Naloxone Administration and Survival in Overdoses Involving Opioids and Stimulants: An Analysis of Law Enforcement Data from 63 Pennsylvania Counties

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Funding:

Funding is reported from the National Institutes of Health (PI Abenaa Jones: K01 DA051715).

Conflicts of interest:

Frank LoVecchio, DO, MPH: NIH grants, speaker bureau ABBVIE for antibiotics only.

No other conflicts of interest were reported.

Abstract

Background: In consideration of rising deaths from opioid-stimulant-involved overdoses in the United States, this study explored rates of naloxone administration and survival in opioid overdoses with versus without stimulants co-involved.

Methods: The study used data from the Pennsylvania Overdose Information Network, focusing on 26,635 suspected opioid-involved overdose events recorded by law enforcement and other first responders in 63 Pennsylvania counties from January 2018 to July 2024. Relative frequencies and chi-square tests were first used to compare suspected opioid overdoses with, versus without, stimulants (cocaine or methamphetamine) co-involved. Next, mediation analyses tested naloxone administration as a mediator of the association between stimulant co-involvement (in opioid overdoses) and survival.

Results: Naloxone was reportedly administered in 72.2% of the opioid-no-cocaine overdoses, compared to 55.1% of the opioid-cocaine-involved overdoses, and 72.1% of the opioid-no-methamphetamine overdoses vs. 52.4% of the opioid-methamphetamine-involved overdoses. With respect to survival rates, 18.0% of the opioid-no-cocaine overdoses ended in death, compared to 41.3% of the opioid-cocaine overdoses; 18.1% of the opioid-no-methamphetamine overdoses ended in death, versus 42.9% of the opioid-methamphetamine overdoses. In mediation analyses (adjusted for demographics, county, year, and other drug co-involvement), naloxone administration mediated 38.7% (95% Confidence Interval [CI], 31.3%-46.0%) of the association between cocaine co-involvement and survival and 39.2% (95% CI, 31.3%-47.1%) of the association between methamphetamine co-involvement and survival.

Conclusions: Among suspected opioid overdose events recorded in the Pennsylvania Overdose Information Network, stimulant co-involvement was associated with lower naloxone administration and higher fatality, with naloxone partially mediating the association between stimulant co-involvement and death.

Keywords: opioids, stimulants, cocaine, methamphetamine, overdose, naloxone

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The current phase ("fourth wave") of the United States' (US) overdose crisis is characterized by rising numbers of overdoses involving synthetic opioids (e.g., non-pharmaceutical fentanyl) and stimulants (e.g., cocaine and methamphetamine) (Ciccarone, 2021). Rising opioid-stimulant co-use or co-exposure in the US has been documented across data from emergency department visits, postmortem toxicology, drug seizures, substance use treatment admission records, case reports, and population-based or community-based surveys (Jones et al., 2020). Research with individuals who use drugs has identified diverse opioid-stimulant co-use motivations, including: achieving synergistic effects; counteracting unfavorable effects of one drug type by also using another drug type; reducing perceived overdose risk; managing opioid withdrawal symptoms; and adapting to changes in the cost and availability of different drugs (Daniulaityte et al., 2022; Fredericksen et al., 2024; Silverstein et al., 2021; Valente et al., 2020).

Increasing opioid-stimulant co-use represents a growing public health concern for several reasons, including overdose risk; several studies have documented higher rates of non-fatal and fatal overdoses among individuals who co-use opioids and stimulants (relative to those who use opioids only; Karamouzian et al., 2024; Korthuis et al., 2022; Palis et al., 2022). Between 2015 and 2022, the proportion of US overdose deaths involving stimulants rose from 23% to 53% (Centers for Disease Control and Prevention, 2024a), and opioids were co-involved in 78.6% and 65.7% of overdose deaths involving cocaine and psychostimulants (e.g., methamphetamine), respectively (in 2021; Spencer et al., 2023).

In cases of opioid-stimulant overdose, timely naloxone administration and supportive care is recommended to counteract the effects of the opioids involved in the overdose (Ahmed et

al., 2022; Britch & Walsh, 2022; Rzasa Lynn & Galinkin, 2018). Naloxone, an opioid overdose reversal medication, is used to restore breathing in cases of opioid-induced respiratory depression (Davis & Carr, 2020; Morris & Kleinman, 2020). Naloxone can be administered by medical personnel, bystanders, or nonmedical first responders, and because time is of the essence when responding to an opioid-involved overdose (Davis & Carr, 2020), increasing naloxone access for first responders and community members represents a public health priority (Centers for Disease Control and Prevention, 2024b).

As opioid-related overdose deaths continue to increase nationally, there have been efforts to expand access to naloxone among law enforcement, who are often first responders at the scene of an overdose (Ray et al., 2015; Wagner et al., 2016). In Pennsylvania, the setting of the present study, legislation first enacted in 2014 (Act 139) enables police to administer naloxone and complete online training, and in a survey of 980 Pennsylvania police four years after the legislation's implementation, 91% reported access to naloxone and 73% indicated that they were typically first on the scene of an overdose (Jacoby et al., 2020).

Opioid-stimulant-involved overdoses may be particularly complex and risky (Pergolizzi et al., 2021; Shastry et al., 2024), as these overdoses involve multiple substances, each with unique as well as potentially interactive effects (Shastry et al., 2024). A 2024 study of opioid overdose patients in nine US emergency departments found that cases of opioid-stimulant co-exposure required more doses of naloxone than opioid-only cases (Shastry et al., 2024). Moreover, research suggests that the signs/symptoms/clinical presentations of overdoses involving opioid-stimulant combinations can differ from those observed in cases of opioid-only or stimulant-only toxicity (Glidden et al., 2023), potentially contributing to first responders' or bystanders' difficulty identifying what drugs may be involved and how best to respond.

