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Psychostimulant drug co-ingestion in non-fatal opioid overdose☆

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HIGHLIGHTS

- Over half of study patients with opioid overdose were also exposed to psychostimulants, indicating a high prevalence of opioid and psychostimulant co-exposure.
- Patients with opioid and psychostimulant co-exposure required significantly higher doses of naloxone to reverse respiratory depression, suggesting a higher severity of overdose in these patients.
- Opioid and psychostimulant co-exposure was not predictive of increased incidence of intubation or cardiac arrest.

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ABSTRACT

Introduction: In 2019, there were over 16,000 deaths from psychostimulant overdose with 53.5% also involving an opioid. Given the substantial mortality stemming from opioid and psychostimulant co-exposure, evaluation of clinical management in this population is critical but remains understudied. This study aims to characterize and compare clinical management and outcomes in emergency department (ED) overdose patients with analytically confirmed exposure to both opioids and psychostimulants with those exposed to opioids alone.
Methods: This was a secondary analysis of a prospective consecutive cohort of ED patients age 18+ with opioid overdose at 9 hospital sites from September 21, 2020 to August 17, 2021. Toxicologic analysis was performed using liquid chromatography quadrupole time-of-flight mass spectrometry. Patients were divided into opioid-only (OO) and opioid plus psychostimulants (OS) groups. The primary outcome was total naloxone bolus dose administered. Secondary outcomes included endotracheal intubation, cardiac arrest, troponin elevation, and abnormal presenting vital signs. We employed t-tests, chi-squared analyses and multivariable regression models to compare outcomes between OO and OS groups.
Results: Of 378 enrollees with confirmed opioid overdose, 207 (54.8%) had psychostimulants present. OO patients were significantly older (mean 45.2 versus 40.6 years, $p < 0.01$). OS patients had significantly higher total naloxone requirements (mean total dose 2.79 mg versus 2.12 mg, $p = 0.009$). There were no significant differences in secondary outcomes.
Conclusion: Approximately half of ED patients with confirmed opioid exposures were also positive for psychostimulants. Patients in the OS group required significantly higher naloxone doses, suggesting potential greater overdose severity.

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1. Introduction

Since 2015, there has been a marked increase in psychostimulant and opioid overdose deaths, with over 75,000 opioid overdose deaths in 2021 (CDC, 2021) and over 16,000 psychostimulant overdose deaths in 2019 (Hedegaard, 2021). This concurrent rise in opioid and psychostimulant overdose deaths has been termed the "fourth wave" of the opioid epidemic. Psychostimulants and opioids are commonly used together, with 53.5% of reported psychostimulant overdose deaths in 2019 also involving an opioid (Hedegaard, 2021).

In the past, the combination of diacetylmorphine (heroin) and cocaine has been colloquially referred to as a "speedball". Previous reports have described a unique synergistic profile of effects, outside of those caused by either drug alone (Duvauchelle et al., 1998; Foltin and Fischman, 1992). Coincident use of cocaine and opioid is known to be a predictor of accidental fatal drug overdose (O'Driscoll et al., 2001).

There has been a proliferation of synthetic opioids, such as fentanyl, fentanyl analogs (fentalogs) and other opioid agonists in the drug supply in the past decade (CSFRE, 2021). Synthetic opioid overdose deaths increased by over 50% from 2019 to 2020 and were responsible for over 82% of opioid-involved deaths in 2020 (CDC, 2023). This trend is temporally associated with increasing rates of mortality from combined opioids and stimulants among multiple racial and ethnic demographic groups (Townsend et al., 2022). Estimates indicate that approximately 1 in 5 opioid overdose deaths also included cocaine or another stimulant (Jones et al., 2018). Reports of individuals who use primarily stimulants, such as cocaine and methamphetamines, having accidental self-reported exposed to opioids due to fentanyl contamination have increased (DiSalvo et al., 2021). This combination of psychostimulants with synthetic opioids can impact overdose severity and ultimately mortality.

