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Long-term wastewater-based surveillance and impacts of the COVID-19 pandemic on drug use trends in a U.S. Northeast rural town

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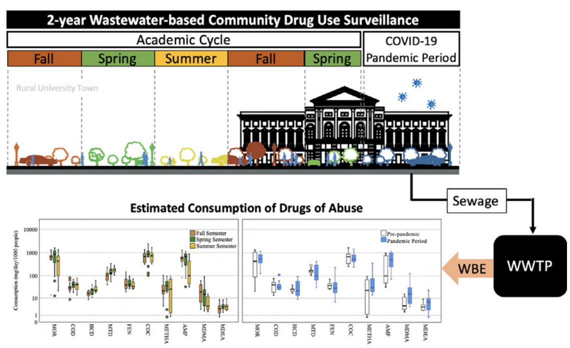
HIGHLIGHTS

- Two-year wastewater-based surveillance of drug use in a university town
- First report on rural town drug use via WBE monitoring during COVID-19 pandemic
- 100 % detection of abused drugs, including fentanyl, in sewage
- Notable differences in drug use on weekdays/weekends and during academic cycles
- Notable increase in MDMA consumption during pandemic period

GRAPHICAL ABSTRACT



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ABSTRACT

Herein we discuss the findings of a two-year wastewater-based drug use surveillance from September 2018 to August 2020 and present objective evidence on the impacts of the COVID-19 pandemic on drug use in a rural community. 24-h composite wastewater samples were collected twice each month from a university town in Northeastern United States and were analyzed for ten priority opioids and stimulants: morphine, codeine, hydrocodone, methadone, fentanyl cocaine, methamphetamine, amphetamine, 3,4-methylenedioxymethamphetamine (MDMA), and 3,4-methylenedioxy-N-ethylamphetamine (MDEA). All target drugs were detected at 100 % frequency in wastewater samples. On a mass basis, the average estimated per capita drug consumption were highest for cocaine, morphine, and amphetamine, and lowest for MDMA, MDEA, and hydrocodone. Furthermore, the estimated per capita consumption of fentanyl was higher than previous reports from rural and university settings in the U.S. Generally, drug consumption was higher during the spring semesters, with year-on-year semester increases also noted over the 2-y study period. Except for methadone and cocaine, the estimated average per capita consumption of drugs increased over the pandemic period, with the highest increase noted for MDMA (286 % increase compared to baseline, $p = 0.016$). Estimated average consumption of methadone and cocaine decreased slightly by 6 % and 7 %, respectively. These results demonstrate the utility and strength of wastewater-based approaches in capturing long-term and evolving trends in drug use within communities. Our study findings reflect the regionwide problem with opioid-related overdoses and increasing stimulant prescription rates. Our findings also provide objective data and insights for health policymakers on the effects of the pandemic period on community drug use in a rural U.S. town.

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1. Introduction

Drug abuse and misuse is a global health crisis that has been exacerbated by the COVID-19 pandemic. According to a recent report from the United Nations, nearly half a million lives in 2019 were lost due to drug use and 18 M healthy lives were lost due to drug use disorders, mainly attributed to opioids (United Nations Office on Drugs and Crime, 2021). Drug use continues to increase worldwide and has reached 275 M people in 2019 (United Nations Office on Drugs and Crime, 2021). Consumption rates across age groups are also increasing for certain drugs (e.g., opioids, stimulants) (National Institute on Drug Abuse, 2021). This trend is more pronounced in the United States (U.S.), where over 88,000 drug overdose deaths occurred in 2020, up by 27 % from 2019 (Kiernan, 2021). States in Northeastern U.S. have among the highest drug use rates in the country.

The highest levels of drug use are seen among young adults (18–25 years old) (United Nations Office on Drugs and Crime, 2021). There is increasing research on prescription drug misuse among university students (Bennett and Holloway, 2017), highlighting the importance of understanding and monitoring drug use behaviors in university settings. However, data on drug use in rural areas are scarce (Dombrowski et al., 2016). Rural areas tend to have limited access to health services (Substance Abuse and Mental Health Services Administration, 2019), and alternative tools for drug use surveillance are desirable to guide and evaluate policies for strategic health interventions.

Drug use intervention and treatment programs rely on timely availability of drug use data, which are traditionally obtained via survey-based methods. In recent years, wastewater analysis (i.e., wastewater-based epidemiology or WBE) has been developed and piloted for community drug use surveillance (Daughton, 2001; Gao et al., 2015). In this method, measured drug concentrations in wastewater are used to back-calculate average community consumption (Daughton, 2001). WBE is rapid compared to survey data, cost-efficient, and generates objective drug use data that can complement traditional drug use surveillance (Pagsuyoin et al., 2015). WBE has been widely implemented in tracking evolving drug use trends in Europe (Hummel et al., 2006; Valcarcel et al., 2012; Zuccato et al., 2008a; Zuccato et al., 2008b), Asia (Kim et al., 2015), and Australia (Lai et al., 2016; Lai et al., 2018). Recent applications in the U.S. focused on monitoring drug use in dorms and campuses (Gushgari et al., 2018; Heuett et al., 2015), prisons (Brewer et al., 2016), small towns and cities (Banta-Green et al., 2009; Bishop et al., 2020; Foppe et al., 2018; Subedi and Kannan, 2014), and during sports events (Montgomery et al., 2020).

In the present work, we performed a 2-y drug use surveillance in a small rural university town in the U.S. Northeast. Specifically, we aimed to examine temporal trends in drug consumption over academic seasons and weekends/weekdays, and identify co-occurrence trends across drugs. Incidentally, the monitoring period coincided with the onset of the COVID-19 pandemic period, thus a subset analysis was carried out to examine drug use changes during the pandemic. A total of 10 priority drugs of abuse (Table 1) were included in the study based on their reported high consumption in populations: the opioids morphine, codeine, hydrocodone, methadone, fentanyl; and the stimulants cocaine, methamphetamine, amphetamine, 3,4-methylenedioxymethamphetamine (MDMA), and 3,4-methylenedioxy-N-ethylamphetamine (MDEA). These drugs are abused through illicit routes or misused prescription. Except for MDMA and MDEA, these drugs are classified as Schedule II controlled substances in the United States, indicating they currently have known medical uses but also have high potential for abuse. MDMA and MDEA are amphetamine-type stimulants commonly used as recreational drugs and have no currently accepted medical use (United States Controlled Substances Act, 2012).

