseline, which was not the case in both other groups, where these sub-scores remained below the cutoffs.

With respect to the baseline CSHQ scores, our results are in line with numerous other studies and reviews indicating a clear association between ADHD and sleep problems. Cortese et al. conducted a meta-analysis encompassing what they called subjective (i.e., based on questionnaires) and objective (i.e., using polysomnography or actigraphy) studies that compared sleep in children with ADHD to controls[14]. Their findings indicated that children with ADHD displayed significantly greater impairment than controls across various subjective and some objective sleep measures/parameters. Specifically, with regard to subjective measures, they found children with ADHD to have higher bedtime resistance, more sleep onset difficulties, more night awakenings, more sleep disordered breathing, more daytime sleepiness, and more difficulties with morning awakenings compared to controls. Regarding objective parameters, ADHD patients showed an extended sleep onset latency (as assessed by actigraphy), a greater frequency of stage shifts per hour of sleep, and a heightened apnea-hypopnea index. In addition to the meta-analysis by Cortese et al. a series of further studies and reviews also found clear associations between sleep issues and ADHD including a more recent meta-analysis focusing on adult patients[10].

While the association between sleep issues and ADHD appears evident, reasons for this association are less well understood and likely to be complex[9]. On one hand, untreated ADHD symptoms could contribute to sleep problems. Conversely, sleep issues might also lead to or “imitate” ADHD symptoms. Moreover, sleep problems and ADHD symptoms may interact with bidirectional causation; their relationship could be influenced by concurrent comorbid symptoms and/or they might share common underlying etiology. Further research would be needed to gain a better understanding of these likely complex interrelations. Furthermore, it is important to acknowledge that findings at group level might offer limited insights, given that the underlying reasons for the concurrent presence of ADHD symptoms and sleep problems may significantly vary on an individual basis.

As part of the ADDUCE study, we investigated the extent to which sleep problems changed during the 2-year observation period within the three distinct groups. Specifically, we focused on changes of

CSHQ scores in the MPH group compared the no MPH group. Although there is comprehensive evidence that sleep problems and in particular different types of insomnia are a common side effect of MPH treatment[16], there was no evidence of a worsening of sleep patterns at a group level in participants in the MPH group for either the total sleep score or any of the CSHQ subscales in our sample. Indeed, the parents of the MPH group reported improved total sleep, bedtime resistance and parasomnia scores at 24 months. Interestingly, the only group to show a statistically significant negative change in any aspect of sleep from baseline to 24 months was the control group for whom the sleep duration score increased after the 2-year observation period.

In summary, our findings suggest that long-term effects of MPH on sleep were rather minimal, and that those changes that did occur tended to show a positive direction, which could indicate a possible improvement of sleep. In conclusion, our results rather support that MPH is likely to be well-tolerated in terms of its long-term effects on sleep.

Nonetheless, this does not negate the possibility that certain individuals might experience long-lasting negative effects on sleep due to MPH. Therefore, it remains important for clinicians to carefully address and monitor sleep-related issues among their ADHD patients. The use of methods such as interviews, specific validated questionnaires, and/or sleep diaries should be carefully considered. Assessment should be performed before starting pharmacotherapy, and should be continued or repeated during ongoing treatment. This may also help to counteract the consequences of sleep problems at an early stage.

Strengths and limitations

The present findings need to be interpreted in the context of some limitations. First, a significant loss-to-follow-up occurred over the two-year observation period, with only 53.5% of participants attending at 24 months visit. While it is crucial to highlight this limitation and note that our findings should be interpreted with caution, it is also important to acknowledge that long-term outcomes hold relevance only for those individuals who continue treatment. Second, the observation period of the study was 2 years, however, in routine care, many children and adolescents with ADHD get treatment with MPH for a longer period. Third, as most of the participants were males, we were not able to perform gender-specific analyses. Indeed, there is evidence suggesting gender-specific differences in ADHD, e.g., with girls being more commonly effected by sleep problems than boys[11]. Fourth, the ADDUCE study adopted an observational approach, allowing clinicians to select the most suitable treatment for individual patients. The treatment form was not constrained in terms of preparation, formulation, or dosage. Dose was documented using a free-text entry and treatment adherence was not assessed. Since an intention-to-treat approach was used in the analysis, the estimates may be biased towards the null due to exposure misclassification. However, this approach reflected the true effectiveness of the treatment-allocation throughout the observation period. Fifth, the study did not assess objective markers of sleep, but solely collected data based on a validated parent-reported sleep questionnaire. Seventh, the study investigated long-term effects of MPH only. To compare the long-term effects of MPH with other approved ADHD medications, further comparative prospective studies are needed. Finally, we have not yet explored the frequency of transitions between good and bad sleep quality in patients undergoing MPH treatment. Data from the adult population indicate that the effects of MPH treatment can vary in both directions equally[25]. Furthermore, to advance clinical care, it would be helpful to identify predictors for transitions in both directions. In this context, further research and

additional analyses are required. Clear strengths of the study are the prospective, controlled design, the long observation period and the large sample size.

Conclusion

Sleep difficulties represent a common problem among children and adolescents with ADHD. Findings of our naturalistic, prospective, longitudinal, controlled ADDUCE study support this, as both ADHD groups within our sample showed Children's Sleep Habits Questionnaire (CSHQ) total scores above the clinical cutoffs at baseline. Although MPH is known to potentially impair sleep in some individuals, no evidence of such effects was observed at the group level for either the total sleep score or any of the CSHQ subscales in our study. Indeed, the MPH group reported improvements in the total sleep score, bedtime resistance and parasomnia scores at 24 months. In conclusion, our results suggest long-term effects of MPH on sleep in children and adolescents to be rather positive than negative.

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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.

Declaration of Conflicting interests

AH has received compensation for serving as consultant or speaker for Shire–Takeda and Medice, unrelated to this work. KKCM reports grants from the CW Maplethorpe Fellowship, the UK National Institute for Health and Care Research (NIHR), the EU Horizon 2020 Framework, and the Hong Kong Research Grant Council, and personal fees from IQVIA Holdings, outside the submitted work. JB has been in the past 3 years a consultant, member of advisory board, or speaker for Takeda–Shire, Roche, Medice, Angelini, Janssen, and Servier. SC reports collaboration on projects from the EU Seventh Framework Programme and on clinical trials sponsored by Shire Pharmaceutical Company, Lundbeck, Otsuka, Janssen-Cilag, and Angelini. MD has received research funding from Takeda–Shire, outside the submitted work. RWD - For the past 3 years, he has no conflicts of interest to report. As a former company employee, he has been a stock holder of Eli Lilly & Co. BF has been a consultant or 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. CH reports research funding from the NIHR including the Health Technology Assessment SATURN trial (grant ref: NIHR128472) comparing MPH with guanfacine for children and young people with ADHD and tics. CH was chair of the NICE Guideline (CG155) for psychosis and

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