Association between methylphenidate treatment and risk of seizure: A population-based self-controlled case series study

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Research in context

Evidence before this study

We searched PubMed for studies published from January 1, 1966, to January 30, 2020, with the following terms: (methylphenidate OR stimulant OR ritalin) AND (seizure OR epilepsy) AND (attention deficit hyperactivity disorder or ADHD or hyperkinetic disorder). The search yielded 160 articles.

We excluded articles that we deemed to be not relevant on the basis of their titles. We reviewed abstracts of the remaining articles to identify potentially relevant articles and scanned reference lists of relevant articles. The primary criteria was that the study reported the risk of seizure as adverse event related to methylphenidate treatment. Four studies were identified; three from the US and one from Sweden. None of these previous studies found evidence for an increased risk of seizures associated with the use of ADHD treatment over six months or longer follow-up periods.

Added value of this study

In this population-based self-controlled case series study of 269 patients with incident seizure identified from 30 453 patients prescribed methylphenidate medication, the risk of incident seizure was 4-fold higher during the 30-day period after methylphenidate treatment was first initiated, which returned to baseline levels during the ongoing treatment.

Implications of all the available evidence

These findings indicate there is an increased risk of seizures associated with methylphenidate following medication initiation. Although this elevated risk was not sustained with long-term use, the acute increased short-term risk should be considered and discussed with patients and families in clinical practice.

Abstract

Background: Patients with attention-deficit/hyperactivity disorder (ADHD) are at increased risk of seizures. Stimulant medications such as methylphenidate are the most commonly prescribed treatment for ADHD, but the association between their therapeutic use and the risk of seizures is unclear. This study aims to investigate the association between methylphenidate treatment and the risk of seizure in patients with ADHD.

Methods: We conducted an observational study using population-based, electronic medical record database from the Hong Kong Clinical Data Analysis & Reporting System to identify individuals aged 6 to 25 years who were treated with methylphenidate between January 1, 2001, and December 31, 2017. Patients treated with methylphenidate who had seizures were included in the subsequent analyses and a self-controlled case series design was used to control for time-invariant patient characteristics. Additional analysis was conducted using skin infection as a negative control outcome. Relative incidence of seizure during periods when patients were exposed to methylphenidate was compared with non-exposed periods.

Findings: Among 29,604 patients prescribed methylphenidate, 269 had incident seizures during the study period. The mean (SD) age at baseline was 6·66 (2·01) years and 199 (74·0%) were male. The overall incidence of seizure during methylphenidate treatment was 4·4 per 10 000 patient-years. An increased risk of seizure was detected during the 30-day period following initiation of methylphenidate compared to non-exposed periods, with an incidence rate ratio (IRR) of 4·01 (95% CI, 2·09-7·68). No increase in risk was identified during the 31 to 180 days of the treatment (IRR, 1·13; 95% CI, 0·56-2·25) or during subsequent treatment (IRR, 1·38; 95% CI, 0·92-2·07). No increased risk was identified in all risk windows for the negative control outcome analysis. No patient died due to seizure.

Interpretation: The incidence of seizures was higher in the period immediately after the start of the methylphenidate treatment compared to the non-exposed period. The risk returned to baseline levels during continuation of methylphenidate treatment. The association between methylphenidate treatment and seizures immediately following initiation of medication can be seen as a potential safety signal. Monitoring of

neurological outcomes in methylphenidate users is essential when they first start on medication is recommended.

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Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common neurodevelopmental disorders in children, with a worldwide prevalence of 5% to 7%.[1,2] In Hong Kong (HK), ADHD prevalence is estimated at around 6·4% in children and adolescents.[3] Guidelines for ADHD from North America, the UK, and Europe recommend the use of stimulant medications, such as methylphenidate (MPH) and amphetamines, when pharmacological intervention is considered appropriate for management of ADHD and that MPH is recommended as a first-line therapy in many countries.[4-8] Recent studies have shown the prevalence of ADHD medication is increasing over the past decade, and that MPH is the most commonly prescribed ADHD medication in many countries.[9,10]

Although MPH is effective for managing ADHD symptoms,[11] there have been long-standing concerns that stimulant therapy may have negative impacts on neurological functioning and in particular that it may lower the seizure threshold increasing the risk of seizures and seizure-related morbidities.[12,13] In 2007, the European Commission requested a referral to the Committee for Medicinal Products for Human Use (CHMP) for MPH because of safety concerns,[13,14] and in 2009, the CHMP concluded that further research on its safety is needed.[14]

