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ORIGINAL ARTICLE

Characterization of Nonfatal Opioid, Cocaine, Methamphetamine, and Polydrug Exposure and Clinical Presentations Reported to the Toxicology Investigators Consortium Core Registry, January 2010–December 2021

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Abstract

Introduction To characterize and compare opioid-only, cocaine-only, methamphetamine-only, opioid-and-cocaine exposure, and opioid-and-methamphetamine exposure and to examine clinical presentations, leading to a better understanding of overdose effects involving these drug exposures.

Methods We examined drug exposures in the Toxicology Investigators Consortium (ToxIC) Core Registry from January 2010 to December 2021, a case registry of patients presenting to participating healthcare sites that receive a medical toxicology consultation. Demographic and clinical presentations of opioid-only, cocaine-only, methamphetamine-only, and opioid-and-cocaine exposure, and opioid-and-methamphetamine exposure consultations were described; differences between single and polydrug exposure subgroups were calculated to determine statistical significance. Clinical presentations associated with exposures were evaluated through calculated adjusted relative risk.

Results A total of 3,883 consultations involved opioids, cocaine, methamphetamine, opioid-and-cocaine exposure, or opioid-and-methamphetamine exposure. Opioid-only ($n=2{,}268$, 58.4%) and methamphetamine-only ($n=712$, 18.3%) comprised most consultations. There were significant differences in clinical presentations between exposure subgroups. Opioid-and-cocaine exposure consultations were 8.15 times as likely to present with a sympathomimetic toxidrome than opioid-only. Conversely, opioid-and-cocaine exposure and opioid-and-methamphetamine exposure were 0.32 and 0.42 times as likely to present with a sympathomimetic toxidrome compared to cocaine-only and methamphetamine-only consultations, respectively. Opioid-and-cocaine exposure was 0.67 and opioid-and-methamphetamine exposure was 0.74 times as likely to present with respiratory depression compared to opioid-only consultations. Similarly, opioid-and-cocaine exposure was 0.71 and opioid-and-methamphetamine exposure was 0.78 times as likely to present with CNS depression compared to opioid-only consultations.

Conclusions Used in combination, opioids and stimulants may mask typical clinical presentations of one another, misattributing incorrect drugs to overdose in both clinical treatment and public health surveillance.

Keywords Polydrug · Drug overdose · Stimulants · Polysubstance · Medical toxicology

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Introduction

Polydrug exposure is a common and growing concern for clinicians and public health practitioners due to increased risk for nonfatal and fatal drug overdose. A study utilizing data from the National Epidemiologic Survey on Alcohol and Related Disorders found that more than 90% of individuals with opioid use disorder (OUD) reported exposure of two or more additional substances, and more than 50% had an additional substance use disorder diagnosis [1]. In 2019, both opioids and stimulants were among the more common drugs involved with nonfatal polydrug overdose. An investigation of emergency department (ED) visits submitted to the National Syndromic Surveillance Program found that, of all nonfatal opioid overdoses reported, cocaine was involved in 23.6%, while amphetamine was involved in 17.1% of cases [2]. Similarly, a 2021 study examining nonfatal ED visits found that 15% of drug overdose-related visits in 2018 included two or more drug poisoning-related discharge diagnosis codes [3]. Additionally, a report investigating Healthcare Cost and Utilization Project data found cocaine and opioid-involved nonfatal overdose rates increased approximately 15% per year from 2006 to 2016, while psychostimulants with abuse potential (e.g., methamphetamine) and opioid-involved nonfatal overdose rates increased almost 50% per year from 2006 to 2016. In 2016, 27% of nonfatal cocaine- and 14% of psychostimulant-involved overdoses included a reported opioid [4].

Death rates for both cocaine and psychostimulants, with and without illicitly manufactured fentanyl and fentanyl analogs (IMFs), have continuously increased since 2013 [5, 6]. A recent report using data from the State Unintentional Drug Overdose Reporting System (SUDORS) found approximately two in five IMF-involved deaths also involved a stimulant in 2020 [7]. Similarly, in 2020, more than one-third of overdose deaths reported through SUDORS involved opioids and stimulants (34.9%). In comparison, approximately one-half of overdose deaths involved opioids without stimulants (48.1%) and one-eighth involved stimulants without opioids (12.6%) [8]. Of the 91,799 drug overdose deaths reported by the National Vital Statistics System (NVSS) in 2020 16.7% ($n = 15{,}372$) involved opioids and cocaine and 16.3% ($n = 14{,}983$) involved opioids and psychostimulants with abuse potential (e.g., methamphetamine) [9]. More recently, provisional data from NVSS predict an estimated 108,022 overdose deaths over 12 months, ending in May 2022 [10].

