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Risk of suicidal event with stimulant treatment: a self-controlled case series study

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Key points

Question: Is treatment with methylphenidate associated with an increased risk of suicide attempt?

Findings: In this population-based self-controlled case series study of 154 patients with suicide attempt identified from 25 629 patients prescribed methylphenidate medication, the risk of suicide attempts was 6.5-fold higher during the 90-day period before methylphenidate was first initiated, remained elevated 4-fold during the first 90-days of treatment, and returned to baseline levels during ongoing treatment.

Meaning: These findings indicate that the increased risk of suicide attempts preceding the initiation of medication is not causally related to the effects of methylphenidate. The elevated risk of suicide attempts observed prior to the start of treatment may be linked to emerging psychiatric symptoms which also may lead to medical consultations that were associated with the decision to initiate ADHD treatment.

Abstract: (332 words)

IMPORTANCE: Patients with attention-deficit/hyperactivity disorder (ADHD) are at increased risk of attempting suicide. Stimulants such as methylphenidate (MPH) are the most common treatment for ADHD but the relationship between their therapeutic use and suicide is unclear.

OBJECTIVE: To investigate the association between MPH and the risk of suicide attempt.

DESIGN, SETTING, AND PARTICIPANTS: We used a population-based electronic medical records database from the Hong Kong Clinical Data Analysis & Reporting System to identify individuals aged 6-25 years who were treated with MPH between 2001 and 2015. Individuals who had attempted suicide were included in the analysis. We applied a self-controlled case series design to control for time-invariant characteristics of the patients.

MAIN OUTCOME MEASURE: Relative incidence of suicide attempt during periods when patients were exposed to MPH compared with non-exposed periods.

RESULTS: Among 25 629 patients with MPH prescriptions, 154 had their first recorded suicide attempt within the study period. The overall incidence of suicide attempt during MPH treatment was 9.27 per 10 000 patient-years. An increased risk of suicide attempt was detected during the 90-day period before MPH was first initiated, with an incidence rate ratio (IRR) of 6.55 (95%CI 3.37-12.72). The IRR remained elevated during the first 90-days of treatment with IRR of 3.91 (95%CI 1.62-9.42), before returning to baseline levels during ongoing treatment (IRR=1.35; 95%CI 0.77-2.38). When the risk during the first 90-days of treatment was compared with the 90-days preceding first treatment, the incidence of suicide attempt was not elevated (IRR=0.78; 95%CI 0.26-2.35).

CONCLUSION: The incidence of suicide attempt was higher in the period immediately before the start of MPH treatment. The risk remains elevated immediately after the start of MPH treatment and returns to baseline levels during continuation of MPH treatment. The observed higher risk of suicide attempt prior

to the start of treatment may reflect emerging psychiatric symptoms that trigger medical consultations which result in a decision to begin ADHD treatment. Our results, therefore, do not support a causal association between MPH treatment and suicide attempts.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorders in children with worldwide prevalence rates in school-aged children estimated at 5-7%.[1,2] In Hong Kong (HK), the reported prevalence of ADHD is estimated to be 6.1% in schoolboys and 3.9% in early adolescents.[3,4] ADHD is associated with a diverse range of mental health comorbidities and adverse health, academic and psychosocial outcomes.[5-8] Individuals with ADHD are at increased risk of both attempted and completed suicide, even if comorbid psychiatric disorders are clinically treated.[9]

National guidelines recommend psychostimulant medication for the treatment of ADHD.[10-12] Over the past two decades, the rate of medication use for ADHD has risen rapidly worldwide.[13-18] The prevalence of ADHD medication use in HK is around 1% in school-aged children and adolescents and has increased 14-fold over the past decade.[18] Methylphenidate (MPH), in particular, is commonly used as the first-line therapy. In 2009, the European Medicines Agency conducted a review of the safety of MPH. The review concluded further research on the association between MPH and psychiatric adverse effects, including suicide risk was needed.[19]

Although there has been some concern about a potential association between MPH and suicide-related events,[20] few studies have addressed this issue directly. One Swedish register-based study investigated the risk of suicidal behaviour among MPH/stimulant users.[21] When comparing treated and non-treated ADHD patients, this study found that MPH/stimulant use was associated with a 31% increase in the rate of suicide-related events.[21] However, this analysis did not adjust for potential confounding factors that may account for this association. For instance, a recent study on suicide in school-aged children and adolescents showed that ADHD was over-represented in suicide victims.[22] Previous studies have also suggested that comorbid disorders and familial/social factors may all play an important role in the relationship between ADHD and suicide.[9,23-25]. Indeed, in a follow up analysis in the register study mentioned above, when periods on and off treatment were compared within the same patient, no

increased risk of suicide-related events during the treatment periods was found.[21] Therefore, at present, there is still uncertainty around potential effects of MPH on the suicidal behaviour of patients. Hence the aim of this study was to examine the association between MPH and the risk of suicide attempt.

Method

Data source

This study utilised data from the Clinical Data Analysis & Reporting System (CDARS), an electronic health record database developed by the HK Hospital Authority (HA), a statutory body that manages all public hospitals and their ambulatory clinics in HK. The service is available to all HK residents (over 7.3 million) and covers about 80% of all hospital admissions in HK.[26] Data from CDARS have been validated and used for various investigations of medication safety.[26-33] Patient-specific data in CDARS includes diagnosis, prescription, information on hospital admissions/discharges, payment method, prescription and dispensing information.[34] CDARS contains in-patient, out-patient and emergency room admissions records, anonymised to protect patient confidentiality.

