European Addiction Research

Research Article

Eur Addict Res
DOI: 10.1159/000526144

Received: February 17, 2022
Accepted: July 13, 2022
Published online: September 22, 2022

Key Interpretation Challenges for Wastewater-Based Epidemiology of Illicit Drugs: A Norwegian Three-City Case Study

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Keywords
Wastewater-based epidemiology · Illicit drugs · Amphetamines · MDMA · Cocaine

Abstract
Introduction: Wastewater-based epidemiology (WBE) has emerged as a timely, non-invasive, and cost-effective indicator of illicit drug consumption. It is increasingly used by international organizations as a proxy measure for estimates of drug prevalence and related trends. Nevertheless, the literature exploring the limitations of WBE remains limited. This paper aims to shed further light on important shortcomings of WBE with recommendations on moving forward. ***Method:*** Utilizing case study and statistical analysis, the paper critically reviews methodological challenges associated with WBE results related to (i) levels, (ii) trends, and (iii) between-city comparisons of drug use. Data from raw influent wastewater samples from wastewater plants in the cities of Oslo, Bergen and Stavanger/Sandnes were analysed for amphetamine, methamphetamine, MDMA, and cocaine (benzoylecgonine) over a 3-year period. Normalized population loads were calculated and variation in daily loads analysed with plots and estimation of means, confidence intervals, and coefficient of variation. Linear regression models examined trends and between-city differences. ***Results:*** Plots and statistical analyses revealed extensive variation in daily loads, with min/max values of 6.1/453.9 mg/day per 1,000 inhabitants 15–64 years for amphetamine and correspondingly 9.4/675.9 mg for methamphetamine. Substantial differences in load levels and patterns across time and plants were also observed. A carefully designed sampling procedure and a relatively large number of daily samples are required to obtain estimates of sufficient precision for determining trends in space or time. Cross-referencing with alternative trend variables can improve the interpretation of WBE trend indicators. Finally, when using mean load levels for different wastewater-treatment plants to assess spatial variation in drug use, the representativeness of the catchment area should be evaluated before interpreting observed changes as city differences. ***Conclusion:*** Although WBE is a useful supplementary indicator of illicit drug consumption, important methodological issues and potential shortcomings should be taken into account when designing sampling procedures and interpreting the analytical results.

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Introduction

As European and global patterns of illicit drug use are recognized as becoming increasingly dynamic and complex, the measures used to monitor patterns and trends have needed to rapidly develop to keep pace. During the last decade, more established methodologies for monitoring drug use, such as population surveys, treatment service data, seizures, and registry data have increasingly been complemented by new methods and approaches. An important addition to the traditional epidemiological toolkit has been wastewater-based epidemiology (WBE), which has emerged as a popular supplementary indicator of illicit drug use [1–6].

The WBE method is primarily used to monitor and compare patterns of use of illicit drugs at the city level, with the potential to provide real-time and comparable information on a broad range of substances. The approach is used to identify types and quantities of illicit drugs that reflect drug-taking patterns, trends, and geographical variations [7], and commentators suggest it can prove particularly useful in times when obtaining survey data is difficult [8, 9]. More specifically, WBE quantifies illicit drugs, or their metabolites, in wastewater samples collected at wastewater-treatment plants (WWTPs), with the results typically reported as estimates of the quantity (in mg) present per 1,000 inhabitants within a defined period at a WWTP. In some cases, results are back-calculated to estimates of quantities consumed per 1,000 inhabitants in the catchment area of a WWTP [1, 10–12]. In spite of its benefits, a number of shortcomings of the WBE approach have been widely discussed. In this context, this study aims to both illustrate and deepen the discussion of some of the more important challenges, focusing specifically on interpretation of results related to (i) levels, (ii) trends, and (iii) between-city comparisons of drug consumption, and highlighting key implications for policy and practice.

Since the first publications on WBE by Zuccato et al. [4, 5], studies have been conducted in many European countries with an increasing global literature development [13]. An important series of city-level studies based on an annual week-long sampling regime has generated information about levels and trends for amphetamine, methamphetamine, MDMA, and cocaine, across several European WWTPs since 2011 [14, 15]. Other studies included longer sampling periods and various longitudinal sampling strategies of illicit drug use in urban and rural areas in Washington State [16]; detailed analyses of several Slovakian cities [17]; 7-year trends of methamphetamine residues in two cities in Queensland, Australia [18]; day-by-day variations in measurements of cocaine (as benzoylecgonine) and methamphetamine over a 1-month period in Oslo [19]; weekly, seasonal, and long-term trends over 4 years for multiple drugs in South Australia [20]; and consumption of multiple drugs during a 1-year period in Brussels, Belgium [21]. The observed differences in levels and trends of analytical results have, implicitly or explicitly, been assumed to reflect the differences in drug consumption across cities and over time.

A number of criticisms of the WBE approach focus on what the method is not able to deliver. An example being that WBE estimates do not offer any individual-level information, such as individual drug-use patterns, user characteristics, drug-use history, user context, etc. Similarly, the method has been criticized for not providing information on issues such as drug-related harms, and for encouraging a shift in focus from drug-related harm to the issue of drug use per se [22]. Further, the method raises some significant ethical issues when used in smaller catchment areas (entertainment venues, prisons, schools, or workplaces) where results may potentially be misused to the detriment of the population under study [23]. Such ethical concerns are reduced when WBE is utilized to monitor illicit drug use in large populations, and its proponents would argue that findings at this level can helpfully complement established drug epidemiological methods and prove beneficial for improving our understanding and analysis of drug-use patterns and trends.

