Acute toxicity related to psychoactive substance abuse and the impact of emergency department interventions on drug-related reattendance

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Final Research Report

Project Title

Acute toxicity related to psychoactive substance abuse and the impact of emergency department interventions on drug-related reattendance

Project Reference No.: BDF 190053

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Abstract

Introduction and background

Despite the popularity of methamphetamine, cocaine and cannabis among recreational drug abusers and the significant associated harms, local studies on the trends of use, acute toxicities, emergency department (ED) interventions, and ED reattendance are lacking.

Objectives

The objectives of this study were: 1) to characterise the trends and patterns of acute toxicity related to methamphetamine, cocaine and cannabis in drug abusers presenting to EDs in Hong Kong; 2) to evaluate the impact of the pattern of drug use and severity of acute toxicity; and 3) to review the current practice of ED interventions, including psychosocial interventions and case referrals to non-governmental organisation (NGO) substance abuse services, and their impact on ED reattendance for drug-related problems.

Methods

We conducted a retrospective study of all consecutive patients reported to the Hong Kong Poison Information Centre (HKPIC) by public EDs in Hong Kong between 1 January 2010 and 31 December 2019 for acute toxicity related to the recreational use of methamphetamine, cocaine, cannabis and novel psychoactive substances (NPSs). The electronic medical records of the included cases were reviewed with data extracted by trained research personnel according to a standardised coding manual. We ranked the severity of acute toxicity using the Poison Severity Score (PSS) and the patient outcome with reference to the American Association of Poison Control Centers' National Poison Data System. The primary outcome was the time interval between the index ED attendance (the first drug-related presentation within the study period) and the first ED reattendance for drug-related problems. The secondary outcome was a composite outcome of severe complications reflecting end-organ toxicity.

We studied the trend of acute toxicity using a negative binominal model, accounting for the volume of ED attendance. We also evaluated the correlation between the trends of methamphetamine, cocaine and cannabis abuse reported to the HKPIC with data from the Narcotics Division of the Security Bureau and drug seizure data from law enforcement. Univariate analysis, followed by multivariable logistic regression analysis, were conducted to identify independent predictors for the secondary outcome. Cox regression analysis was performed to identify factors associated with a higher risk of drug-related ED revisits after the index presentation.

Results

In total, 1,629 episodes involving 1,348 patients were included. During the study period, the median annual incidence of acute toxicities related to methamphetamine, cocaine and cannabis abuse were 5.64 (interquartile range [IQR] 4.14–6.72), 1.32 (IQR 0.96–2.14), and 0.67 (IQR 0.54–1.01) per 100,000 ED attendances, respectively. No rising trend of use was observed. The majority of the episodes involved men (70.6%) and the median age was 32.0 years. More than half of the episodes involved polysubstance abuse, with methamphetamine, cocaine and cannabis involved in 1,225, 328 and 172 episodes, respectively. Nineteen NPSs were identified in 23 episodes.

Over 70% of the cases had a previous history of drug abuse and a significant proportion had a history of drug-induced psychosis (35.6%). Only a minority of the patients had received detoxification treatment (17.1%), social worker follow-up (22.1%) and NGO drug services (7.6%) before the index presentation. Most patients were triaged to a higher acuity in the ED (Category 3 or the more urgent category) with prominently neurological and cardiovascular presentations, including sinus tachycardia, hypertension, confusion and agitation. Psychotic features, including hallucination and delusion, were more commonly seen in methamphetamine abusers. Hypokalaemia was found in around one-fifth of all cases. Rhabdomyolysis and acute kidney injury occurred in many methamphetamine and cocaine abusers. Acute toxicity was often accompanied by disorganised behaviours, self-harm, aggression and injuries. Supportive treatment was the mainstay and a significant proportion required physical and/or chemical restraints. Irrespective of the drug used, the majority of the patients were managed and discharged from the ED. In total, 96 patients required intensive care unit (ICU) admission and 18 patients died of acute toxicity. Methamphetamine-related episodes had a higher proportion of psychiatric ward admission, urgent psychiatric consultation and referral to psychiatric services upon discharge.

Overall, the median PSS of the whole cohort was 2, and 24.1% of the cases developed one of the end-organ toxicities defined as secondary outcome. Patients with any of the following were at a higher risk of developing severe complications: a triage temperature > 39°C (odds ratio [OR] 7.59, 95% confidence interval [CI] 2.10–27.49, p=0.002); diaphoresis (OR 2.30, 95% CI 1.42–3.71, p=0.001); agitation (OR 1.87, 95% CI 1.32–2.64, p<0.001); a triage ranking of a higher acuity (OR 1.86, 95% CI 1.48–2.33, p<0.001); concurrent use of cough mixture or pills (OR 1.81, 95% CI 1.09–3.00, p=0.023); co-ingestion of other medications (OR 1.68, 95% CI 1.07–2.63, p=0.026); sluggish or non-reactive pupils (OR 1.61, 95% CI 1.02–2.52, p=0.039); associated injury (OR 1.56, 95% CI 1.04–2.35, p=0.032); and tachycardia >120 beats per minute (OR 1.55, 95% CI 1.09–2.19, p=0.015). Patients who presented with auditory hallucination (OR 0.54, 95% CI 0.35–0.85, p=0.007) and drowsiness (OR 0.31, 95% CI 0.19–0.52, p<0.001) were less likely to develop severe complications. Predictors of severe outcome varied in episodes that involved methamphetamine, cocaine and cannabis.

Over half of the patients reattended ED for drug-related problems, especially among the methamphetamine abusers (58.9%), and over 50% of these revisits manifested with psychotic symptoms. In total, 1,195 patients were included in the Cox regression analysis. After controlling for gender, social allowance status, past physical health status and the length of stay of the index hospitalisation, methamphetamine abuse (hazard ratio [HR] 2.10, 95% CI 1.64–2.68, $p<0.001$) and the need for urgent psychiatric consultation (HR 1.60, 95% CI 1.31–1.95, $p<0.001$) remained significantly associated with a higher risk of reattendance, whereas a major effect of acute toxicity was associated with a lower risk (HR 0.54, 95% CI 0.33–0.88, $p=0.013$).

Conclusions

Data from the EDs extended our current understanding of the trends, patterns, harms and burden of methamphetamine, cocaine and cannabis abuse in Hong Kong. Although we could not identify a significant trend of increased ED presentations of acute toxicity, there is no room for complacency. Methamphetamine remains a major public health burden and threat to physical and mental health. More resources should continue to be channelled to educate youths about its harms and to prevent its use. Although most cases of acute methamphetamine, cocaine and cannabis toxicity can be managed in the ED, end-organ toxicities are frequently encountered and their risk factors should be actively looked for early in the clinical course. The optimal ED care model for methamphetamine, cocaine and cannabis drug abusers remains unknown. There is a need to bring drug services from different agencies to the patients while they are still in hospital to ensure maximum engagement in order to motivate behavioural change.

Declaration

The following work was completed by the research team led by the principal investigator, Dr Rex Pui Kin Lam at the Emergency Medicine Unit, Li Ka Shing Faculty of Medicine, The University of Hong Kong with collaboration with the Hong Kong Poison Information Centre of the Hospital Authority and Hong Kong Lutheran Social Service.

The research was conducted in accordance with the Declaration of Helsinki. Ethics approval was obtained from the Institutional Review Board of The University of Hong Kong/Hong Kong West Cluster of the Hospital Authority (Reference no. UW 20-597) and the Research Ethics Committee of the Kowloon Central/ Kowloon East Cluster of the Hospital Authority (Reference no. KC/KE-20-0270/ER-2) prior to data collection.

We declare that no work resembling the current study has been published before. We certify that we have reviewed and approved the content of the report.

Acknowlegdements

The research team would like to express our heartfelt gratitude to Ms Ho Ching Chan and Ms Agatha Ho for their help in data collection and preparation of the manuscript.

We sincerely thank our colleagues working in emergency departments of Hong Kong and the Hong Kong Poison Information Centre for their expert care of the patients described in this study and we dedicate the study to them all for their tireless efforts in looking after our ED patients with acute recreational drug toxicity.

This study was supported by the Beat Drugs Fund Association (Project Reference No. BDF190053).

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List of abbreviations

1P-LSD	1-Propionyl-d-lysergic acid diethylamide
25B-NBOMe	2-(4-bromo-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine
25C-NBOMe	2-(4-chloro-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine
2-Oxo PCE	Deschloro-N-ethyl-ketamine
5F-MDMB-PICA	Methyl-2-[[1-(5-fluoropentyl) indole-3-carbonyl]amino]-3,3-dimethyl-butanoate
5-MeO-DIPT	5-methoxy-N,N-diisopropyltryptamine
A&E	Accident and emergency department
AAPCC	American Association of Poison Control Centers
ABFUBINACA	N-[(2S)-1-amino-3-methyl-1-oxobutan-2-yl]-1-[(4-fluorophenyl)methyl]indazole-3-carboxamide
ACS	Acute coronary syndrome
ADB-FUBINACA	N-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-[(4-fluorophenyl)methyl]indazole-3-carboxamide
AKI	Acute kidney injury
ALP	Alaine phosphatase
ALT	Alaine aminotransferase
AMI	Acute myocardial infarction
ARDS	Adult respiratory distress syndrome
AST	Aspartate aminotransferase
CI	Confidence interval
CK	Creatine kinase
CMS	Clinical Management System
CNS	Central nervous system
CPR	Cardiopulmonary resuscitation
CRDA	Central Registry of Drug Abuse
CSSA	Comprehensive Social Security Assistance
CVS	Cardiovascular System
DAWN	Drug Abuse Warning Network
DBP	Diastolic blood pressure
DI	Diabetic insipidus
DIC	Disseminated intravascular coagulation
DILI	Drug-induced liver injury
ECMO	Extracorporeal membrane oxygenation
ED	Emergency department
EMW	Emergency Medicine Ward
ePR	Electronic patient record
Euro-DEN	European Drug Emergencies Network
GCS	Glasgow Coma Scale
GGT	γ-glutamyl transferase
GI	Gastrointestinal
HA	Hospital Authority
HKPIC	Hong Kong Poison Information Centre
HR	Hazard ratio
ICH	Intracranial haemorrhage
ICU	Intensive care unit

IQR	Interquartile range
IV	Intravenous
IVH	Intraventricular haemorrhage
KDIGO	Kidney Disease: Improving Global Outcomes
LOS	Length of stay
LSD	Lysergic acid diethylamide
MAP	Mean arterial blood pressure
MDMA	3,4-methylenedioxy-methamphetamine
MOF	Multi-organ failure
MRSA	Multi-drug resistant *Staphylococcus* aureus
MSM	Men who have sex with men
MSW	Medical social worker
N/A	Not applicable
NGO	Non-governmental organisation
NPS	Novel psychoactive substances
NSTEMI	Non-ST-elevation myocardial infarction
OR	Odds ratio
PE	Pulmonary embolism
PI	Principal investigator
PICMS	Poison Information and Clinical Management System
PMMA	paramethoxymethamphetamine
PMA	Paramethoxyamphetamine
PSA	Psychoactive substance abuse
PSS	Poison Severity Score
RR	Respiratory rate
SaO2	Oxygen Saturation
SBP	Systolic blood pressure
SD	Standard deviation
SPSS	Statistical Package for the Social Sciences
STEMI	ST-elevation myocardial infarction
SVT	Supraventricular tachycardia
TFMPP	1–(3-trifluoromethylphenyl)piperazine
TRL	Toxicology Reference Laboratory
ULN	Upper limit of normal
URL	Upper reference limit
VT	Ventricular tachycardia

1. Introduction

1.1 Background

Psychoactive substance abuse (PSA) is a major public health problem worldwide. At the global level, it is estimated that 1 in 20 adults used at least one drug in 2014.[1] PSA can lead to significant morbidity and mortality. Often patients with acute toxicity due to PSA present to emergency departments (EDs),[2,3] which serve as the first contact points for drug users with the healthcare system. It is clear that EDs have an important role to play in monitoring the changing pattern of recreational drug use and the associated toxicity. ED-based sentinel networks for recreational drugs have been established in many countries. Examples include the Drug Abuse Warning Network (DAWN) in the United States and the European Drug Emergencies Network (Euro-DEN) in Europe.[4–7] These networks provide complementary information to other indicators of drug-related harm and help build a bigger picture of the public health implications of recreational drug use.[7]

In Hong Kong, recreational drug use statistics are provided by the Central Registry of Drug Abuse (CRDA) of the Narcotics Division of the Security Bureau, which collates information voluntarily reported by law enforcement departments, treatment and welfare agencies, hospitals, clinics and tertiary institutions.[8] However, the CRDA data do not specify the number of drug users who develop acute toxicity. The Hong Kong Poison Information Centre (HKPIC), which provides poison information and toxicology management advice to health care professionals, has published annual reports on local poisoning incidents since 2006.[9] Recreational drug use/abuse accounts for 13–14% of all poisoning incidents reported to the centre and this figure has remained stable since 2007.[10–19] However, these reports do not provide detailed information about the drug harms related to PSA.

Clearly, more information about the harms of psychoactive substances is needed. EDs are important sources of information regarding the acute toxicity associated with abuse of psychoactive substances and other related problems, including withdrawal, mental and behavioural problems, trauma, and infection. Yet local studies have been sparse despite substance abuse being a common encounter in EDs. A relatively small study in an ED located close to the Hong Kong–Shenzhen border showed that ecstasy (the street name for 3, 4-methylenedioxymethamphetamine) was the most commonly abused drug among users with the majority taking it in mainland China.[20] However, that study was conducted more than 15 years ago and might not reflect the current pattern of recreational drug use. Ng et al. reviewed the medical records of 233 cases of ketamine users presenting to 15 local EDs.[21] Systemic local studies on methamphetamine, cocaine and cannabis, which have gained prevalence in Hong Kong in recent years, are currently lacking.

ED visits by PSA patients provide an opportunity for physicians to actively engage them in discussion and reflection about their drug abuse, motivate behavioural change, and connect them with appropriate substance abuse services. Barriers to effective ED interventions include competing priorities, inadequate staff training and stigma.[22] In Hong Kong, there has been a lack of studies on ED interventions, including psychosocial interventions and referrals to substance abuse services after management of the acute toxicities or medical problems related to PSA. The impact of ED-based interventions on reducing reattendance for drug-related presentations after discharge remains largely unknown in the local setting.

1.2 Knowledge gaps

In summary, knowledge gaps exist in the following areas:

1. the trends and characteristics of patients who present to EDs with acute toxicity related to abuse of methamphetamine, cocaine and cannabis in Hong Kong

2. the current practices of ED interventions, including psychosocial interventions and referrals to substance abuse services, such as non-governmental organisation (NGO) service providers, for patients presenting with methamphetamine, cocaine and cannabis abuse, and their impact in reducing subsequent ED reattendance for drug-related problems

This information has important implications not only for clinical practice regarding the management of acute drug toxicity but also for policy-making and future research related to ED interventions for PSA in Hong Kong. It could also provide data to support initiatives that strengthen the role of EDs in fighting drug abuse.

Supported by a Beat Drugs Fund research grant, this retrospective study included all consecutive patients who were reported to the HKPIC by public accident and emergency departments (A&Es) in Hong Kong over the 10-year period between 1 January 2010 and 31 December 2019. Here, we report the study objectives, methodology and results, and discuss the implications of the findings for future policies to fight drug abuse in Hong Kong.

In order to reduce recurrent drug-related ED attendance, it will be essential to reach out to different stakeholders working in the field of substance abuse and explore effective strategies that engage drug abusers early in the hospital setting, facilitate case referral and strengthen continued care after ED discharge in a multi-sectoral platform. To that end, we plan to organise a knowledge exchange forum at the end of this project to share the knowledge generated from this research.

2. Study objectives

This study focused on methamphetamine, cocaine and cannabis. Surprisingly, despite their popularity among recreational drug abusers and the significant associated harms, local studies on their acute toxicities and ED interventions are lacking.

The objectives of this study were as follows:

1. To characterise the trends and patterns of acute toxicity related to methamphetamine, cocaine and cannabis abuse in individuals presenting to EDs in Hong Kong, and to evaluate the impact of the pattern of drug use and severity of acute toxicity on ED reattendance for drug-related problems

2. To evaluate the current practice of ED interventions, including psychosocial interventions and case referrals to substance abuse services, and their impact on reducing subsequent drug-related ED reattendance

During the case review process, we identified a number of cases of acute toxicities related to the misuse of novel psychoactive substances (NPSs), which have rapidly emerged and proliferated around the world. Designed to mimic existing established recreational drugs, NPSs are often sold online as 'legal highs'. These compounds comprise a wide array of drugs ranging from stimulants (such as mephedrone), cannabinoids (such as 'spice'), hallucinogens (including dissociatives and psychedelics) and depressants (including novel benzodiazepines and novel opioids).[23] These compounds pose unique challenges for drug control and clinical management. This report also briefly describes the NPSs captured in the HKPIC database within the study period.

3. Methods

This was a retrospective study on all consecutive patients reported to the HKPIC by public A&Es in Hong Kong over the 10-year period between 1 January 2010 and 31 December 2019.

3.1 Research ethics

The study was approved by the Institutional Review Board of The University of Hong Kong/Hong Kong West Cluster of the Hospital Authority (HA; reference no. UW 20-597) and the Research Ethics Committee of the Kowloon Central/Kowloon East Cluster of the HA (reference no. KC/KE-20-0270/ER-2). Informed consent from the recruited subjects was waived because of the retrospective nature of the study and anonymity in the data analysis.

3.2 Study setting and data source

The HKPIC is an information hub of poisoning in Hong Kong. It provides a round-the-clock phone consultation service to health care professionals in Hong Kong, and collects epidemiological data on poisoning voluntarily reported by all A&Es in the city. Data on each poisoning case, received from either consultation or reporting, are entered into the Poison Information and Clinical Management System (PICMS) by trained staff and routinely verified by senior team members.[19] This database contains territory-wide data that are representative of the local PSA pattern.

3.3 Study population

All patients with acute toxicity related to the recreational use of methamphetamine, cocaine, cannabis and NPSs within the study period were included. Drug use was defined based on clinical diagnosis with or without confirmation by a urine toxicology immunoassay or laboratory liquid chromatography and mass spectrometry. The following criteria were used to exclude subjects from the descriptive analysis:

1. Recreational abuse of other drugs that were not the focus of the current study, such as cough mixture and ketamine, without the involvement of methamphetamine, cocaine, cannabis or NPSs (although patients with polysubstance abuse that involved other recreational drugs were still included in the analysis)
2. Unintentional exposure
3. Malicious exposure in which the patients were victims of another person's intention to harm them

4. ‘Body packing’ of methamphetamine, cocaine and cannabis; however, individuals who had swallowed drugs hastily to avoid law enforcement arrest (‘body stuffer’) were still included as they were considered likely to be drug abusers.
5. Unrelated cases in which clinical presentations were explained by alternative medical or psychiatric diagnoses, or social or non-medical reasons
6. Confirmed non-exposure with objective evidence that the initially suspected involvement of methamphetamine, cocaine, cannabis or NPSs had not occurred
7. Non-ED cases

3.4 Data collection

Electronic medical records of all eligible cases were retrieved from PICMS using appropriate poison vocabularies and codes in the HKPIC (Appendix 1). The electronic medical records of all eligible cases were then retrieved from the Clinical Management System (CMS) of the HA using patient identifiers for review. Once a data file had been built up for an individual subject, his or her personal identifiers were permanently erased from the study database to protect the subject’s privacy. Data were retrieved and collected by two research assistants independently in parallel based on a standardised data-entry coding manual (Appendix 2). Any discrepancies were resolved by the principal investigator (PI). All data were entered into an Excel spread sheet. The following data were collected:

1. Demographic data, including age, gender and social allowance status
2. Poison data, including the type of drug, dose, route, time, place and reason for exposure
3. Clinical data, including triage category, clinical features and investigation results; triage clinical variables included the Glasgow Coma Scale (GCS), blood pressure, pulse rate, respiratory rate, oxygen saturation, body temperature and pupil size
4. Data on associated problems, including injuries, self-harm behaviour and aggressive behaviour
5. Management data, including the use of decontamination, antidotes and other specific treatments such as endotracheal intubation, mechanical ventilation and electrical therapy
6. Data on severe complications, including cardiac arrest, acute myocardial injury, heart failure, shock, respiratory failure, acute kidney injury (AKI), liver injury, rhabdomyolysis, seizure, coma, acute ischaemic stroke, intracranial bleeding and severe hyperthermia
7. Outcome data, including hospitalisation, intensive care unit (ICU) admission, psychiatric admission, length of stay, episode death, time to reattendance for drug-related presentations after ED discharge and the frequency of ED reattendance within 1 year of the index ED presentation
8. ED interventions, including psychiatric consultation, referral to medical social worker and case referral to NGO substance abuse services

We evaluated the whole clinical course of individual cases from presentation to hospital discharge or death for the index ED attendance and ranked the severity of toxicity using the Poison Severity Score (PSS). The PSS classifies the severity of poisoning into five categories: (0) none, (1) minor, (2) moderate, (3) severe, and (4) fatal poisoning, based on the most severe clinical features identified in the index presentation. We checked the occurrence of a particular symptom or sign against the PSS chart and assigned a severity grading for each case (Appendix 3).[24] The PSS is commonly used in similar studies on PSA in other countries and has been validated.[24-26] It allows comparison of the severity of acute toxicity of methamphetamine, cocaine, cannabis and NPSs across different centres. To ensure reliability of PSS grading, all grading was performed by an experienced emergency physician with post-graduate training in clinical toxicology (PI) and crossed-checked randomly by another emergency physician with a similar training background. Any discrepancies were resolved by discussion with the third investigator, who was a full-time clinical toxicologist in the HKPIC.

We classified the outcome of acute poisoning into five categories: no effect, mild effect, moderate effect, major effect or death, with reference to the American Association of Poison Control Centers' National Poison Data System (Appendix 4).[27] The relationship between exposure to the poison and clinical outcomes was graded as definite, probable, possible, not related or undetermined/not applicable according to the judgement of the clinical toxicologists in the HKPIC.

3.5 Sample size calculation

According to the annual reports of the HKPIC, the number of amphetamines, cocaine and cannabis poisonings reported were around 170, 50, and 25, respectively. There was no breakdown of the cases that involved amphetamines and we assumed that methamphetamine accounted for around 60% of the amphetamine cases.[9–20] The estimated total sample size over 10 years would be around 2,400, including around 1,000 methamphetamine abusers, 500 cocaine abusers, and 250 cannabis abusers who presented to EDs for acute toxicity. For the Cox regression model, which predicted the ED reattendance, it was sufficiently powered with 10–20 events per predictor variable.[28] We listed about 40 predictor variables above (data collection) and assuming that, at most 20 variables were selected for the multivariable analysis, there would be sufficient power to estimate the independent effect of the predictors for methamphetamine, cocaine and cannabis abusers.

3.6 Outcome

Primary Outcome

The primary outcome was the time interval between the index ED attendance (the first drug-related presentation within the study period) and the first ED reattendance for a drug-related

problem. We defined a drug-related problem as presentation directly related to the acute toxicities of drug abuse or acute withdrawal.

Secondary Outcome

The secondary outcome was a composite outcome of severe complications, including cardiac arrest, acute myocardial injury, ventricular dysrhythmias, heart failure, shock, respiratory failure, AKI, liver injury, rhabdomyolysis, seizure, coma, acute ischaemic stroke, intracranial bleeding that was not due to injury and disseminated intravascular coagulation (DIC).

We followed the Forth Universal Definition of Myocardial Infarction in defining acute myocardial injury as an elevated cardiac troponin value above the 99th percentile of the upper reference limit (URL) with a rise and fall of the value.[29] The occurrence of ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), unstable angina and heart failure after recreational drug use was recorded as documented in the medical notes. Shock was defined by a systolic blood pressure (SBP) <90 mmHg or a mean arterial blood pressure (MAP) <65 mmHg or a clinical diagnosis of circulatory shock in the clinical notes when the blood pressure readings were above the cut-off points.[30]

In this study, we defined drug-induced liver injury (DILI) based on the following thresholds proposed by an international expert group: (a) alanine transferase (ALT) value ≥5 × upper limit of normal (ULN), (b) alanine phosphatase (ALP) value ≥2 × ULN or (c) ALT value ≥3 × ULN and total bilirubin ≥2 × ULN.[31] However, since elevation of aminotransferase including aspartate aminotransferase (AST) and ALT is common in the setting of rhabdomyolysis,[32] we carefully evaluated the trajectory of serum creatine kinase (CK) and aminotransferases of each case with rhabdomyolysis. Only those patients with a concurrently elevated bilirubin or γ-glutamyl transferase (GGT) level, which are inconsistent with isolated muscle injury, were considered to be suffering from DILI in this study.[33]

AKI was defined based on the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for Acute Kidney Injury.[34]

We defined rhabdomyolysis as a CK level >1,000 IU/L in the absence of myocardial infarction/CK elevation with cardiac aetiology, chronic renal failure and neuromuscular disease with myopathies, based on the findings and recommendations of Stahl et al.[35] We did not include symptoms in the definition because many patients were intoxicated at the time of presentation and they might not have been able to report muscle pain or weakness accurately.

Other severe complications, including ventricular dysrhythmias, respiratory failure, coma, acute ischaemic stroke, intracranial bleeding and DIC were recorded as clinically documented.

3.7 Data analysis

We initially studied the overall trend of patients who presented to EDs with acute toxicity related to abuse of methamphetamine, cocaine and cannabis in Hong Kong from 2010 to 2019. We calculated the median annual incidence of methamphetamine-, cocaine-, and cannabis-related visits per 100,000 ED attendances over the study period. We then evaluated the time trend using a Poisson regression/negative binomial regression model (depending on the dispersion of data) with the logarithm of total ED attendance as the offset term. We tested the time trend using a linear or quadratic term to allow for potential non-linear trends. To study the trend of drug use among young substance abusers, we repeated the same analysis for those who were aged ≤21 years at the time of ED presentation. We also evaluated the correlation between the trend of methamphetamine, cocaine and cannabis abuse reported from local A&Es with the CRDA data and drug seizure data reported by the Customs and Excise Department. Furthermore, we compared the levels of drug-related ED visits with overseas data by determining the annual rates of ED visits per 100,000 population. All population estimates were based on the mid-year population data provided by the Census and Statistics Department of the Government of the Hong Kong Special Administrative Region.

We then evaluated the characteristics of cases of acute toxicities related to abuse of methamphetamine, cocaine and cannabis presenting to local A&Es. Descriptive statistics were used to analyse the distribution of characteristics of the study population. Missing values were not imputed. We stratified patients into groups based on abuse of methamphetamine, cocaine and cannabis. Pearson's chi-square test (or Fisher's exact test where appropriate) was used to study the differences in proportions between groups. For variables with a normal distribution, we compared the mean values across different groups using the Student's t-test. For variables that did not follow a normal distribution, we calculated the median and interquartile range (IQR) and compared group differences using the Mann-Whitney U test. We then performed univariate analysis to identify factors associated with severe complications (secondary outcome). The factors considered were based on an extensive literature search of potential risk factors and the main hypothesis. Factors that were significantly associated with serious complications ($p<0.05$) in the univariate analysis were then entered into a multivariable logistic regression model to control for the confounding factors and to identify independent predictors for severe complications.

Furthermore, we analysed the current ED practice, including psychosocial interventions and case referrals to NGO substance abuse services. To evaluate the impact of the pattern of drug use, severity of acute toxicity, and ED interventions on the time of ED re-visits for drug-

related problems, we treated the first ED attendance within the study period as the index attendance and calculated the time interval between the index ED presentation and the first ED reattendance. Patients who died at the time of the index attendance or subsequently, and those who were identified as tourists or non-local residents were excluded from this analysis because their inclusion would have falsely lowered the reattendance rate. We followed up all patients till 23:59 hours on 31 December 2020, and drug-related ED reattendance that had not happened by that date was censored. Cox regression survival analysis was used to control for the effect of confounding factors such as gender, socio-economic status (receiving social allowance as a surrogate) and the length of index hospitalisation. This was intended to identify factors that were associated with drug-related ED reattendance of methamphetamine, cocaine and cannabis abusers.

