

# Descriptive analysis of poisoning cases involving attention deficit hyperactivity disorder medications in Hong Kong

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## ABSTRACT

**Introduction:** The number of poisoning cases involving attention deficit hyperactivity disorder (ADHD) medications has reportedly risen with their increased use. However, there is limited relevant evidence from Asia. We analysed the characteristics of poisoning events involving these medications in Hong Kong.

**Methods:** We retrieved data regarding ADHD medication-related poisoning cases from the Hong Kong Poison Information Centre and conducted a descriptive analysis of the demographic information and poisoning information including sources of cases, exposure reason, exposure location, and outcome. The HKPIC data were linked with the Hospital Authority Clinical Data Analysis and Reporting System (CDARS) via de-identified Accident and Emergency numbers of public hospitals to investigate clinical characteristics. We also retrieved ADHD medication prescription records from the CDARS, then compared trends between poisoning cases and ADHD medication use.

**Results:** We identified 72 poisoning cases involving ADHD medications between 2009 and 2019, of which approximately 70% occurred in the affected individual's residence; most were intentional poisoning events (65.3%). No statistically significant association was observed between ADHD medication prescription trends and poisoning events involving ADHD medications. Of the 66 cases (91.7%) successfully linked to CDARS, 40 (60.6%) occurred in individuals with ADHD (median age: 14 years); 26 (39.4%) occurred in individuals who lacked ADHD (median age: 33 years) but displayed higher rates of other mental disorders including depression and anxiety.

**Conclusion:** No significant correlation was evident between ADHD medication prescriptions and poisoning events involving ADHD medications. However, medication management and caregiver education must be emphasised to prevent potential poisoning events.

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## New knowledge added by this study

- The number of prescriptions for attention deficit hyperactivity disorder (ADHD) medications increased by 2.6-fold between 2009 and 2019 (from 32 497 to 84 037).
- In total, 72 poisoning cases involving ADHD medications between 2009 to 2019 were confirmed by the Hong Kong Poison Information Centre, and there was no clear trend regarding the annual number of such cases.
- No statistically significant correlation was evident between ADHD medication prescriptions and poisoning events involving ADHD medications.

## Implications for clinical practice or policy

- The management and safe storage of ADHD medications should be strengthened in both ADHD and non-ADHD populations.
- Appropriate interventions and/or social support for individuals with psychiatric disorders should be planned and implemented to reduce the risk of poisoning.

## Introduction

Acute poisoning by medicines or chemicals is common worldwide; it can lead to death and other serious outcomes. Globally, poison centres are estimated to receive millions of calls each year regarding acute poisoning reports or consultations.<sup>1</sup> According to the Hong Kong Poison Information Centre (HKPIC) annual reports from 2009 to 2018, >3000 events of poisoning in Hong Kong each year are potentially caused by medications or chemicals (excluding food poisoning and bites or stings).<sup>2-11</sup>

Attention deficit hyperactivity disorder (ADHD) is the most prevalent neurodevelopmental disorder in childhood and adolescence.<sup>12,13</sup> Because of its inattentiveness, hyperactivity, and impulsivity characteristics, individuals with ADHD have higher risks of intentional and accidental poisoning.<sup>14</sup> A recent study showed that ADHD medication use increased in many countries and regions from 2001 to 2015, including the United States (US), the United Kingdom, Australia, and Hong Kong.<sup>15</sup> Descriptive analyses of poisoning cases reported to the US<sup>16</sup> and Australian poison centres<sup>17</sup> showed trends similar to the reported increases in ADHD medication prescriptions. Accordingly, we hypothesised that an increase in ADHD medication prescriptions would lead to an increase in the number of poisoning cases involving ADHD medications in Hong Kong.

To our knowledge, there have been no relevant studies regarding trends in poisoning cases involving ADHD medications in Hong Kong; it is unclear whether the increased use of ADHD medications is associated with an increased risk of overall poisoning in Hong Kong. Therefore, this study analysed the trends and characteristics of poisoning events involving ADHD medications in Hong Kong.