Importantly, there are a range of potential shortcomings of WBE that require consideration in the context of analysis and interpretation of results. One important issue is how to correctly handle the substantial short-term variation often seen in WBE results [12, 18, 20, 21, 24, 25]. Such variations may correctly reflect changes in drug use but may also be influenced by leaks, overflows, and biological processes in the body and in the sewer system affecting drugs or their metabolites. Variation caused by the sampling procedure, plant characteristics (representativeness, storage, preparation, water-flow estimation), and the process of chemical analysis in laboratories [1–3] have more recently been addressed, and a number of procedures have been established to minimize the impact [1, 2, 26]. Yet some basic measurement problems mentioned above remain. In addition, the results will be sensitive to the direct disposal of drugs in sewage water [8, 27], to variations in use across weekdays and seasons, and to peaks in drug use on special occasions such as music festivals [2]. For stimulant drugs, however, chiral analysis as

part of enantiomeric profiling has a potential to distinguish what has been consumed and what has been directly disposed of in wastewater although the results are sometimes hard to interpret [28].

Furthermore, WBE is often used to compare quantity estimates for the same plant across time and thus be a useful tool for evaluating trends in drug use [18, 20, 29]. However, beyond demonstrating changes in mean drug quantity per 1,000 inhabitants over time, a more comprehensive understanding of trends is challenging. An increasing trend in the quantity of a substance detected may be caused by an increase in consumption per user, an increase in the number of users, or a combination of the two. In this context, additional data sources will be needed for further interpretation of the findings. Observed trends may additionally be influenced by time-varying and unobserved factors, such as changes in drug purity over the observation period [2, 18, 30–33]. In this respect, an observed increase in daily loads may have a negligible association with street volume/weight units, but rather the increased purity of the product on the market.

Finally, geographical location is a key consideration with some plants processing sewage water from an entire city or district, whereas other plants only process from smaller enclaves [34]. If drug users in a given catchment area are not representative of a city's drug-using population, the observed differences in population-standardized quantity estimates across plants may be incorrectly interpreted as differences in drug consumption across cities. Also, if the small enclaves include a non-representative proportion of business areas, nightclubs, shopping districts etc., there will be variations in movements in and out of the catchment area, and the number of inhabitants may not well represent those who actually contribute to the wastewater being analysed.

The Norwegian Three-City Study

Using a data set collected from September 2014 to January 2017 from three WWTPs situated in three Norwegian cities as a case study, this paper aims to illustrate and discuss a number of key methodological challenges associated with WBE. Specifically, the analytical results are utilized to explore challenges in interpreting: (i) substantial short-term variation in quantities found at the same plant, (ii) long-term variation (trends), and (iii) observed differences across plants. Based on our findings, we suggest measures to improve the use and interpretation of WBE.

Materials and Methods

Biomarkers for amphetamine, methamphetamine, MDMA, and cocaine (benzoylecgonine) were sampled from three wastewater plants:

1. Vestfjorden WWTP (VEAS): The catchment area covered 76% of Oslo's population (455,000 inhabitants), two large adjoining municipalities (180,000 inhabitants) and parts of two small municipalities. Sixty-one samples were collected between November 2014 and December 2016.
2. Knappen WWTP: The catchment area mainly covered two administrative units outside Bergen city centre, including 25% of the population (approximately 70,000 inhabitants). Thirty-six samples were collected between June 2015 and January 2017.
3. Nord-Jæren WWTP (SNJ): The catchment area covered the cities of Stavanger (135,000 inhabitants) and Sandnes (75,000 inhabitants), plus three adjoining municipalities comprising a total of 50,000 inhabitants. Seventy-six samples were collected between September 2014 and January 2017.

Composite raw wastewater samples were collected on weekdays and weekends and analysed according to a validated procedure [35]. The analytical quality assessment for the target compounds presented in this study was performed as part of an annual inter-laboratory exercise [26].

Variables

Quantities for each biomarker were calculated from the measured concentration (ng/l) and the total daily flow in cubic litres (72 h at weekends). On weekdays, the 24-h sampling period started and finished at 08:00. Weekend day quantities were calculated as one-third of the quantity for the whole weekend, which lasted from 08:00 on Friday to 08:00 on Monday. Ideally, we would have wanted daily measurements also for the weekend days but that was not feasible. Quantity values in this study are presented as mg per 24-h period per 1,000 inhabitants aged 15–64 years, i.e., population-normalized loads (*daily loads* for short). WBE results are usually presented per 1,000 inhabitants, while we applied an age range that is considered more relevant for the drug-using part of the population.

Date and day of the week were registered. A dummy variable for weekend (value 1) and weekdays (value 0) was applied because large differences across days of the week have been found for some illicit drugs [19, 29]. Public holidays and the day before public holidays were defined as weekends.

To estimate daily loads over time, the number of inhabitants on a given day of wastewater sampling was estimated using a linear function between the population on 1 January of the sampling year and that of the following year. Statistics Norway provided population figures for 1 January each year.

Statistical Analyses

Variation in daily loads is described using plots and by estimating means and confidence intervals (CI), coefficient of variation, and minimum and maximum values for each biomarker (amphetamine, methamphetamine, MDMA, and benzoylecgonine/cocaine). Separate means for weekdays and weekends are shown.

