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Article

Time-Dependent Intrinsic Correlation Analysis Reveals Positive Relationship between Drug Types in Wastewater: Antidepressants vs Illicit Drugs and Analgesics vs Antibiotics/Antivirals

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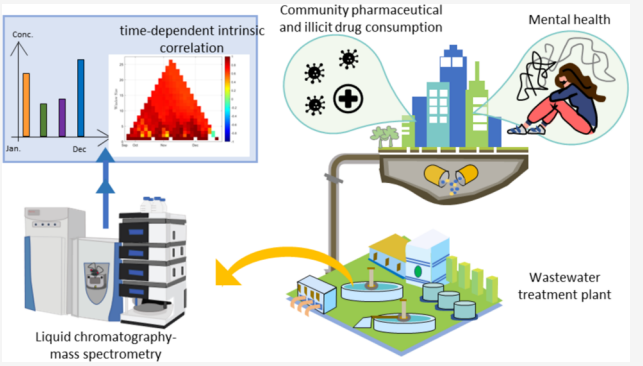
ABSTRACT: The connection between mental health and illicit substance use disorder is intricate and poorly understood but may potentially be unraveled by examining residues of antidepressants and illicit drugs through wastewater-based epidemiology (WBE). In this study, we assessed time-dependent intrinsic correlations (TDIC) between the concentrations of antidepressants and illicit drugs and their metabolites in untreated sewage samples during three sampling campaigns, from September 2022 to May 2024. Notable positive correlations (+medium in 2022; +weak in 2023; +medium in 2024) were observed between illicit drugs (e.g., methamphetamine, cocaine, and its benzoylecgonine metabolite) and bupropion (an antidepressant). For other psychoactive drugs examined (citalopram, venlafaxine, and its metabolite desvenlafaxine), +medium correlations were observed with illicit drugs in the 2023 and 2024 sampling campaigns. This is the first time WBE demonstrates the interconnection between prescription psychoactive drugs, such as antidepressants, and illicit drugs, underscoring TDIC's strength in extracting information from complementary data. We applied similar data analytics using residues of antivirals and antibiotics in untreated sewage and their correlation with acetaminophen; the expected results were obtained. TDIC between acetaminophen and antibiotics showed a strong correlation during the whole sampling event, supporting the applicability of TDIC in WBE research.



KEYWORDS: *pharmaceuticals, opioids, data analytics, community health, liquid chromatography−high-resolution mass spectrometry, wastewater-based epidemiology*

1. INTRODUCTION

In recent years, wastewater-based epidemiology (WBE) has emerged as a highly effective and robust approach for disentangling the complex interplay between human behavior and public health dynamics within communities. As a cost-effective technique with minimal ethical concerns, WBE has been predominantly employed to decipher patterns of community use of illicit drugs such as cocaine, methamphetamine, and opioids. However, the scope of WBE applications has significantly broadened to a vast array of public health concerns, including other performance-enhancing substance use,[1−3] disease prevalence,[4,5] antimicrobial resistance,[6,7] and exposure to chemical contaminants.[8,9] This evolution in the scope of WBE studies is particularly timely and significant given the ongoing health challenges posed by the escalating prevalence of mental health disorders and the emerging and reemerging infectious diseases, underscoring the pressing need for a deeper understanding of community health dynamics.

Mental health disorders affect global well-being and have profound economic and societal consequences. The influence of mental health disorders is far-reaching, as they consistently rank among the primary causes of disability across diverse populations, often intertwining with alarming rates of suicidal tendencies.[10,11] Of particular concern is the escalating growth of depression among young individuals posing a critical public health challenge that demands urgent attention.[12,13] Another concerning facet that arises in the context of mental disorders is the connection between these disorders and the use of illicit or abusive substances because mental health problems and substance use disorders sometimes occur together.[14] A

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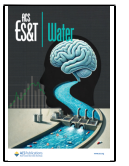

previous study has shown that individuals with depression are twice as likely to engage in self-medication.[15] It has also been reported that drug abuse was highest among adolescents with prior anxiety disorders and behavior disorders.[16] This phenomenon aligns with the self-medication hypothesis, which suggests that individuals may turn to illicit or abusive substances in order to alleviate symptoms associated with trauma, anxiety, or depression.[17] Despite the evident connection between public health and substance use, effective strategies to track and address this intricate connection remain challenging. The knowledge provided by the WBE offers a unique opportunity to understand the use of illicit and abusive drugs in a community and its potential association with mental health. This can promote intervention efforts and develop targeted approaches to address the interconnected challenges of mental health and substance use within communities.