The study protocol was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (Reference number: UW12-136).

Self-Controlled Case Series Design

We used the self-controlled case series (SCCS)[35] study design to investigate the association between MPH and suicide attempt. In this design, used previously to investigate the MPH effects on trauma and psychosis risk,[30,31] each patient serves as their own control.[36] It relies on within-person comparisons in a population of individuals who have experienced both the outcome and exposure of interest.[36] Incidence rate ratios (IRR) are derived by comparing the rate of events during periods of medication exposure with those during all other observed time-periods (i.e. off medication). A major

advantage of this design, over the classic design, is that it controls for potential effect of measured and unmeasured time-invariant confounders that vary between individuals (i.e. genetic factors, disease severity and socio-economic factors). Furthermore, we also adjusted for time varying factors such as age and season which are known to affect MPH treatment prescribing.[37,38] In addition to the standard SCCS analysis, the non-parametric SCCS was also applied to investigate risk changes over the observation period.[39,40]

Case identification

Individuals aged 6 to 25 years who received at least one prescription of MPH and who had made at least one suicide attempt during the study period (01/2001-12/2015) were identified in CDARS. The suicide attempt codes were identified through the diagnostic codes from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) E950-E959.[41] The statistical modelling of the SCCS analysis requires incident cases to fulfil the model assumption;[36] therefore, patients who had made a suicide attempt before the study period were excluded. Only MPH and atomoxetine are licensed for the treatment of ADHD in HK, therefore the observation periods were censored by atomoxetine treatment to avoid co-prescribing situations that could affect comparisons.

The age range was 6-25 years. We commenced follow-up at 6 years of age, as MPH is not recommended for younger children.[42] Recently, there is an increasing trend of MPH use in college-aged young adult (age 18-25).[43] Observation periods commenced on 1st January 2001 or the 6th birthday of the patient (whichever was later); and ended on 31st December 2015, the 26th birthday of the patient, date of receiving atomoxetine treatment, or the date of registered death (whichever was earlier). As the aim of this study was to investigate the association between MPH and suicide attempts, all MPH users, regardless of the presence of a formal diagnosis of ADHD, were included.

Exposures and outcomes

For each included participant, all MPH prescriptions and suicide attempts were identified. All MPH formulations (standard and extended release), and all strengths were included in the analysis. "Exposed periods" were defined as time on medication - the duration between prescription start and end date recorded in CDARS for each prescription. Over 99% of prescriptions had the intended start and end date as recorded in our dataset. Daily dosages and the quantity prescribed were used to determine the duration of treatment if prescription end date was not available. Median values for exposure duration were imputed when the above information was missing. We divided patient time into four discrete categories: absence of MPH (baseline period, including patient-time before MPH and after-MPH exposure); 90-day before the first MPH exposure (pre-exposure period); first 90-day of MPH use; and subsequent MPH use. We did not assume participants received continuous treatment upon initiation of MPH. This is because clinicians may offer drug holidays to ADHD patients during school holidays and treatment may be stopped and started for various reasons.[30,31] The pre-exposure period was defined as the period before the first MPH prescription and thus there were no pre-exposure periods before the second or subsequent MPH periods. A pictorial presentation of the study design and timeline for a single hypothetical participant is given in Figure 1. Suicide attempts were identified through ICD-9-CM codes E950-E959. The corresponding date of suicide attempt was identified as an event date and only the first recorded suicide attempt for each patient was included in the analysis. In SCCS designs, there should be no censoring by the outcome of interest, as this would violate their assumption and invalidate the results.[36] We conducted a validation analysis by reviewing the information in CDARS. Through doing this, we identified that in 153 of 154 (99.3%) cases, the ICD diagnosis code of a suicide attempt was confirmed in the medical records by an emergency room clinician, hospital paediatrician and/or psychiatrist. Consequently, the risk of misclassification is considered to be low.

Statistical Analysis

The relationship between MPH treatment and suicide attempts was calculated by comparing the rate of suicide attempt during exposure periods to that during baseline periods. Adjusted IRR and the corresponding 95% CIs were calculated using conditional Poisson regression, adjusting for age, in one-year bands, and season. A 90-day pre-exposure period was added to take account of the possibility that the suicide attempt itself may impact on the likelihood of MPH treatment, which in turn may introduce bias into the risk estimate during treatment. We separated the first 90-day of MPH use to allow the detection of any temporary change in the IRR of suicide attempts, and we also compared the rate of suicide attempts between pre-exposure period and the MPH exposed periods. To investigate if emergent psychiatric disorders could lead to MPH treatment, post-hoc analyses were conducted, employing the same setting as the original analysis, to test the association between MPH treatment and other psychiatric conditions (ICD-9-CM: 290-319). A significance level of 5% was used in all statistical analyses. SAS v9.4 (SAS Institute) and R v3.3.1 (www.R-project.org) were used for data manipulation and analysis.

