Preventive Medicine Reports 36 (2023) 102494

Contents lists available at ScienceDirect

Preventive Medicine Reports

journal homepage: www.elsevier.com/locate/pmedr

Polysubstance use and post-discharge mortality risk among hospitalized patients with opioid use disorder

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ARTICLE INFO

Keywords:
Polysubstance use
Opioid use disorder
Sedatives
Overdose
Substance use disorder
Hospitalized patients

ABSTRACT

Polysubstance use is becoming increasingly common and presents several harms. This study aimed to examine the association of comorbid cocaine, alcohol (binge drinking), and sedative use with mortality among hospitalized patients with opioid use disorder (OUD).

A subsample of adult medical/surgical hospital patients with OUD who were seen by a hospital addiction consultation service in Baltimore City and enrolled in a randomized trial of a patient navigation intervention were included in this study ($N = 314$; 45 % female; 48 % White; mean age = 44). Death certificate data from the Maryland Division of Vital Records was used, covering 3.3–5.5 years post-discharge. Multivariable proportional hazards Cox regression and competing risks regression were used to estimate all-cause mortality and overdose mortality, respectively, as a function of concurrent use of cocaine, alcohol (binge drinking), and non-prescribed sedatives at baseline.

In the 30 days prior to hospital admission, 230 (73 %) participants used cocaine, 64 (20 %) binge drank, and 45 (14 %) used non-prescribed sedatives. Nearly one-third ($N = 98$; 31 %) died during the observation period. Drug overdose caused 53 % ($N = 52$) of deaths. Older age (HR = 1.03 [1.01,1.05]; $P = 0.001$), less than high school education (HR = 0.36 [0.24,0.54]; $P < 0.001$), and past 30-day sedative use (HR = 2.05 [1.20,3.50]; $P = 0.008$) were significantly associated with all-cause mortality. The risk of overdose mortality was 62 % lower (HR = 0.38 [0.22,0.66]; $P = 0.001$) for those who completed high school. No other characteristics were significantly associated with overdose mortality.

The concurrent use of opioids and sedatives increases the post-discharge mortality risk among hospitalized patients with OUD. Interventions are needed to prevent mortality among this high-risk population.

1. Introduction

The opioid overdose crisis is compounded by polysubstance use – the use of more than one substance over a defined period of time. In a national sample of people entering treatment for opioid use disorder (OUD), 96 % reported past-month use of at least one non-opioid drug. (Cicero et al., 2020) In another national sample of people who used heroin, 93 % reported using at least one other drug in addition to heroin and 41 % reported using three or more drugs in the past year. (Winkelman et al., 2018) More than 80 % of drug overdose deaths in the United States involve opioids, and an estimated 63 % of all opioid deaths involve at least one non-opioid drug (Gladden et al., 2019).

Concurrent use of opioids with other central nervous system depressants, such as sedatives and alcohol, compounds the respiratory depressant effect of each drug and increases the risk of overdose. (Jones et al., 2012; Garg et al., 2017; Cho et al., 2020) Benzodiazepines are prescription sedatives commonly misused for nonmedical purposes in combination with opioids. (Gudin et al., 2013) Research demonstrates that people who use prescription opioids and benzodiazepines concurrently are at increased risk of an emergency department visit, being admitted to a hospital for opioid overdose, (Sun et al., 2017) and fatal overdose. (Park et al., 2015; Dasgupta et al., 2016) A cohort study in North Carolina found that the overdose death rate among patients prescribed both benzodiazepines and opioid analgesics was ten times higher than among those prescribed opioids alone. (Dasgupta et al., 2016) Another study among U.S. veterans with an opioid prescription

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https://doi.org/10.1016/j.pmedr.2023.102494
Received 20 July 2023; Received in revised form 31 October 2023; Accepted 1 November 2023
Available online 4 November 2023

found that receiving a benzodiazepine prescription was associated with increased risk of death from drug overdose in a dose-dependent manner. (Park et al., 2015) Despite the Food and Drug Administration's 2016 warning about the risks of co-prescribing of opioids and benzodiazepines, the problem persists. (U.S. Food and Drug Administration, 2016) In 2021, nearly 14 % of overdose deaths involving opioids also involved benzodiazepines. (National Institute on Drug Abuse, 2022) Despite benzodiazepine prescriptions remaining relatively stable, illicit benzodiazepine-involved overdose deaths increased 517 % from 2019 to 2020. (Liu, 2021) This spike raises concern and warrants further investigation into the harms associated with concurrent use of opioids and non-prescribed sedatives.