Data analytics can reveal the interrelationships between different chemical residues detected during WBE studies. Pearson correlation is generally used to analyze correlations between two variables globally, assuming that the variables are stationary and linear. Most phenomena in nature, however, are nonstationary and nonlinear, thus requiring a more comprehensive quantitative method for evaluation. Consequently, time-dependent intrinsic correlation (TDIC) can be employed, allowing the intrinsic correlation between two variables to be localized by varying the sliding window size.[18] It has been shown that TDIC can be applied to environmental science studies, including an attempt to correlate hydro-meteorological factors with Dengue fever incidences.[19] Additionally, TDIC has been used to investigate potential sources of fine particulate matter (PM 2.5) and how their concentrations change over time,[20] river dust pollution,[21] and wildfires.[22] These studies highlighted the versatility of TDIC in assessing dynamic environmental factors and their correlations.

In this study, TDIC is introduced to WBE for the first time to evaluate how the concentration time series of residues of psychoactive drugs, such as antidepressants that are prescribed to manage mental health issues, may be related to illicit drug use in a defined community. In this study, we limited our analysis to illicit drugs with residues that are frequently detected in sewage water such as cocaine and its metabolite benzoylecgonine, methamphetamine, morphine, and oxycodone. To validate the strength of TDIC in revealing correlations between drug residues from WBE, we also examined correlations between residues of antibiotics, antivirals, and analgesics (painkiller), which we anticipated to be positively correlated due to the well-known use of acetaminophen in managing symptoms of pathogenic infection. The objectives of this study are (1) to employ liquid chromatography coupled to high-resolution mass spectrometry (LC-HRMS) for targeted analysis and suspect screening of drug residues, including antidepressants, antivirals, antibiotics, pain medication drugs, and illicit drugs in untreated sewage, (2) to investigate the time-dependent correlations between detected drug concentrations in sewage, and (3) to evaluate the potential viability of drug residues in community-based WBE analysis to assess prevalence of mental health, use of illicit drugs, and bacterial or viral infections in a community-level.

2. MATERIALS AND METHODS

2.1. Sample Collection and Extraction. Twice each week (within weekdays), 24 h time-weighted composite untreated wastewater samples (450 ± 50 mL; a total of 50 samples) were collected from a participating sewage treatment facility in Western New York in precleaned (with 10% nitric acid) Nalgene polypropylene bottles. The sample collection was carried out during the following sampling campaigns: September−December 2022 (sampling 1), and February−May 2023 (sampling 2). To further test the applicability of TDIC in revealing relationships between the concentrations of antidepressants and illicit drugs for an extended period, additional weekly samples were collected from May to August 2024 (sampling 3). To ensure proper sample preservation, we carefully transported the collected samples to the laboratory under cold conditions (4 °C) for further analysis.

Upon receipt, the samples immediately underwent a cleanup and preconcentration following a previously validated and published solid-phase extraction (SPE) method.[23] In brief, samples were filtered through a 0.7 μm pore size GF/F glass microfiber filter, followed by 0.45 μm pore size nylon membrane filter. The filtered samples were then acidified with H_3PO_4 to pH 2−3 and spiked with 2 mL of 5% w/v Na_2EDTA. Prior to conducting the extraction, the samples were fortified with 50 μL of 1 mg/L of an isotopically labeled surrogate standards mix. We added an internal standard after filtration because we intended to measure only the dissolved portion of the drug residues; any adsorbed pharmaceuticals were not measured. This approach eliminates the potential variability caused by the differences in the nature of suspended particulate matter that might sorb variable portions of the drug residues. All analytes included in the targeted analysis and suspect screening with the isotopically labeled surrogate standards used are listed in the Supporting Information. A tandem extraction approach was employed for the SPE, which included passing the samples through a hydrophilic−lipophilic balance (HLB) sorbent, followed by mixed-mode cation exchange (MCX). To preserve the analytes from potential degradation, the SPE cartridges were stored at −40 °C until the elution process. Each HLB SPE cartridge was eluted sequentially with 3 mL of: (i) methanol, (ii) acetonitrile, and (iii) (1:1, v:v) mixture of acetonitrile:ethyl acetate. Separately, each MCX sorbent was eluted sequentially to the same collection vessel using 3 mL of (i) 5% NH_4OH in methanol, (ii) 5% NH_4OH in acetonitrile, and (iii) 5% NH_4OH in (1:1, v:v) acetonitrile:ethyl acetate. Eluates were evaporated to complete dryness by passing a gentle flow of nitrogen gas. Dried eluates were reconstituted up to 1 mL, with the starting mobile phase used in the LC-HRMS analysis and 50 μL of 1 mg/L instrumental internal standard (d3-diphenhydramine) such that the final concentration of d3-diphenhydramine in the vial is 50 μg/L. Before injection to the instrument, sample extracts were filtered with 0.45 μm pore size nylon syringe filters. Information regarding the performance of the analytical method, including analyte extraction recoveries, method detection limits, and method reproducibility for the targeted analytes are presented in Table S1.[23]