Sensitivity Analyses

Sensitivity analyses were planned to test the validity and robustness of the initial study results. Specifically analyses to test the effects of; 1) different drug non-adherence scenarios; 2) restricting the sample to a 6-month age band; 3) of more than 10 weeks of MPH exposure; 4) removing patients with a diagnosis of substance misuse/dependence; 5) restricting observation periods to the date of prescription of any antidepressant or antipsychotic medications; 6) removing patients where event occurred on the first day of prescription; 7) of redefining the observation period to 1st January 2001, the 6th birthday of the patient, the first observed date of ADHD diagnosis or the first date of MPH treatment, whichever occurred later and 8) restricting to incident MPH users only. The details of these can be found in eAppendix 1.

Results

Among 25 629 patients with MPH prescriptions, 19 had attempted suicide prior to the observation period and were therefore removed from the analysis, as per protocol. 154 had their first recorded suicide attempt within the observation period (eFigure 1), of which 111 were male and 43 were female. The mean age at commencement of observation was 7.15 years (range from 6 to 16.47) and the mean duration of follow-up per participant was 12.15 years. Mean MPH exposure was 2.22 years per participant. The median length of each prescription was 70 days and 85% of these prescriptions were short-acting MPH. Out of a total of 154 patients, 112 (72.7%) had an ADHD diagnosis, and the median age at diagnosis was 10.4 years (interquartile range [IQR] 8.3 to 13.4). Of the 154 patients, 72 had at least one prescription for an antidepressant or antipsychotic during the study period in which 17 of them started on an antidepressant or antipsychotic before their first MPH treatment and 55 started after initiation of MPH. Broader psychiatric comorbidities for these patients are shown in eTable 1. Among patients without an ADHD diagnosis, 92.9% had at least one other psychiatric diagnosis (ICD-9-CM: 290-319), 38% of these had a diagnosis of autism spectrum disorder (eTable 2). Of the 154 suicide attempts, 44 occurred during MPH treatment and 110 occurred off-treatment period (Table 1). The median age of the index suicide attempt was 15.4 years (IQR 12.7 to 18.1) (eFigure 2). The overall incidence of suicide attempt during MPH treatment was 9.27 per 10 000 patient-years. The crude incidence of suicide attempt in the different risk windows are summarised in Table 2. No participants in the SCCS died of completed suicide during the study period.

The analysis indicated some association between the decision to start MPH treatment and suicide attempt (Table 3). After adjusting for age and season, an increased risk of suicide attempts was detected during the 90-days period before MPH initiation, with an IRR of 6.55 (95%CI 3.37 to 12.72). The IRR remained elevated during the first 90-days of MPH treatment with IRR of 3.91 (95%CI 1.62 to 9.42), before returning to baseline levels during prolonged treatment (IRR=1.35; 95%CI 0.77 to 2.38) (Table 2). A direct comparison between the risk of suicide attempt during the pre-exposure period and the MPH treatment period showed the corresponding risk was not increased during the first 90-days of MPH

treatment (IRR=0.78; 95%CI 0.26 to 2.35). However, a 72% lower risk was found in the subsequent period of MPH treatment (IRR=0.28; 95%CI 0.08 to 0.94) compared to pre-exposure period. Further analysis using non-parametric spline-based SCCS showed that the risk of suicide attempt increased significantly before the initiation of MPH treatment and reached a peak within 100 days before MPH treatment (Figure 2). The age and gender stratified results showed a similar pattern to the overall analysis (eTable 3). Post-hoc analysis revealed an increased risk of any psychiatric disorders was detected during the 90-days period before MPH initiation (IRR=22.14; 95%CI 21.31 to 22.99). The risk remained elevated during the first 90-days of MPH treatment with IRR of 9.40 (95%CI 8.94 to 9.88), and during prolonged treatment (IRR=1.53; 95%CI 1.44 to 1.62) (eTable 4). The additional sensitivity analyses did not change this general picture of results (eFigure 3-5 and Table 3).

Discussion

In this population-based retrospective study, the incidence of MPH-related suicide attempts demonstrated a 6.5- and a 4-fold elevation during the 90-day periods before and after the start of treatment, respectively. This suggests that the decision to start MPH treatment follows the period of increasing risk for suicide attempts, with the risk remaining elevated and then beginning to fall after initiation of MPH. The most parsimonious interpretation of this pattern of temporal association is that the observed increased risk of suicide attempt is not due to MPH but precedes it, perhaps reflecting changes in behavioural and mental health symptoms or associated impairment that lead to a medical consultation, which in turn may contribute to the decision to prescribe MPH. This fits with the finding that the incidence of suicide attempt just after treatment initiation was comparable to that just before it, while after more than 90 days' of MPH use it was similar to that during the baseline period. In addition, the spline-based SCCS analysis showed the incidence of suicide attempts was decreasing upon the initiation of MPH treatment. However, our results cannot be interpreted as demonstrating that MPH has an immediate effect on lowering the risk of suicide attempt. The increased risk of suicide attempt pre-treatment may have been missed in a classic cohort study, in which patients with either events or exposures before the

commencement of study are usually excluded. This is the first study investigating the risk of suicide attempts before and after commencement of MPH treatment. The study results thus provide new evidence with which to interpret reports of an elevated risk of suicide attempts after initiation of MPH treatment.