Recent population-based studies have investigated the risk of seizures related to ADHD treatment.[15-18] Although none of them found evidence for an increased risk of seizures associated with the use of ADHD treatment, all of these studies accessed the association over a relatively long period with six months or longer follow-up periods.[15-18] However, when evaluating drug-induced acute adverse drug reactions, it is essential to take temporal relationships into account.[19] The risk of an adverse drug reaction is usually greatest during the period immediate after the initiation of offending drug. Therefore, it is important to specifically evaluate seizure risk in the period immediate after the initiation of ADHD treatment.[20] Furthermore, during periods in which individuals were taking ADHD medication, they were also more likely to be receiving and complying with other treatments for their psychiatric comorbidities,[21] in particular, antipsychotics and antidepressants medications, that could potentially lower seizure threshold,[22] and which are often prescribed concurrently with ADHD treatments in clinical practice.[23] The current literature does

not provide clear evidence on the potential interaction of these medications with MPH regarding to the risk of seizure.

Seizures must be considered as serious adverse effects. A better understanding of the MPH-related seizure risk in ADHD patients is necessary to prevent these serious adverse effects. To address these issues we conducted a self-controlled case series (SCCS) analysis of a population-based cohort to assess the association between MPH exposure and seizures in different risk periods and interaction between antidepressants and antipsychotic medications.

Methods

Data source

This study used data from the Clinical Data Analysis and Reporting System (CDARS), an electronic health record database developed by the HK Hospital Authority, a statutory body that manages all public hospitals and their ambulatory clinics in HK. The HA health services is available to all HK residents (over 7·4 million people) and cover about 80% of all hospital admissions in HK.[24] Data from CDARS has been validated and used in a variety of epidemiological studies, including studies of medication safety study on seizure[25] and of MPH and other health outcomes.[21,26,27] Patient-specific data in CDARS includes diagnoses, information on hospital admissions and discharges, payment method, and prescription and dispensing information.[28] The study protocol was approved by the Institutional Review Board of the HKU/HA HK West Cluster.

Self-controlled case series design

We investigated the association between MPH use and the risk of seizure using the SCCS study design.[29] In this design, used previously to investigate the effects of MPH on trauma, psychosis and suicide risk,[21,26,27] patients serve as their own control and comparisons were conducted within-person in a population of individuals who have experienced both the outcome and exposure of interest.[29] Incidence rate ratios (IRR) are derived by comparing the rate of events during periods of medication exposure with the rate during all other observed time periods (i.e. without medication) using conditional Poisson regression. A major advantage of the SCCS design over the classic design is that it implicitly controls for all the measured and unmeasured time-

invariant confounders that vary between individuals, such as genetic factors, socioeconomic status and underlying disease severity.[29] Furthermore, we adjusted for time-varying factors, such as age and season, which are known to affect MPH treatment prescribing.[9,30] Concurrent use of antidepressants and antipsychotics were also adjusted as time-varying factors.

Case identification

Individuals aged 6 to 25 years who had received at least one MPH prescription and experienced an incident seizure event, i.e. first record of non-febrile seizure or epilepsy, during the study period (1 January 2001 to 31 December 2017). Individuals with previous records of seizure or epilepsy before the study period were excluded. The outcome codes were identified through the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic codes: 333·2, 345, 649·4, 780·39, 779. Only MPH and atomoxetine are licensed for the treatment of ADHD in HK,[9] and atomoxetine has a different pharmacological action from MPH; therefore, if an individual received both MPH and atomoxetine, the observation periods were ended at the date of receiving atomoxetine treatment to avoid co-prescribing situations that would affect comparisons.

We commenced follow-up at 6 years of age, as MPH is not recommended for younger children.[31] Also, we defined the follow-up to age 25 years as there has been an increasing trend of MPH use in college-aged young adults up to age 25 years, whereas there were not many of those above 25 received MPH.[32] As the aim of this study was to investigate the association between MPH and seizures all MPH users, regardless of the presence of a formal diagnosis of ADHD, were included. Individual observation periods began on 1 January 2001 or on the patient's 6th birthday, whichever was later, and ended on 31 December 2017 or on the patient's 26th birthday or on the registered date of death, whichever was earlier.

