Journal of Hazardous Materials 476 (2024) 135020

Contents lists available at ScienceDirect

Journal of Hazardous Materials

journal homepage: www.elsevier.com/locate/jhazmat

Wastewater-based epidemiology to monitor 68 NPS/conventional drug use in Taipei metropolitan area in Taiwan during and after COVID-19 pandemic

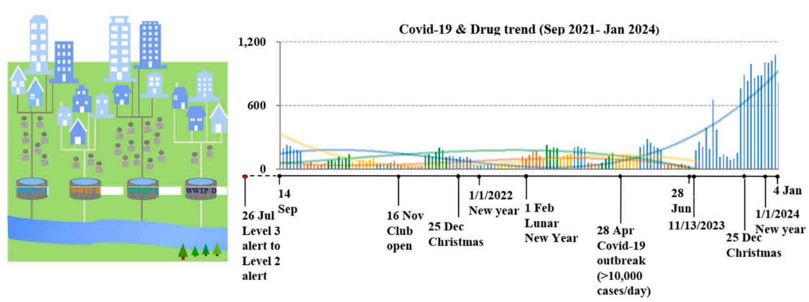
Te-Tien Ting [a,1], Pin-Chuan Chen [b,1], Ya-Chi Chang [c], Pin-Ju Chiang [c], Hsu-Cheng Li [d], Shih-Hsun Chen [c], Pei-Chieh Chen [c], Hai-Tien Chu [d], Ping-Yu Chuang [d], Yi-Hsin Liu [d,*], Pai-Shan Chen [c,*]

[a] Department of Data Science, School of Big Data Management, Soochow University, Taipei, Taiwan
[b] Department of Mechanical Engineering, National Taiwan University of Science and Technology, Taipei, Taiwan
[c] Graduate Institute of Toxicology, National Taiwan University College of Medicine, National Taiwan University, Taipei, Taiwan
[d] Department of Chemistry, National Taiwan Normal University, Taipei, Taiwan

HIGHLIGHTS

- 38 conventional drugs and 30 NPS were monitored in 4 northern Taiwan WWPTs. sewage.
- WBE was adopted to understand policy impact during and after COVID-19 (2021-2024).
- Tramadol, zolpidem, CMA, and MDPV were newly detected NPS in Taiwanese sewage.
- Hard drugs showed persistent use reflecting daily use despite COVID-19 measures.
- No correlation is shown between drug consumption and the particular day of the week.

GRAPHICAL ABSTRACT



ARTICLE INFO

Keywords:
Drug abuse
New psychoactive substances (NPS)
COVID-19 pandemic
Liquid chromatography-tandem mass spectrometry (LC-MS/MS)
Wastewater-based epidemiology

ABSTRACT

Amidst far-reaching COVID-19 effects and social constraints, this study leveraged wastewater-based epidemiology to track 38 conventional drugs and 30 new psychoactive substances (NPS) in northern Taiwan. Analyzing daily samples from four Taipei wastewater plants between September 2021 and January 2024—encompassing club reopenings, holidays, Lunar New Year, an outbreak, and regular periods—thirty-one drugs were detected, including 5 NPS. Tramadol, zolpidem tartrate, CMA, and MDPV were newly detected in Taiwanese sewage with frequency of 1.4 %– 89.0 %. Conventional drug use typically increased post-pandemic, aside from benzodiazepines and methadone. Methamphetamine showed 100 % frequency, indicating ongoing daily consumption despite COVID-19 measures. Methamphetamine and morphine's consumption dipped then rose around club reopening, hinting at limited access. The consumption trend of methadone appeared to compensate for the use of morphine. Ketamine and NPS demonstrated similar patterns throughout the entire period. NPS as party drugs seemed influenced by an unstable supply chain and complexities in implementation. Benzodiazepines, commonly abused alongside synthetic cathinones in Taiwan exhibited an opposing trend to NPS while aligned with

* Corresponding authors.
E-mail addresses: frfkimo@gmail.com (Y.-H. Liu), paishanchen@ntu.edu.tw (P.-S. Chen).

[1] The authors have contributed equally to this study.

https://doi.org/10.1016/j.jhazmat.2024.135020
Received 20 September 2023; Received in revised form 18 May 2024; Accepted 22 June 2024
Available online 29 June 2024

acetaminophen, suggesting elevated stress and anxiety levels during the pandemic. No significant differences were observed in drug consumption between weekdays and weekends, potentially indicating that COVID-19 measures blurred the traditional distinctions between these timeframes.

Environmental Implication: New psychoactive substances refer to chemically modified variants of controlled drugs designed to mimic the effects of the original drugs while evading modern detection methods, categorizing them as hazardous materials. The study presents a sewage monitoring project conducted from 2021 to 2024, collecting samples from four WWTPs to analyze NPS and conventional drug trends during and after the COVID-19 pandemic. The findings uncovered connections between drug consumption patterns and pandemic-related policies. In light of the persistent drug abuse and their environmental presence, the results bear critical importance for both environmental and public health. We provide a thorough assessment of these relationships and prioritize areas for future research.

1. Introduction

In February 2020, the rapid global spread of COVID-19 had resulted in more than 118,000 cases across 114 countries, with over 4000 lives lost and thousands more hospitalized. Consequently, on 11 Mar 2020, the World Health Organization (WHO) declared the pandemic situation [1]. In response, many countries implemented varying levels of restrictions on socialization, mobility, and daily activities to curb virus transmission. These unprecedented measures to control the COVID-19 pandemic have had profound effects on public health, society, and the economy, affecting the well-being of people worldwide [2]. Research by Liu et al. [3] and Zeegers Paget et al. [4] has highlighted the elevated levels of physical and mental stress experienced by individuals due to these measures. Coping with concerns about the coronavirus, economic challenges, and social isolation has led to increased substance use and abuse during the pandemic [5,6]. Additionally, several studies [5,7,8] further demonstrated that this situation has exacerbated substance crisis during the COVID-19 pandemic, particularly among individuals with acute health effects and substance use disorders, who face social isolation and economic hardships. However, the quantitative impacts of COVID-19 measures on substance use or abuse, including various new psychoactive substances (NPS), are unclear. Monitoring trends in both conventional drugs and emerging NPS during this period remains challenging, as NPS may differ significantly from conventional drugs in terms of usage patterns, effects, and associated risks.

Over the past two decades, there has been rapid emergence of over a thousand different NPS in the global market, creating a legal grey area. This proliferation of NPS has contributed to increased drug overdose cases and drug-related crimes [9]. Taiwan is no exception, since it plays a major role in substance smuggling, as noted by Lo [10] and the UNODC [11]. In the 1990s, drugs use in Taiwan expanded from conventional opioids and methamphetamines to encompass barbiturates, inhalants like glue, and flunitrazepam. In subsequent years, a shift in drug use preferences among young adults was observed, moving away from barbiturates and glue towards ecstasy, and notably, ketamine, classified as an NPS. Since 2005, ketamine has become one of the top 3 abused drugs in Taiwan, alongside methamphetamine and opioids due to its rising popularity [12,13]. This prompted amendments to the Narcotics Hazard Prevention Act 2009 and dictated higher criminal charges for the use or possession of ketamine. Note that this corresponded to a surge in ketamine abuse in the following six years. Additionally, synthetic drugs like cathinones have recently gained popularity in Taiwan [14,15]. Therefore, it is crucial to understand the trends and patterns of drug abuse during the COVID-19 pandemic, especially the change patterns of NPS. Implementing a monitoring system that considers the correlation with specific time-events and drug use will aid in evaluating the effectiveness of drug control measures and addressing challenges posed by the ever-evolving landscape of drug consumption, including NPS.

Wastewater-based epidemiology (WBE) has emerged as a proposed method for probing drug prevalence in recent years [16]; even though traditional approaches such as urine analysis, interviews, and self-reported questionnaires have been commonly used for gathering practicality and flexibility in detailed information. However, these traditional approaches may introduce important biases, including selection bias, as drug users may be concealed within the general population and difficult to reach [17]. Additionally, there is self-report bias, where individuals may over- or under-report their drug use behaviors [18,19]. There is also bias due to the intentional mislabeling of drug packaging, which omits ingredients and quantities [19,20]. Although quantifying drug consumption through urinalysis is much more objective [21], it is complicated by the timing of the sample collection relative to the last drug use. Moreover, urine analysis, which typically involves collecting one-time samples from individuals, limits the ability to track the trajectory of drug use behaviors and capture diverse information about drug use in communities [22]. Therefore, it is imperative to establish a real-time monitoring system for drugs abuse. WBE offers a direct method of measuring human excretion products and biomarkers in untreated wastewater, allowing for back-calculation of substance consumption and exposure [23]. WBE has been widely adopted over the past decade in various regions for estimating illicit drug consumption through instrument detection [24-27]. For the analysis of trace amounts of illicit drugs or their metabolites in complex wastewater, sensitive and comprehensive analytical techniques are crucial.

Liquid chromatography-mass spectrometry (LC-MS) is widely recognized for its effectiveness in identifying and quantifying diverse substances across multiple fields [28,29]. This technique allows for comprehensive analysis in a single run following appropriate sample preparation methods. LC-MS has been effectively utilized to detect various types of compounds in pharmaceutical studies [30,31], food analysis [32], and environmental research [33]. Therefore, LC-MS is well-suited for the detection a wide range of conventional drugs and NPS [13,34]. To address the complexity of wastewater and the low concentrations of drugs found at the ng/L level, sample pretreatment and concentration are essential prior to LC-MS analysis. This process commonly involves coupling with solid phase extraction (SPE) due to its capability of removing interferences from wastewater [35,36,27]. However, the sample preparation is time-consuming and labor-intensive. Moreover, using a single type of SPE cartridge typically only allows for the extraction of drugs with chemical similarities. This significantly limits the range of detectable drugs, particularly given that the emergence of various NPS has posed significant challenges to existing drug control measures. This highlights the need for a monitoring system to assess the effectiveness of current methods, particularly in response to the evolving landscape of NPS during the Covid-19 pandemic.

Prior research has highlighted several key gaps: (1) the absence of suitable techniques and designs for detecting multiple drugs to compare traditional and new psychoactive substances; (2) the challenge of monitoring drug use behaviors among hidden populations to understand substance use cycles and potential complementary behaviors amidst significant societal changes; (3) the potential of LC-MS integration to yield more insights than prior studies; and (4) the lack of real-time substance use information in the densely populated Taiwan Metropolitan Area, known for its numerous nightclubs and high incidence of drug-related crimes. To address these gaps, this study seeks to develop the first analysis of 38 conventional drugs/metabolites and 30 NPS commonly seized at Taiwan's borders, using wastewater samples to track evolving drug use patterns over time. Liquid-liquid micro-extraction coupled with LC-MS was employed for effectively detection, conducting monitoring from 2020 to 2024, which spans significant time-event series including the COVID-19 pandemic and post-pandemic phases. Daily sampling will be conducted at four major wastewater treatment plants (WWTPs) serving 6 million residents in Metropolitan Taipei (North Taiwan), enabling analysis of trends across different periods and WWTPs, particularly during and after COVID-19, to understand how pandemic-related policies influence drug consumption patterns. WBE serves as a comprehensive tool to complement official drug surveys, providing valuable insights into drug prevalence and usage patterns within the community.