A linear regression analysis estimated the trends in daily loads, controlled for weekend measurements for each biomarker and plant. Since weekend data were measured as averages over 3 days and therefore had a reduced statistical uncertainty compared to

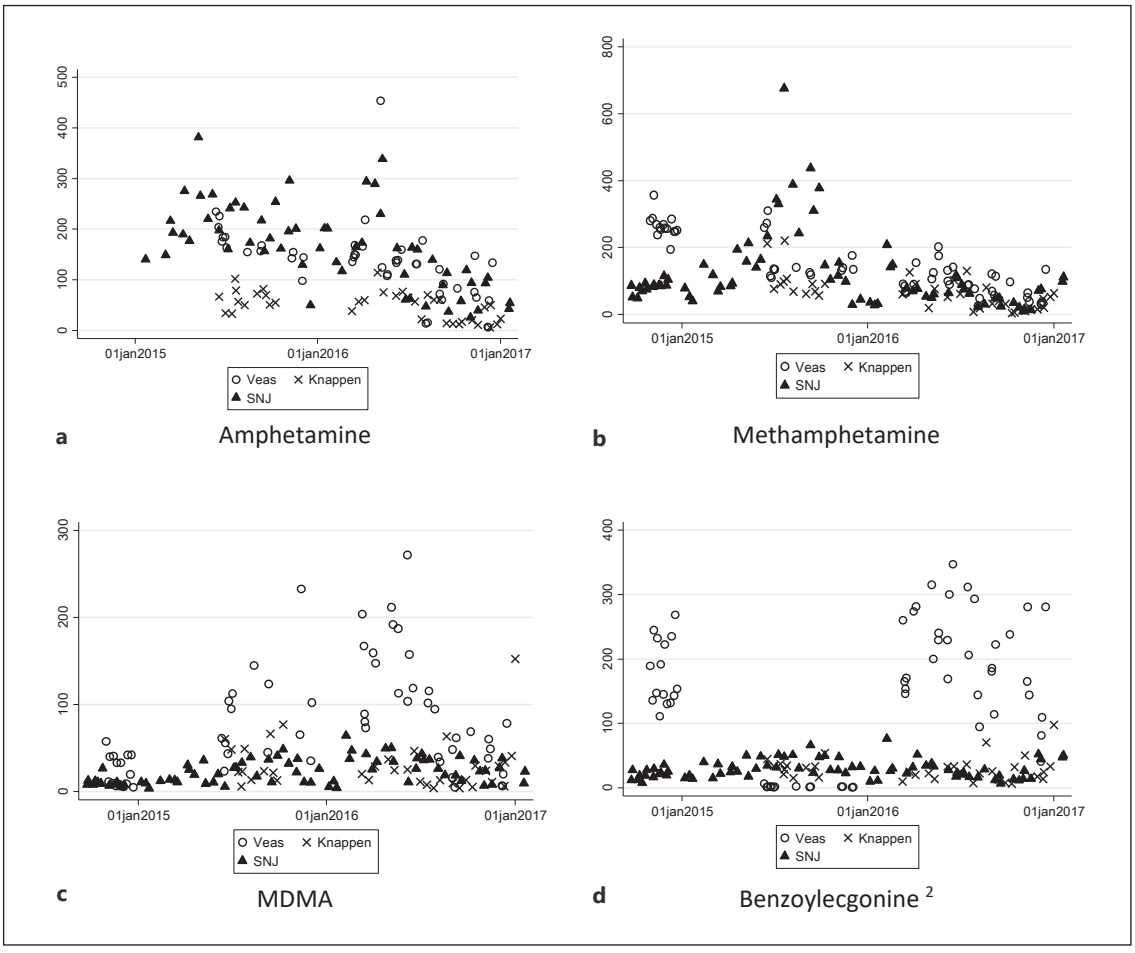

Fig. 1. Amphetamine, methamphetamine, MDMA, and benzoylecgonine (cocaine)[1] daily loads according to plant and calendar time. mg/day per 1,000 inhabitants 15–64 years of age. [1]Benzoylecgonine is a metabolite of cocaine. [2]At VEAS, benzoylecgonine measurements were very low from June to December 2015. An analysis of additional cocaine biomarkers (ecgonine methyl ester, cocaethylene, and cocaine itself) in the same samples confirmed the results from benzoylecgonine (data not shown). We have chosen to show results that include the very low measurements in the analyses, since there are no other indicators or information confirming or denying such low consumption levels for the period.

single-day measurements, analytic weights were applied to adjust for this. Trends were operationalized as calendar days (1 January 2016 as day zero). Skewness and kurtosis tests (sktest) assessed the normality assumption of residuals and lvr2plots (leverage vs. squared residual plots) were used to identify influential measurements. This is a useful tool for examining how a given point influences the data analysis. The most influencing points have a high leverage and a high residual. Influential measurements have the potential to change the significance of the results, for both trends and comparisons of levels. Results were reported that both included and excluded influential measurements if excluding or including them changed the results.

National purity figures per year, based on seizures by the police and customs, were applied in order to run purity-adjusted regressions. The purity of amphetamine decreased by 40% from 2014 to 2016 (from 35% to 21%), while the purity of methamphetamine increased by 25% from 2014 to 2016 (36–45%). The purity of cocaine gradually increased by 44% from 2014 to 2016 (32–46%) [36]. The purity of MDMA powder was high (85–95%) over the period. MDMA tablets have increased in purity, however, from an average of 100 mg/tablet at the beginning of the century to an average of 165 mg/tablet in 2021 [37]. This means that the average increase of MDMA purity in tablets may have been approximately 10% between 2014 and 2016, based on a non-verifiable assumption of a linear increase from 2000 to 2021. Recalculated to tablets, the MDMA amount of powder seized equalled approximately three times the number of tablets seized. A very uncertain estimate of increase 2014–2016 will thus be less than 10%. An assumption of "no change" was used in this study.

Linear regression models, accounting for trend and weekends as well as drug purity, were applied to compare drug use across WWTPs.