Alcohol is another respiratory depressant and is involved in an estimated 31 % of opioid overdose deaths (Phillips et al., 2023). Research indicates that approximately 23–26 % of people with OUD have a concurrent alcohol use disorder (Hser et al., 2017; Jones and McCance-Katz, 2019). Compared with nondrinkers, people who binge drink (defined as more than five drinks for men or more than four drinks for women within a two-hour period) are twice as likely to misuse prescription opioids, and the prevalence of prescription opioid misuse increases significantly with binge drinking frequency. (Esser et al., 2019) While prior studies have documented the heightened risk of overdose from combining opioids with alcohol, (Buckley et al., 2022) there is little known about how binge drinking influences overdose risk in the context of polysubstance drug use.

Opioids are also increasingly being used in combination with stimulants, primarily cocaine and amphetamines, which also have high potential for misuse and contribute to the rising number of opioid-involved overdose deaths (Favrod-Coune and Broers, 2010; Ellis et al., 2018; Ahmed et al., 2022). In the first half of 2019, approximately 40 % of opioid overdose deaths involved stimulants, primarily cocaine and/or methamphetamine. (O'Donnell, 2020) National data from 2015 to 2017 indicate that 12.5 % of people with OUD meet DSM-IV criteria for a co-occurring cocaine use disorder and 10.6 % meet criteria for a co-occurring methamphetamine use disorder. (Jones and McCance-Katz, 2019) The co-use of stimulants with synthetic opioids such as fentanyl, either intentionally or through drug contamination, has increased the number of stimulant-involved overdose deaths. (Ahmed et al., 2022). The opposing effects of increased arousal from stimulants and sedation from opioids on the body can make the outcomes of co-use less predictable and raise the risk of overdose. Thus, more research is needed to understand how the combined use of stimulants and opioids impacts overdose risk.

The increasing rate of opioid use has been associated with sharp increases in drug-related hospitalizations, (Rajbhandari-Thapa, 2019; Singh and Cleveland, 2020) and mortality rates among opioid-related hospitalizations have risen significantly. (Singh and Cleveland, 2020; Song, 2017) Post-discharge mortality is high among patients treated in the emergency department for nonfatal opioid overdose (Weiner et al., 2020) and hospital inpatients admitted for opioid-related conditions. (Ashman et al., 2014) More than half of patients who are hospitalized and have a substance use disorder use more than one substance, and nearly 70 % of hospitalized patients who use opioids also report recent (past 30 day) polysubstance use, including alcohol, cocaine, or amphetamines. (King et al., 2020) Patients who use multiple substances, or with comorbid substance use disorders, often present with complex medical, behavioral, and social issues and frequently face multiple barriers to care after hospital discharge (Gryczynski et al., 2021). Thus, understanding and addressing hospitalized patients' risks associated with polysubstance use is critical for developing interventions and preventing adverse post-discharge outcomes.

One study that used a large Medicaid claims database to compare all-cause and opioid-related mortality among individuals with OUD found that compared to individuals with OUD alone, individuals with a co-occurring substance use disorder were 76 % more likely to experience all-cause mortality and 48 % more likely to experience opioid-related poisoning, with the highest risk among patients with comorbid opioid and cocaine use disorder (O'Brien et al., 2021). However, this study only followed individuals for one year, preventing the understanding of long-term mortality. Other studies describing the association between overdose risk and polysubstance use primarily focus on the combination of opioids with just one other drug of interest. As polysubstance use increases and people with OUD are exposed to new drug combinations that may involve three or more substances, studies are needed that comprehensively assess use of multiple substances. Understanding the risk of death associated with polysubstance use among hospitalized patients is essential for the development and delivery of hospital services and interventions that aim to prevent post-discharge health risks and rehospitalization. This study aimed to estimate the added risk of death conferred by binge drinking and use of non-prescribed sedatives and cocaine among hospitalized patients with OUD during an extended follow-up period of 3.3–5.5 years.

2. Methods

2.1. Participants

This study included adult medical/surgical hospital patients with OUD who were seen by a hospital addiction consultation service and enrolled in a randomized trial of a patient navigation intervention, the Navigation Services to Avoid Rehospitalization (NavSTAR) study. The NavSTAR study was a parallel two-group randomized controlled trial that examined the effectiveness of NavSTAR patient navigation (continued for three months post-discharge) compared to Usual Care on measures of hospital service use (readmissions and ED visits), substance use disorder treatment linkage, substance use, HIV risks, and quality of life. A total of 400 adult hospital patients with substance use disorder were enrolled into the NavSTAR study at a large, urban academic medical center in Baltimore, Maryland from 2016 to 2018. Additional details on the design, recruitment, randomization, study groups, and intervention effectiveness are available elsewhere. (Gryczynski et al., 2021; Nordeck et al., 2020) The current study includes 314 participants who were aged 18 years or older and met *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* criteria for OUD.