Polydrug exposure to opioids and stimulants can be intentional or unintentional (i.e., without the user's knowledge). Some individuals may intentionally mix these drugs to balance the tranquillizing effects of opioid exposure and central nervous system agitation of stimulant exposure [11]. While polydrug exposure may help mitigate undesirable drug side effects and symptoms (e.g., drowsiness from opioids), one also potentially increases the lethality of the other by exacerbating cardiovascular and pulmonary toxicity [12]. Additionally, contamination and adulteration of the illicit stimulant drug supply with opioids such as IMFs has been reported utilizing the National Forensic Laboratory Information System data. The Drug Enforcement Administration (DEA) reported that the presence of fentanyl in both cocaine and methamphetamine supplies increased from 2014 (fentanyl and cocaine, $n = 155$ samples; fentanyl and methamphetamine, $n = 13$ samples) to 2019 (fentanyl and cocaine, $n = 3{,}419$ samples; fentanyl and methamphetamine, $n = 1{,}618$ samples) [13]. Additionally, in April 2022, the DEA released a letter responding to multiple mass-overdose events related to incidents in which persons, while ingesting what they thought was cocaine, were exposed to fentanyl resulting in 58 overdoses and 29 overdose deaths [14].

Regardless of whether polydrug exposure to opioids and stimulants is intentional or unintentional, it is important to better understand the clinical signs of these drug overdoses among persons presenting in healthcare settings (e.g., hospitals and clinics). Studies exploring the differences in clinical presentations among these drug interactions are limited, potentially due to lack of available data. Understanding the complex presentations of these counter-effect-producing drug combinations is imperative in both clinical diagnosis and treatment of drug overdose as well as in tracking and addressing the drug overdose crisis.

Diagnostically, bedside consultations are an invaluable tool allowing physicians to ascertain a detailed patient assessment (e.g., patient interview, history, and physical examinations) [15–17]. These interactions and the accuracy of information collected during them are imperative in cases of polydrug exposures, where typical clinical presentations may be masked by one another. For instance, clinical signs associated with opioid toxicity include bradypnea, hypotension, and depressed mental status [18], whereas stimulant toxicity is associated with tachypnea, hypertension, and agitated mental status [18]. It is important for clinicians to be able to recognize and manage both presentations. The current study is the first to examine data captured during bedside consultations from the Toxicology Investigators Consortium (ToxIC) Core Registry to better understand the clinical presentations of opioid-and-stimulant polydrug exposure (i.e., opioid-and-cocaine and opioid-and-methamphetamine) compared to opioid- or stimulant-only exposure. Using this detailed clinical data source, we aim to evaluate clinical presentations of single and polydrug

exposure among patients presenting with a drug exposure of interest. We characterized and compared bedside consultations from the ToxIC Core Registry that involved opioids, cocaine, methamphetamine, opioids-and-cocaine, and opioids-and-methamphetamine to evaluate differences in clinical presentations. Findings from this study may help to fill the knowledge gaps surrounding specific presentations of these polydrug exposures, leading to better understanding and identification of overdoses involving these drugs as well as subsequent treatment options.

Methods

Data

We performed a secondary analysis of data collected through the ToxIC Core Registry from January 2010 through December 2021 across 21 states ($N = 88{,}559$). The ToxIC Core Registry is a case registry of patients presenting to participating healthcare sites that receive a bedside medical toxicology physician consultation [19]. Deidentified data, such as demographics, exposures, clinical presentation, and outcomes, are collected and entered into the registry by medical toxicologists [20].

Demographic variables are collected by the reporting clinician and include age (grouped for analysis into the following ranges for age in years: 15–24, 25–34, 35–44, 45–54, 55 +), sex (i.e., female, male), and race and ethnicity (grouped for analysis as: Hispanic, non-Hispanic Black, non-Hispanic White, and non-Hispanic and any other race (i.e., American Indian or Alaskan Native, Asian, Australian Aboriginal, Native Hawaiian or Pacific Islander, mixed, unknown or uncertain) reported). Race and ethnicity data are limited to 2014–2021 due to collection of these variables beginning in 2014. Similarly, drug exposures are assessed during the consultation by the clinician utilizing available evidence (e.g., patient self-report, presence of the product of exposure, clinical presentation, physical examination, and ancillary data). The ToxIC Core Registry was reviewed by the Western Institutional Review Board (IRB) and participating sites have obtained approval from their respective IRBs.

Sample and Case Definitions

Our analytical sample included only patients who were not deceased at the time of consultation and where the patient reported an intentional exposure (i.e., use with the knowledge of the exposed person) involving single and polydrug exposures of interest ($n = 9{,}338$). Single-drug exposures included opioids, cocaine, or methamphetamine, while polydrug exposures included either opioid-and-cocaine or opioid-and-methamphetamine. Cases involving additional other exposures were further excluded. This left a final analytic sample of 3,883 total consultations ($n = 2{,}268$ opioid-only; $n = 380$ cocaine-only; $n = 712$ methamphetamine-only; $n = 343$ opioid-and-cocaine exposure; and $n = 180$ opioid-and-methamphetamine exposure consultations) (see Fig. 1).