Several factors may explain why the initiation of MPH treatment tends to coincide with the times of increased risk of suicide attempt. The initiation of new medication often occurs at a time of specific concerns about patients' health. ADHD patients are at higher risk of suicide-related events.[9,21,44] The decision to start treating with MPH may be a response to changes in behavioural or related psychiatric problems. These could be transient psychiatric disorders with ADHD or clinical observation in the period leading up to initiation of MPH. It is also well recognised that patients with ADHD are prone to cognitive, emotional and behavioural comorbidities, for example depression or disruptive behavioural disorders.[8] These comorbidities may increase the likelihood of suicide attempt, which may consequently increase both the likelihood of medical/psychiatric consultation and being prescribed MPH. This position is further supported by the post-hoc analysis which found an increased risk of other psychiatric disorders before MPH initiation. Interestingly, a previous study investigating the relationship between antidepressant medication and suicide also found the peak incidence of suicide attempt to be immediately before initiation of an antidepressant, suggesting that the attempt was a precipitant for initiation of antidepressant treatment.[45] It is also important to note that only two subjects died within our study period and neither of them was being prescribed MPH treatment at the time of death. Furthermore, the cause of death was not recorded as suicide. Therefore, in our cohort, death by suicide while on the treatment MPH is a rare outcome.

The suicidal ideation that precedes a suicide attempt may not be an acute event as patients with suicidal ideation may not carry out the attempt immediately.[46] Therefore, there may be a time-lag between the beginning of suicidal ideation and the suicide attempt event. This could possibly contribute to the increased risk during the first 90-days of MPH treatment (IRR=3.91; 95%CI 1.62 to 9.42).

Only one published report evaluated the risk of suicidal behaviour in MPH/stimulant users.[21] Chen et al. identified an increased risk of suicidal behaviour in patients with ADHD medications (hazard ratio [HR]=1.31; 95%CI 1.19 to 1.44) when compared with non-treated ADHD patients.[21] Chen et al. further applied a within-individual methodology, i.e. comparing patient-time with and without medication, and found no increased risk of suicide-related events (HR=0.89; 95%CI 0.79 to 1.00). Among stimulant users, a reduced within-patient rate of suicide-related events was seen during treatment periods (HR=0.81; 95%CI 0.70 to 0.94).[21] Chen et al. assumed the risk of suicidal behaviour to be constant in non-treatment periods.[21] However, in the current study, we found an increased risk of suicide attempt before the initiation of treatment. This suggests, therefore, that the estimate of risk derived by Chen et al. may need to be re-evaluated.

There are a number of limitations to our study. First, CDARS does not have linkage to data from private medical practitioners. However, in HK, the public sector is the main provider of specialist care[47] and there are very few private child and adolescent psychiatrists.[18,48] As a consequence, the vast majority of patients on MPH are likely to have been included in this study, our sample should be highly representative of Hong Kong population. In addition, our cohort only included clinically-referred patients who had sufficiently severe ADHD symptoms and/or impairment to have received MPH treatment. Therefore, our cohort may have a higher baseline risk than non-medicated patients. However, as we applied a SCCS design, individual baseline risk does not affect our study results and conclusion. Second, CDARS provides data on drug prescription, but not on adherence, and this may lead to misclassification of exposure periods. Third, as we had a comparatively long follow-up time, other time-varying cofounding factors may affect our study results. Therefore, we conducted various sensitivity analyses to explore the potential effects of non-adherence and various confounding factors and the results were consistent.

Conclusions

The incidence of suicide attempt peaked before the start of MPH treatment, remained high immediately after the start of MPH treatment, and declined during continuation of treatment. Our data, therefore, does not support a causal association between MPH treatment and suicide attempts.

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Access to Data and Data Analysis: Mr Man and Professor Wong had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Competing Interest: We have read and understood the policy on declaration of interests and declare the following interests: support from the European Community's 7th framework programme for the submitted work; Prof Wong reports grants from European Union FP7 programme, during the conduct of the study; grants from Shire, grants from Janssen-Cilag, grants from Eli-Lily, grants from Pfizer, outside the submitted work; and Prof Wong was a member of the National Institute for Health and Clinical Excellence (NICE) ADHD Guideline Group and the British Association for Psychopharmacology ADHD guideline group and acted as an advisor to Shire; Dr Coghill reports grants and personal fees from Shire, personal fees from Janssen-Cilag, personal fees from Lilly, grants and personal fees from Vifor, personal fees from Novartis, personal fees from Flynn Pharma, personal fees from Medice, personal fees from Oxford University Press, outside the submitted work; Professor Hollis was chair of the National Institute

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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).

Reference:

1. Polanczyk GV, Willcutt EG, Salum GA, Kieling C, Rohde LA. ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis. *Int J Epidemiol* 2014; **43**(2): 434-42.
2. Thomas R, Sanders S, Doust J, Beller E, Glasziou P. Prevalence of attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. *Pediatrics* 2015; **135**(4): e994-1001.
3. Leung PW, Luk SL, Ho TP, Taylor E, Mak FL, Bacon-Shone J. The diagnosis and prevalence of hyperactivity in Chinese schoolboys. *Br J Psychiatry* 1996; **168**(4): 486-96.
4. Leung PW, Hung SF, Ho TP, et al. Prevalence of DSM-IV disorders in Chinese adolescents and the effects of an impairment criterion: a pilot community study in Hong Kong. *Eur Child Adolesc Psychiatry* 2008; **17**(7): 452-61.
5. Biederman J, Faraone SV. Attention-deficit hyperactivity disorder. *Lancet* 2005; **366**(9481): 237-48.
6. Harstad E, Levy S, Abuse CS. Attention-Deficit/Hyperactivity Disorder and Substance Abuse. *Pediatrics* 2014; **134**(1): E293-E301.
7. Connor DF, Doerfler LA. ADHD With Comorbid Oppositional Defiant Disorder or Conduct Disorder Discrete or Nondistinct Disruptive Behavior Disorders? *J Atten Disord* 2008; **12**(2): 126-34.
8. Lambek R, Tannock R, Dalsgaard S, Trillingsgaard A, Damm D, Thomsen PH. Executive dysfunction in school-age children with ADHD. *J Atten Disord* 2011; **15**(8): 646-55.
9. Ljung T, Chen Q, Lichtenstein P, Larsson H. Common etiological factors of attention-deficit/hyperactivity disorder and suicidal behavior: a population-based study in Sweden. *JAMA Psychiatry* 2014; **71**(8): 958-64.
10. National Institute for Health and Clinical Excellence. Attention deficit hyperactivity disorder - Disagnosis and management of ADHD in children, young people and adults. 2008. http://publications.nice.org.uk/attention-deficit-hyperactivity-disorder-cg724/26/2012).
11. Subcommittee on Attention-Deficit/Hyperactivity Disorder Steering Committee on Quality Improvement Management, Wolraich M, Brown L, et al. ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics* 2011; **128**(5): 1007-22.
12. Pliszka S, AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2007; **46**(7): 894-921.
13. Garfield CF, Dorsey ER, Zhu S, et al. Trends in Attention Deficit Hyperactivity Disorder Ambulatory Diagnosis and Medical Treatment in the United States, 2000-2010. *Acad Pediatr* 2012.
14. Brault MC, Lacourse E. Prevalence of Prescribed Attention-Deficit Hyperactivity Disorder Medications and Diagnosis Among Canadian Preschoolers and School-Age Children: 1994-2007. *Can J Psychiatry* 2012; **57**(2): 93-101.
15. McCarthy S, Wilton L, Murray ML, Hodgkins P, Asherson P, Wong IC. The epidemiology of pharmacologically treated attention deficit hyperactivity disorder (ADHD) in children, adolescents and adults in UK primary care. *BMC Pediatr* 2012; **12**(1): 78.
16. Wong IC, Murray ML, Camilleri-Novak D, Stephens P. Increased prescribing trends of paediatric psychotropic medications. *Arch Dis Child* 2004; **89**(12): 1131-2.
17. Garbe E, Mikolajczyk RT, Banaschewski T, et al. Drug treatment patterns of attention-deficit/hyperactivity disorder in children and adolescents in Germany: results from a large population-based cohort study. *J Child Adolesc Psychopharmacol* 2012; **22**(6): 452-8.

18. Man KKC, Ip P, Chan EW, et al. Attention-Deficit/ Hyperactivity Disorder (ADHD) Drug Prescribing Trend is Increasing Among School-aged Children and Adolescents. *J Atten Disord* 2014 doi: 10.1177/1087054714536047.
19. EMA. European Medicines Agency makes recommendations for safer use of Ritalin and other methylphenidate-containing medicines in the EU London: European Medicines Agency Press Office; 2009.
20. Cortese S, Holtmann M, Banaschewski T, et al. Practitioner review: current best practice in the management of adverse events during treatment with ADHD medications in children and adolescents. *J Child Psychol Psychiatry* 2013; **54**(3): 227-46.
21. Chen Q, Sjolander A, Runeson B, D'Onofrio BM, Lichtenstein P, Larsson H. Drug treatment for attention-deficit/hyperactivity disorder and suicidal behaviour: register based study. *BMJ* 2014; **348**: g3769.
22. Sheftall AH, Asti L, Horowitz LM, et al. Suicide in Elementary School-Aged Children and Early Adolescents. *Pediatrics* 2016; **138**(4).
23. Chronis-Tuscano A, Molina BSG, Pelham WE, et al. Very Early Predictors of Adolescent Depression and Suicide Attempts in Children With Attention-Deficit/Hyperactivity Disorder. *Arch Gen Psychiat* 2010; **67**(10): 1044-51.
24. Impey M, Heun R. Completed suicide, ideation and attempt in attention deficit hyperactivity disorder. *Acta Psychiat Scand* 2012; **125**(2): 93-102.
25. Meza JI, Owens EB, Hinshaw SP. Response Inhibition, Peer Preference and Victimization, and Self-Harm: Longitudinal Associations in Young Adult Women with and without ADHD. *J Abnorm Child Psych* 2016; **44**(2): 323-34.
26. Chan EW, Lau WCY, Leung WK, et al. Prevention of Dabigatran-Related Gastrointestinal Bleeding With Gastroprotective Agents: A Population-Based Study. *Gastroenterology* 2015; **149**(3): 586-95.
27. Chui CSL, Man KKC, Cheng CL, et al. An investigation of the potential association between retinal detachment and oral fluoroquinolones: a self-controlled case series study. *J Antimicrob Chemother* 2014; **69**(9): 2563-7.
28. Wong AYS, Root A, Douglas IJ, et al. Cardiovascular outcomes associated with use of clarithromycin: population based study. *BMJ* 2016; **352**.
29. He Y, Chan EW, Man KKC, et al. Dosage Effects of Histamine-2 Receptor Antagonist on the Primary Prophylaxis of Non-Steroidal Anti-Inflammatory Drug (NSAID)-Associated Peptic Ulcers: A Retrospective Cohort Study. *Drug Saf* 2014; **37**(9): 711-21.
30. Man KK, Chan EW, Coghill D, et al. Methylphenidate and the risk of trauma. *Pediatrics* 2015; **135**(1): 40-8.
31. Man KK, Coghill D, Chan EW, et al. Methylphenidate and the risk of psychotic disorders and hallucinations in children and adolescents in a large health system. *Transl Psychiatry* 2016; **6**(11): e956.
32. Chui CS, Chan EW, Wong AY, Root A, Douglas IJ, Wong IC. Association between oral fluoroquinolones and seizures: A self-controlled case series study. *Neurology* 2016; **86**(18): 1708-15.
33. Man KKC, Chan EW, Ip P, et al. Prenatal antidepressant use and risk of attention-deficit/hyperactivity disorder in offspring: population based cohort study. *BMJ* 2017; **357**: j2350.
34. HAHO/ITD. Clinical Data Analysis & Reporting System (CDARS) User's Manual. In: Authority H, editor. 2.0 ed. Hong Kong; 2003. p. 3.
35. Lao KS, Chui CS, Man KK, Lau WC, Chan EW, Wong IC. Medication safety research by observational study design. *Int J Clin Pharm* 2016 doi: 10.1007/s11096-016-0285-6.
36. Whitaker HJ, Farrington CP, Spiessens B, Musonda P. Tutorial in biostatistics: the self-controlled case series method. *Stat Med* 2006; **25**(10): 1768-97.
37. Oner O, Yilmaz ES, Karadag H, et al. ADHD Medication Trends in Turkey: 2009-2013. *J Atten Disord* 2014 doi: 10.1177/1087054714523129.