## Methods

### Participants and databases

The data used in this study include HKPIC poisoning records for the period between 1 January 2009 and 31 December 2019, consisting of consultations (poisoning cases in which healthcare professionals consulted the HKPIC for poison information and management advice) and poisoning cases reported to the accident and emergency (A&E) departments under Hospital Authority (HA).<sup>11</sup>

We used A&E numbers, which are de-identified codes generated by the HA, to link data from the HKPIC with poisoning data acquired from the A&E module of the Clinical Data Analysis and Reporting System (CDARS) of the HA. The CDARS is an electronic health records system that contains patient demographic and clinical information from inpatient, outpatient, and A&E settings. It captures data from all public hospitals and clinics in Hong Kong<sup>18-20</sup> and has been extensively used

## 香港專注力不足過度活躍症藥物中毒事例的描述性分析

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**簡介：**隨着治療專注力不足過度活躍症（ADHD）藥物的使用量上升，涉及這些藥物的中毒事例也有所增加。然而在亞洲地區，相關的研究證據有限。本項研究分析了香港ADHD藥物中毒事例的臨床特徵。

**方法：**本研究從香港中毒諮詢中心檢索了涉及ADHD藥物相關中毒事件的記錄，並描述了中毒案例的人口特徵以及分析中毒相關的資料，包括個案來源、中毒原因、中毒事件發生地點和中毒結果。本研究利用去除識別的公立醫院急症室編碼，將這些中毒記錄與醫院管理局臨床數據分析和報告系統的醫療電子病歷連接，以分析臨床特徵。最後，我們在臨床數據分析和報告系統中檢索了ADHD藥物的處方記錄，並比較發生ADHD藥物中毒事例及ADHD藥物使用之間的趨勢。

**結果：**我們發現在2009至2019年間共有72宗涉及ADHD藥物的中毒事例，其中約70%發生在病人家中，並且大多數（65.3%）為非意外中毒事例。分析顯示，ADHD藥物處方和涉及ADHD藥物的中毒事例的趨勢並無關聯。在成功連接到電子病歷的66宗中毒事件（91.7%）之中，有40宗（60.6%）的病人患有ADHD（中位年齡：14歲）；26宗（39.4%）發生在沒有ADHD（中位年齡：33歲）但患抑鬱和焦慮等其他精神疾病的比例較高的患者。

**結論：**研究顯示，ADHD藥物處方和涉及ADHD藥物的中毒事件的趨勢並沒有顯著關聯。然而，藥物管理和對相關患者及家屬的教育在預防潛在中毒方面仍至關重要。

for safety studies regarding ADHD and ADHD medications.<sup>21-25</sup> Reference keys (ie, de-anonymised identifiers in the CDARS) were used for matched individuals to retrieve relevant diagnostic and prescription information. The data presented are fully anonymised, and the risk of identification is minimal.

### Statistical analysis

The annual prevalence of poisoning cases involving ADHD medications was calculated, along with the annual prevalence of ADHD medication prescriptions dispensed by the HA; the relationship between the two prevalence trends was examined using a cross-correlation function.<sup>26</sup> Demographic and clinical details were summarised to include the exposure reason, exposure location, and clinical outcome of each case. Definitions and classifications of clinical outcomes were acquired from the HKPIC (Table 1).<sup>11</sup> Subgroup analyses were conducted to examine the association between the annual prevalence of poisoning related to ADHD medications in individuals with ADHD (ie, individuals with an ADHD diagnosis or a prescription for ADHD medication), and the annual prevalence of

TABLE 1. Definitions of clinical outcomes<sup>11</sup>

No effect	The patient did not develop any signs or symptoms.
Mild effect	The patient developed some signs or symptoms that were minimally bothersome and generally resolved rapidly without residual disability or disfigurement. Examples are self-limiting gastrointestinal symptoms, drowsiness, skin irritation, first-degree dermal burn, sinus tachycardia without hypotension, and transient cough.
Moderate effect	The patient exhibited signs or symptoms that were more pronounced, more prolonged, or more systemic in nature, compared with a mild effect. Usually, some form of treatment is required. Symptoms were not life-threatening, and the patient had no residual disability or disfigurement. Examples are corneal abrasion, acid-base disturbance, high fever, disorientation, hypotension that rapidly responds to treatment, and isolated brief seizures that readily respond to treatment.
Major effect	The patient exhibited signs or symptoms that were life-threatening or resulted in significant residual disability/disfigurement. Examples are repeated seizures or status epilepticus, respiratory compromise requiring intubation, ventricular tachycardia with hypotension, cardiac or respiratory arrest, oesophageal stricture, and disseminated intravascular coagulation.
Death	The patient died.
Unknown effect	The clinical outcome cannot be determined from the information available.

