

Methylphenidate and the Risk of Trauma

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abstract

BACKGROUND AND OBJECTIVE: Children and adolescents with attention-deficit/hyperactivity disorder (ADHD) are prone to sustaining trauma that requires emergency department (ED) admission. Methylphenidate (MPH) can reduce ADHD symptoms and may thus theoretically reduce the risk of trauma-related ED admission, but previous studies do not make this association clear. This study examines this association.

METHODS: A total of 17 381 patients aged 6 to 19 years who received MPH prescriptions were identified by using the Clinical Data Analysis & Reporting System (2001–2013). Using a self-controlled case series study design, the relative incidence of trauma-related ED admissions was compared with periods of patient exposure and nonexposure to MPH.

RESULTS: Among 17 381 patients prescribed MPH, 4934 had at least 1 trauma-related ED admission. The rate of trauma-related ED admission was lower during exposed periods compared with nonexposed periods (incidence rate ratio [IRR]: 0.91 [95% confidence interval (CI): 0.86–0.97]). The findings were similar only when the incident trauma episode was assessed (IRR: 0.89 [95% CI: 0.82–0.96]). A similar protective association was found in both genders. In validation analysis using nontrauma-related ED admissions as a negative control outcome, no statistically significant association was found (IRR: 0.99 [95% CI: 0.95–1.02]). All sensitivity analyses demonstrated consistent results.

CONCLUSIONS: This study supports the hypothesis that MPH is associated with a reduced risk of trauma-related ED admission in children and adolescents. A similar protective association was found in both male and female patients. This protective association should be considered in clinical practice.

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WHAT'S KNOWN ON THIS SUBJECT: Children and adolescents with attention-deficit/hyperactivity disorder are prone to sustaining trauma that requires emergency department (ED) admission. Methylphenidate can reduce attention-deficit/hyperactivity disorder symptoms and thus theoretically may reduce the risk of trauma-related ED admission, but previous studies did not provide a clear association.

WHAT THIS STUDY ADDS: For patients treated with methylphenidate, on-medication periods were associated with lower rates of trauma-related ED admission compared with off-medication periods. A similar protective association was found in both genders. Potential treatment benefit was greater for age ≥ 16 years.

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www.pediatrics.org/cgi/doi/10.1542/peds.2014-1738

DOI: 10.1542/peds.2014-1738

Accepted for publication Oct 6, 2014

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder that is common among school-aged children and adolescents. It is characterized by pervasive and impairing hyperactivity, inattention, and impulsiveness¹ and has a worldwide prevalence of ~5%.² ADHD can have a profound effect on relationships with family and friends, as well as hamper academic performance.³ Therefore, behavioral intervention and/or drug treatment is usually required to mitigate these symptoms and impairments. Guidelines from the National Institute for Health and Clinical Excellence in the United Kingdom recommend the use of methylphenidate (MPH), dexamfetamine, and atomoxetine when drug intervention is considered appropriate for the management of ADHD symptoms.⁴ In the past 2 decades, ADHD prescribing trends have risen rapidly in the United States,⁵ Canada,⁶ the United Kingdom,^{7,8} and Hong Kong.⁹ Clearly, it is important to evaluate the benefits versus the risks (ie, adverse effects) of ADHD medications in clinical practice.

It is well recognized that patients with ADHD are prone to accidents and are more likely to visit the emergency department (ED).¹⁰ Previous studies show that patients with ADHD have a higher tendency of sustaining trauma and other injuries that result in ED admissions.¹⁰⁻¹⁶ Studies also suggest that poor concentration in some patients with ADHD may contribute to the high incidence of ED admissions^{10,11,17} and traffic accidents.¹⁸ ADHD medications have been demonstrated to effectively reduce ADHD symptoms (eg, by improving concentration).^{17,19-22} Theoretically, ADHD medications could therefore reduce the likelihood of trauma-related ED admissions. Recent studies evaluated the effect of ADHD treatment on driving performance,^{23,24} medically attended