2.2. Baseline data

Participants completed a baseline study assessment at the time of enrollment into the NavSTAR trial to collect baseline measures of sociodemographic, substance use, medical, and mental health characteristics. Type and frequency (number of days in the past 30 prior to hospital admission) of substance use at baseline was measured using the Addition Severity Index (ASI)- Lite. (McLellan et al., 1997) Substance use was dichotomized into whether they used the substance in the past 30 days (yes/no) due to a highly skewed distribution in the days of use. Non-prescribed substances assessed included alcohol (binge drinking, defined as consuming 5 or more drinks on an occasion for men or 4 or more drinks on an occasion for women), sedatives/hypnotics/tranquilizers (hereafter, "sedatives"), cocaine, amphetamines, and hallucinogens. The current study focuses on cocaine use, binge drinking, and sedative misuse, as use of amphetamines and hallucinogens was very infrequent in this sample.

2.3. Outcome data

Death certificate data from the Maryland Division of Vital Records was used to identify participants who died 3.3–5.5 years post-discharge. In this study, we examine the number of days between the initial hospital discharge date and the date of death for deaths due to (a) any cause and (b) drug overdose. Deaths were determined to be drug overdoses if the Medical Examiner classified the cause of death on the death certificate as overdose or intoxication. All overdose deaths are assumed to be

accidental because suicide was not listed as a cause of death on any overdose deaths that occurred in this study. We also describe the most common causes of death for participants who died from causes other than drug overdose.

2.4. Statistical analysis

Pearson's chi-square, Fisher's exact, and t-tests were used to compare demographics and baseline prognostic variables between those who did not die and those who died from (a) any cause and (b) drug overdose. Covariates that were decided *a priori* to potentially influence risk of death (age, sex, race, and NavSTAR randomization arm) and that were significantly different between those who died and those who did not die were included in multivariate regression models. A proportional hazards Cox regression model was used to estimate the impact of the concurrent use of opioids with other substances on all-cause mortality. A competing risks regression model was used to estimate the impact on overdose mortality, with overdose death as the event of interest and non-overdose (i.e., other) death as the competing event. Survival curves were created to demonstrate survival estimates for any statistically significant effects of concurrent substance use on mortality. Statistical significance was defined as $P < 0.05$. Data were analyzed using Stata/SE, version 17 (StataCorp).

2.5. IRB approvals and data and safety monitoring

The study was approved by the Friends Research Institute and University of Maryland Institutional Review Boards (IRB). The study was registered at ClinicalTrials.gov (NCT02599818). A federal Certificate of Confidentiality was obtained to protect the confidentiality of participants' data.

3. Results

3.1. Participant characteristics

There were 314 adults with OUD enrolled in the NavSTAR trial and included in this analysis. The most common admission/discharge diagnoses, as categorized by the Medical Dictionary for Regulatory Activities (MedDRA), (Welcome to MedDRA | MedDRA. Accessed October 11, 2023) included infections and infestations (n = 182); injury, poisoning, and procedural complications (n = 32); cardiac disorders (n = 25); respiratory, thoracic, medistatinal disorders (n = 17); vascular disorders (n = 14); and gastrointestinal disorders (n = 10). All other diagnosis groups had cell counts less than 10. Among these 314 individuals, 45 % were female, 48 % were White, and the mean age was 44. In the 30 days prior to study enrollment, 230 (73 %) participants used cocaine, 64 (20 %) binge drank, 45 (14 %) used non-prescribed sedatives, 12 (4 %) used hallucinogens, and 2 (1 %) used non-prescribed amphetamines. Table 1 provides demographic and substance use characteristics at baseline, comparing those who did not die to those who died from (a) any cause and (b) drug overdose.

3.2. All-cause mortality

Nearly one-third ($N = 98$; 31 %) of participants died during the observation period. Bivariate analyses found that compared to those who did not die, participants who died from any cause were older (mean

Table 1
Sociodemographic and substance use characteristics of those who did not die and those who died from (a) any cause and (b) drug overdose; 2016–2021.