In light of the complexity of opioid-stimulant-involved overdoses (Pergolizzi et al., 2021; Shastry et al., 2024) and the recent increases in opioid-stimulant fatalities across the US (Ciccarone, 2021), this study examines naloxone administration and survival in overdoses involving opioids with or without stimulants (cocaine or methamphetamine). The study uses data from nonfatal and fatal overdose events recorded by law enforcement or other first responders in Pennsylvania's Overdose Information Network (ODIN). The study investigates the following questions:

a) How do rates of naloxone administration and survival compare between suspected opioid-stimulant and opioid-no-stimulant overdoses recorded in ODIN?
b) To what extent might naloxone administration mediate the association between suspected stimulant co-involvement in opioid overdose and whether or not the individual survived the overdose event?

Methods

Data Source

The Arizona State University Institutional Review Board designated the present study as exempt based on Federal Regulations 45CFR46(4). All data were drawn from the Pennsylvania State Police's publicly available Overdose Information Network (ODIN) dataset (Pennsylvania State Police, 2024). The ODIN comprises overdose incidents recorded by participating law enforcement agencies who responded to the scene of a suspected overdose, as well as overdose incidents reported on a voluntary basis by other first responders (e.g., firefighters, emergency medical personnel). Due to the voluntary nature of third-party first responder reporting in the ODIN, ODIN data do not include, nor represent, all overdoses reported to emergency services in Pennsylvania. At the time of the study, the list of agencies recording events in ODIN included

752 law enforcement entities (Pennsylvania State Police, 2024), primarily (but not exclusively) city/township/borough police departments and state police.

Identifying Unique Records. Considering that any overdose event ("incident") in ODIN may have involved multiple persons who suffered an overdose at the same time and place, we used the ODIN "victim ID" code to identify unique persons in each incident. Because each ODIN record in the publicly available dataset includes only one data field for the drug type, multiple records can be used to record different drugs suspected in an overdose. Therefore, for records with the same victim ID, incident ID, and date/time, we merged all data corresponding to the unique combination of victim ID and incident ID to maintain only one record for each person's overdose incident. We coded separate variables for each of the multiple different drugs recorded and reviewed the original data to ensure that all other measures examined in the study, apart from the multiple drug responses, were identical within records assigned the same victim ID and incident ID.

We did not locate any instances of the same victim ID with different incident IDs (which would represent the same person experiencing separate overdose incidents recorded in the ODIN). Considering that repeat overdoses are relatively common, the lack of multiple incident IDs for the same victim ID suggested that some of the same individuals may possibly have been assigned different victim IDs on different occasions in the public-access ODIN; as such, we consider our analyses to be at the overdose *event* level, rather than the *individual* level.

Analytic Sample and Measures

The publicly accessible ODIN dataset is updated monthly, and the data used in the present study (Pennsylvania State Police, 2024) spanned January 1, 2018-July 15, 2024. The study included 63 (of 67) Pennsylvania counties. We excluded Philadelphia County (which accounted for 1,242 [4.5%] of the ODIN opioid overdoses) because the only listed ODIN-

reporting agencies from Philadelphia County were Drexel University Police and Philco; without the Philadelphia Police Department as an ODIN reporter, we considered the limited ODIN data from Philadelphia not comparable with the data from the other counties whose county/city/borough/township police forces were ODIN reporters. We also excluded three counties (Cameron, Forest, and Sullivan) with populations below 7,000 and relatively low numbers (0, 6, and 3, respectively) of ODIN-recorded opioid overdoses.

The study's analytic sample comprised 26,635 suspected opioid-involved overdoses (each with a unique victim ID/incident ID combination). We identified opioid-involved overdoses via any opioid-related ODIN category (heroin, fentanyl, carfentanil, fentanyl analog/other synthetic opioid, pharmaceutical opioid, methadone, or suboxone) recorded as a "suspected drug." *Suspected drugs* in each ODIN overdose report are determined by law enforcement/first responders based on sources such as interviews with the person who overdosed or others present, drug field testing, and other evidence (e.g., drugs and paraphernalia) found at the scene of the overdose (Barboza & Angulski, 2020).

Our primary *outcome* of interest was whether the individual survived the overdose (binary indicator), as reported in the ODIN system. We also examined a binary indicator for whether naloxone was administered to the individual at the scene of overdose, as reported in the ODIN system. Our two primary *exposures* of interest comprised binary indicators for whether A) cocaine or B) methamphetamine, respectively, were listed as one of the drugs "suspected" to be co-involved in the opioid overdose. We also examined available demographic measures: the individual's age category (0-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, and 70+), gender (man, woman, "unknown"), race (White, Black, Hispanic, American Indian, Asian, or unknown) and ethnicity (Hispanic, Non-Hispanic, or unknown). In addition, we examined the county where the

overdose occurred and the year of occurrence, as well as other "suspected drug" categories (binary indicators) listed in the overdose: heroin, fentanyl, carfentanil, other synthetic opioids/fentanyl analogs, pharmaceutical opioids, benzodiazepines, and alcohol.

Statistical Analyses

We first examined opioid-stimulant co-involvement in ODIN-recorded overdoses over time and across counties. We used line graphs to depict percentages of opioid overdoses that also co-involved cocaine or methamphetamine, respectively, per year, and used choropleth maps to depict these percentages at the county level. We also used descriptive statistics to summarize (and Pearson's chi-square tests to compare) the characteristics of suspected opioid overdoses with and without cocaine and methamphetamine also co-involved, separately for a) opioid overdoses with versus without cocaine and b) opioid overdoses with versus without methamphetamine.

Next, we focused on naloxone administration and survival in suspected opioid overdoses with and without cocaine and methamphetamine co-involved. We used flow charts to depict: the proportion of opioid overdoses with and without suspected involvement of stimulants (cocaine or methamphetamine, respectively); the proportions of each of these types of overdoses in which naloxone was or was not administered; and the proportions of survival and death in each of these types of overdoses with, versus without, naloxone administered.

