



High prevalence of co-occurring substance use in individuals with opioid use disorder

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ABSTRACT

Objective: Funding to address the current opioid epidemic has focused on treatment of opioid use disorder (OUD); however, rates of other substance use disorders (SUDs) remain high and non-opioid related overdoses account for nearly 30% of overdoses. This study assesses the prevalence of co-occurring substance use in West Virginia (WV) to inform treatment strategies. The objective of this study was to assess the prevalence of, and demographic and clinical characteristics (including age, gender, hepatitis C virus (HCV) status) associated with, co-occurring substance use among patients with OUD in WV.

Methods: This retrospective study utilized the West Virginia Clinical and Translation Science Institute Integrated Data Repository, comprised of Electronic Medical Record (EMR) data from West Virginia University Medicine. Deidentified data were extracted from inpatient psychiatric admissions and emergency department (ED) healthcare encounters between 2009 and 2018. Eligible patients were those with OUD who had a positive urine toxicology screen for opioids at the time of their initial encounter with the healthcare system. Extracted data included results of comprehensive urine toxicology testing during the study timeframe.

Results: 3,127 patients met the inclusion criteria of whom 72.8% had co-occurring substance use. Of those who were positive for opioids and at least one additional substance, benzodiazepines were the most common co-occurring substances (57.4% of patients yielded a positive urine toxicology screen for both substances), followed by cannabis (53.1%), cocaine (24.5%) and amphetamine (21.6%). Individuals who used co-occurring substances were younger than those who were positive for opioids alone ($P < 0.001$). There was a higher prevalence of individuals who used co-occurring substances that were HCV positive in comparison to those who used opioids alone ($P < 0.001$). There were limited gender differences noted between individuals who used co-occurring substances and those who used opioids alone. Among ED admissions who were positive for opioids, 264 were diagnosed with substance toxicity/overdose, 78.4% of whom had co-occurring substance use (benzodiazepines: 65.2%; cannabis: 44.4%; cocaine: 28.5%; amphetamine: 15.5%). Across the 10-year timespan, the greatest increase for the entire sample was in the rate of co-occurring amphetamine and opioid use (from 12.6% in 2014 to 47.8% in 2018).

Conclusions: These data demonstrate that the current substance use epidemic extends well beyond opioids, suggesting that comprehensive SUD prevention and treatment strategies are needed, especially for those substances which do not yet have any evidence-based and/or medication treatments available.

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1. Introduction

In 2019, it was estimated that 10.5 million people in the United States (U.S.) misused opioids (Substance Abuse and Mental Health Services Administration, 2020). Opioid overdoses in the U.S. have quadrupled since 2000, contributing to over 46,800 overdose deaths in 2018 and accounting for nearly 70% of all drug overdose deaths (Center for Behavioral Health Statistics and Quality, 2019; National Institute on Drug Abuse, 2020). The morbidity and mortality secondary to the opioid epidemic is arguably one of the greatest public health problems that the nation currently faces. Particularly hard hit by the opioid crisis is Appalachia (Rossen et al., 2014). Drug overdose deaths are the number one cause of accidental death in West Virginia (WV) and, in 2018, the opioid overdose rate in WV (51.5 deaths per 100,000) far surpassed the national average (21.7/100,000) (Hedegaard et al., 2020). In a recent survey of people who inject drugs (PWID) in WV (Schneider et al., 2020), 42% percent of respondents reported an overdose in the past 6 months, significantly higher than the national and global overdose rates among PWIDs (14% and 17% in the past year, respectively) (Martins et al., 2015; Robinson et al., 2020). As a result of the upsurge of intravenous injection, WV is experiencing significant increases in infectious diseases. WV ranks first in the nation in rates of acute hepatitis B and hepatitis C (HCV) infections (West Virginia Department of Health and Human Resources, 2017).

While we are clearly in the midst of an opioid epidemic, we must be attentive to the additive burden caused by co-occurring substance use among individuals with opioid use disorder (OUD). Results from a nationally representative database, which included 356 individuals with OUD, revealed that 57.3% of those individuals also met criteria for at least one other substance use disorder (SUD). Of those individuals with OUD, information obtained via semi-structured interview revealed that 51% self-reported the use of cannabis, 41% self-reported the use of sedatives, and 31% self-reported the use of cocaine or other stimulants over the past year (Hassan and Le Foll, 2019). Also, recent use of co-occurring substances is elevated among individuals with OUD presenting to the ED, as 47–55% reported use of sedatives, cannabis, and/or cocaine within the previous month (D'Onofrio et al., 2015). In addition, co-occurring substance use is also associated with an increased prevalence of fatal overdose, as 85% of overdoses involving benzodiazepines, 74% of overdoses involving cocaine, and 50% of overdoses involving psychostimulants also included opioids in 2018 (Center for Behavioral Health Statistics and Quality, 2019). Among opioid-involved hospitalizations, approximately 50% had multiple SUD diagnoses, most commonly cocaine (21.7%), cannabis (18.5%), and sedative use disorder (18.1%) (Zhu & Wu, 2020). In addition to OUD, having multiple comorbid SUDs is one of the most prominent risk factors associated with opioid overdose (Betts et al., 2015; Bohnert et al., 2012; Kerr et al., 2007). Furthermore, the rate of highly potent synthetic opioids (e.g. illicitly manufactured fentanyl) is also a major contributing factor, accounting for and/or contributing to 47% of all overdose deaths and 67% of all opioid-related overdose deaths in 2018 (Wilson et al., 2020). In the survey of PWID in WV previously mentioned, those who used multiple substances (specifically opioids and stimulants) had the highest probability of having experienced an overdose (Schneider et al., 2020).