2. Materials and methods

2.1. Materials and reagents

The solvents used in this study included methanol (LC-MS grade), formic acid (MS grade), acetone (LC grade), dichloromethane (DCM, LC grade), and sodium chloride, all purchased from Fluka (Buchs, Switzerland). The Milli-Q® Integral Water Purification machine was acquired from Millipore (Darmstadt, Germany). Formic acid (MS grade) and sodium chloride (NaCl) were obtained from Sigma-Aldrich (St. Louis, MO, USA). All reference standards and four isotopes of drugs of abuse (1 mg/mL in methanol) were purchased from Cerilliant (Austin, TX, USA).

2.2. The source of wastewater sample

Wastewater influent samples were collected from four WWTPs across metropolitan Taipei. In Taipei City with a population of 2500,022 inhabitants, there exist WWTP A serving for 2216,000 inhabitants (88.6 %) and WWTP B serving for 282,000 (11.3 %). In the neighboring New Taipei City with 4.02 million inhabitants, there exist WWTP C serving 3830,000 inhabitants (95.3 %) and WWTP D serving 15,000 inhabitants (0.4 %). The daily flow rate is reported on the website of Ministry of Environment Taiwan [37]. Within the sampling period, the average daily flow rates (m^3/day) were 408059, 197869, 470130 and 50408, respectively. Daily influent samples of 100 mL were collected hourly using time-proportional autosamplers, specifically the WS Porti 24 mobile sampler (Water-Sam GmbH & Co, KG, Germany).

2.3. The process of sample collection

During the pandemic, wastewater sampling commenced on 14 Sep and continued until 28 Jun 2022. Society gradually resumed normalcy thereafter. Post-COVID-19 sampling occurred from 13 Nov 2023 to 4 Jan 2024. Samples were collected consecutively over 7 days at each WWTP on a rotational basis within a key time point. In the post-COVID-19 period, sampling was confined to WWTP A from 13 Nov 2023, to 4 Jan 2024 due to limited time, manpower and funding. After collection, all samples were filtered through 0.45 μm cellulose acetate membrane filters (Advantec, Toyo Roshi Kaisha, Ltd., Japan) without pH adjustment. All samples were kept in dark and stored at − 20 °C. The analysis of the samples took place within three days after collection.

2.4. Sample pretreatment

A 15 mL tube was filled with 10 mL of filtered wastewater sample, and 0.4 g of NaCl was added to the sample. The sample was then vortexed until the salt dissolved, and 100 μL of internal standard (25 ng/mL of 7-aminoclonazepam-d_4, amphetamine-d_8, and methamphetamine-d_5, and GHB-d_6 in 50 % methanol) was added. A mixture of 3 mL of acetone as the dispersant and 3 mL of DCM as the extractant was prepared and mixed well. This mixture was rapidly injected into the sample, resulting in a cloudy mixture. The solution was vortexed for 30 s using a vortex mixer (scale 5, Vortex Genie 2, VWR, Chicago, IL, USA). The sample was centrifuged at 3500 rpm for 20 min. The sediment phase was collected and transferred to an Eppendorf tube, then dried under a rotary evaporator at 30 °C. The residue was reconstituted with 50 μL of 10 % methanol. The sample was then centrifuged at 13000 rpm for 30 min. Finally, the reconstituted sample was transferred to a vial for LC-MS analysis. Drug standards at nine final concentrations (0.001, 0.005, 0.01, 0.02, 0.05, 0.1, 0.2, 0.5, 1.0, and 2.0 ng/mL) were used to spike to matrix-matched blank samples for the establishment of calibration curves. In situations where the drug concentration was over the highest calibrator, samples were diluted with water to bring concentrations to within the calibration range. The limit of detection (LOD), linearity, and repeatability were shown in Table S1 (see in supplementary). The method validation was based on "protocol of Action for monitoring illicit drugs in wastewater" by the European Monitoring Centre for Drug and Drug Addiction (EMCDDA) [38].

2.5. Instrument analysis

An LC-MS/MS method was employed using a TSQ Altis triple quadrupole MS system (Thermo Fisher Scientific, MA, USA) coupled with an LC system Vanquish Flex UPLC (Thermo Fisher Scientific, MA, USA) to detect 68 abused drugs. The ionization source conditions were configured as follows: electrospray voltage of 3500 V, sheath gas at 60 Arb, aux gas at 15 Arb, sweep gas at 2 Arb, ion transfer tube temperature at 380 °C, and vaporize temperature at 350 °C. For chromatographic separation, a Restek Ultra PFPP column (50 mm × 2.1 mm, 5 μm) (Restek®, PA, USA) was utilized. A 25 μL injection volume was employed. The mobile phase consisted of two components: mobile phase A, which contained 0.1 % formic acid in 2 % methanol (in ultrapure water), and mobile phase B, consisting of 0.1 % formic acid in methanol. The chromatographic separation utilized a gradient elution program with specific time intervals and conditions. During the first 0 to 10 min, a linear gradient was applied, gradually transitioning from 5 % to 90 % mobile phase B. The flow rate ranged from 0.5 to 1.0 mL/min throughout this interval. From 10 to 12 min, a constant flow rate of 1.0 mL/min was maintained while the mobile phase B composition increased from 90 % to 95 %. Between 12 and 12.5 min, the flow rate was adjusted from 1.0 to 0.5 mL/min, while the mobile phase B remained constant at 95 %. For the subsequent 12.5 to 13 min, a constant flow rate of 0.5 mL/min was maintained as the mobile phase B decreased from 95 % to 5 %. Finally, from 13 to 15 min, the system was re-equilibrated to the initial conditions. To identify the analytes, ion ratios were calculated for each drug using three pairs of transitions. the ion ratios of the detected compounds were compared to the average ratios of the calibrators. A ± 20 % relative difference was set as the acceptance criteria for determining the accuracy of the measurements. For quantitative analysis, each batch of samples included at least one positive control and one negative control, making up 10 % of the total samples. Positive controls containing drugs were prepared at two concentrations: 0.2 ng/mL and 1.0 ng/mL. The results obtained from these controls were deemed acceptable if they fell within a range of ± 20 %. Data processing and demonstration were carried out using Tracefinder TM software (Thermo Fisher Scientific, US). Detailed information regarding the optimized LC-MS/MS method parameters for the compounds can be found in Table S2 (see in supplementary).

2.6. Back calculation of illicit drug consumption

The estimation of drug consumption (mg/day/1000 inhabitants) was conducted using the following equation:

$$\textbf{Drug consumption} = \frac{\textbf{Cbiomarker} \times \quad \textbf{F} \quad \times \textbf{CF}}{\text{P}/1000} \times \left(1 \middle/ 10^6\right) (\text{mg} \middle/ \text{ng})$$

Here, $C_{biomarker}$ represents the concentration of biomarkers in wastewater (ng/L), F is the daily flow provided on the website of each WWTP (L/Day), and CF is the corresponding correction factor for each drug. The correction factor is determined based on the excretion profile of biomarkers and the molar mass ratio of biomarkers and parent drugs, as provided in Table S3 (see in supplementary). P represents the catchment population of each WWTP. Utilizing this information, drugs consumed by 1000 inhabitants every day can be estimated through back-calculate.

2.7. Timeframe design throughout COVID-19 timeline

To establish an appropriate timeline for examining the impact of pandemic-related policies on drug use patterns, several key events that may either limit or enhance public gatherings throughout Taiwan's COVID-19 timeline have been observed: (1) Pre-25 Jul 2021: Taiwan enforced Level 3 restrictions, including school closure, non-essential businesses shutdowns, limits on public gatherings, work-from-home arrangements, face mask mandates, enhanced social distancing, and travel restrictions. Daily COVID-19 cases remained below 100. (2) On 26 Jul 2021, alert level reduced to Level 2, allowing schools to reopen and giving flexibility for work settings. Most businesses resumed operations with mandatory mask-wearing. (3) After 16 Nov 2021, nightclubs reopen; limited festive activities (i.e., Christmas, New Year, and Lunar New Year) permitted with mask. (4) On 24 Feb 2022, quarantine for arrivals was shortened to 10 days. However, late March saw a surge in coronavirus cases. (5) From 28 Apr 2022, cases exceeded 10,000 daily, while the alert level remained at Level 2. (6) After 1 May 2023: Epidemic measures transitioned toward normalization, discontinuing "vaccination leave" and shifting command center responsibilities to standard leave requirements.

2.8. Data analysis and statistics

To achieve the study objectives, the piecewise polynomial regression models were used to identify nonlinear changes in drug use patterns, including conventional drugs, NPS, and controlled medications, at significant time points (i.e., the time points objectively defined in Section 2.7) during Taiwan's COVID-19 timeline. This analysis was based on wastewater concentration data collected form approximately 6 million people in Metropolitan Taipei. Statistical analyses were conducted using STATA 17 (Stata Corporation, College Station, TEXAS, USA).

$Y_{i\_substanc} = \beta_{01} + \beta_{11}x_{1i}$, if $2021\text{–}09\text{–}14 \le x_{1i} < 2021\text{–}11\text{–}15$ (schools reopen and work from home)

$+ \beta_{12}x_{2i}$, if $2021\text{–}11\text{–}16 \le x_{2i} < 2022\text{–}01\text{–}20$ (nightclub reopen with festive activities)

$+ \beta_{13}x_{3i}$, if $2022\text{–}01\text{–}20 \le x_{3i} < 2022\text{–}04\text{–}27$ (quarantine for arrivals and before outbreak)

$+ \beta_{14}x_{4i}$, if $2022\text{–}04\text{–}28 \le x_{4i} < 2022\text{–}06\text{–}08$ (outbreak to the end of 2022 study)

$+ \beta_{15}x_{5i}$, if $2023\text{–}11\text{–}13 \le x_{5i} < 2024\text{–}12\text{–}04$ (Post-epidemic era of Covid 19)

$+ \beta_{16}x_{6i}$, if $2023\text{–}12\text{–}22 \le x_{6i} < 2024\text{–}01\text{–}04$ (Post-epidemic era of Covid 19 with festive activities to the end of 2024 study) $+ \varepsilon_i$

where $Y_{i\_substanc}$ is the concentration of each substance detected from four WWTPs (i.e., methamphetamine, NPS, acetaminophen, morphine, ketamine, benzodiazepines and methadone), $_i$ is from 1 to n sampling records of wastewater, $x$time, $_i$ is the interval time including some special events; $\beta_{1,\quad time}$ is the coefficient for each time interval to represent the concentration changing over time, and ε_i is the error term.

3. Results and discussion

The innovative findings of this study include the simultaneous analysis of 68 conventional substances and NPS in daily wastewater samples collected from 2021 to 2024. This period encompasses both during and after the COVID-19 pandemic. The study explored the relationship between drug abuse and stress levels related to COVID-19, as well as the impact of lockdown measures on daily activities, building upon prior research [5,7,8]. Using the piecewise polynomial regression, the findings revealed patterns of multiple drugs consumption and highlighted potential factors such as drug access and market circulation influenced by pandemic-related restrictions on mobility, aligning with earlier studies [25,38], in Metropolitan Taipei with 6 million residents served by major WWTPs. The following content presents four important parts to provide unprecedented insights into drug consumption trends, aiding public health strategies and deepen our understanding of societal impacts associated with both conventional and emerging drugs during global health crises.