Finally, we conducted mediation analyses, considering overdose survival as our outcome, naloxone administration as mediator, and cocaine or methamphetamine co-involvement (respectively) as the exposure variable. We used Stata/MP 18.5's *mediate* suite of commands (StataCorp, 2023) based on the potential-outcomes framework (Imai et al., 2011; MacKinnon et al., 2020). This mediation approach is comparable to Baron and Kenny's (1986) classical

mediation in the context of a linear model with no exposure-mediator interaction, yet the *mediate* command provides additional flexibility and allowed us to examine a binary mediator and binary outcome (with a logit specification) and model an exposure-mediator (stimulant involvement × naloxone administration) interaction (based on prior research; Shastry et al., 2024). We examined two separate mediation models, one with cocaine co-involvement as exposure, and the other with methamphetamine co-involvement as exposure, with both models including controls for age, gender, race, county (fixed effect), year (categorical), and other drug co-involvement (with each drug as a binary indicator). Listwise deletion was used for missing data (6.2% total). We expressed results in terms of "total effect," "average direct effect," "average indirect effect," and proportion mediated (the indirect effect as a percentage of the total effect). Although we use terms such as "direct effect" and "indirect effect," as conventional in mediation analyses, our results are not causal in nature.

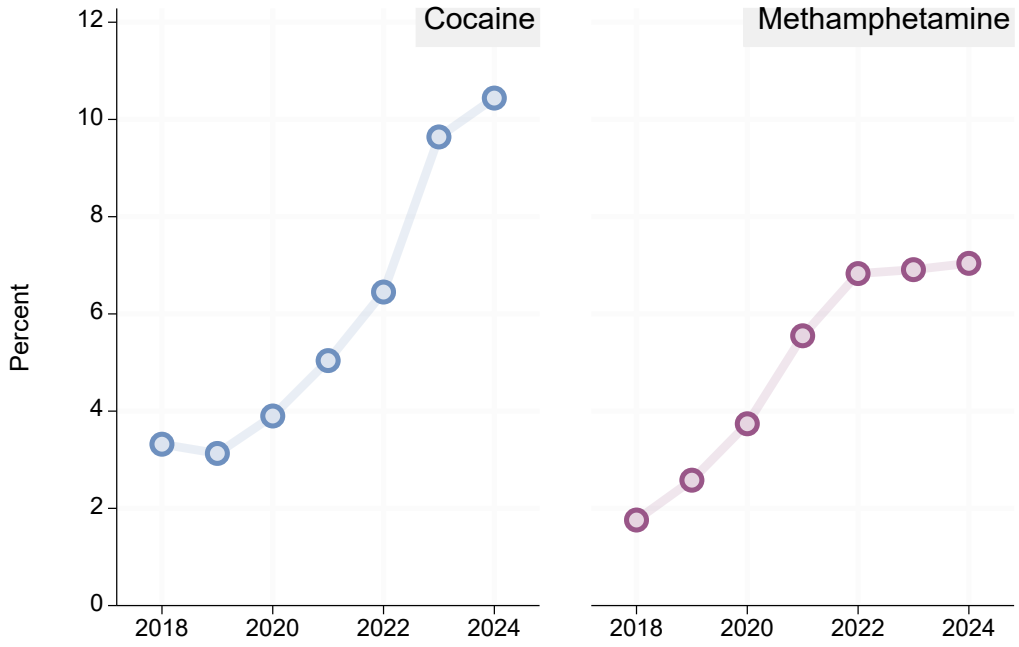
Supplemental Analyses

Stimulant co-use may be more common in individuals who use fentanyl, as opposed to other opioids (Daniulaityte et al., 2020), and fentanyl presents heightened overdose risks. Therefore, we conducted additional analyses focusing on suspected fentanyl-related overdoses (involving fentanyl, carfentanil, or other fentanyl analogs/synthetic opioids) instead of opioid overdoses in general. In these supplemental analyses, we compared fentanyl-stimulant and fentanyl-no-stimulant overdoses in terms of naloxone administration and survival; we also repeated the mediation models with this subset of overdoses involving fentanyl/other synthetic opioids.

Results

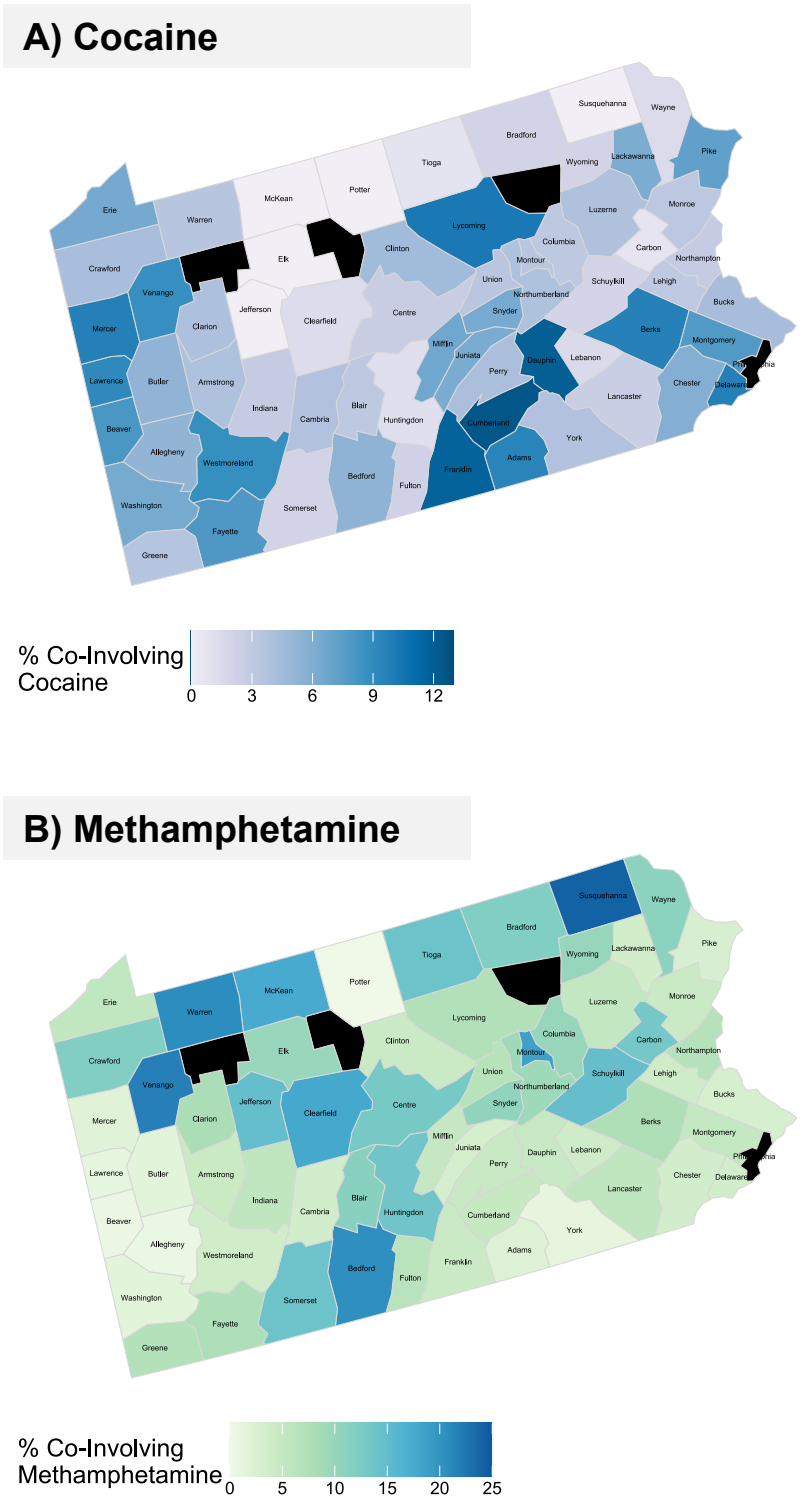
As depicted in Figure 1, the proportion of ODIN-recorded opioid overdoses that reportedly co-involved cocaine rose from 3.3% in 2018 to 10.4% in the first half of 2024, and the proportion of the opioid overdoses reportedly co-involving methamphetamine increased from 1.8% in 2018 to 7.0% in the first half of 2024. The percentage of ODIN-recorded opioid overdoses co-involving cocaine or methamphetamine varied widely between counties (Figure 2), ranging from 0.0% to 12.5% co-involving cocaine and 0.0% to 24.2% co-involving methamphetamine.