Demographic variable	All-cause death (N = 98), n (%)	No death (N = 216), n (%)	P-value	Overdose death (N = 52), n (%)	No Death (n = 216), n (%)	P-value
Female sex	44 (44.9)	98 (45.4)	0.938	25 (48.1)	98 (45.4)	0.725
Mean (SD) age	46.9 (11.8)	42.1 (12.3)	0.001*	44.0 (11.1)	42.1 (12.3)	0.303
Race			0.448			1.00
White	44 (44.9)	107 (49.5)		26 (50.0)	107 (49.5)	
Black	53 (54.1)	103 (47.7)		25 (48.1)	103 (47.7)	
Other	1 (1.0)	6 (2.8)		1 (1.9)	6 (2.8)	
Completed High School	39 (39.8)	148 (68.5)	<0.001*	20 (38.5)	148 (68.5)	<0.001*
Marital status			0.842			0.762
Never married	56 (57.1)	131 (60.7)		30 (57.7)	131 (60.7)	
Married	9 (9.1)	18 (8.3)		6 (11.5)	18 (8.3)	
Widowed, Separated, or Divorced	33 (33.7)	67 (31.0)		16 (30.8)	67 (31.0)	
Homeless	40 (40.8)	107 (49.5)	0.151	23 (44.2)	107 (49.5)	0.492
Employment pattern, past 3 years[a]			0.004*			0.058
Full- or part-time work	13 (13.4)	50 (23.6)		6 (11.5)	50 (23.6)	
Unemployed	41 (42.3)	106 (50.0)		25 (48.1)	106 (50.0)	
Retired or disability	43 (44.3)	56 (26.4)		21 (40.4)	56 (26.4)	
NavSTAR arm	47 (48.0)	116 (53.7)	0.345	26 (50.0)	116 (53.7)	0.631
Mean (SD) number of times hospitalized	10.3 (15.6)	8.8 (16.5)	0.450	13.0 (20.5)	8.8 (16.5)	0.116
Chronic medical problem(s)[b]	85 (86.7)	164 (75.9)	0.028*	45 (86.5)	164 (75.9)	0.097
Prescribed medication(s)[b]	61 (62.2)	103 (47.7)	0.017*	31 (59.6)	103 (47.7)	0.122
Non-opioid substances used in past 30 days						
Alcohol (binge drank)	17 (17.4)	47 (21.8)	0.368	8 (15.4)	47 (21.8)	0.307
Sedatives	19 (19.39)	26 (12.0)	0.085	11 (21.2)	26 (12.0)	0.087
Cocaine	71 (72.5)	159 (73.6)	0.829	43 (82.7)	159 (73.6)	0.172
Amphetamines	0 (0.0)	2 (0.9)	1.00	0 (0.0)	2 (0.9)	1.00
Hallucinogens	2 (2.0)	10 (4.6)	0.353	1 (1.9)	10 (4.6)	0.697
Mean (SD) number of times treated for drug use	4.9 (6.1)	5.3 (8.1)	0.706	4.8 (5.5)	5.3 (8.1)	0.653
Any mental health disorder	26 (26.5)	65 (30.1)	0.519	15 (28.9)	65 (30.1)	0.860

Fisher's exact test was used when cell size < 6.
SD = Standard Deviation
* = statistically significant ($P < 0.05$).
[a] Does not include 4 individuals: 3 students and 1 in a controlled environment.
[b] The ASI defines a chronic medical problem as a serious physical condition that requires regular care, preventing full advantage of the person's abilities. Prescribed medications are defined as medication prescribed for a medical problem. Thus, these definitions do not include psychiatric problems or medications.

age 42 vs 47; $P = 0.001$), less likely to have completed high school (40 % vs 69 %; $P < 0.001$) and be employed (13 % vs 24 %; $P = 0.004$), and more likely to have chronic medical problems (87 % vs 76 %; $P = 0.028$) and be prescribed medications (62 % vs 48 %; $P = 0.017$). Because employment and high school completion were correlated, only high school completion was included in the regression analyses. In the multivariate proportional hazards Cox regression analysis (Table 2), individuals who used sedatives were twice as likely to die from any cause (HR = 2.05 [1.20,3.50]; $P = 0.008$; Fig. 1) and those who completed high school were 0.36 times less likely to die (HR = 0.36 [0.24,0.54]; $P < 0.001$). The risk of all-cause mortality increased by 3 % (HR = 1.03 [1.01,1.05]; $P = 0.001$) for each additional year in age.

There were 46 participants who died from causes other than drug overdose. The most common other causes of death included: 13 organ failures (most often due to sepsis), 11 cardiovascular events (e.g., cardiovascular disease, sudden cardiac arrest), 6 respiratory events (e.g., respiratory arrest/failure), 5 cancer deaths, and 11 other causes (with 3 or fewer cases in any one category).

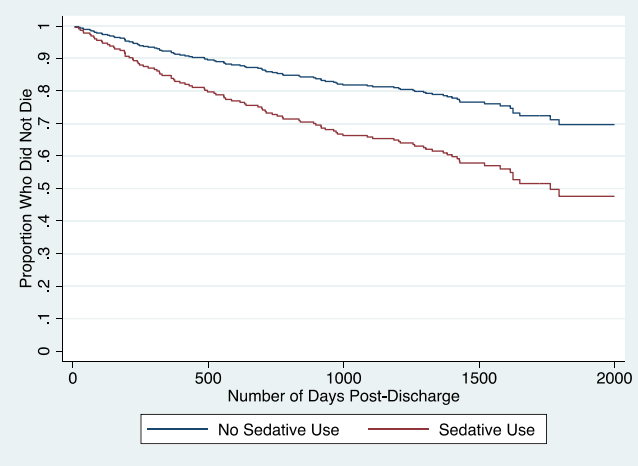

Fig. 1. Cox proportional hazards regression survival curves among hospitalized patients with OUD (N = 314), by concurrent sedative use; 2016–2021.