injuries,²⁵⁻²⁷ and serious traffic accidents.²⁸ The results provided both positive and negative evidence that injuries or trauma in general can possibly be prevented by the use of medications. However, prevention of trauma has not been recognized as a benefit of ADHD pharmacotherapy in clinical practice guidelines. A reduction in ED admissions not only represents significant savings in health care costs but is also a proxy indicator for diminished harm from injury events. Classic epidemiologic methods and study designs, which made comparisons between patients with or without MPH treatment, may be biased due to confounding by indication and ADHD severity. This bias creates difficulties in the research of ADHD and the risk of trauma with respect to medications. Previous studies have compared the incidence of ED admission or trauma-related hospitalization of patients with and without MPH treatment.^{17,27} However, these studies were inconclusive because sample size and methodologic and data source limitations made it difficult to determine whether positive results were due to treatment or other important differences between patients.

In the present study, we hypothesized that the use of MPH can reduce the risk of ED admission due to trauma in children with ADHD. Consequently, the aim of the study was to assess the association between MPH and the risk of trauma-related ED admission by using the self-controlled case series (SCCS) method. With this method, comparisons are made within subjects with trauma-related ED admission who have been prescribed MPH in the setting of a territory-wide hospital database in Hong Kong.

METHODS

The Clinical Data Analysis and Reporting System

This study was conducted by using the Clinical Data Analysis and

Reporting System (CDARS), an electronic health record database developed by the Hong Kong Hospital Authority (HA), a statutory body that manages all public hospitals and their ambulatory clinics in Hong Kong. The service is available to all Hong Kong residents (>7 million). CDARS has been used previously for various epidemiologic studies, including MPH-prescribing trends in Hong Kong^{9,29,30} and trauma-related ED admissions,³¹⁻³³ and has proved to be a reliable database for research. Patient-specific data, which are recorded by trained clinicians, typically include basic demographic information, payment method, prescription information, pharmacy dispensing information, diagnosis, and admission and discharge information.³⁴ CDARS contains the records of all inpatient, outpatient, and ED admissions in Hong Kong Hospital Authority clinics and hospitals since 1995. Records are anonymized to protect patient confidentiality, and unique patient reference numbers were generated to facilitate data retrieval. Detailed descriptions of CDARS can be found elsewhere.⁹ This study protocol was approved by the institutional review board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (reference number: UW 12-136).

SCCS Design

The SCCS study design³⁵ was specifically selected to investigate the association between MPH and trauma-related ED admissions. This method has been used previously to investigate the safety of vaccines³⁶ and other drugs.³⁷ In SCCS, each patient serves as his or her own control, and the modeling is conditional in that all cases will experience the outcome of interest at some stage.³⁵ This study design relies on within-person comparisons in a population of subjects who have both the outcome and the exposure of interest.³⁵ Incidence rate ratios

(IRRs) were derived by comparing the rate of events during exposed periods (on medication) with the rate during all other observed time periods (off medication). A major advantage of this design is that the potential time-invariant confounding effect of both recorded and unrecorded fixed characteristics that vary between individuals (eg, genetic factors, underlying disease severity, socioeconomic factors) are removed. Furthermore, we are able to adjust for factors that vary with time, particularly age and seasonal effects. However, unmeasured time-varying confounders (eg, nonpharmacologic treatment, parental supervision, school factors) may still affect the study results.

Case Identification

Subjects aged 6 to 19 years who received at least 1 prescription of MPH with at least 1 trauma-related ED admission during the study period (January 2001–December 2013) were identified in CDARS. Individual observation periods commenced on January 2001 or the sixth birthday of the patient (whichever was later) and ended on December 2013, the 20th birthday of the patient, or the date of registered death (whichever was earlier). We commenced follow-up at 6 years of age because MPH is not recommended for younger children.³⁸ Patients with at least 1 prescription of atomoxetine were excluded from the analysis to avoid coprescribing situations, which may affect comparisons. Only MPH and

atomoxetine are licensed for the treatment of ADHD in Hong Kong.