The Statistical Package for the Social Sciences (SPSS) for Window version 27.0 (IBM Corp., Armonk, NY, USA) or R version 3.6.1 or later (R Foundation for Statistical Computing, Vienna, Austria) were used for data analysis. A two-tailed p value <0.05 was considered statistically significant.

4. Results

In total, 1,905 episodes of acute toxicities were retrieved from the PICMS. After case review, 1,629 episodes were included in the descriptive analysis and 276 episodes were excluded based on pre-defined criteria. The patient flow and reasons for exclusion are shown in Figure 1.

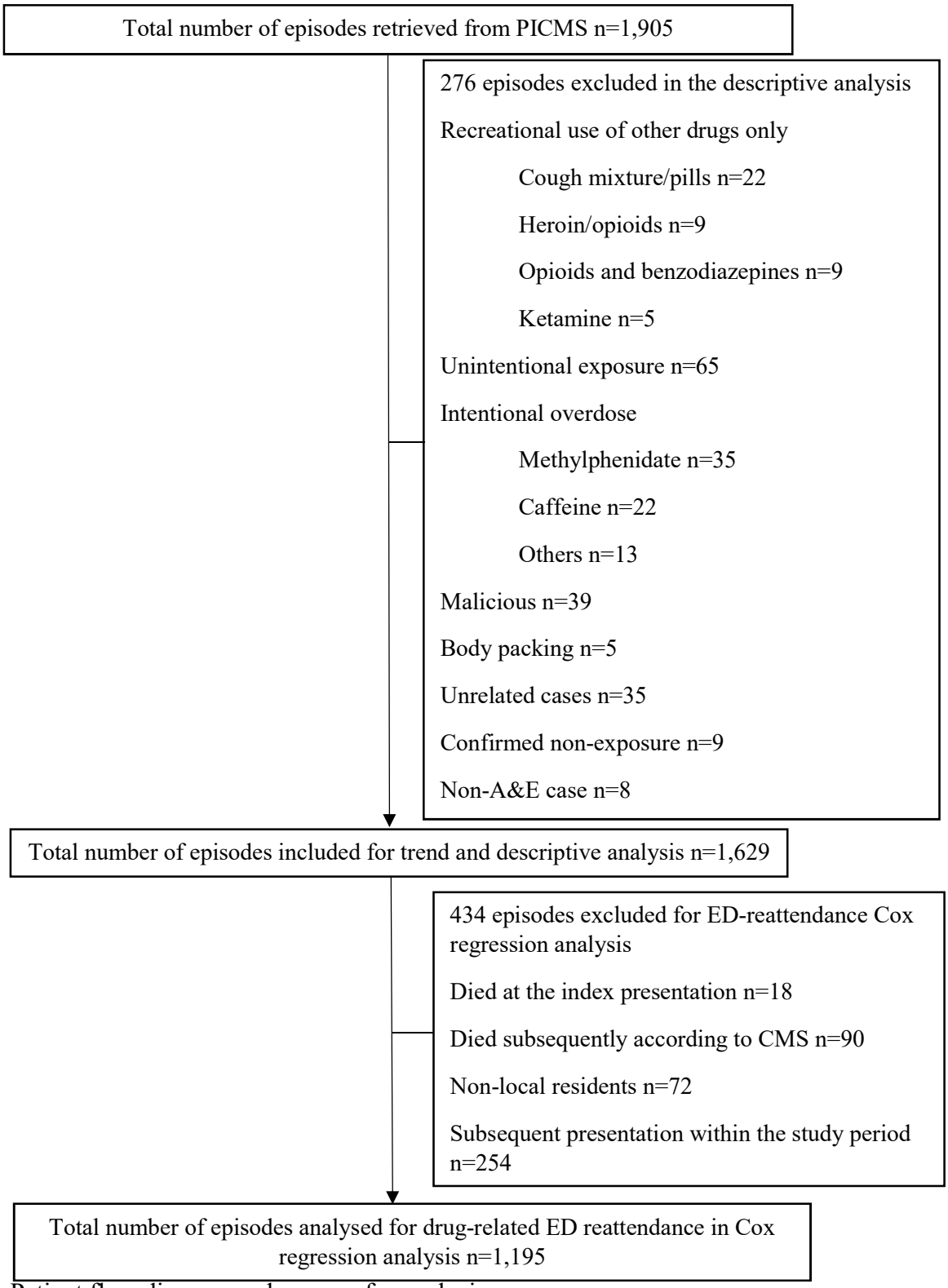


Figure 1. Patient flow diagram and reasons for exclusion.

4.1 Trend analysis

Over the study period, the median annual incidence of acute toxicities related to methamphetamine, cocaine and cannabis abuse were 5.64 (IQR 4.14–6.72), 1.32 (IQR 0.96–2.14) and 0.67 (IQR 0.54–1.01) per 100,000 ED attendances, respectively. The median annual incidence rates of methamphetamine-, cocaine- and cannabis-related ED visits were 1.63 (IQR 1.31–2.06), 0.41 (IQR 0.30–0.60) and 0.21 (IQR 0.17–0.30) per 100,000 population, respectively.

Figure 2 illustrates the trend of acute toxicities related to methamphetamine, cocaine and cannabis abuse reported to the HKPIC from 2010 to 2019. Negative binomial regression was performed because the count data was over-dispersed. As for the linear trend, acute toxicities that involved methamphetamine (OR 1.10, 95% CI 0.86–1.40, p=0.46), cocaine (OR 1.13, 95% CI 0.91–1.40, p=0.27) and cannabis (OR 1.16, 95% CI 0.93–1.45, p=0.20) did not increase significantly during the study period. For drug abusers ≤21 years old, no significantly increasing trend was observed for methamphetamine (OR 0.93, 95% CI 0.72–1.19, p=0.55) and cocaine (OR 1.03, 95% CI 0.81–1.31, p=0.80). For cannabis, an upward trend was seen but the number of cases reported was too small to reach statistical significance (OR 1.30, 95% CI 0.99–1.71, p=0.057).

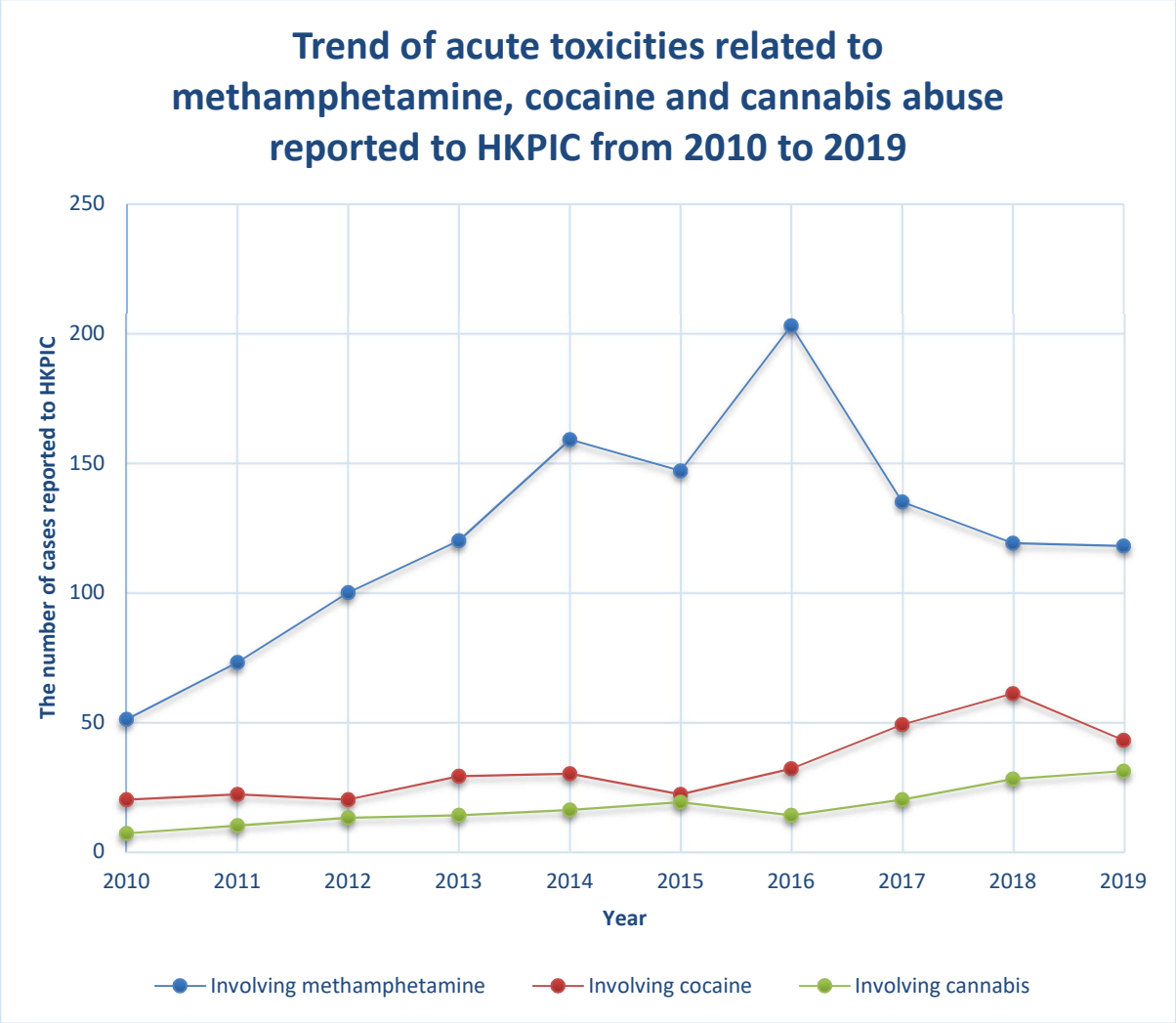


Figure 2. Trend of acute toxicities related to methamphetamine, cocaine and cannabis abuse reported to the HKPIC from 2010 to 2019.

Figures 3–5 show the comparison of acute toxicities captured by the HKPIC and the number of drug abusers reported by the CRDA for methamphetamine, cocaine and cannabis, respectively. The number of acute toxicities reported to the HKPIC was significantly associated with the number of users reported in the CRDA for methamphetamine (Spearman's rho 0.82, p=0.004), but not for cocaine (Spearman's rho 0.43, p=0.22) and cannabis (Spearman's rho 0.26, p=0.46).

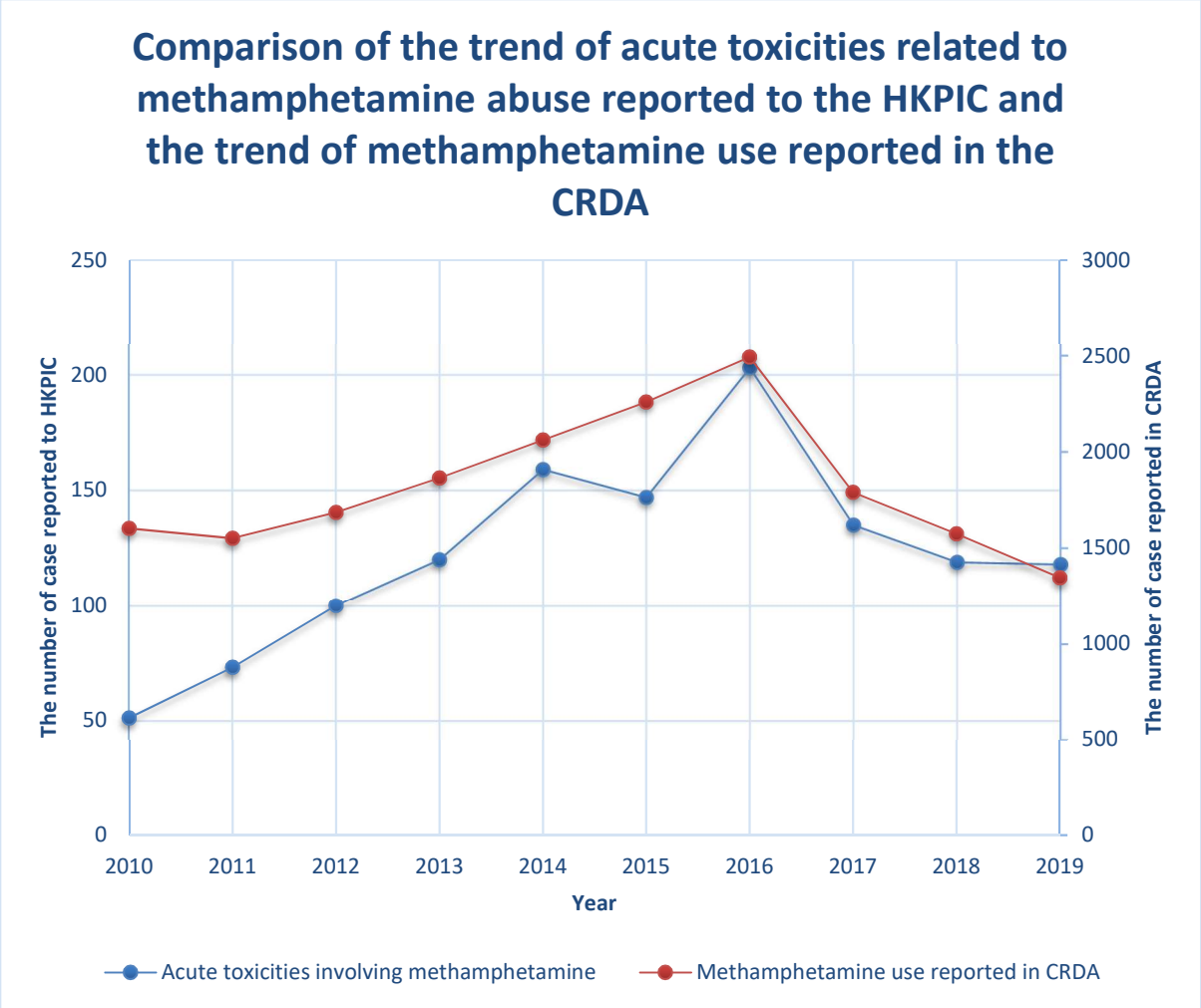


Figure 3. Comparison of the trend of acute toxicities related to methamphetamine abuse reported to the HKPIC and the trend of methamphetamine use reported in the CRDA.

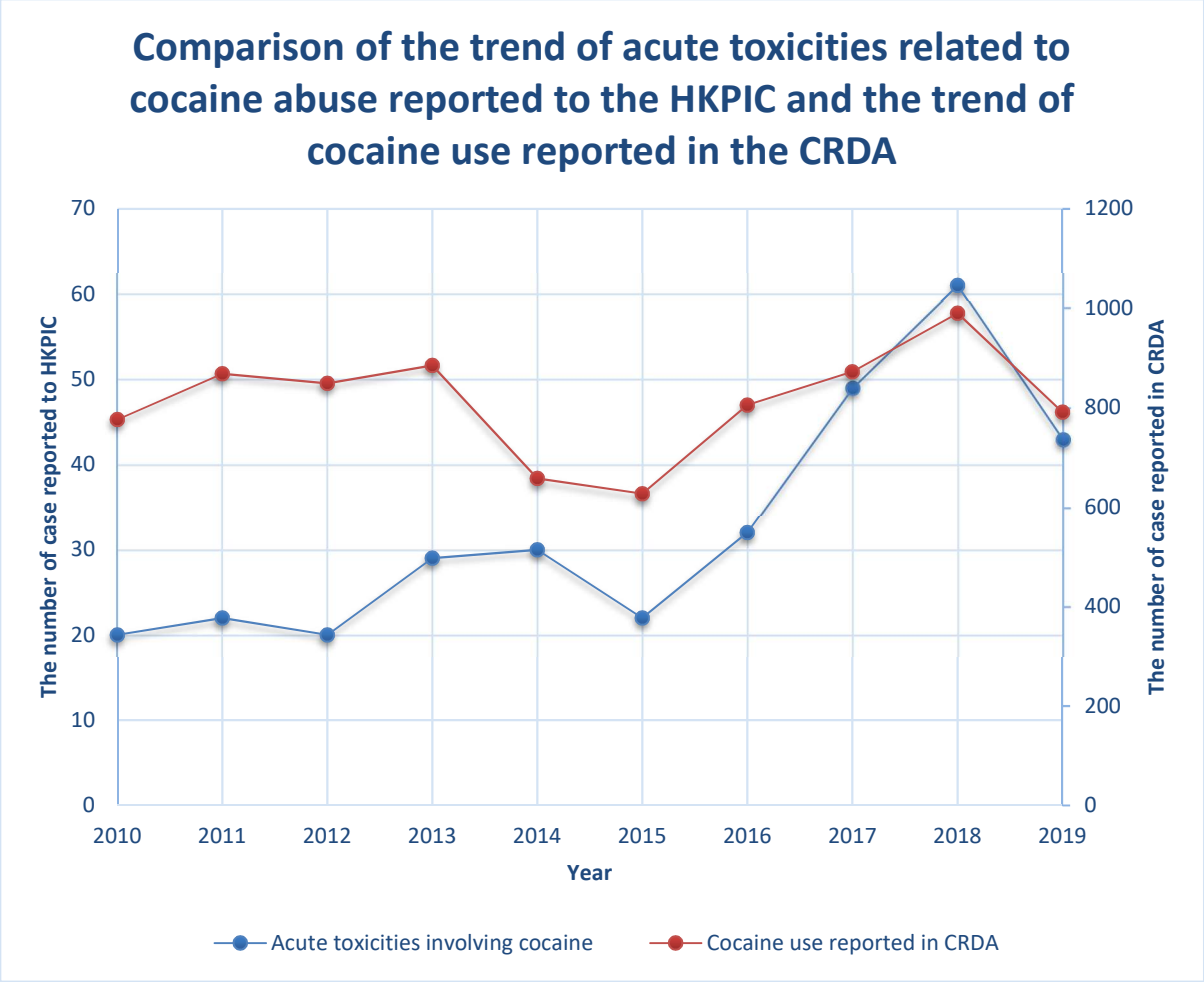


Figure 4. Comparison of the trend of acute toxicities related to cocaine abuse reported to the HKPIC and the trend of cocaine use reported in the CRDA.

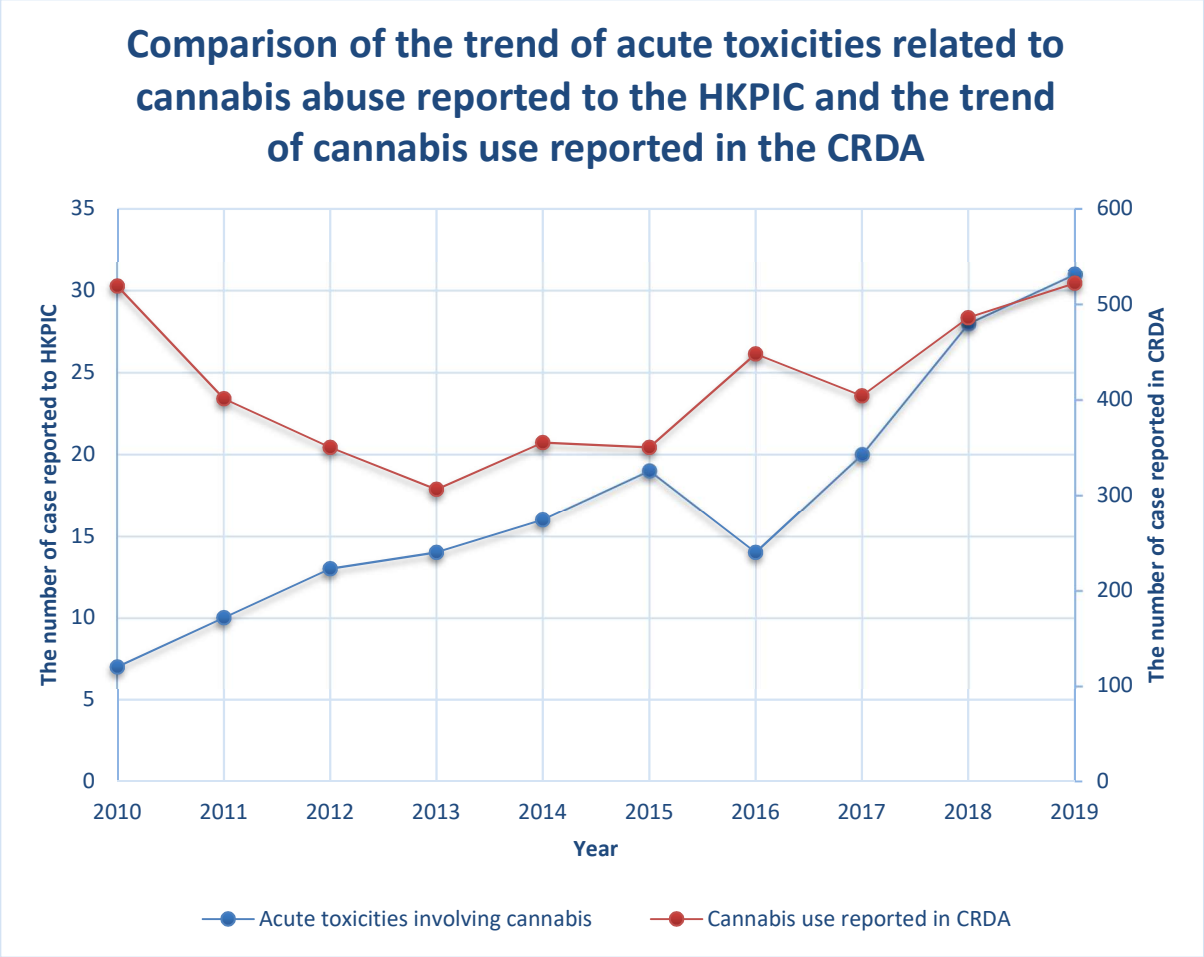


Figure 5. Comparison of the trend of acute toxicities related to cannabis abuse reported to the HKPIC and the trend of cannabis use reported in the CRDA

Figures 6–8 depict the trend of acute toxicities captured by the HKPIC and the market value of drugs seized as reported by the Customs and Excise Department for methamphetamine, cocaine and cannabis, respectively. The number of acute toxicities reported to the HKPIC was significantly correlated with the market value of drugs seized by law enforcement for cannabis (Spearman's rho 0.87, p=0.001), but not for methamphetamine (Spearman's rho 0.33, p=0.35) and cocaine (Spearman's rho –0.18, p=0.63).

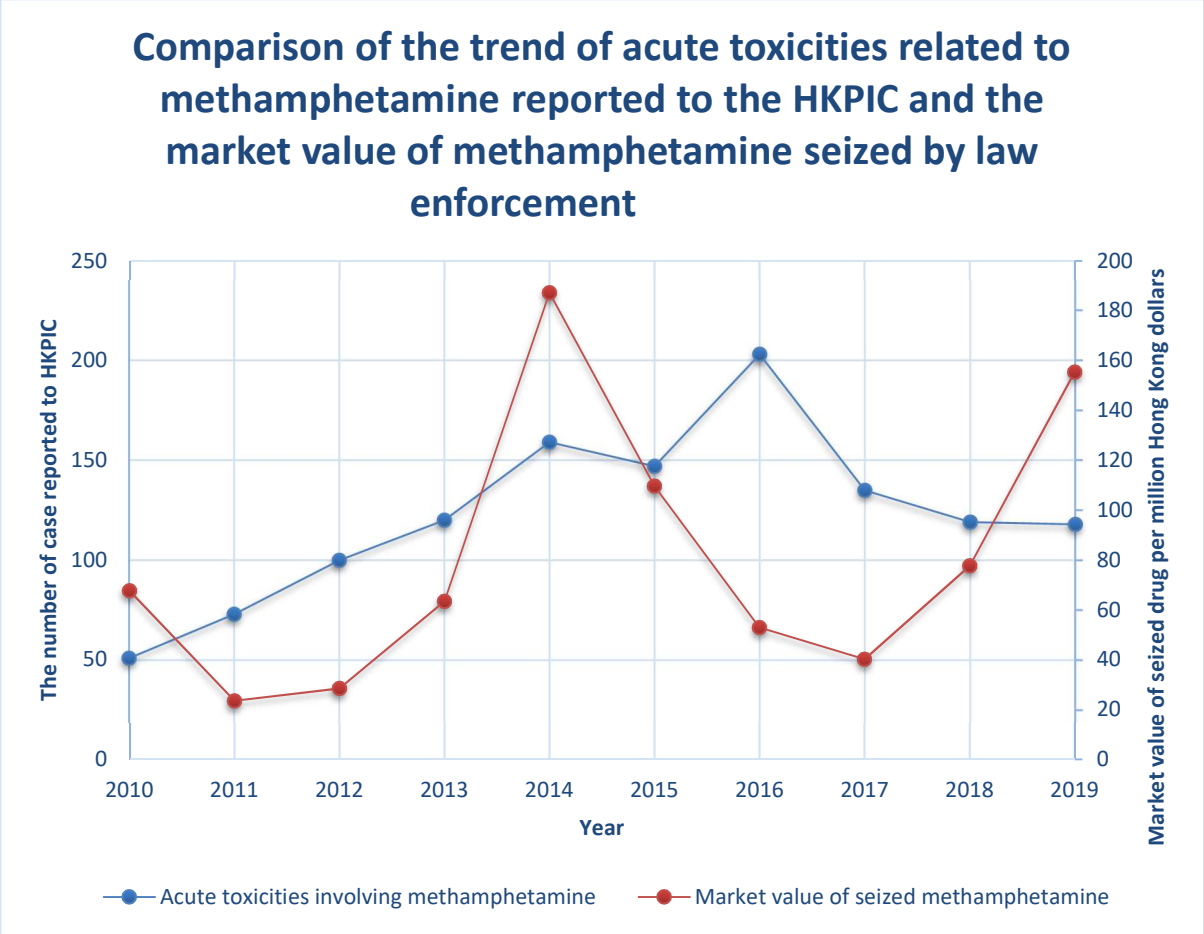


Figure 6. Comparison of the trend of acute toxicities related to methamphetamine reported to the HKPIC and the market value of methamphetamine seized by law enforcement

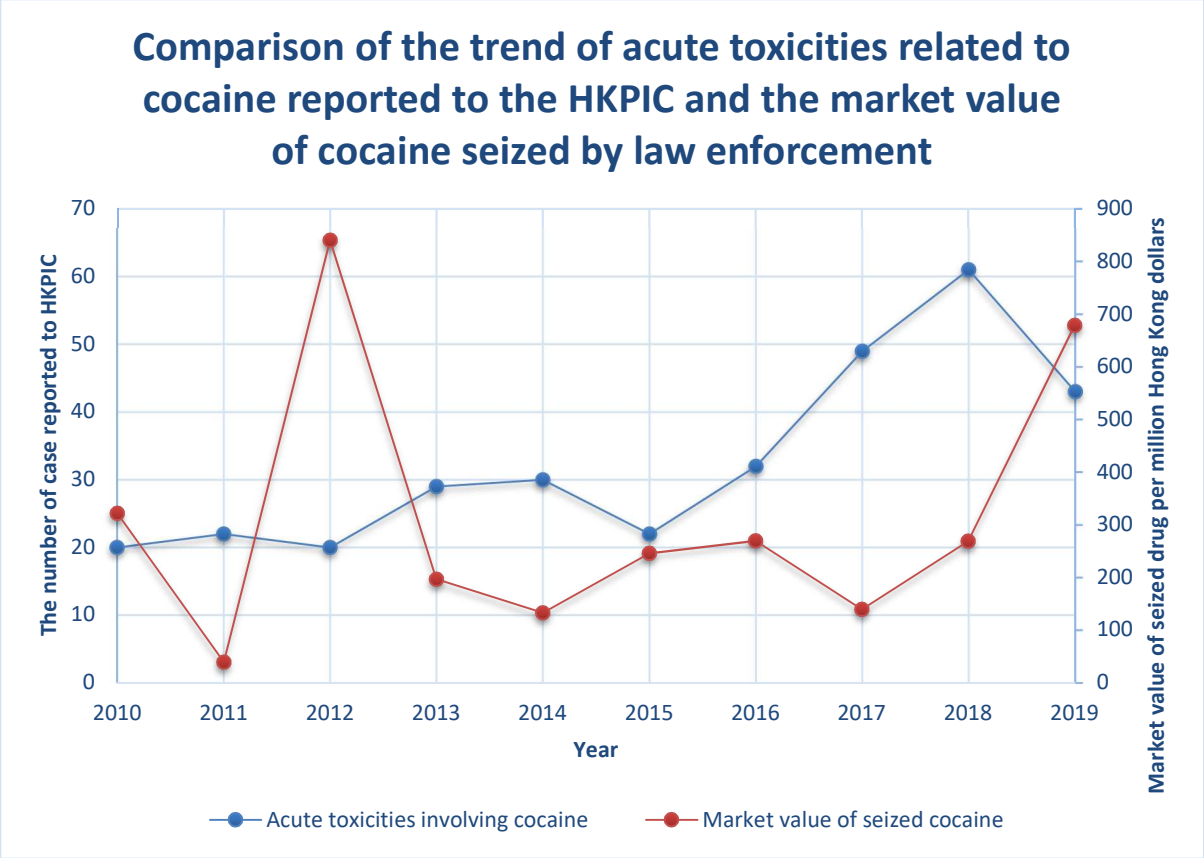


Figure 7. Comparison of the trend of acute toxicities related to cocaine reported to the HKPIC and the market value of cocaine seized by law enforcement