3.3. Overdose mortality

Drug overdose or intoxication was listed as a direct or precipitating cause in 53 % ($N = 52$) of deaths. Nearly all overdose deaths (50/52; 96 %) involved an opioid In bivariate analyses, those who died from drug overdose were less likely to complete high school (38 % vs 69 %; $P < 0.001$) than those who did not die. In the competing risks regression analysis, the risk of overdose mortality was 62 % lower (HR = 0.38 [0.22,0.66]; $P = 0.001$) for those who completed high school. No substances or other prognostic variables examined were statistically significantly associated with overdose mortality.

4. Discussion

This study was unique in that it examined polysubstance use and long-term post-discharge mortality among medical/surgical patients with OUD. Overall, there was a high rate of mortality, with nearly one-third of participants dying within 3.3–5.5 years post-discharge, despite a young average age of 44 years at enrollment. The concurrent use of opioids and non-prescribed sedatives as measured at baseline doubled the risk of all-cause mortality compared to opioid use alone among this study population. This finding supports our hypothesis and the existing literature describing the increased risk of death from combined opioid and sedatives use. (Jones et al., 2012; Garg et al., 2017; Cho et al., 2020) However, the association between overdose mortality and the concurrent use of opioids and non-prescribed sedatives was not statistically significant. The lack of statistical significance may be due to the small sample size and limited power. Alternatively, non-prescribed sedative use may be associated with broader detrimental health outcomes that lead to other types of deaths. For example, people with OUD who use sedatives non-medically may engage in other behaviors harmful to their health; the combined use of opioids and non-prescribed sedatives may cause other health problems; or it is possible that people with OUD in poorer health (i.e., who are already at higher risk of mortality) seek out sedatives illicitly to address symptoms of existing health conditions. Further research is needed to understand contributing risk factors for mortality other than overdose among hospitalized patients with OUD using sedatives extra-medically. An important consideration is that concurrent use of sedatives was measured in a fairly coarse way, at the time of the index hospitalization. Concurrent use of non-prescribed sedatives among hospital patients with OUD may thus be a clinically useful prognostic for subsequent risk of death.

Interventions to reduce post-discharge mortality risk associated with the concurrent use of opioids and non-prescribed sedatives should be implemented and investigated. For example, educational interventions may teach patients about the risks of combining opioids with sedatives. Teaching people how to identify illicitly manufactured sedatives, which can be far more dangerous than prescription sedatives, (Mahase, 2020) may prevent the unintentional use of non-prescribed sedatives. Additionally, safe storage, use, and disposal of prescription sedatives among those prescribed sedatives may prevent drug diversion. Lastly, increasing the availability of local drug checking services and raising awareness of the availability of these programs will allow people who use drugs, including opioids and sedatives bought on the street/black market, to understand the composition of their substances prior to use and avert unintended overdoses. Further research is needed that focuses on the development and evaluation of such interventions for preventing concurrent and simultaneous use of opioids and non-prescribed

Table 2
Results of (a) proportional hazards cox regression and (b) competing risks regression analyses among hospitalized patients with OUD; 2016–2021.

	(a) All-cause death (n = 98) vs no death (n = 216)			(b) Overdose death (n = 52) vs no death (n = 216)		
	Hazard ratio	95 % CI	P-value	Hazard ratio	95 % CI	P-value
Sedatives[a]	2.05	1.20–3.50	0.008*	1.73	0.85–3.52	0.131
Cocaine[a]	1.11	0.69–1.80	0.660	1.85	0.86–3.98	0.118
Alcohol (binge)[a]	0.64	0.37–1.09	0.100	0.57	0.25–1.26	0.163
Sex	1.09	0.72–1.67	0.674	1.08	0.60–1.96	0.797
Age	1.03	1.01–1.05	0.001*	1.01	0.98–1.03	0.456
White race	1.21	0.76–1.90	0.421	1.10	0.58–2.11	0.769
Completed high school	0.36	0.24–0.54	<0.001*	0.38	0.22–0.66	0.001*
NavSTAR Study Arm	0.80	0.53–1.21	0.290	0.92	0.52–1.61	0.763
Chronic Medical Problems	1.12	0.57–2.22	0.746	1.29	0.52–3.16	0.585
Prescribed medication	1.66	0.99–2.77	0.054	1.53	0.78–3.02	0.218

* = statistically significant ($P < 0.05$).
[a] Any use in past 30 days.

sedatives.