Table 1. Stimulant consumption for WWTPs; biomarker daily loads (total and weekday/weekend) and distributional properties; mg/day per 1,000 inhabitants 15–64 years

Plant/city[1] and biomarker/metabolite	Sample size	Mean	CI of mean	Coefficient of variation	Min.	Max.	Means	
							Weekday (*n*)	Weekend (*n*)
VEAS – Oslo								
Amphetamine	46	136.4	114.8–158.1	54	6.1	453.9	120.7 (23)	152.2 (23)
Methamphetamine	61	149.5	127.5–171.5	57	24.9	357.0	143.6 (30)	155.5 (31)
MDMA	61	77.4	61.0–93.9	83	4.6	272.0	63.3 (30)	92.1 (31)
Benzoylecgonine	61	152.1	125.7–178.4	68	0.3	346.8	125.0 (30)	180.1 (31)
Knappen – part of Bergen								
Amphetamine	36	50.0	40.8–59.1	54	6.1	113.9	49.3 (16)	50.7 (29)
Methamphetamine	36	66.7	49.6–83.8	76	3.7	220.7	62.3 (16)	72.3 (29)
MDMA	36	29.9	20.3–39.5	95	3.8	152.3	19.6 (16)	42.9 (29)
Benzoylecgonine	36	28.5	22.4–34.7	64	6.1	97.9	20.4 (16)	38.7 (29)
SNJ – Stavanger								
Amphetamine	58	166.8	145.4–188.3	49	25.6	381.5	158.3 (23)	179.9 (35)
Amphetamine, including extreme value	59	214.0	117.2–310.7	58	25.6	2,950.0	235.8 (24)	179.9 (35)
Methamphetamine	76	117.7	92.2–143.3	95	9.4	675.9	120.1 (23)	114.3 (35)
MDMA	76	22.5	19.2–25.7	63	3.7	64.3	19.1 (23)	27.4 (35)
Benzoylecgonine	76	28.8	25.5–32.0	50	6.6	76.3	24.8 (23)	34.5 (35)

[1] VEAS includes central Oslo/west Oslo plus two large municipalities and parts of two small municipalities to the west of Oslo. Knappen mainly covers two administrative districts outside Bergen city centre. SNJ includes Stavanger, one large (Sandnes) and three smaller municipalities outside Stavanger.

Results

The plots in Figure 1 show the calculated 24-h loads for the four drugs over the sampling periods at each of the three WWTPs.

If the results are interpreted as indicators of drug consumption patterns, then they could be summarized to show:

1. There is extensive variation in drug use in all cities. For example, at Knappen WWTP, a daily load of 130 mg of methamphetamine was registered on a weekday in July 2016, while a corresponding figure of 8 mg was found 13 days later. Further, on a weekday in November 2016, a load of 281 mg of benzoylecgonine (cocaine) was found at VEAS, and the calculated load a few weeks later amounted to 41 mg.
2. There are drug-specific trends over the sampling period: the use of amphetamines in Bergen, Oslo, and Stavanger/Sandnes goes down, the use of MDMA in Oslo and Stavanger/Sandnes increases, as does the use of cocaine in Oslo.
3. There is substantial variation in drug use across the three cities. For instance, the benzoylecgonine load values for VEAS seem to be far larger than corresponding load values from Knappen and SNJ.

The findings of Figure 1 were examined in more detail, and results are presented in Tables 1–3. Table 1 shows measures of statistical variation and uncertainty. Over and above the weekend/weekday differences in mean loads, the minimum and maximum values show wide ranges of daily loads over the study period, see Table 1.

The coefficient of variation was lowest for amphetamine, indicating relatively stable use on a day-to-day basis (value range 49–54) and highest for MDMA (value range 63–95), indicating more varied use. The mean load values for all drugs were higher at VEAS than at Knappen, whereas the load values for amphetamines were higher at SNJ than at VEAS and Knappen.

Possible trends in drug use were examined and Table 2, column three, presents the linear regression coefficients. The estimations controlled for weekend versus weekday sampling (see online suppl. Table S1 for a complete set of results; see www.karger.com/doi/10.1159/000526144 for all online suppl. material). There were significant trend indicators in eight out of 12 regression models. To check whether the results were influenced by single extreme values, for instance caused by drugs directly disposed in the wastewater/toilet, all models were run both with and without influential measurements identified by the lvr2plots. The procedure changed only one of the trend coefficients: the coefficient

Table 2. Trends in daily loads[1] for each WWTP and stimulant, unadjusted and adjusted for annual purity levels; coefficient estimates from linear regression[2]

	N	Trend	Trend adjusted with average purity per year
VEAS			
Amphetamine	46	−0.19 (−0.08 to −0.31)*	−0.13 (−0.35 to 0.08)
Methamphetamine	61	−0.28 (−0.23 to −0.32)*	−0.30 (−0.34 to −0.26)*
MDMA	61	0.06 (0.01–0.12)*	–[3]
Benzoylecgonine	61	0.11 (0.01–0.21)*	−0.00 (−0.09 to 0.08)
Knappen			
Amphetamine	36	−0.07 (−0.03 to −0.11)*	−0.06 (−0.13 to −0.02)
Methamphetamine	36	−0.19 (−0.12 to −0.27)*	−0.18 (−0.24 to −0.12)*
MDMA	36	−0.024 (−0.066 to 0.016)[4]	–[3]
Benzoylecgonine	36	−0.036 (−0.028 to 0.089)	−0.036 (−0.052 to 0.010)
SNJ			
Amphetamine	58	−0.29 (−0.21 to −0.37)*	−0.27 (−0.41 to −0.13)*
Methamphetamine	76	−0.08 (−0.17 to 0.01)	−0.09 (−0.17 to −0.01)*
MDMA	76	0.025 (−0.015 to 0.035)*	–[3]
Benzoylecgonine	76	0.003 (−0.009 to 0.015)	−0.016 (−0.023 to 0.000)

* Significance based on normal assumptions, $p < 0.05$. [1] mg/day per 1,000 inhabitants 15–64 years. [2] The regression analyses were controlled for the weekend. Online supplementary Table S1 shows the complete results for the unadjusted analysis for yearly purity levels. [3] No yearly purity change. [4] Excluding one influential measurement yielded a significant result for trend, −0.036, CI (−0.005 to −0.068).