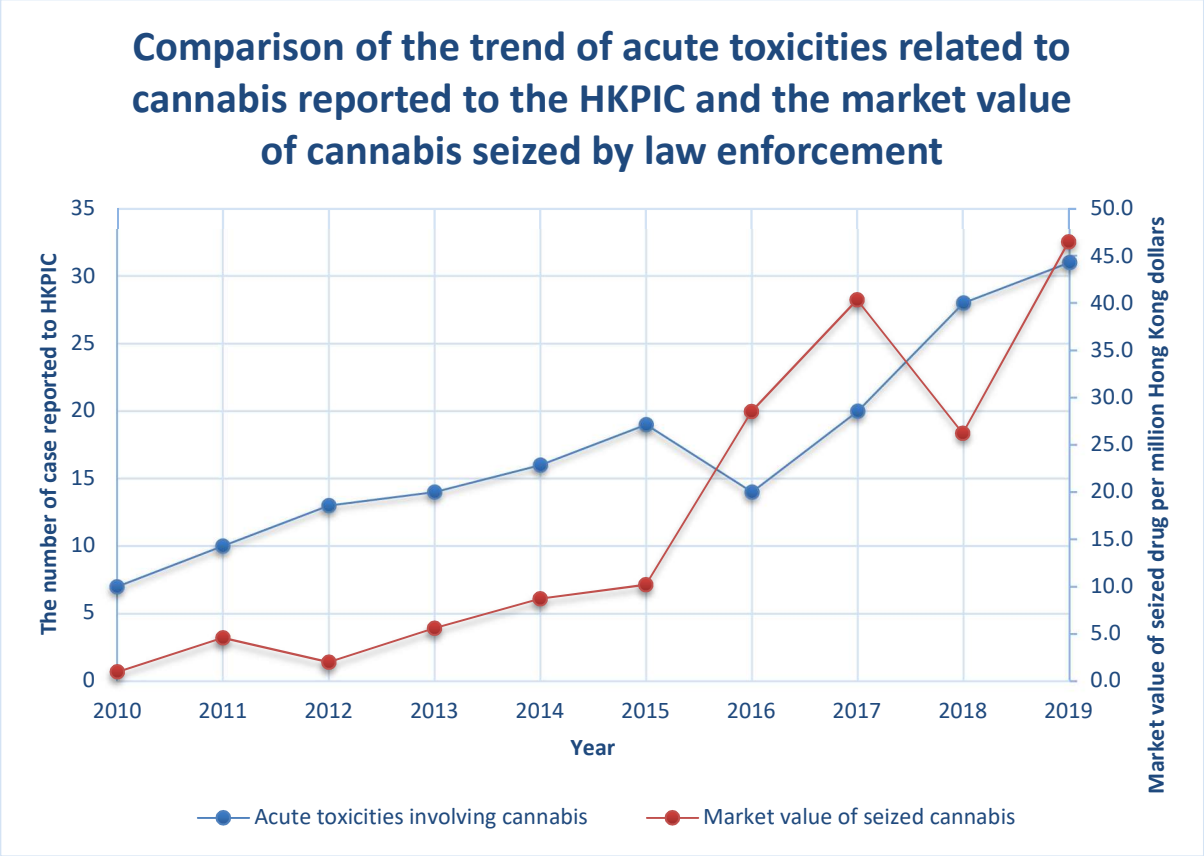


Figure 8. Comparison of the trend of acute toxicities related to cannabis reported to the HKPIC and the market value of cannabis seized by law enforcement

4.2 Pattern and clinical presentations

In total, 1,629 episodes of acute toxicities that involved 1,348 patients were included in the descriptive analysis. The majority of the patients (n=1,168, 86.6%) were reported to the HKPIC once within the study period for acute toxicities related to methamphetamine, cocaine or cannabis abuse. The number of episodes captured by the HKPIC was two in 123 patients (9.1%), three in 32 patients (2.4%), four in 13 patients (0.01%) and five in nine patients (0.007%). Notably, one patient had six episodes and two patients had eight episodes of drug-related acute toxicities reported to the HKPIC within the study period.

The median age of the patients at the time of presentation in the 1,629 episodes was 32.0 years (IQR 25.0–39.0 years). The majority of episodes involved men (n=1,152, 70.6%) and two episodes involved patients who identified themselves as transgender in the clinical notes. As for the socio-economic status, 291 episodes (17.9%) involved patients who received social allowance. Ambulance transportation to A&E was required in 1,191 (73.1%) episodes. Overall, 73 episodes (4.5%) involved non-local residents such as tourists, 10 episodes (0.6%) occurred in pregnant patients and 56 episodes (3.4%) involved men who were reported to have sex with another men.

More than half of the reported episodes involved polysubstance abuse. Methamphetamine, cocaine and cannabis were the only drug abused in 605 (37.1%), 63 (3.9%) and 61 (3.7%) of episodes, respectively. The most common combination was methamphetamine with alcohol (n=141, 8.7%), followed by methamphetamine with ketamine (n=116, 7.1%) and methamphetamine with cough mixture (n=109, 6.7%). For episodes that involved methamphetamine and cannabis, inhalation/smoking was the most common route of drug intake. For cocaine, both inhalation and insufflation were common routes. In most episodes, the place of drug abuse was not documented in the medical record. Drug abuse in places outside of Hong Kong was reported in 11 episodes, of which three occurred in mainland China, two in Thailand, one in Macau and one in Cambodia before the patients returned to Hong Kong to seek medical advice.

The demographic characteristics and the pattern of drug use at the time of presentation are summarised in Table 1 for the whole cohort and for the subgroups that involved methamphetamine, cocaine and cannabis.

Table 1. Demographic characteristics and pattern of drug abuse

	The whole cohort n=1,629	Episodes that involved methampheta mine n=1,225	Episodes that involved cocaine n=328	Episodes that involved cannabis n=172
Age—median (IQR), year	32.0 (25.0-39.0)	33.0 (27.0-40.0)	30.0 (25.0-36.3)	26 (21-32)
Sex—n (%)				
Female	475 (29.2)	379 (30.9)	90 (27.4)	35 (20.3)
Male	1,152 (70.6)	844 (68.9)	238 (72.6)	137 (79.7)
Transgender	2 (0.2)	2 (0.2)	0 (0)	0 (0)
Social allowance—n (%)	291 (17.9)	279 (22.8)	15 (4.6)	9 (5.2)
Ambulance case—n (%)	1,191 (73.1)	931 (76.0)	223 (68.0)	107 (62.2)
Police involvement—n (%)	499 (30.6)	416 (34.0)	84 (25.6)	38 (22.1)
Non-local resident—n (%)	73 (4.5)	37 (3.0)	25 (7.6)	12 (7.0)
Pregnant at the time of presentation—n (%)	10 (0.6)	9 (0.7)	3 (0.9)	0 (0)
MSM—n (%)	56 (3.4)	52 (4.2)	1 (0.3)	2 (1.2)
Drug abused at presentation—n (%)				
Methamphetamine	1,225 (75.2)	N/A	97 (29.6)	29 (16.9)
Cocaine	328 (20.1)	97 (7.9)	N/A	23 (13.4)
Cannabis	172 (10.6)	29 (2.4)	23 (7.0)	N/A
MDMA	46 (2.8)	4 (0.3)	22 (6.7)	6 (3.5)
Ketamine	191 (11.7)	116 (9.5)	87 (26.5)	9 (5.2)
Heroin	52 (3.2)	46 (3.8)	9 (2.7)	2 (1.2)
Cough mixture or pills	134 (8.2)	109 (8.9)	19 (5.8)	13 (7.6)
Zopiclone or zolpidem	98 (6.0)	80 (6.5)	18 (5.5)	7 (4.1)
Benzodiazepine	81 (5.0)	59 (4.8)	22 (6.7)	2 (1.2)
Novel psychoactive substances	23 (1.4)	5 (0.4)	8 (2.4)	1 (0.6)
Co-ingestion of alcohol—n (%)	284 (17.4)	141 (11.5)	111 (33.8)	53 (30.8)
Co-ingestion of other medications—n, (%)	209 (12.8)	145 (11.8)	46 (14.0)	19 (11.0)
Primary route of exposure—n (%)				
Inhalation	823 (50.5)	679 (55.4)	85 (25.9)	119 (69.2)
Insufflation	100 (6.1)	29 (2.4)	69 (21.0)	5 (2.9)
Oral ingestion	150 (9.2)	78 (6.4)	43 (13.1)	25 (14.5)
Intravenous	15 (0.9)	13 (1.1)	1 (0.3)	1 (0.6)
Others	2 (0.1)	2 (0.2)	2 (0.6)	0 (0)
Unspecified	539 (33.1)	424 (34.6)	128 (39.0)	22 (12.8)
Place of drug abuse—n (%)				
Home	94 (5.8)	65 (5.3)	19 (5.8)	11 (6.4)
Workplace	1 (0.1)	0 (0)	0 (0)	1 (0.6)
Public place	68 (4.2)	33 (2.7)	24 (7.3)	15 (8.7)
Unknown	1,466 (90.0)	1,127 (92.0)	285 (86.9)	145 (84.3)
Place outside of Hong Kong	11 (0.7)	9 (0.7)	1 (0.3)	1 (0.6)

Abbreviations: IQR, interquartile range; MSM, men who have sex with men; N/A, not applicable; MDMA, 3,4-methylenedioxy-methamphetamine

During the process of case review, we also identified 19 different NPSs (Table 2) in 24 episodes, including TFMPP (1–(3-trifluoromethylphenyl)piperazine) in six episodes, PMMA (paramethoxymethamphetamine) and PMA (paramethoxyamphetamine) in five episodes, and 5-MeO-DIPT (5-methyoxy-*N,N*-diisopropyltryptamine), 25B-NBOMe and 25C-NBOMe in two episodes. Other NPSs that were involved in single episodes of acute toxicity included ethylone, N-ethylpentylone, 4-fluoroamphetamine, 2-/3-fluoroethylamphetamine, 1-propionyl-d-lysergic acid diethylamide (IP-LSD), 2-methoxydiphenidine, deschloro-*N*-ethyl-ketamine (2-oxo-PCE), 5-methoxy-*N,N*-methylisopropyltryptamine/5-methoxy-*N,N*-diethyltryptamine, 5F-MDMB-PICA, AB-FUBINACA and ADB-FUBINACA and tiletamine. A brief description of each NPS is included in Appendix 5.

Table 2. Novel psychoactive substances reported to the HKPIC from 2010 to 2019

Year	Novel psychoactive substances (n)
2010	TFMPP (3)
2011	TFMPP (2)
2012	
2013	25B-NBOMe and 25C-NBOMe (2), PMMA and PMA (2)
2014	
2015	2-Methoxydiphenidine (1), 4-fluoroamphetamine (1)
2016	PMMA/PMA (1), 5-MeO-DIPT (1), AB-FUBINACA and ADB-FUBINACA (1)
2017	PMMA/PMA (2), TFMPP (1), 2-oxo PCE (1), 5-MeO-DIPT (1), 5F-MDMB-PICA metabolites (1), N-ethylpentylone (1)
2018	5-Methoxy-*N,N*-methylisopropyltryptamine/5-methoxy-*N,N*-diethyltryptamine (1)
2019	1P-LSD (1), 2-/3-fluoroethylamphetamine (1), tiletamine (1)

Table 3 shows the pattern of past recreational drug use, and the psychiatric and medical history of the recruited subjects. Over 70% of the cases in the ED had a previous history of drug abuse. The most common drug abused in our cohort was methamphetamine (58.0%), followed by ketamine (34.0%) and cannabis (23.0%). As for the episodes that involved methamphetamine, cocaine and cannabis, the respective drugs were the most commonly reported drugs abused in the past, indicating loyalty of the drug abusers to individual substances.

Table 3. Past drug abuse, and psychiatric, medical and treatment history

	The whole cohort n=1,629	Episodes that involved methamphetamine n=1,225	Episodes that involved cocaine n=328	Episodes that involved cannabis n=172
Past history of drug abuse—n (%)	1,25332 (76.9)	1,047 (85.5)	209 (63.7)	78 (45.3)
Methamphetamine	945 (58.0)	898 (73.3)	89 (27.1)	26 (15.1)
Cocaine	336 (20.6)	225 (18.4)	153 (46.6)	17 (9.9)
Cannabis	374 (23.0)	309 (25.2)	38 (11.6)	54 (31.4)
MDMA	256 (15.7)	230 (18.8)	32 (9.8)	9 (5.2)
Ketamine	554 (34.0)	466 (38.0)	98 (29.9)	27 (15.7)
Heroin	292 (17.9)	281 (22.9)	23 (7.0)	9 (5.2)
Cough mixture or pills	211 (13.0)	196 (16.0)	13 (4.0)	13 (7.6)
Sedative or hypnotics	324 (19.9)	299 (24.4)	35 (10.7)	7 (4.1)
History of alcohol dependence—n (%)	73 (4.5)	64 (5.2)	12 (3.7)	5 (2.9)
Past medical history—n (%)				
Good past health	744 (45.7)	511 (41.7)	181 (55.2)	100 (58.1)
Hypertension	106 (6.5)	85 (6.9)	14 (4.3)	7 (4.1)
Diabetes mellitus	26 (1.6)	25 (2.0)	4 (1.2)	2 (1.2)
Ischaemic heart disease	5 (0.3)	5 (0.4)	2 (0.6)	0 (0)
History of drug-induced psychosis—n (%)	580 (35.6)	546 (44.6)	43 (13.1)	17 (9.9)
History of psychiatric disease—n (%)				
Schizophrenia	131 (8.0)	120 (9.8)	3 (0.9)	7 (4.1)
Depression	112 (6.9)	87 (7.1)	24 (7.3)	10 (5.8)
Anxiety	22 (1.4)	15 (1.2)	9 (2.7)	3 (1.7)
Bipolar affective disorder	26 (1.6)	15 (1.2)	9 (2.7)	5 (2.9)
History of personality disorder—n (%)				
Antisocial personality disorder	51 (3.1)	51 (4.2)	1 (0.3)	0 (0)
Borderline personality disorder	47 (2.9)	45 (3.7)	5 (1.5)	1 (0.6)
Previous psychiatry follow-up—n (%)				
Regular	374 (23.0)	354 (28.9)	27 (8.2)	14 (8.1)
Defaulted	318 (19.5)	287 (23.4)	37 (11.3)	14 (8.1)
Never	937 (57.4)	583 (47.6)	263 (80.2)	144 (83.7)
Previous psychiatric treatment—n (%)				
Regular	227 (13.9)	213 (17.4)	18 (5.5)	9 (5.2)
Defaulted	215 (13.2)	197 (16.1)	19 (5.8)	7 (4.1)
Poor compliance	91 (5.6)	88 (7.2)	10 (3.0)	5 (2.9)
Never	1,092 (67.0)	723 (59.0)	281 (85.7)	151 (87.8)
Previous detoxification treatment—n (%)	278 (17.1)	253 (20.7)	25 (7.6)	10 (5.8)
Followed-up by social worker—n (%)	360 (22.1)	333 (27.2)	37 (11.3)	9 (5.2)
Followed-up by NGO service provider for drug abuse—n (%)	123 (7.6)	107 (8.7)	20 (6.1)	6 (3.5)

Abbreviations: MDMA, 3,4-methylenedioxy-methamphetamine; NGO, non-governmental organisation

Almost half of the episodes involved patients who had unremarkable past physical health but a significant portion had a history of drug-induced psychosis (35.6%). Compared with cocaine and cannabis, the proportion of patients who had drug-induced psychosis, schizophrenia, anti-social and borderline personality disorder was higher in methamphetamine users. A higher proportion of methamphetamine abusers had received psychiatric follow-up. However, among those who had received psychiatric treatment, only half were compliant. In this cohort, only a minority of the patients had received detoxification treatment (17.1%), social worker follow-up (22.1%) and NGO services for drug abuse (7.6%) before their index drug-related ED presentation.

As for the clinical presentation, most patients were triaged to a higher acuity (Category 3 or the more urgent category) with prominently neurological and cardiovascular presentations. Sinus tachycardia and hypertension were common across different stimulants. Confusion and agitation were the most common neurological presentations at the ED. Notably, a significant proportion of methamphetamine abusers had psychotic features such as hallucination (29.6%) and/or delusion (16.7%). Auditory hallucination (23.8%) and paranoid delusion (21.1%) were frequently reported in methamphetamine abusers in the ED. Cocaine abusers often complained of dizziness (19.2%), chest pain or discomfort (13.4%) and shortness of breath (14.9%). Dizziness (34.2%), nausea and vomiting (18.6%), and shortness of breath (13.4%) were seen in many cannabis abusers in A&E.

Interestingly, hypokalaemia was commonly found in around one-fifth of all cases in the cohort. Rhabdomyolysis was common among drug abusers, especially those with methamphetamine abuse (17.2%). AKI was seen in a significant portion of drug abusers of methamphetamine (9.4%) and cocaine (10.1%) in the ED. Metabolic acidosis was found in 4.3% of the episodes that involved methamphetamine and 6.4% that involved cocaine. Acute myocardial injury was found in 4.7% of the episodes that involved methamphetamine and 4.9% that involved cocaine. Other severe conditions identified during the index presentation included ventricular dysrhythmia (n=5), acute myocardial infarction (n=4), heart failure (n=1), coma (n=49), seizure (n=55), acute ischaemic stroke (n=4), acute haemorrhagic stroke (n=3), respiratory failure (n=24) and severe hyperthermia (n=24). Cardiac arrest occurred in 16 episodes that involved methamphetamine and six with cocaine. Overall, the median PSS of the whole cohort was 2, which was similar for subgroups that involved methamphetamine, cocaine and cannabis, although episodes that involved cannabis did not result in fatality.

Table 4. Clinical presentations and Poison Severity Score of different organ systems

	The whole cohort n=1,629	Episodes that involved methamphetamine n=1,225	Episodes that involved cocaine n=328	Episodes that involved cannabis n=172
Triage category—n (%)				
Category 1—Critical	149 (9.1)	108 (8.8)	37 (11.3)	7 (4.1)
Category 2—Emergent	472 (29.0)	350 (28.6)	93 (28.4)	44 (25.6)
Category 3—Urgent	920 (56.5)	710 (58.0)	173 (52.7)	111 (64.5)
Category 4—Semi-urgent	86 (5.3)	55 (4.5)	25 (7.6)	10 (5.8)
Category 5—Non-urgent	2 (0.1)	2 (0.2)	0 (0)	0 (0)
Triage vital signs				
Systolic blood pressure—mean (SD), mm Hg	136.6 (25.3)	136.2 (25.1)	137.5 (24.9)	138.8 (23.0)
Diastolic blood pressure—mean (SD), mm Hg	83.1 (17.9)	83.7 (18.0)	82.8 (17.0)	81.2 (15.5)
Pulse rate—mean (SD), beat per minute	107.4 (26.3)	107.6 (25.0)	102.3 (26.8)	111.4 (28.3)
Respiratory rate—mean (SD), breath per minute	18.5 (4.9)	18.5 (4.8)	18.3 (5.1)	19.4 (5.3)
SpO2—median (IQR), %	99.0 (97.0-100.0)	99.0 (97.0-100.0)	98.0 (97.0-100.0)	99.0 (98.0-100.0)
Supplemental oxygen required at triage—n (%)	107 (6.6)	68 (5.6)	32 (9.8)	10 (5.8)
Glasgow Coma Scale—median (IQR)	15 (14-15)	15 (14-15)	15 (14-15)	15 (14-15)
Temperature—median (IQR)	36.7 (36.3-37.2)	36.7 (36.3-37.2)	36.7 (36.2-37.2)	36.7 (36.3-37.3)
Pupil size—median (IQR)	3.0 (3.0-4.0)	3.0 (3.0-4.0)	3.0 (3.0-4.0)	3.0 (3.0-4.0)
Pupil reactivity—n (%)				
Reactive	959 (58.9)	719 (58.7)	197 (60.1)	114 (66.3)
Sluggish or non-reactive	143 (8.8)	107 (8.7)	33 (10.1)	6 (3.5)
Not specified	527 (32.4)	399 (32.6)	98 (29.9)	52 (30.2)
Cardiac arrest—n (%)	21 (1.3)	16 (1.3)	6 (1.8)	0 (0)
Cardiovascular presentations—n (%)				
Chest pain/discomfort	144 (8.8)	96 (7.8)	44 (13.4)	18 (10.5)
Palpitation	160 (9.8)	96 (7.8)	41 (12.5)	28 (16.3)
Hypertension	579 (35.5)	412 (33.6)	133 (40.5)	60 (40.1)
Sinus tachycardia	957 (58.7)	729 (59.5)	160 (48.8)	111 (64.5)
Supraventricular tachycardia	8 (0.5)	5 (0.4)	2 (0.6)	2 (1.2)
Ventricular dysrhythmia	5 (0.3)	2 (0.2)	3 (0.9)	0 (0)
Acute myocardial injury	78 (4.8)	57 (4.7)	16 (4.9)	2 (1.2)
Myocardial infarction	4 (0.2)	3 (0.2)	0 (0)	0 (0)
Shock	32 (2.0)	25 (2.0)	8 (2.4)	1 (0.6)
Heart failure	1 (0.1)	1 (0.1)	0 (0)	0 (0)
Cardiovascular PSS—median (IQR, range)	1 (0–1, 0–4)	1 (0–1, 0–4)	1 (0–1, 0–4)	1 (1–1, 0–3)

Neurological presentations—n (%)				
Agitation	528 (32.4)	440 (35.9)	78 (23.8)	45 (26.2)
Confusion	572 (35.1)	483 (39.4)	74 (22.6)	46 (26.7)
Headache	85 (5.2)	57 (4.7)	22 (6.7)	12 (7.0)
Dizziness	265 (16.3)	159 (13.0)	63 (19.2)	59 (34.2)
Seizure	55 (3.4)	33 (2.7)	17 (5.2)	4 (2.3)
Syncope	73 (4.5)	42 (3.4)	20 (6.1)	9 (5.2)
Drowsiness	195 (12.0)	143 (11.7)	45 (13.7)	18 (10.5)
Coma	49 (3.0)	36 (2.9)	10 (3.0)	1 (0.6)
Weakness	27 (1.7)	13 (1.1)	8 (2.4)	7 (4.1)
Numbness	28 (1.7)	19 (1.6)	8 (2.4)	4 (2.3)
Restlessness	91 (5.6)	71 (5.8)	16 (4.9)	9 (5.2)
Involuntary limb movement/tremor	100 (6.1)	70 (5.7)	25 (7.6)	12 (7.0)
Unstable emotion	180 (11.0)	164 (13.4)	20 (6.1)	13 (7.6)
Anxiety	79 (4.8)	52 (4.2)	17 (5.5)	14 (8.1)
Auditory hallucination	316 (19.4)	292 (23.8)	26 (7.9)	16 (9.3)
Visual hallucination	158 (9.7)	130 (10.6)	17 (5.2)	15 (8.7)
Tactile hallucination	21 (1.3)	19 (1.6)	1 (0.3)	2 (1.2)
Paranoid delusion	272 (16.7)	259 (21.1)	24 (7.3)	9 (5.2)
Referential delusion	45 (2.8)	42 (3.4)	1 (0.3)	7 (4.1)
Any hallucination	407 (25.0)	363 (29.6)	37 (11.3)	27 (15.7)
Any delusion	221 (13.6)	204 (16.7)	20 (6.1)	11 (6.4)
Acute ischaemic stroke	4 (0.2)	3 (0.2)	0 (0)	0 (0)
Acute haemorrhagic stroke	3 (0.2)	2 (0.2)	0 (0)	0 (0)
Nervous system PSS—median (IQR, range)	2 (1–2, 0–4)	2 (1–2, 0–4)	2 (1–2, 0–4)	1 (1–2, 0–3)
Gastrointestinal presentations				
Nausea/vomiting	152 (9.3)	85 (6.9)	35 (10.7)	32 (18.6)
Diarrhoea	15 (0.9)	11 (0.9)	3 (0.9)	0 (0)
Abdominal pain	87 (5.3)	62 (5.1)	18 (5.5)	4 (2.3)
Gastrointestinal system PSS—median (IQR, range)	0 (0–0, 0–2)	0 (0–0, 0–2)	0 (0–0, 0–1)	0 (0–0, 0–1)
Respiratory presentations—n (%)				
Shortness of breath	164 (10.1)	110 (9.0)	49 (14.9)	23 (13.4)
Hyperventilation	43 (2.6)	31 (2.5)	8 (2.4)	5 (2.9)
Cough	10 (0.6)	8 (0.7)	2 (0.6)	0 (0)
Bronchospasm	4 (0.2)	2 (0.2)	2 (0.6)	0 (0)
Pneumothorax	1 (0.1)	1 (0.1)	0 (0)	0 (0)
Pneumomediastinum	2 (0.1)	1 (0.1)	1 (0.3)	0 (0)
Respiratory failure	24 (1.5)	17 (1.4)	8 (2.4)	0 (0)
Respiratory system PSS—median (IQR, range)	0 (0–0, 0–3)	0 (0–0, 0–3)	0 (0–0, 0–3)	0 (0–0, 0–1)
Metabolic presentation—n (%)				
Metabolic acidosis	81 (5.0)	53 (4.3)	21 (6.4)	4 (2.3)
Hyperkalaemia	18 (1.1)	14 (1.1)	3 (0.9)	0 (0)
Hypokalaemia	375 (23.0)	294 (24.0)	57 (17.4)	36 (26.9)
Hypernatraemia	13 (0.8)	10 (0.8)	2 (0.6)	1 (0.6)
Hyponatraemia	39 (2.4)	27 (2.2)	12 (3.7)	3 (1.7)
Hyperglycaemia	9 (0.6)	6 (0.5)	2 (0.6)	2 (1.2)

Hypoglycaemia	16 (1.0)	14 (1.1)	3 (0.9)	2 (1.2)
Hyperthermia (temperature>37.8°C)	200 (12.3)	151 (12.3)	41 (12.5)	14 (8.1)
Severe hyperthermia (temperature> 40°C)	24 (1.5)	13 (1.1)	7 (2.1)	2 (1.2)
Metabolic system PSS—median (IQR, range)	0 (0–1, 0–3)	0 (0–1, 0–3)	0 (0–1, 0–3)	0 (0–1, 0–3)
Acute liver injury—n (%)	11 (0.7)	7 (0.6)	1 (0.3)	0 (0)
Liver PSS—median (IQR, range)	0 (0–0, 0–3)	0 (0–0, 0–3)	0 (0–0, 0–3)	0 (0–0, 0–1)
Acute kidney injury—n (%)	148 (9.1)	115 (9.4)	33 (10.1)	11 (6.4)
Kidney PSS—median (IQR, range)	0 (0–0, 0–3)	0 (0–0, 0–3)	0 (0–0, 0–3)	0 (0–0, 0–2)
Rhabdomyolysis—n (%)	271 (16.6)	211 (17.2)	47 (14.3)	21 (12.2)
Disseminated intravascular coagulopathy—n (%)	12 (0.7)	8 (0.7)	3 (0.9)	0 (0)
Blood PSS—median (IQR, range)	0 (0–0, 0–3)	0 (0–0, 0–3)	0 (0–0, 0–3)	0 (0–0, 0–0)
Other presentations—n (%)				
Diaphoresis	158 (9.7)	119 (9.7)	35 (10.7)	19 (11.0)
Serotonin syndrome	2 (0.1)	0 (0)	1 (0.3)	0 (0)
Overall PSS—median (IQR)	2 (1–2, 0–4)	2 (2–2, 0–4)	2 (1–2, 0–4)	2 (0–2, 0–3)

Abbreviations: IQR, interquartile range; PSS, poison severity score

Disorganised behaviours were commonly reported at the time of ED presentation for acute toxicity related to methamphetamine, cocaine and cannabis abuse. Many drug abusers were found wandering, lying on the floor, or streaking or exposing their body indecently in public areas before they were sent to the ED. Drug-driving was found in 17 episodes, involving methamphetamine in seven episodes, cocaine in eight episodes, cannabis in one episode, both methamphetamine and cannabis in one episode. In one episode of cocaine-related drug-driving, the patient collapsed while driving a minibus and collided with the truck in front. He was trapped in the vehicle and developed cardiac arrest before ED arrival.