Exposures and Outcomes

For each included participant, prescription records of all MPH and trauma-related ED admission records were identified. All formulations of MPH (standard and extended release) and all strengths were included in the analysis. Exposed periods were defined as time on medication and were estimated by the duration between prescription start and the end date recorded in CDARS for each prescription. More than 99% of prescriptions have the intended start and end date of the treatment recorded in our data set. Daily dosages and quantity prescribed were used to determine the length of treatment if prescription end dates were not available. Median imputation was conducted when the aforementioned prescription information was missing. Periods within the observation phase other than exposure periods were classified as baseline periods. We did not assume participants received continuous treatment upon initiation of MPH. We avoided this assumption because clinicians may offer drug holidays to ADHD patients during school holidays.

A pictorial presentation of the study design for a single hypothetical participant timeline is illustrated in Fig 1. Physicians defined trauma-related admissions upon participants' attendance at hospital ED

departments. An identification code in CDARS (traumatic case = yes) was used for data retrieval. The corresponding date of ED admission was identified as an event date. All admission episodes were included in the analysis.

Statistical Analysis

The primary analysis investigated the relationship between MPH treatment and the occurrence of trauma-related ED admissions by comparing the rate of events during exposed periods versus the rate of events during baseline periods. Adjusted IRR and the corresponding 95% confidence intervals (CIs) were calculated by using conditional Poisson regression, adjusting for age in 1-year bands and seasonal effect. The gender and age effects were assessed by using a stratified analysis. The number needed to expose to cause 1 less event was calculated by using the formula developed by Wilson and Hawken.³⁹ A significance level of 5% was used in all statistical analyses. Microsoft Excel (Microsoft Corporation, Redmond, WA) and SAS version 9.3 (SAS Institute, Inc, Cary, NC) were used for data manipulation and analysis.

Sample Size Calculation

With reference to the equation developed by Musonda et al,⁴⁰ an IRR of 0.9 with 80% power (2-sided 95% CI) could be detected with a minimum of 4062 trauma-related ED admissions.

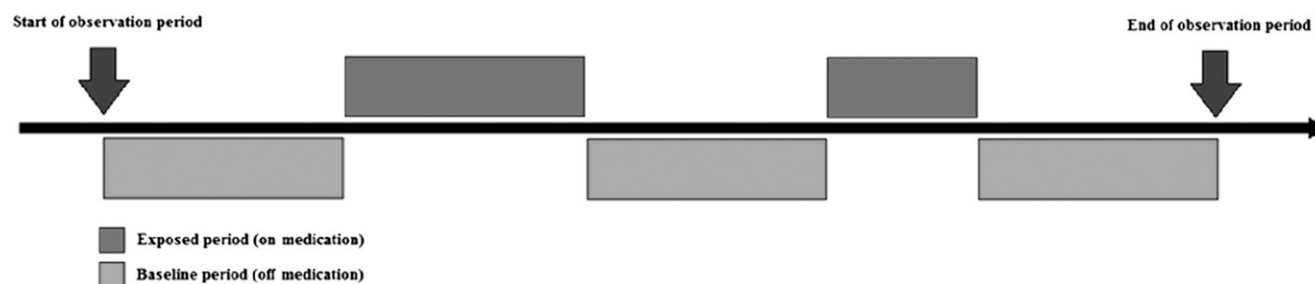


FIGURE 1

Illustration of SCSS study design to evaluate the association of MPH treatment and the risk of trauma-related ED admission.

