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RESEARCH ARTICLE

Tracing consumption patterns of stimulants, opioids, and ketamine in China by wastewater-based epidemiology

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Abstract

Illicit drug use has long been a key issue of international concern, and the true situation is unknown to the relevant authorities. To develop a profile of comprehensive consumption patterns of illicit drugs in China, data from 34 wastewater treatment plants in 25 cities were collected to analyze four classes of drugs, including amphetamine-type stimulants, opioids, ketamine, and cocaine. They were identified and quantified in samples using methods based on gas chromatography coupled to mass spectrometry. According to the wastewater-based epidemiology (WBE) approach, an analysis of the consumption pattern was performed regarding per inhabitant consumption based on the revised metabolic rate. The consumption quantity of illicit drug and precursor was divided into four categories based on statistical difference analyses: methamphetamine and ephedrine (precursor) were the predominant drugs in the first category, followed by ketamine and heroin in the second category, methcathinone and 3,4-methylenedioxymethamphetamine (MDMA) in the third category, and cocaine and methadone in the fourth category. There were distinctive spatial patterns: heroin and cocaine consumption was higher in Southern China than in Northern China, heroin consumption was higher in Western China than in Eastern China, and the consumption of each drug differed across seven regions of China, especially with ephedrine and methcathinone consumption higher in North China; heroin consumption higher in Southwest, Central, and Northwest China; and ketamine and MDMA consumption higher in East, South, and Central China. Compared with findings in previous studies, there were temporal patterns, in which ketamine consumption presented a downward trend but heroin remained stable. Based on correlation analyses, there were the polydrug abuse patterns between heroin and cocaine, methcathinone and ketamine, and cocaine and MDMA. In general, this study based on WBE provides a comprehensive evaluation of drug consumption in China.

Keywords Drug analysis · Wastewater-based epidemiology · Meta-analysis · Comprehensive weights · Monte Carlo simulation

Highlights

•The climate, geography, economy, and use history would lead to spatial differences.
•The quantity of drug consumption was divided into four categories statistically.
•Significant correlations were shown between several drugs.
•About 175 t/a illicit drugs were consumed in China based on mathematical models.
•A new excretion factor (77.0%) was constructed for ephedrine by meta-analysis.

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Introduction

According to the 2020 World Drug Report, the expansion and rapid change of the market make the situation of illicit drug use increasingly severe (United Nations Office on Drugs and Crime 2020a). For China, although work against illicit drug use has achieved remarkable results, the number of users is still relatively large, and the complex consumption situation is unknown (Office of China National Narcotic Control Commission 2020).

Wastewater-based epidemiology (WBE) is a powerful means for grasping the reality of illicit drug use. It was first proposed in 2001 (Daughton and L Jones-Lepp 2001) and implemented in 2005 (Zuccato et al. 2005), and then, it developed in terms of the three aspects of regional scope, drug type, and estimation of consumption. The regional scope has gradually broadened on different spatial scales and extended from small regional units, such as entertainment venues (Causanilles et al. 2018; Fr. Schröder et al. 2010), prisons (Postigo et al. 2011), and campuses (Ginsberg and Burgard 2014), to cities (Khan et al. 2014; Zuccato et al. 2008) and even countries (Du et al. 2015; Lai et al. 2016). There are few countries (such as Australia and New Zealand) conducting studies at the national level due to the difficulties of large-scale sampling activities. For drug type, detection methods of various drugs have been developed and applied in the past several years. For estimation of consumption, the determination of excretion factors (EFs) is the most important procedure (Baker et al. 2014; Du et al. 2020b; Gracia-Lor et al. 2016; Khan and Nicell 2011; Thai et al. 2016, 2019).

The WBE approach was introduced relatively late in China but has been frequently applied in recent years. The first WBE study for illicit drug use was performed in Hong Kong by Lai et al. (2013b) and then in four Chinese megacities (Beijing, Shanghai, Guangzhou, and Shenzhen) by Khan et al. (2014). In addition to studies in small regional units, national-level researches through WBE have been implemented to estimate illicit drug use. Major Chinese cities were investigated for the use of methamphetamine (METH) and ketamine (KET) sampled in 2014 (Du et al. 2015; Li et al. 2019), heroin (HR) in 2014 (Du et al. 2017), methadone (MTD) and heroin in 2016 (Du et al. 2019), methamphetamine in 2014 and 2015 (Xu et al. 2017), methamphetamine and ketamine in 2012–2016 (Li et al. 2019), and methamphetamine in 2018 (Shao et al. 2020). Until now, a large-scale survey of methcathinone (MTCA), 3,4-methylenedioxymethamphetamine (MDMA), cocaine (COC), and ephedrine (EPH, a precursor for the manufacture of illicit drugs) has not yet been included in the above WBE campaigns.

In general, there is still a lack of national research on multiple types of drugs to fully grasp the drug consumption pattern in China. In addition, metabolic rates are vital to back-calculate population-normalized consumption, and studies considered only the average or population-weighted average to estimate the overall level of consumption in the whole region, which all could lead to uncertainty and inaccuracy of the analysis results. Therefore, the aims here were, first, to collect wastewater samples from major Chinese cities and select drug target residues (DTRs) to investigate. A secondary aim was to back-calculate the population-normalized consumption of target drugs based on appropriate metabolic rates that were reconfirmed or originated. Additionally, to obtain the consumption pattern, the per inhabitant (inh) consumption of illicit drugs was analyzed considering the aspects of space, time, amount, and relationship. The final aim was to accurately estimate the annual consumption of target drugs.