To the authors' knowledge, this study is the first report of a long-term wastewater-based surveillance of community drug use in a rural university town that covers the COVID-19 pandemic period. The pandemic presented unique and complex challenges in addiction treatment and in the drug market dynamics, including disruptions to treatment services for substance abuse patients (Volkow, 2020) and disruptions in the drug supply chain (United Nations Office on Drugs and Crime, 2020). Recent data suggest that the drug overdoses in the United States worsened during the pandemic, including in already vulnerable rural areas (American Medical Association, 2021). The findings of the present study provide objective data and insights on the effects of the pandemic period on community drug use in a rural U.S. town and support the adoption of WBE as a monitoring tool to complement traditional drug use surveillance methods.

2. Methods

2.1. Chemicals and reagents

High purity reagent chemicals (HPLC-grade methanol, ethyl acetate, formic acid, ammonium hydroxide) were purchased from Sigma Aldrich (St. Louis, MO). Drug analyte standards and their individual labeled analogs were sourced from Cerilliant as solutions in methanol or acetonitrile. Individual analyte stock solutions were prepared in methanol at a concentration of 10 or 100 μg/mL and stored in the dark at −20 °C until use. Mixed standard solutions were prepared in methanol and diluted as necessary to prepare working solutions on the day of use. Ultrapure water was prepared on site and was used in analyte extractions and chromatographic analyses.

2.2. Sewershed area and sample collection

The study area is a rural town in Northeastern U.S. that is home to one large university and four smaller colleges. Two of these academic institutions (university and one college) discharge sewage to the WWTP. The census-estimated resident population is approximately 25,000 (United States Census Bureau, 2020), of which 55.7 % are within the ages of 18 to 24 years old (United States Census Bureau, 2010). Based on their historical flow data, the WWTP estimates that transient student populations contribute an additional 20,000–30,000 to the town population during regular academic calendars (September–December and mid-January to mid-May). The university offers on-campus housing to approximately 60 % of its student population; off-campus housing is also available in the northern and southern parts of the town. The WWTP receives an average flow of approximately 2–4 MGD, which is almost entirely residential with very little

Table 1
Target drug analytes and their common uses.

Drug class	Drug analyte (CODE)	CSA schedule[a]	Uses
Opioids	Morphine (MOR)	II	Treatment for moderate to severe pain
	Codeine (COD)	II	Treatment for mild to moderately severe pain and cough relief
	Hydrocodone (HCD)	II	Treatment for severe pain
	Methadone (MTD)	II	Treatment for pain relief and drug addiction detoxification
	Fentanyl (FEN)	II	Treatment for moderate to severe chronic pain
Stimulants	Cocaine (COC)	II	Stimulant often abused as a recreational drug
	Methamphetamine (METHA)	II	Treatment for attention deficit hyperactivity disorder and obesity
	Amphetamine (AMP)	II	Treatment for attention deficit hyperactivity disorder
	3,4-methylenedioxymethamphetamine (MDMA)	I	Stimulant often abused as a recreational drug
	3,4-methylenedioxy-N-ethylamphetamine (MDEA)	I	Stimulant often abused as a recreational drug

[a] Source: US Department of Justice Drug Enforcement Administration ((United States Controlled Substances Act, 2012).

commercial and industrial inputs. The sewer drain system is separate. Statewide travel restrictions during COVID pandemic took effect on March 24, 2020 (Massachusetts Department of Public Health, 2021), nearly 2 weeks after Spring break started although students were advised not to return to campus after their break. Phased re-opening began on May 18, 2020 for essential businesses (manufacturing, construction) and July 6, 2020 for other sectors (retail, restaurants) (Commonwealth of Massachusetts, 2023). Schools remained mostly remote the following Fall 2020 semester outside the study monitoring period.

Influent wastewater samples were collected from the WWTP twice each month (Monday and Thursday of the second week of each month) over two years (September 2018–August 2020). Samples were collected on dry days, i.e., no recorded precipitation on ~85 % of sampling days and with maximum recorded precipitation of only 0.5–0.6 in on 6 % of sampling days. Local climate is characterized as humid continental, with annual precipitation of 48 in (National Oceanic and Atmospheric Administration Centers for Environmental Information, 2021). The Monday sample from September 2018 was missed due to miscommunication (sample was not set aside by WWTP personnel). Samples were collected in the early morning and represented a volume-averaged composite of the past 24 h. As such, Monday samples represented weekend sampling and Thursday samples represented mid-week sampling. Samples were collected in 1 L amber glass bottles from the outflow of the preliminary screen and were preserved on-site via addition of 1 mL 0.2 g/L sodium azide and were kept at 4 °C during transport and prior to processing in the laboratory. The sampling bottles were acid-washed, triple-rinsed in ultrapure water, and rinsed with methanol prior to sample collection. Wastewater samples were processed within 24 h of collection. Additional operational data (daily flow, carbonaceous biological oxygen demand or cBOD) for each sampling date were provided by the wastewater facility.

2.3. Sample processing and analysis

Influent samples were shaken, and 250 mL aliquots were filtered through 1.0 μm glass fiber filters (type A/E; VWR, PA, USA). Filtered samples were each spiked with 30 ng labeled standards and then analytes were extracted via solid phase extraction with Strata-X (200 mg/6 mL) cartridges. The cartridges were pre-conditioned with 10 mL methanol, equilibrated with 10 mL ultrapure water, loaded with filtered wastewater at a flow rate of 2 mL/min, washed with 10 mL 5 % methanol in water, and sequentially eluted with 5 mL methanol with 2 % formic acid, 2 mL ethyl acetate: isopropanol (85:15, v/v), and 3 mL methanol with 5 % ammonium hydroxide. The eluted samples were evaporated to dryness in a vacuum oven and then reconstituted in 0.5 mL of methanol:water (1:9, v/v).