Of note, a significantly portion of the patients had concomitant self-harm behaviours (15.7%), including drug overdose or self-poisoning, self-inflicted sharp injuries (e.g. cuts to the wrist) and blunt injuries (e.g. banging the head on a hard surface). Many patients were brought to the ED because of a gesture of attempting to jump from a building or high structure (3.6%) and four patients did jump, resulting in major trauma with multiple injuries. Under the influence of drugs, a number of patients demonstrated extraordinary self-harm behaviours, including four cases of attempted self-strangulation/hanging, one case of amputation of the penis with broken glass, one case of an open cut injury to the scrotum, one case of insertion of sharp objects into the vagina and rectum, one case of attempted electrocution, and one case of attempted self-burning after pouring thinner onto the body. Although not consistently documented in the clinical notes, many drug abusers either acted impulsively because of their frustration with the discomfort caused by the psychotic experience or misjudged the risk of their reckless behaviour under the influence of drugs.

Equally prominent among drug abusers were violent behaviours to others during their acute presentation, especially among methamphetamine abusers. Violent behaviours were documented in 13.3% of episodes, of which 1.0% reported verbal violence alone, 4.1% exhibited violent gestures (e.g., brandishing sharp instruments), 5.1% demonstrated violent behaviour to objects (e.g., breaking furniture at home) and 5.0% perpetuated physical violence against other people. The patient's family members were the most common target of physical violence, followed by police officers and healthcare workers.

Table 5. Injuries and behavioural problems associated with drug intoxication

	The whole cohort n=1,629	Episodes that involved methamphetamine n=1,225	Episodes that involved cocaine n=328	Episodes that involved cannabis n=172
Disorganised behaviours—n (%)				
Steaking or indecent exposure of body	41 (2.5)	35 (2.9)	5 (1.5)	5 (2.9)
Wandering	88 (5.4)	81 (6.6)	4 (1.2)	8 (4.7)
Found lying on the floor	81 (5.0)	67 (5.5)	15 (4.6)	3 (1.7)
Drug-driving—n (%)	17 (1.0)	8 (0.7)	8 (2.4)	2 (1.2)
Deliberate self-harm—n (%)	255 (15.7)	201 (16.4)	48 (14.6)	18 (10.5)
Drug overdose/self-poisoning	104 (6.4)	76 (6.2)	24 (7.3)	6 (3.5)
Self-inflicted physical injuries				
Sharp injuries	46 (2.8)	39 (3.2)	8 (2.4)	2 (1.2)
Blunt injuries	43 (2.6)	35 (2.9)	6 (1.8)	5 (2.9)
Gesture to jump from a height	59 (3.6)	49 (4.0)	10 (3.0)	3 (1.7)
Actual jump from a height	4 (0.2)	4 (0.3)	0 (0)	0 (0)
Attempted hanging oneself	4 (0.2)	3 (0.2)	1 (0.3)	0 (0)
Violent behaviours to others—n (%)	216 (13.3)	194 (15.8)	26 (7.9)	14 (8.1)
Verbal violence to others only	16 (1.0)	16 (1.3)	1 (0.3)	0 (0)
Violent gesture to others	67 (4.1)	63 (5.1)	8 (2.4)	3 (1.7)
Physical violence to objects	83 (5.1)	78 (6.4)	9 (2.7)	2 (1.2)
Physical violence to other people	81 (5.0)	68 (5.6)	12 (3.7)	9 (5.2)
Family members	46 (2.8)	41 (3.3)	4 (1.2)	5 (2.9)
Police officers	11 (0.7)	6 (0.5)	2 (0.6)	3 (1.7)
Healthcare workers	10 (0.6)	8 (0.7)	2 (0.6)	0 (0)
Others	11 (0.7)	10 (0.8)	4 (1.2)	1 (0.6)
Unspecified	3 (0.2)	3 (0.2)	0 (0)	0 (0)
Associated injury—n (%)	250 (15.3)	183 (14.9)	61 (18.6)	22 (12.8)
Abrasion	84 (5.2)	60 (4.9)	24 (7.3)	8 (4.7)
Laceration/cut	52 (3.2)	40 (3.3)	14 (4.3)	4 (2.3)
Contusion	36 (2.2)	26 (2.1)	8 (2.4)	5 (2.9)
Fracture	11 (0.7)	7 (0.6)	3 (0.9)	1 (0.6)

Associated injuries were common among drug abusers who presented to the ED with methamphetamine, cocaine or cannabis abuse. The most frequent injuries documented were abrasions, followed by laceration/cut injuries and contusion. A small number of patients had fractures due to injuries sustained under the influence of drugs. Table 5 summarises the disorganised behaviours and associated injuries reported in our cohort.

Regarding the clinical management in the ED, supportive treatment was the mainstay with supplemental oxygen and intravenous fluid administered to 10.0% and 43.0% of cases, respectively. A significant proportion of patients required physical and chemical restraint both in the ED and in the hospital. As for chemical restraint, diazepam was the most frequently used, followed by midazolam and lorazepam. Haloperidol was used in a small number of episodes with acute psychosis. Gastrointestinal decontamination and other antidotes were rarely needed.

In the ED, intubation and mechanical ventilation were initiated in 55 cases (3.4%). Administration of anti-arrhythmic, electrical therapy for arrhythmia and infusion of inotrope were initiated in the ED in nine, four and seven cases, respectively. Ten patients required cardiopulmonary resuscitation (CPR) in the ED. Veno-arterial extracorporeal membrane oxygenation (ECMO) was initiated in one case in the ED (Table 6).

Table 7 shows the treatment given in the hospital, including those interventions provided in the observation ward, general ward and ICU. Treatment provided during psychiatric admission was not recorded. Many of the drug abusers continued to require supportive treatment, and physical and chemical restraint after ED management. Respiratory support with mechanical ventilation was required in 59 of cases (3.6%). Circulatory support with inotrope infusion was administered to 23 cases and 12 patients required renal replacement therapy. CPR was performed in 11 cases. In addition to the ECMO case initiated in the ED, one other patient was put on veno-venous ECMO for acute respiratory distress syndrome and diffuse alveolar haemorrhage after admission.

Table 6. Treatment offered in the emergency department

	The whole cohort n=1,629	Episodes that involved methamphetamine n=1,225	Episodes that involved cocaine n=328	Episodes that involved cannabis n=172
Supplemental oxygen—n (%)	163 (10.0)	113 (9.2)	47 (14.3)	13 (7.6)
Intravenous fluid—n (%)	700 (43.0)	526 (42.9)	130 (39.6)	79 (45.9)
Physical restraint—n (%)	583 (35.8)	481 (39.3)	86 (26.2)	53 (30.8)
Chemical restraint—n (%)	392 (24.1)	317 (25.9)	64 (19.5)	33 (19.2)
Diazepam	342 (21.0)	278 (22.7)	65 (19.8)	30 (17.4)
Lorazepam	35 (2.1)	27 (2.2)	8 (2.4)	1 (0.6)
Midazolam	156 (9.6)	110 (9.0)	36 (11.0)	20 (11.6)
Haloperidol	37 (2.3)	33 (2.7)	3 (0.9)	1 (0.6)
Dexmedetomidine	1 (0.1)	0 (0)	0 (0)	1 (0.6)
Propofol	8 (0.5)	5 (0.4)	3 (0.9)	0 (0)
Gastrointestinal decontamination—n (%)	33 (2.0)	24 (2.0)	9 (2.7)	2 (1.2)
Gastric lavage	6 (0.4)	5 (0.4)	2 (0.6)	0 (0)
Activated Charcoal	30 (1.8)	22 (1.8)	7 (2.1)	2 (1.2)
Other antidotes—n (%)				
Naloxone	50 (3.1)	45 (3.7)	11 (3.4)	1 (0.6)
Flumazenil	4 (0.2)	4 (0.3)	1 (0.3)	1 (0.6)
Inotrope—n (%)	7 (0.4)	5 (0.4)	2 (0.6)	0 (0)
Intubation and mechanical ventilation—n (%)	55 (3.4)	34 (2.8)	15 (4.6)	2 (1.2)
Administration of anti-arrhythmic—n (%)	9 (0.6)	4 (0.3)	2 (0.6)	2 (1.2)
Electric therapy for arrhythmia—n (%)	4 (0.2)	2 (0.2)	1 (0.3)	1 (0.6)
Cardiopulmonary resuscitation—n (%)	10 (0.6)	7 (0.6)	2 (0.6)	0 (0)
ECMO—n (%)	1 (0.1)	1 (0.1)	0 (0)	0 (0)
Administration of thiamine—n (%)	7 (0.4)	2 (0.2)	5 (1.5)	2 (1.2)
Administration of sodium bicarbonate—n (%)	15 (0.9)	12 (1.0)	2 (0.6)	1 (0.6)
Replacement of potassium—n (%)	15 (0.9)	12 (1.0)	3 (0.9)	0 (0)
Wound management—n (%)				
Anti-tetanus	38 (2.3)	25 (2.0)	10 (3.0)	4 (2.3)
Wound dressing	37 (2.3)	27 (2.2)	10 (3.0)	6 (3.5)
Suturing/sterile strips	20 (1.2)	13 (1.1)	6 (1.8)	3 (1.7)

Abbreviations: ECMO, extracorporeal membrane oxygenation; IV, intravenous

Table 7. Treatment offered after admission to the observation ward, general ward or intensive care unit

	The whole cohort n=1,629	Episodes that involved methamphetamine n=1,225	Episodes that involved cocaine n=328	Episodes that involved cannabis n=172
Intravenous fluid—n (%)	511 (31.4)	401 (32.7)	94 (28.7)	47 (27.3)
Physical restraint—n (%)	323 (19.8)	285 (23.3)	34 (10.4)	26 (15.1)
Chemical restraint—n (%)	178 (10.9)	155 (12.7)	17 (5.2)	10 (5.8)
Diazepam	166 (10.2)	148 (12.1)	23 (7.0)	8 (4.7)
Lorazepam	29 (1.8)	26 (2.1)	5 (1.5)	2 (1.2)
Midazolam	90 (5.5)	73 (6.0)	12 (3.7)	9 (5.2)
Haloperidol	54 (3.3)	51 (4.2)	2 (0.6)	2 (1.2)
Dexmedetomidine	15 (0.9)	13 (1.1)	0 (0)	2 (1.2)
Propofol	14 (0.9)	7 (0.6)	4 (1.2)	2 (1.2)
Gastrointestinal decontamination—n (%)	12 (0.7)	9 (0.7)	1 (0.3)	0 (0)
Gastric lavage	5 (0.3)	3 (0.2)	1 (0.3)	0 (0)
Activated Charcoal	9 (0.6)	8 (0.7)	0 (0)	0 (0)
Other antidotes—n (%)				
Naloxone	9 (0.6)	9 (0.7)	1 (0.3)	0 (0)
Flumazenil	0 (0)	0 (0)	0 (0)	0 (0)
Inotrope—n (%)	23 (1.4)	16 (1.3)	9 (2.7)	0 (0)
Intubation and mechanical ventilation—n (%)	59 (3.6)	41 (3.3)	15 (4.6)	2 (1.2)
Renal replacement therapy—n (%)	12 (0.7)	7 (0.6)	4 (1.2)	0 (0)
Administration of anti-arrhythmic—n (%)	1 (0.1)	1 (0.1)	0 (0)	0 (0)
Electric therapy for arrhythmia—n (%)	3 (0.2)	2 (0.2)	1 (0.3)	0 (0)
Cardiopulmonary resuscitation—n (%)	11 (0.7)	8 (0.7)	4 (1.2)	0 (0)
ECMO—n (%)	2 (0.1)	1 (0.1)	0 (0)	0 (0)
Administration of thiamine—n (%)	22 (1.4)	11 (0.9)	7 (2.1)	1 (0.6)
Administration of sodium bicarbonate—n (%)	36 (2.2)	24 (2.0)	8 (2.4)	3 (1.7)
Replacement of potassium—n (%)	71 (4.4)	62 (5.1)	6 (1.8)	4 (2.3)
Antibiotics—n (%)	105 (6.4)	80 (6.5)	23 (7.0)	5 (2.9)
Surgical or any invasive procedure—n (%)	28 (1.7)	21 (1.7)	8 (2.4)	0 (0)

Abbreviations: ECMO, extracorporeal membrane oxygenation

Overall, 24.1% of the cases developed one of the defined severe complications and 18 patients died of acute toxicity from drug abuse during the index presentation. A brief clinical summary of the fatal cases is shown in Supplementary Table 1. The AAPCC outcome classification was comparable between episodes that involved methamphetamine and cocaine. Episodes that involved cannabis appeared to be less lethal compared with those involving methamphetamine and cocaine, with no deaths reported for the former (Table 8).

Table 8. Patient disposal and clinical outcome

	The whole cohort n=1,629	Episodes that involved methamphetamine n=1,225	Episodes that involved cocaine n=328	Episodes that involved cannabis n=172
Severe complications*—n (%)	392 (24.1)	310 (25.3)	76 (23.2)	28 (16.3)
AAPCC outcome classification				
Death	18 (1.1)	14 (1.1)	5 (1.5)	0 (0)
Major effect	72 (4.4)	44 (3.6)	19 (5.8)	3 (1.7)
Moderate effect	415 (25.5)	325 (26.5)	78 (23.8)	38 (22.1)
Minor effect	1,083 (66.5)	809 (66.0)	215 (65.5)	130 (75.6)
No effect	41 (2.5)	33 (2.7)	11 (3.4)	1 (0.6)
Direct discharge from the ED—n (%)	158 (9.7)	95 (7.8)	43 (13.1)	32 (18.6)
Discharge against medical advice/patient walked away before or after consultation—n (%)	240 (14.7)	172 (14.0)	56 (17.1)	20 (11.6)
Managed in emergency medicine ward or observation ward in the ED—n (%)	1,012 (62.1)	779 (63.6)	195 (59.5)	102 (59.3)
LOS in the emergency medicine ward or observation ward in the ED—median (IQR), hour	18.6 (11.2–29.8)	19.6 (12.6–33.8)	14.2 (7.4–24.7)	13.2 (8.6–21.9)
Admission to the general ward—n (%)	465 (28.5)	355 (29.0)	90 (27.4)	37 (21.5)
LOS in general ward—median (IQR), day	2.6 (1.4-4.6)	2.7 (1.6-4.7)	2.2 (1.1-4.1)	1.9 (1.5-2.7)
Admission to the ICU—n (%)	96 (5.9)	66 (5.4)	24 (7.3)	4 (2.3)
Admission to psychiatry ward/hospital—n (%)	416 (25.5)	382 (31.2)	32 (9.8)	26 (15.1)
LOS in psychiatry ward/hospital—median (IQR), day	15.2 (8.6–27.0)	15.8 (8.9–27.8)	14.4 (5.8–26.4)	14.9 (6.0–27.0)
Total LOS of hospitalisation—median (IQR), day	1.9 (0.8-8.6)	2.6 (0.9–12.1)	1.0 (0.5–3.0)	0.9 (0.5–3.2)
Psychiatric consultation during the index episode—n (%)	1,028 (63.1)	869 (70.9)	144 (43.9)	76 (44.2)
Referred psychiatry follow-up service after discharge—n (%)	411 (25.2)	345 (28.2)	63 (19.2)	29 (16.9)
Referral to social worker—n (%)	278 (17.1)	228 (18.6)	55 (16.8)	18 (10.5)
Referral to NGO drug abuse service—n (%)	68 (4.2)	59 (4.8)	9 (2.7)	2 (1.2)

Abbreviations: ED, emergency department; ICU, intensive care unit; LOS, length of stay, NGO, non-governmental organisation

*A composite outcome including cardiac arrest, acute myocardial injury, ventricular dysrhythmias, heart failure, shock, respiratory failure, acute kidney injury, liver injury, rhabdomyolysis, seizure, coma, acute ischaemic stroke, intracranial bleeding that was not due to injury and disseminated intravascular coagulation.

As for patient disposal after ED consultation, 9.7% of the cases were discharged directly from the ED and the direct discharge rate was the highest for cannabis abusers (18.6%). It is

noteworthy that many drug abusers left the ED or hospital against medical advice (14.7%), particularly those abusing cocaine (17.1%). Irrespective of the drug used, the majority of the patients were managed in the emergency medicine ward or observation ward by emergency physicians and nurses. Around a quarter of the episodes were admitted to the general ward or psychiatric ward. The number of patients who required ICU care were 96 (5.9%) for the whole cohort, 66 (5.4%) for methamphetamine-related episodes, 24 (7.3%) for cocaine-related episodes and four (2.3%) for cannabis-related episodes. The overall median length of stay in the hospital was 1.9 (IQR 0.8–8.6), 2.6 (IQR 0.9–12.1), 1.0 (IQR 0.5–3.0), and 0.9 (IQR 0.5–3.2) days for the whole cohort, methamphetamine-, cocaine- and cannabis-related episodes, respectively.

Compared with episodes that involved cocaine and cannabis, methamphetamine-related episodes had a higher proportion of psychiatric ward admission, psychiatric consultation during the index presentation and referral to psychiatric services upon discharge. Around one in six cases were referred to social workers upon discharge and only a small number of episodes had documented referral to NGO drug abuse services.

Table 9 summarises the pattern of drug-related ED reattendance after the index ED presentation. For the whole cohort, half of the patients reattended ED, especially among methamphetamine abusers (58.9%). The median number of ED reattendance within 1 year was 1 (IQR 0–3) but the range was wide. One patient reattended 97 times within 1 year, of which 71 episodes were related to drug abuse. The median time interval between the first drug-related ED reattendance and the index ED presentation was 132.5 days (IQR 31.0–422.3 days) and episodes that involved methamphetamine tended to have a shorter time interval before the first reattendance compared with cocaine and cannabis.

As for the drug used during the ED reattendance, the most common was still methamphetamine (78.0%), followed by cocaine (10.5%) and cannabis (4.5%). Again, addiction to individual drugs was observed with the same substances being the most likely to be abused at the time of reattendance. Over half of these drug-related ED reattendances involved psychotic symptoms after drug abuse, especially among methamphetamine abusers. Around a third reattended because of acute intoxication after drug abuse. Like the index ED presentation, a sizable portion of these reattendances was associated with self-harm behaviours (9.6%), violence behaviours to others (9.4%) and injuries (6.4%).

Table 9. Characteristics of drug-related reattendance to the emergency department before the censor date

	The whole cohort n=1,629	Episodes that involved methamphetamine n=1,225	Episodes that involved cocaine n=328	Episodes that involved cannabis n=172
ED reattendance for drug-related problems—n (%)	822 (50.5)	721 (58.9)	113 (34.5)	44 (25.6)
Total number of ED attendance within 1 year of index ED presentation—median (IQR, range)	1.0 (0–3, 0–97)	1.0 (0–3, 0–97)	0 (0–1.0, 0–25)	0 (0–2.0, 0–12)
Total number of drug-related ED attendance within 1 year of index ED presentation—median (IQR, range)	0 (0–1, 0–71)	0 (0–1, 0–71)	0 (0–0, 0–12)	0 (0–0, 0–11)
Time interval between the index ED presentation and first drug-related ED reattendance—median (IQR, range), day	132.5 (31.0–422.3, 0–2903)	126.0 (32.0–402.0, 0–2903)	200.0 (37.0–538.5, 0–2903)	170.0 (8.3–404.0, 0–1997)
Drug abused at the time of first ED reattendance—n/total n of reattendance (%)				
Methamphetamine	641/822 (78.0)	621/721 (86.1)	42/113 (37.2)	17/44 (38.6)
Cocaine	86/822 (10.5)	41/721 (5.7)	65/113 (57.5)	2/44 (4.5)
Cannabis	37/822 (4.5)	23/721 (3.2)	3/113 (2.7)	22/44 (50.0)
Presentation of the first drug-related ED reattendance—n/total n of reattendance (%)				
Acute intoxication	221/822 (26.9)	189/721 (26.2)	40/113 (35.4)	13/44 (29.5)
Psychotic features	413/822 (50.2)	388/721 (53.8)	33/113 (29.2)	15/44 (34.1)
Acute withdrawal	4/822 (0.5)	3/721 (0.4)	1/113 (0.9)	0/44 (0)
Associated with injuries	53/822 (6.4)	47/721 (6.5)	6/113 (5.3)	3/44 (6.8)
Associated with self-harm	79/822 (9.6)	75/721 (10.4)	8/113 (7.1)	3/44 (6.8)
Associated with violence to others	77/822 (9.4)	68/721 (9.4)	8/113 (7.1)	5/44 (11.4)

Abbreviations: ED, emergency department; IQR, interquartile range

4.3 Predictors of severe complications

Altogether, 99 clinical variables were selected for univariate analysis (Supplementary Table 2) and those with a statistically significant association with the secondary outcome were entered into a multivariable logistic regression model to control for the confounding effects. Variables with overlapping meaning or significant collinearity were not entered into the multivariable regression model.

Table 10. shows the result of univariate and multi-variable logistic regression for the whole cohort. Eleven factors were independently associated with severe complications of methamphetamine, cocaine or cannabis abuse. Patients with a triage temperature > 39°C (odds ratio [OR] 7.59, 95% CI 2.10–27.49, p=0.002), diaphoresis (OR 2.30, 95% CI 1.42–3.71, p=0.001), agitation (OR 1.87, 95% CI 1.32–2.64, p<0.001), a triage ranking of a higher acuity (OR 1.86, 95% CI 1.48–2.33, p<0.001), concurrent use of cough mixture or pills (OR 1.81, 95% CI 1.09–3.00, p=0.023), co-ingestion of other medications (OR 1.68, 95% CI 1.07–2.63, p=0.026), sluggish or non-reactive pupils (OR 1.61, 95% CI 1.02–2.52, p=0.039), associated injury (OR 1.56, 95% CI 1.04–2.35, p=0.032), or tachycardia >120 beats per minute (OR 1.55, 95% CI 1.09–2.19, p=0.015) were at a higher risk of developing severe complications.

Patients who presented with auditory hallucination (OR 0.54, 95% CI 0.35–0.85, p=0.007) and drowsiness (OR 0.31, 95% CI 0.19–0.52, p<0.001) were less likely to develop severe complications.

Table 10. Multiple variable logistic regression of factor associated with severe complications of methamphetamine, cocaine and cannabis abuse in the emergency department

	Un-adjusted OR (95% CI)	P value	Adjusted OR (95% CI)*	P value
Triage temperature > 39°C	26.97 (9.46–76.92)	<0.001	7.59 (2.10–27.49)	0.002
Diaphoresis	3.19 (2.28–4.47)	<0.001	2.30 (1.42–3.71)	0.001
Agitation	2.61 (2.07–3.30)	<0.001	1.87 (1.32–2.64)	<0.001
Triage category	2.44 (2.08–2.87)	<0.001	1.86 (1.48–2.33)	<0.001
Current abuse of cough mixture or pills	2.23 (1.55–3.22)	<0.001	1.81 (1.09–3.00)	0.023
Co-ingestion of other medications	1.63 (1.19–2.24)	0.002	1.68 (1.07–2.63)	0.026
Sluggish or non-reactive pupils	2.64 (1.84–3.79)	<0.001	1.61 (1.02–2.52)	0.039
Associated injury	1.84 (1.38–2.46)	<0.001	1.56 (1.04–2.35)	0.032
Tachycardia > 120 beats per minute	2.46 (1.94–3.13)	<0.001	1.55 (1.09–2.19)	0.015
Auditory hallucination	0.71 (0.52–0.96)	0.028	0.54 (0.35–0.85)	0.007
Drowsiness	0.66 (0.45–0.97)	0.034	0.31 (0.19–0.52)	<0.001
Ambulance case	2.76 (2.02–3.76)	<0.001		
Current abuse of MDMA	2.28 (1.26–4.15)	0.007		
Current abuse of heroin	1.86 (1.04–3.31)	0.035		
Confusion	1.78 (1.41–2.24)	<0.001		
Past history of hypertension	1.76 (1.16–2.68)	0.008		
Male sex	1.56 (1.19–2.03)	0.001		
Previous history of heroin abuse	1.47 (1.11–1.94)	0.008		
Deliberate self-harm	1.39 (1.03–1.87)	0.030		
Current abuse of methamphetamine	1.33 (1.01–1.75)	0.042		
Age	1.02 (1.01–1.03)	0.001		
Previous history of ketamine abuse	0.76 (0.59–0.97)	0.025		
Previous history of cocaine abuse	0.68 (0.50–0.91)	0.011		
Shortness of breath	0.59 (0.39–0.91)	0.017		
Abdominal pain	0.49 (0.26–0.91)	0.024		
Palpitation	0.45 (0.28–0.72)	0.001		
Anxiety	0.44 (0.23–0.87)	0.018		
Dizziness	0.41 (0.28–0.61)	<0.001		
Current abuse of cannabis only	0.21 (0.08–0.59)	0.003		

Abbreviations: CI, confidence interval; OR, odds ratio

*Variables ranked according to the descending order of adjusted ORs

We repeated the same univariate and multivariable analysis for the subgroups that involved methamphetamine, cocaine and cannabis. As for episodes that involved methamphetamine,

seven factors were independently associated with severe complications: a triage temperature >39°C (OR 5.55, 95% CI 1.46–21.12, p=0.012), agitation (OR 2.13, 95% CI 1.47–3.08, p<0.001), diaphoresis (OR 1.90, 95% CI 1.13–3.19, p=0.015), a triage ranking of higher acuity (OR 1.77, 95% CI 1.38–2.26, p<0.001), sluggish or non-reactive pupils (OR 1.67, 95% CI 1.03–2.72, p=0.038), tachycardia >120 beats per minute (OR 1.51, 95% CI 1.03–2.21, p=0.036) and auditory hallucination (OR 0.63, 95% CI 0.40–0.99, p=0.046). Table 11 summarises the un-adjusted and adjusted ORs of different variables in the regression analysis.