Exposures and outcomes

For each included participant, all MPH prescriptions and non-febrile seizure events were identified. All MPH formulations and all strengths were included in the analysis. Exposed periods were defined as time receiving medication, with the duration between prescription start and end dates recorded in CDARS for each prescription. More than 99% of the prescriptions recorded the intended start and end dates. Daily

dosages and the quantity prescribed were used to determine the duration of treatment if the prescription end date was not available. Median values for exposure duration were imputed when the above information was missing. We divided patient time into 5 discrete windows: absence of MPH (baseline period, including patient-time before starting and after completing MPH exposure), 90 days before the first MPH exposure (pre-exposure period), first 30 days of MPH use, days 31 to 180 of MPH use and subsequent MPH use (> 180 days). We did not assume that participants received continuous treatment on initiation of MPH, because clinicians may offer drug holidays to patients with ADHD during school holidays and treatment may be stopped and started for various other reasons.[21] The pre-exposure period was defined as the time before the first MPH prescription; thus, there were no pre-exposure periods before the second or subsequent MPH treatments. The study design and timeline for a single hypothetical participant is given in Figure 1a. The corresponding date of the seizure was identified as the event date. In SCCS designs, there should be no censoring by the outcome of interest as this would violate the assumptions and invalidate the results.[29]

Statistical analysis

Risk of incident seizure

The association between MPH treatment and risk of seizure was evaluated by comparing the rate of seizure during exposure periods with that during baseline periods. Adjusted IRR and the corresponding 95% confidence intervals (CIs) were calculated using conditional Poisson regression and adjusted for: age in 1-year bands, season, and use of antidepressants and/or antipsychotics. A 90-day pre-exposure period was added to take into account the possibility that a recent seizure event may affect the likelihood of the MPH treatment, which in turn may introduce bias into the risk estimate during the treatment. We separated the first 30 days and days 31 to 180 of MPH use to allow the detection of any temporary change in the IRR of the risk of seizure. Although both age and gender effect were addressed in our primary analysis, previous studies looked into MPH and other health outcomes suggested potential difference in the effect of MPH with respect to age and gender.[21,26,33] Therefore, stratified analyses were conducted to evaluate the effect by sex and age (below 12 years and 12 years or above). The interaction between MPH and other psychotropic medications on the seizure risk were further evaluated with the interaction model that

included all combinations of MPH concurrent with i) antidepressants and ii) antipsychotics.

Risk of recurrent seizure

Further analyses investigated the association between MPH and the risk of recurrent seizures. Patients with at least two seizure events where the incident and second seizure events were recorded during the individual observation period were included. The follow-up period began on the 30-day after the incident seizure,[25] and the IRR of subsequent seizures were evaluated during the exposure and non-exposure periods using the same analysis as those outlined above. The study design and timeline for a single hypothetical participant are given in Figure 1b.

A significance level of 5% was used in all statistical analyses. SAS version 9·4 (SAS Institute Inc.) was used for data manipulation and analysis. With reference to the equation developed by Musonda et al.,[34] the sample size required, at 5% level of significance and 80% statistical power, for 50% increased risk of MPH will be 241 cases. Multiple comparisons are not adjusted in the analyses as seizure is a serious adverse event, it is more important to be cautious and not to increase type II error. Also, not making adjustments for multiple comparisons is preferable in population-based epidemiological study.[35] Post-hoc analysis adjusted for antiepileptic drugs and benzodiazepines as time-varying variables were conducted.

Sensitivity and negative control analyses

Sensitivity analyses were conducted to test the validity and robustness of the initial study results: (1) different drug non-adherence scenarios; (2) removing patients with diagnosis of febrile seizures; (3) redefining the start observation period to January 1, 2001, the sixth birthday of the patient, the first observed date of ADHD diagnosis, or the first date of methylphenidate treatment, whichever occurred last; (4) restricting to incident user of MPH treatment; (5) more than 120 days of methylphenidate exposure. (6) A negative control analysis to validate our results using skin infection as an alternative outcome (ICD-9-CM: 680-686). (7) To further assess the potential impact of any unmeasured confounding by computing the E-value, defined as the minimum strength of association that an unmeasured confounder would need to have with both treatment and outcome, conditional on the measured covariates, to explain away an

observed association.[36] Detail description of sensitivity analyses and the negative control analysis are in eAppendix 1.