2.2. Sample Analysis and Quantification. A Dionex UltiMate 3000 ultrahigh-performance liquid chromatography (UHPLC) system with QExactive Focus Orbitrap HRMS (Waltham, MA) was used for the analysis of the sample extracts. An XSelect charge-surface hybrid (CSH) C18 (2.1 mm × 150 mm, particle size 2.5 μm) analytical column was used to achieve chromatographic separations. The mobile phases consisted of 5 mM ammonium formate and 0.1% formic acid in water (mobile phase A), and the same additives

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in methanol (mobile phase B). The gradient method started with 15% mobile phase B for 3 min, followed by a linear ramp up until 22 min to 100% mobile phase B. At the 25th minute, the gradient was switched back to the starting mobile phase composition. The column was equilibrated at the end of the run, making the total run time 41 min. The LC-HRMS analysis was performed under a full-scan data-dependent MS^2 (ddMS2) method with positive mode electrospray ionization. Other method-specific parameters are as follows: scan range 80−1000 m/z; resolution 17 500; and collision energies at 10, 30, and 60 eV.

The XCalibur 2.1 software (Thermo Scientific, San Jose, CA) was used for data acquisition and processing. The isotope dilution method was used for the quantification of the analytes with corresponding isotopically labeled surrogate standards spiked to the sample prior to SPE. Further, a suspect screening strategy was employed, utilizing an in-house database[24] that encompassed additional pharmaceutical residues. The screening process was conducted using TraceFinder version 4.1 software (Thermo Scientific, San Jose, CA). Concentrations of the analytes detected via suspect screening were estimated using a 7-point external calibration curve prepared in an influent wastewater matrix.

To address the gaps in measurements from Sampling 3 (May−August 2024), we supplemented the missing data using ordinary kriging interpolation. Kriging, a widely adopted and statistically robust technique, takes advantage of spatial autocorrelation within georeferenced data. As the best linear unbiased predictor (BLUP), it leverages the sample's sufficient statistics, operating similarly to an expectation-maximization (EM) approach.[25] The interpolation, conducted via the PyKrige library in Python using an exponential variogram model, covered the period from May 2024 to August 2024. Ordinary kriging assumes a constant but unknown mean within the search neighborhood of x_0.

2.3. TDIC Analysis. Chen et al.[26] proposed the TDIC algorithm to analyze nonstationary and nonlinear data. TDIC conducts localized correlation analysis within adaptive windows, capturing short-term relationships and accounting for multiscale components and variations in a signal frequency over time. The correlation coefficients can thus be estimated locally. The TDIC algorithm estimates the correlation between the time series of two variables on a similar time scale. As presented in eq 1, this algorithm determines the general correlation coefficient R_j between the time series of two variables c_{1j} and c_{2j} by changing the sliding window width at any time. The window size t_w^n is expressed in eq 2, in which n is any positive number. Moreover, the minimum t_d in eq 2 is defined in eq 3, in which $T_{1j}(t_k)$ and $T_{2j}(t_k)$ are the instantaneous period of any two time series (signals).

$$R_j(t_k^n) = \mathrm{corr}[c_{1j}(t_w^n),\ c_{2j}(t_w^n)] \tag{1}$$

$$t_w^n = \left[t_k - n\frac{t_d}{2},\ t_k + n\frac{t_d}{2}\right] \tag{2}$$

$$t_d = \max\left(T_{1j}(t_k),\ T_{2j}(t_k)\right) \tag{3}$$

Incorporating statistical significance testing ensures the reliability of the identified correlations, distinguishing meaningful relationships from random occurrences. TDIC's visual representation as triangular plots simplifies interpretation, and its iterative approach allows in-depth exploration of correlations across diverse segments of the data set. The peak of the triangular plot corresponds to the Global (Pearson) correlation coefficient, simplifying interpretation while retaining the complexity of underlying relationships, as depicted in Figure S1.

Apart from providing a global correlation value, the TDIC method can also assess the TDIC between two variables using different time window sizes, typically represented by a numerical range. Table 1 summarizes the categories of correlations. It can be classified into different categories: strongly correlated (S) (when the TDIC range exceeds 0.7), moderately correlated (0.4 < TDIC < 0.7), weakly correlated (0.2−0.4), and uncorrelated (<0.2). For the present study, only the pharmaceuticals with consistent detection frequencies (>50%) and signal intensities (>10^5) that are significantly higher than the noise were included in the TDIC analyses. To validate the findings from the TDIC analysis, we performed autocorrelation and cross-correlation analyses. The results are presented in Figures S2 and S3, with additional discussion.