Table 11. Multiple variable logistic regression analysis of factor associated with severe complications of methamphetamine abuse in the emergency department

	Un-adjusted OR (95% CI)	P value	Adjusted OR (95% CI)*	P value
Triage temperature > 39 °C	13.57 (4.53–40.67)	<0.001	5.55 (1.46–21.12)	0.012
Agitation	2.51 (1.93–3.27)	<0.001	2.13 (1.47–3.08)	<0.001
Diaphoresis	2.98 (2.03–4.39)	<0.001	1.90 (1.13–3.19)	0.015
Triage category	2.31 (1.92–2.77)	<0.001	1.77 (1.38–2.26)	<0.001
Sluggish or non-reactive pupils	2.47 (1.63–3.75)	<0.001	1.67 (1.03–2.72)	0.038
Tachycardia > 120 beats per minute	2.26 (1.72–2.98)	<0.001	1.51 (1.03–2.21)	0.036
Auditory hallucination	0.71 (0.51–0.97)	0.033	0.63 (0.40–0.99)	0.046
Removal of clothing	2.28 (1.15–4.50)	0.018		
Ambulance case	2.27 (1.60–3.23)	<0.001		
Past history of hypertension	1.98 (1.25–3.12)	0.003		
Co-ingestion of other medications	1.85 (1.28–2.66)	0.001		
Current use of cough mixture or pills	1.82 (1.20–2.75)	0.005		
Confusion	1.61 (1.24–2.09)	<0.001		
Male sex	1.61 (1.20–2.16)	0.002		
Deliberate self-harm	1.56 (1.13–2.17)	0.008		
Associated injury	1.50 (1.07–2.11)	0.02		
Previous history of heroin abuse	1.45 (1.08–1.95)	0.013		
Age	1.02 (1.00–1.03)	0.015		
Previous history of ketamine abuse	0.69 (0.52–0.90)	0.007		
Previous history of cocaine abuse	0.69 (0.49–0.99)	0.044		
Dizziness	0.57 (0.37–0.88)	0.01		

Abbreviations: CI, confidence interval; OR, odds ratio

*Variables ranked according to the descending order of adjusted ORs

As for the episodes that involved cocaine, tachycardia >120 beats per minute (OR 3.18, 95% CI 1.28–7.89, p=0.012) and a triage ranking of higher acuity (OR 1.89, 95% CI 1.22–2.93,

p=0.005) were independently associated with a higher risk of severe complications. Shortness of breath was associated with a lower risk (OR 0.18, 95% CI 0.04–0.84, p=0.029). The unadjusted and adjusted ORs of the included variables are shown in Table 12.

Table 12. Multiple variable logistic regression of factors associated with severe complications of cocaine abuse in the emergency department

	Un-adjusted OR (95% CI)	P value	Adjusted OR (95% CI)*	P value
Tachycardia > 120 beats per minute	3.43 (1.93–6.10)	<0.001	3.18 (1.28–7.89)	0.012
Triage category	2.35 (1.68–3.30)	<0.001	1.89 (1.22–2.93)	0.005
Shortness of breath	0.26 (0.09–0.74)	0.011	0.18 (0.04–0.84)	0.029
Current abuse of cough mixture or pills	6.56 (2.48–17.35)	<0.001		
Current abuse of heroin	4.37 (1.14–16.69)	0.031		
Ambulance case	3.52 (1.77–7.00)	<0.001		
Diaphoresis	3.27 (1.59–6.74)	0.001		
Non-reactive pupils	2.92 (1.37–6.22)	0.005		
Confusion	2.61 (1.49–4.60)	0.001		
Associated injury	2.44 (1.34–4.45)	0.003		
Non-local resident	2.39 (1.03–5.58)	0.043		
Temperature > 38°C	12.62 (4.80–33.20)	<0.001		
Agitation	1.84 (1.05–3.24)	0.035		
Previous history of cocaine abuse	0.55 (0.32–0.94)	0.028		
Followed-up by social worker	0.26 (0.08–0.88)	0.031		
Palpitation	0.07 (0.01–0.52)	0.009		

Abbreviations: CI, confidence interval; OR, odds ratio
*Variables ranked according to the descending order of adjusted ORs

In episodes that involved cannabis, backward multivariable logistic regression was performed because of the relatively large number of candidate variables identified in univariate analysis compared with the low event rate. We found that cannabis abusers who presented with paranoid delusion in the ED (OR 45.57, 95% CI 3.62–573.47, p=0.003), diaphoresis (OR 7.60, 95% CI 1.87–30.89, p=0.005), agitation (OR 5.54, 95% CI 1.57–19.50, p=0.008), and those with associated injury (OR 5.26, 95% CI 1.13–24.61, p=0.035) had a significantly higher risk of severe complications (Table 13).

Table 13. Multiple variable backward logistic regression analysis of factors associated with severe complications of cannabis abuse in the emergency department

	Un-adjusted OR (95% CI)	P value	Adjusted OR (95% CI)*	P value
Paranoid delusion	4.63 (1.61–18.50)	0.03	45.57 (3.62–573.47)	0.003
Diaphoresis	8.33 (2.99–23.25)	<0.001	7.60 (1.87–30.89)	0.005
Agitation	9.58 (3.90–23.56)	<0.001	5.54 (1.57–19.50)	0.008
Associated injury	6.11 (2.31–16.17)	<0.001	5.26 (1.13–24.61)	0.035
Male sex	8.35 (1.09–63.71)	0.041		
Previous history of sedative/hypnotic abuse	7.83 (1.65–37.21)	0.01		
Confusion	5.07 (2.17–11.85)	<0.001		
Restlessness	4.63 (1.16–18.50)	0.03		
Current abuse of methamphetamine	3.66 (1.47–9.09)	0.005		
Previous history of methamphetamine abuse	3.54 (1.38–9.07)	0.008		
Current abuse of cocaine	3.44 (1.29–9.16)	0.013		
Previous history of cocaine abuse	3.30 (1.11–9.83)	0.032		
Temperature > 38°C	28.0 (5.55–141.31)	<0.001		
Previous history of cannabis abuse	2.60 (1.14–5.94)	0.023		
Triage category	2.05 (1.11–3.79)	0.021		
Previous history of heroin abuse	12.82 (2.99–55.02)	0.001		
Sluggish or non-reactive pupils	10.67 (1.82–62.65)	0.009		
Age	1.05 (1.00–1.09)	0.031		
Current abuse of cannabis only	0.25 (0.08–0.77)	0.016		
Dizziness	0.19 (0.05–0.65)	0.009		

Abbreviations: CI, confidence interval; OR, odds ratio

*Variables ranked according to the descending order of adjusted ORs

4.4 Cox regression analysis of drug-related ED reattendance

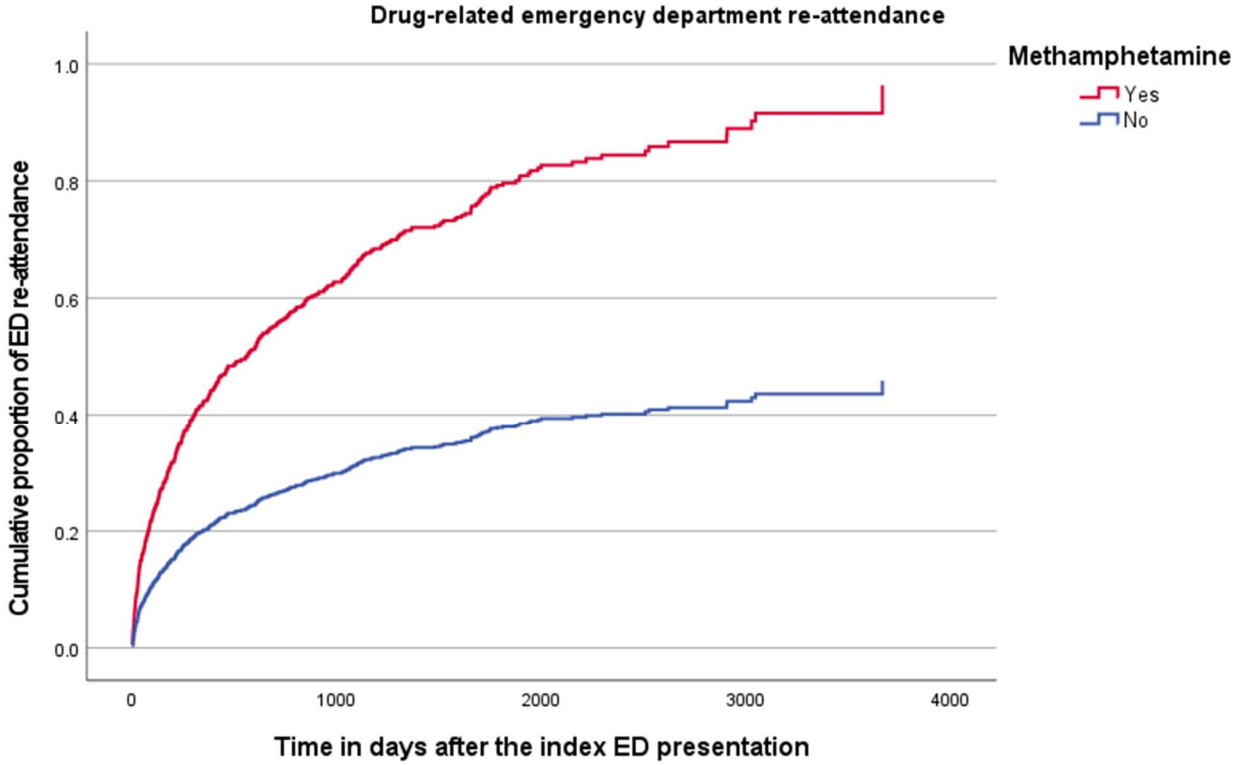
In total, 1,195 patients were included in the Cox regression analysis on drug-related ED reattendance after the index presentation after exclusion of 18 patients who had died at the time of index ED attendance, 90 patients who died subsequently based on CMS records, 72 non-local residents and 254 episodes of subsequent attendance (Figure 1). Among these 1,195 patients, 583 patients (48.8%) reattended ED for drug-related problems with a median time interval between the index presentation and the first ED drug-related reattendance of 170 days (IQR 33–565 days).

Cox regression showed that receiving social allowance (hazard ratio [HR] 2.15, 95% CI 1.77–2.62, p<0.001), acute toxicity involving methamphetamine as compared with cocaine and cannabis (HR 2.41, 95% CI 1.76–3.29, p<0.001), patients who required urgent psychiatric consultation during the index ED attendance (HR 2.13, 95% CI 1.76–2.57, p<0.001) were associated with a higher risk of ED reattendance for drug-related problems, whereas male gender (HR 0.80, 95% CI 0.67–0.95, p=0.011), good past health (HR 0.53, 95% CI 0.45–0.63, p<0.001) and a major effect of acute toxicity at the index ED presentation (HR 0.53, 95% CI 0.33–0.86, p=0.010) were associated a lower risk. The relevant Kaplan Meier curves are showed in Supplementary Figures 1–6.

Other ED discharge interventions, such as referral to social workers (HR 1.18, 95% CI 0.97–1.45, p=0.10) or NGO substance abuse services (HR 1.31, 95% CI 0.91–1.90, p=0.15), were not significantly associated with ED reattendance. However, it is important to note that the number of referrals to social worker in hospital (278, 17.1%) and NGO drug abuse services (68, 4.2%) was small. Because of the small number of such referrals, the statistical power to reveal statistical significance was likely inadequate. Patients who discharged themselves against medical advice or absconded before or after medical encounters did not have a higher risk of reattendance (HR 1.05, 95% CI 0.83–1.32, p=0.68).

Since the length of stay in the hospital following the index ED presentation affected the time interval of ED reattendance (i.e., those who stayed longer in the hospital were less likely to reattend sooner than those who had a shorter stay), we controlled for this confounding factor, alongside gender, past medical health and social allowance status by entering these factors into the multivariable Cox regression model. Methamphetamine abuse (HR 2.10, 95% CI 1.64–2.68, p<0.001) and the need for urgent psychiatric consultation during the index ED presentation (HR 1.60, 95% CI 1.31–1.95, p<0.001) remained significantly associated with a higher risk of reattendance. A major effect of acute toxicity at the index presentation was associated with a lower risk of drug-related ED reattendance (HR 0.54, 95% CI 0.33–0.88, p=0.013) (Figure 9).

Figure 9. Kaplan-Meier curve showing drug-related ED reattendance as a complex function of methamphetamine abuse, female gender, major toxic effect, psychiatric consultation required and the length of hospital stay.



5. Discussion

This study provided detailed information about the clinical characteristics of acute toxicity related to methamphetamine, cocaine and cannabis abuse in patients presenting to local EDs, as well as their patterns of drug misuse in the past, present and future attendance. We also evaluated the medical needs, health consequences and patterns of health service utilisation of these patients and identified a number of factors that are associated with a higher risk of severe complications and ED reattendance for drug-related problems. To the authors' knowledge, this is the largest local cohort representing methamphetamine, cocaine and cannabis acute toxicity in Hong Kong over the past decade. The consistency of the reporting system of acute poisoning throughout the study period also allowed us to study the trend of individual PSAs over a decade. The results of this study provide important real-world data to inform clinical decision and drug-control policy, as well as the members of the public about the harms of methamphetamine, cocaine and cannabis abuse.

5.1 Overall trends of acute methamphetamine, cocaine and cannabis toxicity

Acute toxicity related to methamphetamine misuse was more frequently encountered than that for cocaine in local A&Es. This finding was consistent with a higher estimated annual prevalence of methamphetamine usage compared with cocaine (0.61% vs 0.05% of the adult population) in East Asia reported by the United Nations Office on Drug and Crime (UNODC)[36] and local CRDA statistics.[37] Despite being widely used in East Asia (with an estimated annual prevalence of 1.19% in the adult population)[38] and being popular among drug abusers ≤21 years of age in Hong Kong,[37] acute toxicity related to cannabis abuse was less frequently encountered in the ED. This could be explained by the milder severity of acute toxicity associated with cannabis use in general, which is further supported by the findings of less severe clinical presentations compared with those of methamphetamine and cocaine in our study.

During the study period, the median annual incidence rates of methamphetamine-, cocaine- and cannabis-related ED visits were 1.63, 0.41 and 0.21 per 100,000 population in Hong Kong, respectively. These figures were notably lower than that reported in the United States. According to the Drug Abuse Warning Network (DAWN), in 2011, the annual rates of ED visits per 100,000 United States (US) population for methamphetamine, cocaine and cannabis were 33.0, 162.1 and 146.2, respectively.[39] Unfortunately, the DAWN ceased to publish further data after 2011. Another study by Winkelman et al. showed a similar magnitude of drug abuse in the US from 2011 until 2015.[40] In Europe, such a population-level estimate has not been published. In 2017, the European Drug Emergency Network (Euro-Den) reported 1,700 cases of cocaine, 1,550 cases of cannabis and 864 cases of amphetamine misuse from 31 sentinel hospital centres in 21 European countries.[41] There is a lack of systematic collection of relevant data in other Asia-Pacific countries for comparison. We believe the difference in the magnitude of drug-related ED visits can be explained by differences in local

drug supply, consumption patterns, access to healthcare systems and methods of data collection. Our study provides population-level estimates for benchmarking and monitoring the impact of drug-control interventions.

It is important to note that our study identified a greater number of methamphetamine-, cocaine-, and cannabis-abuse episodes compared with previous studies that utilised diagnostic codes in case searching. For instance, the number of methamphetamine-related episodes identified in our study was 1,225 over 10 years, whereas only 592 cases of amphetamine abuse were identified over 12 years (2004–2016) in a study that used diagnostic codes to identify patients.[42] The difference could be explained by the fact that not all A&Es in Hong Kong use diagnostic codes and under-reporting is possible. The inherent limitations of diagnostic code-based case retrieval[43] highlight the value of the poison database in the HKPIC. Although not every poisoning from local A&Es is reported to the HKPIC, prospective and consistent data collection with verification by on-site clinical toxicologist results in a more accurate database for analysis. We believe that the findings from our study are closer to the true picture encountered in local EDs.

In this study, we could not identify a significant trend of methamphetamine-, cocaine- and cannabis-related ED visits over the study period when we subjected the data to statistical analysis that offset the confounding effect of total ED attendance during the same period of time. However, for drug abusers younger than 21 years at the time of presentation, there was an apparent rising trend of cannabis-related ED visits, although it did not reach statistical significance given the small number of cases.

It was interesting to see the relationship between the reported statistical data from different agencies. For methamphetamine, the correlation between the number of acute toxicities reported to the HKPIC and the number in the CRDA was strong and significant. Indeed, the number of acute toxicities reported to the HKPIC was roughly one-tenth of that for methamphetamine abusers in the CRDA, indicating an ‘iceberg phenomenon’. This strong correlation could be explained by the fact that methamphetamine abusers were more likely to be in contact with various drug service providers, including psychiatrists, social workers, NGOs and law enforcement agencies (because of criminal offences). The opportunity to be identified by the CRDA reporting network was thus higher.

For cannabis, the number of acute toxicities reported to the HKPIC was strongly correlated with the market value of the drugs seized, but not with the CRDA statistics. This indicated a potential under-reporting of cannabis abusers in the community by the current reporting mechanism. It is noteworthy that the amount of cannabis seized by the Hong Kong Customs and Excise Department surged threefold in 2019.[44] Given the strong correlation between the market value and acute toxicity, the increasing popularity of cannabis among students

according to a local survey[37] and the apparent trend of increasing cannabis-related ED visits observed in our study, there is a need to continue close monitoring of the trend of local cannabis abuse especially among young drug abusers.

As for cocaine, no significant correlation between the statistics of the HKPIC, the CRDA and the market value of the drugs seized by the Customs and Exercise Department was found. Cocaine abusers were less likely to be receiving social allowances or psychiatric and NGO services, and a higher proportion of them were non-local residents. They were less likely to be captured by the current reporting mechanism in the community until they presented to the ED with acute toxicities. This poses challenges to accurate drug surveillance in our community and indicates the importance of having multiple data sources to provide complementary information.

5.2 Drug use pattern and clinical presentations

In our study, polysubstance abuse was the most common pattern encountered in the ED. Methamphetamine was frequently combined with alcohol, ketamine and cough mixture in our cohort. Although the reasons for drug use were not systematically reported in the clinical notes, we found that many drug abusers used methamphetamine along with other drugs (such as ketamine or cough mixture) to achieve the desired effect or to reduce the undesirable effects of methamphetamine (e.g. insomnia) alongside with zopiclone and benzodiazepines. A number of heroin users were also abusing methamphetamine to 'balance drug effects' or curb opioid withdrawal,[45] which is a high-risk combination that has been reported to be rising in the US.[46, 47] This combination poses a challenge to the ED because of the more complicated presentation (a mixture of opioid and sympathomimetic syndromes) and potentially worse health consequences. Of note, many drug abusers also reported using methamphetamine to replace ketamine (because of ketamine-associated bladder dysfunction) and heroin (possibly driven by behavioural economic mechanism with methamphetamine being an inexpensive substitute for heroin).[47]

On the whole, the use of NPSs constituted only a minority in our cohort, as confirmed by a local study on NPS use published by the Toxicology Reference Laboratory (TRL) of the HA.[48] However, it is likely that the abuse of NPSs is underestimated in our locality because of the current 'case referral' approach by the treating doctors to TRL and non-exhaustive analytical coverage of NPSs within the laboratory. Right now, only the TRL has the capability and validated analytic tool of screening for emerging NPSs in Hong Kong.[49] In our cohort, only 117 cases (7.2%) were referred to the TRL for emerging drug screening. Given the rising trend of the number of NPSs reported from 2009–2015 at the global level and widespread use,[50,51] the magnitude of NPS abuse presented in this report should be interpreted with caution.

In our study, more than half of the patients had a past history of drug abuse. In particular, 73.3% of methamphetamine drug users had abused the same drug before. For those who reattended the ED, 86.1% involved methamphetamine again. These proportions are higher than that for cocaine and cannabis, signifying that methamphetamine is highly addictive among local drug abusers. Consistent with previous studies,[52,53] a higher proportion of methamphetamine abusers in our cohort had psychiatric comorbidities, including drug-induced psychosis, schizophrenia, antisocial personality disorder, and had received psychiatric service. Methamphetamine abuse has been associated with a higher risk of schizophrenia than cocaine, opioids and alcohol except cannabis.[54] Increase in frequency, duration and severity of methamphetamine abuse are associated with a higher risk of psychotic symptoms,[55, 56] whose clinical course might last for months even after drug abstinence.[57] Early and heavy cannabis use has also been associated the risk of psychosis in vulnerable youths,[58–60] but the number who received psychiatric service in our cohort was not large. It is concerning that methamphetamine abusers generally had a very poor compliance with psychiatric follow-up appointment and treatment. It is also noticeable that across different drugs in our cohort, only a minority of patients had received detoxification treatment, social service and NGO drug service in the past. These findings highlight the need to strengthen the current referral system for drug service providers from different sectors and to develop strategy to reinforce patient compliance to treatment.

Overall, the acute toxicities of methamphetamine, cocaine and cannabis are comparable with those reported in studies that were based in the ED on recreational drugs as a whole [25, 61] and on methamphetamine,[62–66] cocaine, [67–70] and cannabis individually.[71–74] Consistent with previous studies, acute toxicity related to methamphetamine and cocaine abuse is predominantly characterised by sympathomimetic toxidrome with hyperactivity of the central nervous system (CNS) and cardiovascular system due to adrenergic stimulation. They are often triaged to a higher acuity.[64, 67] Methamphetamine abuse was more often associated with agitation, psychotic symptoms, acute behavioural disturbance and aggression,[62, 75, 76] requiring chemical and physical restraints,[77] police and ambulance service [62, 75, 78] and is resource intensive.[62, 65, 78, 79] Compared with methamphetamine, cocaine users were more likely to have alcohol co-ingestion, associated injury and self-discharge.[80] Cannabis abusers presented to the ED primarily due to gastrointestinal and psychiatric complaints with a relatively minor toxicity.[71–74] It is important to note that despite the well-described stimulant toxidrome, the clinical picture is typically not stereotypical.[67] Drug abusers presented with a myriad of presentations, sometimes non-specific. No single sign or symptom predominated in our cohort and emergency physicians should maintain a high index of suspicion especially when handling novice drug abusers.

Our study adds to the literature by showing that up to one-fifth of the patients with methamphetamine- and cannabis-related presentations developed hypokalaemia, which is not well reported in previous large case series on respective drugs. Hypokalaemia has been rarely

reported after cocaine and cannabis abuse, [81–83] with intracellular shift of potassium due to β2-adrenergic stimulation and activation of Na-K-ATPase being an explanation for cocaine. To the authors' knowledge, hypokalaemia after methamphetamine abuse has not been well-reported in the literature. In this study, we also found that one-sixth of the methamphetamine and cocaine abusers developed rhabdomyolysis, which is consistent with the proportions reported in previous studies.[62, 84, 85] One-tenth of the acute toxicity was complicated with AKI (both methamphetamine and cocaine users) and almost 5% had evidence of myocardial injury, of whom 4 developed myocardial infarction. For episodes involving cannabis, the proportions with rhabdomyolysis, AKI and acute myocardial injury were 12.2%, 6.4% and 1.2%, respectively. It is well acknowledged that these abnormalities cannot be predicted with history and physical examination reliably.[85] Based on the results of our study, we recommend routine checking of serum potassium, creatinine, creatine kinase and cardiac troponins for all patients who present to the ED with acute toxicity related to methamphetamine and cocaine abuse, and for selected cases of cannabis abuse. We also concur with Richards et al. that patients with unexplained rhabdomyolysis should be screened for methamphetamine or other illicit drugs.[84]

Another challenge healthcare workers in the ED need to face is the violent behaviours of these patients under the influence of drug intoxication, paranoia and other psychotic symptoms, especially among methamphetamine abusers. Our study showed that around one-sixth of methamphetamine abusers presented with deliberate self-harm and aggression concurrently in addition to physical problems and one out of six came with associated injuries. Self-harm behaviours and injuries were also seen in a sizable portion of cocaine and cannabis abusers. It has been well reported in the literature that methamphetamine users are significantly more agitated, violent and aggressive than other drug users,[86] posing a higher risk to people around.[87] Greater methamphetamine consumption has been associated with more self-reported impulsivity (tendency to act without thinking)[88] and alcohol co-ingestion may further increase aggression.[89] Consistent with previous findings, our study shows that among those who displayed physical violence to other people, patients' family members were always the most common target.[90] This highlights the need for an effective strategy to protect cohabiting family members of the patients in case of aggression.

Despite these challenges, the majority of cases were managed in the EDs or short-stay observation units run by emergency physicians with supportive treatment such as intravenous fluids, supplemental oxygen, and correction of electrolyte disturbances, similar to the current practice reported in the literature.[62, 67, 68, 71] Physical and chemical restraints were applied at similar rates as reported elsewhere. Most cases of rhabdomyolysis and AKI responded to intravenous fluid or alkaline diuresis and only 12 cases required renal replacement therapy. In total, 59 patients required endotracheal intubation and mechanical ventilation because of either coma or respiratory failure. ECMO was initiated in two patients, of whom only one survived. The overall ICU admission rate (5.9%) and death rate (1.1%) were marginally higher than the respective international figures.[62, 67, 71] The discrepancies can be explained by

difference in sample selection. In our study, EDs treating patients with milder toxicity might not consult or report to the HKPIC, which might result in a smaller denominator of patients at-risk of outcome.

5.3 Predictors of severe complications

Despite the widespread abuse of methamphetamine, cocaine and cannabis and the serious health outcomes that follow, there is a surprising lack of studies looking into the prognostication of acute toxicities in the literature, especially in the ED setting.

For methamphetamine, Lan et al. compared five ED patients who died with 13 survivors and found that coma, shock, convulsions, oliguria, high body temperature, higher blood urea nitrogen and serum creatinine, and lower values of arterial pH were associated with fatality. The patients who died developed multiorgan failure resembling that from heatstroke.[91] However, the authors did not conduct multivariable logistic regression to control for the effects of confounding variables. Paydar et al. reported that age, suicidal history, route of poisoning, and pulmonary system manifestations were independently predictive of patient outcome, but the definition of patient outcome and pulmonary manifestations were not clear.[92] Rahimi et al. suggested a partial pressure of carbon dioxide (PCO_2) ≥51 mm Hg, serum bicarbonate ≤22.6 mEq/L, and loss of consciousness on admission as prognostic factors of mortality in acute methamphetamine poisoning.[93] All these previous studies were limited by single-centre study and small sample size, which limited the number of variable that could be identified as independent predictors in multivariable logistic regression.

A poison centre study on methamphetamine stuffers showed that a pulse rate > 120 beats/min or temperature >38.0°C were more commonly seen in patients with end-organ toxicity.[94] It is not known whether these factors are valuable in predicting end-organ toxicity in other methamphetamine abusers. For cocaine and cannabis acute toxicity, to the best of our knowledge, we are not aware of any studies on outcome prognostication in the ED.

In this study, we did not choose mortality as the secondary outcome because the number of deaths was too small for identification of a reasonable number of predictors. We also did not want to duplicate the work of other investigators before. We defined poor outcome as a composite of a number of end-organ toxicities to reflect the severity of the poisoning. We did not include ICU admission or the need for certain interventions e.g. intubation in our definition because they are affected by other non-clinical factors such as ICU bed availability, clinicians' belief and practice. When we conducted univariate and multivariable analysis, clinical and laboratory variables with a clear relationship with the outcome (e.g. GCS and coma, pH value and AKI) were not included to avoid overestimating the predicting values of individual parameters.

Our study adds to the literature by identifying a number of independent predictors of severe complications. For the whole cohort, a triage temperature > 39°C, diaphoresis, agitation, sluggish or non-reactive pupil response to light, tachycardia > 120 beats per minute were independent predictors of end-organ toxicity. These physiological derangements suggest a more pronounced adrenergic stimulation due to drug poisoning, which may lead to a higher chance of body decompensation. Concurrent use of cough mixture, which may contain codeine, ephedrine/pseudoephedrine, promethazine and dextromethorphan, and other non-recreational medications, were also high-risk factors because they complicate the clinical course. The presence of auditory hallucination was associated with a lower risk because the patients at least needed to talk for such a presentation to be registered, indicating a relatively higher level of sensorium. The finding of drowsiness as a low-risk factor is interesting. In the context of polysubstance abuse, it can be explained by the alleviating effect of concurrent intake of sedatives (e.g. overshooting of benzodiazepine taken to reduce the undesirable effects of methamphetamine) or the stimulant not being be the main culprit of current presentation (e.g. patient might have drunken a lot of alcohol with some exposure to cocaine).