Results

Among 29 943 patients with MPH prescriptions, 339 had seizures before the observation period and were not included in the analysis, as per protocol. A total of 269 patients had their incident seizure within the observation period (eFigure 1); of these, 199 (74·0%) were male and 70 (26·0%) were female. The mean (SD) age at commencement of observation was 6·66 (2·01) years (range, 6-22·5 years), and the mean duration of the follow-up per participant was 10·69 (4·44) years (Table 1). The average MPH exposure was 2·19 (2·49) years per participant. The median length of each prescription was 70 days (interquartile range [IQR], 35-105 days). Of the included participants, 157 (58·4%) had ADHD with a median age at diagnosis of 9·2 years (IQR, 7·82-11·70 years). During the study period, 32 (11·9%) and 72 (26·8%) patients had at least one prescription for antidepressants and antipsychotics respectively. Recorded psychiatric comorbidities for these patients are reported in eTable 1 in the Supplement. Of the 269 incident seizure events, 69 occurred during the MPH treatment period and 200 occurred during off-treatment periods (Table 1). The median age at the event was 9·69 years (IQR, 7·62-12·99 years) (eFigure 2 in the Supplement). Among 29 604 patients with MPH, the overall incidence of seizures during the MPH treatment was 4·4 per 10,000 patient-years. The crude incidence of seizures in the different risk windows is summarised in Table 2. No participants in the SCCS analysis died during the study period.

The analysis indicated association between the use of MPH treatment and seizure (Table 2). After age, season and the use of other psychotropic medications were adjusted, no increased risk of seizure was found in the 90-day period before the initiation of MPH treatment (IRR, 1·60; 95%CI, 0·88-2·92). However, an increased risk of seizure was detected during the first 30-day of MPH treatment (IRR, 4·01; 95%CI, 2·09-7·68). Non-significant IRR was observed during 31-180 days of MPH treatment (IRR, 1·13; 95% CI, 0·56-2·25) and remained at similar level during the prolonged treatment (IRR, 1·38; 95%CI, 0·92-2·07) (Table 2). Similar effects were observed in both sex and age stratified analyses, with no significant difference between the IRRs in all risk windows (eTable 2). Also, no increased risk was

identified when treated with antidepressant and antipsychotic treatments (IRR for antidepressants, 0·67; 95%CI, 0·15-3·07; IRR for antipsychotics, 1·14; 95%CI, 0·61-2·13). Further analysis showed no interactions between MPH, antidepressants and antipsychotics (Table 3). Our results identified 69 patients had seizure during MPH treatment period (Table 2), 11 (15·9%) of them had recurrent seizures with 7 events occurred during subsequent MPH treatment and 1 event occurred during a treatment period with MPH, antipsychotics and antidepressants together (eTable 4). When using skin infection as outcome in the negative control analysis, no association was found in all risk windows (Table 2). The additional sensitivity analyses did not change the overall findings and E-value analysis indicated that the results are unlikely to be affected by unmeasured confounding factors. (eFigures 3-6 and eAppendix 2 in the Supplement). Post-hoc analysis adjusted for antiepileptic drugs and benzodiazepines as time-varying variables showed similar results (eTable 5).

Of those 269 individuals with incident seizure events within the observation period, an increased risk of recurrent seizure was detected during the first 30-day of MPH treatment (IRR, 5·00; 95%CI, 1·09-22·96). Nevertheless, the increased risk of recurrent seizures was not significant during subsequent use of MPH treatment (IRR, 2·09; 95% CI, 0·85-5·13) (Table 4).

Discussion

We observed in a 4-fold increase in the incidence of MPH-related seizures during the first month of treatment, but no increase in the risk of seizure with long-term MPH treatment. The findings suggest that an acute but transient increase in the risk of seizures during the initial period of prescribing. However, the overall risk of seizure during MPH treatment (69 cases, incidence of 4·4 per 10,000 patient-years) was remained low.

For many years, there has been much concern about the use of stimulants such as MPH that may increase the risk of seizures. Seizures generally occur as a result of either inadequate inhibitory neurotransmitter influences (e.g., gamma aminobutyric acid [GABA]) or excessive excitatory stimulation (e.g. glutamate) although many other neurotransmitters, including dopamine, play a role.[37] In view of the pharmacological mechanism of action for stimulant medications, initiation of MPH, which inhibits the dopamine transporter elevates synaptic dopamine levels,[38] that in

turn mediates GABAergic and glutamatergic neurotransmission, may increase excitatory of the neural activity and lower the seizure threshold soon after.[39] However, most drug-induced seizures are self-limited and do not cause permanent sequelae,[37] as observed in this study, the IRR at the first 30-day was 4·01 where the IRR dropped to 1·13 and 1·38 for 31 to 180 days of MPH and subsequent MPH which indicated that no increased risk of in the long-term use of MPH.