Table 1. Time-Dependent Correlation Range Classification

(S)	strong	>0.7	(+)	positive correlated globally
(M)	moderate	0.4−0.7	(−)	negative correlated globally
(W)	weak	0.2−0.4	(U)	uncorrelated globally

3. RESULTS AND DISCUSSION

3.1. Correlations between Illicit Drug Residues and Other Drug Classes. The current investigation unveiled the presence of active ingredients of illicit drugs, including cocaine, its primary metabolite benzoylecgonine, and methamphetamine, in untreated sewage samples at high detection frequencies. Notably, benzoylecgonine was detected at concentrations reaching as high as 1661 ng/L, while cocaine itself was consistently detected (100% frequency; n = 50) at levels up to 650 ng/L (Figure 1), which uses data collected from the first two sampling events (September 2022 and May 2023). Furthermore, the presence of opioid pain medications known for their potential for misuse, namely, oxycodone (59% detection frequency; n = 50) and morphine (63% detection frequency; n = 50), were also confirmed in the samples. Morphine levels were observed to reach as high as 132 ng/L, while oxycodone levels reached a maximum of 92 ng/L in untreated sewage samples.

A concerning surge in illicit drug usage and opiate abuse has been documented in the United States (US). In 2019, the US experienced around 70 630 individuals tragically succumbing to drug overdoses, and approximately half of these fatalities were linked to opioids.[27] This trend is mirrored in Western New York, where a previous report originating from Erie County's Medical Examiner's Office revealed a 2-fold increase compared to the number of opioid-related deaths documented during the same period in 2022 and 2023.[28] A recent report from the county's Department of Health revealed a distressing count of 85 confirmed and 106 suspected opioid-related overdose fatalities as of June 2024.[29] Furthermore, a 2023 report highlights the exceptionally high drug overdose death rates in the US. According to the report, between 2019 and 2022, there was a staggering 50% increase in drug overdose deaths, with the second-ranking country, Scotland, experiencing only a 3% increase during the same period.[30] However, recent surveys of the Centers for Disease Control and Prevention indicate a roughly 10% decline in drug overdose

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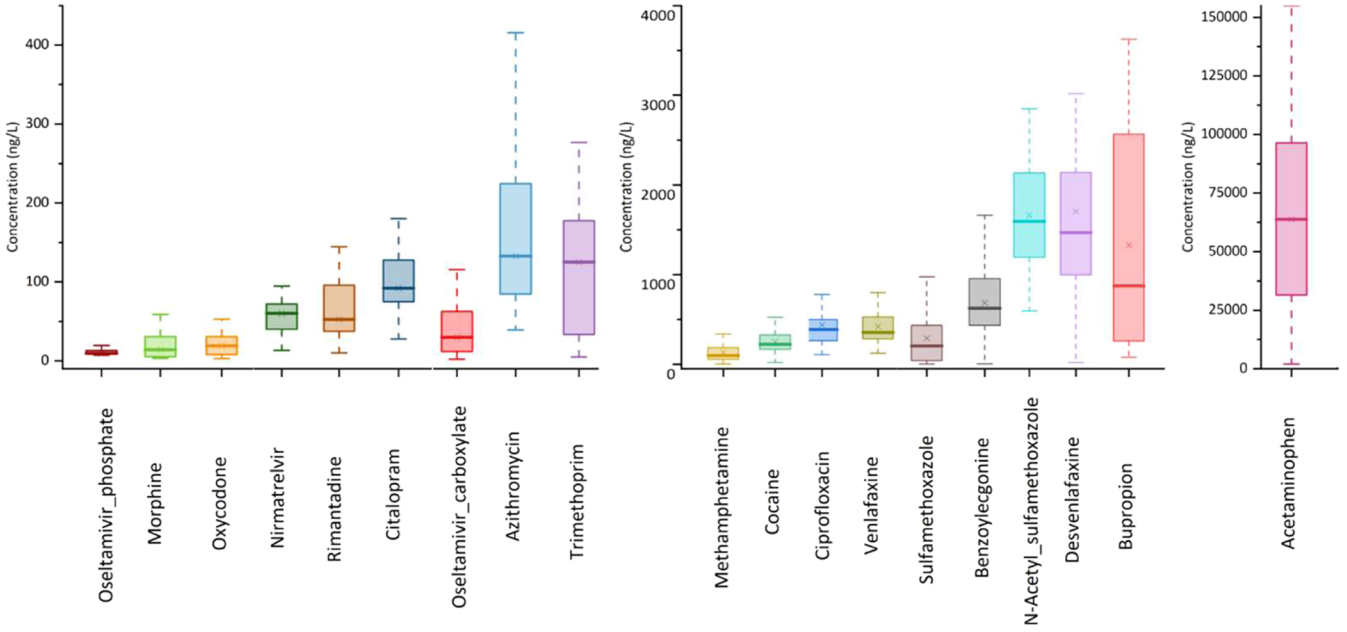