Co-occurring SUDs have been associated with worse treatment outcomes, including lower treatment retention, increased legal consequences, and poorer health outcomes overall (Betts et al., 2016; Morgan, Schackman, Leff, Linas, & Walley, 2018; Samples, Williams, Olfson, & Crystal, 2018). However, for those receiving treatment, findings have shown that medication for OUD (MOUD) may also be indirectly beneficial in reducing co-occurring non-opioid substance use. For example, individuals receiving inadequate doses of MOUD are at elevated risk to abuse other substances such as benzodiazepines and amphetamines (Heikman et al., 2017). Despite this, individuals with additional SUD diagnoses in combination with OUD are less likely to receive buprenorphine and methadone treatment (Lin et al., 2020). The current study

assesses the prevalence of, and demographic and clinical characteristics (including age, gender, HCV status) associated with, co-occurring substance use, assessed via urine toxicology, among individuals with OUD in WV. Given that the statistics detailed previously generally involved co-occurring or comorbid SUDs assessed via self-report or clinical interview, the current approach is unique in that it reflects the actual toxicological assessment of recent substance use independent from SUD diagnoses. While this approach is not free from limitations discussed at the conclusion of this manuscript, the outcomes provide valuable information to complement the already existing literature.

2. Methods

This retrospective study used the EMR data warehouse, created by the WV Clinical and Translational Science Institute (WVCTSI), which is comprised of deidentified data from the West Virginia University Medicine healthcare system (the largest health system in WV). EMR data from 1/1/2009–12/31/2018 were analyzed for unique individuals with either inpatient psychiatric admissions and/or emergency department visits. Subject inclusion criteria required: 1) lifetime diagnosis of OUD and 2) a positive urine toxicology for opioids at the time of the initial healthcare system encounter. Following the data extraction, if there were repeated episodes of care for a single patient, only the data from the encounter that he/she was positive for opioids was included. If a single patient had more than one encounter in which they were positive for additional substances in combination with opioids, the data from the time point in which they tested positive for the highest number of cumulative substances was included.

Frequency distributions regarding urine toxicology results (substance positive/negative assessed via qualitative testing) for opioids (opiates, buprenorphine, oxycodone, methadone), cannabis, benzodiazepines, cocaine, and amphetamine were calculated for patients meeting inclusion criteria presenting to two care settings (e.g., emergency department (ED) and inpatient psychiatry service). Frequency distributions for blood alcohol level (BAL) and co-occurring substance use were also calculated for those patients with available BAL data. Those presenting to the ED were stratified by presence or absence of overdose/toxicity (ICD-10 Code T40). Patient characteristics, including age, gender, and HCV status, of those who used only opioids and co-occurring substances were also determined. Chi-square test (gender and HCV status) and *t*-test analyses (age) were used to determine differences between those who use opioids alone versus those who use co-occurring substances. Mantel-Haenszel Test was used to assess odds ratios taking into account the stratification. With regard to overdose (presence or non-presence of substance toxicity/overdose), chi-square test was used to determine differences between those who use opioids alone versus those who use co-occurring substances and specific co-occurring substance.

With regard to specific opioid type (opiates, buprenorphine, oxycodone, methadone), chi-square test was used to determine differences between those who use opioids alone versus those who use co-occurring substances and specific co-occurring substance. Regression analysis was used to identify statistically significant changes in the proportion of positive urine screens by substance between 2009 and 2018. Cochran Armitage test was used in the trend data analysis for ordinal data, Year as a continuous variable was included in the regression model to assess the outcome variable over time, and Spearman's rank test were used to assess the correlation between ordinal and continuous variables. All data were analyzed using SPSS 21.0 and R software, version R 3.6.0.

3. Results

Patient characteristics of the entire sample can be found in Table 1. A total of 3,127 patients with OUD met the inclusion criteria (ED admissions: *n* = 2350; psychiatric inpatient: *n* = 777), of whom 41.5% were women and 95.8% were White, with an average age of 36.2 ± 13.0 years

Table 1

Patient Characteristics of Emergency Department and Psychiatric Inpatient Admissions.

	Entire Sample <i>n</i> = 3,127	ED (<i>n</i> = 2,350)	Psychiatric Inpatient (<i>n</i> = 777)
Age	36.2 ± 13.0	36.6 ± 13.4**	34.8 ± 11.4
Gender			
Male	1,830 (58.5%)	1,407 (59.9%)*	423 (54.4%)
Female	1,297 (41.5%)	943 (40.1%)	354 (45.6%)
Race (White)	2,996 (95.8%)	2,245 (95.5%)	751 (96.7%)
HCV+ ¹	535 (17.1%)	402 (17.1%)	133 (17.1%)