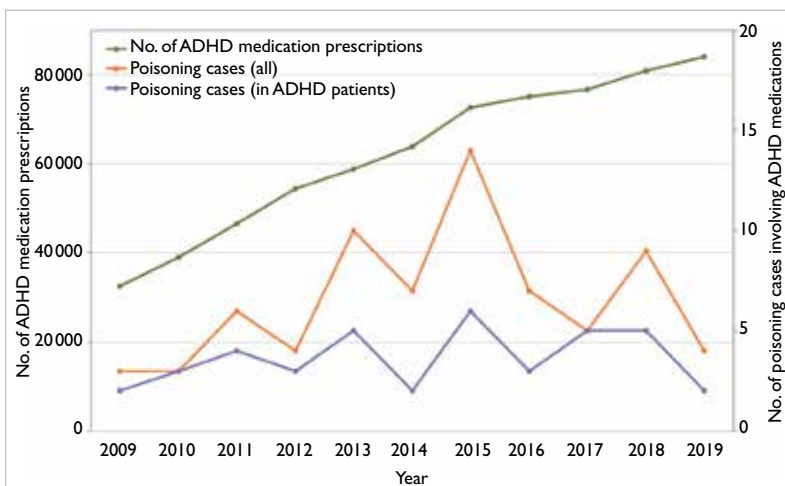


FIG 1. Trends in attention deficit hyperactivity disorder (ADHD) medication prescriptions and poisoning cases involving ADHD medications in Hong Kong from 2009 to 2019