Figure 1. Box and whisker plots of the concentrations (ng/L) of the detected pharmaceuticals in all collected influent wastewater samples (n = 50) between September 2022 and May 2023. The whiskers, represented as vertical lines, span from the minimum to the maximum values. Within the box, the data extend from the first quartile to the third quartile, with the median indicated by the solid center line. Due to varying concentration ranges among compounds, the plots are segmented into three sections, arranged in ascending order of concentration, enhancing clarity in analyte concentration visualization.

fatalities in the US.[31] These reports are reflected in the high concentrations and detection frequencies of the illicit drugs and opioids observed in the present study.

An extensive range of prescription psychoactive drugs were also detected in the collected samples, with desvenlafaxine concentrations reaching as high as 4375 ng/L and bupropion as high as 3625 ng/L (Figure 1). The primary contributor to the prescription psychoactive drugs detected was bupropion, a well-known antidepressant and smoking cessation aid, with a detection frequency of 72% (n = 50). Furthermore, the antidepressant venlafaxine and its major metabolite desvenlafaxine were also detected in the samples at a detection frequency of 85% (n = 50). The notable and recurring presence of antidepressants in wastewater may be attributed to the escalating prevalence of compromised mental well-being in the US. The mental health crisis across the nation has been further intensified by the far-reaching impacts of the COVID-19 pandemic,[32] which likely fueled the rise in medication use and abuse.

To further address the correlation between illicit drug use and antidepressants, a more detailed TDIC analysis was applied (Figure 2). By examining individual components of the identified antidepressants, Figure 2A,D showcases the TDIC outcomes for bupropion in conjunction with the total concentrations of illicit drugs. It is noteworthy that positive correlations between bupropion concentrations and combined illicit drug concentrations were observed across both sampling events, in September−December 2022 (event 1) and February−May 2023 (event 2). During sampling event 1, a moderately positive correlation (global correlation of +0.40) was evident, and during sampling event 2, a relatively weaker positive correlation (global correlation of +0.29) was observed (Table S1). To verify if these observed positive correlations are consistent and will hold true in a different month and year of sampling, additional samples were collected between May and August 2024. Figure 2G shows a moderately positive correlation (global correlation of +0.86, Table S1) between the concentrations of bupropion and illicit drugs, which is consistent with previous observations. These results demonstrate TDIC's capability to handle nonlinear, nonstationary data through adaptive window sizes, allowing us to extend the analysis across all collected samples within a unified framework.[16]

Bupropion's connection to illicit drug use is intricate and multifaceted. Functionally, bupropion acts as a norepinephrine and dopamine reuptake inhibitor (NDRI) antidepressant.[33] Moreover, it serves as a noncompetitive nicotine receptor antagonist. Bupropion finds prescription use in the treatment of major depression, seasonal affective disorder, and smoking cessation.[34] Off-label applications include addressing sexual dysfunction caused by antidepressants, obesity, attention-deficit hyperactivity disorder, and depression associated with bipolar disorder.[35] Notably, instances of bupropion abuse have been reported, with some referring to it as the "poor man's cocaine" due to its purported ability to induce a sensation akin to that experienced with cocaine or amphetamine use.[36]

The residues of venlafaxine and desvenlafaxine, another class of antidepressants, were also examined relative to the combined concentrations of illicit drugs in the sewage. Venlafaxine is typically utilized as a serotonin-norepinephrine reuptake inhibitor (SNRI), often prescribed to address diverse mental health issues including major depressive disorder, generalized anxiety disorder, and social anxiety disorder.[37] Furthermore, antidepressants such as venlafaxine are recognized for being prone to prescription drug misuse.[38] In sampling event 1, the correlation between venlafaxine and desvenlafaxine concentrations (Figure 2B) with illicit drug concentrations displayed a weakly negative correlation (global correlation of −0.16, Table S1). In contrast, during sampling events 2 and 3, moderately positive correlations (global