Mutually exclusive coding was applied to identify consultations with polydrug exposures of interest (i.e., ≥ 1 opioid and ≥ 1 cocaine exposure or ≥ 1 opioid and ≥ 1 methamphetamine exposure per consultation); single-drug exposure data were similarly delineated (i.e., ≥ 1 opioid, cocaine, or methamphetamine exposure per consultation).

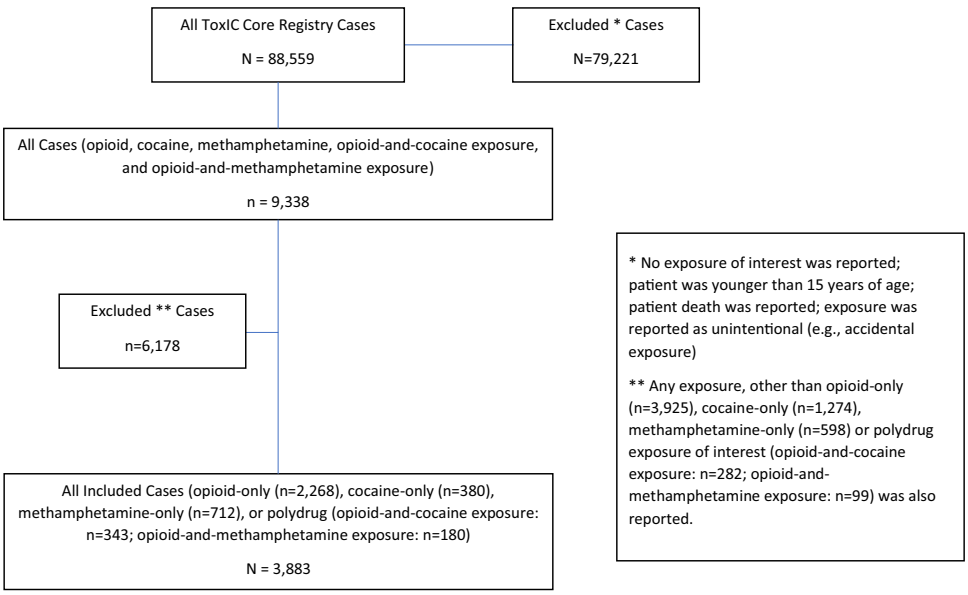

Fig. 1 Case inclusion flowchart.

Clinical Presentations

Several variables were used to determine clinical presentations. The type of toxic syndrome (toxidrome) noted by the physician included either sympathomimetic (e.g., agitation, tachycardia) or opioid toxidrome (e.g., central nervous system (CNS) depression, respiratory depression, and miosis) [18]. Additionally, related notable vital sign abnormalities (i.e., hypertension, tachycardia, and bradypnea), pulmonary signs (i.e., respiratory depression), nervous system-related signs (i.e., CNS stimulation (i.e., agitation and delirium/toxic psychosis), coma or CNS depression, and seizures), and renal signs (i.e., acute kidney injury (AKI) and rhabdomyolysis) were assessed.

Statistical Analysis

Statistical analyses include chi-square and Mantel–Haenszel testing, with significance set at $p < 0.05$, to evaluate differences between single and polydrug exposure subgroups. Investigators also ran multivariable modified Poisson regression models [21] to determine whether differences between single and polydrug exposure-related clinical presentations are statistically significant by calculating relative risk with corresponding 95% confidence intervals (CI), adjusting for sex and age group. Investigators explored 9 clinical presentations in adjusted analyses due to their clinical significance related to drug overdose [18], including sympathomimetic toxidrome, opioid toxidrome, hypertension, tachycardia, respiratory depression, CNS stimulation, coma or CNS depression, AKI, and rhabdomyolysis. Cell sizes with less than 10 cases are suppressed and not analyzed. All analyses are conducted using SAS 9.4.

Results

Descriptive Analysis

Overall

Opioid-only consultations comprised nearly 60% ($n = 2{,}268$, 58.4%) of all consultations included in this analytical sample; cocaine-only ($n = 380$, 9.8%) and methamphetamine-only ($n = 712$, 18.3%) comprised fewer consultations (Table 1). Opioid-and-cocaine exposure accounted for 8.8% of included consultations ($n = 343$), proportionally almost more than double that of opioid-and-methamphetamine exposure ($n = 180$, 4.6%). Table 1 provides a description of the exposure breakdown by demographic characteristics.