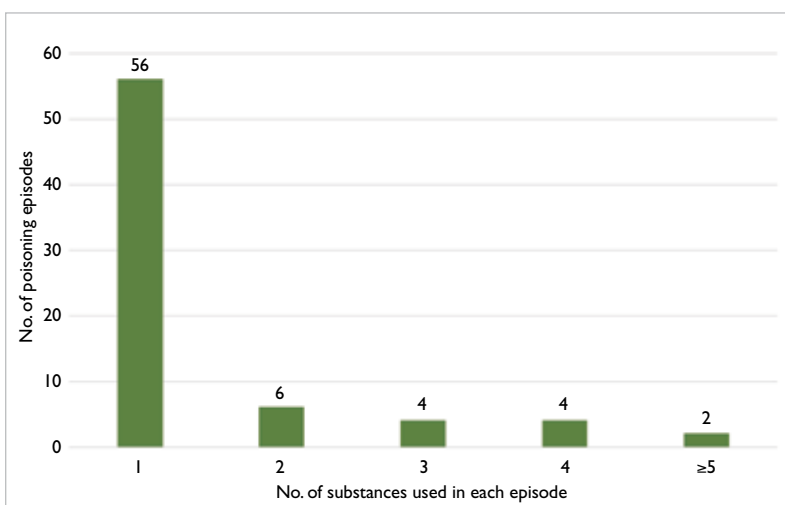


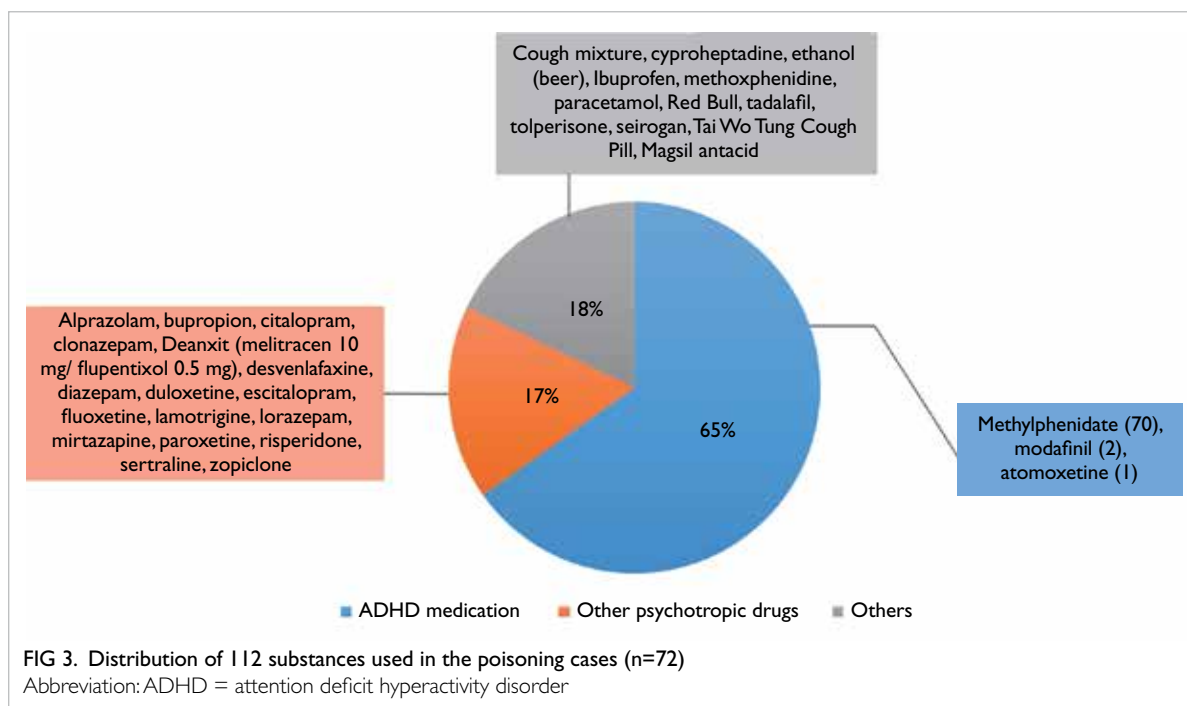
FIG 2. Summary of substances used in the poisoning cases (n=72)

prescriptions dispensed by the HA. These analyses were conducted using information from the CDARS, including prescriptions and diagnoses. R software (version 4.0.3) and Microsoft Excel 2019 were used for analyses.

This descriptive analysis has been reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist for cross-sectional studies.

## Results

In total, 72 poisoning cases involving ADHD medications were confirmed by the HKPIC during the period from 2009 to 2019. The trends in all poisoning cases involving ADHD medications and the annual number of ADHD medication prescriptions are shown in Figure 1. The number of ADHD medication prescriptions is increasing annually, from 32 497 in 2009 to 84 037 in 2019; in contrast, although the number of poisoning cases involving ADHD medications has fluctuated, there has been no upward trend. There were similar findings with respect to poisoning cases involving ADHD medications in patients with an ADHD diagnosis or prescription (Fig 1). Notably, from 2014 to 2015, when the rate of increase in ADHD medication prescriptions was faster than in the previous year, the number of poisoning cases involving ADHD medications showed an upward trend. In contrast, when the rate of increase in ADHD medication prescriptions was slower in the previous year, the number of poisoning cases decreased (eg, from 2015 to 2016). However, cross-correlation analysis did not reveal any significant correlation between the number of poisoning cases and the number of ADHD medication prescriptions. At a time lag of 0, the correlations were approximately 0.442 and 0.326 for all poisoning cases involving ADHD medications



and poisoning cases involving ADHD medications in patients with ADHD, respectively; these values were within the range of -0.59 to 0.59, indicating the absence of a significant correlation. At a time lag of 1 (ie, 1 year), the correlations were 0.176 and 0.063, respectively; neither correlation was statistically significant.

Among the 72 poisoning cases involving 112 substances, most (n=56; 77.8%) were caused by a single ADHD medication (Fig 2). The 112 substances used in the poisoning cases are shown in Figure 3. Each case included at least one type of ADHD medication, the most common of which was methylphenidate (n=70; 95.9%). Furthermore, 17% of the substances that caused poisoning were psychotropic drugs.

The main characteristics of all poisoning cases involving ADHD medications are shown in Table 2. The two main sources of these poisoning cases were consultation (54.2%) and reporting (40.3%); most exposures occurred in the affected individual's residence. The exposure reason was intentional poisoning in 47 cases, accidental poisoning in 20 cases, and an adverse reaction in one case. Overall, a minor effect or no adverse effect occurred in 63 cases (87.5%); a moderate effect occurred in five cases, and a major effect occurred in four cases. Detailed information regarding the four cases with major effects is provided in Table 3. The age distribution of affected individuals (among all 72 cases) is

**TABLE 2. Characteristics of all poisoning cases involving attention deficit hyperactivity disorder medications in Hong Kong from 2009 to 2019\***