Table 3. Comparison of stimulant daily loads[1] across WWTPs according to linear regression, unadjusted and adjusted for yearly purity change[2, 3]

Type of drug/metabolite	Obs., *n*	Knappen versus VEAS	SNJ versus VEAS	Knappen versus SNJ
Unadjusted				
Amphetamine	140	−87.2 (−60.4 to −113.9)*	17.7 (−6.5 to 41.8)[4]	−87.2 (−113.9 to −60.4)*
Methamphetamine	173	−57.3 (−23.6 to −90.9)*	−44.3 (−17.2 to −71.5)*	−12.9 (−46.4 to −20.6)
MDMA	173	−53.4 (−36.9 to −69.8)*	−57.0 (−43.7 to −70.3)*	3.6 (−12.8 to 20.0)
Benzoylecgonine	173	−139 (−110 to −167)*	−130 (−107 to −153)*	−8.0 (−36.3 to 20.3)
Adjusted				
Amphetamine	140	−141.2 (−187.0 to −95.4)*	20.6 (−20.7 to 62.0)[5]	−161.8 (−207.1 to −116.5)*
Methamphetamine	173	−52.6 (−83.1 to −22.0)*	−44.7 (−69.4 to −20.0)*,[6]	−7.9 (−38.3 to 22.6)
Benzoylecgonine	173	−102 (−125 to −79)*	−102 (−120 to −83)*	−0.1 (−22.9 to 22.7)

* Significance based on normal assumptions, $p < 0.05$. [1] mg/day per 1,000 inhabitants 15–64 years. [2] The regression analysis controlled for calendar trend and weekend sampling. Online supplementary Table S2 shows the complete results. [3] VEAS as the reference plant. [4] Excluding one influential measurement yielded a significant result, 27.6, CI (7.3–47.9). [5] Excluding one influential point yielded a significant result, 38.9, CI (5.5–72.4). [6] Excluding one influential point yielded no significant result 4.8, CI (−23.4 to 33.1).

for MDMA at Knappen WWTP (from non-significant to significant), see footnote in Table 2.

Further, in order to examine the influence on trends of additional time-varying factors of assumed relevance, the regression models were re-run, adjusting for drug purity. Results presented in Table 2, fourth column, suggest that three out of eight trend estimates were no longer statistically significant after this adjustment.

Finally, the differences across WWTP were statistically assessed. Table 3 indicates that there were significant differences in mean loads across the WWTPs.

Both unadjusted and purity-adjusted coefficients suggested lower mean daily loads for all drugs examined at Knappen (located in Bergen) compared to VEAS (based in Oslo). At SNJ (Stavanger/Sandnes), the estimates for methamphetamine, MDMA, and benzoylecgonine point-

ed in the same direction, indicating lower mean daily loads at this plant compared to VEAS. Finally, the comparison of Knappen to SNJ suggested a significant difference in amphetamine loads only. A complete set of results, including weekday and trend estimates, are shown in online supplementary Table S2.

Before interpreting these results as *city* differences, the representativeness of each plant's catchment area should be assessed. Unfortunately, no ideal indicator for representativeness was available for this project. Still, for illustrative purposes only, we conducted a simple assessment based on a less-than-ideal variable. The chosen indicator was the number of designated living quarters for high-risk drug users, and the idea was the following: if a catchment area covered the same proportion of the city population and of the per capita number of beds in such living quarters, mean daily loads from the WWTP could be assumed representative of the city's high-risk drug use.

The VEAS catchment area covered approximately the same proportion of beds as the population aged 15–64 years in Oslo (73% of beds vs. 76% of the population). SNJ covered all beds and the entire population of Stavanger/Sandnes, while the Knappen catchment area covered 12% of the designated beds and 25% of the population aged 15–64 years. According to this rather over-simplified indicator, the catchment area of Knappen may not be representative of Bergen city, while comparison of the overall use of stimulants between Oslo and Stavanger (VEAS vs. SNJ) would be valid.

Discussion

This study has aimed to illustrate some critical challenges in interpreting WBE results related to (i) levels, (ii) trends, and (iii) between-city comparison of drug use by in-depth analysis of treatment plant level data sets over a 3-year time period. The essential question was whether, or to what extent, load levels and variation in these reflected levels in drug consumption as well as temporal and spatial changes.

Estimation of Levels and Short-Term Variation

The plots (Fig. 1) and statistical measures (Table 1) showed large short-term variation in population-normalized daily load levels (quantity per 1,000 inhabitants 15–64 years of age) for each of the four substances being studied. Daily load measurements varied by several hundred per cent within a short period of time, e.g., min/max values for daily population-normalized loads were 6.1/453.9 for amphetamine and 9.4/675.9 for methamphetamine. Similar variations have been observed in several other studies [12, 18, 20, 21, 24, 25]. However, whether the revealed variation at the three WWTPs reflects actual fluctuations in drug consumption is not possible to fully assess, as there is no existing data source that could confirm or validate the observed drug-using pattern. An ideal validation would require detailed consumption data for a representative sample of persons using drugs in a catchment area, preferably measured on a daily basis, and for the same observation period.