3.1. Occurrence of conventional drugs and NPS in wastewater

During the entire collection time, a total of 31 drugs and metabolites were detected in the wastewater samples at different frequencies in Table 1. The detected drugs include 9 benzodiazepines and metabolites (alprazolam, 7-aminoclonazepam, estazolam, 7-aminoflunitrazepam, midazolam, bromazepam, diazepam, nitrazepam, and flurazepam), 7 stimulants (methamphetamine, amphetamine, ephedrine, pseudoephedrine, cocaine, PMA, and MDMA), 6 opioids (acetylcodeine, acetylmorphine, methadone, codeine, heroin and morphine), 7 NPS and metabolites (ketamine, norketamine, dehydronorketamine, tramadol, zolpidem tartrate, CMA, and MDPV), and 2 analgesic drugs (diclofenac and acetaminophen). Three substances, ketamine, methamphetamine, and diclofenac (excluding their metabolites), were 100 % detected in all wastewater samples in Table 1. Moreover, 6 compounds (alprazolam, acetaminophen, 7-aminoclonazepam, codeine, methadone and pseudoephedrine) were detected in more than 90 % of 145 samples. The detection rates of morphine, amphetamine, estazolam, tramadol, 7-aminoflunitrazepam, zolpidem tartrate, and dehydronorketamine were within the range of 90 % to 70 %. NPS excluding ketamine showed lower detection frequencies, including PMA (17.9 %), MDMA (30.3 %), CMA (9.7 %), and MDPV (1.4 %). Methamphetamine (183.71 ± 239.50 mg/day/1000 inhabitants), ketamine (30.17 ± 31.41 mg/day/1000 inhabitants), benzodiazepines (27.96 ± 17.64 mg/day/1000 inhabitants), morphine denoted opiate use, including heroin (14.16 ± 10.42 mg/day/1000 inhabitants), and NPS excluding ketamine (30.91 ± 50.16 mg/day/1000 inhabitants), were the major kinds of substances consumed in the four WWTPs (i.e., WWTP A, B, C, and D) in Fig. 1. The specific concentrations of substances detected from four WWTPs are detailed in Table 2.

The average consumption of commonly used substances within intervals 5 and 6 (i.e., post-COVID-19) showed significantly higher levels compared to the average levels in intervals 1 to 4. Specifically, methamphetamine use increased by 1.8 times, morphine by 1.2 times, ketamine by 1.6 times, non-ketamine NPS by 3.2 times, and acetaminophen by 2.2 times. Meanwhile, benzodiazepines (0.9-fold decrease) and methadone (0.9-fold decrease) showed relatively low levels in the post-COVID-19 pandemic period (2023–2024). The change are consistent with national surveys, indicating that methamphetamine, opiate, and ketamine are still the most commonly abused drugs in Taiwan [39]. The ratio of amphetamine/methamphetamine levels was 0.10 ± 0.09, suggesting that amphetamine detected in wastewater samples was mainly

Table 1
Daily mass loads of detected drugs and metabolites in sewage.

	Daily mass load (mg/day/1000 inhabitants)				Detection frequency (n = 145, %)
Compound	Average	SD	Min	Max	
6-acetylcodeine	0.38	NA	0.38	0.38	0.7
6-acetylmorphine	0.58	0.06	0.55	0.75	7.6
7-aminoclonazepam	4.09	3.49	0.20	15.53	93.1
7-aminoflunitrazepam	4.82	3.73	0.34	14.12	81.4
Acetaminophen	375.46	801.80	0.52	4540.37	95.2
Alprazolam	15.12	9.73	2.50	35.48	99.3
Amphetamine	49.43	83.73	6.48	380.75	82.1
Bromazepam	1.73	0.09	1.55	1.87	21.4
CMA	2.17	0.35	1.79	2.66	9.7
Cocaine	16.51	NA	16.51	16.51	0.7
Codeine	56.24	38.61	1.59	191.09	95.2
Diazepam	22.22	11.63	9.82	37.37	4.8
Diclofenac	289.08	2981.99	8.37	35945.35	100.0
Dehydronorketamine	2.46	1.71	0.17	7.10	76.6
Ephedrine	650.13	992.07	0.00	3554.34	56.6
Estazolam	2.98	1.85	0.98	7.24	89.0
Flurazepam	1.07	1.75	0.19	7.06	9.7
Heroin	1.31	NA	1.31	1.31	0.7
Ketamine	30.17	31.41	4.91	197.89	100.0
MDMA	10.15	5.48	3.62	28.18	30.3
MDPV	3.49	0.05	3.46	3.52	1.4
Methadone	9.11	7.14	0.60	25.54	99.3
Methamphetamine	183.71	239.50	6.18	1081.67	100.0
Midazolam	2.13	1.92	0.19	7.06	46.9
Morphine	14.16	10.42	2.16	56.01	85.5
Nitrazepam	1.30	0.49	0.96	1.65	1.4
Norketamine	47.53	52.27	4.87	214.65	22.1
PMA	5.98	4.70	0.00	14.08	17.9
Pseudoephedrine	759.73	1324.55	10.83	6289.70	99.3
Tramadol	29.39	52.39	0.14	260.20	89.0
Zolpidem tartrate	4.25	1.91	0.38	8.37	80.7

NA: not applicable

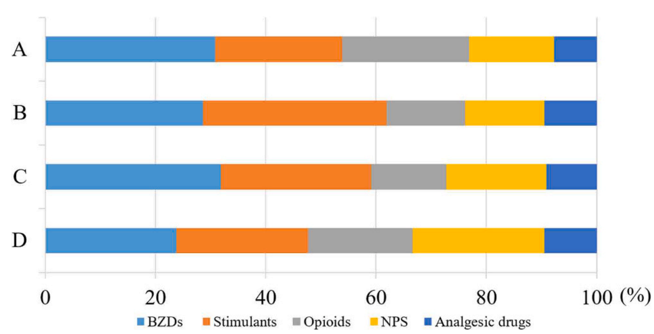


Fig. 1. The composition of five kinds of drugs from WWTPs A, B, C, and D. BZDs: alprazolam, 7-aminoclonazepam, diazepam, estazolam, 7-aminoflunitrazepam, midazolam, bromazepam, nitrazepam, and flurazepam; Stimulants: amphetamine, cocaine, ephedrine, methamphetamine, MDMA, pseudoephedrine, and PMA; Opioids: acetylcodeine, acetylmorphine, codeine, heroin, methadone, morphine; NPS: CMA, ketamine, MDPV, tramadol, and zolpidem tartrate; Analgesic drugs: diclofenac, acetaminophen.

converted from methamphetamine. This phenomenon has been previously reported in Australia [40] and China [27]. Regarding to ketamine consumption, out of 145 samples, 111 were determined to contain dehydronorketamine, while norketamine was found in 32 samples. The data suggests that dehydronorketamine may be a more stable marker of ketamine in wastewater. In the case of clonazepam detection, only 7-aminoclonazepam was found, not its precursor form. Similar observations were made for 7-aminoflunitrazepam, indicating that amino-metabolites may be the appropriate markers for these substances.

In terms of opiate consumption, heroin and its primary biomarker, 6-acetylmorphine, along with the secondary metabolic marker, morphine, were monitored. The rapid conversion of both heroin and 6-acetylmorphine to morphine through biological processes within 24 to 48 h makes it challenging to distinguish morphine originating from heroin use or morphine alone [41]. The latter may also originate from cold medicine. Another alkaloid, codeine, is a common component in both herbal medicine and is sometimes converted from acetylcodeine, which is a common impurity in illicit heroin [41]. The average consumption of codeine (56.24 ± 38.61 mg/day/1000 inhabitants) was approximately 4.0 times higher than morphine (including heroin). Although abuse of codeine-containing medicine has been reported [27], the codeine abuse was not observed in Taiwan [42]. This increase in codeine consumption may be a result of over-the-counter cough medicine consumption during the COVID-19 pandemic. However, it cannot be completely ruled out that it partly originated from illicit heroin use [41].

3.2. Consumption patterns during and following the period of COVID-19 impact

During the COVID-19 pandemic in Taiwan, restrictions were gradually eased from Level 3 to Level 2 measures starting on 26 Jul 2021. Despite this, most people maintained precautionary behaviors such as minimizing outings, working from home, and avoiding gatherings up to Christmas 2021. An outbreak occurred on 28 Apr 2022, leading to widespread infection but ultimately enabling a return to normalcy. The study aimed to compare drug consumption patterns during and after the pandemic in Taiwan. As part of this effort, samples were additionally collected from WWTP A between 13 Nov 2023 and 4 Jan 2024, after society had fully reopened and stabilized.

To assess the trend of illicit drug consumption throughout the COVID-19 policy timeline, the study periods were divided into six intervals based on significant events and government responses to COVID-19, as well as the post-COVID-19 period: (1) 14 Sep 2021 (schools reopened) to 15 Nov 2021, (2) 16 Nov 2021 (clubs reopened) to 20 Jan 2022 including Christmas and New Year, (3) 21 Jan to 27 Apr including Lunar New Year on 1 Feb 2022, (4) 28 Apr (outbreak) to 28 Jun 2022,

Table 2
Average concentration, range, and detection frequency of influent samples from each WWTP.