	Male	Female	Total
No. of cases	49 (68.1%)	23 (31.9%)	72 (100%)
<b>Sources</b>			
Consultation	28 (57.1%)	11 (47.8%)	39 (54.2%)
Pre-hospital	1 (2.0%)	3 (13.0%)	4 (5.6%)
Reporting	20 (40.8%)	9 (39.1%)	29 (40.3%)
<b>Location of exposure</b>			
Residence	34 (69.4%)	17 (73.9%)	51 (70.8%)
Others	15 (30.6%)	6 (26.1%)	21 (29.2%)
<b>Exposure reason</b>			
Adverse reaction	1 (2.0%)	0	1 (1.4%)
Intentional	28 (57.1%)	19 (82.6%)	47 (65.3%)
Accidental	17 (34.7%)	3 (13.0%)	20 (27.8%)
Others	3 (6.1%)	1 (4.4%)	4 (5.6%)
<b>Outcome</b>			
No effect	17 (34.7%)	7 (30.4%)	24 (33.3%)
Minor effect	27 (55.1%)	12 (52.2%)	39 (54.2%)
Moderate effect	2 (4.1%)	3 (13.0%)	5 (6.9%)
Major effect	3 (6.1%)	1 (4.4%)	4 (5.6%)
Cases successfully linked to CDARS	43 (87.8%)	23 (100%)	66 (91.7%)

Abbreviation: CDARS = Clinical Data Analysis and Reporting System  
\* Data are shown as No. (%)



TABLE 3. Clinical characteristics of cases with major effects

Case No.	Exposure reason	Recorded substances	Clinical symptoms/laboratory results
1	Intentional	Methylphenidate	Tachycardia; coma (GCS score <8/15)
2	Intentional	Duloxetine, Deanxit (melitracen 10 mg/ flupentixol 0.5 mg), diazepam, clonazepam, risperidone, paracetamol, ibuprofen, methylphenidate, tolperisone, cough mixture	Vomiting $\leq$ 4 times; dizziness/lethargy
3	Intentional	Alprazolam, paracetamol, mirtazapine, desvenlafaxine, methylphenidate, tadalafil	Hypotension; AST, ALT abnormal and $\leq$ 1000 IU/L (peak); coma (GCS score <8/15); miosis
4	Malicious	Methylphenidate, methoxphenidine	No detailed records available

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; GCS = Glasgow Coma Scale

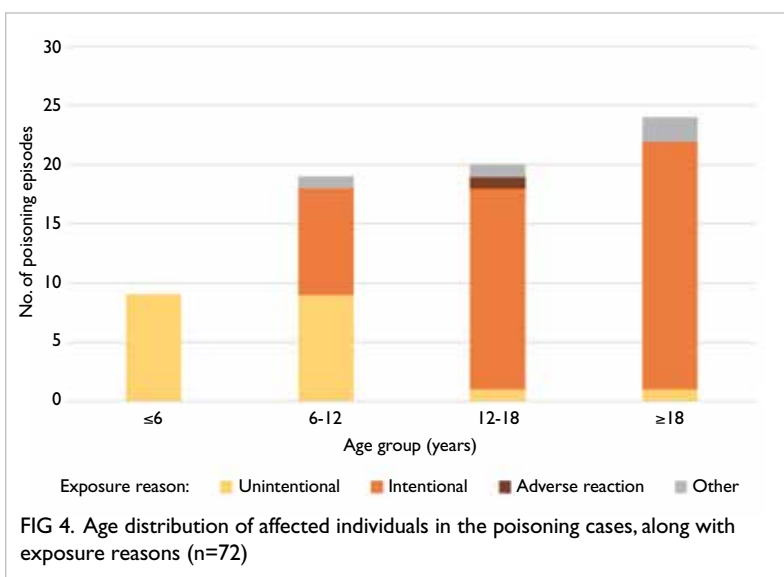


FIG 4. Age distribution of affected individuals in the poisoning cases, along with exposure reasons (n=72)

shown in Figure 4. Most poisoning cases (66.67%) involving ADHD medications occurred in children and adolescents; intentional poisoning occurred in a much larger proportion of cases among older individuals.