Based on clinical observation, we hypothesized that patients with co-exposure to opioids and psychostimulants may require higher doses of naloxone for opioid reversal. This may be in part due to use of higher quantities of opioids when used in combination with psychostimulants. Accordingly, our primary study aim is to compare naloxone dosing requirements in patients with opioid and psychostimulant exposure with patients with opioid exposure alone. Secondary aims include comparing overdose severity in opioid and psychostimulant co-exposure with opioid exposure alone.

2. Materials and methods

2.1. Study design

This was a secondary data analysis of the Toxicology Investigators Consortium (ToxIC) Fentalog Study, an ongoing, multicenter study across 8 healthcare sites in the United States. Emergency department (ED) patients with a presumed acute opioid overdose and residual blood samples were enrolled into this cohort study between September 21, 2020 to August 17, 2021. A chart review and comprehensive blood toxicology analyses were performed. Data on clinical stay and characteristics were collected by chart review up until discharge or death. The WCG IRB provided approval and a waiver of informed consent.

2.2. Study setting and population

Patients aged 18 and older were screened for inclusion if they had a suspected opioid overdose and had waste blood leftover from specimens sent as part of routine clinical care. Suspected opioid overdose was identified via chart review in three ways: (1) chief complaint or discharge diagnosis; (2) receipt of naloxone for overdose reversal in the ED; or (3) self-reported opioid use resulting in overdose. Study inclusion criteria were: age 18 and over, suspected opioid overdose as per criteria above with positive confirmatory opioid serum drug screen and available waste blood specimen. Exclusion criteria were age under 18, co-occurring trauma/burns, custody of law enforcement, or non-toxicological diagnoses (e.g. sepsis).

Patients were split into opioid-only (OO) and opioid plus psychostimulants (OS) groups. Patients with serum-analyte confirmed exposure to psychostimulants (classic stimulants, novel stimulants, or sympathomimetics) were included in the OS group while patients who tested negatively for psychostimulants were included in the OO group.

2.3. Study protocol

Patients at participating sites were screened and assessed for eligibility by research staff (medical toxicology physicians, fellows, or trained research assistants) using the criteria above. *A priori* data collection consisted of demographic variables (e.g., age, sex, race/ethnicity), past medical and psychiatric history, suspected opioid and other substances exposure, clinical characteristics (e.g., relevant laboratory data, specific organ toxicity), treatments received (naloxone treatment, non-pharmacological interventions, etc.), and disposition (i.e., discharge, admit, ICU). Data were de-identified and entered into a secure, web-based software platform (Research Electronic Data Capture [REDCap]) by research staff at each site. De-identified clinical data was linked to toxicology blood analysis using a unique study ID code. Database quality assurance was maintained by dedicated centralized ToxIC staff in accordance with current best-practices including database logical checks, quality assurance personnel, automated data cleaning, data tracking, encryption, and data abstractor training.

Waste blood samples obtained as part of routine clinical care were transferred to deidentified cryogenic tubes, and stored at temperatures between −4 and −80°C until toxicology analysis. Toxicology analysis was performed quarterly by the Center for Forensic Science Research and Education (Horsham, PA). Qualitative molecular identification consisted of liquid chromatography quadrupole time-of-flight mass spectrometry analysis, with secondary analysis by liquid chromatography tandem quadrupole mass spectrometry when necessary. The drug library used contains over 1000 substances, including traditional illicit drugs, pharmaceutical drugs, novel psychoactive substances, adulterants, metabolites, and other compounds. Toxicological analysis was performed blinded to clinical outcomes. Samples were considered to be positive for opioids based on the presence of morphine, codeine or papaverine serum analytes.

2.4. Outcomes

The primary study outcome was the difference in total naloxone dose requirements between the OS group and OO groups. Total naloxone dose was calculated by summing total prehospital doses (if any), bolus doses, and cumulative infusion doses (if any). Total naloxone dose was chosen as the primary outcome as a pragmatic, real-world surrogate measure of overdose severity (Boyer, 2012). Secondary outcomes were various markers of overdose severity, including the difference in in-hospital mortality, cardiac arrest (defined as loss of pulse requiring cardiopulmonary resuscitation), intensive care unit (ICU) admission and hospital length of stay.