Methods

Reagents and materials

Standards of MDMA, methcathinone, and 6-acetylmorphine (6-AM) were purchased from Cerilliant (Round Rock, TX, USA). Standards of ephedrine, morphine (MOR), codeine (COD), methadone, ketamine, norketamine (NK), and benzoylecgonine (BE) were purchased from A ChemTek, Inc. (Worcester, MA, USA). Standard solutions of N, O-bis (trimethylsilyl) trifluoroacetamide (BSTFA) with 1% trimethylchlorosilane (TMCS) and trifluoroacetic anhydride (TFA) were purchased from Aladdin (Shanghai, China). Naphthalene-d8 (Nap-d8) used as an internal standard was obtained from Supelco Co., Ltd. (Bellefonte, USA). HPLC grade (HPLC ≥ 99.8%) solutions of methanol (MeOH), acetonitrile (ACN), and ethyl acetate (EAC) were purchased from TEDIA Co., Ltd. (TEDIA, USA). Hydrochloric acid (HCl), sodium bicarbonate ($NaHCO_3$), and sodium hydroxide (NaOH), which were all in reagent grade, were obtained from Kemiou Chemical Reagent Co., Ltd. (Tianjin, China). Oasis MCX (60 mg, 3 mL) solid-phase extraction (SPE) cartridges and vacuum pump manifold with twenty connections were acquired from Waters Corporation (Waters, USA).

Wastewater sampling

The sampling campaign was conducted during 2018 and 2019 in China. For influent samples, 24-h composite domestic wastewater was collected from 34 WWTPs of 25 cities in Qingdao (QD), Jinan (JN), Weihai (WH), Hefei (HF), Chengdu (CD), Harbin (HRB), Xi'an (XA), Beijing (BJ), Zhengzhou (ZZ), Hohhot (HHHT), Changzhou (CZ), Guiyang (GY), Guangzhou (GZ), Xiangtan (XT), Chongqing (CQ), Yinchuan (YC), Lanzhou (LZ), Dingxi (DX), Baoding (BD), Qamdo (CAD), Kunming (KM), Shanghai (SH), Shenzhen (SZ), Changzhi (CZI), and Dalian (DL). In addition to QD, CD, CZ, LZ, DX, and DL (DL1 and DL3), other wastewater samples were collected on weekdays. Details of sample information in each wastewater treatment plant (WWTP) are provided in Appendix A.

A time proportional mode was applied during sampling with 60 mL collected every 30 min using an auto-sampler. After collection, the samples were immediately acidified to pH 2 with HCl, carried back to the laboratory in a frozen state, and stored at − 20 °C until analysis.

Extraction and analysis

The determination of the concentration of NH_4-N in all samples was performed using standard methods 350.1 from the United States Environmental Protection Agency (USEPA) with the Nessler Method (EPA 1993), and each sample was analyzed in duplicate.

For ten target drugs in the samples, a procedure based on SPE was developed to isolate and to concentrate target compounds from wastewater. First, MCX SPE cartridges were conditioned with 6 mL MeOH and 9 mL ultrapure water, consecutively. Fifty milliliters of wastewater was loaded on the cartridges after passed through 0.45-μm and 0.22-μm glass filters to remove the solid particles. Next, the cartridges were dried under vacuum, followed by the column eluted with 4 mL MeOH and 4 mL 5% ammonia/methanol. The eluate was dried under a soft stream of nitrogen and re-dissolved using 200 μL of ACN. For the first step of derivatization, 25 μL BSTFA with 1% TMCS was added into the solution and incubated for 30 min at 70 °C. Then, 20 μL silylated solutions were taken out into another chromatographic bottle and was added an internal standard. They were directly injected into the instrument for analysis. Next, residues from the initial bottle were dried under vacuum and 180 μL EAC was added as a new solvent. For the second step of derivatization, 25 μL TFA was also added into the initial bottle and incubated for 60 min at 45 °C. After the reaction, 10% $NaHCO_3$ solutions were used to remove the remaining derivative reagents. The mixture was centrifuged at 2000 rad/s for 3 min. Last, the upper organic phase was transferred to a chromatographic bottle, followed by adding NAP-d8 before analysis.

The samples were analyzed by an Agilent 7890B gas chromatography connected to an Agilent 5977A mass spectrometer (GC-MS). Separations were carried out in a capillary column (HP-5MS, 30 m × 0.25 mm × 0.25-μm film thickness, J & W Scientific). Helium (99.999%) was employed as the carrier gas maintaining at 1.0 mL/min in constant flow mode. The GC-MS interface and the injector port temperatures were set at 290 °C and 280 °C, respectively. The GC oven temperature conditions divided into two parts (silylation and acylation) were as follows: For silylation, the initial temperature of 90 °C for 2 min, increased to 290 °C at 20 °C/min, and held for 5 min giving a total run time of 17 min. For acylation, the initial temperature of 90 °C increased to 290 °C at 10 °C/min and held for 5 min giving a total runtime of 25 min. The GC-MS was programmed to perform a 2 μL splitless injection. The samples were analyzed by using a selected ion monitoring program to monitor the target analytes. Detailed method validation information is presented in Appendix A.

Estimation of consumption

Population-normalized consumption

The per inhabitant daily consumption of drugs (mg/d/1000 inhs) at a specific WWTP was estimated by using the following equation:

$$m_{j,i} = \frac{C_{j,i} \times F_i \times f_j}{P_i} \quad (1)$$

where $C_{j,i}$ (ng/L) is the concentration of drug of j at a specific WWTP of i, F_i (10,000 m^3/d) is the flow rate of influent wastewater in a WWTP of i, and P_i (10,000 inh) is the population served by a WWTP of i. f_j is the correction factor (CF) for drugs of type j showed in Table 1.