In total, 66 cases with an A&E number were matched to CDARS data for 62 individuals (Table 4). Among the remaining six cases which were not successfully linked, three did not have an A&E number in the poisoning record. In total, 40 poisoning cases (median age: 14 years) occurred in 39 individuals with either an ADHD diagnosis or ADHD prescription, and 26 poisoning cases (median age: 33 years) occurred in 23 individuals without ADHD. The sources of poisoning reports and locations of exposure were similar between the two groups. With respect to exposure reason, there were more cases of intentional poisoning among individuals without ADHD (76.9% among individuals without ADHD vs

60.0% among individuals with ADHD); there were also sex-related differences. Among female ADHD patients and among both male and female non-ADHD individuals, more than three-quarters of poisoning events were intentional. However, among male ADHD patients, intentional and accidental poisoning each constituted approximately half of all cases. Furthermore, the distribution of poisoning outcomes differed between individuals with and without ADHD. Among individuals with ADHD, a minor effect or no adverse effect occurred in most cases; a major effect did not occur in any cases. Among individuals without ADHD, a minor effect occurred in >65% of cases; a major effect occurred in four cases. The proportions of poisoning cases caused by a single ADHD medication were 82.5% among individuals with ADHD and 69.2% among individuals without ADHD. Analysis of psychiatric co-morbidities retrieved from the CDARS revealed that individuals without ADHD more frequently had mental disorders such as depression, anxiety, or schizophrenia.

## Discussion

### Comparison with other studies

In this study, we analysed the characteristics of poisoning cases involving ADHD medications reported to the HKPIC between 2009 and 2019. Overall, 72 cases were included in our analysis. The most common location of poisoning was the affected individual's residence, and most cases occurred in children and adolescents. These results are similar to the findings in previous studies, including reports from poison control centres of the US<sup>16</sup> showing that 94.5% of cases occurred in the affected individual's residence, and a report from the Australian New South Wales Poisons Information Centre<sup>17</sup> revealing a median age of 17 years among individuals with intentional poisoning involving ADHD medications. These results may be explained by the increased likelihood of household exposure to various drugs,

TABLE 4. Characteristics of cases with successful linkage to the Clinical Data Analysis and Reporting System\*

	Individuals with ADHD			Individuals without ADHD		
	Male	Female	Total	Male	Female	Total
No. of cases	30 (75.0%)	10 (25.0%)	40 (100%)	13 (50.0%)	13 (50.0%)	26 (100%)
Median age, y	11	14.5	14	39	30	33
Sources						
Consultation	15 (50.0%)	5 (50.0%)	20 (50.0%)	7 (53.9%)	6 (46.2%)	13 (50.0%)
Pre-hospital	1 (3.3%)	1 (10.0%)	2 (5.0%)	0	2 (15.4%)	2 (7.7%)
Reporting	14 (46.7%)	4 (40.0%)	18 (45.0%)	6 (46.2%)	5 (38.5%)	11 (42.3%)
Location of exposure						
Residence	18 (60.0%)	9 (90.0%)	27 (67.5%)	11 (84.6%)	8 (61.5%)	19 (73.1%)
Others	12 (40.0%)	1 (10.0%)	13 (32.5%)	2 (15.4%)	5 (38.5%)	7 (26.9%)
Exposure reason						
Adverse reaction	0	0	0	0	0	0
Intentional	15 (50.0%)	9 (90.0%)	24 (60.0%)	10 (76.9%)	10 (76.9%)	20 (76.9%)
Accidental	14 (46.7%)	1 (10.0%)	15 (37.5%)	1 (7.7%)	2 (15.4%)	3 (11.5%)
Others	1 (3.3%)	0	1 (2.5%)	2 (15.4%)	1 (7.7%)	3 (11.5%)
Outcome						
No effect	14 (46.7%)	3 (30.0%)	17 (42.5%)	1 (7.7%)	4 (30.8%)	5 (19.2%)
Minor effect	14 (46.7%)	4 (40.0%)	18 (45.0%)	9 (69.2%)	8 (61.5%)	17 (65.4%)
Moderate effect	2 (6.7%)	3 (30.0%)	5 (12.5%)	0	0	0
Major effect	0	0	0	3 (23.1%)	1 (7.7%)	4 (15.4%)
No. of substances used						
1	26 (86.7%)	7 (70.0%)	33 (82.5%)	10 (76.9%)	8 (61.5%)	18 (69.2%)
2	4 (13.3%)	1 (10.0%)	5 (12.5%)	1 (7.7%)	0	1 (3.9%)
≥3	0	2 (20.0%)	2 (5.0%)	2 (15.4%)	5 (38.5%)	7 (26.9%)
No. of patients						
With ADHD diagnosis	26 (83.9%)	5 (16.1%)	31 (100%)	NA	NA	NA
With ADHD prescription	27 (75.0%)	9 (25.0%)	36 (100%)	NA	NA	NA
Psychiatric co-morbidities						
Depression	1 (3.5%)	1 (10.0%)	2 (5.1%)	2 (20.0%)	4 (30.8%)	6 (26.1%)
Anxiety	0	1 (10.0%)	1 (2.6%)	1 (10.0%)	4 (30.8%)	5 (21.7%)
Bipolar disorder	1 (3.5%)	1 (10.0%)	2 (5.1%)	0	1 (7.7%)	1 (4.4%)
Substance use disorder	7 (24.1%)	2 (20.0%)	9 (23.1%)	7 (70.0%)	3 (23.1%)	10 (43.5%)
Personality disorder	4 (13.8%)	6 (60.0%)	10 (25.6%)	0	0	0
Schizophrenia	0	1 (10.0%)	1 (2.6%)	1 (10.0%)	0	1 (4.4%)
Adjustment disorder	2 (6.9%)	3 (30.0%)	5 (12.8%)	2 (20.0%)	2 (15.4%)	4 (17.4%)