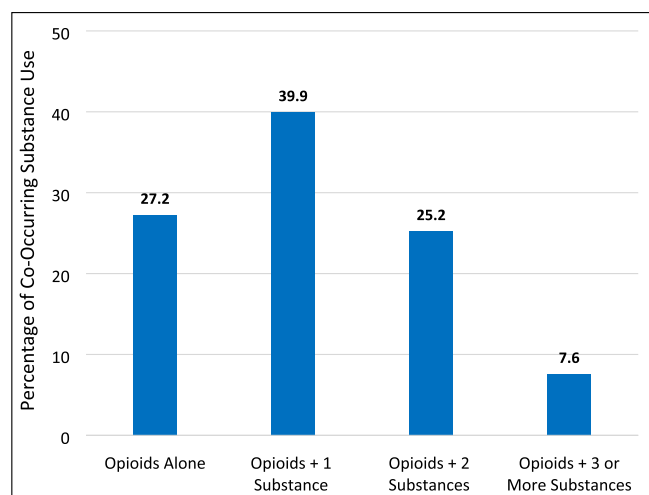
¹ Hepatitis C Seropositivity.Data Reflect Mean ± SD or *n* (%).

Asterisk indicates significant differences between ED and psychiatric inpatient admissions.

P* < 0.01; *P* < 0.001.

(Mean ± Standard Deviation). In comparison to psychiatric inpatients, those who presented to the ED were older (36.6 ± 13.4 vs. 34.8 ± 11.4 , $t(3125) = 3.36$, $P < 0.001$) and more likely to be male (59.9% vs. 54.4%; $\chi^2 = 6.88$, $P = 0.009$). Regarding substance use characteristics, of the entire sample, 27.2% were positive for opioids alone while 72.8% were positive for opioids and at least one other substance. In addition to opioids, 39.9% were positive for one additional substance, 25.2% were positive for two additional substances, and 7.6% were positive for three or more additional substances (Fig. 1a). In comparison to those who presented to the ED, psychiatric inpatients were more likely to be positive for opioids and 2 or more additional substances (38.1% vs. 31.1%; $\chi^2 = 12.78$, $P < 0.001$). There were no differences in the specific co-occurring substances (cannabis, amphetamine, cocaine, benzodiazepine) between those who presented to the ED and psychiatric inpatients.

When compared to those who were positive for opioids alone, those who used co-occurring substances were significantly younger (35.1 ± 12.1 vs. 38.8 ± 14.7 ; $P < 0.01$) and age decreased as the cumulative numbers of co-occurring substances increased (e.g. opioids alone, +1, +2, +3 or more additional substances; 38.8 ± 14.7 vs. 37.2 ± 13.4 vs. 33.3 ± 10.4 vs. 30.7 ± 7.4 ; $P < 0.001$). When compared to those who were positive for opioids alone, those who used co-occurring substances were more likely to be HCV+ (18.7% vs. 12.8%, $P < 0.05$) and rates of HCV+ increased as the cumulative number of co-occurring substances increased (e.g. opioids alone, +1, +2, +3 or more additional substances; 12.8% vs. 16.2% vs. 21.7% vs. 22.4%; $P < 0.001$). There were no gender differences between those who used opioids alone and those with co-occurring substance use (% female: 40.6% vs. 41.8%; $P = 0.57$) (Table 2a).

**Fig. 1a.** Total Number of Different Substances Present on Urine Toxicology in Individuals Positive for Any Opioid (*n* = 3,127).**Table 2a**

Differences in Patient Characteristics by Total Number of Co-Occurring Substances Present on Urine Toxicology.

	Only Opioid+ <i>n</i> = 852	1 Substance <i>n</i> = 1,249	2 Substances <i>n</i> = 789	≥3 Substances <i>n</i> = 237
Age	38.8 ± 14.7	37.2 ± 13.4**	33.3 ± 10.4***	30.7 ± 7.4***
Gender				
Male	506 (59.4%)	715 (57.2%)	464 (58.8%)	145 (61.2%)
Female	346 (40.6%)	534 (42.8%)	325 (41.2%)	92 (38.8%)
HCV+ ¹	109 (12.8%)	202 (16.2%)*	171 (21.7%)	53 (22.4%)***

¹ Hepatitis C Seropositivity.Data Reflect Mean ± SD or *n* (%).

Asterisk indicates significant differences between those who use opioids alone versus those who use co-occurring substances in addition to opioids.

P* < 0.05; *P* < 0.01; ****P* < 0.001.

Of those who were positive for opioids and at least one additional substance, benzodiazepines were the most common co-occurring substances (57.4%) followed by cannabis (53.1%), cocaine (24.5%) and amphetamine (21.6%) (Fig. 1b). There were no significant differences between specific types of co-occurring substances between ED admissions and psychiatric inpatients (all *P*'s > 0.05). Regarding age differences, when compared to those who were positive for opioids alone (38.8 ± 14.7), those with co-occurring use of benzodiazepines (36.3 ± 12.7), cannabis (32.6 ± 10.8), cocaine (33.0 ± 9.6), and amphetamine (33.5 ± 9.4) were significant younger (all *P*'s < 0.001). Regarding prevalence rates of HCV+, when compared to those who were HCV+ and used opioids alone (12.8%), there was a higher prevalence of those who were HCV+ and used opioids with co-occurring use of amphetamine (29.7%; $P < 0.001$), cocaine (25.1%; $P < 0.001$), cannabis (17.1%; $P = 0.01$) and benzodiazepines (16.6%; $P = 0.02$). There was also a higher percentage of women with co-occurring benzodiazepine and opioid use when compared to women who used opioids alone (45.5% vs. 40.6%; $P = 0.028$) (Table 2b).