Demographic Characteristics

Males accounted for 77.1% of cocaine-only ($n = 293$) versus 65.6% of opioid-and-cocaine exposure consultations ($n = 225$), and 75.6% of methamphetamine-only consultations ($n = 538$) versus 66.1% of opioid-and-methamphetamine exposure ($n = 119$) (Table 1). Patients aged 15–34 years comprised 36.6% of cocaine-only ($n = 146$) compared to 42.6% of opioid-and-cocaine exposure consultations (Table 1). While patients aged 55 years and older comprised 15.5% of opioid-only consultations ($n = 352$), they comprised only 4% of opioid-and-methamphetamine exposure consultations ($n = 8$, 4.4%). Non-Hispanic Black patients comprised 29.5% of cocaine-only ($n = 112$) and 19% of opioid-and-cocaine exposure consultations ($n = 65$); conversely, non-Hispanic White patients presented similarly, but reversed categories (cocaine-only: $n = 82$, 21.6%; opioid-and-cocaine exposure: $n = 95$, 27.7%, respectively). Non-Hispanic Black patients accounted for only 6% of methamphetamine-only consultations ($n = 43$).

Non-Hispanic White patients comprised the largest proportion of opioid-only ($n = 953$, 42.0%), opioid-and-cocaine exposure ($n = 95$, 27.7%), methamphetamine-only ($n = 340$, 47.8%), and opioid-and-methamphetamine exposure consultations ($n = 121$, 67.2%). Patients who were identified as non-Hispanic and any other or multiple races comprised 17.4% of opioid-only ($n = 395$), 9.2% of cocaine-only ($n = 35$), 14.5% of methamphetamine-only ($n = 103$), 18.1% of opioid-and-cocaine exposure ($n = 62$), and 11.7% of opioid-and-methamphetamine exposure consultations ($n = 21$). Hispanic patients comprised less than 10% of opioid-only ($n = 191$, 8.4%), cocaine-only ($n = 34$, 8.9%), and opioid-and-cocaine exposure consultations ($n = 33$, 9.6%). Conversely, Hispanic patients comprised 13.8% of methamphetamine-only ($n = 98$) and 11.1% of opioid-and-methamphetamine exposure consultations ($n = 20$).

Clinical Presentations

Clinical Toxidrome

More than 44% of opioid-only consultations ($n = 837$, 44.8%) presented with an opioid toxidrome compared to 26.6% of opioid-and-cocaine exposure consultations ($n = 67$). Only slightly more than 1% of opioid-only consultations presented with an apparent sympathomimetic toxidrome ($n = 21$, 1.1%), compared to 12.3% of opioid-and-cocaine exposure consultations ($n = 31$); conversely, 47.7% of cocaine-only consultations ($n = 112$) presented with a sympathomimetic toxidrome. Similarly, 70.4% of methamphetamine-only presented with a sympathomimetic toxidrome ($n = 449$), compared to 31% of opioid-and-methamphetamine exposure consultations ($n = 48$) (Table 2).

Table 1 Descriptive characteristics of single and polydrug exposures captured in ToxIC Core Registry, January 2010–December 2021.

Characteristic	Combined use vs opioid-only and cocaine-only			Combined use vs opioid-only and methamphetamine-only		
	Opioid-only	Cocaine-only	Opioid and cocaine	Opioid-only	Methamphetamine-only	Opioid and methamphetamine
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Overall	2,268 (58.4)	380 (9.8)	343 (8.8)	2,268 (58.4)	712 (18.3)	180 (4.6)
Sex						
Female	830 (36.6)	**86 (22.6)**	118 (34.4)	830 (36.6)	**171 (24.0)**	60 (33.3)
Male	1,432 (63.1)	**293 (77.1)**	225 (65.6)	1,432 (63.1)	**538 (75.6)**	119 (66.1)
Missing	6 (0.3)	**1 (0.0)**	0 (0.0)	6 (0.3)	**3 (0.4)**	1 (0.6)
Age Ranges						
15–24	529 (23.3)	**44 (11.6)**	47 (13.7)	**529 (23.3)**	115 (16.2)	28 (15.6)
25–34	632 (27.9)	**95 (25.0)**	99 (28.9)	**632 (27.9)**	259 (36.4)	65 (36.1)
35–44	397 (17.5)	**88 (23.2)**	93 (27.1)	**397 (17.5)**	192 (27.0)	59 (32.8)
45–54	300 (13.2)	**89 (23.4)**	56 (16.3)	**300 (13.2)**	88 (12.4)	18 (10.0)
55 +	352 (15.5)	**55 (14.5)**	44 (12.8)	**352 (15.5)**	39 (5.5)	8 (4.4)
Missing	58 (2.6)	**9 (2.4)**	4 (1.2)	**58 (2.6)**	19 (2.7)	2 (1.1)
Race/Ethnicity[a]						
Non-Hispanic Black	**231 (10.2)**	**112 (29.5)**	65 (19.0)	**231 (10.2)**	**43 (6.0)**	8 (4.4)
Non-Hispanic White	**953 (42.0)**	**82 (21.6)**	95 (27.7)	**953 (42.0)**	**340 (47.8)**	121 (67.2)
Non-Hispanic other[b]	**395 (17.4)**	**35 (9.2)**	62 (18.1)	**395 (17.4)**	**103 (14.5)**	21 (11.7)
Hispanic	**191 (8.4)**	**34 (8.9)**	33 (9.6)	**191 (8.4)**	**98 (13.8)**	20 (11.1)
Missing	**96 (4.2)**	**16 (4.2)**	19 (5.5)	**96 (4.2)**	**38 (5.3)**	4 (2.2)