Sensitivity Analyses

Several sensitivity analyses were conducted to test the validity and robustness of the study results. First, we assessed the association between MPH treatment and nontrauma-related ED admissions. To our knowledge, there is no published evidence or pharmacologic/biological hypothesis to support MPH-associated reduction of nontrauma-related ED admission. Thus, nontrauma-related ED admissions were selected as a negative control for validation purposes. If a harmful or protective association were found in this analysis, it would raise the possibility that our study design is prone to bias. Second, only the first incident episode of ED admission was considered a relevant outcome to test whether recurrent outcomes are independent because this test is an important assumption underpinning the SCCS method. Third, alternative analyses were conducted based on different drug nonadherence scenarios. Each exposed period was further extended by adding 1 to 10 weeks after the end of an exposed period to assess this effect. Fourth, because the event may potentially precipitate MPH exposure, a 7-day pre-exposure period was added to remove the short-term impact of this effect. Fifth, to assess the sensitivity of age banding used, an analysis with a 6-month age band rather than annual bands were used to reaffirm the results. Finally, additional analysis was conducted by restricting patients to those with >1 prescription to ensure a reasonable length of medication use.

RESULTS

From 17 381 eligible participants in the CDARS database, 4934 were included in the primary analysis (Fig 2). Of these participants, 4309 (87%) were male and 625 were female (13%). The mean age at commencement of observation was

6.9 years, and the mean duration of follow-up per participant was 8.3 years. On average, each participant was exposed to MPH for 1.95 years. The median length for 1 prescription was 70 days. There were 8428 trauma-related ED admissions, of which 6416 occurred at baseline periods and 2012 during the MPH treatment period. The overall incidence of trauma-related admissions in the participants during the study period was 21 per 100 patient-years (Table 1). No participants died during the study period. ADHD diagnosis and psychiatric comorbidities in this group of patients are shown in Table 2.

The primary analysis indicated a protective association of MPH treatment and trauma-related ED admissions. After adjusting for age (in 1-year bands) and season, the IRR was 0.91 (95% CI: 0.86–0.97). There was no evidence of this effect varying by gender, as a similar protective association was found in male (IRR: 0.92 [95% CI: 0.86–0.98]) and female (IRR: 0.83 [95% CI: 0.68–1.00]) participants. No significant difference was found between genders ($P = .16$).

The age-stratified analysis showed that the potential treatment benefit was greater for age ≥ 16 years (IRR: 0.68 [95% CI: 0.53–0.86]) compared with those aged < 16 years (IRR: 0.93 [95% CI: 0.87–0.99]). In the validation analysis, no statistically significant association was found between the use of MPH and nontrauma-related ED admissions. The IRR, after adjusting for age and season, was 0.99 (95% CI: 0.95–1.02) (Table 3). The number needed to expose was 88.

The robustness of the effect estimates was assessed in subsequent sensitivity analyses. An analysis using the first episode of admission produced similar results. The adjusted IRR for the first trauma-related ED admission was 0.89 (95% CI: 0.82–0.96); the results were again consistent for both male and female subjects (male: 0.9 [95% CI: 0.83–0.99]; female: 0.73 [95% CI: 0.57–0.94]). The estimate for nontrauma-related admission was 0.93 (95% CI: 0.87–1.00), which was consistent with the results found when considering all episodes.