The safety of neurological and psychiatric adverse effects are some of the major concerns regarding the long-term use of MPH.[40] Although short-term risk of seizure have not been well studied previously, recent evidence suggests that the long-term use of stimulant treatments is safe. Wiggs and colleagues[18] examined health insurance claim data in the United States to investigate the risk of seizures in individuals aged 5 to 64 years with newly diagnosed ADHD or prescribed ADHD medication. Comparing non-medicated and medicated months among all ADHD patients, the odds of seizure occurrence were approximately 40% lower during medicated months. They also found that the prescription of ADHD medications for two cumulative years was not associated with seizure risk. Another similar study[17] that investigated the association between ADHD medication and the risk of seizures in individuals with epilepsy in Sweden found no differences in the risk of seizure during the 24 weeks before and after the initiation of ADHD medication, which was about 27% lower during the treatment period. Partly consistent with these results, the current study did not identify an increased risk of seizure during the long-term use of MPH. However, neither of the earlier studies[17,18] looked for an acute increase in seizure risk following the initiation of the ADHD treatment. It is also important to note that these previous studies reported lower risk of seizures during treatment periods.[17,18] This is, however, unlikely to be explained by a direct pharmacological neuroprotective effect. One potential explanation could be that patients with ADHD who are on MPH are less likely to suffer injuries, in particular traumatic brain injury,[39] during the MPH treatment period,[26,33 41] Given that traumatic brain injury could be a common aetiology for seizures,[42,43] lowering the risk of head injury could lower the likelihood of having seizures. This may have masked the acute transient adverse effects of initiating MPH treatment. Furthermore, participants in our study were seizure-naïve children and adolescents, and the differing age groups included in the studies makes it difficult to compare our results directly with these studies.[17,18] Over 95% of

population in HK is of Chinese descent; previous studies have mainly been conducted in the Caucasian population so we cannot exclude the possibility of genetic differences lead to different response.

It has been suggested that both antidepressants and antipsychotics are associated with increases in seizure rates.[44,45] In this study, reassuringly, we found no increased risk of incident or recurrent seizure occurrence when antidepressants and/or antipsychotics were used concurrently MPH treatment.

With the results observed in this study, one of the important questions yet to be answered is whether the seizures occurred following the initiation of MPH treatment continued afterwards. Among patients who had their incident seizure during MPH treatment period, 58 of them (84·1%) do not have further seizures and only 11 (15·9%) of patients had recurrent seizures. Thus we do not have an adequate sample size to investigate the subsequent risk of seizures in these patients. Up to September 2019, the European Medical Agency EudraVigilance database of adverse drug reaction reports has 423 recorded seizure cases and 121 epilepsy cases related to the use of MPH.[46] Of those with outcomes reported in the database (253 in seizure cases and 66 in epilepsy cases), 207 in the seizure cases (81·8%) and 55 in the epilepsy cases (83·3%) were reported to be recovered or resolved (efigure 7). With a similar rate observed in our study, it suggests that about 80% of patients who had seizures during MPH treatment may not have further seizures.

The half-life of MPH is relatively short (2.5-3.5 hours, a little longer for extended-release formulations). Based on this, some would argue that the first dose of each day constitutes a brand new exposure. If this is so, the risk of seizure should be more or less similar throughout MPH treatment and if a patient were to stop the medication for any length of time (e.g. school breaks) would there be an increased risk of seizure upon restarting. Our results suggested the otherwise, that the incident seizure risk only attained during the first 30 days of treatment. This suggests MPH may have a heterogeneous effect on the risk of seizure throughout the treatment period. However, further study is warranted to evaluate this corresponding risk in detail.

Strengths and Limitations

The cases for the SCCS analysis were extracted from a population-based cohort, representative of HK population, with a within-individual design, which renders the underlying differences between people less important. Accurate ascertainment of MPH treatment and seizure was possible by linking data in the CDARS within primary, secondary, and tertiary healthcare services. On the other hand, the validation analysis, using skin infection cases as the negative control, found no evidence to suggest that MPH treatment is associated with skin infection in all exposure windows as hypothesised. This finding further strengthens our conclusion that the increased risk of seizure in the first month is associated to MPH medication rather than other factors that vary with time. Our findings also provide detailed investigation on the risk of seizures when MPH is used concurrently with other psychotropic medications that substantially expands on the current literature. While ADHD itself is associated with an increased risk of seizures,[18,47] the short-term increase in risk following initiation of MPH treatment should not be neglected in clinical practice.