$\alpha \leq 0.05$: referent-categories are single-drug subgroups (opioid-only, cocaine-only, or methamphetamine-only) compared to opioid-and-cocaine exposure or opioid-and-methamphetamine exposure. Statistically significant findings are bolded

[a]Race and ethnicity data collection from 2014 to 2021

[b]Patients who identified as non-Hispanic and any other or multiple races

Notable Vital Sign Abnormalities

Only 1.6% of opioid-only ($n = 30$) and 17.4% of cocaine-only consultations ($n = 41$) presented with hypertension, compared to 5.2% of opioid-and-cocaine exposure consultations ($n = 13$). Tachycardia was reported in 29.4% of cocaine-only (n = 69) and 5.8% of opioid-only consultations ($n = 108$) compared to 11.5% of opioid-and-cocaine exposure consultations ($n = 29$). Similarly, 47.3% of methamphetamine-only consultations (n = 302) presented with tachycardia compared to 16.1% of opioid-and-methamphetamine exposure consultations (n = 25). Opioid-only consultations ($n = 356$, 19.1%) presented with bradypnea proportionally more often than both opioid-and-cocaine exposure ($n = 34$, 13.5%) and opioid-and-methamphetamine exposure consultations ($n = 18$, 11.6%) (Table 2).

Pulmonary Clinical Signs

Opioid-and-cocaine exposure ($n = 69$, 27.9%) and opioid-and-methamphetamine exposure consultations ($n = 35$, 25.4%) presented with respiratory depression proportionally more often than cocaine- ($n = 11$, 4.7%) and methamphetamine-only consultations ($n = 43$, 6.7%) (Table 2).

Nervous System Clinical Signs

CNS stimulation was reported in 57.9% of cocaine-only ($n = 136$) and 78.8% of methamphetamine-only ($n = 503$), compared to 30.2% of opioid-and-cocaine exposure ($n = 76$) and 52.9% of opioid-and-methamphetamine exposure consultations ($n = 82$). Comparatively, only 12.2% of opioid-only consultations ($n = 228$) presented with CNS stimulation. Coma or CNS depression was the most common nervous system clinical presentation in opioid-involved exposure categories; 62.5% of opioid-only consultations ($n = 1{,}168$) compared to 50% of opioid-and-cocaine exposure ($n = 126$) and 46.5% of opioid-and-methamphetamine exposure consultations ($n = 72$) (Table 2). Conversely, 20.4% cocaine- ($n = 48$) and 13.3% methamphetamine-only consultations ($n = 85$) presented with coma or CNS depression. More than 8% of cocaine- ($n = 19$. 8.1%) and nearly 5% of methamphetamine-only consultations ($n = 31$, 4.9%) presented with seizures (Table 2).

Table 2 Clinical presentations of single and polydrug exposures captured in the ToxIC Core Registry ($n = 3{,}148$), January 2010–December 2021.

Clinical characteristic(s) presentations	Combined use vs opioid-only and cocaine-only			Combined use vs opioid-only and methamphetamine-only		
	Opioid-only	Cocaine-only	Opioid and cocaine	Opioid-only	Methamphetamine-only	Opioid and methamphetamine
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Overall	1,868 (59.3)	235 (7.5)	252 (8.0)	1,868 (59.3)	638 (20.3)	155 (4.9)
Clinical toxidrome						
Sympathomimetic syndrome	**21 (1.1)**	**112 (47.7)**	31 (12.3)	**21 (1.1)**	**449 (70.4)**	48 (31.0)
Opioid	**837 (44.8)**	-	67 (26.6)	837 (44.8)	-	51 (32.9)
Notable/major vital sign abnormalities						
Hypertension[a]	**30 (1.6)**	**41 (17.4)**	13 (5.2)	30 (1.6)	**64 (10.0)**	0 (0.0)
Tachycardia[b]	**108 (5.8)**	**69 (29.4)**	29 (11.5)	**108 (5.8)**	**302 (47.3)**	25 (16.1)
Bradypnea[c]	**356 (19.1)**	-	34 (13.5)	**356 (19.1)**	-	18 (11.6)
Pulmonary						
Respiratory depression	706 (37.8)	**11 (4.7)**	71 (28.2)	706 (37.8)	**43 (6.7)**	41 (26.5)
Nervous system						
CNS stimulation	**228 (12.2)**	**136 (57.9)**	76 (30.2)	**228 (12.2)**	**503 (78.8)**	82 (52.9)
Coma/CNS depression	**1,168 (62.5)**	**48 (20.4)**	126 (50.0)	**1,168 (62.5)**	**85 (13.3)**	72 (46.5)
Seizures	132 (7.1)	**19 (8.1)**	0 (0.0)	132 (7.1)	**31 (4.9)**	0 (0.0)
Renal/muscle						
Acute kidney injury[d]	**158 (8.5)**	**19 (8.1)**	36 (14.3)	**158 (8.5)**	70 (11.0)	12 (7.7)
Rhabdomyolysis[e]	**174 (9.3)**	44 (18.7)	35 (13.9)	**174 (9.3)**	**171 (26.8)**	25 (16.1)