The adjusted IRR did not change substantially after adding 1 to

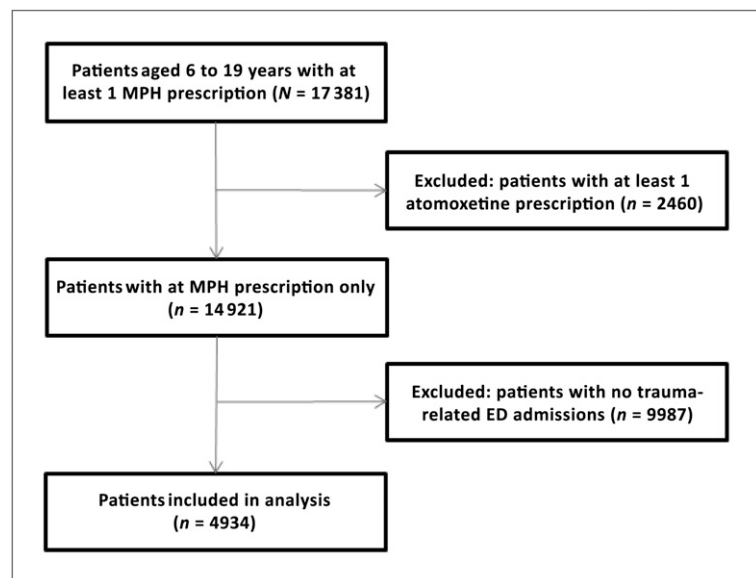


FIGURE 2
Flowchart of patients included.

TABLE 1 Characteristics of Study Population

Patients	No. (%) of Patients	Mean ± SD Age at Baseline (y)	Median Daily Dosage (mg)	IQR of Daily Dosage (mg)	Median Length of Prescription (d)	Exposed Period		Unexposed Period	
						No. of Events	Total Follow-up Time (Patient-Years)	No. of Events	Total Follow-up Time (Patient-Years)
All	4934 (100)	6.9 ± 1.6	20	20	70	2012	9599	6416	31 236
Male	4309 (87.3)	6.9 ± 1.6	20	20	70	1821	8539	5658	27 347
Female	625 (12.7)	6.8 ± 1.4	20	15	70	191	1060	758	3889

IQR, interquartile range.

TABLE 2 ADHD Diagnosis and Psychiatric Comorbidities of the Study Cohort

Diagnosis and Psychiatric Comorbidity	ICD-9-CM	No. (%) of Patients %
ADHD	314	3809 (77.2)
Acute reaction to stress	308	72 (1.46)
Adjustment disorder	309	70 (1.42)
Anxiety disorder	293.84, 300	81 (1.64)
Autism spectrum disorder	299	628 (12.7)
Disturbance of conduct not elsewhere classified	312	118 (2.39)
Disturbance of emotions specific to childhood and adolescence	313	538 (10.9)
Specific delays in development	315	600 (12.2)
Other psychiatric comorbidities ^a	290-319	436 (8.84)

ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

^a Other psychiatric comorbidities included all other disorders from ICD-9-CM code 290 to 319, which were not included in the table.

TABLE 3 SCGS Analyses for Association Between MPH and ED Admissions

Variable	IRR	LCL	UCL	P Value
Trauma-related ED admission (n = 4934)				
All episodes	0.91	0.86	0.97	<.01
Gender				
Male (n = 4309)	0.92	0.86	0.98	<.01
Female (n = 625)	0.83	0.68	1.00	.05
Age, y				
<16	0.93	0.87	0.99	.03
≥16	0.68	0.53	0.86	<.01
First episode only	0.89	0.82	0.96	<.01
Gender				
Male (n = 4309)	0.90	0.83	0.99	.03
Female (n = 625)	0.73	0.57	0.94	.02
Age, y				
<16	0.90	0.82	0.98	.02
≥16	0.51	0.34	0.78	<.01
Nontrauma-related ED admission (n = 8489)				
All episodes	0.99	0.95	1.02	.44
First episode only	0.93	0.87	1.00	.05

LCL, 95% lower confidence limit of IRR; UCL, 95% upper confidence limit of IRR.

10 weeks to the end of each exposed period. The estimates ranged from 0.91 to 0.92 for models considering all episodes and 0.88 to 0.90 for first episodes only, with all attaining a statistically significant result (Fig 3). After including a pre-exposure period of 7 days, a similar IRR during MPH treatment was observed [all episodes IRR: 0.90 [95% CI: 0.84–0.95]; first episode only IRR: 0.89 [95% CI:

0.82–0.97]] (Table 4). Other sensitivity analyses also produced similar results. All analyses consistently indicated that MPH was associated with a reduced risk of trauma-related ED admission.