Target analyte concentrations were quantified via isotope dilution using a Shimadzu ultra-fast liquid chromatograph interfaced to a triple quadrupole mass spectrometer (AB SCIEX API 4000) equipped with an electrospray ionization source. Chromatographic separation was achieved in a C18 column (Kinetex® 2.6 μm, 100 mm × 4.6 mm) using a gradient mobile phase consisting of 0.1 % formic acid in water and 0.1 % formic acid in methanol (Supporting information, Table SI.A). MRM transitions for each drug analyte are summarized in Table SI·B (Supporting Information). Quantitation was performed in Analyst software (version 1.7, AB SCIEX), using the internal standard method (by plotting the ratio of peak areas of the analyte/internal standard of each target analyte vs. the ratios of concentrations of analyte/internal standard). Analyte recoveries ranged from 87 %–116 % and are summarized in Table SII alongside analyte detection and quantification limits.

2.4. Back-calculation of community drug use

The averaged consumption rate of each drug i (CR_i) was estimated using the mass load model in Eq. (1) (Zuccato et al., 2008a; Zuccato et al., 2008b).

$$CR_i = \frac{C_i \times Q \times CF_i}{P} \tag{1}$$

where C_i is concentration of the parent drug or main metabolite in the influent, Q is the influent flowrate, CF_i is a correction factor that accounts for pharmacokinetics and drug stability in sewage, and P is the sewershed population. The CF values for the drug analytes are taken from Zuccato et al. (Zuccato et al., 2008a; Zuccato et al., 2008b) and are summarized in Table SIII. Different methods have been previously used to estimate mobile sewershed population; commonly used population proxies include hydrochemical parameters (e.g., oxygen demand, nutrients) (Zheng et al., 2019), anthropogenic biochemical markers (e.g., creatinine; (Centazzo et al., 2019)), and cellular signal (Thomas et al., 2017). The advantages and limitations of these methods have been discussed elsewhere (Croft et al., 2020; Thomas et al., 2017). Van Nuijs et al. (Van Nuijs et al., 2011) noted good agreements between population estimates from oxygen demand and nutrients. For simplicity and considering the availability of temporal wastewater data from the WWTP and the dry days during the sampling period, this study adopted the method from Castiglioni et al. (Castiglioni et al., 2013) which uses biological oxygen demand, and assuming a daily per capita cBOD load of 0.2 lb. (Castiglioni et al., 2013; Pagsuyoin et al., 2019a; Pagsuyoin et al., 2019b).

2.5. Statistical analysis

Datasets comprised drug consumption estimates and wastewater data from the WWTP. Drug data subsets were formed to analyze co-occurrence patterns and compare trends among specific time periods. For the academic cycle, the fall semester spanned from September to December, spring semester spanned from January to April, and summer spanned from May to August. The COVID-19 pandemic period occurred during the second year of this surveillance study, and spanned from April 2020 to August 2020 (i.e., shorter spring semester in 2019). Each drug data subset was tested for normality (Shapiro-Wilk test) and homogeneity (Levene's test). To compare between data subsets, independent samples t-test and one-way ANOVA (with Tukey's post-hoc test) were performed for normally distributed datasets, while Mann-Whitney and Kruskal Wallis tests (Dunn's post-hoc test) were performed for non-normally distributed datasets, all at 95 % confidence level. Comparisons were done without p-value adjustments since only a few comparisons were performed (academic semesters, weekend/weekday, with/without pandemic). Drug co-occurrence patterns were evaluated using Spearman (due to non-normally distributed data) correlation analysis. All statistical analyses were performed in SPSS (ver. 25, IBM).

3. Results and discussion

3.1. Population estimates

Expectedly, population estimates indicate higher sewershed population during the academic semesters than in summer when schools were not in session (Fig. 1). We note that the summer months in year 2 of this surveillance study occurred within the COVID-19 pandemic period. Population estimates for the fall semester were higher in year 1 than in year 2, with a notable difference between weekend and weekday in November and December in year 1 (indicated by vertical bars). Generally, we aimed to collect influent samples during the Mondays and Thursdays of the second week of the month, however, some sampling days were adjusted when these coincided with holidays when the WWTP was closed to public access or samples were not collected at the WWTP. For example, the October 2018 sampling week covered a holiday long weekend, whereas the October 2019 sampling week did not. The November 2018 sampling also included a Monday coinciding with the start of Thanksgiving recess when most students started their week-long break; whereas this break only started after sampling was completed in November 2019. Furthermore, we note the sharp decline in population estimates in April 2020 during the pandemic period when schools and business establishments shifted to remote operation several days following enforcement of statewide stay-at-home order beginning on March 24, 2020 (Commonwealth of Massachusetts, 2020). Google mobility