Some cases in the initial sample may not have presented with clinical signs of significance to drug effect or overdose ($n = 735$) and were subsequently removed from clinical analysis

Cases can report multiple clinical presentations

$\alpha \leq 0.05$: referent-categories are single-drug subgroups (opioid-only, cocaine-only, or methamphetamine-only) compared to opioid-and-cocaine or opioid-and-methamphetamine exposure. Statistically significant findings are bolded

Symbol "–" indicates insufficient data ($n < 10$ cases)

[a]Hypertension = systolic blood pressure > 200 and/or diastolic blood pressure > 120

[b]Tachycardia = pulse > 140

[c]Bradypnea = respiratory rate < 10

[d]Acute kidney injury = creatinine > 2

[e]Rhabdomyolysis = creatine phosphokinase > 1,000

Relative Risk

Polydrug Opioid-and-Cocaine Exposure Compared to Single-Drug Exposure

The regression analysis results are presented in Table 3. Opioid-and-cocaine exposure consultations were 8.15 (95% CI = 4.85–13.69) and 0.32 (95% CI = 0.22–0.46) times as likely to present with a sympathomimetic toxidrome compared to opioid- and cocaine-only consultations, respectively. Conversely, opioid-and-cocaine exposure were 0.54 (95% CI = 0.44–0.68) times as likely to present with an opioid toxidrome compared to opioid-only consultations.

Opioid-and-cocaine exposure consultations were 2.49 (95% CI = 1.31–4.75) times as likely to present with hypertension and 1.89 (95% CI = 1.29–2.77) times as likely to present with tachycardia compared to opioid-only. Conversely, opioid-and-cocaine exposure consultations were 0.30 (95% CI = 0.17–0.55) times as likely to present with hypertension and 0.43 (95% CI = 0.29–0.64) times as likely to present with tachycardia compared to cocaine-only. Opioid-and-cocaine exposure consultations were 0.67 (95% CI = 0.54–0.83) times as likely to present with respiratory depression compared to opioid-only.

Opioid-and-cocaine exposure consultations were 1.97 (95% CI = 1.56–2.48) times as likely as opioid-only and 0.54 (95% CI = 0.43–0.69) times as likely as

Table 3 Adjusted relative risk of clinical presentations and signs of single and polydrug exposures captured in the ToxIC Core Registry, January 2010–December 2021.

Clinical presentations[a]	Opioid and cocaine polydrug exposure				Opioid and methamphetamine polydrug exposure			
	Polydrug vs opioid[b]		Polydrug vs cocaine[b]		Polydrug vs opioid[b]		Polydrug vs methamphetamine[b]	
	aRR[c]	95% CI	aRR[c]	95% CI	aRR[c]	95% CI	aRR[c]	95% CI
Toxidrome								
Sympathomimetic	**8.15**	**4.85–13.69**	**0.32**	**0.22–0.46**	**22.42**	**13.95–36.03**	**0.42**	**0.33–0.53**
Opioid	**0.54**	**0.44–0.68**	-	-	**0.78**	**0.62–0.99**	-	-
Notable vital sign abnormality								
Hypertension	**2.49**	**1.31–4.75**	**0.30**	**0.17–0.55**	-	-	-	-
Tachycardia	**1.89**	**1.29–2.77**	**0.43**	**0.29–0.64**	**2.70**	**1.80–4.06**	**0.33**	**0.23–0.47**
Pulmonary								
Respiratory depression	**0.67**	**0.54–0.83**	-	-	**0.74**	**0.56–0.98**	**3.66**	**2.48–5.40**
Nervous system								
CNS stimulation	**1.97**	**1.56–2.48**	**0.54**	**0.43–0.69**	**3.93**	**3.18–4.85**	**0.62**	**0.53–0.74**
CNS depression/coma	**0.71**	**0.62–0.82**	**2.34**	**1.78–3.08**	**0.78**	**0.65–0.94**	**3.22**	**2.50–4.17**
Renal/muscle								
Acute kidney injury	**1.51**	**1.07–2.12**	**2.22**	**1.32–3.72**	0.98	0.55–1.75	0.70	0.39–1.25
Rhabdomyolysis	1.27	0.90–1.81	0.85	0.56–1.29	1.52	0.99–2.31	**0.54**	**0.36–0.82**