Figure 1. Percent of suspected opioid-overdoses also involving (a) cocaine or (b) methamphetamine, in Pennsylvania's Overdose Information Network (ODIN) data, 2018-2024.[1]



Note. [1]Data do not include Philadelphia, Cameron, Forest, and Sullivan counties. Data for 2024 are through July 15, 2024.

Figure 2. Percentages of ODIN-recorded suspected opioid overdoses co-involving cocaine or methamphetamine, 2018-2024, by county.



Notes. Data are from the Pennsylvania Overdose Information Network (ODIN) from January 1, 2018-July 15, 2024. Counties in black (Philadelphia, Cameron, Forest, and Sullivan) are not included in the analyses.

Table 1. Selected characteristics of suspected opioid-related overdoses (*n*=26,635) co-involving cocaine or methamphetamine, from Pennsylvania's Overdose Information Network (ODIN),[1] 2018-2024.

	Opioid & cocaine (*n*=1,490)	**Opioid, no cocaine** (*n*=25,145)	P value	**Opioid & metham-phetamine** (*n*=1,236)	**Opioid, no methamphet amine** (*n*=25,399)	P value
Age, years			<0.001			<0.001
0-9	0.2	0.2		0.3	0.2	
10-19	0.9	1.4		1.1	1.4	
20-29	20.5	27.7		22.3	27.5	
30-39	34.2	38.3		39.6	38.0	
40-49	22.6	18.5		21.6	18.6	
50-59	15.0	9.7		11.7	9.9	
60-69	6.2	3.7		3.4	3.9	
70+	0.5	0.5		0.2	0.6	
Gender			<0.001			0.991
Man	65.4	69.9		69.8	69.7	
Woman	34.6	29.8		29.9	30.1	
Unknown	0.1	0.3		0.2	0.3	
Race			<0.001			<0.001
White	80.5	89.4		94.7	88.6	
Black	17.4	8.4		4.3	9.2	
AI	0.1	0.1		0.2	0.1	
Asian	0.7	0.3		0.1	0.3	
Unknown	1.3	1.8		0.7	1.8	
Ethnicity			<0.001			<0.001
Hispanic	7.1	5.6		3.4	5.8	
Non-Hispanic	87.5	86.5		94.6	86.2	
Unknown	5.4	7.8		2.0	8.0	
Year of incident			<0.001			<0.001
2018	10.1	17.5		6.5	17.6	
2019	8.5	15.7		8.5	15.6	
2020	11.7	17.2		13.6	17.0	
2021	12.8	14.2		16.9	14.0	
2022	14.5	12.5		18.5	12.3	
2023	30.8	17.1		26.6	17.5	
2024[a]	11.5	5.9		9.4	6.0	
Other drugs co-involved						
Heroin	55.6	80.3	<0.001	57.5	80.0	<0.001
Fentanyl	63.9	38.5	<0.001	60.5	38.9	<0.001
Carfentanil	1.1	1.0	0.623	0.7	1.0	0.404
Other synth. opioids	10.5	6.5	<0.001	13.8	6.3	<0.001
RX opioids	4.8	6.8	0.002	4.9	6.8	0.008
Benzodiazepines	4.6	1.9	<0.001	4.2	2.0	<0.001
Alcohol	8.4	2.2	<0.001	3.6	2.5	0.016
Naloxone administered?			<0.001			<0.001
Yes	55.1	72.2		52.4	72.1	
No	44.9	27.9		47.6	27.9	
Survived overdose?			<0.001			<0.001
Yes	54.6	77.6		52.4	77.5	
No	41.3	18.0		42.9	18.1	
Unknown	4.1	4.4		4.8	4.4	