While data related to alcohol/ethanol use was only available for < 15% of the entire sample (*n* = 421), 72% of whom had a blood alcohol level (BAL) of greater than 0.08 (*n* = 304), there were elevated rates of co-occurring non-opioid substance use noted in combination with both opioids and alcohol. Specifically, of those with a BAL > 0.08, 55.9% were also positive for opioids and at least one additional substance. In addition to opioids and alcohol, 43.3% were also positive for cannabis, 37.1% were also positive for benzodiazepines, and 12.1% and 7.6% were also positive for cocaine and amphetamine, respectively.

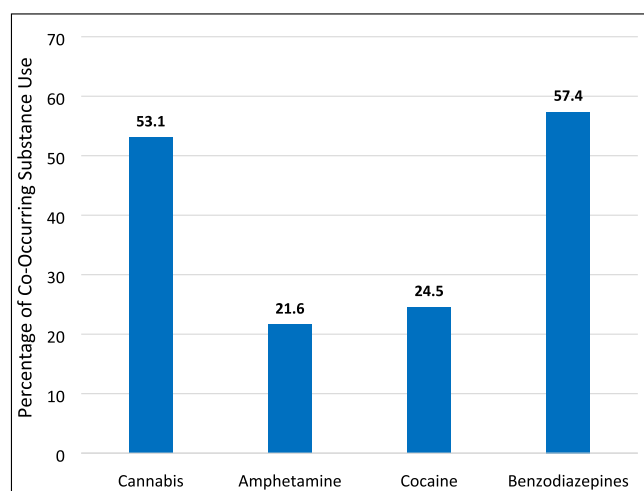
**Fig. 1b.** Specific Co-Occurring Substances Present on Urine Toxicology in Addition to Any Opioids (*n* = 2,275).

Table 2b

Differences in Patient Characteristics by Specific Type of Co-Occurring Substance Present on Urine Toxicology (in addition to Opioids).

	<i>Co-occurring Substance Use</i> <i>Opioid+ & Positive for Specific Substances</i>				
	Only Opioid+ <i>n</i> = 852	Benzodiazepines <i>n</i> = 1,305	Cannabis <i>n</i> = 1,207	Cocaine <i>n</i> = 558	Amphetamine <i>n</i> = 491
Age	38.8 ± 14.7	36.3 ± 12.7***	32.6 ± 10.8***	33.0 ± 9.6***	33.5 ± 9.4***
Gender					
Male	506 (59.4%)	711 (54.5%)	759 (62.9%)	333 (59.7%)	292 (59.5%)
Female	346 (40.6%)	594 (45.5%)*	448 (37.1%)	225 (40.3%)	199 (40.5%)
HCV+ ¹	109 (12.8%)	216 (16.6%)*	206 (17.1%)*	140 (25.1%)*	146 (29.7%)*

¹Hepatitis C Seropositivity.

Data Reflect Mean ± SD or n (%).

Asterisk indicates significant differences between those who use opioids alone versus those who use co-occurring substances in addition to opioids.

P* < 0.05; *P* < 0.01; ****P* < 0.001.

Among the 2,350 ED admissions who were positive for opioids at the time of the encounter, 264 were diagnosed with substance toxicity/overdose. 21.6% of these individuals were positive for opioids alone and 78.4% were positive for opioids and at least one other substance. In addition to opioids, 44.7% were positive for opioids and one additional substance, 26.1% were positive for two additional substances, and 7.6% were positive for three or more additional substances. In comparison to those with substance toxicity, those who presented to the ED without substance toxicity were more likely to be positive for opioids alone (29.0% vs. 21.6%; $\chi^2 = 5.93$; *P* = 0.015) (Fig. 2a). Of those who presented to the ED with substance toxicity and were positive for opioids and at least one additional substance, benzodiazepines were the most common co-occurring substances (65.2%) followed by cannabis (44.4%), cocaine (28.5%), and amphetamine (15.5%). In comparison to those diagnosed with substance toxicity, those who presented to the ED without substance toxicity were more likely to be positive for opioids and cannabis (53.4% vs. 44.4%; $\chi^2 = 5.45$; *P* = 0.02). In addition, those who were diagnosed with substance toxicity were more likely to be positive for opioids and benzodiazepines when compared to those without substance toxicity (65.2% vs. 55.1%; $\chi^2 = 7.11$; *P* = 0.008) (Fig. 2b).

Regarding poly-opioid use (e.g. heroin, morphine, buprenorphine, oxycodone, methadone), 80.0% were positive for only one opioid at the time of presentation, 17.2% were positive for two opioids, and 2.8% were positive for three or more opioids. Of those who were positive for more than one opioid, 87.9% were positive for opiates (heroin or

morphine), 68.8% were positive for buprenorphine, 46.0% were positive for oxycodone, and 11.5% were positive for methadone. When comparing only those who were positive for one opioid at time of presentation (Fig. 3a), those who were positive for buprenorphine were more likely to be positive for 3 or more additional non-opioid substances than those positive for other opioids (*P* < 0.001). Those who were positive for oxycodone alone were less likely to use co-occurring non-opioid substances in comparison to those who were positive for the other opioids (*P* < 0.001).