	WWTP A (SEP.2021-JAN.2024)			WWTP B (SEP.2021-JUN.2022)		
Compounds	Average (ng/mL)	Min - Max (ng/mL)	Frequency (%, n = 64 days)	Average (ng/mL)	Min - Max (ng/mL)	Frequency (%, n = 32 days)
6-acetylcodeine	0.002	0.002-0.002	2	ND	ND	NA
6-acetylmorphine	0.003	0.003-0.004	17	ND	ND	NA
7-aminoclonazepam	0.637	0.002-0.024	100	0.019	0.008 - 0.034	78
7-aminoflunitrazepam	0.58	0.003-0.017	83	0.015	0.014 - 0.017	56
Acetaminophen	279.524	0.013-23.611	97	5.391	0.015 - 16.420	84
Alprazolam	0.521	0.001-0.011	100	0.008	0.004 - 0.012	100
Amphetamine	4.597	0.001-0.445	78	0.093	0.009 - 0.209	75
Bromazepam	0.243	0.005-0.009	48	ND	ND	NA
CMA	0.035	0.005-0.005	11	ND	ND	NA
Cocaine	ND	ND	NA	0.001	0.001 - 0.001	3
Codeine	2.113	0.015-0.071	100	0.030	0.020 - 0.049	78
Diazepam	ND	ND	NA	ND	ND	NA
Diclofenac	3.8213	0.029-0.103	100	0.718	0.028 - 20.961	100
Dehydronorketamine	0.313	0.001-0.020	92	0.003	0.002 - 0.004	38
Ephedrine	413.095	0.733-14.476	100	6.663	0.387 - 15.027	100
Estazolam	0.457	0.004-0.040	89	0.005	0.003 - 0.007	78
Flurazepam	0.011	0.001-0.003	8	0.004	0.004 - 0.005	25
Heroin	0.007	0.007-0.007	2	ND	ND	NA
Ketamine	5.13	0.021-0.344	100	0.058	0.028 - 0.087	100
MDMA	1.436	0.013-0.151	53	0.042	0.019 - 0.078	16
MDPV	ND	ND	ND	ND	ND	NA
Methadone	0.208	0.002-0.005	100	0.002	0.002 - 0.004	100
Methamphetamine	68.298	0.117-2.490	100	0.761	0.081 - 1.406	100
Midazolam	0.125	0.001-0.005	67	0.007	0.004 - 0.012	34
Morphine	3.253	0.017-0.164	81	0.063	0.028 - 0.103	81
Nitrazepam	0.014	0.005-0.009	3	ND	ND	NA
Norketamine	0.301	0.001-0.044	39	0.026	0.015 - 0.032	22
PMA	1.043	0.035-0.098	25	0.039	0.017 - 0.103	28
Pseudoephedrine	582.848	0.301-30.274	100	7.162	0.160 - 18.461	100
Tramadol	11.507	0.136-0.451	89	0.159	0.015 - 0.289	78
Zolpidem tartrate	0.373	0.003-0.020	78	0.006	0.003 - 0.012	56
	WWTP C (SEP.2021-JUN.2022)			WWTP D (SEP.2021-JUN.2022)		
Compounds	Average (ng/mL)	Min – Max (ng/mL)	Frequency (%, n = 24 days)	Average (ng/mL)	Min - Max (ng/mL)	Frequency (%, n = 25 days)
6-acetylcodeine	ND	ND	NA	ND	ND	NA
6-acetylmorphine	ND	ND	NA	ND	ND	NA
7-aminoclonazepam	0.014	0.001-0.025	100	0.032	0.006 - 0.069	100
7-aminoflunitrazepam	0.017	0.014-0.019	96	0.021	0.015 - 0.027	100
Acetaminophen	4.751	0.006-22.513	100	5.030	0.024 - 14.690	100
Alprazolam	0.008	0.004-0.012	100	0.010	0.006 - 0.015	100
Amphetamine	0.164	0.004-0.649	92	0.111	0.006 - 0.257	100
Bromazepam	0.033	0.005-0.068	100	ND	ND	NA
CMA	0.003	0.003-0.004	33	0.008	0.008 - 0.008	28
Cocaine	0.014	0.001-0.025	100	ND	ND	NA
Codeine	0.017	0.014-0.019	96	0.058	0.022 - 0.380	100
Diazepam	4.751	0.006-22.513	100	ND	ND	NA
Diclofenac	0.075	0.044-0.223	100	0.084	0.035 - 0.171	100
Dehydronorketamine	0.007	0.002-0.015	71	0.008	0.002 - 0.019	96
Ephedrine	9.059	0.297-20.267	96	8.095	0.901 - 14.408	100
Estazolam	0.005	0.004-0.008	92	0.006	0.004 - 0.009	100
Flurazepam	0.004	0.004-0.004	8	ND	ND	NA
Heroin	0.080	0.035-0.111	100	ND	ND	NA
Ketamine	0.045	0.029-0.066	17	0.043	0.028 - 0.065	100
MDMA	9.059	0.297-20.267	96	0.041	0.033 - 0.049	8
MDPV	0.003	0.002-0.003	8	ND	ND	NA
Methadone	0.003	0.002-0.005	100	0.003	0.002 - 0.004	100
Methamphetamine	1.859	0.040-3.388	100	1.654	0.416 - 2.631	100
Midazolam	0.003	0.002-0.003	33	0.002	0.002 - 0.003	28
Morphine	0.093	0.027-0.186	96	0.060	0.025 - 0.085	100
Nitrazepam	0.105	0.099-0.111	8	ND	ND	NA
Norketamine	11.278	0.196-26.612	100	ND	ND	NA
PMA	0.180	0.105-0.241	92	0.003	0.003 - 0.003	28
Pseudoephedrine	0.004	0.002-0.008	100	14.094	1.712 - 26.694	100
Tramadol	0.003	0.002-0.005	100	0.245	0.185 - 0.312	100
Zolpidem tartrate	1.859	0.040-3.388	100	0.008	0.002 - 0.026	100

ND: not detectable; NA: not applicable.

(5) 13 Nov to 4 Dec 2023 (after the COVID-19 pandemic), and (6) 22 Dec 2023 to 4 Jan 2024 including Christmas and New Year. We employed a cubic polynomial for virtual observations in Fig. 2 and Fig. 3. Additionally, piecewise polynomial regression analyses were utilized to evaluate all consumption trends over time in Table S4 (see in supplementary).

3.2.1. *Methamphetamine*

The consumption trends of methamphetamine exhibited a significant decline during period 1 ($\beta_{1,\ \text{interval 1}} = -1.25$, $p < 0.05$), followed by an increase around period 2 ($\beta_{1,\ \text{interval 2}} = 2.01$, $p < 0.05$), a decrease during period 3, a significant decrease within period 4 ($\beta_{1,\ \text{interval 4}} = -2.94$, $p < 0.001$). Subsequently, a significant increase was observed in

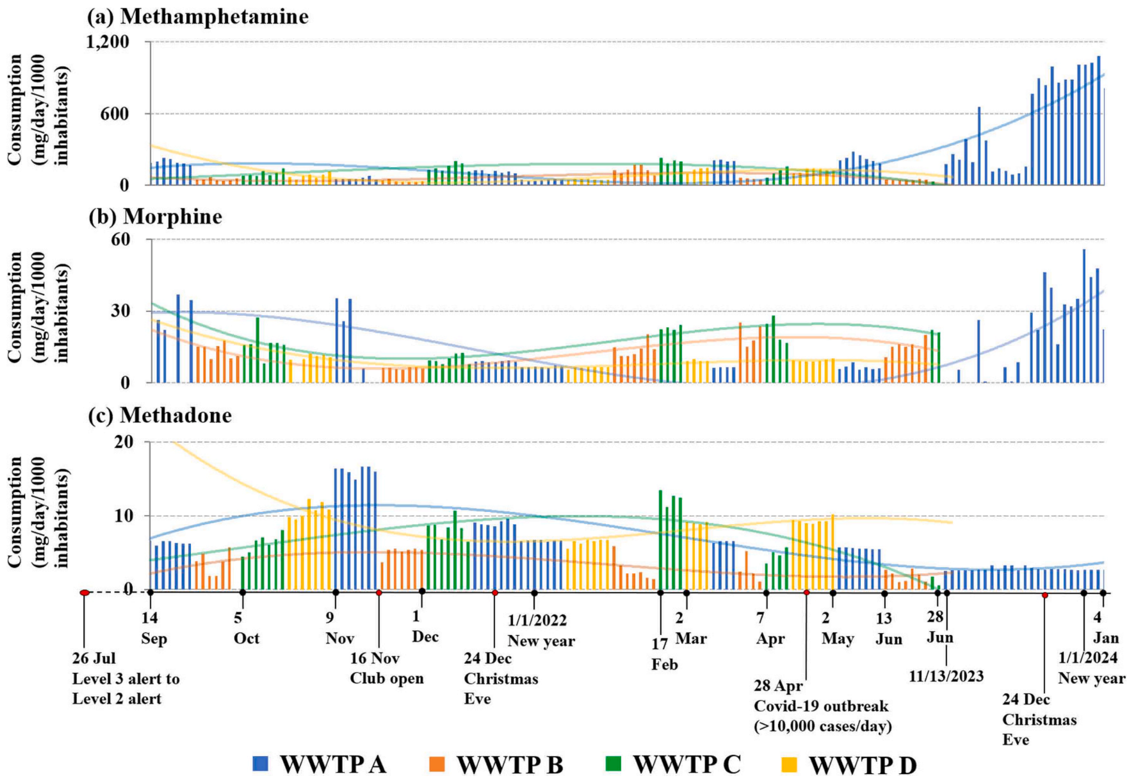


Fig. 2. The trend of illicit drug consumption throughout the COVID-19 policy timeline modeled by a cubic polynomial: (a) methamphetamine; (b) morphine; and (c) methadone.

the post-COVID-19 pandemic period of 2023 ($\beta_{1,\ \text{interval }5} = 2.66$, $p < 0.001$) and continued through the holiday season ($\beta_{1,\ \text{interval }6} = 28.33$, $p < 0.001$), as shown in Fig. 2(a). Specifically, for the biggest WWTP A (blue curve) in capital Taipei city and WWTP C (green curve) in New Taipei city, which together serve nearly 6.5 million residents, the consumption trend showed a distinct increase after the reopening of clubs on 16 Nov 2021. Subsequently, the curves of WWTP A demonstrated a significant rise during the holiday period, encompassing Christmas 2021, New Year 2022, Lunar New Year 2022, and continuing through the COVID-19 outbreak (periods 2 to 3, with $p < 0.05$). A pronounced holiday increase in methamphetamine consumption was also observed in interval 6 from WWTP A, covering the period including Christmas 2023 and New Year 2024, following the post-COVID-19 pandemic. This indicates that methamphetamine consumption was greatly influenced by the lifting of COVID-19 measures, such as the reopening of nightclubs, which may have eased social isolation and promoted holiday gatherings. After the outbreak on 28 Apr 2022, during period 4, there was a significant decrease in the total consumption of methamphetamine once more as additional COVID-19 measures were enacted. These included working from home and another round of school closures at all levels to halt the spread of the virus. The measures imply a connection between drug consumption and the restrictions placed on citizens' movement and social assembly. These restrictions effectively limited the distribution and availability of methamphetamine, leading to users reporting higher prices for illicit drugs during this period. This situation likely influenced how the drug was accessed and used. The decline in availability can also be attributed to the shortage of essential precursors required to synthesize methamphetamine; nevertheless, the significance of local production has been acknowledged [12]. This scenario seems to reflect a short-term influence on the drug markets, as the removal of these measures allowed the markets to revert back to their pre-COVID-19 state. Concurrently, the seizure of methamphetamine at the Taiwan border slightly increased after December 2021 when more COVID-19 measures were gradually eased in 2023 and 2024, the seizure amount of methamphetamine and positive urine cases were also increased in national drug reports [39,43]. These findings align with observations made by EMCDDA [44]. Notably, methamphetamine exhibited the highest concentration among all substances, reflecting its status as the dominant abused substance in Taiwan, with the possibility of local production [45].

3.2.2. *Opiate*

In Taiwan, morphine, a conventional drug denoting opiate use (including heroin), ranks among the top 3 abused substances. It is predominantly imported from Southeast Asia [45]. In Fig. 2(b), the findings revealed a significant decrease in the trend of opiate consumption prior to the reopening of nightclubs ($\beta_{1,\ \text{interval }1} = -0.17$, $p < 0.05$), followed by a subsequent increase until interval 4. A slight decrease in substance consumption was observed in interval 5, despite the return to normal life post-pandemic. However, during the holiday season, specifically in interval 6, a sharp increase was noted ($\beta_{1,\ \text{interval }6} = 1.36$, $p < 0.001$). This pattern consists with the shift observed in methamphetamine consumption during period 6 as mentioned in Section 3.2.1. It indicates a possible correlation between increased citizen mobility after COVID-19 pandemic and the heightened consumption of highly addictive drugs like opiates and methamphetamine. Regarding the wastewater treatment plants (WWTPs), A, B, and C all exhibited a significant decrease during period 1 ($p < 0.05$). However, during periods 2 and 3, WWTP A displayed a slight decline ($\beta_{1,\ \text{interval }2} = -0.29$, $p < 0.05$) in period 2 and a slight increase ($\beta_{1,\ \text{interval }3} = 0.48$, $p < 0.001$) during period 3. In contrast, WWTP C followed a different trend, with a minor increase ($\beta_{1,\ \text{interval }2} = 0.78$, $p < 0.05$) during period 2 and a slight decline ($\beta_{1,\ \text{interval }3} = -0.39$, $p < 0.05$) in period 3. The variation in trends between WWTPs A and C exhibited a combination of the recreational industry and associated social behaviors. This phenomenon could be attributed to the limited availability of opiates during the reopening of the recreational industry in certain districts of metro Taipei City. Simultaneously, illegal drug stockpiling could have potentially met the demand in WWTP