There are limitations to this study. First, although we have identified an increased risk of seizure during the first 30-day of MPH treatment, we cannot exclude the possibility that the decision to start MPH treatment could potentially raise clinical attention in the patient and thus increase the chance of detection. This may potentially confounded the risk estimates. However, we have calculated the E-value in our sensitivity analysis that our estimate could be explained away by such a confounding effect if it is associated with both the treatment and the outcome by a risk ratio of 7·48-fold each, on top of the confounders that were addressed, but weaker confounding could not do so. Furthermore, all seizure episodes identified in our study had received care in hospital. Therefore, even if we raised the sensitivity to detect seizure when the patients just started MPH, seizure did occur during that period of time. It is unlikely that detection bias could fully explain the results obtained in our study. Second, CDARS does not contain data from the private healthcare sector. Therefore, it is possible that patients were prescribed MPH by a private clinician, which would not have been recorded in CDARS. However, we anticipate that this is unlikely because the HA hospitals and clinics provide the majority of the specialist care in HK[48] and children with long-term neurodevelopmental disorders such as ADHD are likely to seek treatment from public hospitals.[48]

Similar to all database studies, CDARS provides data on drug prescriptions but not drug adherence, which may lead to misclassification of exposure periods. Additionally, as we had a comparatively long follow-up period, there could be time-varying confounding factors that may influence the study results. The various sensitivity analyses that explored the potential effects of non-adherence and the observed time-varying confounding factors were consistent with the primary analyses suggesting that this is unlikely.

Patients developed seizures with methylphenidate were mostly young children (median age at the event was 9·7 years). It is important to determine if there were other risk factors e.g. prematurity, traumatic birth histories, early central nervous system illness (e.g. meningitis, encephalitis) and head trauma which predisposed these patients to seizures and that may modify the effect of MPH in these vulnerable patients and not others. Although these factors were unable to be identified in the current study, they will not affect our study results based on the self-controlled nature of the study design. However, further study is necessary to investigate this important issue.

We observed not many cases were on both MPH and antidepressants in our study. As mentioned, the interaction between MPH and antidepressants is clinically important, that have not been investigated in previous study. The small number of cases may reflect the situation in real life practice that the absolute risk is not high. However, further study with a larger size is warranted provide more in-depth investigation.

The dosages of MPH treatment and type of seizures have been considered as possible moderating factors in the association between MPH use and the risk of seizure. However, information on the type of seizure is not available in the diagnosis records. There is no difference for the median daily dose in those without seizure (median=20mg; IQR: 15-30). The dosage of MPH use in Hong Kong is generally lower than most the western countries but there was no difference in dosage between those with and without seizure in our study. On the other hand, the prescribed dosage will be highly correlated to the exposure time windows, as the dosage is usually lower when the patients just initiate MPH. Among the 269 patients included in the analysis, the prescribed dosage in the first prescription, with a median of 10mg (IQR: 10-15), were significantly lower than that in subsequent prescription (median of 20mg; IQR: 15-35), with median two-sample test $p<0.0001$, and therefore was not included in the

analysis to avoid collinearity. Future studies, preferably with brain imaging and details dosage data, would be beneficial in investigating these potential moderating effects.

Conclusions

The incidence of seizures peaked during the short period immediately after the first 30 days of MPH treatment initiation and returned to baseline levels during the continuation of MPH treatment. Despite the increase in risk observed in the first 30 days of MPH treatment, the overall risk of seizure remain low. The association between methylphenidate treatment and seizures immediately following initiation of medication can be seen as a potential drug safety signal. Monitoring of neurological outcomes in MPH users is essential, especially when they first started the treatment.

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Ethical approval: 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).

Contributors:

KKCM, PI, and ICKW had full access to the aggregate analysis data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. ICKW, KKCM, and PI were responsible for the study concept, and ICKW, PI, and KKCM were responsible for the study design. KKCM, ICKW, and PI were involved in the acquisition, KKCM, and WCYL were involved in statistical analysis. All authors were involved in the interpretation of data. KKCM drafted the manuscript. All authors critically revised the manuscript for important intellectual content.

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Figure 1a: Illustration of Self-controlled Case Series Study Design (Incident Seizure)