Regarding specific co-occurring non-opioid substance use (Fig. 3b), there was a significantly higher prevalence of amphetamine use in those positive for buprenorphine (37.7%) when compared to those who were positive for opiates (12.5%; $\chi^2 = 138.12$, *P* < 0.001), oxycodone (11.2%; $\chi^2 = 28.54$, *P* < 0.001), and methadone (4.7%; $\chi^2 = 36.35$, *P* < 0.001). There was also a higher prevalence of amphetamine use in those positive for opiates relative to methadone (12.5% vs. 4.7%; $\chi^2 = 4.51$, *P* = 0.034). There was a higher prevalence of benzodiazepine use in those who were positive for methadone (81.2%) relative to those positive for opiates (59.1%; $\chi^2 = 15.95$, *P* < 0.001), buprenorphine (48.8%; $\chi^2 = 31.26$, *P* < 0.001), and oxycodone (62.6%; $\chi^2 = 7.90$, *P* = 0.005). There was also a higher prevalence of benzodiazepine use in those positive for opiates (59.1%; $\chi^2 = 16.01$, *P* < 0.001) or oxycodone (62.6%; $\chi^2 = 6.90$, *P* = 0.009) relative to buprenorphine (48.8%). There was a higher prevalence of cocaine use in those positive for opiates (23.8%; $\chi^2 = 6.30$, *P* = 0.012) or buprenorphine (21.6%; $\chi^2 = 4.07$, *P* = 0.044) relative to oxycodone (13.1%). There was also a higher prevalence of

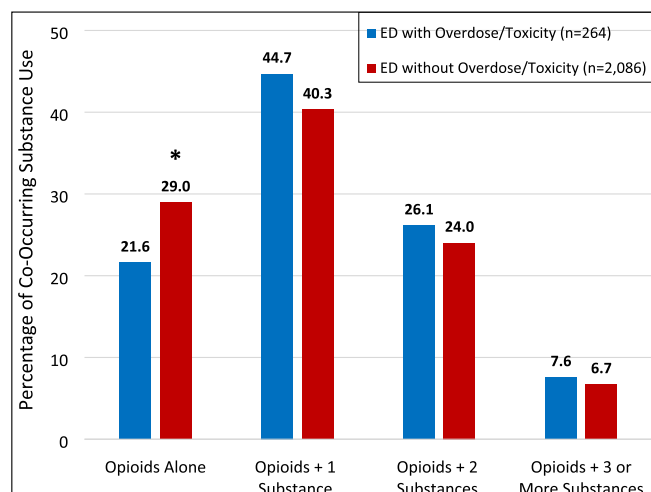


Fig. 2a. Total Number of Different Substances Present on Urine Toxicology in Individuals Positive for Any Opioid – ED Admissions With and Without Substance Toxicity (*n* = 2,350). Asterisk indicates significant differences between those who presented to the ED with versus without substance overdose/toxicity. **P* < 0.05.

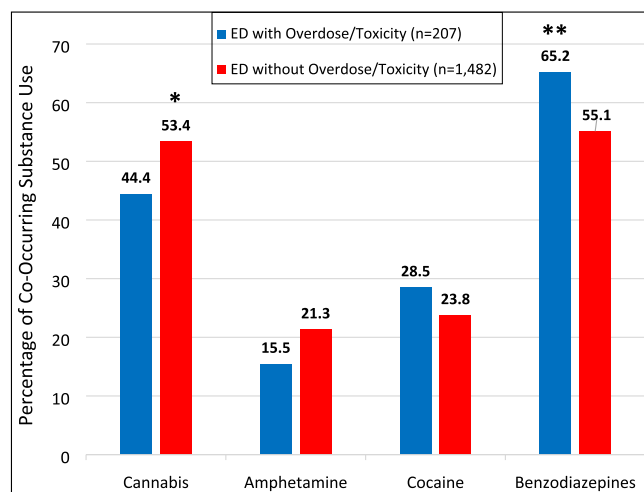


Fig. 2b. Specific Co-Occurring Substances Present on Urine Toxicology in Addition to Any Opioids – ED Admissions With and Without Substance Toxicity (*n* = 1,689). Asterisk indicates significant differences between those who presented to the ED with versus without substance overdose/toxicity. **P* < 0.05; ***P* < 0.01.

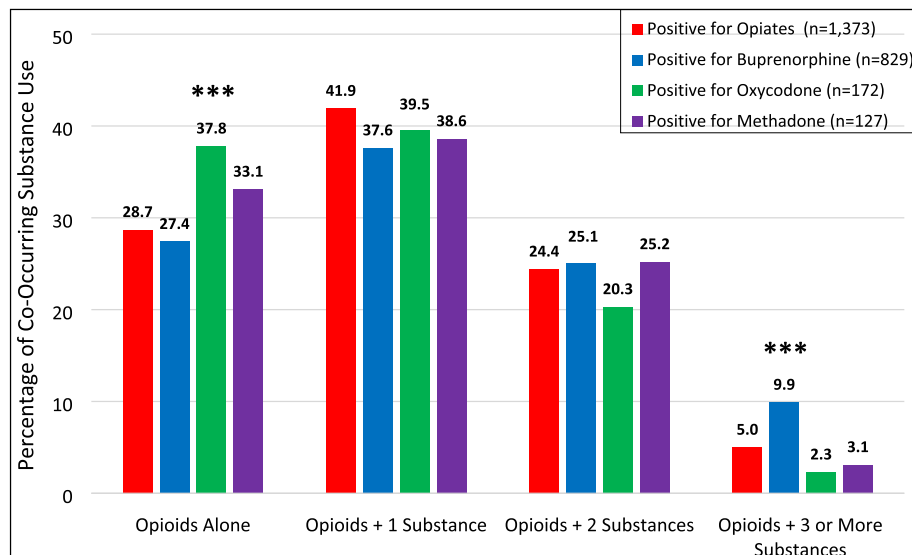


Fig. 3a. Total Number of Different Substances Separated by Specific Opioids Present on Urine Toxicology (n = 2,501). Individuals positive for more than one opioid (e.g. opiates AND methadone, oxycodone AND buprenorphine, etc.) are excluded. Asterisk indicates significant differences between specific opioid type. *** $P < 0.001$.