In this study, NH_4-N is used as a biomarker of the population (Been et al. 2014). The population estimated by NH_4-N was calculated as follows:

$$P_i = \frac{C_{NH_4-N,i} \times F_i}{m_{NH_4-N,i}} \quad (2)$$

Table 1 Excretion profiling of target drugs

Compound	DTR	EF (%)	Molar ratio parent/DTR	CF	Reference
EPH	EPH	77.0	1.00	1.30	This study[a]
MTCA	MTCA	36.0	1.00	2.78	(Markantonis et al. 1986)
	EPH	48.0	0.988	2.06	(Markantonis et al. 1986)
MDMA	MDMA	22.5	1.00	4.44	(Gracia-Lor et al. 2016)
HR	MOR	42.0	1.29	3.07	(Zuccato et al. 2008)
MOR	MOR	77.7	1.00	1.29	(Khan and Nicell 2011)
COD	COD	30.0	1.00	3.33	(Thai et al. 2016)
	MOR	6.00	1.05	17.5	(Khan and Nicell 2011)
MTD	MTD	27.5	1.00	3.64	(Thai et al. 2016)
KET	KET	20.0	1.00	5.00	(Du et al. 2020b)
	NK	4.00	1.06	26.5	(Du et al. 2020b)
COC	BE	29.2	1.05	3.59	(Castiglioni et al. 2013)

[a] This study conducted a meta-analysis to provide a new excretion factor for ephedrine in Appendix C

where $C_{NH4\text{-}N,\ i}$ (mg/L) is the concentration of NH_4-N measured in wastewater from WWTPs of i and $m_{NH4\text{-}N,\ i}$ (g/d/inh) is the average amount of daily NH_4-N production of each inhabitant. The value of $m_{NH4\text{-}N,\ i}$ is determined by the book of Census data of Pollution Sources (The First National Pollution Source Census Data Compilation Committee 2011). Hence, Eq. (1), used to calculate the drug consumption at specific WWTPs, can be simplified as below:

$$m_{j,i} = \frac{C_{j,i} \times m_{NH_4-N,i} \times f_j}{C_{NH_4-N,i}} \tag{3}$$

Population-normalized consumption in heroin and ephedrine

Taking all the sources into account as same as a previous study from Du et al. (2017), pure heroin consumption was estimated through measuring morphine concentrations and subtracting therapeutically used amounts of morphine (Appendix D). Therapeutical sources of morphine were determined by the Chinese Medicine Statistics Year Book of 2014 (Ministry of Industry and Information Technology 2015) as Appendix I shows. Similarly, taking the source of methcathinone into account, pure ephedrine consumption can also be estimated by deducting concentrations of ephedrine metabolized from methcathinone. It was estimated according to the principle of Formula (3) as follows:

$$m_{EPH,i} = \frac{C_{EPH-EPH,i} \times m_{NH_4-N,i} \times f_{EPH-EPH}}{C_{NH_4-N,i}} \tag{4}$$

where $f_{EPH\text{-}EPH}$ is the correction factor for drugs of ephedrine back-calculated by the parent drug showed in Table 1. $C_{EPH\text{-}EPH,\ i}$ is the concentration of ephedrine derived from ephedrine at a specific WWTP of i which can be estimated as follows:

$$C_{EPH-EPH,i} = C_{EPH,i} - C_{MTCA-EPH,i} \tag{5}$$

where $C_{EPH,i}$ is the concentration of ephedrine in wastewater determined by GC-MS at a specific WWTP of i, and $C_{MTCA\text{-}EPH,i}$ is the ephedrine concentration derived from methcathinone which can be estimated by Eq. (6):

$$C_{MTCA-EPH,i} = \frac{CF_{MTCA-MTCA}}{CF_{MTCA-EPH}} \times C_{MTCA,i} \tag{6}$$

where $C_{MTCA,\ i}$ is the concentration of methcathinone detected straightly in GC-MS. $CF_{MTCA\text{-}EPH}$ and $CF_{MTCA\text{-}MTCA}$ are the correction factor for methcathinone metabolizing to ephedrine and methcathinone, respectively (Table 1).

Annual consumption

The annual consumption (AC) of drugs in China was estimated by using the following equation:

$$m_{annual,j} = m_{average,j} \times P \times 365 \tag{7}$$

where P is the population of China in 2018 (1395 million) from the Statistical Yearbook in China (National Bureau of Statistics of China 2018) and $m_{average,\ j}$ (mg/d/1000 inh) is the average consumption of China in a kind of drug of j which can be estimated by Eq. (8):

$$m_{average,j} = \sum_{k=1}^{n} m_{k,j} \times w_{k,j} \tag{8}$$

where $m_{k,\ j}$ (mg/d/1000 inh) is the drug consumption of j calculated in a specific city of k. n is the number of cities from 1 to 25, and $W_{k,\ j}$ is the average weight of city of k determined by the mean of the weights of city calculated by analytic hierarchy process, principal components analysis, grey relational analysis, entropy weight method, independent weighting method, and coefficient of variation method as Appendix F shows.

Determination and excretion profiling of target residues

To profile the illicit drug use in China, this study chooses four classes of illicit drugs including amphetamine-type stimulants (ATS), opioids, ketamine, and cocaine. In addition to illicit drugs, this study also selected a typical precursor, ephedrine. According to the annual report from the International Narcotics Control Board, ephedrine and pseudoephedrine are both used in China as legal medicines widely and the major precursors for the manufacture of methamphetamine as well (International Narcotics Control Board 2019). Since no standard of pseudoephedrine was purchased, ephedrine was only tested in this study. As a precursor, ephedrine can indirectly reflect the degree of abuse of some illicit drugs.

The selection of the appropriate target metabolites to track consumption of illicit drugs of interest was based on the traits of ideal metabolites suggested by Khan and Nicell (Khan and Nicell 2011) (Appendix B). This study also selected the suitable correction factor as Table 1 shows (Appendix C). In particular, this study reviewed pharmacokinetic studies of ephedrine and then conducted a comprehensive meta-analysis to reconstruct profiles of excretion using 77.0% as a newly derived excretion factor (Table 2).