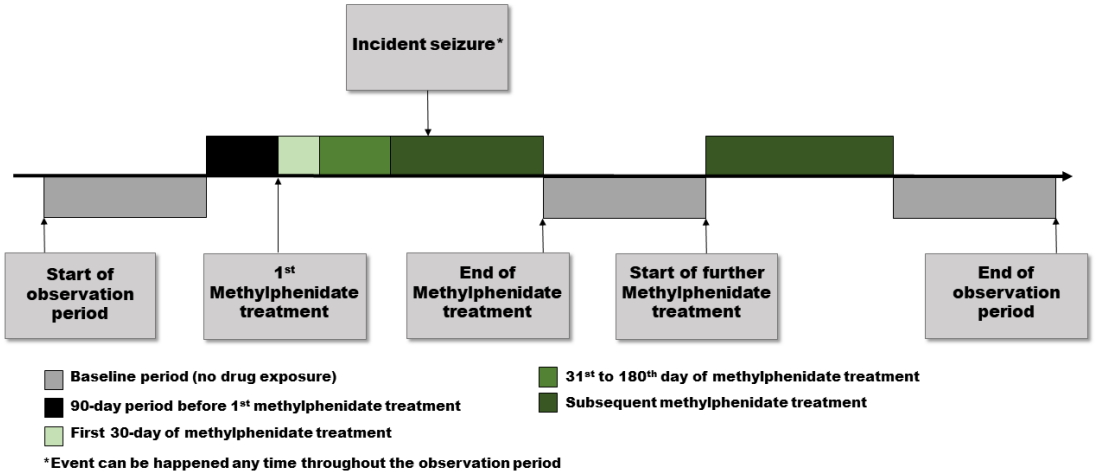

Figure 1b: Illustration of Self-controlled Case Series Study Design (Recurrent Seizure)

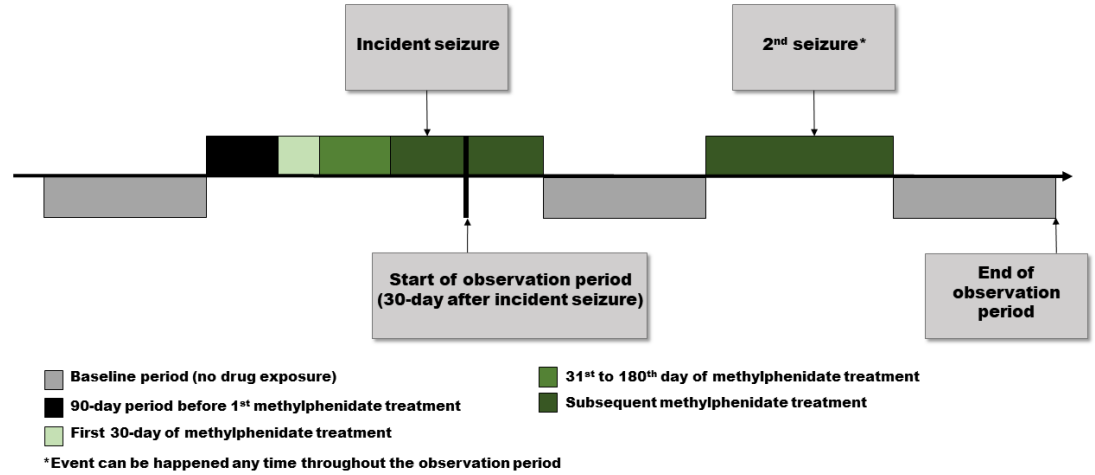

Table 1: Patient characteristics

	No. of Patients	(%)	Mean age at baseline (years)	SD[a]	Median daily dosage (mg)	IQR[b] of daily dosage (mg)	Median length of prescription (days)	IQR of length of prescription (days)	Exposed period		Unexposed period	
									No. of events	Total follow-up time (patient-years)	No. of events	Total follow-up time (patient-years)
All	269	100	6·66	2·01	20	15-30	70	35-105	69	588·9	200	2286·2
Male	199	74·0	6·64	2·06	20	15-35	70	42-107	55	463·2	144	1085·4
Female	70	26·0	6·71	1·90	20	10-30	56	28-96	14	125·7	56	444·2