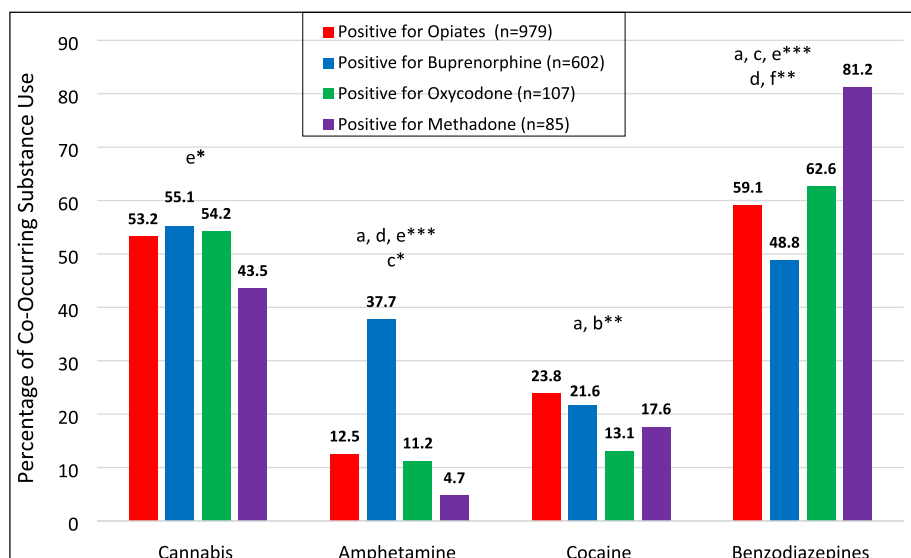


Fig. 3b. Specific Co-Occurring Substances Separated by Specific Opioids Present on Urine Toxicology (n = 1,773). Individuals positive for more than one opioid (e.g. opiates AND methadone, oxycodone AND buprenorphine, etc.) are excluded. Asterisk indicates significant differences between specific opioid type. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$. ^aOpiates vs. Buprenorphine, ^bOpiates vs. Oxycodone, ^cOpiates vs. Methadone, ^dBuprenorphine vs. Oxycodone, ^eBuprenorphine vs. Methadone, ^fOxycodone vs. Methadone.

cannabis use in those positive for buprenorphine relative to methadone (55.1% vs. 43.5%; $\chi^2 = 4.05$, $P = 0.044$).

Logistic regression model was used to assess the rates of the specific co-occurring substance use from 2009 to 2018, which included cannabis, amphetamine, cocaine, and benzodiazepines as response variables (positive/negative) and the time (year, a continuous variable) as the independent variable in the regression model (Fig. 4). Therefore, the rate of a substance is increasing over time if the regression coefficient of independent variable (time) is greater than zero. In particular, this coefficient was 0.336 ($P < 0.001$) for amphetamine, indicating that co-occurring opioid and amphetamine use represented the most significant increase over time. There was also a significant increase in co-occurring opioid and cocaine use (coefficient 0.086, $P < 0.001$), while co-occurring cannabis use remained relatively stable (coefficient 0.022, $P = 0.18$) and co-occurring benzodiazepine use significantly decreased over time (coefficient = -0.159, $P < 0.001$).

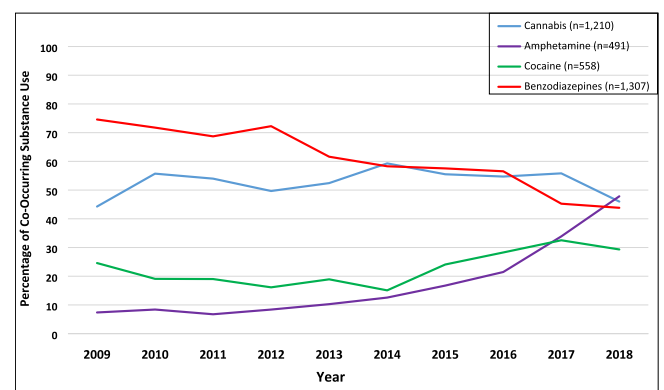


Fig. 4. Co-Occurring Substance Use in Individuals with Opioid Use Disorder by Year (n = 2,275).