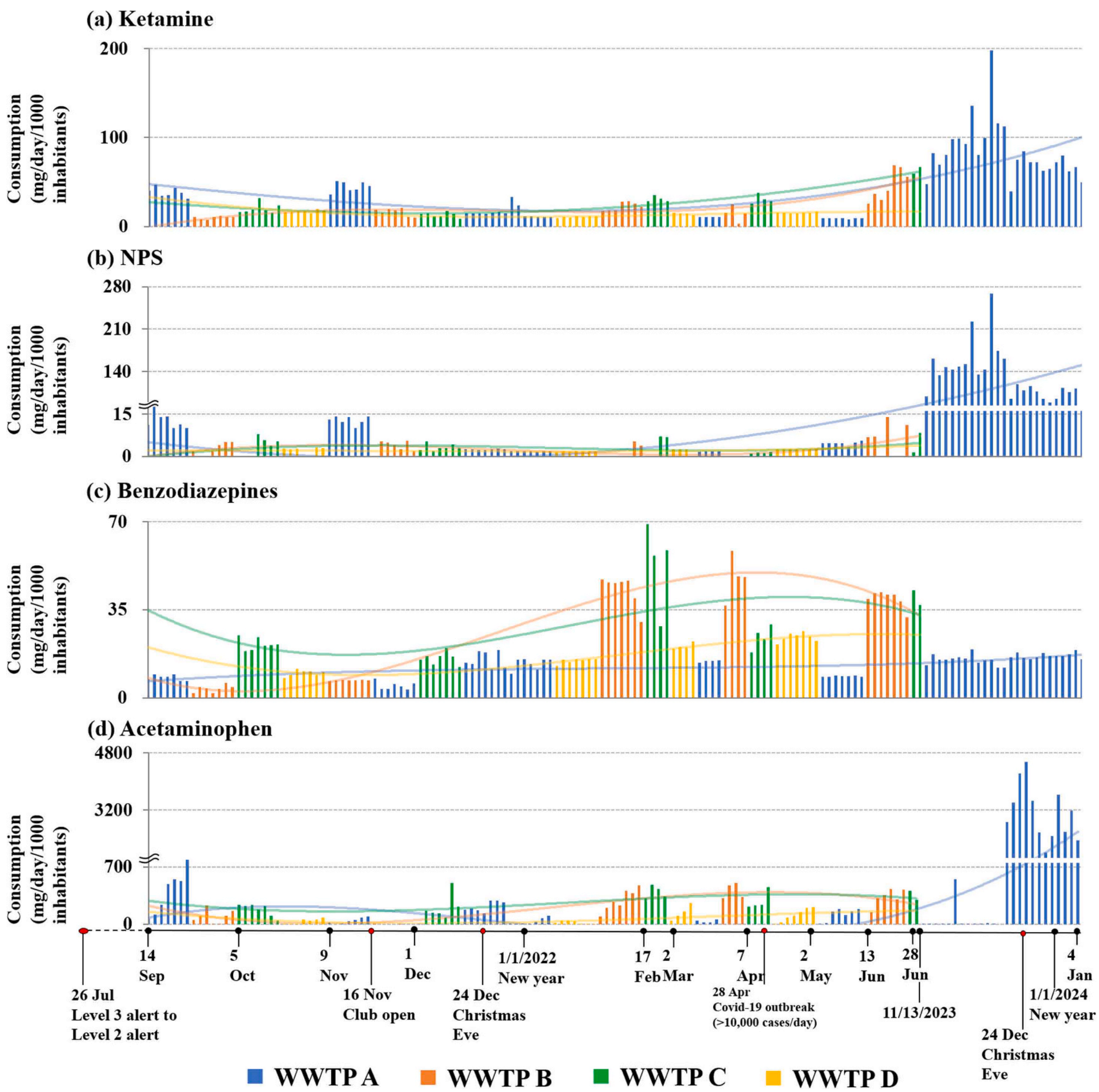


Fig. 3. The trend of illicit drug consumption throughout the COVID-19 policy timeline modeled by a cubic polynomial: (a) ketamine; (b) NPS (excluding ketamine); (c) benzodiazepines; and (d) acetaminophen.

C. The findings suggest that a mix of elements may contribute to shifts in drug use. They can range from the localized impact of COVID-19 restrictions and the influence of unique social sub-cultures with varied drug preferences, to uneven law enforcement efforts and varied social responses to stressors related to pandemic protocols [25,46]. However, the consumption trend of methadone differed from that of morphine, exhibiting an opposite pattern. Methadone consumption increased in period 1 ($\beta_{1,\ \text{interval 1}} = 0.12$), decreased in period 2 as clubs reopened for Christmas and New Year ($\beta_{1,\ \text{interval 2}} = -0.23$), rose slightly in period 3 during the Lunar New Year ($\beta_{1,\ \text{interval 3}} = 0.14$), then declined in period 4, coinciding with the COVID-19 outbreak ($\beta_{1,\ \text{interval 4}} = -0.14$). It increased again in period 5 ($\beta_{1,\ \text{interval 5}} = 0.12$) and decreased slightly in period 6 ($\beta_{1,\ \text{interval 6}} = -0.01$), as shown in Fig. 2(c). All periods except interval 6 exhibited statistical significance with $p < 0.001$. The government reports indicate that before and within this period, seized methadone ranked outside of the top 10 drugs with only a few grams seized [47,48,43,39]. Therefore, it is reasonable to assume that the primary source of methadone originates from prescriptions issued by addiction treatment units in hospitals. The trend of methadone consumption appears to have compensated for the need for morphine, including heroin, particularly in period 1 and 2. This trend compensated for morphine was consistently observed in intervals 5 and 6. However, during the outbreak, patients may have avoided returning to hospitals, resulting in a subsequent decline in methadone consumption. Upon returning to normal life, methadone consumption remained relatively stable, with average daily consumption at 0.9 times the level of periods 1–4 during intervals 5 and 6. Only slight changes were observed in the slopes (in supplementary Table S5).

3.2.3. *Ketamine and NPS*

Ketamine, classified as a NPS and known as a common party drug among young groups, has rapidly gained popularity throughout the country within just six years since 2009 in Taiwan [12]. It has ascended to rank among the top 3 abused drugs, alongside conventional drugs like methamphetamine and opiates, and has been under monitoring since then. The consumption trend of ketamine exhibited a slight increase in period 1, followed by a decrease in period 2, another slight increase in period 3, and a continuation into period 4 in Fig. 3(a). The change observed in period 4 displayed statistical significance ($\beta_{1,\ \text{interval 4}} = 0.68$, $p < 0.001$), a slight decline in interval 5 ($\beta_{1,\ \text{interval 5}} = -0.57$, $p < 0.001$) and a decrease in interval 6 ($\beta_{1,\ \text{interval 6}} = -1.53$, $p < 0.001$). As society gradually reopens, a relatively high consumption trend is observed compared to periods 1–3. This is likely due mainly to the holiday seasons, including Christmas, New Year, and Lunar New Year, which foster increased social and family gatherings, consequently leading to heightened citizen movement. In Taiwan, ketamine production involves a combination of local synthesis and smuggling precursor compounds, primarily sourced from East Asia [49]. The marginal decrease in consumption subsequent to nightclub re-openings might reflect potential limitations in unstable supply chain or precursor availability. A similar consumption pattern has been observed in the case of non-ketamine NPS Fig. 3(b). The overall consumption pattern of non-ketamine NPS demonstrated a slight increase in period 1, followed by a significant decrease ($\beta_{1,\text{ interval 2}} = -0.10$, $p < 0.05$) in period 2. Notably, period 3 witnessed a substantial increase ($\beta_{1,\text{ interval 3}} = 0.11$, $p < 0.05$). Minor increases were observed during period 4 and 5 ($\beta_{1,\text{ interval 5}} = 0.25$, $p < 0.05$), and a significant decrease occurred in interval 6 ($\beta_{1,\text{ interval 6}} = -2.77$, $p < 0.001$). Considering that the concurrent use of non-ketamine NPS is commonly linked with ketamine use [13], and the production sources of non-ketamine NPS, similar to ketamine, involve a blend of local synthesis and smuggling mainly from East Asia [49], their scarcity pattern could contribute to a reduction in local production before/after the club-reopening. Border closures especially highlight the issue, as they impact the acquisition of raw materials, resulting in reduced purity and usage. Similar trends have been confirmed in other research [25,46]. In terms of ketamine consumption, WWTP A showed a significant decrease ($\beta_{1,\text{ interval 2 | WWTP A}} = -0.76$, $p < 0.001$) during period 2, followed by a slight increase during period 3 ($\beta_{1,\text{ interval 3 |WWTP A}} = 0.78$, $p < 0.001$), while WWTP C displayed a slightly different profile. It showed a decrease during period 1 ($\beta_{1,\text{ interval 1 | WWTP C}} = -0.46$, $p < 0.05$), followed by an increase ($\beta_{1,\text{ interval 2 | WWTP C}} = 0.90$, $p < 0.05$), a decrease again in period 3 ($\beta_{1,\text{ interval 3 | WWTP C}} = -0.43$, $p < 0.05$), and an increase in period 4 ($\beta_{1,\text{ interval 4 | WWTP C}} = 0.52$, $p < 0.05$). Similarly, with non-ketamine NPS, WWTP A displayed a significant decrease during period 2 ($\beta_{1,\text{ interval 2 | WWTP A}} = -0.23$, $p < 0.001$), succeeded by a notable increase during period 3 ($\beta_{1,\text{ interval 3 | WWTP A}} = 0.30$, $p < 0.001$). For WWTP C, the longitudinal profile of non-ketamine NPS consumption showed a similar trend to that of ketamine. However, the changes observed at different time intervals did not achieve statistical significance in the other two WWTPs (i.e.,WWTPs B and D). This reveals local disparities, as WWTPs A and B are located in Capital Taipei City. WWPT A serves several areas with recreational nightclubs and illegal gambling houses, while a Science and Industrial Park is within the service areas of WWTP B. Regarding to WWTP C located in a satellite city around the capital, it serves the largest population among the four WWTPs, and its service area includes a major psychiatric center for drug rehabilitation. These variations underscore the local disparities in ketamine and non-ketamine NPS consumption across the four WWTPs, highlighting regional inconsistencies shaped by local conditions. Varied patterns of ketamine use point to complex societal responses to COVID-19 measures. Such complexity might lead to reduced use of this generally recreational substance, influenced by demographic variances, limited opportunities for social consumption, and restricted social interactions. Non-ketamine NPS, are primarily associated with recreational use in nightclubs, similarly to ketamine. After the post-COVID-19 pandemic, specifically during interval 6, the consumption of ketamine and non-ketamine NPS in sewage declined. This decline may be attributed to the large quantities of these substances that were seized by law enforcement [39,43]. This situation is also reflected in the relatively low number of urine cases detected [43]. Although the consumption patterns of non-ketamine NPS and ketamine share similarities, the average consumption level of ketamine was five times higher than that of non-ketamine NPS during the pandemic periods 1–4. It is worth noting that in intervals 5 and 6, the consumption of non-ketamine NPS, mainly tramadol and zolpidem, showed a relatively higher total value compared to ketamine. This observation does not dismiss the potential medical use for these substances, which are commonly prescribed. This is also reflected by the low amounts seized and few urine cases detected by law enforcement [43]. Nevertheless, this indicates that ketamine remains the predominant NPS in Taiwan, a finding that is consistent with urinary results from Taiwan [13].