For methamphetamine, our findings concurred with those published by West at al.[93] that a triage temperature >39°C and pulse rate >120 beats per minute were associated with end-organ toxicity, along with other features of sympathetic overdrive including agitation, diaphoresis and sluggish and non-reactive pupils. The presence of auditory hallucination was associated with a lower risk. Co-ingestion and drowsiness were no longer independent predictors. It is interesting to note that the magnitude of association between temperature and end-organ toxicity was the largest among different predictors, suggesting a role of hyperthermia in acute methamphetamine toxicity. The exact mechanism underlying methamphetamine-induced hyperthermia remains to be determined, but it is likely that both central and peripheral mechanisms beyond the norepinephrine, dopamine and serotonin neurotransmitter systems are involved. No single pharmacological agent is current indicated for treatment of methamphetamine-induced hyperthemia.[95]

For cocaine, we found that tachycardia > 120 beats per minute and a higher triage category were independent predictors for poor outcome. Unexpectedly, shortness of breath, which might indicate hyperventilation in response to cocaine exposure, was associated with a lower risk. For cannabis, paranoid delusion had the largest magnitude of association with end-organ toxicity. This can be explained by co-exposure to other stimulants in the context of polysubstance abuse or uncontrolled intake of cannabis in patients with psychosis. Other independent predictors included diaphoresis, agitation and associated injury. These findings need confirmation in future prospective studies.

It is noteworthy that a higher triage acuity was an independent predictor of poor outcome for methamphetamine and cocaine acute toxicity, indicating the robustness of the current local A&E triage system in picking up high-risk drug abuse patients.

5.4 Drug-related ED reattendance

Looking at the trajectory of methamphetamine, cocaine and cannabis abusers after the discharge from the index ED presentation is important in evaluating the impact of ED interventions in preventing drug-related reattendance. However, few ED-based studies in the literature offer such relevant data and the estimations vary across different studies.

For methamphetamine, Gray et al. reported that 45.5% of abusers had previous amphetamine-related ED presentations, but they did not follow up the patients after the index ED discharge.[64] Cunningham et al. reported 65% of the patients with cocaine-associated chest pain returned within 1 year, of whom 23% returned for chest pain; among these, 66% had a positive cocaine screening result.[96] By contrast, Galicia et al. reported a much lower 1-year ED drug-related reattendance rate of 18.9% in a multicentre ED cohort of cocaine users.[97] To the best of our knowledge, there have been no ED-based studies on cannabis that reported a specific drug-related ED reattendance rate.

The findings of this study extend our current understanding of the pattern of drug-related ED revisits after the index presentation by providing estimates of the number of revisits within 1 year and the time to the first revisit. After controlling for the confounding effects of gender, physical health condition, social allowance status, and the length of index hospitalisation on unscheduled ED revisits and utilisation,[98, 99] methamphetamine abuse still remained significantly associated with a higher risk of reattendance, indicating that it is highly addictive. As for the whole cohort, our data showed that for index ED presentations involving methamphetamine, 73.3% of the patients reported previous use and 86.1% abused methamphetamine when they returned. The relevant figures for cocaine were 46.6% and 57.5%; and for cannabis 31.4% and 50.0%, respectively.

The need for urgent psychiatric consultation during the index ED presentation was also associated with a higher risk of reattendance, which could be attributed to the fact that mental illness is associated with frequent ED use.[98, 99] Methamphetamine abusers with concurrent psychotic disorders have higher levels of psychiatric symptomatology across multiple domains over time and increased health service utilisation.[100]

The finding of an association between major toxic effect experienced during the index presentation and a lower risk of ED reattendance is worthy of further discussion. Major toxic

effect from recreational drug abuse could be a life-changing event that might alter the perceived risk of harm of drug abuse and thus influence the future intention to use.[101] However, the number of patients who developed major toxic effect in the entire cohort was small and we could not wait until the major effect to occur to change drug abusers' behaviour. There is a need to take pre-emptive action to motivate behavioural change by demonstrating the serious physical and mental health consequences to both potential and current drug users.[102] Yet, methamphetamine addiction is associated with impaired cognitive function and altered decision making with less focus on riskiness of behaviour.[103,104] More research is needed to determine best strategy to tailor the message to current methamphetamine abusers.

In this study, referral to social worker or NGO drug services was not associated with drug-related ED reattendance. However, it is important to note that the number of such referrals was too small within the entire cohort and the statistical power was too low to reveal a significant association. It would be inappropriate to draw conclusion on the impact of such referrals on drug-related ED reattendance based on the current data. Caution is advised when interpreting these findings. Also, the practice of referring patients with acute recreational drug toxicities to social worker or NGO drug services varied considerably between different clinicians. Without a standardised referral pathway to these services, it is not possible to properly evaluate the true impact of such referrals on ED revisits. More research is needed to evaluate the best care pathway to link all the available services together in the ED. That would require a study with a prospective design to evaluate the relative risk of future reattendance in a structured manner.

6. Strengths and limitations of the study

6.1 Strengths

To the best of our knowledge, this is the largest reported local case series of acute methamphetamine, cocaine and cannabis toxicity, and the first to evaluate factors associated with drug-related ED reattendance beyond 1 year. The database in the HKPIC offers access to territory-wide data that are representative of the contemporary drug abuse pattern for the whole of Hong Kong. The consistency in the reporting mechanism of acute poisonings from local A&Es throughout the study period also allowed us to conduct trend analysis on drug use patterns over a decade.

Compared with studies based on administrative data and diagnostic codes, the current work provides more accurate and detailed information on individual cases covering demographic, past drug use pattern, clinical and laboratory data at the index presentation, outcome and future attendance records. The data quality was ensured by manual checking by qualified specialists with training in clinical toxicology.

Owing to the large sample size, we were able to identify events with a low rate of occurrence in this study, including rare complications and NPSs with a low frequency of use. We were also able to identify more independent predictors in the multivariable logistic regression compared with those reported in previous studies with a smaller sample size.

6.2 Limitations

This study had several limitations. First, it was a retrospective study with the inherent weaknesses of information bias and missing data. Clinical data were not recorded in a standardised manner in the medical notes. It was likely that only the main signs and symptoms were documented by the treating clinicians. We could only assume the absence of certain features when they were not documented.

Second, there was no standard criterion for the determination of drug use and its relationship with an ED visit. We could only rely on the clinical judgement of the treating physicians with subsequent vetting during data collection.

Third, there was no standardised protocol for ordering toxicology screens in different A&Es. Not all cases underwent toxicology screening. It is well known that the self-reporting rate of drug abuse is low—around 50% for both methamphetamine and cocaine.[105] Diagnosis could be missed if history was not forthcoming or if the clinicians did not consider stimulant

toxicity in their differential diagnosis. It was likely that acute toxicity of cannabis and NPSs was under-reported, especially when only a small number of samples were sent to TRL for screening for emerging drugs of abuse. However, this represents the current ED practice in Hong Kong, where management of patients with acute recreational drug toxicity is mainly based on clinical judgement and self-reporting, supported by laboratory analyses to confirm exposure.

Fourth, we did not study the impact of different forms of drug (e.g. powder vs crack cocaine)[67], nor did we study the pattern, quantity and time of drug use as they were in general inconsistently documented in the medical notes. We could not confidently extract such data in a standardised manner and factor them in during regression analysis.

Fifth, presentations of individual drugs were possibly affected by co-ingestion of substances such as heroin and alcohol; however, this reflects real clinical situations in which polysubstance abuse predominates.

Sixth, we were not able to reliably retrieve non-clinical data that might affect ED reattendance, such as imprisonment and travel records. It has been shown that methamphetamine users have more extensive criminal records and are more likely than other drug users to commit property crimes.[106] Imprisoned drug abusers would have a falsely lower ED utilisation during their time of incarceration. We were also unable to ascertain whether patients referred to social workers or NGO drug services actually booked an appointment. Equally, for patients who were not referred upon discharge, it was still possible that they might have self-referred to see social workers and NGO substance abuse service providers.

Finally, because of the retrospective nature of the study, we were unable to quantify the severity of addiction using validated tools, such as the Addiction Severity index.[107] The current cohort contained a mixture of causal drug abusers and patients with drug dependence disorder who might had a significantly different trajectories for future drug use and outcome.

7. Implications of the research

Despite the limitations, this study provides real-world data collected over the past decade and offers a unique insight into the acute health harms of recreational use of methamphetamine, cocaine, cannabis and NPSs in our locality. The findings of this study have multiple implications for future drug-control policy, clinical management and research.

7.1 Implications for drug-control policy

Our study shows that from 2010 to 2019, the number of acute toxicities related to methamphetamine abuse encountered in local EDs was greater than those of cocaine and cannabis combined. Methamphetamine abuse was characterised by a trajectory of strong addiction, a high acuity in the ED, and a high proportion of mental health co-morbidities, acute psychosis, self-harm, violence, and injuries. Methamphetamine abuse is devastating not only to the drug abusers, but also to their family members, who often are the target of physical violence. Once the abusers develop psychotic symptoms, the risk of ED return for methamphetamine-related problems is even higher.

With methamphetamine now being the most commonly abused soft drug in Hong Kong,[108] the threat of having more cases of psychosis over time is growing,[56,109] even though we do not see a signficiant rising trend of methamphetamine abuse. In the absence of effective treatment for methamphetamine-dependence disorder,[110] more resources should continue to be channelled to educate youths on its harms to prevent the use of methamphetamine in the first place. Public education should focus on the major effects and psychiatric consequences, as there is a general lack of understanding of risks.[101] For methamphetamine users who are already receiving psychiatric treatment, there is a need to reinforce compliance by bringing drug services from various agencies to them while they are still in the hospital. Tailoring the risk message to methamphetamine abusers who might have a heightened impulsivity and lower risk perception is important to ensure effective risk communication.

For cocaine, no single drug-surveillance system seems to capture the entire use pattern. Cocaine abusers in the ED are less likely to be already in contact with social workers or NGO drug services, and are more likely to self-discharge without completing treatment and drug abuse assessment. Given the similar acute toxicity of methamphetamine and cocaine, premature termination of care represents a higher risk to cocaine users. The ED remains an important sentinel point for cocaine-use surveillance. ED consultation represents an important opportunity to link cocaine abusers to various anti-drug services.

For cannabis, we believe that the current figures both in our study and in the official registry are under-reported, given its milder toxicity in general. By its nature, figures in the official

registry (CRDA) do not measure the exact size of the drug abusing population in Hong Kong at any particular time, but they are rather indicators of the trends of drug abuse over time. This study showed an apparent rising trend of abuse among youths. The increased market value of cannabis seized by law enforcement, which were significantly correlated with the number of acute toxicity cases in the ED, indicates a need to closely monitor the trend of cannabis use locally. Given the non-specific presentations of some cannabis abusers (such as cyclical vomiting in those with cannabinoid hyperemesis syndrome)[111], frontline healthcare workers should be more vigilant.

For NPSs, the overall magnitude of the problem appears to be small. However, the low detection rate locally might have been the result of low awareness among drug abusers and healthcare providers and limited access to diagnostic services. Although the global rise of NPSs has appeared to stablise since 2015, wide regional variability has been observed.[112] There is a need to continue to strengthen the current surveillance system for emerging drugs of abuse and improve clinical awareness and access to laboratory testing for NPSs.

7.2 Implications for clinical management

Most cases of methamphetamine-, cocaine- and cannabis-related acute toxicities are managed and discharged from the ED, which remains a critical point in the patient help-seeking journey. Given the high prevalence of hypokalaemia among stimulant abusers, and the presence of rhabdomyolysis, AKI and acute myocardial injury in many patients, we recommend routine checking of serum potassium, creatinine, creatine kinase and cardiac troponins for all patients who present to the ED with acute toxicity related to methamphetamine and cocaine abuse, and for selected cases of cannabis abuse. Patients with unexplained rhabdomyolysis should be screened for methamphetamine or other illicit drugs.

At ED presentation, for patients with undifferentiated presentations of stimulant abuse, a triage temperature > 39°C, diaphoresis, agitation, sluggish or non-reactive pupil response to light, tachycardia > 120 beats per minute, and concurrent use of cough mixture and other non-recreational medications predict a higher risk of end-organ toxicity. Predictive factors of poor outcome vary for methamphetamine, cocaine and cannabis. A higher level of care in a facility capable of organ support should be arranged earlier for patients at risk of end-organ toxicity.

Methamphetamine is associated with psychiatric comorbidities and a higher risk of acute psychosis. Therefore, it is necessary to screen for psychotic symptoms when methamphetamine abusers present to the ED with acute toxicity.[52] Our data show that methamphetamine users generally have poor compliance with follow-up advice and psychiatric treatment. Cocaine and cannabis abusers are not connected with social workers

and NGO drug services frequently. ED presentation represents a unique opportunity to engage drug abusers and motivate abstinence through communication of the risks of major harms. Such messages should be tailored to drug abusers who have heightened impulsivity and altered risk perception.

There is a need to integrate the network of service providers at the ED and bring them to the patients while they are still in the hospital to maximise contact. More resources should be provided to train medical social workers in hospitals to handle patients with acute recreational drug toxicities. In addition to the current practice of arranging residential placement for patients after hospital discharge and assisting them in applying for social allowance, medical social workers can play an important role in referring patients-in-need to various anti-drug NGOs for treatment and rehabilitation, counselling and other follow up services.

7.3 Implications for future research

It remains unclear which care model in the ED would have an impact on the trajectory of drug use and prevention of associated harms. The efficacy of any ED care programme can only be evaluated properly with a prospective study with standardised follow-up and data collection.

The coronavirus disease 2019 (COVID-19) pandemic has also brought new trends of drug trafficking and use worldwide, characterised by increases in use of cannabis and non-medical use of pharmaceutical drugs such as benzodiazepines.[113] Social isolation and disrupted access to detoxification and anti-drug services during the pandemic cause additional psychological distress, pushing addicts to seek for alternative psychotropic drugs.[114]

The true impact of the COVID-19 pandemic on local drug use pattern remains to be elucidated. Future studies should factor in the impact of the COVID-19 pandemic.

8. Conclusions

Data from the EDs extended our current understanding of the trends, patterns, harms and burden of methamphetamine, cocaine and cannabis abuse in Hong Kong. Although we could not identify a significant trend of increased ED presentations, there is no room for complacency. Methamphetamine remains the major health burden. Besides focusing our anti-drug work on preventing the abuse of other prevalent drugs such as opioid and ketamine, more resources should continue to be channelled to educate young people about the harms of methamphetamine and to prevent its use. Although most cases of acute methamphetamine, cocaine and cannabis toxicity can be managed in the ED, end-organ toxicities are frequently encountered and their risk factors should be actively looked for and managed early in the clinical course. While the optimal ED care model for drug abusers remains unknown, there is a need to enhance collaboration with other agencies providing anti-drug services in order to provide the most appropriate services to address the needs of the patients while they are still in hospital, to ensure maximum engagement and assistance in order to motivate behavioural changes, with the aim to help the abusers quit drugs.

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Supplementary tables

Supplementary Table 1. Brief summary of fatal cases

Year of presentation	Gender	Age (year)	Drug involved	Clinical presentation	Complications
2011	M	32	Methamphetamine	Eyelid twitching and sweating after swallowing a pack of drug	Shock, altered mental status, repeated seizure, hyperthermia (42°C), metabolic acidosis, AKI, rhabdomyolysis
2012	M	41	Methamphetamine, cough mixture	Found comatose and lying on the street with shock and hyperthermia	STEMI, shock, ARDS with respiratory failure, hyperkalaemia, metabolic acidosis, rhabdomyolysis, AKI with acute renal failure, acute liver failure, DIC, recurrent hypoglycaemia, complicated with MRSA septicaemia
2013	M	41	PMMA, PMA, cocaine, ketamine	Found comatose and lying in park with sinus tachycardia, hyperthermia (40.3°C) and limb rigidity	Coma, acute myocardial injury, AKI, acute liver injury, metabolic acidosis, rhabdomyolysis
2013	M	31	PMMA, PMA, methamphetamine, cocaine	Found lying on the street with limb twitching and SVT (HR 176) and hyperthermia (41.7°C)	Shock, VT, acute myocardial injury, AKI, rhabdomyolysis, metabolic acidosis, DIC
2014	M	39	Methamphetamine, cough mixture	Suspected seizure followed by cardiac arrest before ED arrival, hyperthermia (40.9°C)	hypoxic brain damage with poor neurological recovery, acute myocardial injury, AKI, rhabdomyolysis,
2014	M	30	Methamphetamine, heroin, codeine, zopiclone, promethazine	Found collapsed in a public toilet with cardiac arrest before ED arrival	Repeated episodes of cardiac arrest, shock, acute myocardial injury, AKI, acute liver injury, metabolic acidosis, hyperkalaemia, rhabdomyolysis
2015	M	42	Methamphetamine	Shortness of breath, chest discomfort, agitation with sinus tachycardia (HR 126)	Hyponatraemia, hypoglycaemia, AKI, acute liver injury, metabolic acidosis, rhabdomyolysis, sudden cardiac arrest after admission
2015	M	43	Methamphetamine	Found hanging himself with prehospital cardiac arrest	hypoxic brain damage, acute myocardial injury, metabolic acidosis, AKI, acute liver injury, rhabdomyolysis
2015	M	41	Methamphetamine	Sudden cardiac arrest after abusing methamphetamine intravenously with friend	acute myocardial injury, shock, hyperkalaemia, metabolic acidosis, AKI, acute liver injury, rhabdomyolysis, DIC

2016	M	38	Methamphetamine, ketamine	Sudden collapse with VT cardiac arrest soon after ED arrival and hyperthermia (41.5°C)	Shock, VT, acute myocardial injury, seizure, metabolic acidosis, hyperkalaemia, AKI, acute liver injury, rhabdomyolysis, DIC, right calf compartment syndrome
2016	M	36	Methamphetamine, cough mixture	Found collapsed in a cemetery with head injury, hyperthermia (41.1°C) and bradycardic cardiac arrest soon after ED arrival	hyperkalaemia, hyponatraemia, metabolic acidosis
2016	M	46	Methamphetamine, sildenafil	Found lying on the floor	Massive right ICH/IVH, acute myocardial injury, rhabdomyolysis
2016	M	26	Cocaine	Sudden cardiac arrest while driving a minibus which collided with a truck	Coma, myoclonus, metabolic acidosis, AKI, rhabdomyolysis complicated with septic shock
2017	M	35	Methamphetamine	Acute confusion with aggressive behaviour and vomiting	cerebral oedema, coma, acute myocardial injury, shock, sudden cardiac arrest twice, MOF, DI, metabolic acidosis
2017	M	27	MDMA	Sudden collapse in a music festival with VF cardiac arrest soon after ED arrival and hyperthermia (42°C), failed resuscitation in the ED	Acute myocardial injury, hyperkalaemia, metabolic acidosis
2018	M	46	Methamphetamine	Acute confusion and agitation with violent behaviour	Shock, bradycardia, VF, suspected PE, metabolic acidosis, AKI, rhabdomyolysis
2019	M	58	Methamphetamine	Chest discomfort followed by sudden cardiac arrest before ED arrival	Acute coronary syndrome, AKI, metabolic acidosis
2019	F	30	Cocaine, ketamine	Altered mental status with rapid deterioration to coma, hypertension and tachycardia	cerebral oedema, tachycardia, shock, severe hyponatremia, torsade de pointes cardiac arrest, AKI, brain death

Abbreviations: AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; DI, diabetes insipidus; DIC, disseminated intravascular coagulation; ED, emergency department; HR, heart rate; ICH, intracranial haemorrhage; IVH, intraventricular haemorrhage; MDMA, 3,4-methylenedioxy-methamphetamine; MRSA, mutli-drug resistant *Staphylococcus aureus*; PMA, paramethoxyamphetamine; PMMA, paramethoxymethamphetamine; PE, pulmonary embolism; MOF, multi-organ failure, STEMI, ST-segment elevation myocardial infarction; SVT, supraventricular tachycardia; VT, ventricular tachycardia

Supplementary Table 2. Results of univariate analysis

	The whole cohort n=1,629	Episodes that involved methampheta mine n=1,225	Episodes that involved cocaine n=328	Episodes that involved cannabis n=172
Age—median, year	0.001^	0.026^	0.094^	0.027^
Sex	0.003*	0.004*	0.086*	0.016*
Female				
Male				
Transgender				
Social allowance	0.759*	0.683*	0.027**	1.000**
Ambulance case	<0.001*	<0.001*	<0.001*	0.272*
Non-local resident	0.215*	0.313*	0.038*	1.000**
Pregnant at the time of presentation	0.467**	0.463**	0.548**	N/A
MSM	0.422*	0.354*	1.000**	1.000**
Drug abused at presentation				
Methamphetamine	0.041*	N/A	0.892*	0.010**
Cocaine	0.672*	0.535*	N/A	0.016**
Cannabis	0.012*	0.250*	0.171*	N/A
MDMA	0.006*	0.267**	0.129*	0.253**
Ketamine	0.210*	0.154*	0.218*	1.000**
Heroin	0.032*	0.246*	0.034**	0.300**
Cough mixture or pills	<0.001*	0.004*	<0.001**	0.231**
Zopiclone or zolpidem	0.919*	0.641*	0.264**	0.319**
Benzodiazepine	0.504*	0.346*	0.959*	0.300**
Novel psychoactive substances	0.819*	1.000**	1.000**	1.000**
Co-ingestion of alcohol	0.203*	0.888*	0.304*	0.539*
Co-ingestion of other medications	0.002*	0.001*	0.532*	0.202**
Primary route of exposure	0.146*	0.562*	0.221*	0.989*
Inhalation				
Insufflation				
Oral ingestion				
Intravenous				
Others				
Unspecified				
Place of drug abuse	0.067*	0.293*	0.018*	0.464*
Home				
Workplace				
Public place				
Unspecified				
Place outside Hong Kong	0.309**	0.242**	0.232**	1.000**

Methamphetamine only	0.960*	0.351*	N/A	N/A
Cocaine only	0.962*	N/A	0.894*	N/A
Cannabis only	0.001*	N/A	N/A	0.01*
Past history of drug abuse	0.667*	0.665*	0.039*	0.028*
Methamphetamine	0.173*	0.795*	0.174*	0.017**
Cocaine	0.011*	0.043*	0.027*	0.037**
Cannabis	0.783*	0.525*	0.742*	0.02*
MDMA	0.226*	0.086*	0.855*	0.641**
Ketamine	0.025*	0.007*	0.439*	0.050**
Heroin	0.007*	0.013*	0.731*	0.001**
Cough mixture or pills	0.578*	0.914*	0.084**	0.447**
Sedative or hypnotics	0.307*	0.838*	0.423*	0.014**
History of alcohol dependence	0.071*	0.156*	0.483**	1.000**
History of drug-induced psychosis	0.368*	0.523*	0.124*	1.000**
History of psychiatric disease				
Schizophrenia	0.598*	0.422*	0.135**	0.600**
Depression	0.639*	0.997*	0.825*	1.000**
Anxiety	0.723*	0.549**	1.000**	0.415**
Bipolar affective disorder	0.906*	0.773**	0.438**	1.000**
History of personality disorder				
Antisocial personality disorder	0.215*	0.309*	0.232**	N/A
Borderline personality disorder	0.650*	0.628*	1.000**	1.000**
Past medical history				
Good past health	0.483*	0.214*	0.780*	0.048*
Hypertension	0.007*	0.003*	0.746**	1.000**
Diabetes mellitus	0.731*	0.754*	1.000**	0.300**
Ischaemic heart disease	0.094**	0.106**	0.053**	N/A
Previous psychiatry follow-up	0.253*	0.426*	0.155*	0.851*
Regular				
Defaulted				
Never				
Previous psychiatric treatment	0.852*	0.903*	0.455*	0.549*
Regular				
Defaulted				
Poor compliance				
Never				
Previous detoxification treatment	0.987*	0.997*	0.377*	1.000**
Followed-up by social worker	0.104*	0.129*	0.021*	1.000**
Followed-up by NGO service provider for drug abuse	0.147*	0.237*	0.054**	1.000**
Triage category	<0.001*	<0.001*	<0.001*	0.001*
Category 1—Critical				
Category 2—Emergent				
Category 3—Urgent				

Category 4—Semi-urgent				
Category 5—Non-urgent				
Triage vital signs				
Pulse rate—mean, beat per minute	<0.001#	<0.001#	0.016#	0.160#
Temperature—median	<0.001^	<0.001^	0.001^	0.019^
Pupil size—median	0.692^	0.962^	0.514^	0.169^
Pupil reactivity	<0.001*	<0.001*	0.004*	0.01**
Reactive				
Sluggish or non-reactive				
Not specified				
Tachycardia > 120 beats per minute	<0.001*	<0.001*	<0.001*	0.807*
Tempeature > 40 ºC	<0.001**	<0.001**	0.001**	0.026**
Tempeature > 39 ºC	<0.001*	<0.001*	<0.001**	0.004**
Tempearture > 38 ºC	<0.001*	<0.001*	<0.001*	<0.001**
Cardiovascular presentations				
Chest pain/discomfort	0.118*	0.752*	0.107*	0.741**
Palpitation	0.001*	0.124*	0.001*	0.260**
Hypertension	0.519*	0.251*	0.753*	0.456*
Sinus tachycardia	<0.001*	0.027*	0.009*	0.405*
Neurological presentations				
Agitation	<0.001*	<0.001*	0.033*	<0.001*
Confusion	<0.001*	<0.001*	0.001*	<0.001*
Headache	0.052*	0.045*	0.637*	0.109**
Dizziness	<0.001*	0.01*	0.127*	0.004*
Syncope	0.903*	0.392*	0.584**	0.641**
Drowsiness	0.033*	0.06*	0.587*	0.313**
Weakness	0.112*	1.000**	0.206**	0.60**
Numbness	0.035*	0.185**	0.206**	1.000**
Restlessness	0.073*	0.09*	0.77**	0.04**
Involuntary limb movement/tremor	0.478*	0.716*	0.552*	0.693**
Unstable emotion	0.243*	0.148*	1.000**	0.231**
Anxiety	0.015*	0.093*	0.135**	0.130**
Auditory hallucination	0.027*	0.032*	0.143*	0.300**
Visual hallucination	0.169*	0.536*	0.378**	0.470**
Tactile hallucination	0.978*	0.795**	0.232**	0.300**
Paranoid delusion	0.703*	0.569*	0.220*	0.040**
Referential delusion	0.952*	0.820*	0.232**	0.086**
Any hallucination	0.045*	0.046*	0.813*	0.395**
Any delusion	0.224*	0.179*	1.000**	1.000**
Gastrointestinal presentations				
Nausea/vomiting	0.777*	0.093*	0.963*	0.912*
Diarrhoea	0.766**	0.484**	1.000**	N/A
Abdominal pain	0.021*	0.160*	0.017**	0.512**
Respiratory presentations				

Shortness of breath	0.016*	0.180*	0.007*	0.131**
Hyperventilation	0.900*	0.629*	0.206**	1.000**
Cough	0.711**	0.425**	0.410**	N/A
Bronchospasm	1.000**	0.442**	1.000**	N/A
Other presentations				
Diaphoresis	<0.001*	<0.001*	0.001*	<0.001**
Disorganised behaviours				
Removal of clothing in public area	0.057*	0.015*	0.594**	1.000**
Wandering	0.327*	0.234*	1.000**	1.000**
Lying on the floor	0.352*	0.393*	0.756**	0.415**
Deliberate self-harm	0.030*	0.007*	0.248*	0.179**
Violent behaviours to others	0.391*	0.870*	0.637*	0.704**
Drug-driving	1.000**	1.000**	1.000**	1.000**
Associated injury	<0.001*	0.019*	0.003*	<0.001**