DISCUSSION

In this study, we found that use of MPH medication was associated with

a statistically significant reduction in the risk of trauma-related ED admission. This finding supports the hypothesis that for those treated with MPH, the treatment is associated with a reduced the risk of trauma. This protective effect was clearly present among participants aged 6 to 19 years with the rate of their trauma-related ED admissions significantly lower during MPH treatment periods compared with nontreatment periods. As hypothesized, the validation analysis, using nontrauma cases as the negative control, found no evidence to suggest that MPH treatment reduces the risk of nontrauma-related ED admissions. This finding further strengthens our conclusion that the reduction in risk of traumatic admission was due to MPH medication rather than other factors that vary with time. The results were shown to be robust and minimally affected by changes in outcome and exposure classification, performed to test robustness to the SCGS study design assumptions.

The effectiveness of MPH in preventing trauma for female subjects was not clear in the literature, and whether there is a gender difference on the effect of medication on trauma was not known.^{17,20–22,26} Because our study had a considerably larger sample size and power than these previous studies, we were also able to evaluate the effects of medication according to gender and found similar benefits for both male and female subjects. There were no significant differences in reduction of trauma risk between

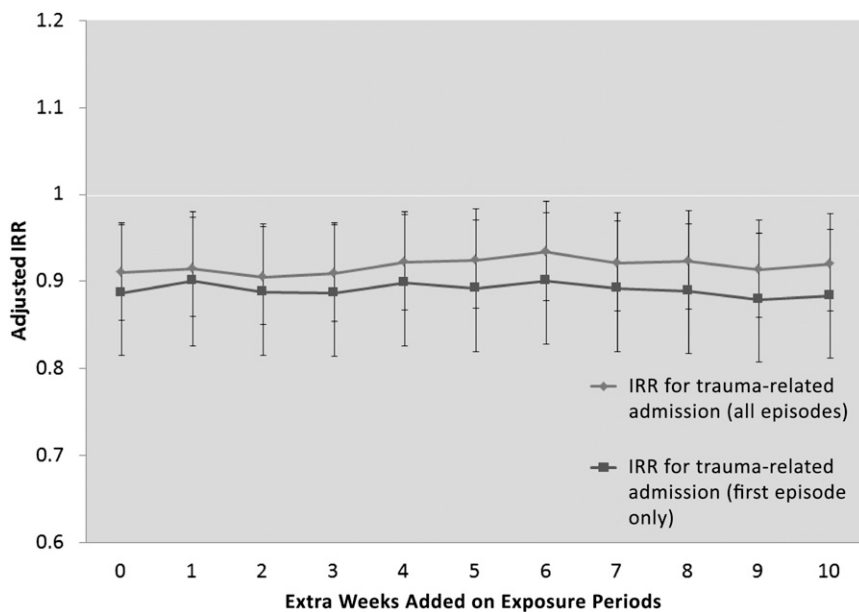


FIGURE 3 Sensitivity analyses on exposure periods by adding 1 to 10 weeks after the end of each exposed period.

male and female participants. A moderate effect of risk reduction was observed (~9% reduction overall). This finding highlighted a decreased risk of trauma-related ED admission as a potential benefit of medication in all patients.

Apart from gender, it has also been unclear whether the benefit of MPH in preventing trauma varies according to age.^{17,20-22,26} Our age-stratified analysis showed that patients aged <16 years had a 7% risk reduction, whereas the group aged ≥16 years had a greater reduction of 32%. The results suggest that the risk reduction in trauma-related ED admission was greater in older adolescents.