One may only speculate on whether the observed pattern reflects changes in drug-use preferences, e.g., increased use during festivals or local celebrations (differences across weekdays/weekends are already accounted for). Notably, such changes may have greater impact on observation in daily loads in smaller (in terms of population size) compared to larger catchment areas. The catchment areas in this study are however of comparable size of many plants in, e.g., the pan-European SCORE study that includes more than 140 cities (https://www.emcdda.europa.eu/publications/html/pods/waste-water-analysis_en#sourceData), and the coefficients of variation (Table 1) do not support the claim that plants/catchment areas covering fewest people show the largest variation. The observed pattern could of course, alternatively, be explained by changes on the supply side, like short-time shortages of drug availability. The varying pattern may also illustrate some of the above-mentioned problems of wastewater-based technology such as leak, overflows, plant characteristics of chemical procedures, or a combination of the three.

Irrespective of causes, however, it is essential to take the substantial variation in mean load levels into account when designing sample collection protocols. The SCORE wastewater study is based on a common protocol where samples are collected daily in one designed week [38]. A similar sampling procedure was used in a recent study examining the effect of COVID-19 lockdowns on drug use in seven cities [9]. Figure 1 suggests that the outcome for amphetamines in Oslo would differ extensively depending on the week of data collection, whether one compares weeks across the calendar year or compare the same week/dates across years. While large short-term variation in load values does not devalue WBE as a useful supplement to other drug monitoring tools, it should influence decisions made on sample collection procedures. Several samples over a relatively large time period will be required to obtain precise estimates. A power calculation ahead of data collection start-up could help ensuring that

estimated consumption levels are based on a sufficient number of samples to achieve an acceptable degree of uncertainty (not too wide confidence intervals).

Trends and Purity Adjustment

Figure 1 further suggests trends in drug use over the study period, and Table 2 presents the trend estimates. Both unadjusted and adjusted figures for changes in drug purity are shown. As with the mean load calculations, the precision of trend estimates was influenced by the substantial variation in daily loads and by extreme values. Again, increasing the number of samples and carefully examining the effects of influential points would likely improve the usefulness of WBE. Finally, the significance of several trends and weekend/weekday estimates in trend analyses changed after removal of one influential measurement (see Tables 2, 3; online suppl. Tables S1, S2). As a sufficiently large number of data points may not always be available, interpretation of trend estimates should keep these well-known statistical facts in mind.

In terms of interpretation, it is key to recognize that an increasing trend in volumes of a substance detected is complex and can be linked to a range of consumption and market-related factors [18, 20, 29, 32]. Importantly, there is a need to explore the factors underpinning the increase (more consumers, increased individual consumption, drug purity increases, or any combination of these). Triangulation with additional trend indicators may help to better understand and validate the findings.

National purity data for each of the four drugs were used in this paper. Local purity trends would have been preferable but were not available in this case. Further, it is not clear to what extent the mean purity level of drug seizures accurately reflects the purity level of the drugs being consumed. In case of a general increase in purity, drug tolerance may lead drug users to consume about the same *weight* of drugs over time. If so, an increasing trend in load levels can be observed without a corresponding increase in the number of users. When some of our trend estimates remained significant after the purity adjustment, it may suggest that the increase, at least partly, was due to an increased number of users. Alternative interpretations are of course possible too [31], and additional, local indicators would be required to better validate any interpretation. The point we make is simply to bear in mind the possible influence of unobserved factors when assessing trends in calculated loads and add, if possible, more drug-using variables into the models for trend analysis.

Comparison across WWTP

An important role of WBE has been to compare results across plants. Observed differences have been interpreted as between-city variation in drug use [39–42]. The results in Table 3 suggest that there were significant differences in loads for VEAS WWTP compared to Knappen and SNJ WWTPs. However, whether it is reasonable to interpret the results as being indicative of differences in overall consumption of stimulants in Oslo, Bergen, and Stavanger/Sandnes is disputable. Disregarding potential measurement biases, this would depend on whether the catchment area of each plant was representative of drug users for the city in which it was located.

Representativeness of WWTPs is only an issue when two or more plants cover separate districts of the same city. A study from Milan, Italy, provides an example of such a case [34]. There were three WWTPs in the city, and the WBE results for three WWTPs varied substantially, implying that the overall city estimate would differ correspondingly if it was based on results from one plant alone. When two or more plants exist, their representativeness should be examined before results from one plant are used to represent the city average. As obvious as this may sound and although the representativeness of a WWTPs catchment area for a city is being increasingly acknowledged, comparisons that disregard this aspect are commonly seen in the WBE literature [15, 41, 43].

One pronounced problem is finding local indicators for drug use that follow the boundaries for catchment areas. Relevant indicators will vary by drug, local drug-using cultures, and data availability. The indicator of designated beds was simply used to illustrate the methodological point of interest, and other, likely better, local indicators may be applied in other settings.

Conclusions

WBE that is ethically and carefully integrated to complement other drug epidemiological methods offer a useful tool for comprehensive and agile drug monitoring systems. It is non-invasive, timely, cost-effective, and has the potential to provide useful local indicators of drug-use patterns and trends. Nevertheless, a carefully designed sampling procedure and a relatively large number of daily samples will be required to obtain estimates of sufficient precision to be useful, and analysis alongside additional trend variables will improve the interpretation of WBE findings. Finally, when using mean load levels for different WWTPs to assess spatial variation in drug use,

the representativeness of the catchment area needs to be evaluated before interpreting observed changes as city differences.

Acknowledgments

The authors gratefully acknowledge the important contributions to this work by Kevin V. Thomas (NIVA), Malcolm Reid (NIVA), and Jose Antonio Baz-Lomba (NIVA). Kevin V. Thomas is currently working at the Queensland Alliance for Environmental Health Sciences (QAEHS), University of Queensland. Kevin V. Thomas (NIVA), Malcolm Reid (NIVA), and Jose Antonio Baz-Lomba (NIVA) took part in the conception and design of the data acquisition system and were solely responsible for the data collection and laboratory analyses.