[a]SD = Standard deviation
[b]IQR = Interquartile range

Table 2 Results from the self-controlled case series analysis

Treatment	Risk window	Number of events	Patient-years	Crude incidence (in 100 patient-year)	IRR*	95%CI		p-value
Primary analysis (n=269)								
MPH	90-day before treatment	12	62·32	19·25	1·60	0·88	2·92	0·12
	First 30-day of treatment	10	20·65	48·42	4·01	2·09	7·68	<0·0001
	31 to 180 day of treatment	9	67·82	13·27	1·13	0·56	2·25	0·74
	Subsequent treatment	50	500·46	9·99	1·38	0·92	2·07	0·12
	No MPH	188	2223·88	8·45	1·00	1·00	1·00	--
Other medications adjusted (as time-varying factor)								
AD	during treatment	2	47·23	4·23	0·67	0·15	3·07	0·61
	No AD	267	2827·90	9·44	1·00	1·00	1·00	--
AP	during treatment	23	326·14	7·05	1·14	0·61	2·13	0·68
	No AP	246	2548·99	9·65	1·00	1·00	1·00	--
Negative control analysis with skin infections as outcome (n=438)								
MPH	90-day before treatment	15	102·70	14·61	1·14	0·67	1·93	0·64
	First 30-day of treatment	6	34·57	17·36	1·36	0·60	3·07	0·45
	31 to 180 day of treatment	12	125·02	9·60	0·75	0·42	1·36	0·35
	Subsequent treatment	87	930·20	9·35	0·87	0·64	1·18	0·37
	No MPH	318	3377·20	9·42	1·00	1·00	1·00	--
Other medications adjusted (as time-varying factor)								
AD	during treatment	5	48·93	10·22	1·32	0·43	4·07	0·63
	No AD	433	4520·76	9·58	1·00	1·00	1·00	--
AP	during treatment	17	166·81	10·19	1·21	0·55	2·65	0·64
	No AP	421	4402·87	9·56	1·00	1·00	1·00	--

AD=Antidepressants
AP=Antipsychotics
MPH=Methylphenidate
IRR=Incidence rate ratio
CI=Confidence interval
*All estimates are adjusted for age in 1-year age-band, seasonal effect and other psychotropic medications

Table 3: Interactions between MPH and other medications and the risk of incident seizure

Combination of drugs	Number events	Patient-time (years)	Crude incidence (in 100 patient-year)	IRR*	95%CI		p-value
n=269							
With MPH (1st 30-day treatment of MPH)							
MPH only (1st 30days)	10	18·51	54·04	4·22	2·20	8·10	<0·0001
MPH(1st 30days) + AD	no event	0·16	0	0·00	0·00	·	1·00
MPH(1st 30days) + AP	no event	1·84	0	0·00	0·00	·	0·99
MPH(1st 30days) + AP + AD	no event	0·15	0	0·00	0·00	·	1·00
With MPH (Subsequent MPH treatment)							
MPH only	52	494·64	10·51	1·24	0·84	1·83	0·28
MPH + AD	no event	7·72	0	0·00	0·00	·	0·99
MPH + AP	7	63·19	11·08	2·07	0·74	5·75	0·16
MPH + AP + AD	no event	2·74	0	0·00	0·00	·	0·99
Without MPH							
AD only	1	17·14	5·83	1·19	0·14	9·85	0·87
AP + AD	1	18·53	5·40	1·06	0·12	9·10	0·96
AP only	15	234·66	6·39	1·10	0·53	2·29	0·80
No medication	183	2015·87	9·08	1·00	1·00	1·00	·

AD=Antidepressants

AP=Antipsychotics

MPH=Methylphenidate

IRR=Incidence rate ratio

CI=Confidence interval

*All estimates are adjusted for age in 1-year age-band, seasonal effect and other psychotropic medications

Table 4: Interactions between MPH and other medications and the risk of recurrent seizures

Combination of drugs	Number events	Patient-time (years)	Crude incidence (in 100 patient-year)	IRR*	95%CI		p-value
n=61							
With MPH (1st 30-day treatment of MPH)							
MPH only (1st 30days)	2	5·10	39·23	5·00	1·09	22·96	0·04
MPH(1st 30days) + AD	1	0·09	1106·82	>999	0·00	·	1·00
MPH(1st 30days) + AP	no event	0·72	0·00	0·00	0·00	·	1·00
MPH(1st 30days) + AP + AD	no event	0·13	0·00	0·00	0·00	·	1·00
With MPH (Subsequent MPH treatment)							
MPH only	14	195·05	7·18	2·09	0·85	5·13	0·11
MPH + AD	no event	6·11	0·00	0·00	0·00	·	1·00
MPH + AP	1	16·34	6·12	1·48	0·05	45·69	0·82
MPH + AP + AD	1	1·08	92·94	178·87	0·63	50908·77	0·07
Without MPH							
AD only	no event	7·35	0·00	0·00	0·00	0·00	·
AP + AD	no event	8·39	0·00	0·00	0·00	0·00	·
AP only	4	84·28	4·75	2·63	0·35	19·96	0·35
No medication	38	519·52	7·31	1·00	1·00	1·00	·

AD=Antidepressants

AP=Antipsychotics

MPH=Methylphenidate

IRR=Incidence rate ratio

CI=Confidence interval

*All estimates are adjusted for age in 1-year age-band, seasonal effect and other psychotropic medications