Abbreviations: ADHD = attention deficit hyperactivity disorder; NA = not applicable

\* Data are shown as No. (%), unless otherwise specified

which increases the number of poisoning events that occur in the affected individual's residence.<sup>1</sup> Additionally, children and adolescents are more vulnerable to poisoning involving medications because of their developmental progression, external influences, and inadequate understanding of the relevant dangers.<sup>27</sup> According to the HKPIC 2018 annual report,<sup>11</sup> more than half (64%) of poisoning

events in that year were caused by exposure in the affected individual's residence, and 21.3% occurred among individuals aged <20 years. Poisoning cases occurred among individuals with ADHD at younger ages, compared with cases among individuals without ADHD; a potential explanation for this difference is that, although ADHD is often a lifelong condition, it is currently more commonly diagnosed in children

and adolescents.<sup>28</sup> Because of the limited number of poisoning cases, we could not detect a statistically significant correlation between trends in poisoning cases and the number of ADHD prescriptions. The authors of the New South Wales Poisons Information Centre report<sup>17</sup> compared intentional exposure to ADHD medications with dispensing information for those medications (using Pharmaceutical Benefits Scheme data); their analysis revealed parallel trends.

### Potential explanation of the findings

By using A&E numbers to link poisoning cases with electronic health records from the CDARS, we achieved a high linkage rate (91.7%). Among the poisoning cases that occurred in male individuals with ADHD, intentional and accidental poisoning were equally common; however, among female individuals with ADHD, the most common reason for poisoning was self-harm. This distinction may be related to sex differences in ADHD patients. For example, girls and women are less likely than boys and men to be diagnosed with ADHD; thus, female ADHD patients may have severe symptoms or comorbidities.<sup>29,30</sup> However, with respect to poisoning cases that occurred in individuals without ADHD, exposure reasons were similar among male and female individuals. Although >70% of the poisoning cases were solely caused by ADHD medication, multiple substances (eg, psychiatric medications or other medications) had been used in some cases. Among individuals without ADHD, there were more poisoning cases that involved two or more types of substances. This finding is presumably related to the higher risks of mental disorders (eg, depression, anxiety, and substance use disorders) among individuals without ADHD; all of these mental disorders increase the risk of intentional self-poisoning.<sup>31</sup>

### Strengths and limitations

The main strength of this study is that, to our knowledge, it is the first study in Asia to analyse trends in ADHD prescriptions and poisoning involving ADHD medications. Additionally, we used A&E numbers to link data between the HKPIC and the CDARS, yielding detailed comorbidity and prescription information for affected individuals. The A&E number is a de-identified code generated by the HA, which partially protects each individual's privacy. In this study, we made full use of information available from various databases and conducted preliminary analyses that will facilitate future research.