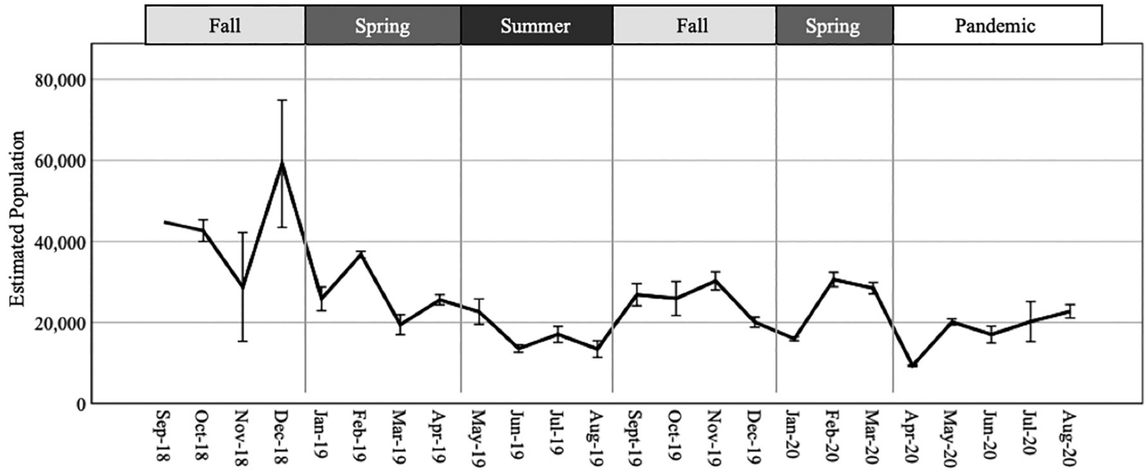

Fig. 1. Population estimates during the 2-year drug surveillance, estimated based on cBOD data provided by the wastewater treatment facility. Vertical bars indicate standard error (SE) of weekend and weekday population estimates for the month. Only the weekday sample was collected in September 2018, hence this data point has no reported SE bar.

data also indicate a sharp decline in population movement within the town for the same period relative to a pre-pandemic baseline (Google, 2022). Collectively, the population trends indicate that population movements within the sewershed are mainly associated with the student population.

3.2. Long-term temporal drug use trends

All target drug analytes were detected in the influent samples at 100 % detection frequency over the 2-y study period. On a mass basis, the average per capita drug consumption rates were highest for cocaine, morphine, and amphetamine, and lowest for MDMA, MDEA, and hydrocodone (Table 2). For comparison, Table 2 also summarizes recently reported WBE estimates of drug consumption in rural towns or university areas in North America, although these previous studies were conducted over a much shorter period. Generally, consumption estimates from the present study are within range of previous studies, with some notable differences. Specifically, this study identified higher fentanyl consumption and lower methamphetamine consumption in the studied rural sewershed. Although local drug overdose data from health centers are limited, opioids, particularly fentanyl and its analogs, are a leading cause of drug overdose fatalities in the region (National Institute on Drug Abuse, 2020; Pagsuyoin et al., 2019a; Pagsuyoin et al., 2019b) mainly via illicit supply routes (Bohler et al., 2019). There have also been anecdotal reports of a recent rise in regional methamphetamine consumption (Padilla, 2019), though this study found relatively stable and low methamphetamine consumption in the rural town.

3.3. Drug co-occurrence trends

Correlation analysis revealed distinct co-occurrence trends for estimated drug consumptions. Among opioids, consumptions of morphine and codeine ($R = 0.77$, $p < 0.01$) and methadone and hydrocodone ($R = 0.86$, $p < 0.01$) were strongly correlated (Supplementary information, Table SIV). Note that while morphine is an opiate commonly used for pain relief, it is also the main metabolite of codeine produced via oxidative demethylation (Thorn et al., 2013), which may partially explain the observed codeine-morphine correlation. Methadone is an opiate analgesic that is also used in medically assisted treatment of drug addiction; alongside hydrocodone, it is among the most common prescription drugs involved in opioid overdose deaths in the U.S. (Centers for Disease Control and Prevention, 2017). Morphine consumption was found to be also strongly correlated with amphetamine consumption ($R = 0.84$, $p < 0.01$) and moderately correlated with cocaine consumption ($R = 0.66$, $p < 0.01$). Combining morphine with powerful stimulants such as amphetamine and cocaine, an example of a "speedball" mixture of opiates and stimulants, is commonly practiced among recreational and addiction users, and is responsible for numerous overdose deaths in recent years (Trujillo et al., 2011).

Table 2
Community Drug Consumption in Rural University Town and in Comparable Areas.

Drug name (code)	This study (in mg/d/1000 people)					Previous Studies in North America (in mg/d/1000 people)	
	Rural university town					University campus	Rural town
	Min.	Max.	Median	Mean	SD	Mean	Mean
Morphine (MOR)	13	1623	611	656	411	18[a]	174, 288[c]; 1780[d]
Codeine (COD)	9	112	32	39	20	50[a]	587, 614, 2000, 2090[c]; 140[d]
Hydrocodone (HCD)	8	95	20	24	17	–	–
Methadone (MTD)	30	421	125	144	86	72[a]	13, 22, 127, 215[c]; 131[d]
Fentanyl (FEN)	7	230	37	49	38	–	1.27[d]
Cocaine (COC)	102	2413	683	758	455	2[b]; 551[a]	3.9[e]; 938[d]
Methamphetamine (METHA)	0.67	354	29	43	55	236[a]	984[c], 6510[c]; 1740[d]
Amphetamine (AMP)	32	1263	573	537	359	2[b]; 256[a]	3.1[e]; 420, 690, 1040, 1710[c]; 967[d]
3,4-methylenedioxy-methamphetamine (MDMA)	2	127	11	21	25	88[a]	1.4[e]; 31, 66[c]
3,4-methylenedioxy-N-ethylamphetamine (MDEA)	0.67	23	4	4	4	–	–

[a] One week of daily sampling per month, over five consecutive months, in a university located in Southwestern U.S. (Gushgari et al., 2018).
[b] Three weeks of daily sampling at the end of spring semester in a university main campus located in Southeastern U.S. (Heuett et al., 2015).
[c] Twenty samples collected over three months from a small micropolitan and a small rural community located in Western U.S. (Bishop et al., 2020).
[d] One week of daily sampling in rural community (predominantly university student population) located in Midwestern U.S. (Skees et al., 2018).
[e] Two weeks of daily sampling in a small city located in Canada. (Yargeau et al., 2014).

For all target drug analytes, monthly averages of estimated drug consumption fluctuated over the 2-y study (Fig. 2). Increases or decreases in the consumption rates for some drugs were observed over certain months within the 2-y period, hence further analyses of drug use over shorter time periods were carried out.