2.5. Data analysis

Descriptive statistics examining patient demographics and clinical characteristics were tabulated. Two sample t-tests (for normally distributed variables) and chi-squared tests (for categorical variables) were employed to compare demographic and clinical characteristics between groups. Chi-squared and Fisher's exact tests for categorical variables, t-tests for normally distributed continuous variables, and Mann-Whitney-U tests for non-normally distributed continuous variables were used to analyze differences in outcomes between groups.

We subsequently fit multivariable models to adjust for demographic and clinical confounding variables. We employed a linear regression model for continuous outcomes (total naloxone dose), logistic regression

models for binary outcomes (death, cardiac arrest, ICU admission), and Poisson regression models for count variables (hospital length of stay).

Relevant demographic and clinical covariates including age, sex, race, ethnicity, prior psychiatric history, and clinical site were selected *a priori* for inclusion in the multivariable models. Analyses were conducted using SAS University Edition v.9.4 (SAS Institute, Cary, NC) and SPSS v. 24 (IBM, Armonk, NY).

2.6. Sample size and power

Based on a fixed sample size of 378 patients (which was the number of eligible patients available in the database for analysis) and sample means and standard deviations, we had 57% power to demonstrate a 0.67 mg mean increase in total naloxone dose in the OS group based on a post-hoc power analysis.

3. Results

3.1. Patient enrollment and baseline characteristics

Out of a total of 1006 patients, following application of study enrollment criteria, a total of 378 patients were included for analysis. 207 patients were in the OS group and 171 patients were in the OO group. Study enrollment and application of study inclusion/exclusion criteria are shown in Fig. 1. Patient demographics and characteristics are summarized in Table 1. Patients in the OO group were significantly older than patients in the OS group (mean age: 45.2 vs 40.6 years, $p < 0.01$). There were no significant differences in sex, race, ethnicity, proportion of patients with fentanyl or fentanyl analogs identified on serum analysis, proportion of patients who received prehospital naloxone and proportion of patients who required a naloxone drip. The most common opioids identified on serum analysis were fentanyl (n=291), methadone (n=73) and tramadol (n=72). The most common psychostimulants identified were methamphetamine (n=114), cocaine (n=102) and amphetamine (n=32). Most common co-exposures in the overall population were benzodiazepines (n=155), anti-depressants (n=114) and anti-psychotics (n=71). Among patients in the OO group, 9 were also exposed to cannabinoids; in the OS group, 3 patients were also exposed to cannabinoids. Most common confirmed opioids and psychostimulants are summarized in Table 2.

3.2. Primary outcome

The mean total dose of naloxone in the OS group was significantly higher than the OO group (2.79 mg (SD: 3.01) versus 2.12 mg (SD: 2.96), $p < 0.01$) with a small effect size (Cohen $d = 0.22$). Results are summarized in Table 3. We subsequently fit a linear regression model to analyze the association between mean total naloxone dose and opioid and psychostimulant co-exposure following adjustment for age, sex, race, ethnicity, prior psychiatric history, and study site. Psychostimulant and opioid co-exposure remained predictive of increased total mean naloxone dose on multivariable linear regression (parameter estimate: 0.70, p=0.04). Results are summarized in Table 4. Psychostimulant and opioid co-exposure also remained associated with increased naloxone

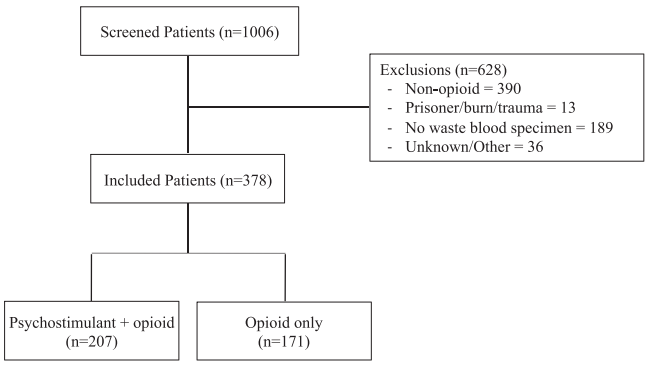

Fig. 1. Patient enrollment and inclusion. Summary of study enrollment and patient inclusion/exclusion.