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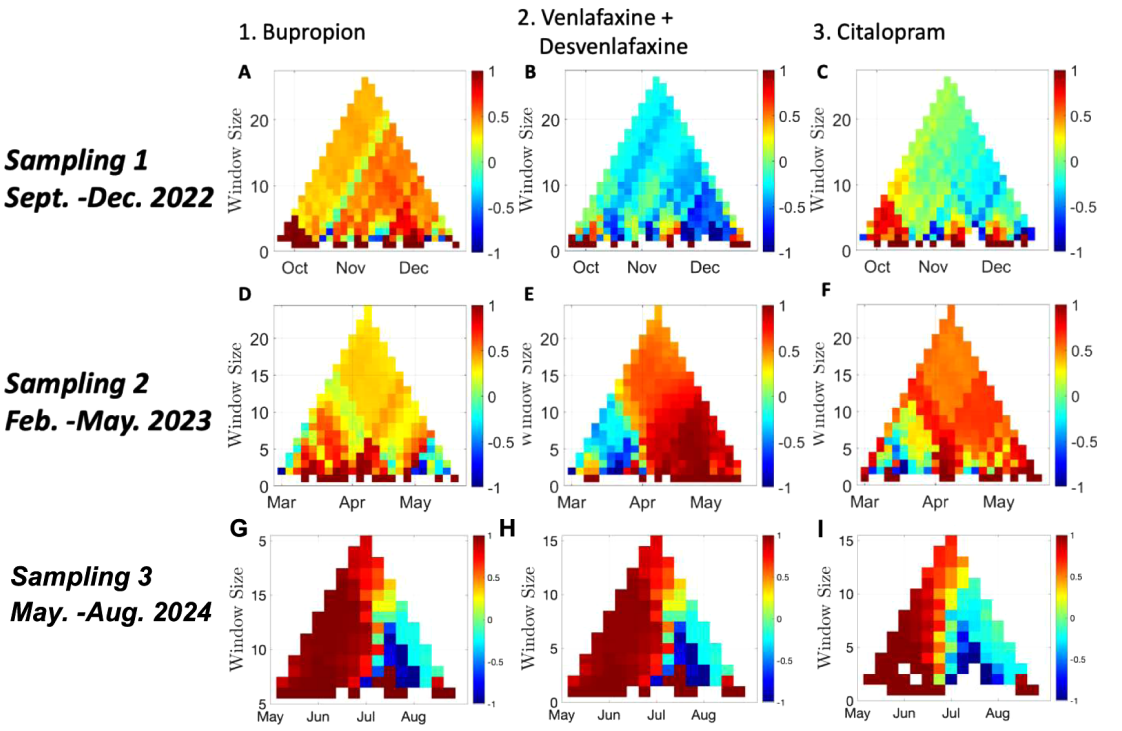

	Sampling 1; Sept. – Dec. 2022	Sampling 2; Feb.-May 2023	Sampling 3; May. -Aug. 2024
Illicit and abusive drugs Vs.	Time- dependent Intrinsic Correlation	Time- dependent Intrinsic Correlation	Time- dependent Intrinsic Correlation
Bupropion (Wellbutrin®)	M+	W+	M+
Venlafaxine (Effexor®) and Desvenlafaxine	W-	M+	M+
Citalopram (Celexa®)	U	M+	M+

Figure 2. TDIC analysis results between illicit and abusive drugs and detected antidepressants. (1) Bupropion, (2) venlafaxine and desvenlafaxine, and (3) citalopram. [Illicit drugs considered = benzoylecgonine, cocaine, methamphetamine, morphine, and oxycodone].

correlation of +0.41 and +0.83, Table S1) were observed, and distinct positive correlations (Figure 2E,H) were particularly evident in the samples collected during April−May (2023) and May−June (2024) for these drug classes. The observed results suggest that the relationship between venlafaxine and desvenlafaxine with illicit drugs may be influenced by factors such as seasonal changes that affect drug use patterns.[39] The seasonal variation of illicit drug use has been challenging to study because of nonresponse bias and artifact of the analytical technique employed.[40] The results of the WBE provide complementary data that could reveal valuable information to help us understand patterns of seasonality displayed by illicit drug use. Similarly, Citalopram, which is another extensively employed antidepressant, exhibited no correlation with illicit drugs in sampling event 1 (Figure 2C), but moderate positive correlations (Figure 2F,I) with the detected illicit drugs in sampling events 2 and 3 (global correlation of +0.55 and +0.70, respectively; Table S1). These positive correlations between citalopram and illicit drugs were also most evident in the samples collected during April−May (2023) and May−June (2024). It will be interesting to investigate if a longer sampling time period could reveal seasonal variations in the observed concentrations of antidepressants and illicit drugs that might align with the occurrences of holidays, changing weather, and current events.