This study found a strong and significant association between high school completion and decreased mortality, including both all-cause mortality and overdose mortality. These results are consistent with prior studies demonstrating a decreased overdose mortality risk associated with increased educational attainment. One study found that from 2013 to 2019, proportionate mortality due to opioid overdose increased by 120 % for the less-than-high-school-diploma education group, whereas the increase was only 60 % and 30 % for groups with bachelor's and graduate-level educations, respectively. (Duan and Hand, 2021) It is possible that premature termination of high school education may lead to more stress or depression and higher likelihood of unhealthy behaviors, including risky substance use. Vice versa, substance use may lead to premature termination of high school education. Future research should examine the directionality of these events to inform interventions that aim to reduce inequities in health. Furthermore, low educational attainment is associated with various other negative social determinants of health, such as low income, insecure housing, and criminal-legal involvement, (Papay et al., 2015; Broton, 2021; Novak, 2019; Weidner and Schultz, 2019; Health, 2020) and these factors may interact and synergistically cause worse health outcomes. Further research is needed on the intersectionality of these characteristics and their impact on overdose mortality. Responses to the drug overdose epidemic should consider disparities in educational attainment, and collecting employment and education levels upon hospital admission may inform the delivery of overdose prevention interventions that target the most vulnerable groups.

This study has several limitations. Generalizability is limited because this study was conducted at a single urban academic medical center in Baltimore. This single-site patient population experienced high levels of unemployment and homelessness, and the use of amphetamines, hallucinogens, and other substances was too low to assess the added risk of death conferred by these substances. Future studies are needed that include larger and more diverse patient populations and geographic regions, such as hospitalized patients from Western U.S. states where methamphetamine use is more common. (Jones, 2020) Another limitation is that this study did not examine which substances contributed to the death and whether participants continued to use the same substances long-term that they reported at baseline. It is possible that patients' substance use and drug preferences changed throughout the study and follow-up period, which occurred during a time in which fentanyl displaced heroin in most U.S. street drug markets and new substances, such as Xylazine, entered the drug supply. (Montero et al., 2022) Additionally, this study focused on the use of multiple substances over a 30 day time period (i.e., concurrent use) because we were unable to assess the simultaneous use of specific substances using the ASI. This common methodological challenge (Connor et al., 2014) prevents us from capturing the rate at which simultaneous polysubstance use occurs and quantifying the added risk of death conferred by ingesting multiple substances at one time compared to using multiple substances at different points in time. However, the fact that concurrent use of non-prescribed sedatives within the past 30 days of the index hospitalization doubled the risk of all-cause mortality over an extended time frame suggests that this variable could be an important prognostic indicator of risk and a target for additional intervention in the hospital setting and post-discharge. Lastly, participants who died outside the state of Maryland would not have been captured.

5. Conclusion

These results highlight the need to address concurrent use of opioids and sedatives as part of comprehensive care for hospitalized adults with OUD. While many providers are addressing the risks of sedative prescriptions (primarily benzodiazepines) among patients with OUD, the non-prescribed use of sedatives is common and significantly associated with post-discharge mortality. Efforts to reduce post-discharge mortality risk should incorporate strategies to prevent, mitigate, and treat the use of multiple substances and target patients most vulnerable.

Funding

This work was supported by the National Institutes of Health National Institute on Drug Abuse [R01DA037942].

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The authors have no conflicts of interest but make the following disclosures that are unrelated to the present study: JG is part owner of COG Analytics LLC and has received research funding from Indivior (paid to his institution and including project-related salary support). JG and RPS were investigators on a NIDA-funded study receiving in-kind medication from Indivior and Alkermes. SGM is MPI on a NIDA study that was provided medication in-kind by Braeburn.

Data availability

The authors do not have permission to share data.

References

Ahmed, S., Sarfraz, Z., Sarfraz, A., 2022. Editorial: a changing epidemic and the rise of opioid-stimulant co-use. Front. Psychiatry. 13, 918197 https://doi.org/10.3389/fpsyt.2022.918197.

Ashman, J.J., Hermer, L., DeFrances, C., Schwartzman, A. Exploring Hospital-Based Mortality - Examples from the 2014 National Hospital Care Survey data linked to the National Death Index. Accessed March 9, 2023. https://www.cdc.gov/nchs/data/nhcs/opioid_involved_hospitalization_NDI.pdf.

Broton, K., 2021. Poverty in American Higher Education: the relationship between housing insecurity and academic attainment. J. Postsecondary Student Succ. 1, 18–45. https://doi.org/10.33009/fsop_jpss129147.

Buckley, C., Ye, Y., Kerr, W.C., et al., 2022. Trends in mortality from alcohol, opioid, and combined alcohol and opioid poisonings by sex, educational attainment, and race and ethnicity for the United States 2000–2019. BMC Med. 20 (1), 405. https://doi.org/10.1186/s12916-022-02590-z.

Cho, J., Spence, M.M., Niu, F., Hui, R.L., Gray, P., Steinberg, S., 2020. Risk of overdose with exposure to prescription opioids, benzodiazepines, and non-benzodiazepine sedative-hypnotics in adults: a retrospective cohort study. J. Gen. Intern. Med. 35 (3), 696–703. https://doi.org/10.1007/s11606-019-05545-y.