449 38. Suhail K, Cochrane R. Seasonal variations in hospital admissions for affective disorders by gender
450 and ethnicity. *Soc Psychiatry Psychiatr Epidemiol* 1998; **33**(5): 211-7.
451 39. Ghebremichael-Weldeselassie Y, Whitaker HJ, Farrington CP. Self-controlled case series method
452 with smooth age effect. *Stat Med* 2014; **33**(4): 639-49.
453 40. Ghebremichael-Weldeselassie Y, Whitaker HJ, Farrington CP. Flexible modelling of vaccine effect
454 in self-controlled case series models. *Biom J* 2016; **58**(3): 607-22.
455 41. Thomas KH, Davies N, Metcalfe C, Windmeijer F, Martin RM, Gunnell D. Validation of suicide and
456 self-harm records in the Clinical Practice Research Datalink. *Br J Clin Pharmacol* 2013; **76**(1): 145-57.
457 42. National Institute for Health and Clinical Excellence. Attention deficit hyperactivity disorder:
458 pharmacological and psychological interventions in children, young people and adults. London: The
459 British Psychological Society and the Royal College of Psychiatrists; 2009.
460 43. Lakhan SE, Kirchgessner A. Prescription stimulants in individuals with and without attention
461 deficit hyperactivity disorder: misuse, cognitive impact, and adverse effects. *Brain Behav* 2012; **2**(5):
462 661-77.
463 44. Ruchkin V, Koposov RA, Koyanagi A, Stickley A. Suicidal Behavior in Juvenile Delinquents: The
464 Role of ADHD and Other Comorbid Psychiatric Disorders. *Child Psychiatry Hum Dev* 2016 doi:
465 10.1007/s10578-016-0693-9.
466 45. Simon GE, Savarino J, Operskalski B, Wang PS. Suicide risk during antidepressant treatment. *Am*
467 *J Psychiatry* 2006; **163**(1): 41-7.
468 46. Carrigan CG, Lynch DJ. Managing Suicide Attempts: Guidelines for the Primary Care Physician.
469 *Prim Care Companion J Clin Psychiatry* 2003; **5**(4): 169-74.
470 47. Leung GM, Tin KY, O'Donnell O. Redistribution or horizontal equity in Hong Kong's mixed public-
471 private health system: a policy conundrum. *Health Econ* 2009; **18**(1): 37-54.
472 48. Chan CW, Lam C, Lau J, et al. Attention Deficit/Hyperactivity Disorder in Children 2007 Position
473 Paper. Hong Kong: The Hong Kong Society of Child Neurology & Developmental Paediatrics; 2007.