4. Discussion

These data demonstrate that the current substance use epidemic in the U.S. extends well beyond opioids, indicating that broader and more inclusive SUD prevention and treatment strategies are needed. Previously published literature has documented the high prevalence of co-occurring substance use via self-report (Center for Behavioral Health Statistics and Quality, 2019; Hassan and Le Foll, 2019) and our findings using urine toxicology results also demonstrate a higher prevalence. While caution is needed when making comparisons to previous findings given that recent use of a substance certainly does not equate to meeting SUD diagnostic criteria (and therefore one-to-one comparisons should not be made), the following examples are provided to highlight the discrepancies strictly for qualitative purposes. For example, co-occurring substance use in our sample was higher compared with self-report data from the National Survey on Drug Use and Health (benzodiazepines: 57% vs. 29%; cocaine: 25% vs. 13%; and amphetamine: 22% vs. 5%) (Wilson et al., 2020). In addition, the percentage of patients positive for two or more substances in addition to opioids was more than six times greater in our sample (33% vs. 5%) relative to the prevalence of co-occurring SUD diagnoses provided by Heikman et al. (2017). A strength of our study, which complements the self-report data referenced above, is the utilization of urine toxicology results which may provide a more quantifiable, and possibly more accurate, reflection of recent use. Also, this method may be better than relying on SUD diagnoses in the EMR which may suffer from both over-reporting (e.g. diagnoses not removed from the EMR after they have resolved) or under-reporting (e.g. diagnoses not entered into the EMR as they were not directly assessed and/or not related to the primary concern at time of presentation).

The recent increase in co-occurring methamphetamine and opioid use is of great concern given the significant increase in U.S. overdose deaths related to psychostimulants (involved in 35% of overdose deaths in 2017 and representing a > 42% increase between 2015 and 2017) (Kariisa et al., 2019; Opioids and Methamphetamine, 2018). In addition, a national sample demonstrated an increase in co-occurring methamphetamine use among individuals with OUD entering a drug treatment program (from 19% in 2011 to 34% in 2017) (Ellis et al., 2018). Similarly, a cross sectional study of urine toxicology results from professionals providing routine care revealed over a five-fold increase in samples positive for methamphetamine between 2013 and 2018 (Twillman et al., 2020). While our sample of patients from WV included those presenting in an acute care setting, we also observed a significant increase in co-occurring opioid and amphetamine use (from 13% in 2014 to 48% in 2018). Also, there was a significantly higher percentage of individuals who were positive for buprenorphine and amphetamine relative to other opioids in combination with amphetamine. While it is unknown whether those who were positive for buprenorphine were in treatment and prescribed MOUD opposed to taking buprenorphine illicitly (described as a limitation below), this does speak to the possibility of “drug switching” (e.g. seeking the reinforcing of other substances due to craving and the positive effects of opioids being controlled with medication). In addition, while the prevalence was relatively low (9.9%), those individuals positive for buprenorphine were more likely to also be positive for 3 or more non-opioid substances relative to those who were positive for opioids other than buprenorphine. As such, incorporating behavioral therapies and community peer support which address addictive processes as a whole rather than a particular substance could better serve this population. Integrating other methods into treatment approaches is especially important for co-occurring substances which do not yet have any proven medication treatment, such as methamphetamine, especially given the increased prevalence. Contingency management has been shown to be an effective treatment for methamphetamine use disorder (Ronsley et al., 2020); however, there remains significant barriers to implementing this intervention into clinical practice.

While the rate of co-occurring opioid and benzodiazepine use has decreased over the years, the overall prevalence of co-occurring use remains very high (>40% were positive for both opioids and benzodiazepines in 2018). This is also of great concern given the extremely high rates of overdose involving benzodiazepines in combination with opioids, which was 65% in our sample. While we are unable to ascertain the rate of individuals whom were prescribed opioids and benzodiazepines in combination, this highlights the detrimental and possibly fatal impact of co-occurring use of these substances. The risks associated with co-occurring use of opioids and benzodiazepines has been well documented in the literature (Griggs et al., 2019; Gomes et al., 2011; Park et al., 2015). The potential negative outcomes of co-occurring use are not surprising given that both cause respiratory suppression which is the primary cause in overdose fatality; however, despite this, the rates of co-occurring opioid and benzodiazepine use remain elevated based on this recent 2018 data.

The findings of the current study also provide insight related to potential predictors and/or demographic and clinical characteristics of those patients with co-occurring substance use versus those who use opioids alone. For example, patients with co-occurring substance use were younger than those who used opioids alone, with age inversely related to the cumulative number of substances detected on urine toxicology. In addition, there was a higher prevalence of HCV+ among those who used co-occurring substances, especially in those also using stimulants (amphetamine and cocaine), with rates of HCV+ increasing as the cumulative number of substances detected on urine toxicology increased. The higher rates of HCV+ among patients with co-occurring opioid and stimulant use, may suggest a higher susceptibility to contracting HCV+ due to intravenous substance use, though this is speculative as route of administration data was not available for this analysis. In addition, literature has emerged indicating that methamphetamine use is associated with immune system dysfunction (Salamanca et al., 2015), potentially making individuals more susceptible to HCV transmission. Another possibility is that patients with co-occurring substance use may be more likely to engage in high risk behaviors putting them at a higher risk for contracting HCV. In support of this, PWID who use both opioids and methamphetamine are more likely to engage in risky injection use and inject more frequently (Al-Tayyib, Koester, Langeegger, & Raville, 2017). Regardless, while providing HCV testing, treatment, and prevention education should be offered to all individuals with SUD, these findings highlight the importance of providing these services to those at higher risk, such as patients with co-occurring substance use. Given the elevated rates of infectious disease and increased risk of HCV/HIV, especially among PWID, there is a continued need for integrated SUD and infectious disease treatment along with the utilization of harm reduction strategies, such as syringe exchange programs and naloxone distribution.