Table 1
Demographics and clinical characteristics of included patients.

Patient Characteristic	Psychostimulant + Opioid (n = 207)	Opioid Only (n = 171)
Age (years), mean (SD)*	40.6 (SD: 12.8)	45.2 (SD: 15.9)
Sex (n,%) *Male*	139 (67.5%)	120 (70.6%)
Race (n, %)+	109 (52.9%)	84 (49.4%)
White	66 (32%)	53 (31.2%)
Black	0	3 (1.8%)
Asian	3 (1.5%)	1 (0.6%)
American-Indian/Alaska Native	25 (12.1%)	29 (17.1%)
Other/Unknown		
Ethnicity (n, %) *Hispanic*	21 (10.9%)	27 (17.4%)
Fentanyl Present (n, %)	167 (80.7%)	124 (72.5%)
Prehospital naloxone given (n, %)	143 (69.1%)	105 (61.4%)
Naloxone infusion (n, %)	14 (8.8%)	15 (6.8%)

* = $p < 0.05$; + = percentages do not sum to 100% due to missing data points.

Table 2
Most common confirmed opioids and stimulants.

Opioids		**Stimulants**	
Analyte	*Frequency*	*Analyte*	*Frequency*
Fentanyl	291	Methamphetamine	114
Methadone	73	Cocaine	102
Tramadol	72	Amphetamine	32
para-Fluorofentanyl	59	PCP	26
Heroin	55	Cocaethylene	18
Oxycodone	34	mCPP	4
Hydrocodone	8	Methylphenidate	3
Phenethyl-4-ANPP	8	Eutylone	2
Codeine	7	MDMA	1

Abbreviations: PCP = Phencyclidine; mCPP = meta-Chlorophenylpiperazine; Phenethyl-4-ANPP = phenethyl-4-anilino-N-phenethylpiperidine; MDMA = 3,4-Methyl enedioxy methamphetamine.

Table 3
Unadjusted analyses of association between psychostimulant and opioid co-exposure with study outcomes.

	Outcome	**Psychostimulant + Opioid**	**Opioid only**	**p-value**
Primary Outcome	Naloxone total dose+* Mean (SD)	2.79 (3.01)	2.12 (2.96)	0.009
Secondary Outcome	Cardiac Arrest N (% (95% CI))	25 (12.1% (8.0–17.3))	13 (7.6% (4.1–12.7))	0.15
	In-Hospital Death N (%, 95% CI)	4 (1.9% (0.5–4.9))	2 (1.2% (0.1–4.2))	0.55
	ICU Admission N (%, 95% CI)	29 (14.0% (9.6–19.5))	28 (16.4% (11.2–22.8))	0.52
	Hospital Length of Stay^ Median (IQR)	9 (25)	10 (42)	0.79

+ = total dose in mg; * = $p < 0.05$; ^ = length of stay in hours.
Definitions: Cardiac arrest = loss of pulse requiring cardiopulmonary resuscitation.
Abbreviations: ICU = Intensive care unit.

Table 4
Adjusted analyses of association between psychostimulant and opioid co-exposure with study outcomes.