Adjusted by sex and age group

[a]Clinical effects and presentations selected based on clinical significance to drug effect or overdose

[b]The sample for opioid-and-cocaine exposure vs opioid-only model (opioid-and-cocaine exposure $n=256$; opioid-only $n=1{,}697$), the sample for opioid-and-cocaine exposure vs cocaine-only (opioid-and-cocaine exposure $n=256$; cocaine-only $n=251$), the sample for opioid-and-methamphetamine exposure vs opioid-only (opioid-and-methamphetamine exposure $n=140$; opioid-only $n=1{,}697$), and the sample for opioid-and-methamphetamine exposure vs methamphetamine-only (opioid-and-methamphetamine exposure $n=140$; methamphetamine-only $n=543$)

[c]*aRR*, adjusted relative risk. Statistically significant findings (aRR confidence intervals ranges both $<$ or >1) for differences in between single vs polydrug exposure are bolded

Symbol "–" indicates insufficient data to calculate aRR

cocaine-only to present with CNS stimulation. Conversely, opioid-and-cocaine exposure consultations were 0.71 (95% CI = 0.62–0.82) times as likely as opioid-only and 2.34 (95% CI = 1.78–3.08) times as likely as cocaine-only to present with coma or CNS depression. Opioid-and-cocaine exposure consultations were 1.51 (95% CI = 1.07–2.12) times as likely as opioid-only and 2.22 (95% CI = 1.32–3.72) times as likely as cocaine-only to present with AKI.

Polydrug Opioid-and-Methamphetamine Exposure Compared to Single-Drug Exposure

Opioid-and-methamphetamine exposure consultations were 22.42 (95% CI = 13.95–36.03) times as likely to report a sympathomimetic toxidrome compared to opioid-only and 0.42 (95% CI = 0.33–0.53) times as likely as methamphetamine-only. Similarly, opioid-and-methamphetamine exposure consultations were 2.70 (95% CI = 1.80–4.06) times as likely as opioid-only and 0.33 (95% CI = 0.23–0.47) times as likely as methamphetamine-only to present with tachycardia. Conversely, opioid-and-methamphetamine exposure consultations were 0.74 (95% CI = 0.56–0.98) times as likely as opioid-only and 3.66 (95% CI = 2.48–5.40) times as likely as methamphetamine-only to present with respiratory depression.

Opioid-and-methamphetamine exposure consultations were 3.93 (95% CI = 3.18–4.85) times as likely as opioid-only and 0.62 (95% CI = 0.53–0.74) times as likely as methamphetamine-only to present with CNS stimulation. Conversely, opioid-and-methamphetamine exposure consultations were 0.78 (95% CI = 0.65–0.94) times as likely as opioid-only and 3.22 (95% CI = 2.50–4.17) times as likely as methamphetamine-only to present with coma or CNS depression. Opioid-and-methamphetamine exposure consultations were 0.54 (95% CI = 0.36–0.82) times as likely as methamphetamine-only to present with rhabdomyolysis.

Discussion

An examination of bedside medical toxicology consultations involving single- and polydrug exposures revealed several important similarities and differences among opioid, cocaine, and methamphetamine exposure consultations and clinical presentations. First, opioid-only consultations were more than half of the sample, and less than one in ten consultations included opioid-and-cocaine exposure or opioid-and-methamphetamine exposure. Though many studies have demonstrated that polydrug opioid with cocaine [22–25] and opioid with methamphetamine exposure [26] is common, these consultations did not make up a majority of our sample. Second, several findings on differences across some patient demographics are consistent with previous literature on both nonfatal and fatal drug overdose. A higher prevalence of men than women using opioids, cocaine, and methamphetamine has been noted in several studies [22, 27, 28] and is consistent with current findings. Our analysis also revealed a relatively lower exposure of methamphetamine in non-Hispanic Black patients compared to non-Hispanic White patients, which is corroborated with results from other data sources [29, 30]. Similarly, our results support previous research exploring racial and ethnic group differences using data from NVSS. For example, Kariisa and colleagues [31–33] found that cocaine-involved overdoses in 2019 were largely driven by opioids, and rates were highest among non-Hispanic Black persons. Additionally, this study provides potential insight and clinical considerations for clinicians in treating patients presenting with polydrug opioid and stimulant toxicity.