Statistical analysis

Statistical difference was tested by Student's t test, one-way ANOVA, Mann-Whitney U test, and independent samples Kruskal-Wallis test. For correlation, Pearson correlation

Table 2 Excretory profile of ephedrine upon various routes of administration

Reference	Route	Dose (mg)	Age (year)	n	Duration (h)	Excretory profile (% of administered dose) of specific metabolites	
						Mean	SD
(Tseng et al. 2006)	Oral	25	Adult	3	24(0-96)	40.9	4.09[a]
(Kawai and Baba 1976)	Oral	49.5	25	1	24	75.1	7.51[a]
(Pickup et al. 1976)	Oral	22	25–51	5	36	83.0	5.50
	Oral	20	25–51	6	36	73.4	11.5
(Sever et al. 1975)	Oral	30	Adult	3	48	96.7	0.794
(Welling et al. 1971)	Oral	25	27–32	3	48	68.3	11.7
	Oral	25	27–32	3	48	70.4	7.37
	Oral	25	27–32	3	48	80.6	4.75
(Beckett et al. 1965)	Oral	27.3	-[b]	1	24	79.3	7.93[a]
(Lefebvre et al. 1992)	Nasal	13.92	21–30	8	10	33.0	9.75
Pooled data						77.03	

[a] SD in these literatures which is not provided or cannot be calculated SD set as 10% × means

[b] The age of the male volunteer was not provided

analysis was firstly used for values with the normal distribution, and then, Spearman correlation analysis was used. They were performed using SPSS 20 (IBM Co., USA), with a p value below 0.05 meaning that the difference was regarded as statistically significant. Details are described in Appendix A.

Comprehensive weights were assigned by using the mean of weights determined by six methods (Appendix F). Before and after averaging weights, this study used Kendall's W test and Spearman correlation analysis to test the combined method of evaluation, respectively.

Based on Oracle Crystal Ball software (Version 7.3.1), the Monte Carlo simulation was used to estimate the average consumption of drugs, and the sensitivity analysis was used to evaluate the uncertainties of estimation.

Results

Occurrence of drugs in wastewater influent

Amphetamine-type stimulants

Ephedrine was the highest content substance in sewage, with a maximum concentration in all investigated samples (mean ± standard deviation, 564 ± 522 ng/L) (Appendix G), followed by methcathinone, with an average concentration of 130 ± 368 ng/L. The highest concentration of methcathinone was found in Changzhi. The concentration that was one or two orders of magnitude higher than the concentration in other cities indicates a high level of methcathinone consumption in Changzhi, which has a history of methcathinone abuse in China (Lucheng Branch of Changzhi Public Security Bureau 2019; Zhao 2020). Except for five WWTPs from Changzhi, the average concentration of methcathinone was 9.22 ± 11.77 ng/L. The lowest concentration of ATS was MDMA with an average of 7.88 ± 11.40 ng/L.

Opioids

Compared to 6-AM, morphine is the most abundant urinary metabolite irrespective of the route of heroin administration (Gracia-Lor et al. 2016; Khan and Nicell 2011). In this study, the average concentration of morphine in all samples was 78.8 ± 67.6 ng/L. Instead, the concentration of 6-AM (1.93 ± 6.78 ng/L) remained at a low level, with only three samples above the LOQ (QD, ZZ, and CQ2), similar to the findings of previous studies (Andrés-Costa et al. 2014; Archer et al. 2018; Baker et al. 2014; Been et al. 2015; Bijlsma et al. 2016; Du et al. 2020a, 2017; Krizman-Matasic et al. 2018; Mastroianni et al. 2017; Nefau et al. 2013; Östman et al. 2014).

In addition to morphine, codeine was the most abundant opioid in sewage, with an average concentration of 56.4 ± 123.7 ng/L, followed by methadone (2.14 ± 4.84 ng/L). There were only nine WWTPs with methadone concentrations above the LOQ.

Ketamine

In accordance with the metabolic ratio of ketamine (20%) and norketamine (4%), the most abundant metabolite of ketamine was the parent drug (27.1 ± 23.3 ng/L), followed by norketamine (5.51 ± 10.53 ng/L), with a lower detection frequency of 35%. The average ketamine/norketamine was 3.72

± 2.20 less than 5.36 (Du et al. 2020b), indicating that ketamine was not directly dumped into the sewers. Furthermore, a strong positive correlation was found between norketamine and ketamine concentration ($p < 0.05$) (Appendix J), which also reveals that they are both from the same source. According to the study by Du et al., the contribution of medical use to ketamine in China was negligible (Du et al. 2015), so it may come from illicit drug abuse.

Cocaine

There were only eight WWTPs with benzoylecgonine concentrations above the LOQ (CQ2, CQ1, CAD, CZI2, CZI1, CZI5, CZI4, and CZI3), and the average concentration of benzoylecgonine was 3.50 ± 8.91 ng/L.

Estimation of drug consumption

Amphetamine-type stimulants

Ephedrine consumption (184 ± 150 mg/d/1000 inh) above 100 mg/d/1000 inh was found across the major Chinese cities, indicating that it is widely consumed due to its wide application as a bronchodilator to treat bronchospasm associated with asthma, bronchitis, and emphysema. In particular, the highest consumption was found at HHHT (550 ± 9 mg/d/1000 inh), where the city plants ephedra used to extract ephedrine, followed by BD (529 ± 1 mg/d/1000 inh), where it produces ephedrine. The specific sampling location from BD was Anguo City, which is nicknamed the "Medicine Capital" and is well known for medicine production. It may indicate that there is a consumption preference for medicine containing ephedrine (Zhang and Chang 2000) or exists an abuse of ephedrine for the manufacture of illicit drugs. Similarly, high consumption of ephedrine was found in Spain (Mastroianni et al. 2017; Postigo et al. 2010) and Canada (Yargeau et al. 2014) because of its legal application.

The average consumption of methcathinone in major Chinese cities was 116 ± 303 mg/d/1000 inh. The highest mean consumption was found in Changzhi in Shanxi province, which has a long history of methcathinone use. To date, methcathinone is one of the main illicit drugs in Changzhi, different from other cities in China, according to a government report (Lucheng Branch of Changzhi Public Security Bureau 2019). Except for WWTPs from Changzhi, the average consumption of methcathinone in other cities was 5.07 ± 5.74 mg/d/1000 inh. In general, methcathinone use suggests an apparent spatial difference, and it was used at a low level in most cities of China, similar to the order found in studies from other countries (González-Mariño et al. 2016; Tscharke et al. 2016).