	Outcome	Parameter Estimate+	Confidence Interval	p-value
Primary Outcome	Naloxone dose*	0.70	0.03– 1.37	0.04
Secondary Outcomes	In-hospital death	1.14	0.14–9.38	0.90
	LOS	1.32	0.92 – 1.89	0.29
	ICU Admission	0.78	0.36–1.66	0.51
	Cardiac Arrest	1.38	0.58–3.28	0.47

* = $p < 0.05$; + = Naloxone dose was modeled using linear regression and LOS with Poisson regression. Death, ICU admission and cardiac arrest parameter estimates are adjusted odds ratios (logistic regression).
Abbreviations: LOS = Length of stay; ICU = intensive care unit.

requirements after two sensitivity analyses, one in which naloxone total dose was analyzed as a binary outcome with a cutoff point of 2.00 mg and a second in which the total naloxone bolus dose was analyzed as a binary outcome with a cutoff point of 2.00 mg. The cutoff point was determined based on the standard starting dose of intranasal naloxone.

3.3. Secondary outcomes

A higher proportion of patients in the OS group experienced cardiac arrest but this finding was not statistically significant (12.1% (95% CI: 8.0–17.3) versus 7.6% (95% CI: 4.1–12.7), p = NS). There were also no significant differences in rates of in-hospital mortality (OS: 1.9% (95% CI: 0.5–4.9) versus OO: 1.2% (95% CI: 0.1–4.2), p = NS), rates of ICU admission (OS: 14.0% (95% CI: 9.6–19.5) versus OO: 16.4% (95% CI: 11.2–22.8), p = NS) and in median hospital length of stay (OS: 82 hours versus OO: 40.9 hours, p = NS). Following adjustment for age, sex, race, ethnicity, prior psychiatric history and study site, psychostimulant and opioid co-exposure was not found to be a significant predictor of cardiac arrest, in-hospital mortality, ICU admission or hospital length of stay. Results are summarized in Tables 3 and 4.

4. Discussion

We found that patients with exposure to both psychostimulants and opioids had significantly increased total naloxone dose requirements when compared with patients who had exposure to opioids alone. The difference in mean naloxone dose between groups was 0.67 mg. This represents a clinically significant difference given the typical starting dose of IV naloxone for opioid overdose is 0.04 mg. The increase in naloxone dose requirements in the OS group is a surrogate of increased opioid overdose severity (Amaducci et al., 2023). We additionally identified overall high rates of cardiac arrest and ICU admission in our patient population but found no significant differences in cardiac arrest, ICU admission or hospital length of stay between patients with opioid and psychostimulant exposure and patients with opioid exposure alone. Our findings suggest that fentanyl is the primary driver of toxicity in these cases.

Our findings represent the first analysis of naloxone dosing in opioid and stimulant co-exposure in the literature to our knowledge. We propose multiple explanations for this phenomenon. It is possible that stimulants may act as an analeptic permitting patients to use higher quantities of opioids before experiencing central nervous system depressant effects. An analeptic refers to an agent which stimulates the central nervous system and can overcome respiratory and cerebral depression caused by other substances (Wang and Ward, 1977). As the stimulant effect decreases, a more severe opioid overdose toxidrome may then be unmasked due to this increased use of opioids, leading to an increase in naloxone requirements.

It is also feasible that stimulant/opioid co-exposed individuals experience higher relative amounts of opioid, requiring greater naloxone dose for reversal. An individual who primarily uses stimulants may accidentally use more opioid due to variable opioid-contaminant concentration in the stimulant product or may inadvertently use stimulants contaminated with opioids. Furthermore, individuals using stimulants and opioids concurrently may be more opioid-naïve relative compared to patients using opioids alone, leading to a more severe opioid toxidrome with increased respiratory depression. Furthermore, the possibility of other co-adulterants with synergistic mechanisms, such as xylazine, could contribute to more severe respiratory depression.

The rates of cardiac arrest and ICU admission identified in the present study are higher than those previously cited in the literature. We found that 12.1% of patients with opioid + stimulant overdose and 7.6% of patients with opioid overdose alone experienced cardiac arrest. This is in contrast to prior studies which have cited opioid overdose associated cardiac arrest rates of 1.4–3.8% (Sakhuja et al., 2017). We similarly found overall high rates of ICU admission in both groups (14% in the OS group and 16.4% in the OO group). This is increased in comparison to prior literature which has noted an ICU admission rate for opioid overdoses of 59 per 10,000 ICU admissions (0.59%) (Stevens et al., 2017). Our findings could be reflective of the evolving trend towards fentanyl/fentalog contamination of the entire opioid drug supply (CSFRE, 2021; Han et al., 2019; Martinez et al., 2021; Bach et al., 2020; Mars et al., 2019).