Clinical presentations within our cohort highlight the complex nature of polydrug exposures where drug effects may mask each other, thus impacting diagnostic and treatment options. Opioid toxicity was present in both opioid-and-cocaine exposure and opioid-and-methamphetamine exposure consultations with roughly one-quarter and one-third of consultations presenting with an opioid toxidrome, respectively. Across polydrug exposure consultations, 12.5% patients presented with bradypnea and more than 25% with respiratory depression. Drug effects of stimulants when combined with drug effects of opioids may lead to unrecognized pulmonary signs, such as respiratory depression and bradypnea [34, 35]. All these findings highlight the need for broadening naloxone administration and provision practices. Comparatively, opioid-and-methamphetamine exposure consultations were more than three and one-half times as likely to present with respiratory depression compared to methamphetamine-only consultations. Coma or CNS depression, while secondary to respiratory depression, is clinically associated with opioid toxicity. Compared to cocaine- and methamphetamine-only, opioid-and-cocaine exposure and opioid-and-methamphetamine exposure consultations were 2.34 and 3.22 times as likely to present with coma or CNS depression, respectively.

Conversely, clinical presentations associated with stimulant toxicity may be masked by polydrug opioid and stimulant exposure, as well. Stimulant drug effects may emerge when opioid drug effects recede. These rapid changes in patient disposition, such as in heart and respiration rates, can lead to arrhythmias, heart failure, or stroke [36]. Compared to both cocaine- and methamphetamine-only consultations, polydrug exposure consultations were one-third and two-fifths as likely to present with a sympathomimetic toxidrome, respectively. Similarly, opioid-and-cocaine exposure and opioid-and-methamphetamine exposure consultations were half as likely and less than two-thirds as likely to develop CNS stimulation compared to cocaine- and methamphetamine-only consultations, respectively.

Among opioid-only consultations, 5.8% presented with tachycardia and 12.2% with CNS stimulation. There may be several reasons for these reported clinical signs. Certain opioids, such as tramadol, are more frequently associated with tachycardia [37]. Additionally, prehospital or early naloxone administration may have led to withdrawal-related signs, including tachycardia and CNS stimulation.

Previous studies on motivations for polydrug opioid and stimulant exposure included mitigation of unwanted drug effects [35–37], specifically CNS stimulation or depression, and may support these findings. CNS stimulation and psychomotor agitation associated with stimulant toxicity is typically treated with benzodiazepines [38]. Polydrug exposure should be considered when treating stimulant toxicity as the addition of benzodiazepines may exacerbate unrecognized opioid-related signs such as respiratory and CNS depression [39].

With the continued increase in both intentional and unintentional polydrug exposure and the complications in diagnosis and treatment due to potential masking of clinical signs, further investigations into different clinical implications among these drug exposure groups are warranted. Our results reinforce that when polydrug opioid and stimulant exposure occurs, clinicians should be aware that signs associated with either drug may be masked by signs associated with the other and to remain vigilant while evaluating, diagnosing, and treating drug toxicities. In addition, clinicians can play an important role in the prevention of future drug overdose among patients under their care by talking to patients about the risks of polydrug opioid and stimulant exposure, especially with the potential for IMFs contamination in the illicit drug supply [13, 14]. Harm reduction strategies, such as the distribution of naloxone and fentanyl test strips, are keys to the prevention of nonfatal and fatal drug overdose [40, 41]. Additionally, improving access to medications for opioid use disorder,

specifically initiation of buprenorphine at bedside, may help to prevent future overdose [42]. While there are currently no medications for persons with a stimulant use disorder, patients can be referred and linked to other treatment options, such as contingency management. Ensuring patients are linked with appropriate addiction medicine treatment and harm reduction resources upon leaving the hospital is also imperative in prevention of future drug overdose [41, 42]. Multi-sectoral partnerships between public health, public safety, and health systems are a key driver for implementing these harm reduction strategies [41, 42].

Limitations

Our study has several limitations. The ToxIC Core Registry is limited to medical toxicology consultations reported by participating sites and providers, potentially limiting and biasing the sample toward more severe presentations and unusual signs and symptoms, as these are more likely to require a consultation. Analyses were limited to nonfatal cases, potentially excluding more severe exposures resulting in drug overdose death. While the ToxIC Core Registry asks participating providers to report all consultation data, these data are voluntarily reported, and completeness of data is not measured. The consultation may have been performed in patients that improved after initial treatment, such as those who received naloxone prior to hospital admission (e.g., first responder administration), leading to a possible underestimation of clinical presentations that are diagnosed by medical toxicology physicians and laboratory methods. Clinical limitations of laboratory testing may require physicians to rely on the clinical presentation, patient history and self-report, and ancillary data collected during treatment. Finally, the data cannot differentiate between potential cases of adulteration, contamination, or purposeful polydrug exposure.

Conclusions

Our results demonstrate that the clinical presentation of opioid, cocaine, or methamphetamine exposure can be altered with polydrug exposure. As polydrug exposure continues to rise, a better understanding of the clinical signs and presentations of opioid and stimulant exposure may help guide clinicians making diagnostic and therapeutic decisions for care, especially when laboratory testing results are unavailable. These findings also highlight the importance of understanding the potential limitations of self-report and clinical diagnoses as adulteration or contamination of the illicit drug supply continues to be a major concern of clinicians and public health officials.

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Declarations

Conflict of Interest None.

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