Cicero, T.J., Ellis, M.S., Kasper, Z.A., 2020. Polysubstance Use: a broader understanding of substance use during the opioid crisis. Am. J. Public Health. 110 (2), 244–250. https://doi.org/10.2105/AJPH.2019.305412.

Connor, J.P., Gullo, M.J., White, A., Kelly, A.B., 2014. Polysubstance use: diagnostic challenges, patterns of use and health. Curr. Opin. Psychiatry. 27 (4), 269–275. https://doi.org/10.1097/YCO.0000000000000069.

Dasgupta, N., Funk, M.J., Proescholdbell, S., Hirsch, A., Ribisl, K.M., Marshall, S., 2016. Cohort study of the impact of high-dose opioid analgesics on overdose mortality. Pain Med. 17 (1), 85–98. https://doi.org/10.1111/pme.12907.

Duan, W.R., Hand, D.J., 2021. Association between opioid overdose death rates and educational attainment – United States, 2010–2019. Prev. Med. 153, 106785 https://doi.org/10.1016/j.ypmed.2021.106785.

Ellis, M.S., Kasper, Z.A., Cicero, T.J., 2018. Twin epidemics: The surging rise of methamphetamine use in chronic opioid users. Drug Alcohol Depend. 193, 14–20. https://doi.org/10.1016/j.drugalcdep.2018.08.029.

Esser, M.B., Guy, G.P., Zhang, K., Brewer, R.D., 2019. Binge drinking and prescription opioid misuse in the U.S., 2012–2014. Am. J. Prev. Med. 57 (2), 197–208. https://doi.org/10.1016/j.amepre.2019.02.025.

Favrod-Coune, T., Broers, B., 2010. The health effect of psychostimulants: a literature review. Pharmaceuticals (Basel) 3 (7), 2333–2361. https://doi.org/10.3390/ph3072333.

Garg, R.K., Fulton-Kehoe, D., Franklin, G.M., 2017. Patterns of opioid use and risk of opioid overdose death among medicaid patients. Med. Care 55 (7), 661–668.

Gladden, R.M., O'Donnell, J., Mattson, C.L., Seth, P., 2019. Changes in opioid-involved overdose deaths by opioid type and presence of benzodiazepines, cocaine, and methamphetamine - 25 States, July-December 2017 to January-June 2018. MMWR Morb. Mortal Wkly Rep. 68 (34), 737–744. https://doi.org/10.15585/mmwr.mm6834a2.

Gryczynski, J., Nordeck, C.D., Welsh, C., Mitchell, S.G., O'Grady, K.E., Schwartz, R.P., 2021. Preventing hospital readmission for patients with comorbid substance use disorder: a randomized trial. Ann. Intern. Med. 174 (7), 899–909. https://doi.org/10.7326/M20-5475.