3.4. Drug use trends during academic cycle

A subset analysis of the drug use trends during the academic cycle was carried out using drug consumption estimates for the pre-pandemic months (September 2018–March 2020). Bi-weekly (weekday and weekend) consumption estimates from September to December in 2018 and 2019 were included in the fall semester dataset ($n = 15$). Estimates from January to April in 2019 and January to March in 2020 were included in the spring semester dataset ($n = 14$). Estimates from May to August in 2019 were included in the summer dataset ($n = 8$). For each of the 10 target drugs, average consumption rates varied over the three periods of the academic cycle (Fig. 3), although the seasonal estimates statistically differ only for hydrocodone and methadone (both $p = 0.012$; Supplementary information, Table SV), both of which had lowest consumption rates during the fall semesters. Except for methadone and MDMA, average drug consumption rates were highest during the spring semesters. The average consumption rate for the following drugs were lowest during the summer months: morphine, fentanyl, amphetamine, and MDMA. Year-on-year analysis of the

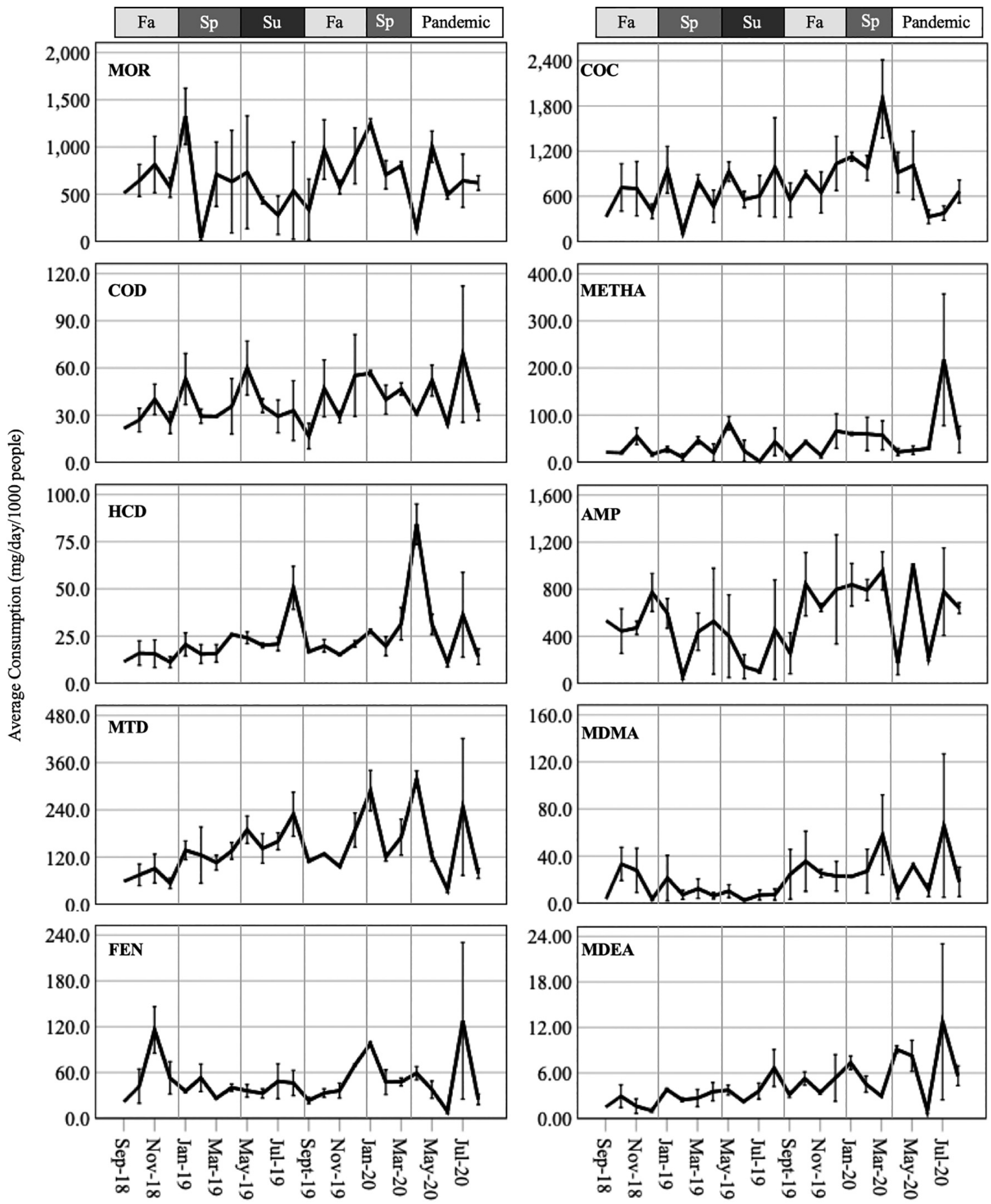

Fig. 2. Temporal trends in average community drug consumption for opioids (left panel) and stimulants (right panel) in a rural university town. Vertical bars indicate standard error of the average weekend and weekday estimates for the month.