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476 **Figures and Tables**

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)	Exposed period		Unexposed period	
								No. of events	Total follow-up time (patient-years)	No. of events	Total follow-up time (patient-years)
All	154	100	7.15	2.19	20	20	70	44	342.1	110	1529.6
Male	111	72.1	7.13	2.05	20	20	70	32	265.4	79	1085.4
Female	43	27.9	7.20	2.54	20	15	70	12	76.7	31	444.2

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

Table 2: Incidence of suicide attempts among MPH users in different risk windows

Risk window	No. of Events	Patient-years	Incidence per 10,000 patient-years	95%CI[a]	
Before Pre-risk	19	65,362	2.91	1.86	4.54
90-day before 1st MPH treatment	12	5,594	21.45	12.28	37.46
First 90 days of MPH	6	4,687	12.80	5.87	27.90
Subsequent MPH	36	42,728	8.43	6.09	11.66
Post-MPH treatment	81	68,636	11.80	9.50	14.66

[a]95%CI=95% confidence interval of incidence

503 **Table 3: Results from the self-controlled case series analyses**

	IRR[b]	95%CI[c]		p-value
Suicide Attempt (n=154)				
90-day before 1st MPH treatment	6.55	3.37	12.72	< 0.01
First 90-day with MPH treatment	3.91	1.62	9.42	< 0.01
Subsequent MPH treatment	1.35	0.77	2.38	0.30
Sensitivity analyses				
6-month age band (n=154)				
90-day before 1st MPH treatment	5.36	2.81	10.23	< 0.01
First 90-day with MPH treatment	4.04	1.87	8.75	< 0.01
Subsequent MPH treatment	1.44	0.88	2.36	0.15
Patients with >10 weeks MPH exposure (n=113)				
90-day before 1st MPH treatment	5.05	2.04	12.48	< 0.01
First 90-day with MPH treatment	3.38	1.15	9.89	0.03
Subsequent MPH treatment	1.38	0.77	2.46	0.28
Censor by antidepressants/antipsychotics (n=154)				
90-day before 1st MPH treatment	8.08	3.88	16.85	< 0.01
First 90-day with MPH treatment	5.79	2.28	14.73	< 0.01
Subsequent MPH treatment	1.14	0.56	2.33	0.72
Remove patients with substance dependence (n=114)				
90-day before 1st MPH treatment	6.91	3.44	13.87	< 0.01
First 90-day with MPH treatment	3.69	1.42	9.60	< 0.01
Subsequent MPH treatment	1.42	0.77	2.61	0.26
Remove cases with event on the 1st day of treatment (n=137)				
90-day before 1st MPH treatment	5.54	2.72	11.29	< 0.01
First 90-day with MPH treatment	3.76	1.56	9.05	< 0.01
Subsequent MPH treatment	1.32	0.75	2.33	0.33
Start of observation at 1st Jan 2001, the 6th birthday of the patient, the first observed date of ADHD diagnosis or the first date of MPH treatment, whichever occurred last (n=126)				
90-day before 1st MPH treatment	7.28	3.22	16.50	< 0.01
First 90-day with MPH treatment	3.65	1.45	9.18	< 0.01
Subsequent MPH treatment	1.25	0.69	2.28	0.46
Incident MPH users only (n=140)				
90-day before 1st MPH treatment	6.57	3.37	12.80	< 0.01
First 90-day with MPH treatment	4.02	1.66	9.73	< 0.01
Subsequent MPH treatment	1.32	0.73	2.40	0.36