This study directly examined the association between MPH treatment and the risk of trauma-related ED admission. Unlike previous studies, our study addressed issues not fully accounted for in the current literature. Two studies^{20,21} compared modified-release MPH and normal-release MPH whereas another²² compared MPH, mixed amphetamine salts, and atomoxetine. The first 2 studies reported that patients receiving modified-release MPH were less likely to present to ED than patients receiving normal-release MPH. Both studies, however, failed to address confounding factors such as duration of treatment. Furthermore, they could not address the key

TABLE 4 SCCS Analyses for Association Between MPH and ED Admissions: Results of Sensitivity Analyses

Variable	IRR	LCL	UCL	P Value
Pre-exposure period included				
All episodes	0.90	0.84	0.95	<.01
First episode only	0.89	0.82	0.97	<.01
6-mo age band				
All episodes	0.92	0.86	0.97	<.01
First episode only	0.89	0.82	0.97	<.01
Patients with >1 prescription				
All episodes	0.91	0.85	0.96	<.01
First episode only	0.87	0.80	0.95	<.01

LCL, 95% lower confidence limit of IRR; UCL, 95% upper confidence limit of IRR.

question of whether ADHD treatments reduced trauma-related ED admissions. The third study²² focused on the cost and resource utilization of 3 different treatments in adult patients with ADHD. However, the association of trauma-related ED admissions and ADHD treatment was not their primary objective.

Leibson et al¹⁷ conducted the first study to compare median frequencies of ED visits per year between treated and nontreated patients. They studied 313 patients from the Rochester Epidemiology Project medical records linkage system with follow-up period to 18 years. Patients on treatment had a lower median frequency of ED visits (0.16 per year) compared with those off treatment (0.4 per year). However, the authors acknowledged study limitations, including a small sample size and single geographic setting (Rochester, Minnesota), hence limiting external generalizability. In addition, the age of subjects and seasons, which are important factors affecting ED admissions, were not adjusted for in the study.⁴¹ Furthermore, confounding may have resulted from unmeasured factors that are associated with ADHD treatment and ED admissions, such as change in severity of ADHD, parental supervision, and personal behavior. Nonetheless, these studies reported an indication of potential association, which warrants further exploration.

Raman et al²⁶ used The Health Improvement Network database to investigate the association between stimulant treatment and injury. There are several potential problems with the information from this database: the injury codes were not validated and the diagnosis date recorded on the database was dependent on the discharge summary from the hospital to the corresponding general practitioner. Because the accurate timing of exposure and outcome is vital when using the SCCS design,

these issues may have affected the accuracy of the study's findings. Our study addresses these issues. We used SCCS, in which unmeasured confounders that are constant over time were controlled by study design. In contrast to previous studies, our data on outcomes came directly from ED admission records from CDARS, a hospital database in which the precise event date was available. Consequently, we were able to avoid issues of data entry delay for the reported ED admissions in the primary care database, which may affect accuracy of the IRR estimate.

There are a number of limitations to our study, however. The first arises from the definition of the trauma-related ED admission outcome. It is standard operating procedure for ED physicians in the Hong Kong Hospital Authority to classify ED admission as "trauma" or "non-trauma." Although previous studies on trauma-related ED admissions have demonstrated the reliability and validity of these records,³¹⁻³³ detailed diagnostic codes for trauma are not available. As a result, we were unable to identify the actual type of trauma (eg, head trauma, hip trauma). However, our aim was to investigate whether MPH treatment was associated with trauma-related ED admission overall;

therefore, the type of trauma was only of secondary interest.

We applied the SCCS design, in which participants were those prescribed MPH. The study results may thus not be generalizable to those with ADHD but were not prescribed MPH. Furthermore, patients prescribed both MPH and atomoxetine were excluded, which may have excluded patients with more severe ADHD.

Data from private medical practitioners were not available in CDARS. Thus, we were not able to include prescriptions from the private sector, which may potentially cause misclassification of the exposed period. However, in our previous study, the public sector was the main provider of specialist care,⁴² with very few private child psychiatrists in Hong Kong.^{9,43} Patients with long-term neurodevelopmental disorders such as ADHD are generally treated in the public health care sector,⁹ and, therefore, the vast majority would be included in this study. Similar to other pharmacoepidemiologic studies using automated databases, CDARS provides prescription data but not adherence (compliance) to medication, which may lead to misclassification of exposure periods. However, the potential for noncompliance in the sensitivity

analysis were addressed, and the results were robust. Moreover, such misclassification would tend to mask any protective effect, leading to a relative risk biased toward 1.