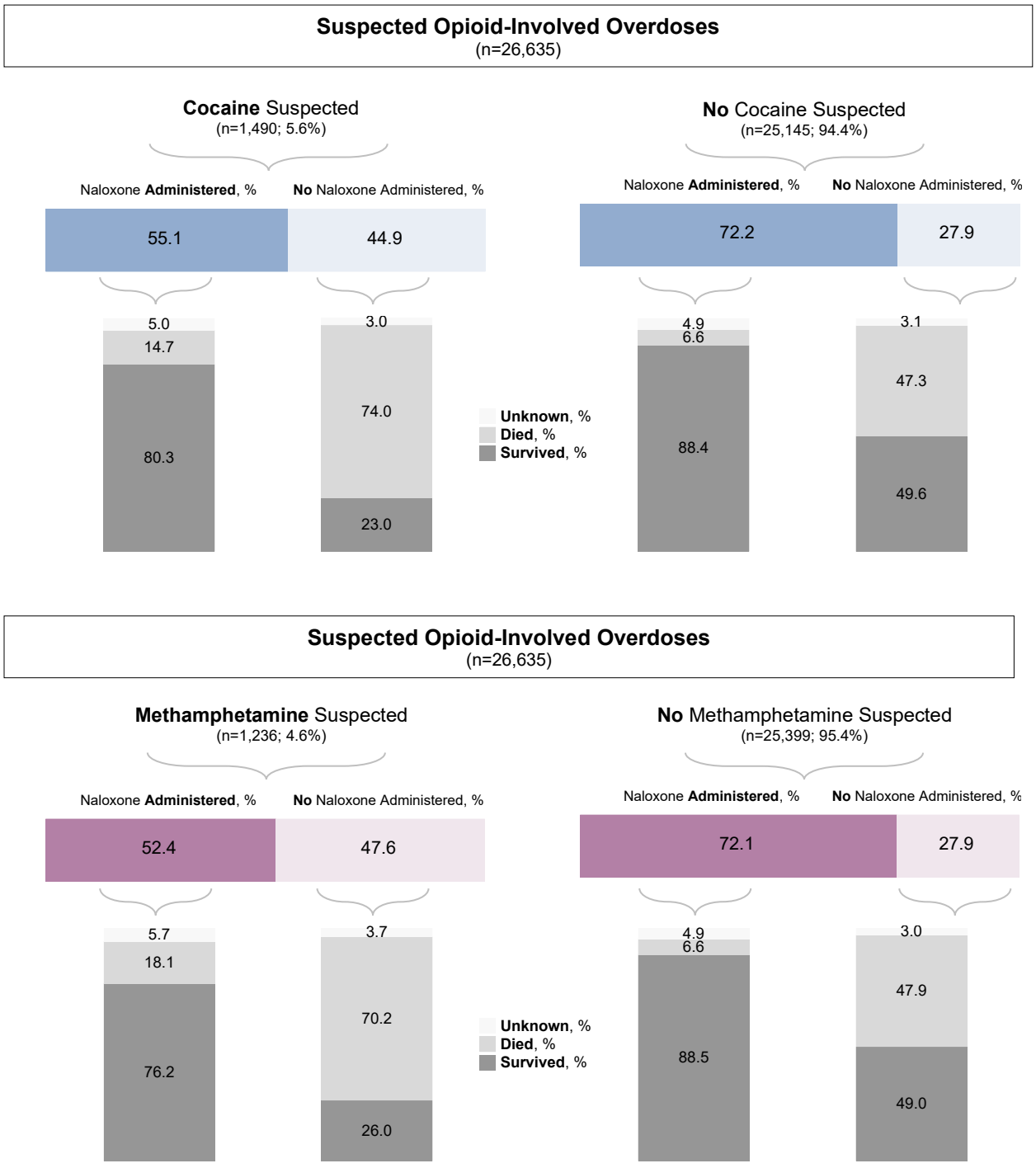
Notes. [1]Data do not include Cameron, Forest, Philadelphia, and Sullivan counties. [a]Denotes partial year. P values based on Pearson's chi-squared tests. *Abbreviations*. AI, American Indian; Synth., synthetic; RX, pharmaceutical.

Table 1 summarizes characteristics of ODIN-recorded overdoses involving opioids with vs. without cocaine, as well as overdoses involving opioids with vs. without methamphetamine. Approximately two thirds of the overdoses occurred in men, ranging from 65.4% men in the opioid-cocaine group to 69.9% men in the opioid-no-cocaine group. Age distributions differed by stimulant co-involvement, although overdoses were concentrated in ages 30-39 in all groups examined. White individuals represented 94.7% of the overdoses with opioids and methamphetamine reported, compared to 88.6% of the overdoses with opioids but no methamphetamine. Black individuals accounted for 8.4% of the overdoses with opioids but no cocaine, compared to 17.4% of the overdoses with opioids and cocaine, and 4.3% of the overdoses with opioids and methamphetamine.

Both heroin and prescription opioids were reported in higher proportions of the overdoses without cocaine or methamphetamine involved, relative to the opioid-cocaine and opioid-methamphetamine overdoses. Conversely, fentanyl, other synthetic opioids/fentanyl analogs, benzodiazepines, and alcohol were recorded in higher proportions of the opioid-cocaine and opioid-methamphetamine groups compared to the opioid-without-cocaine and opioid-without-methamphetamine groups.

Naloxone was reportedly administered in 72.2% of the overdoses involving opioids without cocaine, compared to 55.1% of the overdoses involving opioids with cocaine; similarly, naloxone was administered in 72.1% of the overdoses involving opioids without methamphetamine, versus 52.4% of the overdoses involving opioids with methamphetamine. Finally, 18.0% of the opioid-no-cocaine overdoses ended in death, compared to 41.3% of the opioid-cocaine overdoses; 18.1% of the opioid-no-methamphetamine overdoses ended in death, versus 42.9% of the opioid-methamphetamine overdoses.

Figure 3. Percentages of ODIN overdoses that reportedly ended in survival, death, or an unknown outcome, by naloxone administration and by opioid-stimulant co-involvement category.



Note. Data do not include Philadelphia, Forest, Cameron, and Sullivan counties. Totals may not amount to 100 due to rounding.