Gudin, J.A., Mogali, S., Jones, J.D., Comer, S.D., 2013. Risks, management, and monitoring of combination opioid, benzodiazepines, and/or alcohol use. Postgrad Med. 125 (4), 115–130. https://doi.org/10.3810/pgm.2013.07.2684.
Health, T.L.P., 2020. Education: a neglected social determinant of health. Lancet Public Health 5 (7), e361.
Hser, Y.I., Mooney, L.J., Saxon, A.J., Miotto, K., Bell, D.S., Huang, D., 2017. Chronic pain among patients with opioid use disorder: results from electronic health records data. J Subst Abuse Treat. 77, 26–30. https://doi.org/10.1016/j.jsat.2017.03.006.
Jones, C.M., 2020. Patterns and characteristics of methamphetamine use among adults — United States 2015–2018. MMWR Morb. Mortal Wkly Rep. 69. https://doi.org/10.15585/mmwr.mm6912a1.
Jones, C.M., McCance-Katz, E.F., 2019. Co-occurring substance use and mental disorders among adults with opioid use disorder. Drug Alcohol Depend. 197, 78–82. https://doi.org/10.1016/j.drugalcdep.2018.12.030.
Jones, J.D., Mogali, S., Comer, S.D., 2012. Polydrug abuse: a review of opioid and benzodiazepine combination use. Drug Alcohol Depend. 125 (1–2), 8–18. https://doi.org/10.1016/j.drugalcdep.2012.07.004.
King, C., Nicolaidis, C., Korthuis, P.T., Priest, K.C., Englander, H., 2020. Patterns of substance use before and after hospitalization among patients seen by an inpatient addiction consult service: A latent transition analysis. J. Subst. Abuse Treat. 118, 108121 https://doi.org/10.1016/j.jsat.2020.108121.
Liu, S., 2021. Trends in nonfatal and fatal overdoses involving benzodiazepines — 38 States and the District of Columbia, 2019–2020. MMWR Morb. Mortal Wkly Rep. 70. https://doi.org/10.15585/mmwr.mm7034a2.
Mahase, E., 2020. Doctors warned over "street benzos" linked to hospital admissions and deaths. BMJ 370, m2995. https://doi.org/10.1136/bmj.m2995.
McLellan, T., Cacciola, J., Carise, D., Coyne, T.H., Categories H. Addiction Severity Index Lite. Published online 1997.
Montero, F., Bourgois, P., Friedman, J. Potency-enhancing synthetics in the drug overdose epidemic: Xylazine ("Tranq"), fentanyl, methamphetamine, and the displacement of heroin in Philadelphia and Tijuana. 2022;4(2):204-222. doi: 10.31389/jied.122.
National Institute on Drug Abuse. Benzodiazepines and Opioids. National Institute on Drug Abuse. Published November 7, 2022. Accessed March 10, 2023. https://nida.nih.gov/research-topics/opioids/benzodiazepines-opioids.
Nordeck, C.D., Welsh, C., Schwartz, R.P., et al., 2020. Navigation services to avoid rehospitalization among medical/surgical patients with comorbid substance use disorder: rationale and design of a randomized controlled trial. J. Psychiatr. Brain Sci. 5 (3), e200013.
Novak, A., 2019. The school-to-prison pipeline: an examination of the association between suspension and justice system involvement. Crim. Justice Behav. 46 (8), 1165–1180. https://doi.org/10.1177/0093854819846917.
O'Brien, P., Henke, R.M., Schaefer, M.B., Lin, J., Creedon, T.B., 2021. Adverse events among adult Medicaid enrollees with opioid use disorder and co-occurring substance use disorders. Drug Alcohol Depend. 221, 108555 https://doi.org/10.1016/j.drugalcdep.2021.108555.
O'Donnell, J., 2020. Vital signs: characteristics of drug overdose deaths involving opioids and stimulants — 24 states and the District of Columbia, January–June 2019. MMWR Morb Mortal Wkly Rep. 69. https://doi.org/10.15585/mmwr.mm6935a1.
Papay, J.P., Murnane, R.J., Willett, J.B., 2015. Income-based inequality in educational outcomes: learning from state longitudinal data systems. Educ. Eval. Policy Anal. 37 (1_suppl), 29S–52S. https://doi.org/10.3102/0162373715576364.
Park, T.W., Saitz, R., Ganoczy, D., Ilgen, M.A., Bohnert, A.S.B., 2015. Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study. BMJ 350, h2698. https://doi.org/10.1136/bmj.h2698.
Phillips, A.Z., Post, L.A., Mason, M., 2023. Prevalence of alcohol in unintentional opioid overdose deaths, 2017–2020. JAMA Netw. Open 6 (1), e2252585.
Rajbhandari-Thapa, J., 2019. Opioid-related hospitalization and its association with chronic diseases: findings from the national inpatient sample, 2011–2015. Prev. Chronic Dis. 16 https://doi.org/10.5888/pcd16.190169.
Singh, J.A., Cleveland, J.D., 2020. National U.S. time-trends in opioid use disorder hospitalizations and associated healthcare utilization and mortality. PLoS One 15 (2), e0229174.
Song, Z., 2017. Mortality quadrupled among opioid-driven hospitalizations, notably within lower-income and disabled white populations. Health Aff. 36 (12), 2054–2061. https://doi.org/10.1377/hlthaff.2017.0689.
Sun, E.C., Dixit, A., Humphreys, K., Darnall, B.D., Baker, L.C., Mackey, S., 2017. Association between concurrent use of prescription opioids and benzodiazepines and overdose: retrospective analysis. BMJ 356, j760. https://doi.org/10.1136/bmj.j760.
U.S. Food and Drug Administration. New Safety Measures Announced for Opioid Analgesics, Prescription Opioid Cough Products, and Benzodiazepines. FDA. Published August 31, 2016. Accessed June 20, 2023. https://www.fda.gov/drugs/information-drug-class/new-safety-measures-announced-opioid-analgesics-prescription-opioid-cough-products-and.
Weidner, R.R., Schultz, J., 2019. Examining the relationship between U.S. incarceration rates and population health at the county level. SSM - Population Health 9, 100466. https://doi.org/10.1016/j.ssmph.2019.100466.
Weiner, S.G., Baker, O., Bernson, D., Schuur, J.D., 2020. One-year mortality of patients after emergency department treatment for nonfatal opioid overdose. Ann Emerg Med. 75 (1), 13–17. https://doi.org/10.1016/j.annemergmed.2019.04.020.
Welcome to MedDRA | MedDRA. Accessed October 11, 2023. https://www.meddra.org/.
Winkelman, T.N.A., Chang, V.W., Binswanger, I.A., 2018. Health, polysubstance use, and criminal justice involvement among adults with varying levels of opioid use. JAMA Netw. Open 1 (3), e180558.