The MDMA consumption (11.5 ± 15.9 mg/d/1000 inh) in major Chinese cities was negligible overall, in agreement with previous studies in China (Khan et al. 2014; Zhang et al. 2019). Compared with studies in other countries (Archer et al. 2018; Baker et al. 2014; Du et al. 2020a; Gonzalez-Marino et al. 2017; Lai et al. 2016, 2017; Mastroianni et al. 2017; Nefau et al. 2013; Subedi and Kannan 2014), MDMA consumption in China was at a lower level, which indicates a different MDMA use pattern.

Opioids

Heroin consumption (56.7 ± 56.8 mg/d/1000 inh) in this study was in the same order as previous studies in China by Du et al. (2017, 2019). The highest consumption was found at GY2 (243 ± 7 mg/d/1000 inh), followed by HRB (185 ± 17 mg/d/1000 inh) and CQ1 (184 ± 4 mg/d/1000 inh), indicating high heroin consumption. Heroin consumption was the same as that in Malaysia (Du et al. 2020a) and Canada (Yargeau et al. 2014), but lower than that in Spain (Mastroianni et al. 2017) and England (Baker et al. 2014).

There were only nine WWTPs with methadone consumption above 0.02 mg/d/1000 inh (QD, JN, CD, GY2, CAD, CZ, BJ, LZ, and WH), and the average consumption of methadone was 2.09 ± 5.12 mg/d/1000 inh, which was in the same order as a previous study in China by Du et al. (2019). Compared to studies in other countries (Baker et al. 2014; Been et al. 2015; Du et al. 2020a; Mastroianni et al. 2017; Nefau et al. 2013; Palardy et al. 2015; Skees et al. 2018; Subedi and Kannan 2014; Thai et al. 2016), methadone consumption was at a lower level in China, which may predominantly come from methadone maintenance treatment sources.

Ketamine

Ketamine consumption in major Chinese cities had an average value of 35.3 ± 65.2 mg/d/1000 inh, which was lower than the finding in previous studies in China (Du et al. 2015; Khan et al. 2014; Lai et al. 2013b; Li et al. 2019) and Malaysia (Du et al. 2020a).

Cocaine

There were only eight WWTPs with cocaine consumption above 0.2 mg/d/1000 inh (CQ2, CQ1, CAD, CZI1, CZI2, CZI5, CZI4, and CZI3), and the average consumption of cocaine was 3.28 ± 7.10 mg/d/1000 inh. In most cities in China, cocaine consumption remained at a lower level compared to other studies (Archer et al. 2018; Baker et al. 2014; Bijlsma et al. 2016; Causanilles et al. 2017; Lai et al. 2016; Mastroianni et al. 2017; Nefau et al. 2013; Skees et al. 2018; Subedi and Kannan 2014; Yargeau et al. 2014), which indicates different drug-consumption habits.

Estimation of the drug use market

There are a variety of illicit drugs in China, mainly including ATS, opioids, ketamine, and cocaine. They occupy different market shares of illicit drugs (Office of China National Narcotic Control Commission 2020). Tested by one-way ANOVA ($p < 0.001$) and independent samples Kruskal-Wallis test ($p < 0.001$), the consumption of eight drugs (methamphetamine from Shao et al. (Shao et al. 2020), ephedrine, heroin, ketamine, MDMA, methcathinone, cocaine, and methadone) displayed clear differences. They can be statistically divided into four categories (Fig. 1). First, methamphetamine and ephedrine were the predominant drugs of use, consistent with the reality that methamphetamine was found to be widely used across the country by Du et al. (2015), and ephedrine was widely used as a therapeutic drug for 5000 years in China. Heroin and ketamine also presented high amounts of consumption second to methamphetamine, which was consistent with the 2018 Annual Report on Drug Control in China (Office of China National Narcotic Control Commission 2019). The drugs in the third (MDMA and methcathinone) and fourth (cocaine and methadone) categories were at lower consumption levels. Consumption differences indicate different characteristics of illicit drug use. It means that people in a certain area have their own preferences for drugs. Differences in average daily drug dose levels, purity of the street drugs, the "weekend effect" of recreational drugs, and ways of drug use could also cause the differences in consumption amount. To further estimate market shares of different drugs, this study calculated the annual consumption and compared the results with the actual seizures to verify the reliability of the results.

The calculation processes (Appendix F) based on Monte Carlo simulation and comprehensive weights would give a total annual consumption of drugs in China of approximately 111 t of methamphetamine, 104 t of ephedrine, 31.5 t of heroin, 20.4 t of ketamine, and 14.4 t of others (8.30 t of methcathinone, 3.53 t of MDMA, 1.38 t of methadone, and 1.23 t of cocaine), yielding 175 t of illicit drugs of use in total (Table 3). Among them, cocaine displayed lower estimated data than seizures. It is because China is a transit area to other countries for trafficking cocaine, and the transit of quantities of cocaine from South America was increasing rapidly in 2018 (Office of China National Narcotic Control Commission 2019). Instead, other drugs' estimated consumption was higher than seizures indicating that there was potential drug consumption. In particular, the estimated consumption of MDMA was much larger than seizures compared to the case for other drugs. The government needs to be vigilant and takes appropriate measures. It is also worth noting that the use of ephedrine as a widely therapeutic drug was also higher than the reported value of 18 t (International Narcotics Control Board 2019). These differences may derive from the wastewater from the processes of producing methamphetamine and methcathinone by using ephedrine (International Narcotics Control Board 2019). Besides, sampling dates were concentrated in spring and winter; at that time, there would be a higher prevalence of colds due to the cold climate. It would cause high ephedrine consumption (Mendoza et al. 2014; Paciuszkiewicz et al. 2019; Postigo et al. 2011; Zhang et al. 2017). In addition, Spearman correlation analysis ($p < 0.05$) verifies the correlation between estimated annual consumption and seizures (Appendix J). Hence, this study demonstrates that WBE can estimate the reality of illicit drug use.