Statement of Ethics

This study did not involve human subjects or animals.

Conflict of Interest Statement

The authors declare no conflicts of interest.

Funding Sources

The Norwegian Institute of Alcohol and Drug Research (incorporated into the Norwegian Institute of Public Health [NIPH] in 2016) and the Norwegian Institute for Water Research (NIVA) funded the study. The authors received no other sponsorship or funding for the project. Thus, only the research institutions mentioned above had a role in the study design, collection, analysis or interpretation of the data, writing the manuscript, or the decision to submit the paper for publication.

Author Contributions

Anne Line Bretteville-Jensen took part in the conception and design of data acquisition system and contributed to the statistical analysis and writing and approved the final version. Ellen J. Amundsen took part in the conception and design of data acquisition system, conducted literature searches and the statistical analysis, and contributed to writing and approved the final version. Jane Mounteney contributed to writing the manuscript and approved the final version.

Data Availability Statement

All population-normalized loads data analysed during this study are included in this article. Data on drug purity is publicly available (https://www.politiet.no/globalassets/04-aktuelt-tall-og-fakta/narkotika/narkotikastatistikk-2021.pdf).

References

1 Castiglioni S, Bijlsma L, Covaci A, Emke E, Hernandez F, Reid M, et al. Evaluation of uncertainties associated with the determination of community drug use through the measurement of sewage drug biomarkers. Environ Sci Technol. 2013;47(3):1452–60.
2 Castiglioni S, Thomas KV, Kasprzyk-Hordern B, Vandam L, Griffiths P. Testing wastewater to detect illicit drugs: state of the art, potential and research needs. Sci Total Environ. 2014;487:613–20.
3 Gracia-Lor E, Castiglioni S, Bade R, Been F, Castrignano E, Covaci A, et al. Measuring biomarkers in wastewater as a new source of epidemiological information: current state and future perspectives. Environ Int. 2017;99:131–50.
4 Zuccato E, Chiabrando C, Castiglioni S, Bagnati R, Fanelli R. Estimating community drug abuse by wastewater analysis. Environ Health Perspect. 2008;116(8):1027–32.
5 Zuccato E, Chiabrando C, Castiglioni S, Calamari D, Bagnati R, Schiarea S, et al. Cocaine in surface waters: a new evidence-based tool to monitor community drug abuse. Environ Health. 2005;4:14.
6 Feng L, Zhang W, Li X. Monitoring of regional drug abuse through wastewater-based epidemiology: a critical review. Sci China Earth Sci. 2018;61(3):239–55.
7 Wastewater analysis and drugs: a European multi-city study. 2019. Lisbon. European Monitoring Centre for Drugs and Drug Addiction. Available from: http://www.emcdda.europa.eu/topics/pods/waste-water-analysis.
8 Been F, Emke E, Matias J, Baz-Lomba JA, Boogaerts T, Castiglioni S, et al. Changes in drug use in European cities during early COVID-19 lockdowns: a snapshot from wastewater analysis. Environ Int. 2021;153:106540.
9 Reinstadler V, Ausweger V, Grabher AL, Kreidl M, Huber S, Grander J, et al. Monitoring drug consumption in Innsbruck during coronavirus disease 2019 (COVID-19) lockdown by wastewater analysis. Sci Total Environ. 2021 Feb 25;757:144006.
10 Gracia-Lor E, Zuccato E, Castiglioni S. Refining correction factors for back-calculation of illicit drug use. Sci Total Environ. 2016;573:1648–59.
11 Jones HE, Hickman M, Kasprzyk-Hordern B, Welton NJ, Baker DR, Ades AE. Illicit and pharmaceutical drug consumption estimated via wastewater analysis. Part B: placing back-calculations in a formal statistical framework. Sci Total Environ. 2014;487:642–50.
12 Lai FY, Wilkins C, Thai P, Mueller JF. An exploratory wastewater analysis study of drug use in Auckland, New Zealand. Drug Alcohol Rev. 2017;36(5):597–601.
13 Zarei S, Salimi Y, Repo E, Daglioglu N, Safaei Z, Guzel E, et al. A global systematic review and meta-analysis on illicit drug consumption rate through wastewater-based epidemiology. Environ Sci Pollut Res. 2020;27(29):36037–51.
14 European drug report 2021: trends and developments. Luxembourgh: European Monitoring Centre for Drug and Drug Addiction; 2021.
15 Gonzalez-Marino I, Baz-Lomba JA, Alygizakis NA, Andres-Costa MJ, Bade R, Bannwarth A, et al. Spatio-temporal assessment of illicit drug use at large scale: evidence from seven dears of international wastewater monitoring. Addiction. 2020;115(1):109–20.