Figure 3 depicts the percentages of ODIN overdoses that reportedly ended in survival, death, or an unknown outcome, in cases where naloxone was or was not administered at the scene, separated by opioid-stimulant co-involvement category (opioid-cocaine vs. opioid-without-cocaine, and opioid-methamphetamine vs. opioid-without-methamphetamine). In cases with naloxone administered, more than three of every four overdoses resulted in survival, with percentages ranging from 76.2% in the opioid-methamphetamine group and 80.3% in the opioid-methamphetamine group to 88.4% and 88.5% survival in the opioid-without-cocaine and opioid-without-methamphetamine groups, respectively. When naloxone was not administered, survival percentages differed by stimulant involvement; for example, death was the recorded outcome in 74.0% of the opioid-cocaine overdoses without naloxone administered, compared to 47.3% of the opioid-no-cocaine overdoses without naloxone administered.

Table 2. Results from mediation analyses modeling naloxone administration as a mediator of the relationship between (A) cocaine or (B) methamphetamine co-involvement and overdose survival, for ODIN-recorded opioid overdoses from 63 Pennsylvania counties, 2018-2024.

	(A) Cocaine (n= 24,992)	**(B) Methamphetamine** (n=24,992)
	Logit Coefficient [95% CI]	Logit Coefficient [95% CI]
Total effect	-0.161*** [-0.185, -0.136]	-0.166*** [-0.192, -0.139]
Average direct effect	-0.099*** [-0.118, -0.079]	-0.101*** [-0.124, -0.078]
Average indirect effect	-0.062*** [-0.077, -0.048]	-0.065*** [-0.080, -0.050]
	Proportion [95% CI]	Proportion [95% CI]
Proportion mediated via naloxone administration	**0.387*** [0.313, 0.460]**	**0.392*** [0.313, 0.471]**

Note. Proportion mediated denotes the indirect effect as a percentage of the total effect. Outcome equation includes exposure–mediator interaction. Covariates in outcome and mediator equations: year, incident county, age, gender, race, and drugs co-involved (fentanyl, carfentanil, other synthetic opioids/fentanyl analogs, alcohol, benzodiazepines, heroin, and methamphetamine [in cocaine model]/cocaine[in methamphetamine model]). For convention, the term "effect" is used; nevertheless, results are not causal in nature. ****p*<0.001; p values based on robust standard errors. Data do not include Cameron, Forest, Philadelphia, and Sullivan counties.

Table 2 provides results from the mediation models examining naloxone administration as a mediator of the association between a) cocaine or b) methamphetamine co-involvement and survival, adjusting for age, race, gender, year, county, and other drug co-involvement. Results were similar in the a) cocaine and b) methamphetamine models: naloxone administration mediated 38.7% (95% CI, 31.3%-46.0%) of the "effect" of cocaine co-involvement on survival, and 39.2% (95% CI, 31.3%-47.1%) of the "effect" of methamphetamine co-involvement on survival.

Supplemental Tables S1-S3 detail the analyses focusing on *fentanyl-related* overdoses (instead of opioid overdoses broadly). Naloxone was reportedly administered in 49.9% of the fentanyl-cocaine overdoses and 69.0% of the fentanyl-no-cocaine overdoses. Similarly, naloxone was reportedly administered in 48.3% of the fentanyl-methamphetamine overdoses and 68.8% of the fentanyl-no-methamphetamine overdoses. In these analyses of fentanyl-related overdoses, naloxone administration mediated 46.3% (95% CI, 36.6%-56.0%) of the relationship between cocaine co-involvement and survival, and 42.5% (95% CI, 33.1%-51.9%) of the relationship between methamphetamine co-involvement and survival.

Discussion

Using data from 26,635 law enforcement-attended opioid overdose events recorded in Pennsylvania's Overdose Information Network (ODIN), the present study explored the relationship between naloxone administration and survival in cases of overdose involving opioids with or without stimulants co-involved. Study results indicated that rates of naloxone administration and survival were notably lower in suspected opioid-stimulant overdoses than in opioid-no-stimulant overdoses.

Although stimulants are co-involved in only a portion of opioid-related overdoses, this proportion is increasing over time (Hoots et al., 2020; Spencer et al., 2023). In our study, the proportion of ODIN-recorded opioid overdoses with cocaine reportedly co-involved rose from 3.3% in 2018 to 10.4% in the first half of 2024, and the proportion of opioid overdoses with methamphetamine reportedly co-involved increased from 1.8% in 2018 to 7.0% in the first half of 2024. In consideration of increases in opioid-stimulant co-use nationwide (Jones et al., 2020), our study's finding of higher probabilities of death (and lower probabilities of naloxone receipt) among opioid-stimulant overdoses emphasizes the importance of prioritizing and tailoring overdose prevention and response efforts for opioid-stimulant co-exposure.

Lower Rates of Naloxone Administered in ODIN Opioid-Stimulant-Involved Overdoses

In the ODIN-recorded overdoses in the present study, naloxone was reportedly administered in 72.2% of the overdoses that involved opioids without cocaine, compared to 55.1% of the overdoses involving opioids with cocaine; similarly, naloxone was administered in 72.1% of the overdoses involving opioids without methamphetamine, versus 52.4% of the overdoses involving opioids with methamphetamine. Although our study was unable to examine reasons for this finding, prior research suggests several plausible explanations. Since the clinical presentation and symptoms of opioid-stimulant-involved overdoses may differ from opioid-overdoses in general (Glidden et al., 2023), in some cases of opioid-stimulant involved overdose, it may not be quickly apparent to bystanders or law enforcement whether the person is suffering from an overdose involving opioids. For example, the pupil dilation associated with some stimulants (Substance Abuse and Mental Health Services Administration, 2021) contrasts with the pupil constriction associated with opioids (Williams & Erickson, 2000). Moreover, in cases in which opioids and stimulants may have been used at different times throughout the day, or in

cases of fentanyl-contaminated stimulants (Daniulaityte et al., 2023; Wagner et al., 2023), evidence of opioids (which may prompt bystanders to administer naloxone) may not be readily visible. Although all overdose events examined in the present study reportedly involved opioids, it is not clear what proportion evidenced symptoms of opioid-induced respiratory depression for which naloxone is indicated.