CONCLUSIONS

Our study findings support the hypothesis that MPH is associated with a reduced risk of trauma-related ED admission in children and adolescents of both genders. This outcome has important clinical, resource utilization, and public health implications. Trauma prevention should be considered in the broader clinical assessment of MPH risks and benefits aside from the traditional consideration of improving academic performance.

ACKNOWLEDGMENTS

We thank the Hong Kong Hospital Authority for access to the data from CDARS for research purposes. We thank Miss Wallis C.Y. Lau from Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong for cross checking the analysis. We also thank Mrs Lisa Wong for editing and proofreading the manuscript.

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: Dr Chan reports grants from Janssen (a division of Johnson & Johnson), BMS, Pfizer, The Research Grant Council (RGC, Hong Kong), received for other work. Dr Coghill reports grants and personal fees from Shire and Vifor; personal fees from Janssen-Cilag, Lilly, Novartis, Flynn Pharma, Medice, and Oxford University Press, received for other work. Dr Douglas reports personal fees from GSK and Gilead, received for other work. Prof I.C.K. Wong reports grants from The Research Grants Council (RGC, Hong Kong) (during the study) and grants from Shire, Janssen-Cilag, Eli Lilly, the European Union FP7 programme, received for other work. The other authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Funding received from the Research Grants Council (RGC, Hong Kong) under grant agreement number 781913 for the study (Effects of Attention Deficit Hyperactivity Disorder [ADHD] pharmacotherapy on hospital accident and emergency admission due to injury-related events [ATHAN]).

POTENTIAL CONFLICT OF INTEREST: Dr Coghill reports grants and/or personal fees from Shire, Janssen-Cilag, Novartis, Flynn Pharma, and Medice; and Prof I.C.K. Wong was a member of the National Institute for Health and Clinical Excellence ADHD Guideline Group and the British Association for Psychopharmacology ADHD Guideline Group and acted as an advisor to Shire. The other authors have indicated they have no potential conflicts of interest to disclose.

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ASTITCH IN TIME OR IN RUNNING: *I am not a natural runner. While I periodically run 5 to 10 kilometers, it is never easy for me. Often I develop a sharp pain in my side and have to slow my pace. The pain, commonly referred to as a 'stitch,' has always been a bit mysterious to me. After all, I never get stitches cycling regardless of how hard or long I ride. It seems that stitches, like hiccups, are mysterious not only to ordinary people but medical professionals as well.*

As reported in The Wall Street Journal (A-Hed: November 2, 2014), there has been little research on the condition and no consensus as to the cause. Some suggest that the stitch, also known as exercise-related transient abdominal pain (ETAP), may be due to a multitude of factors, diaphragmatic irritation, or peritoneal irritation. Regardless of the cause, ETAP has been around a long time. Pliny the Elder described ETAP in the first century AD, as did Shakespeare in The Tempest. Evidently, all types of athletes can develop ETAP, including swimmers, runners, equestrians, basketball players, cyclists, and even motorcycle riders. ETAP is more common in younger than older athletes. Regardless of the cause, the effect is the same – athletic performance can be impeded. For some, the pain is fleeting, but others can only control the pain by slowing or entirely stopping the pace of exercise.

The good news is that ETAP is not associated with any long term problems or disability. Prevention seems the key. Some data suggest that core strengthening helps prevent ETAP as does avoidance of fatty or sugary foods immediately before exercise. As for me, I will concentrate on prevention – particularly as Pliny the Elder's advocated treatment (an aural injection of she-goat urine) seems worse than the condition.

Noted by WVR, MD

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