3.2.4. Benzodiazepines and acetaminophen

Benzodiazepines are misused or abused alone, as well as in combination with other drugs [50]. In Taiwan, they are commonly co-used with synthetic cathinones [13]. During the collection time, the drug profile exhibited a decrease in period 1, a slight increase in period 2 ($\beta_{1,\text{ interval 2}} = 0.54$, $p < 0.001$), a slight decrease in period 3 ($\beta_{1,\text{ interval 3}} = -0.49$, $p < 0.001$), and another slight increase ($\beta_{1,\text{ interval 4}} = 0.37$, $p < 0.05$) in period 4 in Fig. 3(c) during the COVID-19 pandemic. However, after the post period, there was a significant drop in interval 5 ($\beta_{1,\text{ interval 5}} = -0.331$, $p < 0.001$) followed by a slight increase in interval 6 ($\beta_{1,\text{ interval 6}} = 0.134$). During periods 1–3, WWTPs A, B, and C exhibited a similar profile as described above with $p < 0.05$. However, in period 4, WWTPs A and B displayed an opposite trend compared to WWTP C. WWTP B demonstrated a slight decrease ($\beta_{1,\text{ interval 4 | WWTP B}} = -0.31$, $p < 0.05$), while WWTP C showed a slight increase ($\beta_{1,\text{ interval 4 | WWTP C}} = 1.02$, $p < 0.001$). In periods 1 and 2, a pattern similar to that of methamphetamine and opiates emerged, where the trend initially decreased and then slightly increased. This could suggest that the ease of COVID-19 restrictions might have alleviated social isolation and facilitated access to drugs [46]. However, periods 3 and 6 included several significant holidays, potentially contributing to increased social gatherings and, consequently, a decrease in the consumption of benzodiazepines, either during the pandemic or afterward. Numerous studies have indicated that during the COVID-19 pandemic, individuals were advised to lockdown and practice social distancing, leading to heightened mental stress, anxiety, and insomnia [51-54]. As a result, the use of benzodiazepines increased to manage these symptoms [50]. With the relaxation of measures, the potential mental stress caused by COVID-19 measures significantly decreased, which might have also led to a reduction in benzodiazepine consumption [50,54]. Our results seem to support the above notion. If assessing the consumption trend from WWTP A only, the slopes within the entire collection period changed slightly, ranging from − 0.22 to 0.30 only, which may reflect on the geographic and sub-culture disparity in a certain area in Supplementary Table S5. It can be inferred that the interplay between COVID-19 measures, both during and after the pandemic, and drug abuse activities has created a more involved social dynamic influencing benzodiazepine consumption. This situation is also evident in the opposing trends observed among different WWTPs. To illustrate this point, the consumption of acetaminophen, which has been widely used as a first-line antipyretic and analgesic for COVID-19 patients, was evaluated Fig. 3 (d). Its profile exhibited similar changes to benzodiazepines. The trends of acetaminophen showed a drop in period 1 ($\beta_{1,\text{ interval 1}} = -3.96$, $p < 0.05$), followed by a clear increase ($\beta_{1,\text{ interval 2}} = 6.95$, $p < 0.05$) in period 2. Subsequently, a significant decrease ($\beta_{1,\text{ interval 3}} = -3.32$, $p < 0.05$) was observed in period 3, followed by an increase with a slope of 2.86 in period 4, and a drop in interval 5 ($\beta_{1,\text{ interval 5}} = -2.56$). Then, a significant increase occurred in interval 6 ($\beta_{1,\text{ interval 6}} = 96.73$, $p < 0.001$). The last increase coincided with a harsh winter and the spread of various flu strains in the community, which likely led to a higher consumption of acetaminophen. The similar trends observed in benzodiazepines and acetaminophen consumption may suggest that the profile of benzodiazepines is influenced by medication usage to reduce mental stress during the COVID-19 pandemic. Consequently, assessing the consumption trends of benzodiazepines as abused drugs could potentially reveal more pronounced changes due to the impact of COVID-19 measures. It is crucial not to underestimate the intricate interplay of social activities and nuanced mental responses, which could together result in more complicated variations.

3.3. Weekly pattern during and after the COVID-19 collection phase

In Fig. 4(a-f), none of the drugs studied exhibited a recognizable weekly consumption pattern using Mondays as reference, with none

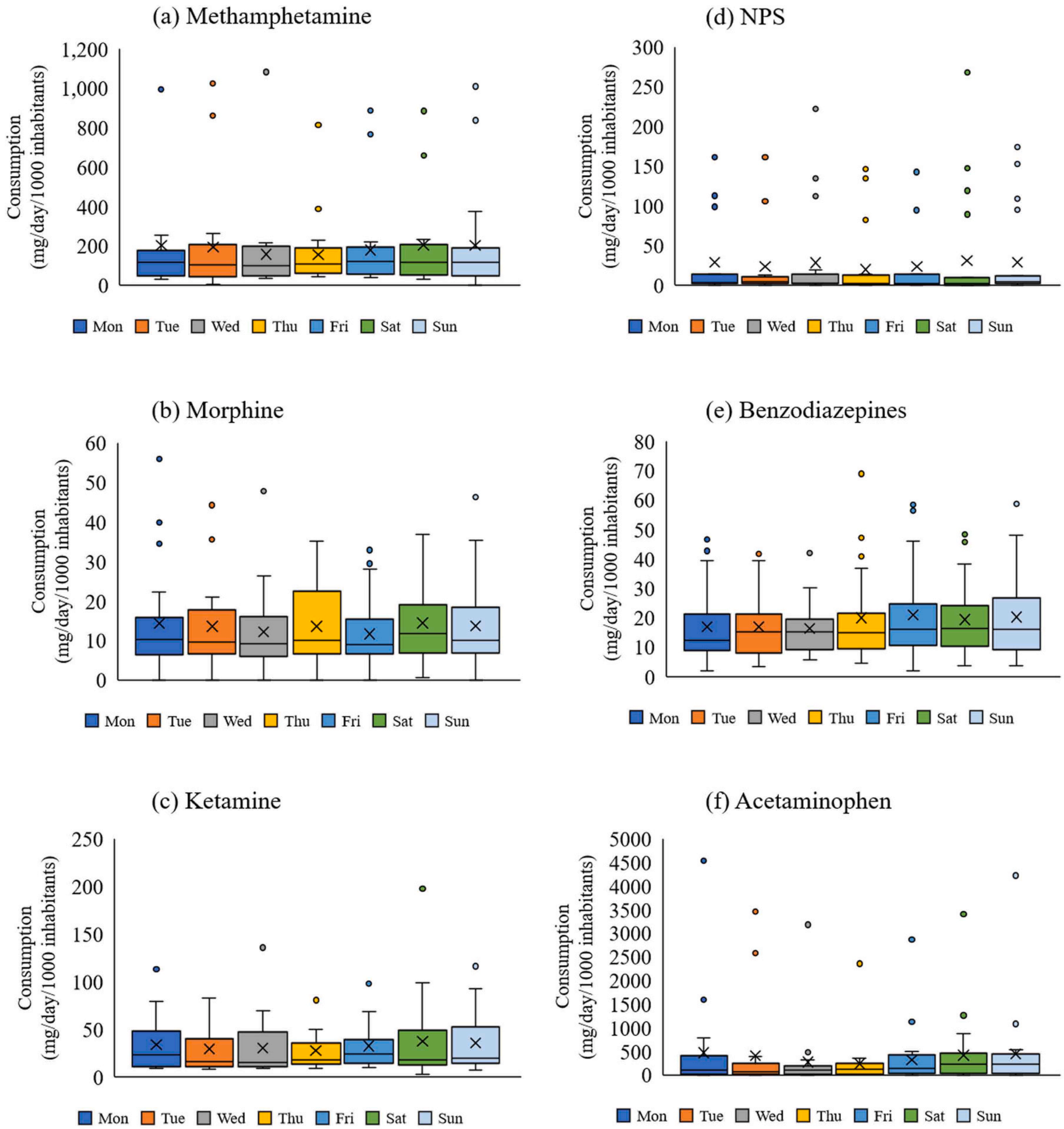


Fig. 4. The weekly patterns during the COVID-19 pandemic (Line: median; x: average; NPS: excluding ketamine).

reaching statistical significance (all $p > 0.05$) in supplementary Table S6. The average daily consumption remained consistent throughout the week. Considering that the majority of non-ketamine NPS are often associated with recreational party use, this leads to a focus on evaluating their consumption differences between weekdays and weekends [46]. In this study, the trend in non-ketamine NPS consumption showed a rise on Saturdays and a slight drop on Sundays; however, no statistically significant variations between these periods were identified, as illustrated in Fig. 4(d). This finding is contrary to other studies [46,25,27]. It may contribute to the reduction in the frequency of recreational drug consumption, limited accessibility and an unstable drug supply chain. Additionally, the impact of the specified period on economic activities should be considered; the loss of income during this time may have further contributed to a decrease in the consumption of these recreational drugs [55].

3.4. Comparison with other WBE studies

Methamphetamine has been consistently identified and analyzed in numerous studies utilizing WBE methods. In the present study, the average detected level was recorded at 183.71 mg/day/1000 inhabitants. This concentration was notably lower than the levels reported in similar studies from various global regions. For instance, the levels reported in Turkey were substantially higher at 322 mg/day/1000 inhabitants [56], while the United States, China, and Northeast Spain reported levels of 1740 mg/day/1000 inhabitants [57], 149 mg/day/1000 inhabitants [58], and 157 mg/day/1000 inhabitants [59], respectively. However, it is worth noting that the consumption level observed in this study still exceeded that seen in the rural university town of the United States during the COVID-19 pandemic, which was 43 mg/day/1000 inhabitants [46], as well as in Iceland (ranging from 47.1 to 106 mg/day/1000 inhabitants) [60] and South Korea (14.9–28.6 mg/day/1000 inhabitants) [61]. Turning to opiates, the consumption of morphine in this study was recorded at 14.16 mg/day/1000 inhabitants, a level lower than that reported in various other regions. For instance, the Midwestern United States showed a notably higher consumption of 1780 mg/day/1000 inhabitants [57], as did the rural university town of the United States

(656 mg/day/1000 inhabitants) [46] and Northeast Spain (228 mg/day/1000 inhabitants) [59]. Comparatively, China exhibited a lower consumption rate of 4.7 mg/day/1000 inhabitants [27].