Abbreviations: NGO, non-governmental organisation

Note:

*Pearson Chi-square test

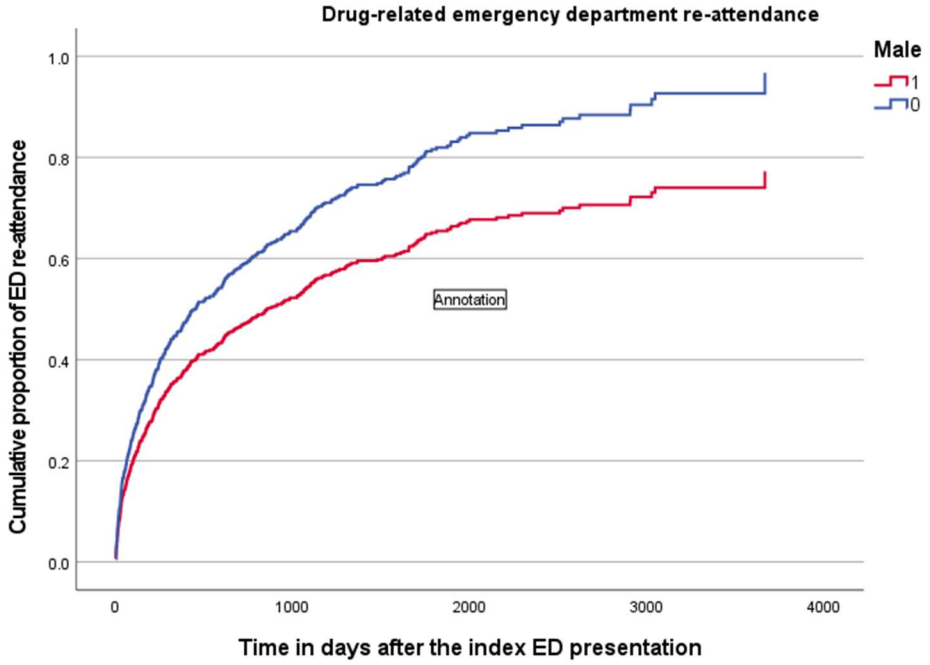
**Fisher's Exact test

#Student t-test

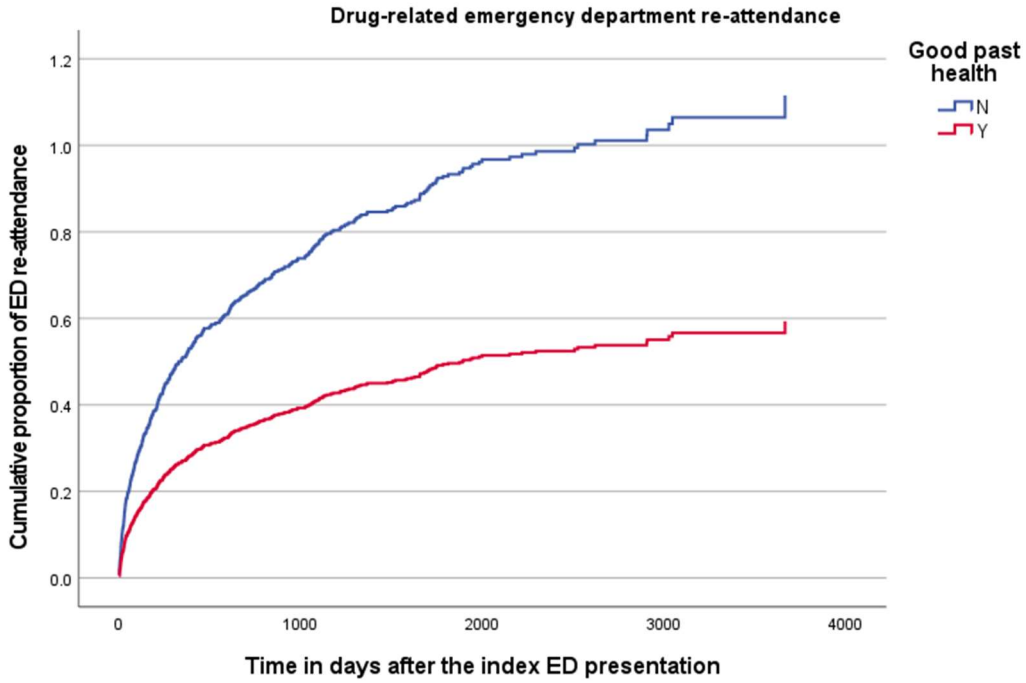
^Mann-Whitney U test

Supplementary figures

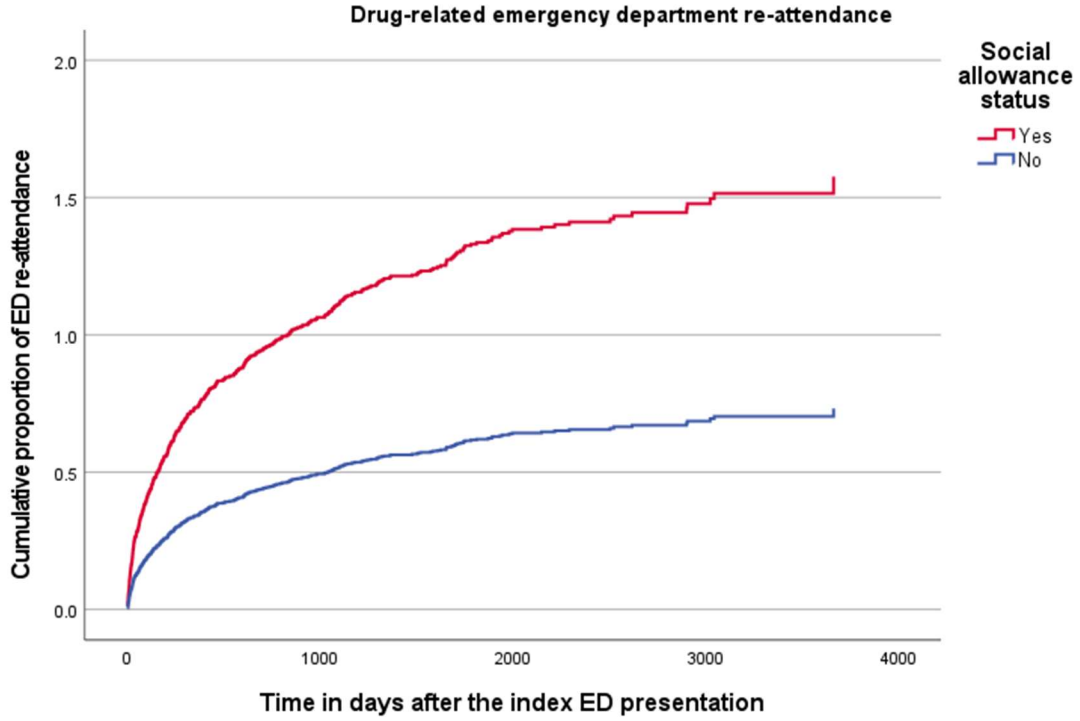
Supplementary Figure 1. Kaplan-Meier curve showing drug-related ED reattendance rate as a function of male gender



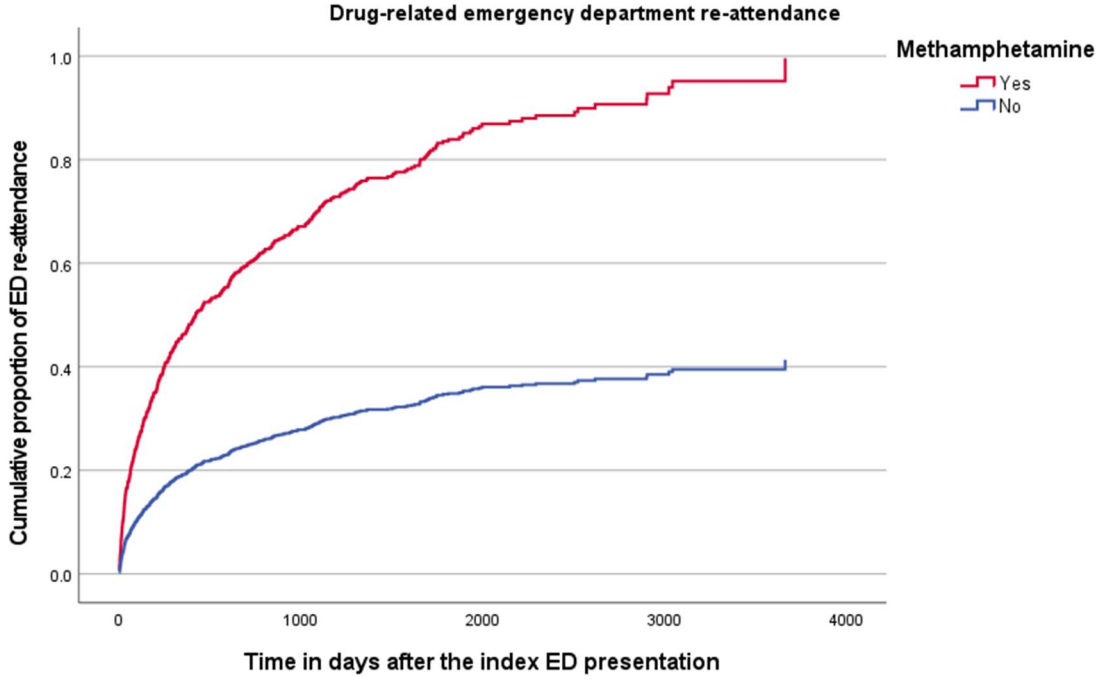
Supplementary Figure 2. Kaplan-Meier curve showing drug-related ED reattendance rate of drug abusers with good past health as compared with those with comorbidities



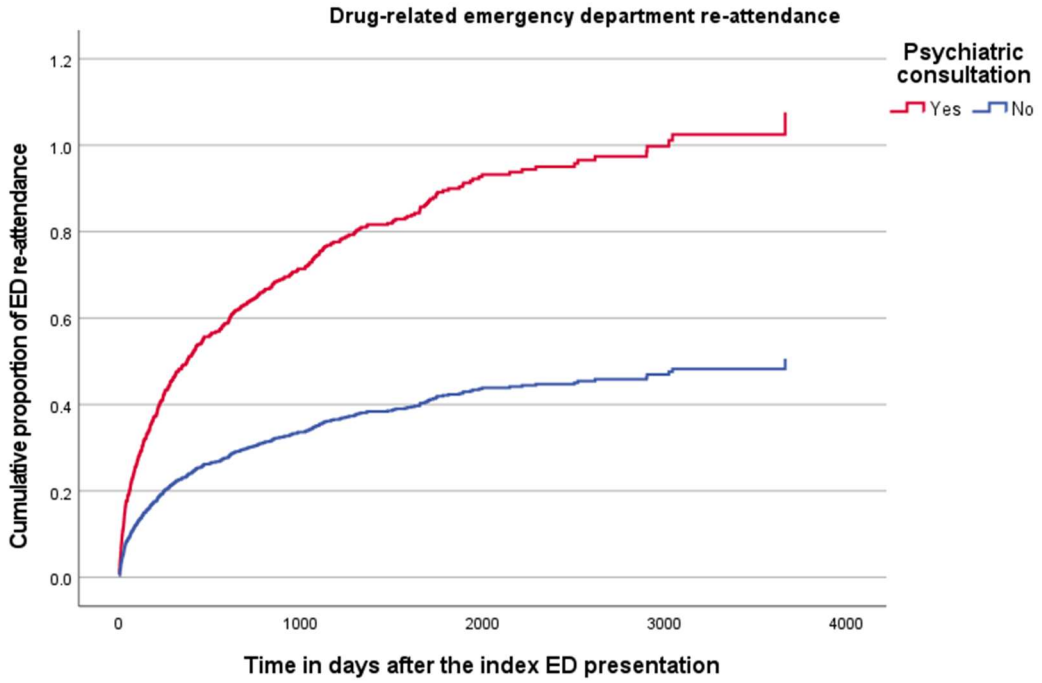
Supplementary Figure 3. Kaplan-Meier curve showing drug-related ED reattendance rate as a function of social allowance status



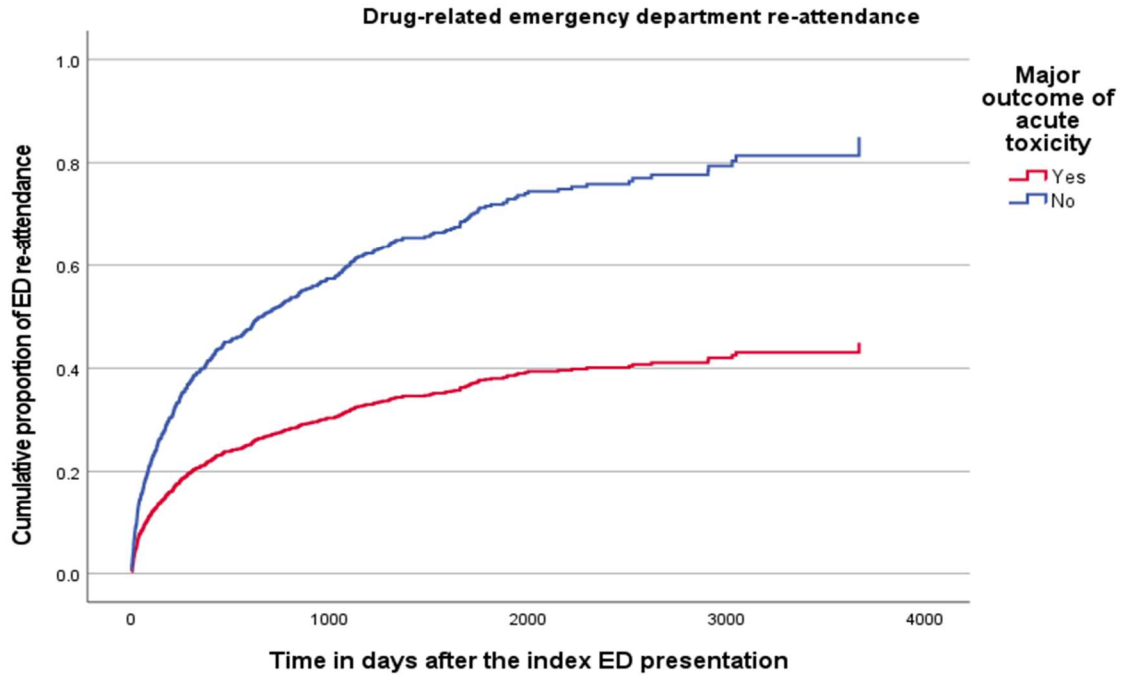
Supplementary Figure 4. Kaplan-Meier curve showing drug-related ED reattendance rate of methamphetamine abusers compared with cocaine and cannabis abusers



Supplementary Figure 5. Kaplan-Meier curve showing drug-related ED attendance rate of durg abusers who required urgent psychiatric consultation during the index ED presentation as compared with those who did not



Supplementary Figure 6. Kaplan-Meier curve showing drug-related ED attendance rate of drug abusers with a major acute toxicity as compared with those with milder toxicity



Appendices

Appendix 1. Search criteria used in the PICMS

1. Time: 1/1/2010 to 31/12/2019
2. Toxins: Poison category (see attached file)
   A19a (amphetamines) – this group should contain all amphetamine-like drugs, including those NPS (e.g. PMMA)

   A19b (Cannabis)

   A19c (Cocaine)

   A19h (others stimulants) – this group may contain cannabinoids and piperazine-based NPS.

3. Poisoning outcome related to the enquired poison (at least possibly related)

4. Excluding information enquiry and overseas consultation.

5. Excluding duplicate records for the same attendance (i.e. reporting and consultation entry): the reporting entry will be deleted

Appendix 2. Data entry code manual

The University of Hong Kong

Emergency Medicine Unit

Beats Drug Fund Project BDF 190053

Acute toxicity related to psychoactive substance abuse and the impact of emergency department interventions on drug-related reattendance

Data Entry Code Manual version 1.1

General rules

1. Retrospective chart review requires a careful review of medical records. Clinicians may not document every symptoms or signs in the clinical notes. Some symptoms and signs require interpretation. The reviewer should be familiarize themselves with how symptoms and signs are recorded as follows:

'cough **+**' – it means the patient had cough

'pain**+++**' – it means the patient had severe pain, with the number of '+' representing the severity of that particular symptoms

'vomiting**o**' – it means the patient did not vomit

2. Sometimes, a symptom is not mentioned specifically in the clinical notes but one can deduce from the information documented in the record. For instance, 'no respiratory symptoms' – it means the patient did not have any respiratory symptoms. So even cough was not mentioned at all in the notes, the review should code the absence of cough.

3. For dichotomized variables (yes/no), enter '1' for yes and '0' for no.

4. For any missing values, enter '999'.

5. For triage vital signs, enter the first set of readings if more than 1 reading are recorded.

6. For date/time variables, follow the format of '**dd/mm/yyyy hh:mm'**.

7. If you are not certain, please highlight the cell with yellow colour and seek advice from the investigators.

8. Data extraction will run in parallel to ensure accuracy of coding.

9. For patients with repeated ED attendance within the study period, the first attendance will be treated as the 'index presentation'.

Variables no. (excel column)	Variable name	Value	Definition
A	Coder 1	Coder initials	The initials of coder 1's name
B	Caseno.	Study code	Assigned study code on the master list
C	Hospital	AHNH	Alice Ho Miu Ling Nethersole Hospital
		CMC	Caritas Medical Centre
		KWH	Kwong Wah Hospital
		NDH	North District Hospital
		NLTH	North Lantau Hospital
		POH	Pok Oi Hospital
		PMH	Princess Margaret Hospital
		PWH	Prince of Wales Hospital
		PYNEH	Pamela Youde Nethersole Eastern Hospital
		QEH	Queen Elizabeth Hospital
		QMH	Queen Mary Hospital
		RH	Ruttonjee Hospital
		SJH	St John Hospital
		TKOH	Tseung Kwan O Hospital
		TMH	Tuen Mun Hospital
		TSH	Tin Shui Wai Hospital
		UCH	United Christian Hospital
		YCH	Yan Chai Hospital
		Others (free text)	Other hospital or clinic
D	HKID	HK ID number	**HK ID number – NOT NEED to enter bracket**
E	AENum	AE number	AE number on the A&E record - **NOT NEED to enter bracket**
F	Age	Age in years	Patient's age in years at the time of A&E presentation
G	Gender	0	Female
		1	Male
H	Date and time	dd/mm/yyyy hh:mm	Date and time of A&E registration
I	Year of presentation	yyyy	Year of A&E registration
J	Ambulance case	0	Not transported by ambulance
		1	Transported by ambulance
K	Police case	0	Not a police case
		1	Police case / brought in by police
L	On CSSA?	0	Not on comprehensive social allowance
		1	Receiving social allowance
M	Triage Category	1	Triage Category 1 'immediate'
		2	Triage Category 2 'emergent'
		3	Triage Category 3 'urgent'
		4	Triage Category 4 'semi-urgent'
		5	Triage Category 5 'non-urgent'
N	SBP	Systolic blood pressure	Triage systolic blood pressure in mm Hg
O	DBP	Diastolic blood pressure	Triage diastolic blood pressure in mm Hg
P	Pulse	Pulse rate	Triage pulse rate in beats per minute

Q	RR	Respiratory rate	Triage respiratory rate
R	SaO2	Oxygen Saturation	Triage oxygen saturation in %
S	O2 flow rate	The flow rate of supplemental oxygen given to the patient	Triage supplemental oxygen flow rate in L/min (If oxygen is not given – **input '0')**
T	Temp	Temperature	Triage temperature
U	APVU	A	Alert
		V	Response to verbal command
		P	Response to pain only
		U	Unresponsive
V	GCS	Glasgow coma score	The first reading documented in the AED notes
W	Pupil size	Pupil size	Triage pupil size in mm (e.g. 3/2 – it means the right pupil was 3 mm and the left pupil 2 mm)
X	Pupil reactivity	1	Pupils reactive to light or '+' following the documented pupil size in the notes. (e.g. +/+ means both pupils were reactive)
		0	Pupils not reactive to light or 'fixed' or '-ve' or '-' or 'sluggish' following the documented pupil size in the notes. (e.g. -/- means both pupils were non-reactive)
Y	Methamphetamine	1	Clinical history or toxicology assays **suggested exposure to methamphetamine** before A&E presentation.
		0	Clinical history or toxicology assays **NOT suggestive of exposure to methamphetamine** before A&E presentation.
Z	MDMA	1	Clinical history or toxicology assays **suggested exposure to MDMA** before A&E presentation.
		0	Clinical history or toxicology assays **NOT suggestive of exposure to MDMA** before A&E presentation.
AA	Other amphetamines	1	Clinical history or toxicology assays **suggested exposure to other amphetamines** before A&E presentation.
		0	Clinical history or toxicology assays **NOT suggestive of exposure to other amphetamines** before A&E presentation
AB	Other amphetamines – free text	Free text of the name of the other amphetamines	
AC	Cocaine	1	Clinical history or toxicology assays **suggested exposure to cocaine** before A&E presentation.

		0	Clinical history or toxicology assays **NOT suggestive of exposure to cocaine** before A&E presentation.
AD	Cannabis	1	Clinical history or toxicology assays suggested **exposure to cannabis** before A&E presentation.
		0	Clinical history or toxicology assays **NOT suggestive of exposure to cannabis** before A&E presentation.
AE	Others (Free text)	Free text	Free text of other recreational drugs exposed
AF	Time of exposure	dd/mm/yyyy hh:mm	
AG	Route of exposure	1	**Smoking/inhalation**
		2	**Snorting/mucosal**
		3	Oral ingestion
		4	Intravenous injection
		5	Others with free text
AH	Recreational use	1	Recreational use was the reason of exposure
		0	Other reasons of exposure
AI	Other reason of use	Free text	
AJ	Site of use	1	Home
		2	Workplace
		3	School
		4	Public space
		999	Unknown
AK	Music festival/ event	1	Drug use in music festival or event
		0	Drug use not associated with music festival or event
AL	Cross-border drug use	1	Drug use across the border with Shenzhen
		0	Drug use in Hong Kong
AM	Use with E-cigarette	1	Drug use associated with E-cigarette
		0	Drug use NOT associated with E-cigarette
AN	Alcohol	1	Drug use with alcohol
		0	NO alcohol use
AO	Tourist/non-local resident	1	The patient is a tourist or not a HK resident
		0	The patient is HK resident
AP	History of drug abuse	1	The patient has a history of drug abuse
		0	The patient has no history of drug abuse
AQ	Known drugs being used in the past	Free text	Name of each drug reported abused in the past
AR	History of drug-induced psychosis	1	The patient has a history of drug-induced psychosis in the past
		0	The patient has NO history of drug-induced psychosis in the past

AS	Previous medical FU for drug-related problem	1	The patient has previous follow up appointment for drug-related problem, defined as outpatient appointment records in epr including psychiatric consultation
		2	The patient defaulted previous medical follow up appointments for drug-related problem. **Only recent default is counted.**
		0	The patient has no previous follow up appointment for drug-related problem
AT	Previous medical treatment for drug-related problem	1	The patient received medication for drug-related problem in the past, including medications for psychiatric symptoms
		2	The patient received non-pharmacological treatment for drug-related problem in the past, including psychotherapy
		3	The patient defaulted treatment for drug-related problem in the past. **Only recent default is counted.**
		0	The patient did not receive any treatment in the past for drug-related problem
AU	Previous detox treatment	1	The patient received professional detoxification treatment in the past
		0	The patient did not receive professional detoxification treatment in the past
AV	Case followed up by social worker	1	The patient had already been followed by a social worker before the index presentation, e.g. brought in by social worker
		0	The patient had NOT been followed by a social worker before the index presentation
AW	Case followed up by NGO	1	The patient had already been followed by a NGO before the index presentation
		0	The patient had NOT been followed by a NGO before the index presentation
AX	Other medical history	Free text	
AY (by doctor)	GIPSS	0-3	Gastrointestinal toxicity as graded with PSS
AZ	Vomiting	1	The presence of vomiting during A&E or hospital admission
		0	The absence of vomiting during A&E or hospital admission
BA	Diarrhoea	1	The presence of diarrhoea during A&E or hospital admission
		0	The absence of diarrhoea during A&E or hospital admission
BB	Abdominal pain	1	The presence of abdominal pain during A&E or hospital admission

		0	The absence of abdominal pain during A&E or hospital admission
BC	GI other symptoms	1	The presence of other gastrointestinal symptoms during A&E or hospital admission
		0	The absence of gastrointestinal symptoms during A&E or hospital admission
			Free text of any gastrointestinal symptoms
BD (by doctor)	RespPSS	0-3	Respiratory toxicity as graded with PSS
BE	SOB	1	The presence of other 'SOB', 'Shortness of Breath', 'dyspnoea' during A&E or hospital admission
		0	The absence of other 'SOB', 'Shortness of Breath', 'dyspnoea' during A&E or hospital admission
BF	Pneumothorax	1	The presence of pneumothorax during A&E or hospital admission
		0	The absence of pneumothorax during A&E or hospital admission
BG	Pneumomediastinum	1	The presence of pneumomediastinum during A&E or hospital admission
		0	The absence of pneumomediastinum during A&E or hospital admission
BH	Respiratory failure	1	The presence of respiratory failure or mechanical ventilation during A&E or hospital admission
		0	The absence of respiratory failure or mechanical ventilation during A&E or hospital admission
BI	Other respiratory symptoms	1	The presence of other respiratory symptoms during A&E or hospital admission
		0	The absence of other respiratory symptoms during A&E or hospital admission
		Free text	Free text of any respiratory symptoms
BJ (by doctor)	CNSPSS	0-3	Neurological toxicity as graded with PSS
BK	Agitation	1	The presence of 'agitation', 'aggressiveness', 'violent act' during A&E or hospital admission
		0	The absence of 'agitation', 'aggressiveness', 'violent act' during A&E or hospital admission
BL	Coma	1	The presence of 'coma', or a GCS<8 during A&E or hospital admission

		0	The absence of ‘coma’, or a GCS<8 during A&E or hospital admission
BM	Dizziness	1	The presence of ‘dizziness’, ‘fainting’, ‘lightheadedness’ during A&E or hospital admission
		0	The absence of ‘dizziness’, ‘fainting’, ‘lightheadedness’ during A&E or hospital admission
BN	Headache	1	The presence of ‘headache’ during A&E or hospital admission
		0	The absence of ‘headache’ during A&E or hospital admission
BO	Seizure	1	The presence of ‘seizure’, ‘convulsion’, ‘fit’ during A&E or hospital admission
		0	The absence of ‘seizure’, ‘convulsion’, ‘fit’ during A&E or hospital admission
BP	Other CNS symptoms	1	The presence of other neurological symptoms during A&E or hospital admission
		0	The absence of other neurological symptoms during A&E or hospital admission
		Free text	Free text of any neurological symptoms
BQ	Ischaemic stroke	1	The presence of ischaemic stroke during index presentation
		0	The absence of ischaemic stroke during index presentation
BR	Haemorrhagic stroke	1	The presence of haemorrhagic stroke during index presentation
		0	The absence of haemorrhagic stroke during index presentation
BS (by doctor)	CVSPSS	0-3	Cardiovascular toxicity as graded with PSS
BT	Shock	1	The presence of ‘shock’, ‘hypotension’, ‘SBP<90’ or ‘MAB<65’ during A&E or hospital admission
		0	The absence of ‘shock’, ‘hypotension’, ‘SBP<90’ or ‘MAB<65’ during A&E or hospital admission
BU	VT	1	The presence of ‘ventricular fibrillation’, ‘ventricular tachycardia’, ‘VF’, VT’, ‘Torsade de pointees’ during A&E or hospital admission
		0	The absence of ‘ventricular fibrillation’, ‘ventricular tachycardia’, ‘VF’, VT’, ‘Torsade de pointees’ during A&E or hospital admission
BV	AF	1	The presence of new-onset atrial fibrillation, irrespective of rate, during A&E or hospital admission
		0	The absence of new-onset atrial fibrillation, irrespective of rate, during A&E or hospital admission