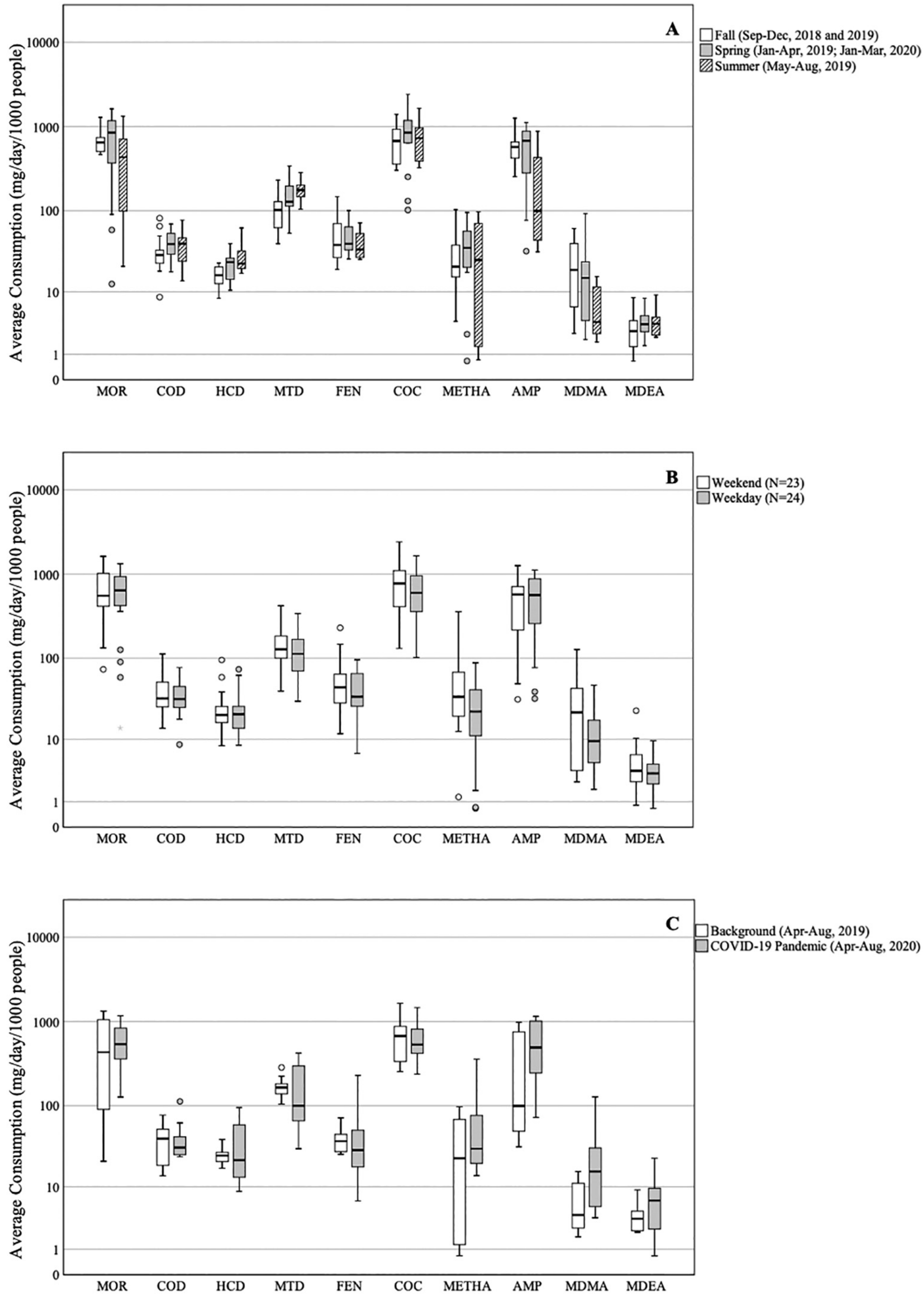

Fig. 3. Comparison of estimated average drug consumption rates within semesters during academic cycle (A), between weekday and weekend (B) and pre- and during COVID-19 pandemic period (C). Horizontal bars in boxes represent median values.

fall semester drug use dataset indicated statistical increase ($p < 0.05$) in consumption rates of methadone and MDEA in year 2 (83 % and 100 % increase, respectively, compared to year 1; Supplementary information, Fig. SI). Year-on-year analysis of the spring semester drug use dataset indicated statistical increase ($p < 0.05$) in consumption rates in year 2 for cocaine (128 % increase), methamphetamine (127 % increase), amphetamine (113 % increase), and MDMA (200 %) (Supplementary information, Fig. SII).

A recent meta-analysis of literature data found that the most prevalent motives for prescription drug misuse among university students are related to health management and sports and academic performance, with fewer than half of users using drugs for pleasure purposes [1]. Increased use of the opioids hydrocodone (Gul et al., 2016) and methadone (Stamper et al., 2016) have been reported during college football events, though no similar pattern was observed for morphine and codeine (Gul et al., 2016). The season for major sports events in our studied rural town occurs during the fall semester; however, our sampling days did not coincide with major sport events, except for a weekend hockey game in a university campus during the Thanksgiving break in 2018. Our WBE data also did not indicate sudden peaks in opioids use during any fall weekend.

Previous WBE studies of on-campus drug use report varying findings with respect to stimulant use. In a Miami, Florida university campus, average amphetamine consumption remained relatively constant at the beginning, middle and end of the semester, although larger variability was observed towards the end of the semester (Heuett et al., 2015). In another

WBE study at a southwestern university, amphetamine consumption was found to increase during exam periods (midterms and finals), with as high as a 760 % increase from baseline levels during finals week (end of the semester) (Burgard et al., 2013). Our study found large variabilities in amphetamine consumption throughout the 2-y surveillance period that no discernable trend (increase or decrease) could be established for exam periods. Nonetheless, our year-on-year WBE data in the rural town reflect the regional trend in stimulant prescription rates, which has shown yearly increases in the last decade. The most recent national registry indicates that the region currently leads in prescription rates in the nation (Bebinger, 2021).

3.5. Drug use trends on weekdays and weekends

A subset analysis of drug use trends for weekends ($n = 23$) and weekdays ($n = 24$) was carried out using drug use estimates from the 2-year study. Although higher estimated weekend consumption was observed for methadone, fentanyl, cocaine, methamphetamine, and MDMA, and higher weekday consumption was observed for morphine and amphetamine (Fig. 3B), the weekend/weekday estimates were not statistically different (at 95 % confidence); Supplementary information, Table SVI). A WBE study in a U.S. university campus also reported no statistically significant difference between weekend and weekday opioid mass loads, though amphetamine mass load was found to be higher on weekdays than on weekends and was attributed to academic-related stress (Gushgari et al., 2018). Higher weekday consumption for amphetamine was also noted at the end of Spring semester (last 3 weeks) in a college campus in Miami, Florida (Heuett et al., 2015). MDMA consumption in a small Canadian city (population of 75,000) peaked on weekends (Yargeau et al., 2014), as did cocaine consumption in European cities (Van Nuijs et al., 2009) and in a municipality in the U.S. Pacific Northwest (Brewer et al., 2012).