Despite the informative findings noted above, there are several important limitations which warrant consideration. One limitation is the generalizability of the data to others regions across the U.S. While treatment admissions for heroin and methamphetamine use have been increasing across the U.S., rates are notably higher in western states (Jones, Underwood, & Compton, 2020) and methamphetamine use is higher in rural areas (Shearer, Howell, Bart, & Winkelman, 2020), such as West Virginia. In addition, another limitation related to generalizability of the data is that these findings likely over-estimate the prevalence of co-occurring substance use in the general population given that data was extracted from inpatient psychiatric hospitalizations and ED presentations. For example, individuals seeking treatment and/or care for their substance use are more likely to be evaluated in these settings and thus are more likely to endorse recent substance use. Also, obtaining comprehensive urine toxicology screens may be prompted by either the patient's self-reported substance use and/or by the provider's behavioral observations possibly also leading to this over-estimation of the actual prevalence.

Limitations related to the assessment of substance use and

availability of data for extraction were also noted. Given the known depressant effects of alcohol, the combination of co-occurring opioid and alcohol use can have significant implications for overdose/toxicity and adverse medical consequences; however, results related to blood alcohol level were only available for < 15% of the sample. Despite this limitation, the prevalence of alcohol in combination with opioids and other non-opioid substances was elevated. The prevalence of alcohol, opioids, and benzodiazepines in combination was particularly elevated (37.1%) which is especially concerning given the respiratory suppression caused by all three of these substances individually. An additional limitation is that urine toxicology results specific to fentanyl were not available which is critical to investigate in future studies given the rise of fentanyl (both knowingly and unknowingly as an adulterant in other drugs). Another limitation is the specificity of automated immunoassay which was the technique used for the urine toxicology performed within the healthcare system from which the current data was extracted. While immunoassay has high sensitivity, it has lower specificity and compounds in the biological specimen other than the actual substance or its metabolite may bind to the assay and subsequently trigger a false-positive result. In addition, immunoassay does not distinguish among drugs within a class (e.g. cannot distinguish between various amphetamines, benzodiazepines, or opiates) (American Society for Addiction Medicine, 2013; Hadland & Levy, 2016). As a result, the available urine toxicology data only tested for amphetamine and we are therefore unable to distinguish whether patients were positive for amphetamine or methamphetamine. Related to this, and as mentioned previously, we were unable to ascertain the percentage of individuals whom were prescribed opioids, benzodiazepines, or amphetamine which is an additional limitation and impedes on determining whether the rates of co-occurring substance use represents licit (e.g. taken as prescribed) versus illicit use. Even if data related to prescribed medications were available, we would still be unable to state with certainty whether the medication was used as prescribed nor would we be able to determine if methamphetamine was also being used illicitly for those who were prescribed amphetamine.

Another limitation includes the half-life of the different substances reported in this study therefore affecting how long the substances can be detected via urine toxicology (further impacted by individual variability of the actual amount of recent use). For example, opioids and stimulants (cocaine and amphetamine), which have a relatively shorter half-life, can be detected in urine for 2–4 days following use while long-acting benzodiazepines and cannabis, which have a much longer half-life, can be detected in urine for up to 30 days following use (Moeller, Lee, & Kissack, 2008). As a result, the prevalence rates of those substances with a shorter half-life may be an underestimation if use occurred more than a few days prior to obtaining the urine toxicology screen. Conversely, those substances with a longer half-life may represent an over-estimation of actual prevalence in relation to toxicity (e.g. benzodiazepine or cannabis use may have occurred weeks prior to presentation and therefore unlikely a contributory factor to toxicity at time of presentation).

5. Conclusions

We posit that the current substance use crisis in the U.S. extends beyond opioids. Most recent policy, funding, and legislative efforts narrowly focus on opioids and fail to take into account that co-occurring substance use is the norm rather than the exception among those with OUD (Cicero, Ellis, & Kasper, 2020). Medications for OUD, such as buprenorphine, have demonstrated benefit in managing OUD; however, there have been no medications with the proven efficacy to address the co-occurring substances cited in this paper. Developing holistic models of care and prevention that address the social, psychological, biological and behavioral underpinnings of all substance use are warranted with strategies tailored to those most at risk (e.g., younger individuals). In summary, focusing solely on treatment of OUD will not solve the

problem of evolving and accelerating substance use patterns and/or co-occurring substance use, thus highlighting the need for comprehensive treatment approaches that address both the social determinants of substance use as well as the treatment of the SUD.

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CRediT authorship contribution statement

James J. Mahoney III: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Supervision, Writing - original draft. **Erin L. Winstanley:** Conceptualization. **Laura R. Lander:** Conceptualization. **James H. Berry:** Conceptualization. **Patrick J. Marshalek:** Conceptualization. **Marc W. Haut:** Conceptualization. **Jennifer L. Marton:** Investigation. **Wesley D. Kimble:** Project administration, Data curation, Resources, Supervision. **Matthew Armistead:** Investigation, Data curation, Resources, Software. **Sijin Wen:** Data curation, Formal analysis, Software. **Yilin Cai:** Data curation, Formal analysis, Software. **Sally L. Hodder:** Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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