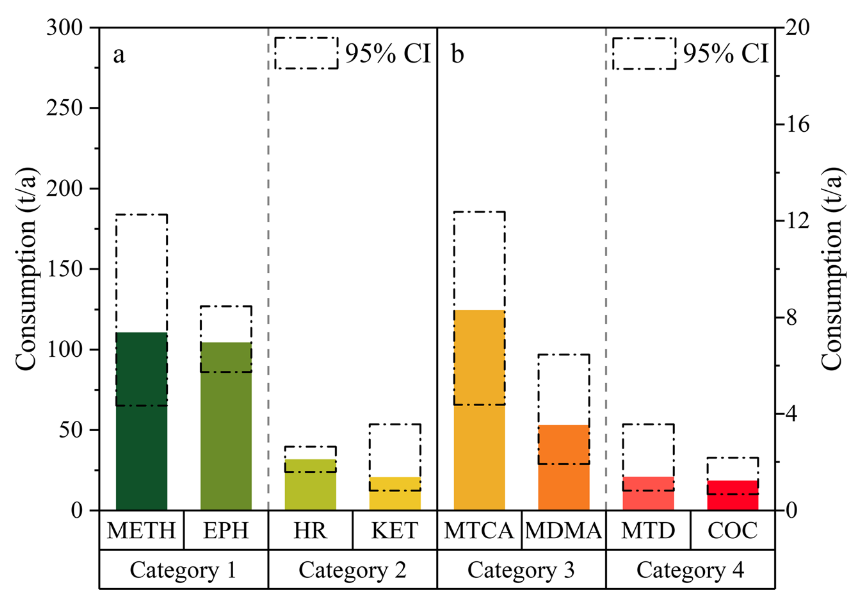

Fig. 1 Annual consumption of drugs in four categories (**a** ephedrine, methamphetamine, heroin, and ketamine; **b** methcathinone, MDMA, methadone, and cocaine)

Table 3 Average consumption of drugs in the investigated area of China and extrapolation to the whole Chinese territory

Drugs	m[a]	AC[b]	Seizures	Ratio of AC/ seizures			Variation[d]		
				Median	2.5%	97.5%	Median	2.5%	97.5%
EPH	205	104	18	5.80	4.78	7.05	− 82.8	− 79.1	− 85.8
METH	217	111	23.5	4.70	2.77	7.82	− 78.7	− 63.9	− 87.2
HR	61.8	31.5	8.07	3.90	2.95	4.90	− 74.4	− 66.1	− 79.6
KET	40.1	20.4	5.74	3.56	2.12	9.31	− 71.9	− 52.8	− 89.3
MDMA	6.94	3.53	0.0641	55.2	29.9	101	− 98.2	− 96.7	− 99.0
MTCA	16.3	8.30	—[c]						
COC	2.41	1.23	1.37	0.899	0.489	1.60	11.3	105	− 37.3
MTD	2.71	1.38	—[c]						

[a] The unit of per inhabitant consumption (m) is mg/d/1000 inh

[b] The unit of annual consumption (AC) is t/a

[c] The data of seizures were not provided

[d] The data of variation (%) were calculated by formula of (seizures/AC-1)*100% to estimate how much the seizure data less than the WBE estimation

Discussion

Spatial pattern

To further explore the potential spatial differences of the seven drugs (Fig. 2 and Appendix K), the consumption of these drugs was compared according to three methods of geographical divisions in China as follows.

Northern and Southern China

When analyzing the consumption of each drug, it can be found that only heroin ($p < 0.05$) and cocaine ($p < 0.05$) showed higher consumption in Southern China than in Northern China, which may be due to economic differences. There are no statistically significant differences in various types of economic indicators (Appendix H) between Southern China and Northern China. The average economic indicators in Southern China are always higher than those in Northern China, implying that the economy in Southern China is superior to that in Northern China (Shao et al. 2020). Furthermore, heroin and cocaine are the two most expensive drugs, except for methamphetamine tablets (United Nations Office on Drugs and Crime 2019). In general, economic factors may be the main reason for the spatial differences in illicit drug use (United Nations Office on Drugs and Crime 2020a).