Individuals who primarily use stimulants may be less likely to carry take-home naloxone (Hughto et al., 2022) that could be administered by a bystander even before the arrival of first responders. It is also possible that some responding law enforcement officers may have heightened concerns in stimulant-involved cases that may reduce their likelihood of prioritizing administering naloxone (e.g., beliefs about aggressive behavior related to methamphetamine, doubts about naloxone or their role in administering it; Bucerius et al., 2022; Murphy & Russell, 2020; Silverstein et al., 2024; Wootson, 2017). Finally, in some ODIN overdose cases in which naloxone was not administered, the overdose victim may have already been deceased by the time a first responder arrived on scene.

Lower Rates of Survival in ODIN Opioid-Stimulant-Involved Overdoses

A recent cohort study from British Columbia, Canada found twice the hazard of fatal overdose among individuals with opioid and stimulant use, compared to opioid use alone (Palis et al., 2022). Consistent with these results, in the ODIN-recorded overdoses examined in the present study, higher proportions of opioid-stimulant overdoses were fatal (i.e., 42.9% of the opioid-methamphetamine overdoses ended in death, compared to 18.1% of the opioid-no-methamphetamine overdoses, and 41.3% of the opioid-cocaine overdoses ended in death, compared to 18.0% of the opioid-no-cocaine overdoses). In mediation models, naloxone administration mediated approximately 39% of the association between stimulant co-

involvement and survival, after adjusting for age, race, gender, year, county, and other drug co-involvement. Notably, these patterns were generally consistent even when examining stimulant co-involvement in fentanyl-related overdoses specifically rather than opioid-related overdoses in general.

Beyond differences in naloxone administration, numerous other factors may potentially contribute to lower survival in opioid-stimulant overdoses. While naloxone addresses opioid-induced respiratory depression, no comparable reversal agent is available to specifically counteract stimulant effects, and stimulant health impacts are often chronic and cumulative (Riley et al., 2022). It is also possible that some individuals who co-use opioids and stimulants may use higher opioid quantities as stimulant effects may temporarily mask some opioid effects (Shastry et al., 2024). Qualitative research indicates that some individuals who use drugs believe that methamphetamine can be used to prevent or reverse an opioid overdose (Daniulaityte et al., 2022). As such, it is also possible that some opioid-methamphetamine ODIN overdoses represented instances in which: a) an individual believed that use of methamphetamine would reduce their opioid overdose risk; or b) a peer injected methamphetamine in someone experiencing fentanyl toxicity as part of an attempt to reverse the overdose (Daniulaityte et al., 2022).

Although *intentional co-use* of opioids and stimulants is likely more common than exposure to stimulants that have been *contaminated* by fentanyl (Jones et al., 2020), fentanyl was detected in 12-15% of powder cocaine or methamphetamine samples analyzed in a cross-state US drug checking program from 2021-2023 (Wagner et al., 2023). Risk of fatality from fentanyl-contaminated stimulants may be particularly pronounced in individuals who primarily use

stimulants, since naloxone carriage rates and opioid tolerance are lower in these individuals compared to persons who regularly use opioids (Hughto et al., 2022).

The overdose survival differences observed in the present study may also be influenced by socioeconomic, racial, and geographic disparities associated with stimulant use. For instance, methamphetamine-involved overdose deaths are disproportionately observed in rural areas of the US (Hedegaard & Spencer, 2021), and a recent nationwide analysis found that counties with the highest psychostimulant (e.g., methamphetamine) and opioid mortality rates generally had higher Social Vulnerability Index scores (Segel et al., 2024). Furthermore, cocaine-involved overdose deaths disproportionately impact Black Americans (Cano et al., 2020, 2022; Jones et al., 2023a), and exposure to fentanyl-contaminated stimulants has been identified as a risk disproportionately impacting Black populations (Ray et al., 2020; Shufflebarger et al., 2024). In the present study, Black individuals accounted for approximately one in six of the opioid-cocaine involved ODIN overdoses, compared to one in twelve of the opioid-no-cocaine overdoses. In addition to disparities in treatment (Barnett et al., 2023; Shufflebarger et al., 2024), Black Americans experience pronounced disparities in drug arrests (Mitchell & Caudy, 2015) which can in turn contribute to hesitancy toward contacting 911 in case of overdose (Watson et al., 2018) as well as increased risk of overdose post-release (Joudrey et al., 2019). National research also indicates that overdose deaths in the Black population are overrepresented among relatively older (e.g., 55-64) age groups (Jones et al., 2023b); age (as well as health status) is considered a particularly salient risk factor in stimulant-involved deaths (Riley et al., 2022).

Prior studies have indicated that individuals who co-use opioids and stimulants are more likely to suffer from poor health and comorbidities (relative to those who use opioids only; Palis et al., 2022), and chronic use of stimulants can contribute to the development of conditions such

as hypertension, atherosclerosis, and cardiovascular disease that may leave individuals more vulnerable to overdose death (Riley et al., 2022). Finally, persons who co-use opioids and stimulants may also face additional stigma and reduced engagement with healthcare systems, as well as lower receipt of medications for opioid use disorder that reduce the risk of fatal overdose (Palis et al., 2022). Although not directly tested in the present study, it is plausible that the disparities and marginalization associated with some types of stimulant or opioid-stimulant use (Daniulaityte et al., 2020; Jones et al., 2023c) may contribute to the elevated fatality rates observed in the opioid-stimulant ODIN overdoses.

Limitations

The data used in this study, from the Pennsylvania public-access ODIN, include only overdose cases in which an ODIN-participating law enforcement agency or other first responder was present at the scene. As such, the data do not include overdose cases in which law enforcement did not respond (e.g., overdoses which were reversed without calling 911) or cases with only first responders who were not ODIN-reporting agencies. Since the Philadelphia Police Department was not listed as an ODIN-reporting agency at the time of the study, all analyses excluded Philadelphia County, the largest county in the state and a particularly racially and ethnically diverse county (Pennsylvania State Data Center, 2022).