Concerning codeine consumption, the average observed rate in Taiwan was 56.24 mg/day/1000 inhabitants, which was lower than the United States' range of 587–2090 mg/day/1000 inhabitants [62]. Nevertheless, it surpassed the consumption in the rural university town of the United States (39 mg/day/1000 inhabitants) [46], China (3.6 mg/day/1000 inhabitants) [27], and Malaysia (22–26 mg/day/1000 inhabitants)[63]. It's important to mention that no detectable levels of fentanyl derivatives beyond the LOD were found in this study. Shifting to ketamine consumption, a prevalent drug of abuse in Southeast and Eastern Asia, the average detected level was 30.17 mg/day/1000 inhabitants. This consumption was below Malaysia's consumption rate of 62 mg/day/1000 inhabitants [63] but exceeded that of China (2.4 mg/day/1000 inhabitants) [27]. It also fell within the range observed in the United States, which was 13–108 mg/day/1000 inhabitants [62]. Among the detected NPS, excluding ketamine but including substances like tramadol, zolpidem tartrate, CMA, and MDPV, the average consumption rate was 30.91 mg/day/1000 inhabitants. Notably, this study marked the first identification of the substances in Taiwanese sewage. It is worth noticing that one of the main NPS commonly used in Taiwan is mephedrone. Although many studies, including this one, attempted to detect it in sewage, none have confirmed its presence [62,64-66]. Existing data from the literature suggests that mephedrone may be converted quickly to metabolites in sewage systems [67,68]. While NPS like methylone were frequently seized in Taiwan before COVID-19 and not detected in our study, this contrasts with findings from regions such as Southern China [27], Australia [66] and the UK [69]. The likely reason for the non-detection of methylone in this study could be the persistent significant effects of social distancing measures, which continued even after the reduction of the social alert level to grade 2, aimed at preventing infection and curtailing recreational or financial activities. In the post-COVID-19 period, the low quantities of methylone seized and the few urine cases detected by law enforcement [43] also corresponded to its low detection in sewage.

3.5. Limitations

The study has several limitations that warrant caution in interpreting its findings. Firstly, the representation of the population in the present is unclear due to daily population changes in Metropolitan Taipei, resulting in uncertain sample compositions (e.g., residents, commuters, travelers, and others). This instability limits real-time profiling of drug use patterns among hidden drug-related populations in Metropolitan Taipei. This ambiguity presents challenges for WBE research. Secondly, inferring individual drug use behaviors from this data is challenging and may lead to ecological fallacies, making it difficult to assess how social demographics and specific environmental factors influence substance consumption patterns. A more comprehensive investigation into these factors could enhance understanding of observed trends. Thirdly, the limited number of samples from each WWTP reduces statistical power for analyzing consumption trends, cautioning against drawing broad conclusions solely from this data. Extending the study to include more samples from various WWTPs nationwide could allow for cross-validation analyses in advance. Additionally, the study's exclusive focus on urban areas from four WWTPs risks oversimplifying results and neglecting varying drug consumption patterns across different neighborhoods or districts within Metropolitan Taipei. Lastly, accurately identifying and quantifying drugs in wastewater samples is challenging due to metabolites and analytical uncertainties, which may lead to misinterpretation of drug consumption patterns.

4. Conclusion

This study presents a comprehensive WBE investigation in Taiwan, spanning the detection of an array of substances, including 30 NPS and 38 conventional drugs, across the COVID-19 pandemic. Among these NPS, the analysis included ketamine, tramadol, zolpidem, CMA, and MDPV, confirming the presence of the latter four for the first time in northern Taiwanese sewage. Certain NPS exhibited generally low detection frequencies, and in many cases, reached non-detectable levels. There was no evidence of a sudden increase in any NPS during or after the COVID-19 periods. Additionally, the detection frequencies of conventional drugs like methamphetamine, opiates, and ketamine—which are highly seized and utilized in Taiwan—remained high throughout, indicating sustained daily consumption despite nationwide COVID-19 social distancing measures. In the post-COVID-19 period, the average consumption of commonly used drugs increased compared to during the pandemic, suggesting that the easing of social restrictions may have enhanced drug access and market circulation. Conversely, benzodiazepines and methadone displayed trends opposite to those of commonly abused drugs both during and after the COVID-19 pandemic. Insights into medicinal treatment demands and pandemic-influenced drug misuse were gleaned from observed trends in the usage of benzodiazepines and acetaminophen. The consumption of benzodiazepines decreased in the post-COVID-19 period as society gradually returned to normalcy. However, the consumption of acetaminophen remained high, likely linked to high rates of flu infection in the winter of 2023. This indicates that both medicinal treatment demands and pandemic-influenced drug misuse interacted, as observed in the usage trends of these substances. The absence of significant correlations between the detection of party drugs and daily consumption suggests that COVID-19 measures may have blurred the distinctions between weekdays and weekends due to reduced activity and social restrictions, a trend also observed with conventional drugs. Furthermore, fluctuations in drug consumption trends, whether upward or downward, possibly tied to specific timeframes shaped by pandemic-controlling governmental policies, or multifaceted interplays of human mental states, social activities, and intricate factors. Encompassing diverse drugs and their detection frequencies, this study enriches the comprehension of COVID-19's impact on drug consumption, highlighting persistent and evolving trends. Additional research is essential to explore multifaceted influences shaping these patterns, aiding targeted interventions and public health policies.

CRediT authorship contribution statement

Ya-Chi Chang: Data curation, Methodology. **Shih-Hsun Chen:** Data curation, Formal analysis, Validation. **Pin-Chuan Chen:** Conceptualization, Data curation, Methodology, Resources, Validation, Writing – original draft. **Te-Tien Ting:** Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review & editing. **Pai-Shan Chen:** Conceptualization, Data curation, Funding acquisition, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Yi-Hsin Liu:** Conceptualization, Data curation, Funding acquisition, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Ping-Yu Chuang:** Data curation, Methodology. **Hai-Tien Chu:** Data curation, Methodology. **Pei-Chieh Chen:** Data curation, Methodology. **Hsu-Cheng Li:** Data curation, Methodology. **Pin-Ru Chiang:** Data curation, Methodology.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests. Pai-Shan Chen reports financial support was provided by National Science and Technology Council.

Data availability

Data will be made available on request.

Acknowledgments

The authors wish to thank the National Science and Technology Council of Taiwan (MOST 111–2627-M-002–002, MOST 110–2627-M-002–005, MOST 109–2627-M-002–001, MOST 108–2627-M-002–001, MOST 111–2113-M-002–021; NSTC 112–2113-M-002–017) for their support. Additionally, the authors would like to express their gratitude to the Institute of Toxicology at National Taiwan University for its instrumental support.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhazmat.2024.135020.