3.2. Infectious Disease-Related Drug Classes. Among the most frequently detected drug residues was acetaminophen (active ingredient of Tylenol and other pain relievers), which was present in all sewage samples at concentrations ranging from 1994 to 154 942 ng/L (Figure 1). In order to demonstrate the reliability of TDIC in data analytics for WBE, we explored its applications in examining correlations between drug residues that are expected to be positively correlated, because of their well-known usage in managing pain and infections. For instance, over-the-counter pain killers, such as acetaminophen, are typically used by patients suffering from symptoms of bacterial or viral infections.[41] It is also likely that patients suffering from viral infections are more prone to bacterial infections due to their weakened immune systems. Hence, we conducted TDIC analysis to explore correlations between the concentrations of antibiotics and antivirals used to treat infectious diseases and the concentrations of acetaminophen residues in sewage. Among the antibiotics analyzed, acetyl-sulfamethoxazole (a major metabolite of the antibiotic

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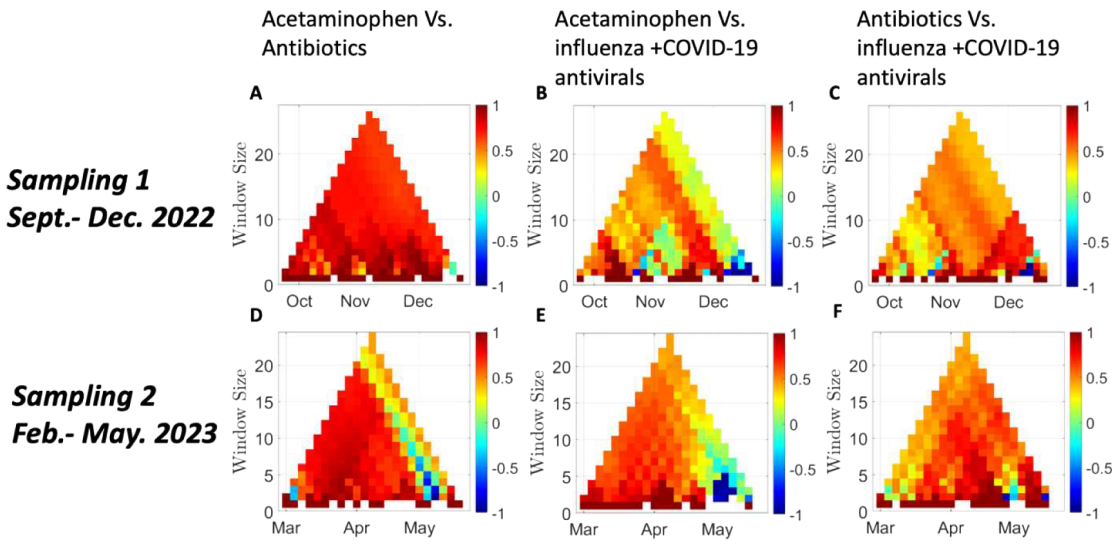

Acetaminophen Vs.	Sampling 1; Sept. – Dec. 2022 Time- dependent Intrinsic Correlation	Sampling 2; Feb.-May 2023 Time- dependent Intrinsic Correlation
Antibiotics	S+	S+
Influenza + COVID-19 antivirals	M+	M+

Antibiotics Vs.	Sampling 1; Sept. – Dec. 2022 Time- dependent Intrinsic Correlation	Sampling 2; Feb.-May 2023 Time- dependent Intrinsic Correlation
Influenza + COVID-19 antivirals	M+	M+

Figure 3. TDIC analysis among acetaminophen, antibiotics, and antivirals. (Antibiotics considered = Azithromycin, Ciprofloxacin, *N*-Acetyl-sulfamethoxazole, Sulfamethazine, Trimethoprim; influenza and COVID-19 related drugs = Nirmatrelvir, Oseltamivir carboxylate, Oseltamivir phosphate, Rimantadine).

sulfamethoxazole) was the most frequently detected (100%; n = 50) and had the highest median concentration of 1593 ng/L (see Figure 1); acetyl-sulfamethoxazole concentration in sewage ranged from 593 to 2847 ng/L. Of the antiviral drugs analyzed, rimantadine (an anti-influenza drug) was most frequently detected (88%; n = 50) and had a median concentration of 53 ng/L; rimantadine concentrations ranged from 10 to 145 ng/L. Figure 3 illustrates the correlations between acetaminophen and total antibiotics, acetaminophen and total influenza drugs combined with COVID-19 antivirals, as well as total antibiotics and total antivirals.