All measures in the study (including suspected drugs involved and overdose fatality or survival) were based on the report of law enforcement or other first responders, using information available at the overdose scene and at the time of the overdose (rather than information from future follow-up). In the absence of data from formal toxicology, the drug involvement measures only reflect the drugs *suspected* to be involved in the overdose based on first responder investigation. It is plausible that *fatal* overdoses may have received more

investigative time and resources from law enforcement than overdoses that were *non-fatal*, which could potentially render the information recorded on fatal overdoses (such as the drugs suspected to be involved) more complete.

Many measures relevant to overdose survival were not available in the dataset; as such, we were unable to account for factors such as the individual's health status, drug use history, quantity of drug used, drug purity and composition, route of drug administration, use of drugs with others or alone, emergency response time, and other emergency care provided (e.g., CPR or rescue breathing). Although we modeled naloxone administration as a potential mediator of the relationship between suspected stimulant co-involvement and survival, it is unclear in which cases the decision regarding whether to administer naloxone at the scene was based on whether the individual was already deceased versus whether naloxone was available and those at the scene were willing and able to administer naloxone. Moreover, although naloxone dosage is recorded in ODIN, we did not include dosage in our analyses in consideration of missing data on this measure, and no information was available regarding route of administration. Overall, the study results are descriptive and correlational rather than causal in nature.

Implications and Conclusions

The present study documented notably lower rates of naloxone administration and survival in opioid-stimulant overdoses (relative to opioid-no-stimulant overdoses) in the Pennsylvania Overdose Information Network. These results underscore the importance of optimizing training and information dissemination regarding recognizing and responding to opioid-stimulant-involved overdoses. Opioid-stimulant overdose response may be strengthened through providing first responders and bystanders with training that specifically discusses opioid-stimulant-involved overdoses, as well as consistent messaging that addresses stigma and

concerns regarding naloxone (Murphy & Russell, 2020). At the same time, increasing harm reduction support and messaging for individuals who use drugs (informed, designed, and/or implemented by individuals with lived experience) may help bolster knowledge regarding the risks of opioid-stimulant co-exposure and strategies to minimize risk, in addition to general harm reduction recommendations such as carrying naloxone and not using drugs alone. Finally, since the study's results highlight persons who experience opioid-stimulant overdoses as a group facing high risk of fatality, results also support upstream efforts to reduce marginalization, social inequities, and barriers to healthcare, treatment, and resources within this group.

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Supplemental Table S1. Percentages of suspected *fentanyl*-related overdoses (n=11,588) that reportedly ended in survival, death, or an unknown outcome, by naloxone administration and *cocaine* co-involvement.

Cocaine Involved?	Naloxone Administered?	% Survived	% Died	% Unknown
Y	Y	77.71	17.05	5.23
Y	N	17.76	80.12	2.12
N	Y	85.89	9.06	5.05
N	N	34.16	63.24	2.60

Notes. *N*=1,034 fentanyl-cocaine overdoses and 10,554 fentanyl-no-cocaine overdoses. Naloxone was reportedly administered in 49.90% of the fentanyl-cocaine overdoses and 69.02% of the fentanyl-no-cocaine overdoses. Data do not include Philadelphia, Forest, Cameron, or Sullivan counties. Totals may not amount to 100 due to rounding. Fentanyl-related refers to overdoses involving fentanyl, carfentanil, or other fentanyl analogs/synthetic opioids.
Abbreviations: Y, yes; N, no; %, percentage

Supplemental Table S2. Percentages of suspected *fentanyl*-related overdoses (n=11,588) that reportedly ended in survival, death, or an unknown outcome, by naloxone administration and *methamphetamine* co-involvement

Methamphetamine Involved?	Naloxone Administered?	% Survived	% Died	% Unknown
Y	Y	72.73	20.88	6.39
Y	N	17.47	78.85	3.68
N	Y	86.04	8.97	4.99
N	N	33.79	63.82	2.39

Notes. *N*=842 fentanyl-cocaine overdoses and 10,746 fentanyl-no-cocaine overdoses. Naloxone was reportedly administered in 48.34% of the fentanyl-cocaine overdoses and 68.80% of the fentanyl-no-cocaine overdoses. Data do not include Philadelphia, Forest, Cameron, or Sullivan counties. Totals may not amount to 100 due to rounding. Fentanyl-related refers to overdoses involving fentanyl, carfentanil, or other fentanyl analogs/synthetic opioids.
Abbreviations: Y, yes; N, no; %, percentage

Supplemental Table S3. Results from mediation analyses modeling naloxone administration as a mediator of the relationship between (A) cocaine or (B) methamphetamine co-involvement and overdose survival, for ODIN-recorded *fentanyl*-related overdoses from 63 Pennsylvania counties, 2018-2024.

	(A) Cocaine (n=10,975)	**(B) Methamphetamine** (n=10,975)
	Logit Coefficient [95% CI]	Logit Coefficient [95% CI]
Total effect	-0.175*** [-0.206, -0.143]	-0.206*** [-0.241, -0.171]
Average direct effect	-0.094*** [-0.120, -0.068]	-0.119*** [-0.149, -0.088]
Average indirect effect	-0.081*** [-0.101, -0.061]	-0.088*** [-0.109, -0.066]
	Proportion [95% CI]	Proportion [95% CI]
Proportion mediated via naloxone administration	**0.463*** [0.366, 0.560]**	**0.425*** [0.331, 0.519]**

Note. Proportion mediated denotes the indirect effect as a percentage of the total effect. Outcome equation includes exposure–mediator interaction. Covariates in outcome and mediator equations: year, incident county, age, gender, race, and drugs co-involved (carfentanil, other synthetic opioids/fentanyl analogs, alcohol, benzodiazepines, heroin, and methamphetamine [in cocaine model]/cocaine[in methamphetamine model]). For convention, the term “effect” is used; nevertheless, results are not causal. ***p*<0.001; p values based on robust standard errors. Data do not include Forest, Philadelphia, Cameron, and Sullivan counties. Fentanyl-related refers to overdoses involving fentanyl, carfentanil, or other fentanyl analogs/synthetic opioids.