References

[1] WHO Director-General's opening remarks at the media briefing on COVID-19–11 March 2020.
[2] Nicola, M., Alsafi, Z., Sohrabi, C., Kerwan, A., Al-Jabir, A., Iosifidis, C., Agha, M., Agha, R., 2020. The socio-economic implications of the coronavirus pandemic (COVID-19): A review. Int J Surg 78, 185–193.
[3] Liu, X., Zhu, M., Zhang, R., Zhang, J., Zhang, C., Liu, P., Feng, Z., Chen, Z., 2021. Public mental health problems during COVID-19 pandemic: a large-scale meta-analysis of the evidence. Transl Psychiatry 11, 384.
[4] Zeegers Paget, D., Allebeck, P., Nagyova, I., 2021. COVID-19: What have we learned? What are the public health challenges? Eur J Public Health 31, iv1–iv2.
[5] Chacon, N.C., Walia, N., Allen, A., Sciancalepore, A., Tiong, J., Quick, R., Mada, S., Diaz, M.A., Rodriguez, I., 2021. Substance use during COVID-19 pandemic: impact on the underserved communities. Discov (Craiova) 9, e141.
[6] Taylor, S., Paluszek, M.M., Rachor, G.S., McKay, D., Asmundson, G.J.G., 2021. Substance use and abuse, COVID-19-related distress, and disregard for social distancing: A network analysis. Addict Behav 114, 106754.
[7] Chiappini, S., Guirguis, A., John, A., Corkery, J.M., Schifano, F., 2020. COVID-19: The hidden impact on mental health and drug addiction. Front Psychiatry 11, 767.
[8] Karamouzian, M., Johnson, C., Kerr, T., 2020. Public health messaging and harm reduction in the time of COVID-19. Lancet Psychiatry 7, 390–391.
[9] Das, P., Horton, R., 2019. The global drug problem: change but not progression. Lancet 394, 1488–1490.
[10] Lo, S., 2009. Cross-border crime between Taiwan and Mainland China: The response from the Taiwan government. Am J Chin Stud 16, 15–32.
[11] UNODC Synthetic drugs in East and Southeast Asia: Latest developments and challenges 2020.
[12] Liu, C., Li, J.-H., Tsay, W.-I., Hsu, J., 2005. Drug use and profile of individuals arrested on drug-related charges in Taiwan. J Food Drug Anal 13, 101–106.
[13] Yang, D.-P., Ting, T.-T., Kuo, Y.-N., Chen, W.-R., Liu, H.-T., Chiu, J.-Y., Jair, Y.-C., Chen, J.-H., Lin, M.-C., Hsu, Y.-H., Chen, H.-W., Chen, P.-S., 2023. The correlation between NPS and polysubstance use in high-risk population: a five-year longitudinal study in Taiwan. Int J Ment Health Addict. https://doi.org/10.1007/s11469-023-01088-w.
[14] Ministry of Justice Taiwan Report on drug control and prevention 2018.
[15] UNODC The world drug report 2020.
[16] Gracia-Lor, E., Castiglioni, S., Bade, R., Been, F., Castrignano, E., Covaci, A., Gonzalez-Marino, I., Hapeshi, E., Kasprzyk-Horden, B., Kinyua, J., Lai, F.Y., Letzel, T., Lopardo, L., Meyer, M.R., O'Brien, J., Ramin, P., Rousis, N., Rydevik, A., Ryu, Y., Santos, M.M., Senta, I., Thomaidis, N., Veloutsou, S., Yang, Z., Zuccato, E., Bijlsma, L., 2017. Measuring biomarkers in wastewater as a new source of epidemiological information: current state and future perspectives. Environ Int 99, 131–150.
[17] Ting, T.T., Chen, C.-Y., Tsai, Y.-S., Chen, Y.-T., Su, L.-W., Chen, W.J., 2015. Using social network as a recruiting tool for research on substance use in the Taipei metropolitan area: study design, implementation, and epidemiological estimates. J Epidemiol 25, 647–655.
[18] Palamar, J.J., Acosta, P., 2015. Synthetic cannabinoid use in a nationally representative sample of US high school seniors. Drug Alcohol Depend 149, 194–202.
[19] Piro, L., Martinotti, G., Santacroce, R., Vannini, C., Montemitro, C., Giorgetti, R., Schifano, F., Fraticelli, S., Baroni, G., Giannantonio, Md, 2019. Substance screening in a sample of "clubbers": discrepancies between self-reporting and urinalysis. Evid -Based Psychiatr Care 5, 10–16.
[20] Johnson, T., Fendrich, M., 2005. Modeling sources of self-report bias in a survey of drug use epidemiology. Ann Epidemiol 15, 381–389.
[21] Chiang, C.-H., Lee, H.-H., Chen, B.-H., Lin, Y.-C., Chao, Y.-Y., Huang, Y.-L., 2019. Using ambient mass spectrometry and LC–MS/MS for the rapid detection and identification of multiple illicit street drugs. J Food Drug Anal 27, 439–450.
[22] Castiglioni, S., Thomas, K.V., Kasprzyk-Hordern, B., Vandam, L., Griffiths, P., 2014. Testing wastewater to detect illicit drugs: state of the art, potential and research needs. Sci Total Environ 487, 613–620.
[23] Huizer, M., Ter Laak, T.L., de Voogt, P., van Wezel, A.P., 2021. Wastewater-based epidemiology for illicit drugs: A critical review on global data. Water Res 207, 117789.
[24] Daughton, C.G., 2001. Illicit Drugs In Municipal Sewage. In: Daughton, C.G., Jones-Lepp, T.L. (Eds.), Pharmaceuticals and Care Products in the Environment. American Chemical Society Inc., New York, pp. 348–364.
[25] Psichoudaki, M., Mina, T., Savvidou, M., Mina, C., Michael, C., Fatta-Kassinos, D., 2023. Wastewater-based monitoring of illicit drugs in Cyprus by UPLC-MS/MS: The impact of the COVID-19 pandemic. Sci Total Environ 854, 158747.
[26] Zarei, S., Salimi, Y., Repo, E., Daglioglu, N., Safaei, Z., Güzel, E., Asadi, A., 2020. A global systematic review and meta-analysis on illicit drug consumption rate through wastewater-based epidemiology. Environ Sci Pollut Res 27, 36037–36051.
[27] Zheng, Q., Ren, Y., Wang, Z., Liu, J., Zhang, Y., Lin, W., Gao, J., Thomas, K.V., Thai, P.K., 2021. Assessing patterns of illicit drug use in a Chinese city by analyzing daily wastewater samples over a one-year period. J Hazard Mater 417, 125999.
[28] Lee, M.S., Kerns, E.H., 1999. LC/MS applications in drug development. Mass Spectrom Rev 18, 187–279.
[29] Pérez-Parada, A., Gómez-Ramos, Md.M., Martínez Bueno, M.J., Uclés, S., Uclés, A., Fernández-Alba, A.R., 2012. Analytical improvements of hybrid LC-MS/MS techniques for the efficient evaluation of emerging contaminants in river waters: a case study of the Henares River (Madrid, Spain). Environ Sci Pollut Res 19, 467–481.
[30] Dahlin, J.L., Palte, M.J., LaMacchia, J., Petrides, A.K., 2019. A rapid dilute-and-shoot UPLC-MS/MS assay to simultaneously measure 37 drugs and related metabolites in human urine for use in clinical pain management. J Appl Lab Med 3, 974–992.
[31] Fan, S.Y., Zang, C.Z., Shih, P.H., Ko, Y.C., Hsu, Y.H., Lin, M.C., Tseng, S.H., Wang, D.Y., 2021. Simultaneous LC-MS/MS screening for multiple phenethylamine-type conventional drugs and new psychoactive substances in urine. Forensic Sci Int 325, 110884.
[32] He, Y., Zhu, L., Ma, J., Wong, L., Zhao, Z., Ye, Y., Fu, P.P., Lin, G., 2020. Comprehensive investigation and risk study on pyrrolizidine alkaloid contamination in Chinese retail honey. Environ Pollut 267, 115542.
[33] Lien, G.W., Chen, J.H., Tien, F.W., Chen, P.C., Chen, H.W., Hwa, H.L., Fang, C.C., Weng, T.I., Chen, P.S., 2018. Dilute-and-shoot enhances sensitivity of phthalate urinary concentrations for assessing the exposure in children. J Hazard Mater 351, 124–130.
[34] Chen, H.-W., Liu, H.-T., Kuo, Y.-N., Yang, D.-P., Ting, T.-T., Chen, J.-H., Chiu, J.-Y., Jair, Y.-C., Li, H.-C., Chiang, P.-J., Chen, W.-R., Lin, M.-C., Hsu, Y.-H., Chen, P.-S., 2023. Rapid and sensitive dilute-and-shoot analysis using LC-MS-MS for identification of multi-class psychoactive substances in human urine. J Pharm Biomed Anal 233, 115443.
[35] Croft, T.L., Huffines, R.A., Pathak, M., Subedi, B., 2020. Prevalence of illicit and prescribed neuropsychiatric drugs in three communities in Kentucky using wastewater-based epidemiology and Monte Carlo simulation for the estimation of associated uncertainties. J Hazard Mater 384, 121306.
[36] van Nuijs, A.L.N., Castiglioni, S., Tarcomnicu, I., Postigo, C., de Alda, M.L., Neels, H., Zuccato, E., Barcelo, D., Covaci, A., 2011. Illicit drug consumption estimations derived from wastewater analysis: A critical review. Sci Total Environ 409, 3564–3577.
[37] Ministry of Environment Taiwan Continuous waste water monitoring open data system. (https://a0-cwms.epa.gov.tw/cwmspublic/ (Accessed: 18 May 2024)).
[38] EMCDDA Common protocol of action for monitoring illicit drugs in wastewater 2013.
[39] Taiwan High Prosecutors Office Annual report of drug abuse cases and laboratory testing of Taiwan 2023.
[40] Gao, J., Xu, Z., Li, X., O'Brien, J.W., Culshaw, P.N., Thomas, K.V., Tscharke, B.J., Mueller, J.F., Thai, P.K., 2018. Enantiomeric profiling of amphetamine and methamphetamine in wastewater: A 7-year study in regional and urban Queensland. Aust Sci Total Environ 643, 827–834.
[41] Chen, W.-R., Kong, P.-H., Sauer, C., Chen, H.-W., Chan, H.-Y., Yang, D.-P., Jair, Y.-C., Liu, H.-T., Lin, T.-Y., Yen, M.-Y., Yen, Y.-F., Chang, S.-H., Li, L.-H., George, C., Chang, Y.-C., Wu, Y.-H., Hwa, H.-L., Chen, C.-Y., Chen, J.-H., Kicman, A.T., Maurer, H.H., Chen, P.-S., 2022. A proposed approach to confirm heroin administration – Regional differences in heroin purity is a major factor. Regul Toxicol Pharmacol 128, 105097.
[42] Lo, M.-Y., Ong, M.W., Lin, J.-G., Sun, W.-Z., 2015. Codeine consumption from over-the-counter anti-cough syrup in Taiwan: A useful indicator for opioid abuse. Acta Anaesthesiol Taiwan 53, 135–138.
[43] Taiwan Food and Drug Administration Annual report of drug abuse cases and laboratory testing of Taiwan 2023.
[44] EMCDDA European drug report 2021.
[45] UNODC The world drug report 2021.
[46] Luo, J., Bello, D., Pagsuyoin, S., 2023. Long-term wastewater-based surveillance and impacts of the COVID-19 pandemic on drug use trends in a U.S. Northeast rural town. Sci Total Environ 877, 162806.
[47] Taiwan Food and Drug Administration Drug abuse cases and testing statistics 2021.
[48] Taiwan Food and Drug Administration Annual report of drug abuse cases and laboratory testing of Taiwan 2022.
[49] UNODC Latest developments and challenges 2023.
[50] Sarangi, A., McMahon, T., Gude, J., 2021. Benzodiazepine misuse: An epidemic within a pandemic. Cureus 13, e15816.

[51] Bäuerle, A., Teufel, M., Musche, V., Weismüller, B., Kohler, H., Hetkamp, M., Dörrie, N., Schweda, A., Skoda, E.M., 2020. Increased generalized anxiety, depression and distress during the COVID-19 pandemic: a cross-sectional study in Germany. J Public Health 42, 672–678.
[52] Lin, L.Y., Wang, J., Ou-Yang, X.Y., Miao, Q., Chen, R., Liang, F.X., Zhang, Y.P., Tang, Q., Wang, T., 2021. The immediate impact of the 2019 novel coronavirus (COVID-19) outbreak on subjective sleep status. Sleep Med 77, 348–354.
[53] Vahratian, A., Blumberg, S.J., Terlizzi, E.P., Schiller, J.S., 2021. Symptoms of anxiety or depressive disorder and use of mental health care among adults during the COVID-19 pandemic - United States, Morb. Mortal. Wkly. Rep, 70, 490–494.
[54] Zaki, N., Brakoulias, V., 2022. The impact of COVID-19 on benzodiazepine usage in psychiatric inpatient units. Australas Psychiatry 30, 334–337.
[55] Benschop, A., van Bakkum, F., Noijen, J., 2021. Changing patterns of substance use during the coronavirus pandemic: Self-reported use of tobacco, alcohol, cannabis, and other drugs. Front Psychiatry 12, 633551.
[56] Mercan, S., Kuloglu, M., Tekin, T., Turkmen, Z., Dogru, A.O., Safran, A.N., Acikkol, M., Asicioglu, F., 2019. Wastewater-based monitoring of illicit drug consumption in Istanbul: Preliminary results from two districts. Sci Total Environ 656, 231–238.
[57] Skees, A.J., Foppe, K.S., Loganathan, B., Subedi, B., 2018. Contamination profiles, mass loadings, and sewage epidemiology of neuropsychiatric and illicit drugs in wastewater and river waters from a community in the Midwestern United States. Sci Total Environ 631-632, 1457–1464.
[58] Zhang, X., Huang, R., Li, P., Ren, Y., Gbao, J., Mueller, J.F., Thai, P.K., 2019. Temporal profile of illicit drug consumption in Guangzhou, China monitored by wastewater-based epidemiology. Environ Sci Pollut Res Int 26, 23593–23602.
[59] Mastroianni, N., López-García, E., Postigo, C., Barceló, D., de Alda, M.L., 2017. Five-year monitoring of 19 illicit and legal substances of abuse at the inlet of a wastewater treatment plant in Barcelona (NE Spain) and estimation of drug consumption patterns and trends. Sci Total Environ 609, 916–926.
[60] Love, A.S.C., Asgrimsson, V., Olafsdottir, K., 2022. Illicit drug use in Reykjavik by wastewater-based epidemiology. Sci Total Environ 803, 149795.
[61] Kim, K.Y., Oh, J.-E., 2020. Evaluation of pharmaceutical abuse and illicit drug use in South Korea by wastewater-based epidemiology. J Hazard Mater 396, 122622.
[62] Bishop, N., Jones-Lepp, T., Margetts, M., Sykes, J., Alvarez, D., Keil, D.E., 2020. Wastewater-based epidemiology pilot study to examine drug use in the Western United States. Sci Total Environ 745, 140697.
[63] Du, P., Liu, X., Zhong, G., Zhou, Z., Thomes, M.W., Lee, C.W., Bong, C.W., Zhang, X., Hao, F., Li, X., Zhang, G., Thai, P.K., 2020. Monitoring consumption of common illicit drugs in Kuala Lumpur, Malaysia, by wastewater-cased epidemiology. Int J Environ Res Public Health 17, 889.
[64] Castiglioni, S., Borsotti, A., Senta, I., Zuccato, E., 2015. Wastewater analysis to monitor spatial and temporal patterns of use of two synthetic recreational drugs, ketamine and mephedrone in Italy. Environ Sci Technol 49, 5563–5570.
[65] Reid, M.J., Derry, L., Thomas, K.V., 2014. Analysis of new classes of recreational drugs in sewage: Synthetic cannabinoids and amphetamine-like substances. Drug Test Anal 6, 72–79.
[66] Thai, P.K., Lai, F.Y., Edirisinghe, M., Hall, W., Bruno, R., O'Brien, J.W., Prichard, J., Kirkbride, K.P., Mueller, J.F., 2016. Monitoring temporal changes in use of two cathinones in a large urban catchment in Queensland. Aust Sci Total Environ 545-546, 250–255.
[67] Cox, G., Rampes, H., 2003. Adverse effects of khat: a review. Adv Psychiatr Treat 11, 456–463.
[68] Uralets, V., Rana, S., Morgan, S., Ross, W., 2014. Testing for designer stimulants: metabolic profiles of 16 synthetic cathinones excreted free in human urine. J Anal Toxicol 38, 233–241.
[69] Mwenesongole, E.M., Gautam, L., Hall, S.W., Waterhouse, J.W., Cole, M.D., 2013. Simultaneous detection of controlled substances in waste water. Anal Methods 5, 3248–3254.