Figure 3A–D depicts correlations between acetaminophen with antibiotics and antiviral drugs. The analysis revealed a strong positive correlation (S+) between the concentrations of acetaminophen and total antibiotics across both sampling events 1 and 2 (global correlations of +0.64 and +0.44, respectively; Table S3). The strong positive correlation revealed by TDIC between acetaminophen and antibiotics is expected, considering that many bacterial infections are frequently linked to symptoms, such as fever or body discomfort. The moderately positive correlations (M+) observed between acetaminophen and antiviral drugs during sampling events 1 and 2 (global correlations of +0.22 and +0.45, respectively; Table S3) can also be rationalized by linking viral infections with symptoms such as pain and fever. Finally, a moderate positive correlation was detected between the concentrations of antiviral drugs and antibiotics in the sewage samples, which suggests the simultaneous emergence and co-occurrence of bacterial and viral infections within the study area. These results provide evidence of the reliability of the TDIC in extracting information from the WBE time series.

The stability of pharmaceuticals and their metabolites in sewer has been investigated at various conditions to determine the influence of sediment processes and presence of biofilm on the transformation and adsorption of these analytes.[42,43] For instance, acetaminophen has been noted to exhibit moderate to high instability under gravity and rising main sewer conditions. The variability in analyte stability across different days pertaining to different sewer conditions, influenced by factors like temperature and rainfall, adds complexity to drawing general conclusions. Nonetheless, the TDIC analysis relies on localized correlations within analyte groups over shorter time frames, thereby minimizing the potential influence of variable in-sewer degradation on correlation outcomes.

4. STUDY LIMITATIONS

An inherent limitation of this approach stems from potential shifts in drug usage patterns within communities, compounded by variations in drug efficacy based on geographical location. For example, the illicit drug landscape is in a constant state of flux with the introduction of performance- and image-enhancing drugs or novel abusive substances. While waste-

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water reflects total consumption in a catchment such that the antidepressants may or may not have been consumed by illicit drug users, studies suggest that mental health disorders often lead to the use of illicit or abusive substances.[14] Therefore, it will be valuable to investigate health and epidemiological data to determine the number of illicit drug users who are also taking antidepressants and vice versa and compare results with the wastewater-based epidemiology data presented in this study. It is desirable to have more significant data availability to enhance TDIC accuracy, as this improves pattern detection over time, reduces noise, and increases reliability across varying conditions such as seasonal changes and drug usage trends, thereby strengthening insights in wastewater-based epidemiology. When applying this methodology across diverse seasons, temperature variations may contribute to varying degrees of in-sewer analyte degradation. An earlier study demonstrated the accelerated degradation of paroxetine and sertraline, two antidepressants exhibiting decay rates of approximately 26 and 36% at 35 °C, respectively, in response to higher temperatures.[44] For this reason, while we detected sertraline and other antidepressants in sewage, we did not include these drug residues in the TDIC analysis.

5. CONCLUSIONS

In this study, TDIC analysis of the concentrations of antidepressants, particularly bupropion, and illicit drugs (benzoylecgonine, cocaine, methamphetamine, morphine, and oxycodone) in untreated wastewater showed positive correlation during the sampling period of September 2022 to August 2024. The very similar patterns observed in the concentrations of antidepressants and illicit drugs in wastewater suggest that mental illness likely co-occurs with substance use. The application of TDIC analysis to analyze the dynamic relationship among antibiotics, antivirals, and analgesics in untreated wastewater illustrated the positive correlation between these drug residues, which is expected, and provides validity to the results revealed by TDIC analysis of antidepressants and illicit drugs. The application of WBE to monitor illicit drugs has increased across the globe in the past decade. The results from our current study could point to the direction of assessing the co-occurrence of antidepressants and illicit drugs on a global scale to further assess the applicability of WBE in understanding the growing crisis of substance abuse among patients with mental health issues.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsestwater.4c00340.

List of analytes included in the targeted analysis and the suspect screening; global correlation analysis results between illicit and abusive drugs and detected antidepressants (Tables S1); summary of the global correlation analysis results of illicit and abusive drugs vs acetaminophen (Table S2); global correlation analysis among acetaminophen, antibiotics, and antivirals (Table S3); and illustration of TDIC calculations, autocorrelation analysis, and cross-correlation analysis (Figures S1−S3) (PDF)

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Author Contributions

CRediT: **Lahiruni M. Halwatura** conceptualization, formal analysis, investigation, methodology, writing - original draft; **Jasmin Y. Tung** formal analysis, visualization, writing - original draft; **Liezel Mari Abaya** formal analysis, investigation; **Cheyanne Witmer** formal analysis, methodology; **Christina W. Tsai** conceptualization, funding acquisition, methodology, supervision, writing - original draft, writing - review & editing; **Diana S Aga** conceptualization, funding acquisition, investigation, project administration, supervision, writing - original draft, writing - review & editing.

Notes

The authors declare no competing financial interest.

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