However, there were some limitations in this study. First, data from the HKPIC were collected from the voluntary poisoning reporting system,<sup>11</sup> which may not cover all poisoning cases involving ADHD medications in Hong Kong. This type of limitation is also present in other poison control

or information centre reports,<sup>16,17</sup> which may omit cases of substance abuse, misuse, or overdose with or without obvious clinical symptoms that are not reported or not detected in electronic health records databases. Additionally, the small sample size limited the statistical power to identify correlations. Second, although we linked HKPIC data to CDARS data, we were only able to obtain all diagnoses and medication records; we could not determine whether subsequent interventions (ie, after poisoning events) were implemented to prevent additional poisoning cases. Finally, medications prescribed in private clinics may not have been recorded, and we could not obtain data regarding the use of unlicensed or illegal medications. However, we expect the numbers of such medications to be relatively low.<sup>22,23</sup> Because HA services are available to all Hong Kong residents<sup>32</sup> and the majority of children and adolescents with chronic conditions are under the care of the HA,<sup>33</sup> our data are likely to be representative of ADHD medications in Hong Kong; however, we currently cannot determine the true rate of poisoning events involving ADHD medications in Hong Kong.

### Clinical implications

Generally, individuals with ADHD have a higher risk of poisoning (both intentional and accidental). Therefore, safe medication storage and management strategies should be implemented to avoid poisoning events involving ADHD medications.<sup>34</sup> Regarding individuals with ADHD, particularly children and adolescents, proper caregiver training is necessary to ensure the safe storage and reasonable disposal of common household medicines.<sup>35</sup> In the present study, accidental poisoning events had occurred in approximately 30% of poisoning cases involving ADHD medications; most of these events occurred among individuals aged <12 years. Thus, at least one-quarter of poisoning cases could be prevented by good medication storage strategies. Furthermore, individuals with mental disorders should be supported in the management of their prescriptions. Appropriate psychological intervention and social/family support can also help to reduce the potential for poisoning events.

### Conclusion

No statistically significant correlation was evident between ADHD medication prescriptions and poisoning events involving ADHD medications. However, it remains important to raise awareness regarding the management and safe storage of medications among individuals with and without ADHD.

### Author contributions

Concept or design: KKC Man, ML Tse, P Ip, ICK Wong.

Acquisition of data: L Gao, ATY Chow, CSL Chui, ML Tse, P Ip, ICK Wong.

Analysis or interpretation of data: All authors.

Drafting of the manuscript: L Gao, KKC Man, KHTW Wong, EW Chan, CSL Chui.

Critical revision of the manuscript for important intellectual content: All authors.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

### Conflicts of interest

L Gao, ATY Chow, ML Tse and KHTW Wong declare no conflict of interest. KKC Man is a recipient of the CW Maplethorpe Fellowship and reports grants from the National Institute for Health Research of the United Kingdom, Research Grants Council (RGC) of Hong Kong, Horizon 2020 Framework of the European Commission, and personal fees from IQVIA Ltd, outside the submitted work. EW Chan reports honorarium from the Hospital Authority, grants from RGC, the Research Fund Secretariat of the Health Bureau (formerly Food and Health Bureau) and the Narcotics Division of the Security Bureau of the Hong Kong SAR Government, the National Natural Science Fund of China, the Wellcome Trust, Bayer, Bristol Myers Squibb, Pfizer, Janssen, Amgen, and Takeda, outside the submitted work. CSL Chui reports grants from Pfizer and personal fees from PrimeVigilance, outside the submitted work. D Coghill reports grants and personal fees from Shire/Takeda, and personal fees from Medice, Servier and Oxford University Press, outside the submitted work. As an editor of the journal, KL Hon was not involved in the peer review process. P Ip reports research grants from the RGC and the Health and Medical Research Fund (HMRF) of the Hong Kong SAR Government, outside the submitted work. ICK Wong reports research funding outside the submitted work from Amgen, Bristol Myers Squibb, Pfizer, Janssen, Bayer, GSK, Novartis, the RGC, the HMRF, the National Institute for Health Research of the United Kingdom, the European Commission and the National Health and Medical Research Council in Australia, as well as speaker fees from Janssen and Medice in the previous 3 years.

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### Ethics approval

The study protocol was approved by the Research Ethics Committee of Kowloon Central Cluster/Kowloon East Cluster (Ref No.: KC/KE-20-0173/ER-3) and the Institutional Review Board of The University of Hong Kong/Hospital Authority Hong Kong West Cluster (Ref Nos.: UW 20-779 and UW 12-136) of Hospital Authority, Hong Kong. The data presented are fully anonymised, and the risk of identification is minimal. This was a pharmacoepidemiology study without patient contact and therefore informed consent was exempted by the Research Ethics Committee/Institutional Review Board.

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