504 [a]MPH=Methylphenidate
505 [b]IRR=Adjusted incidence rate ratio
506 [c]95%CI=95% confidence interval of IRR
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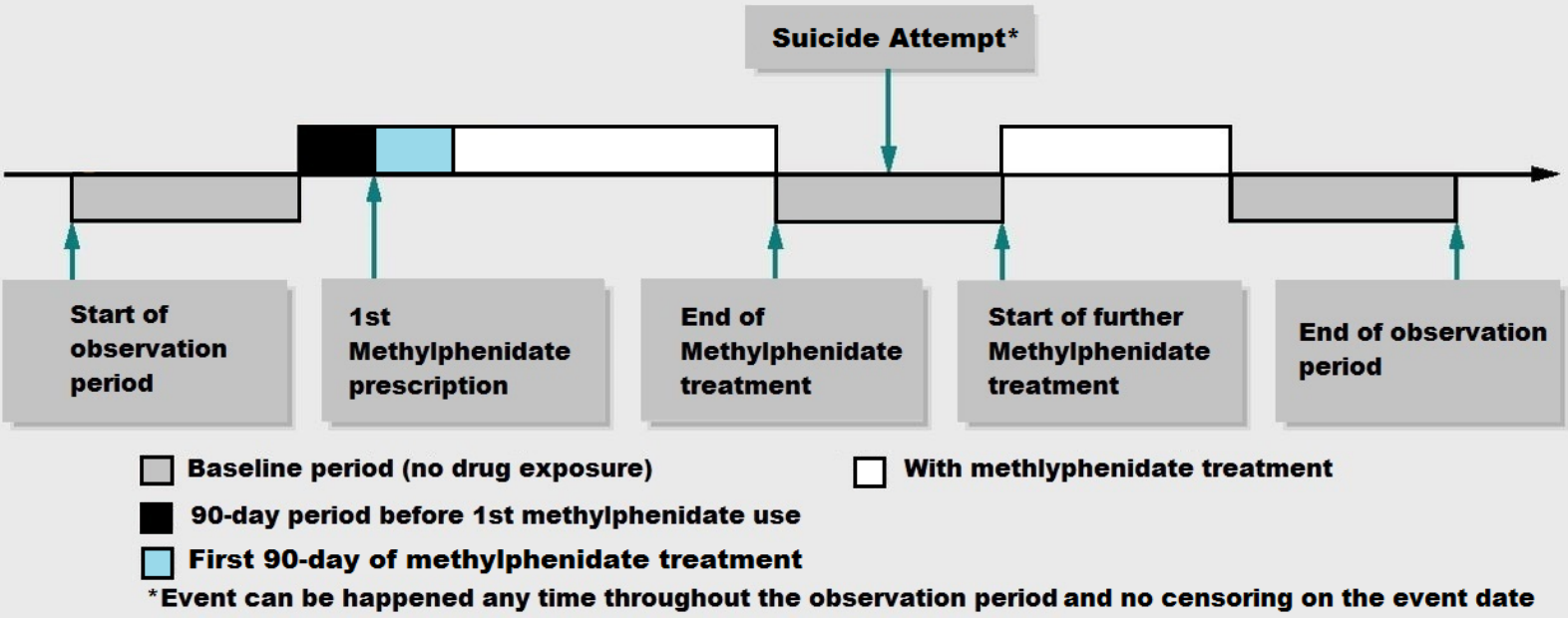
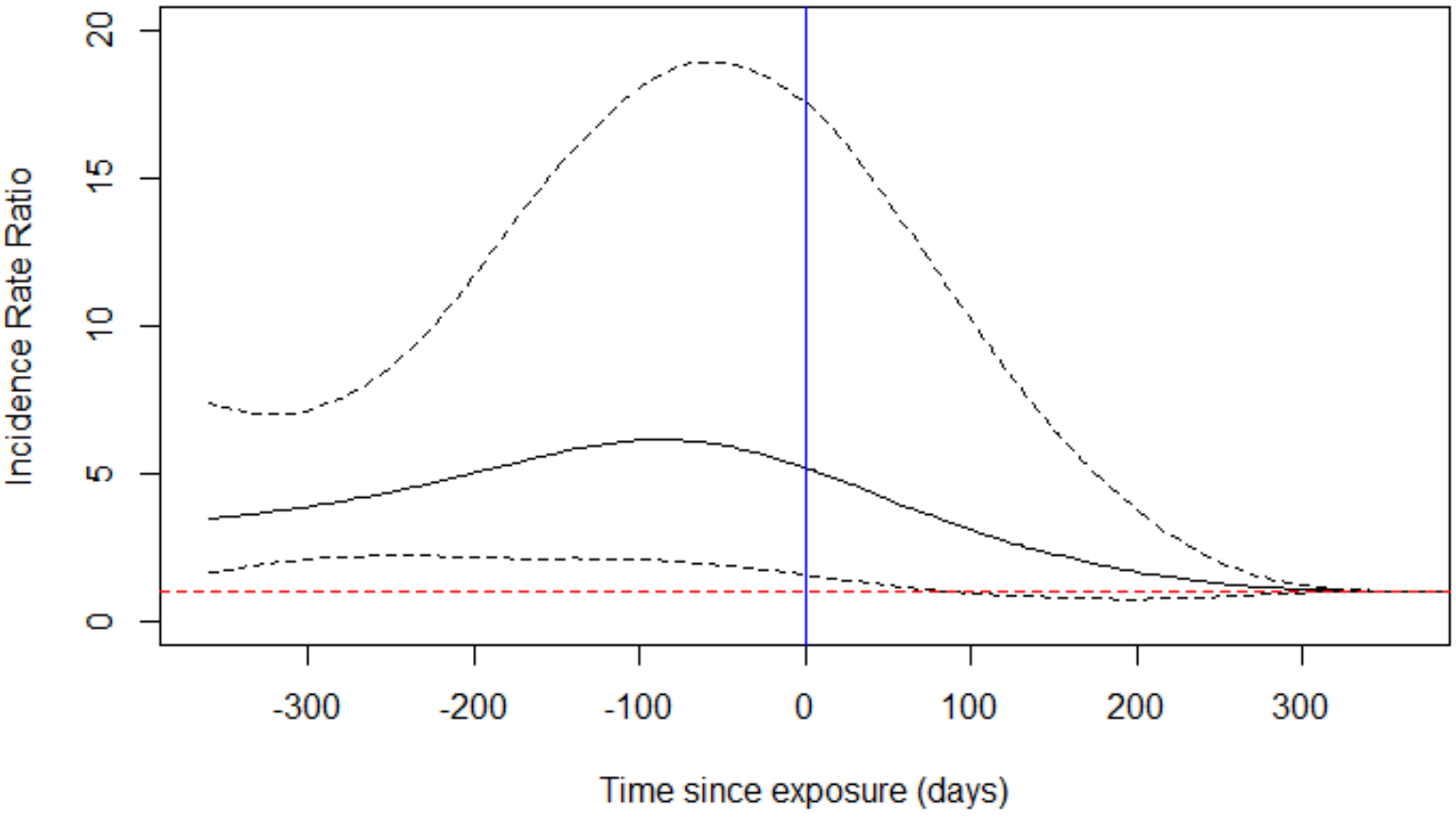

Suicide Attempt*
Start of observation period
1st Methylphenidate prescription
End of Methylphenidate treatment
Start of further Methylphenidate treatment
End of observation period
Baseline period (no drug exposure)
With methlyphenidate treatment
90-day period before 1st methylphenidate use
First 90-day of methylphenidate treatment
*Event can be happened any time throughout the observation period and no censoring on the event date


Incidence Rate Ratio
0
5
10
15
20
-300
-200
-100
0
100
200
300
Time since exposure (days)