16 Banta-Green CJ, Field JA, Chiaia AC, Sudakin DL, Power L, de Montigny L. The spatial epidemiology of cocaine, methamphetamine and 3, 4-methylenedioxymethamphetamine (MDMA) use: a demonstration using a population measure of community drug load derived from municipal wastewater. Addiction. 2009;104(11):1874–80.
17 Bodik I, Mackul'ak T, Faberova M, Ivanova L. Occurrence of illicit drugs and selected pharmaceuticals in Slovak municipal wastewater. Environ Sci Pollut Res. 2016;23(20):21098–105.
18 Lai FY, O'Brien J, Thai PK, Hall WD, Mueller J. Trends in methamphetamine residues in wastewater in metropolitan and regional cities in South-East Queensland, 2009–2015. Med J Aust. 2016;204(4):151–2.
19 Reid MJ, Langford KH, Morland J, Thomas KV. Quantitative assessment of time dependent drug-use trends by the analysis of drugs and related metabolites in raw sewage. Drug Alcohol Depend. 2011;119(3):179–86.
20 Tscharke BJ, Chen C, Gerber JP, White JM. Temporal trends in drug use in Adelaide, South Australia by wastewater analysis. Sci Total Environ. 2016;565:384–91.
21 van Nuijs ALN, Mougel J-F, Tarcomnicu I, Bervoets L, Blust R, Jorens PG, et al. Sewage epidemiology: a real-time approach to estimate the consumption of illicit drugs in Brussels, Belgium. Environ Int. 2011;37(3):612–21.
22 Lancaster K, Ritter A, Valentine K, Rhodes T. "A more accurate understanding of drug use": a critical analysis of wastewater analysis technology for drug policy. Int J Drug Policy. 2019;63:47–55.
23 Hall W, Prichard J, Kirkbride P, Bruno R, Thai PK, Gartner C, et al. An analysis of ethical issues in using wastewater analysis to monitor illicit drug use. Addiction. 2012;107(10):1767–73.
24 Lai FY, O'Brien JW, Thai PK, Hall W, Chan G, Bruno R, et al. Cocaine, MDMA and methamphetamine residues in wastewater: consumption trends (2009–2015) in South East Queensland, Australia. Sci Total Environ. 2016;568:803–9.
25 Ort C, Eppler JM, Scheidegger A, Rieckermann J, Kinzig M, Sorgel F. Challenges of surveying wastewater drug loads of small populations and generalizable aspects on optimizing monitoring design. Addiction. 2014;109(3):472–81.
26 van Nuijs ALN, Lai FY, Been F, Andres-Costa MJ, Barron L, Baz-Lomba JA, et al. Multi-year inter-laboratory exercises for the analysis of illicit drugs and metabolites in wastewater: development of a quality control system. Trac-Trends Anal Chem. 2018;103:34–43.
27 Emke E, Vughs D, Kolkman A, de Voogt P. Wastewater-based epidemiology generated forensic information: amphetamine synthesis waste and its impact on a small sewage treatment plant. Forensic Sci Int. 2018;286:e1–7.
28 Langa I, Goncalves R, Tiritan ME, Ribeiro C. Wastewater analysis of psychoactive drugs: non-enantioselective vs enantioselective methods for estimation of consumption. Forensic Sci Int. 2021;325:110873.
29 Krizman-Matasic I, Senta I, Kostanjevecki P, Ahel M, Terzic S. Long-term monitoring of drug consumption patterns in a large-sized European city using wastewater-based epidemiology: comparison of two sampling schemes for the assessment of multiannual trends. Sci Total Environ. 2019;647:474–85.
30 Banta-Green CJ, Brewer AJ, Ort C, Helsel DR, Williams JR, Field JA. Using wastewater-based epidemiology to estimate drug consumption-statistical analyses and data presentation. Sci Total Environ. 2016;568:856–63.
31 Bruno R, Edirisinghe M, Hall W, Mueller JF, Lai FY, O'Brien JW, et al. Association between purity of drug seizures and illicit drug loads measured in wastewater in a South East Queensland catchment over a six year period. Sci Total Environ. 2018;635:779–83.
32 Goulding N, Hickman M, Reid M, Amundsen EJ, Baz-Lomba JA, O'Brien JW, et al. A comparison of trends in wastewater-based data and traditional epidemiological indicators of stimulant consumption in three locations. Addiction. 2020;115(3):462–72.
33 Jones HE, Goulding N, Hickman M. Commentary on Lai et al (2018): potential and limitations of wastewater-based epidemiology in monitoring substance use. Addiction. 2018;113(6):1137–8.
34 Castiglioni S, Borsotti A, Riva F, Zuccato E. Illicit drug consumption estimated by wastewater analysis in different districts of Milan: a case study. Drug Alcohol Rev. 2016;35(2):128–32.
35 Baz-Lomba JA, Love ASC, Reid MJ, Olafsdottir K, Thomas KV. A high-throughput solid-phase microextraction and post-loop mixing large volume injection method for water samples. J Chromatogr A. 2018;1531:32–8.
36 Narkotika- og dopingstatistikk 2016 (In English: Drug and doping statistics 2016) Oslo: Kripos Den nasjonale enhet for bekjempelse av organisert og annen alvorlig kriminalitet (In English: National Crime Investigation Service). 2017.
37 Narkotika- og dopingstatistikk 2021 (In English: Drug and doping statistics 2021) Oslo: Kripos Den nasjonale enhet for bekjempelse av organisert og annen alvorlig kriminalitet (In English: National Crime Investigation Service). 2021.
38 SCORE SCORE. 2022. Available from: https://score-network.eu/about/.
39 Eurpean drug report 2019: trends and developements. 2019. Luxembourg. European Monitoring Centre for Drugs and Drugs Addiction.
40 Been F, Bijlsma L, Benaglia L, Berset JD, Botero-Coy AM, Castiglioni S, et al. Assessing geographical differences in illicit drug consumption: a comparison of results from epidemiological and wastewater data in Germany and Switzerland. Drug Alcohol Depend. 2016;161:189–99.
41 Love ASC, Baz-Lomba JA, Reid MJ, Kankaanpaa A, Gunnar T, Dam M, et al. Analysis of stimulant drugs in the wastewater of five Nordic capitals. Sci Total Environ. 2018;627:1039–47.
42 Ort C, Van Nuijs ALN, Berset J-D, Bijlsma L, Castiglioni S, Covaci A, et al. Spatial differences and temporal changes in illicit drug use in Europe quantified by wastewater analysis. Addiction. 2014;109(8):1338–52.
43 Krizman I, Senta I, Ahel M, Terzic S. Wastewater-based assessment of regional and temporal consumption patterns of illicit drugs and therapeutic opioids in Croatia. Sci Total Environ. 2016;566-567:454–62.