BW	AMI	1	The presence of 'acute myocardial infarction', 'STEMI', 'non-STEMI' during A&E or hospital admission
		0	The absence of 'acute myocardial infarction', 'STEMI', 'non-STEMI' during A&E or hospital admission
BX	ACS	1	The presence of 'acute coronary syndrome', 'ACS', 'angina' during A&E or hospital admission
		0	The absence of 'acute coronary syndrome', 'ACS', 'angina'during A&E or hospital admission
BY	Heart failure	1	The presence of 'heart failure' during A&E or hospital admission
		0	The absence of 'heart failure' during A&E or hospital admission
BZ	Other CVS symptoms	1	The presence of other cardiovascular symptoms during A&E or hospital admission
		0	The absence of other cardiovascular symptoms during A&E or hospital admission
		Free text	Free text of other cardiovascular symptoms
CA	Metabolic PSS	0-3	Metabolic toxicity as graded with PSS
CB	Hyponatraemia	1	The presence of 'hyponatraemia' during A&E or hospital admission that warranted medical interventions
		0	The absence of 'hyponatraemia' during A&E or hospital admission
CC	Hypokalaemia	1	The presence of 'hypokalaemia' during A&E or hospital admission that warranted medical interventions
		0	The absence of 'hypokalaemia' during A&E or hospital admission
CD	Hyperglycaemia	1	The presence of 'hyperglycaemia' during A&E or hospital admission that warranted medical interventions
		0	The absence of 'hyperglycaemia' during A&E or hospital admission
CE	Hypoglycaemia	1	The presence of 'hypoglycaemia' during A&E or hospital admission that warranted medical interventions
		0	The absence of 'hypoglycaemia' during A&E or hospital admission
CF	Metabolic acidosis	1	The presence of 'metabolic acidosis' during A&E or hospital admission
		0	The absence of 'metabolic acidosis' during A&E or hospital admission
CG	Hyperthermia	1	The presence of 'hyperthemia' or 'temperature > 38°C' during index presentation

		0	The absence of 'hyperthemia' or 'temperature > 38°C' during index presentation
CH	Other metabolic symptoms	1	The presence of other metabolic symptoms during A&E or hospital admission
		0	The absence of other metabolic symptoms during A&E or hospital admission
		Free text	Free text of other metabolic symptoms
CI	Liver PSS	0-3	Liver toxicity as graded with PSS
CJ	KidneyPSS	0-3	Kidney toxicity as graded with PSS
CK	Acute kidney injury	1	The presence of during A&E or hospital admission
		0	The absence of during A&E or hospital admission
CM	BloodPSS	0-3	Haematological toxicity as graded with PSS
CN	Muscle PSS	0-3	Muscle toxicity as graded with PSS
CN	Rhabdomyolysis	1	The presence of during A&E or hospital admission
		0	The absence of during A&E or hospital admission
CO	Peak CK level	Number	
CP	LocalPSS	0-3	Skin or local toxicity as graded with PSS
CQ	OtherPSS	0-3	Other toxicity as grade with PSS with free text
CR	OverallPSS	0-3	Overall Poison Severity Score
CS	Injury	1	The presence of any physical injury or trauma during the index presentation
		0	The absence of any physical injury or trauma during the index presentation
CT	Aggressive act to self	1	Any evidence of physical harm to oneself, including any form of self-inflicted injuries and overdose of medications
		0	No evidence of aggressive act to oneself
CU	Nature of self-harm	Free text	
CV	Aggressive act to other	1	Aggressive act to another person
		0	No evidence of aggressive act to another person
CW	Nature of aggressive act to other	Free text	
CX	Associated infection	1	The presence of infection associated with recreational drug use during the index presentation
		0	The absence of infection associated with recreational drug use during the index presentation
CY	Associated with psychiatric complaints	1	The presence of psychotic symptoms associated with recreational drug use during the index presentation, **defined as the presence of any hallucinations,**

			delusions or clinical diagnosis of psychosis
		0	The absence of psychotic symptoms associated with recreational drug use during the index presentation
		Free text	Free text of any psychotic symptoms
CZ	Urine immunoassay	1	'ABON' or 'ACON' test kit for urine drug screen ordered
		0	No 'ABON' or 'ACON' test kit ordered for urine drug screen
DA	Methamphetamine detected with bedside kit?	1	Methamphetamine detected with 'ABON' or 'ACON' urine kit
		0	Methamphetamine NOT detected with 'ABON' or 'ACON' urine kit
DB	MDMA detected with bedside kit?	1	MDMA detected with 'ABON' or 'ACON' urine kit
		0	MDMA NOT detected with 'ABON' or 'ACON' urine kit
DC	Amphetamine detected with bedside kit?	1	Amphetamine detected with 'ABON' or 'ACON' urine kit
		0	Amphetamine NOT detected with 'ABON' or 'ACON' urine kit
DD	Cocaine detected with bedside kit?	1	Cocaine detected with 'ABON' or 'ACON' urine kit
		0	Cocaine NOT detected with 'ABON' or 'ACON' urine kit
DE	Cannabis detected with bedside kit?	1	Cannabis detected with 'ABON' or 'ACON' urine kit
		0	Cannabis NOT detected with 'ABON' or 'ACON' urine kit
DF	Other drugs detected with bedside kit?	1	Other drugs detected with 'ABON' or 'ACON' urine kit
		0	Other drugs NOT detected with 'ABON' or 'ACON' urine kit
DG	Other drugs detected with bedside kit?	Free text	Free text of other drugs detected with bedside kit
DG	Hospital laboratory toxicology screen done?	1	Hospital laboratory toxicology screen was performed
		0	Absence of hospital laboratory toxicology screening
DI	Which specimens were analyzed in the hospital lab?	1	Urine
		2	Serum
		3	Both urine and serum
		4	Others
DJ	Methamphetamine detected in hospital lab?	1	Methamphetamine detected in hospital lab

		0	Methamphetamine NOT detected in hospital lab
DK	MDMA detected in hospital lab?	1	MDMA detected in hospital lab
		0	MDMA NOT detected in hospital lab
DL	Amphetamine detected in hospital lab?	1	Amphetamine detected in hospital lab
		0	Amphetamine NOT detected in hospital lab
DM	Cocaine detected in hospital lab?	1	Cocaine detected in hospital lab
		0	Cocaine NOT detected in hospital lab
DN	Cannabis detected in hospital lab?	1	Cannabis detected in hospital lab
		0	Cannabis NOT detected in hospital lab
DO	Other drugs detected in hospital lab?	1	Other drugs detected in hospital lab
		0	Other drug NOT detected in hospital lab
DP	Other drugs detected in hospital lab?	Free text	Free text of other drugs detected in hospital lab
DQ	Toxicology Reference Laboratory assay done?	1	Specimen sent to the Toxicology Reference Lab for analysis
		0	Specimen NOT sent to the Toxicology Reference Lab for analysis
DR	Which specimens were analyzed in the TRL lab?	1	Urine
		2	Serum
		3	Both urine and serum
		4	Others
DS	Methamphetamine detected in TRL?	1	Methamphetamine detected in TRL
		0	Methamphetamine NOT detected in TRL
DT	MDMA detected in TRL?	1	MDMA detected in TRL
		0	MDMA NOT detected in TRL
DU	Amphetamine detected in TRL	1	Amphetamine detected in TRL
		0	Amphetamine NOT detected in TRL
DV	Cocaine detected in TRL? (Y=1/N=0)	1	Cocaine detected in TRL
		0	Cocaine NOT detected in TRL
DW	Cannabis detected in TRL? (Y=1/N=0)	1	Cannabis detected in TRL
		0	Cannabis NOT detected in TRL
DX	Other drugs detected in TRL? (Y=1/N=0)	1	Other drugs detected in TRL
		0	Other drug NOT detected in TRL
DY	Other drugs detected in TRL (Free text)	Free text	Free text of other drugs detected in TRL

DZ	Physical restraint?	1	Physical restraint needed in the ED
		0	Physical restraint NOT needed in the ED
EA	Chemical restraint?	1	Chemical restraint needed in the ED
		0	Chemical restraint NOT needed in the ED
EB	IV fluid	1	Intravenous fluid infused in the ED
		0	Intravenous fluid NOT needed in the ED
EC	GI decontamination	1	Gastrointestinal decontamination performed in the ED
		0	Gastrointestinal decontamination NOT performed in the ED
ED	Gastric lavage	1	Gastric lavage performed in the ED
		0	Gastric lavage NOT performed in the ED
EE	Activated charcoal	1	Activated charcoal administered in the ED
		0	Activated charcoal NOT administered in the ED
EF	Antidote	1	Antidote administered in the ED
		0	Antidote NOT administered in the ED
EG	Which antidote?	Free text	The name(s) of the antidote given in the ED
EH	Amiodarone/ antiarrhythmic	1 (free text)	Amiodarone or other antiarrhythmic administered in the ED
		0	Amiodarone or other antiarrhythmic NOT administered in the ED
EI	Electrical shock	1	Electrical therapy given in the ED
		0	Electrical therapy NOT given in the ED
EJ	CPR	1	Chest compression was performed in the ED
		0	Chest compression was NOT performed in the ED
EK	Inotrope	1 (free text)	Inotrope infused in the ED
		0	No inotrope infused in the ED
EL	Renal replacement therapy	1	Renal replacement therapy initiated in the ED
		0	Renal replacement therapy not initiated in the ED
EM	Intubation	1	Intubation performed in the ED, including RSI
		0	Intubation NOT performed in the ED
EN	ECMO	1	Extracorporeal Membrane Oxygenation initiated in the ED
		0	Extracorporeal Membrane Oxygenation NOT initiated in the ED
EO	Other treatment	Free text	
EP	Physical restraint in hospital?	1	Physical restraint needed during index hospitalization after admission
		0	Physical restraint NOT needed during index hospitalization after admission
EQ	Chemical restraint?	1	Chemical restraint needed during index hospitalization after admission
		0	Chemical restraint NOT needed during index hospitalization after admission

ER	IV fluid	1	Intravenous fluid infused during index hospitalization after admission
		0	Intravenous fluid NOT needed during index hospitalization after admission
ES	GI decontamination	1	Gastrointestinal decontamination performed during index hospitalization after admission
		0	Gastrointestinal decontamination NOT performed during index hospitalization after admission
ET	Gastric lavage	1	Gastric lavage performed during index hospitalization after admission
		0	Gastric lavage NOT performed during index hospitalization after admission
EU	Activated charcoal	1	Activated charcoal administered during index hospitalization after admission
		0	Activated charcoal NOT administered during index hospitalization after admission
EV	Antidote	1	Antidote administered during index hospitalization after admission
		0	Antidote NOT administered during index hospitalization after admission
EW	Which antidote?	Free text	The name(s) of the antidote given during index hospitalization after admission
EX	Amiodarone/ antiarrhythmic	1 (free text if yes)	Amiodarone or other antiarrhythmic administered during index hospitalization after admission
		0	Amiodarone or other antiarrhythmic NOT administered during index hospitalization after admission
EY	Electrical shock	1	Electrical therapy given during index hospitalization after admission
		0	Electrical therapy NOT given during index hospitalization after admission
EZ	CPR	1	Chest compression was performed during index hospitalization
		0	Chest compression was NOT performed during index hospitalization
FA	Inotrope	1 (free text if yes)	Inotrope infused during index hospitalization after admission
		0	No inotrope infused during index hospitalization after admission
FB	Renal replacement therapy	1	Renal replacement therapy initiated during index hospitalization after admission
		0	Renal replacement therapy not initiated during index hospitalization after admission
FC	Intubation	1	Intubation performed during index hospitalization after admission, including RSI

		0	Intubation NOT performed during index hospitalization after admission
FD	ECMO	1	Extracorporeal Membrane Oxygenation initiated during index hospitalization after admission
		0	Extracorporeal Membrane Oxygenation NOT initiated during index hospitalization after admission
FE	Other treatment	Free text	
FF	AAPCC	As ranked by HKPIC toxicologist	
FG	ED Disposal	1	Discharge
		2	Admission to general ward
		3	Observation or admission to the Emergency Medicine Ward
		4	Intensive care unit
		5	Psychiatry ward
		6	Discharge against medical advice
		7	Referral to psychiatric specialist outpatient clinic (SOPC)
		8	Referral to other specialist outpatient clinic
		9	Transfer to other hospital
		10	Left before being see
		11	Death
		12	Disappeared after being seen
FH	Date and time of EMW admission	dd/mm/yyyy hh:mm	
FI	Date and time of EMW discharge	dd/mm/yyyy hh:mm	
FJ	LOSED	Not need to fill	Automatic calculation by excel formula
FK	Date and time of ICU admission	dd/mm/yyyy hh:mm	
FL	Date and time of ICU discharge	dd/mm/yyyy hh:mm	
FM	LOSICU	No need to fill	Automatic calculation by excel formula
FN	Date and time of general ward admission	dd/mm/yyyy hh:mm	
FO	Date and time of general ward discharge	dd/mm/yyyy hh:mm	
FP	LOS in general ward	No need to fill	Automatic calculation by excel formula
FQ	Date and time of psychiatry ward admission	dd/mm/yyyy hh:mm	
FR	Date and time of psychiatry ward discharge	dd/mm/yyyy hh:mm	
FS	LOS Psychiatry ward	No need to fill	Automatic calculation by excel formula
FT	LOS hospital	No need to fill	Automatic calculation by excel formula

FU	Psychiatric consultation during index presentation	1	Psychiatrist was consulted during index presentation
		0	Psychiatrist was NOT consulted during index presentation
FV	Referral to psychiatrist	1	The patient was referred to psychiatrist upon hospital discharge
		0	The patient was NOT referred to psychiatrist upon hospital discharge
FW	MSW referral during index presentation (Y=1/N=0)	1	The patient was referred to see medical social worker during index presentation
		0	The patient was NOT referred to see medical social worker during index presentation
FX	NGO referral during index presentation (Y=1/N=0)	1	The patient was referred to non-governmental organization for follow up during index presentation
		0	The patient was NOT referred to non-governmental organization for follow up during index presentation
FY	Episode death? (Y=1/N=0)	1	The patient died in the episode
		0	The patient survived in the episode
FZ	1st ED drug-related attendance date and time	dd/mm/yyyy hh:mm	
GA	Methamphetamine involved in the 1st reattendance	1	Methamphetamine was involved or detected in the 1st reattendance
		0	Methamphetamine was NOT involved or detected in the 1st reattendance
GB	MDMA involved in the 1st reattendance	1	MDMA was involved or detected in the 1st reattendance
		0	MDMA was NOT involved or detected in the 1st reattendance
GC	Cocaine involved in the 1st reattendance	1	Cocaine was involved or detected in the 1st reattendance
		0	Cocaine was NOT involved or detected in the 1st reattendance
GD	Cannabis involved in the 1st reattendance	1	Cannabis was involved or detected in the 1st reattendance
		0	Cannabis was NOT involved or detected in the 1st reattendance
GE	Other drugs involved in the 1st reattendance	1	Other drug(s) was/were involved or detected in the 1st reattendance
		0	Other drug(s) was/were NOT involved or detected in the 1st reattendance
GF	Other drugs involved in the 1st reattendance	Free text	Free text of the other drugs involved
GG	Associated with Trauma	1	1st Reattendance was associated with injuries

		0	1st Reattendance was NOT associated with injuries
GH	Associated with self harm	1	1st Reattendance was associated with self-harm
		0	1st Reattendance was NOT associated with self-harm
GI	Associated with harm to others	1	1st Reattendance was associated with harm to others
		0	1st Reattendance was NOT associated with harm to others
GJ	Associated with infection	1	1st Reattendance was associated with infection related to drug abuse
		0	1st Reattendance was NOT associated with infection related to drug abuse
GK	Associated with psychiatric symptoms?	1	1st Reattendance was associated with psychiatric symptoms
		0	1st Reattendance was NOT associated with psychiatric symptoms
GL	Time interval between the index presentation and 1st ED reattendance	No need to fill	Automatic calculation by excel formula
GM	Total number of AED reattendance within 1 year	Number	Total number of AED attendance within 1 year in epr
GN	Total number of AED attendance because of drug-related problem within 1 year	Number	Total number of AED attendance because of drug-related problem within 1 year in epr

Appendix 3. Poison Severity Score (adapted from Persson et al.)[24]

ORGAN	NONE	MINOR	MODERATE	SEVERE	FATAL
	0	1	2	3	4
	No symptoms or signs	Mild, transient and spontaneously resolving symptoms or signs	Pronounced or prolonged symptoms or signs	Severe or life-threatening symptoms or signs	Death
GI-tract		• Vomiting, diarrhoea, pain	• Pronounced or prolonged vomiting, diarrhoea, pain, ileus	• Massive haemorrhage, perforation	
		• Irritation, 1st degree burns, minimal ulcerations in the mouth	• 1st degree burns of critical localization or 2nd and 3rd degree burns in restricted areas	• More widespread 2nd and 3rd degree burns	
			• Dysphagia	• Severe dysphagia	
		• Endoscopy: erythema, oedema	• Endoscopy: ulcerative transmucosal lesions	• Endoscopy: ulcerative transmural lesions, circumferential lesions, perforation	
Respiratory system		• Irritation, coughing, breathlessness, mild dyspnoea, mild bronchospasm	• Prolonged coughing, bronchospasm, dyspnoea, stridor, hypoxemia requiring extra oxygen	• Manifest respirator insufficiency (due to e.g. severe bronchospasm, airway obstruction, glottal oedema, pulmonary oedema, ARDS, pneumonitis, pneumonia, pneumothorax)	
		• Chest X-ray: abnormal with minor or no symptoms	• Chest X-ray: abnormal with moderate symptoms	• Chest X-ray: abnormal with severe symptoms	

ORGAN	NONE	MINOR	MODERATE	SEVERE	FATAL
	0	1	2	3	4
	No symptoms or signs	Mild, transient and spontaneously resolving symptoms or signs	Pronounced or prolonged symptoms or signs	Severe or life-threatening symptoms or signs	Death
Nervous system		• Drowsiness, vertigo, tinnitus, ataxia	• Unconsciousness with appropriate response to pain	• Deep coma with inappropriate response to pain or unresponsive to pain	
			• Brief apnoea, bradypnoea	• Respiratory depression with insufficiency	
		• Restlessness	• Confusion, agitation, hallucinations, delirium	• Extreme agitation	
			• Infrequent, generalized or local seizures	• Frequent, generalized seizures, status epilepticus, opisthotonus	
		• Mild extrapyramidal symptoms	• Pronounced extrapyramidal symptoms		
		• Mild cholinergic/anticholinergic symptoms	• Pronounced cholinergic/anticholinergic symptoms		
		• Paraesthesia	• Localized paralysis not affecting vital functions	• Generalized paralysis or paralysis affecting vital functions	
		• Mild visual and auditory disturbances	• Visual and auditory disturbances	• Blindness, deafness	

Appendix 4. American Association of Poison Control Centers' National Poison Data System Definition of Medical Outcome (adapted from Mowry et al.)[27]

Outcome	Description
No effect	The patient did not develop any signs or symptoms as a result of the exposure.
Minor effect	The patient developed some signs or symptoms as a result of the exposure, but they were minimally bothersome and generally resolved rapidly with no residual disability or disfigurement. A minor effect is often limited to the skin or mucus membranes (e.g., self-limited gastrointestinal symptoms, drowsiness, skin irritation, firstdegree dermal burn, sinus tachycardia without hypotension and transient cough).
Moderate effect	The patient exhibited signs or symptoms as a result of the exposure that were more pronounced, more prolonged, or more systemic in nature than minor symptoms. Usually, some form of treatment is indicated. Symptoms were not life-threatening, and the patient had no residual disability or disfigurement (e.g., corneal abrasion, acidbase disturbance, high fever, disorientation, hypotension that is rapidly responsive to treatment, and isolated brief seizures that respond readily to treatment).
Major effect	The patient exhibited signs or symptoms as a result of the exposure that were life-threatening or resulted in significant residual disability or disfigurement (e.g., repeated seizures or status epilepticus, respiratory compromise requiring intubation, ventricular tachycardia with hypotension, cardiac or respiratory arrest, esophageal stricture, and disseminated intravascular coagulation).
Death	The patient died as a result of the exposure or as a direct complication of the exposure.

Appendix 5. Brief description of novel psychoactive substances reported to the HKPIC from 2010-2019 from local emergency departments.

Novel psychoactive substance (Full/IUPAC chemical name)	**Brief description**
AB-FUBINACA (N-[(2S)-1-amino-3-methyl-1-oxobutan-2-yl]-1-[(4-fluorophenyl)methyl]indazole-3-carboxamide) and **ADB-FUBINACA** (N-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-[(4-fluorophenyl)methyl]indazole-3-carboxamide)	AB-FUBINACA and ADB-FUBINACA are two closely related synthetic cannabinoids with potent agonist activity at CB1 and CB2 receptors. Both cannabinoids are often sold as 'legal alternatives to marijuana' and mixed with plant materials, tobacco, e-cigarettes and energy drink. The use of AB-FUBINACA and ADB-FUBINACA could be associated with tachycardia, hypertension, confusion, agitation, somnolence, hyperglycaemia and hypokalaemia.[115] Our team has reported a case of transient supraventricular tachycardia after misuse.[116]
Ethylone (1-(1,3-benzodioxol-5-yl)-2-(ethylamino)propan-1-one)	Ethylone is a synthetic cathinone structurally similar to mephedrone (4-methylmethcathinone). Cathinone is the principal psychoactive constituent in the plant Catha edulis (Khat). Synthetic cathinones are emerging drugs of abuse with central nervous system stimulant properties similar to cocaine and MDMA.[117] Fatalities related to ethylone use have been reported.[118]
***N*-Ethylpentylone** (1-(1,3-benzodioxol-5-yl)-2-(ethylamino)pentan-1-one)	*N*-Ethylpentylone, also known as *N*-ethylnorpentylone, is a ring-substituted synthetic cathinone. The clinical features of acute toxicity include tachycardia, agitation, confusion, mydriasis, hallucinations, acidosis and elevated creatine kinase.[118] Fatal intoxication has been reported.[119,120]
4-Fluoroamphetamine (1-[4-fluorophenyl] propan-2-amine)	4-Fluoroamphetamine is a halogenated amphetamine with modes of action similar to those of amphetamine and MDMA. Severity toxicity including fatalities, cerebral haemorrhage, inverted Takostsubo's cardiomyopathy, myocardial infarction and acute heart failure have been reported.[121, 122]

2-/3-Fluoroethylamphetamine	2-/3-Fluoroethylamphetamine are fluorinated analogues of ethylamphetamine that produce entactogenic and stimulant effects. Information about its pharmacological and toxicological effects is limited.[123]
1-Propionyl-d-lysergic acid diethylamide ((6aR,9R)-N,N-diethyl-7-methyl-4-propanoyl-6,6a,8,9-tetrahydroindolo[4,3-fg]quinoline-9-carboxamide)	1P-LSD is a psychedelic substance structurally related to *d*-lysergic acid (LSD) with the addition of a propionyl group at the 1-position. It produces LSD-like serotonergic in animal model but the psychoactive effects in human remains to be invesitgated.[124]
2-Methoxydiphenidine (1-[1-(2-methoxyphenyl)-2-phenylethyl]piperidine)	2-Methoxydiphenidine is a novel dissociative psychoactive substance of the diarylethylamine class which shares structural features with phencyclidine. The reported toxicities are similar to those of other dissociative drugs such as ketamine and methoxetamine, including hypertension, tachycardia, anxiety, confusion, dissociation, hallucination and hallucination.[125] Our team has reported a case with severe rhabdomyolysis and AKI.[126] Deaths associated with 2-Methoxydiphenidinehave been reported in the literature.[127]
5F-MDMB-PICA (Methyl-2-[[1-(5-fluoropentyl) indole-3-carbonyl]amino]-3,3-dimethyl-butanoate)	5F-MDMB-PICA is a synthetic cannabinoid with potent agonist activity at CB1 and CB2 receptors. Observed adverse effects included balance deficiencies, ocular effects such as conjunctival injection, glassy eyes, delayed or unresponsive pupil light reaction, mood disturbances, aggresion, confusion, erratic behaviour, mental leaps, slow reaction and slurred speech. Fatalites associated with its use have been reported [128]

Foxy/5-MeO-DIPT (5-Methoxy-N,N-diisopropyltryptamine)	5-MeO-DIPT, also known as 'Foxy' or 'Foxy methoxy', is a synthetic orally active hallucinogenic tryptamine derivative and 5-HT2 receptor agonist. Clinical effects reported include agitation, hallucinations, tachycardia, hypertension, confusion, tremor and seizure.[129] Fatal poisoning has been reported.[130]
5-Methoxy-*N,N*-methylisopropyltryptamine (N-[2-(5-methoxy-1H-indol-3-yl)ethyl]-N-methylpropan-2-amine) and **5-methoxy-*N,N*-diethyltryptamine** (N,N-diethyl-2-(5-methoxy-1H-indol-3-yl)ethanamine)	5-Methoxy-*N,N*-methylisopropyltryptamine and 5-methoxy-*N,N*-diethyltryptamine are structurally similar to 5-MeO-DIPT, presumably with similar effects.
25B-NBOMe (2-(4-bromo-2,5-dimethoxyphenyl)-*N*-[(2-methoxyphenyl)methyl]ethanamine) and **25C-NBOMe** (2-(4-chloro-2,5-dimethoxyphenyl)-*N*-[(2-methoxyphenyl)methyl]ethanamine)	NBOMes are N-methoxybenzyl analogs of the 2C family of phenethylamines. 25B-NBOMe and 25C-NBOMe, also known as NBOMe-2C-B and NBOMe-2C-C correspondingly, are N-methoxybenzyl derivatives of the phenethylamines 2C-B and 2C-C respectively. They are 5-HT2A receptor agonists. Observe adverse effects after misuse include agitation, tachycardia, hypertension, seizure, elevated creatine kinase, leukocytosis and hyperglycaemia. Fatalities have been reported.[131]
2-oxo-PCE (deschloro-N-ethyl-ketamine)	2-oxo-PCE is an arylcyclohexylamine analgoue with ketamine-like dissociative effects. The main clinical symptoms associated with 2-oxo-PCE include impaired consciousness, confusion, abnormal behaviour, hypertension, tachycardia and seizure.[132] In 2017, 2-oxo-PCE was detected in a cluster of patients, drug driving cases and in drug seizures.[132,133]
PMMA (Paramethoxymethamphetamine) and **PMA** (Paramethoxyamphetamine)	PMMA and PMA are synthetic methoxylated derivatives of methamphetamine and amphetamine, respectively. PMA can be a PMMA metabolite. PMMA and PMA are abused as a MDMA substitute but the toxicity is substantially higher than that of MDMA, earning the street name 'Death'. Severe toxicities, including acute

	respiratory distress, hyperthermia, cardiac arrest, convulsions, sudden collapse and/or multiple organ failure have been reported.[134]
Tiletamine [2-ethylamino-2-(2-thienyl)cyclohexanone]	Tiletamine is a pehncyclidine derivative and an NMDA antagonist with structural similarity with ketamine. Tiletamine is used as a dissociative veterinary anesthetic agent in combination with zolazepam. Reported toxicities include involuntrary choreatic movement, acute psychosis, coma and death.[135–137]
TFMPP (1-(3-trifluoromethylphenyl)piperazine)	TFMPP is a non-selective serotonin receptor agonist of piperzine family with hallucinogenic effect. Combination with 1-benzylpiperzine has been reported in the literature to achieve MDMA-like effects and TFMPP has been found in street ecstasy.[138, 139] Adverse reactions to TFMPP include agitation, bruxism and tachycardia.[140]