3.6. Impacts of COVID-19 pandemic on abused drug use

The early phase of the COVID-19 pandemic overlapped with the last quarter of our 2-y drug use surveillance. Following region-wide travel restrictions, schools and non-essential businesses were closed and transitioned to remote operation on March 24, 2020. This otherwise unfortunate event provided us an opportunity to examine how the pandemic affected drug use trends in the rural town, particularly in the absence of non-local students and commuters (i.e., people who resided outside of the rural town). In a subset analysis, we compared estimated drug consumption rates in the last five months of school closures (April–August in 2020, $n = 10$) with estimates from the same period in the previous year (April–August in 2019, n = 10) as baseline (Fig. 3C). Except for methadone, estimated opioid consumption rates increased (by 8 % -27 %) during the pandemic period compared to the baseline. Except for cocaine, estimated average stimulant consumption rates also increased (by 74 %–286 %). There were notable fluctuations in monthly drug use estimates, and of the observed increases during the pandemic, only the estimate for MDMA was statistically higher than baseline ($p = 0.016$; Supplementary information, Table SVII). Estimated methadone and cocaine average consumption rates decreased only slightly: 6 % and 7 %, respectively.

COVID-19 pandemic disrupted drug supply chains globally and nationally due to travel restrictions and decreased economic activity, leading to increased drug prices, decreased drug purity, and switching to other substances among drug users (United Nations Office on Drugs and Crime, 2020). In the early stages of the pandemic, many U.S. states imposed bans on non-essential travels across state lines. The studied rural town is located near a segment of an interstate highway traversing several Northeastern U.S. states and that is anecdotally referred to locally as the "heroin highway" (i.e., route for drug trade) (Johnson, 2019; WHMP, 2017). Interstate travel restrictions started in the last quarter of this surveillance study and may have impacted the local drug market. Alongside disruptions to drug supply routes, the pandemic also posed challenges to addiction management (United Nations Office on Drugs and Crime, 2021) related to drug switching and disrupted treatment services for substance abuse patients (Volkow, 2020). Nationwide, large increases in drug overdose mortality have been reported within the pandemic period due to combination drug use (speedball mixtures), and driven by several factors such as increased stress due to loss of jobs and loved ones, and opportunistic drug traders introducing and more widely distributing new synthetic drug combinations into the illicit drug market. Regionwide, opioid-related overdose deaths increased in 2020 compared to 2019, mainly in the eastern region and in the areas adjacent to the rural town (Massachusetts Department of Public Health, 2021).

There were distinct drug use trends that were observed within the "pandemic period" of this surveillance study. Except for April 2020, our designated pandemic period represented the summer months when the sewershed demographics and drug use trends are largely dominated by local residents (i.e., absence of transient university population). Coincidentally, this period also encompassed the first wave of COVID-19 infections in town. Fig. 4 shows the normalized daily (7-d average) case counts in the county alongside the estimated drug consumption in the rural town. Infection case counts are only available as aggregated county data, nonetheless, the rural town is the most densely populated town in the county and represents approximately 25 % of the county population. The first pandemic wave lasted three months; cases peaked in the last week of April 2020, with the tail end of the first wave plateauing beginning the first week of June 2020. There was a notable drop consumption rates in April 2020 for morphine, codeine, cocaine, amphetamine, and MDMA. The generally sustained decline in cocaine consumption may be indicative of disruptions in the cocaine supply chain. In contrast, the consumption rates of hydrocodone, methadone, and MDEA rose in April 2020, and followed a similar temporal trend as the infection rate bell curve. For context, opioid prescription rates for the county declined in the second quarter (April–June) compared to the first quarter (January–March) of 2020 (3.4 % (Massachusetts Department of Public Health Bureau of Health Professions Licensure, 2020a) vs 2.8 % (Massachusetts Department of Public Health Bureau of Health Professions Licensure, 2020b). Lastly, we note a sudden increase in estimated drug consumption rates on July 13, 2020 for codeine, hydrocodone, methadone, fentanyl, methamphetamine, MDMA, and MDEA. We looked into potential causes but could not account for these one-off increases. The influent samples represented a weekend composite and were taken a week after a federal holiday, although population estimates for that day remained stable (i.e., no influx of visitors). There were no large scale civic or musical events that weekend as the region was only in the early stages of its phased re-opening that began on June 8, 2020. Other studies hypothesize that sudden surges in drug mass loads in sewersheds may also be due to dumping into sewer systems (Emke et al., 2014).

3.7. Limitations of the study

We acknowledge several methodological limitations in this study. Firstly, the effect of in-sewer sorption of drugs was not accounted for in the back-calculation estimation model in Eq. (1). The effect of sorption to sediments and particulates during in-sewer transport may be significant, particularly for organic compounds that have high octanol-water coefficients (McCall et al., 2016). Secondly, our back-calculation did not account for possible underestimation related to degradation in-sewer (Pagsuyoin et al., 2022) and during wastewater transport prior to lab processing. There have been recent efforts to integrate drug stability in the wastewater to improve the accuracy of mass load estimation models (Subedi and Kannan, 2014). Thirdly, our population estimates used biological oxygen demand as surrogate for per capita load from domestic activities. Decaying organic matter (e.g., dead plants and animals, discharges from food establishments) may increase BOD in sewage, leading to higher population estimates. Nonetheless, given the absence of precipitation during sampling days, the separate sewer system of the study area, and minimal flow inputs from commercial and industrial establishments, the authors view that compounding effects from external BOD sources on population estimates are likely minimal. The use of cellular data has been suggested as a better