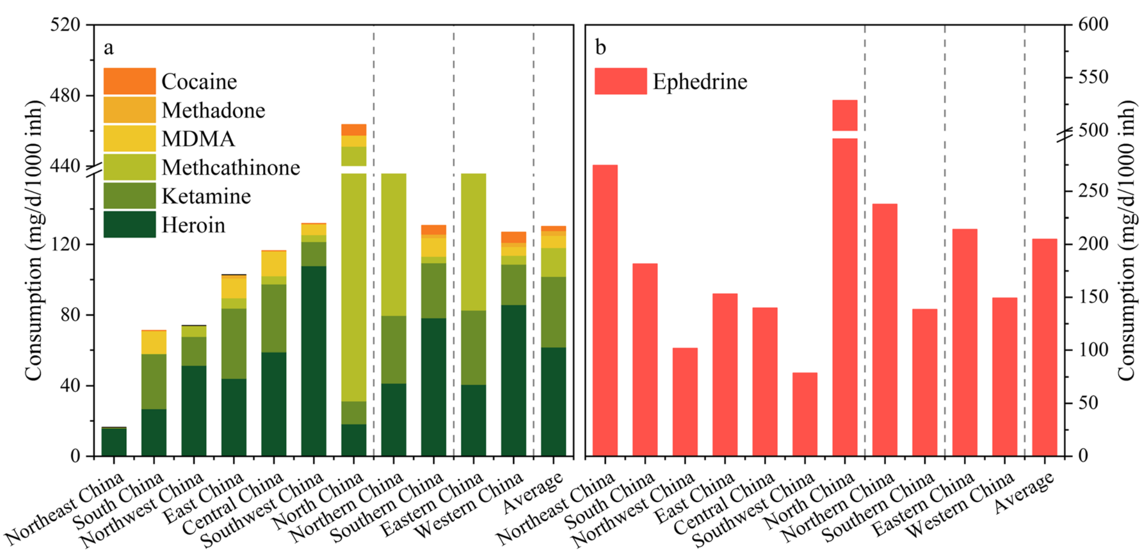

Fig. 2 Average daily consumption of drugs in seven regions, Northern and Southern China, Western and Eastern China, and the whole of China (**a** illicit drugs including cocaine, methadone, MDMA, methcathinone, ketamine, and heroin; **b** ephedrine; Due to non-parametric test conducted in seven regions, the value of median was selected in seven regions, different from the value of mean in others.)

Eastern and Western China

Regarding the differences between Eastern China and Western China in drug consumption, only heroin displayed a clear geographic trend ($p < 0.05$), in which heroin consumption was higher in Western China than in Eastern China, as found in a study by Du et al. (2019). This is mainly attributed to drug input from the "Golden Crescent" and "Golden Triangle" areas to Western China. In addition to the reason of drug input, differences in average daily heroin dose levels, heroin purity, and ways of drug use could cause the geographical pattern (Du et al. 2019).

Seven regions

Furthermore, to deeply explore the influence of regional characteristics on consumption, analysis based on the Kruskal-Wallis test was carried out by a more detailed geographical division. Analysis of seven regions found that each drug presented geographic differences that may relate to the climate, geography, economy, and history of consumption.

The ephedrine consumption in North China (median ± interquartile range) was considered to be the highest, with an average of 529 ± 385 mg/d/1000 inh, followed by other regions ranging from Southwest China to Northeast China (78.7–275 mg/d/1000 inh). Obviously, all regions had high consumption. Ephedrine, which is widely used in the treatment of colds, was consumed more in North China where it is colder than in other regions. The climate affects the prevalence of colds (Mendoza et al. 2014; Paciuszkiewicz et al. 2019; Postigo et al. 2011; Zhang et al. 2017), which in turn affects the use of ephedrine.

Heroin consumption was higher in Southwest China (108 ± 147 mg/d/1000 inh), Central China (59.2 ± 48.0 mg/d/1000 inh), and Northwest China (51.5 ± 50.3 mg/d/1000 inh) than in the other regions. Northwest and Southwest China are close to the "Golden Crescent" and the "Golden Triangle," respectively, and imports led to high consumption in both places, especially in the areas near the "Golden Triangle." Central China, as a region with well-developed transportation, connects to Southwest and Northwest China at the same time. Hence, there was high consumption in Central China.

For ketamine consumption, the highest was East China (39.6 ± 36.2 mg/d/1000 inh), followed by Central China (38.4 ± 25.8 mg/d/1000 inh) and South China (31.2 ± 10.9 mg/d/1000 inh). Similarly, MDMA consumption was high in the same regions (14.2 ± 11.9 mg/d/1000 inh in Central China, 12.8 ± 15.3 mg/d/1000 inh in South China, and 11.3 ± 12.7 mg/d/1000 inh in East China). It is easy to understand that both ketamine and MDMA as recreational drugs are more heavily consumed in economically developed regions.

Methcathinone consumption in North China was considered to be the highest, with an average of 420 ± 829 mg/d/1000 inh, followed by other regions (0.110–6.14 mg/d/1000 inh). The high amount of methcathinone consumption in North China came from Changzhi, which has a long-term habit of use (Zhao 2020). The consumption of cocaine in all regions, except for North China (5.96 ± 9.61 mg/d/1000 inh), and methadone in all regions, except for East China (1.85 ± 11.45 mg/d/1000 inh), was less than 0.1 mg/d/1000 inh. Both of them presented the lowest consumption levels in China.

Relationship

The complexity of illicit drug use is reflected not only in the diversity of drug types but also in the cross-use of different types of drugs, which may increase the risk of side effects and drug-drug interactions. To recognize the cross-use behavior of drug use groups in China, correlation analyses were conducted on the per inhabitant consumption of drugs. As shown in Appendix J, there were three significant correlations (heroin and cocaine, methcathinone and ketamine, and cocaine and MDMA) ($p < 0.05$). Cocaine was co-used with opioid drugs in a variety of different patterns (Leri et al. 2003). For example, heroin and cocaine were often used together in a drug combination known as "speedball" in some countries (Ellinwood Jr. et al. 1976; Gossop 1984). The correlation analysis results of this study indicate that a similar combination also exists in China (Chen and Zhai 2010; Gu 2011). Besides, cocaine, as a recreational drug, was also related to MDMA. They were known as the most used club drugs (Rushing and Burgard 2019). As for methcathinone and ketamine, there were few documents that studied two substances at the same time, and no studies studied co-use between them. The relationship between them was reported firstly in this study. It may be because they were all consumed as recreational drugs (Brown et al. 1995; Busardò et al. 2020; Rice et al. 2020), which needs more studies to verify. In general, the polydrug abuse pattern is common in China (Bao 2015). Furthermore, some drugs without correlations indicate that these types of consumer groups are specific.

In addition to the correlation between drugs, the influencing factors of the drug market are hotspots to explore (Choi et al. 2019). Correlation analyses (Appendix J) were conducted between per inhabitant consumption and indicators of the economy or quality of medical care (Appendix H) after dimensionless processing. The significant correlations with the economy reveal that wealth is linked to drug use. This is also consistent with the 2020 World Drug Report that within countries, the wealthier sectors of society have a higher prevalence of drug use. Besides, the correlation between ephedrine and quality of medical care (Healthcare Access and Quality, HAQ) may be closely related to the widely legal use of ephedrine ($p < 0.05$).