Future studies examining naloxone dosing and overdose severity are needed to validate findings from the present study and may provide adequate power to evaluate for differences in cardiac arrest, ICU admission, in-hospital mortality and hospital length of stay. Future studies may also benefit from providing more detailed and quantitative data on specific fentanyl analogs implicated in overdoses in order to better understand the role of these fentanyl analogs in any observed differences. Similarly, more detailed and quantitative data on novel potent opioids (e.g. nitazenes) involved in overdoses would be beneficial.

Limitations of the present study include the potential for selection bias introduced by the fact that all included patients were required to have additional blood samples available to be sent as waste samples for analysis. This likely selected for patients with more severe overdose presentations as patients with less severe presentations may be less likely to have clinically required blood draws/laboratory studies as part of routine clinical care. However, this bias would have been present in both groups (OO and OS) and would have biased our findings toward the null. Accordingly, this does not detract from our findings on naloxone dosing but may have impacted the overall high rates of ICU admission and cardiac arrest identified in our study population.

Additionally, a relatively small number of patients experienced several of the study's secondary outcomes, limiting our ability to evaluate for differences in these outcomes between study groups. Our study was also limited to clinical sites within the United States, which limits international generalizability. The study was also limited to selected sites within the ToxIC Fentalog Study, which may limit generalizability of our findings to other geographic regions within the United States or to other types of care settings. We also determined race/ethnicity and other demographic variables by chart abstraction rather than patient self-report and this may have led to incomplete information. We ultimately had some races not represented within our study population which again may limit generalizability of our findings. We were unable to analyze differences in opioids detected within the two groups as this analysis would be underpowered; accordingly, it is possible that one group had a higher prevalence of longer-acting opioids. We also did not have individual provider data and were unable to account for potential provider subjectivity in naloxone dosing and infusion duration. Due to technical limitations of the amount of volume that would be required per patient sample, we were unable to pursue quantitative analyses of serum analytes detected. Finally, patients in this study may have used

the opioid and psychostimulants at different times prior to their presentation to the ED.

5. Conclusions

In this large multicenter prospective study of ED patients with confirmed opioid overdose, we found that patients with psychostimulant co-exposure had significantly higher total naloxone dose requirements when compared with patients with fentanyl overdose alone. This does not appear to reflect differences in cardiac arrest, ICU admission, in-hospital mortality or hospital length of stay in those who had psychostimulant and opioid co-exposure. Patients in the OO group were significantly older than patients in the OS group; there were no other significant demographic differences between groups. Additionally, fentanyl was the most prevalent opioid and methamphetamine was the most common psychostimulant. Medical toxicology physicians and ED clinicians should be aware that patients with opioid and psychostimulant co-exposure may require a higher naloxone dose as a result. Further study is needed to elucidate the role of psychostimulant co-exposure on opioid overdose severity.

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Author contributions

AFM, KA, JB and PW conceived and designed the study. AFM was primarily responsible for funding acquisition. KA, AFM and the ToxIC Fentalog Study Group were responsible for clinical data acquisition. SS and AFM analyzed the data. SS, JS and AFM drafted the manuscript and all authors contributed substantially to its revision. AFM takes responsibility for the paper as a whole.

CRediT authorship contribution statement

Jeffrey Brent: Conceptualization. **Kim Aldy:** Conceptualization, Data curation. **Paul Wax:** Conceptualization. **Joshua Shulman:** Writing – original draft, Writing – review & editing. **Siri Shastry:** Formal analysis, Writing – original draft, Writing – review & editing. **Alex F. Manini:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors report no commercial conflicts of interest.

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