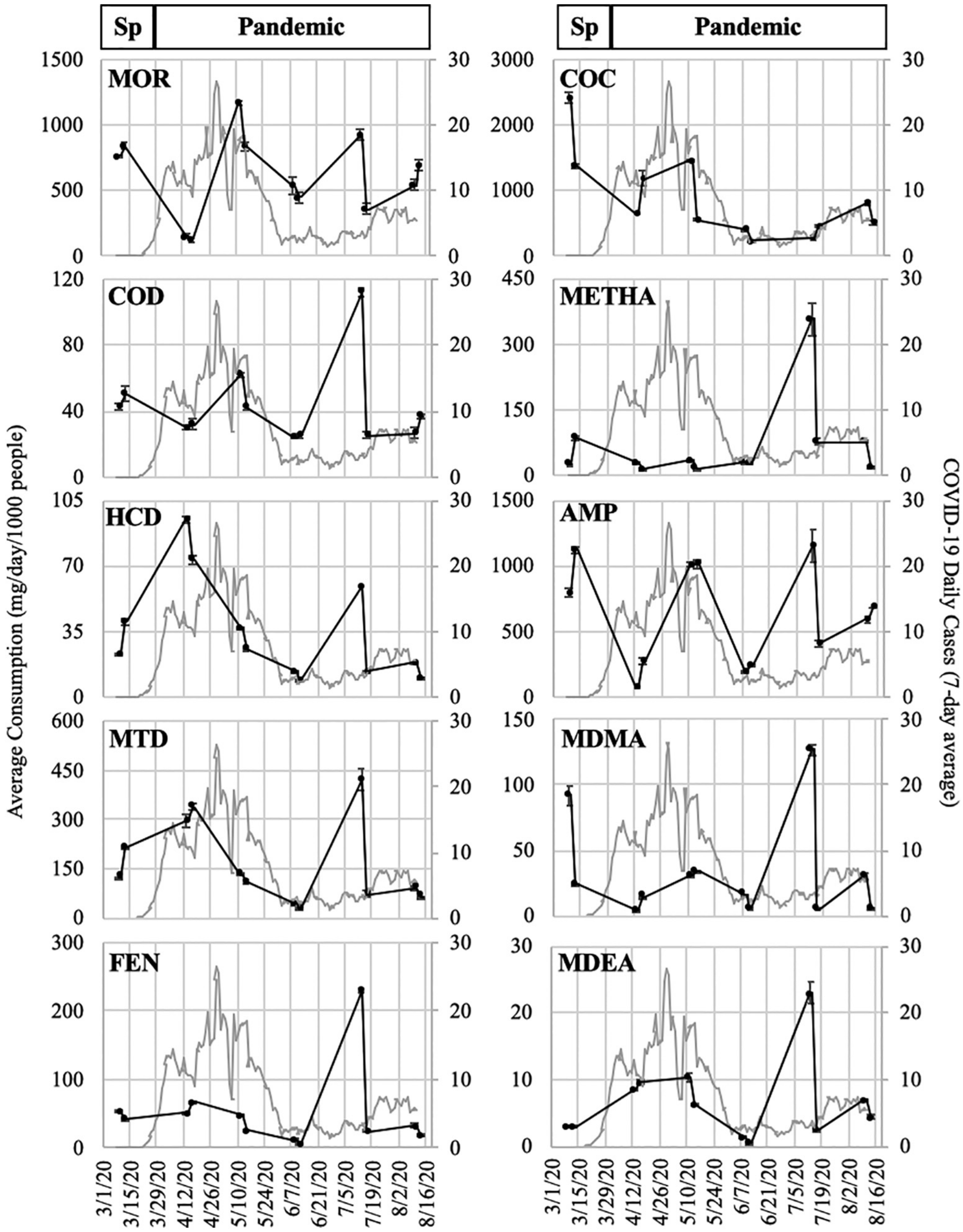

Fig. 4. Estimated average community drug consumption (black solid line, read from left axis scale with units in mg/d/1000 people) and reported daily new COVID-19 cases (gray line, read from right axis scale with units in 7-d average daily case counts). Vertical bars in consumption data points indicate standard error of estimates (from wastewater sample replicates).

measure of near real-time population mobility (Thomas et al., 2017), though the analysis is significantly more complex than when using approaches based on hydrochemical parameters or biomarkers. Lastly, our analysis of drug use trends did not include examination of local demographic and socio-economic profiles nor the causes of observed trends. The population of our studied rural town skews towards a younger and highly educated demographic, has a median household income much higher than the national average, and has relatively low cultural/ethnic diversity. These socio-economic factors contribute to drug use behaviors and trends (United Nations Office on Drugs and Crime, 2021) and will be the subject of future studies.

4. Conclusion

In this study we discuss the findings of a two-year wastewater-based drug use surveillance in a rural community in Northeastern United States, with a focus on opioids and stimulants. The study period spans September 2018 to August 2020 and includes the first wave of the COVID-19 pandemic, providing objective evidence and insights into the effects of the pandemic on drug use trends. All target drugs were detected at 100 % frequency in wastewater samples. Our estimates indicate year-on-year semester increases of per capita drug use over the 2-yr period. Furthermore, estimated per capita consumption of fentanyl was higher than previous reports from rural and university settings in the U.S. We also noted increased drug use during the pandemic period, with the highest increase observed for ecstasy (threefold increase over baseline). These results demonstrate the utility and strength of wastewater-based approaches in capturing long-term, evolving, and emergent trends in drug use within communities. Our study findings reflect the regionwide problem with opioid-related overdoses and increasing stimulant prescription rates. Our findings also provide objective data and insights for health policymakers on the effects of the pandemic period on community drug use in a rural U.S. town.

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Author contributions

JL performed the experiments and data analysis, and contributed in manuscript writing. DB contributed in manuscript review. SP contributed in study design, data analysis, manuscript writing review, and study oversight.

Data availability

Data will be made available on request.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Sheree Pagsuyoin reports financial support was provided by National Science Foundation.

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Appendix A. Supplementary data

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