Annual drug consumption trends

To explore the annual trends of drugs, this study compared the findings regarding heroin and ketamine with the relevant findings of existing national studies by Du et al. (2015, 2019). Comparing the per inhabitant consumption of drugs by conducting Student's t test, the annual trend was analyzed (Fig. 3 and Appendix K). Ketamine consumption in 2018 showed a significant reduction ($p < 0.05$) compared with the finding of Du et al. (2015). This is consistent with the 2018 report (Office of China National Narcotic Control Commission 2019), and it is owing to a series of measures taken by the Chinese government. However, the case for heroin was not significantly different ($p > 0.05$) from a study published by Du et al. (2019), which is also consistent with the data from Du et al. (2017). Obviously, there were also no significant fluctuations in the amount of heroin seizures (8070.3–9519.9 kg) compared to ketamine (19600–5742.9 kg) from 2014 to 2018 (United Nations Office on Drugs and Crime 2020b). In general, compared with the decline in the consumption of synthetic ketamine drugs, traditional heroin drugs remain stable.

Uncertainty analysis

There could be a high variation in drug consumption between days if only one sample collected from each WWTP was used as a representative sample in the estimation of the drug use of an area. In addition, the estimation of drug consumption was based on the average values of the input parameters. They all introduce a certain degree of uncertainty in the estimation of consumption in China. To decrease the influence of these uncertainties and achieve an accurate assessment of consumption, we used the Monte Carlo simulation (Pei et al. 2016). It is based on repeated random sampling (n = 100,000 samples) of the probability distributions defined for the principal factors of variation and the uncertainty of each assumed parameter

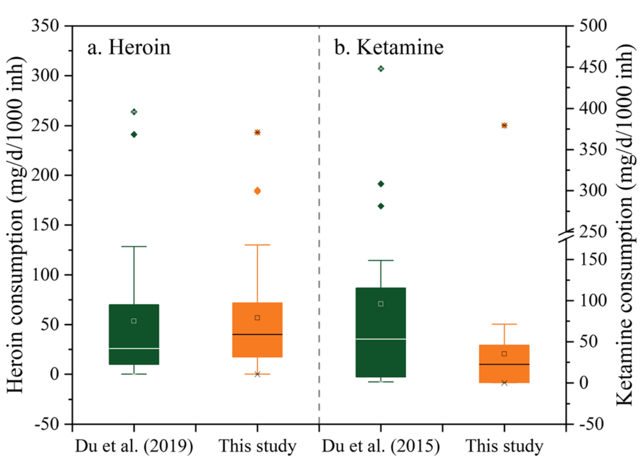

Fig. 3 Annual consumption trends of drugs (**a**: heroin trend between 2016 and 2018; **b**: ketamine trend between 2014 and 2018)

(Appendix F). On the basis of the Monte Carlo simulation, the comprehensive weight was introduced to achieve a more accurate estimation. Four indicators were used to represent the basic situation of a city: gross domestic product (GDP), per capita disposable income of urban households (PI), permanent residents (PP), and GDP of tertiary industry (service industry) were used for illicit drugs and GDP, PI, PP, and HAQ for ephedrine. They were combined by six evaluation methods ("Annual consumption" section), and then, the average of the six groups of weights was extrapolated as the comprehensive weights. The final estimation results were shown in "Estimation of the drug use market" sections.

To evaluate the potential influences of the input parameters, a sensitivity analysis was carried out. The results (Appendix F) showed that EF was the most significant one, which contributes 63.3–97.4% of the total uncertainty of estimation in most drugs but only contributes 2.30% in methcathinone. The comprehensive weight was the second highest, which contributes < 1–24.0% of the total uncertainty of estimation in most drugs but only contributes 95.8% in methcathinone. Hence, the determination of EFs is the most important procedure, and the construction of reasonable weights is an important part of accurately estimating consumption.

In addition, there were the weekend patterns of recreational drugs (e.g., MDMA, cocaine, ketamine) in many WBE studies (Cruz-Cruz et al. 2020; Lai et al. 2013a; Rice et al. 2020; Rushing and Burgard 2019). It is indeed a factor that affects the final estimation owing to some samples collected on weekends ("Wastewater sampling" section). These samples may show higher concentrations than on weekdays. Especially, samples with a concentration above LOD would affect the consumption estimation, including QD, CD, and CZ for MDMA and QD, CZ, LZ, and DX for ketamine. Cocaine was less than LOD in all samples collected on weekends, so it would not affect the final estimation. In the future study, wastewater samples for one week will be collected to analyze the uncertainty from this issue.

Conclusion

A nationwide investigation was performed to analyze the consumption of multiple types of drugs in China, which successfully verified that WBE can be used to analyze human consumption behavior habits and obtain comprehensive patterns of consumption. These consumption patterns were shown in aspects of spatial differences, temporal changes, selective patterns (four categories of the amount of drug consumption), and significant correlations. Furthermore, in our study combining WBE with mathematical models, we estimated the annual consumption (175 t/a) of illicit drugs in the entire country (methamphetamine 111 t/a, heroin 31.5 t/a, ketamine 20.4 t/a, methcathinone 8.30 t/a, MDMA 3.53 t/a, and cocaine 1.23 t/a). In the future, we can utilize more complex models to help WBE mine potential information regarding substance use.

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Authors' contributions Conceptualization: Si-Yu Liu. Methodology: Si-Yu Liu, Wen-Jing Yu, and Yi-Ru Wang. Formal analysis and investigation: Si-Yu Liu. Writing—original draft preparation: Si-Yu Liu. Writing—review and editing: Si-Yu Liu, Xue-Ting Shao, and De-Gao Wang. Funding acquisition: De-Gao Wang. Supervision: De-Gao Wang.

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Data availability All data generated or analyzed during this study are included in this published article (and its supplementary information files).

Compliance with ethical standards

Competing interests The authors declare that they have no competing interests.

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

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