Risk factors of opioid-related overdose among opioid users in an acute care setting: a prospective cohort study

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Abstract

Risk factors of opioid-related overdose among
opioid users in an acute care setting: a prospective cohort study

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Objective: Opioid-related overdoses cause substantial morbidity and mortality in the United States. This prospective cohort analysis investigated the associations between demographics, overdose history, and drug use and future medically attended opioid overdose events (both fatal and non-fatal).

Methods: Baseline data from 241 high-risk opioid users were collected from 2013-2015 in Washington State. These data were linked with medical and death records and analyzed using a Cox proportional hazards model using time to first opioid-related overdose as the outcome of interest. A secondary analysis of all-cause mortality was included.

Results: Participants were mostly male (71.4%), white (52.7%), heroin users not on opioid agonist therapy (58.5%), and homeless (52.5%). Heroin use without opiate agonist therapy (OAT) was associated with future opioid overdose, compared to those who used pharmaceutical opioids or were enrolled in OAT, adjusting for intervention status, age, sex, race, and housing status (adjusted Hazard Ratio (aHR) 1.95; 95% CI 1.07, 3.53). Separate models of lifetime history of a previous opioid overdose (aHR, 3.55; 95% CI 1.71, 6.08), poly drug use with depressants when controlling for uppers, (aHR, 2.99; 95% CI 1.47, 6.08), and proportion of days of opioid use alone when comparing the lowest tertile to the highest tertile (aHR, 1.96; 95% CI 1.03, 3.71) were associated with future opioid overdose while adjusting for intervention status, age, sex, race, housing status, and opioid use type. **Conclusions:** For patients seen in an acute care setting, questions pertaining to one's opioid agonist therapy status, lifetime opioid overdose history, poly drug use with depressants, and proportion of days using opioids alone were most predictive of one's future overdose risk. Drug use habits and enrollment in opiate agonist therapy should be discussed with opioid patients in an effort to intervene, educate, and reduce opioid overdoses.

Introduction

Deaths from opioid-related overdoses have been increasing throughout the United States, with a doubling in the rate of opioid-related deaths from 2000-2014 and 28,647 deaths in 2014 [1] further increasing to 33,091 opioid-related deaths in 2015 [2]. Corresponding with the increase in deaths, hospitalizations from opioid overdoses (including both fatal and non-fatal) have also been increasing [3]. Non-fatal overdoses cause significant morbidities, such as injuries sustained from falls, pulmonary complications, and neurological deficits along with significant psychological distress and monetary losses [4].

Efforts to identify risk factors for opioid overdoses have primarily been limited by their cross-sectional design, and a reliance on self-reported data [5-7]. Coffin et al. identified that history of previous overdose was highly associated with recent overdose, using data collected from surveys of street-recruited drug users [5]. Their study also identified age, poly drug use, and withdrawal symptoms as being associated with recent overdose [5]. Darke and Hall's 2003 systematic review of heroin overdose literature indicated that typically half of opioid users reported a history of previous overdose with many of those reporting more than one previous overdose, as identified through surveys of self-report data [6]. Darke and Hall's review also noted that males, those not enrolled in opioid agonist therapy (OAT) and poly drug use (such as alcohol, downers, and uppers) were most commonly associated with heroin overdose [6]. Additionally, a 2003 study of San Francisco heroin users identified that 68% of heroin fatality victims were reportedly alone, noting that using alone is a risk factor for overdose as no one is able to assist the victim [8].

Few cohort studies of opioid users include non-fatal overdose as an outcome, however, a 2007 study of detox patients also identified prior overdose as the largest predictor of future non-fatal overdose in their opioid user subgroup [9]. Most cohort studies examining opioid overdoses have focused on opioid-related fatalities, as those data are more readily available. A 2001 cohort study of Seattle injection drug users (IDU) noted that homelessness was associated with risk of fatal overdose [10]. Another study following opioid users on OAT found that those who remained on therapy were at lower risk for mortality than those who left their OAT program [11]. A more recent 2016 cohort study from England involving 151,983 opioid users identified enrollment in treatment (OAT) as a protective factor, male gender as a risk factor, and alcohol use as a risk factor for opioid related fatalities [12].

Quality of life (QOL) indicators and their relationship to predicting future opioid overdose risk are not well understood [13]. The WHOQOL-BREF is a shortened version of the WHOQOL-100 self-assessment, and has been shown to be a valid and cross-cultural QOL indicator [14]. Although the WHOQOL-BREF [14] has been explored in a handful of studies examining health metrics of opioid users, there is no known published data regarding its relationship to risk of future overdose and mortality. A study of Lithuanian opioid users indicated that that a higher quality of life score was found in those who continued with methadone maintenance when compared to those who did not [15]. A systematic review of the WHOQOL-BREF in opioid users participating in OAT found increases in their overall QOL for those which remained in their treatment programs [16]. These studies followed patients prospectively but none measured future overdose or mortality risks based on QOL scores [17-24].

The study aimed to examine risk factors of both non-fatal and fatal opioid overdoses using a prospective cohort design. Demographic factors, drug use patterns, opioid use type, and measures of well-being were evaluated.

Methods

Study Population

This prospective cohort analysis utilized data from a randomized controlled trial (RCT) on overdose prevention that combined overdose education, brief behavior change counseling, and free naloxone overdose reversal kits. 241 high-risk opioid users were identified from acute-care settings in Seattle, Washington, from 2013-2015. Initial results from the RCT indicate that the intervention did not have statistically significant results in reducing medically attended opioid overdoses (both non-fatal and fatal). The study was approved by both University of Washington and Washington State Institutional Review Boards.

There were 430 opioid users initially assessed for eligibility. Patients were considered for the study following an acute care visit if they had used heroin at least two times in the last 30 days, or if their daily dose of prescribed opioids was greater than a 10 mg morphine equivalent analgesic dose for at least 15 of the last 30 days. Patients were excluded if they were unwilling to allow access to their electronic medical records, unable to communicate in English, had current suicidal ideation, were significantly cognitively or psychiatrically impaired, or unable to provide contact information.

Data Collection and Linkage

A baseline interview was conducted and participants' medical records were utilized until administrative censoring on December 31, 2015. Participants who entered the study later on were therefore subject to less follow-up time due to the administrative censoring. Entry was defined as date of baseline interview following enrollment in an acute care setting. Baseline interview data were then linked to medical records obtained from University of Washington's Medical System (including in-patient and ER admissions), Washington State's Comprehensive Hospital Abstract Reporting System (CHARS), and Washington State's vital records (death certificates).

Baseline Measures

Demographic factors and drug use patterns were collected from a baseline interview. These data included age, sex, race, housing status, opioid use type, poly drug use, overdose history, and quality of life measures (WHOQOL-BREF). Age was included as a continuous variable. Sex was included as either male or female. Race was defined as white, black, or other. Housing status was categorized as

permanent or stable, temporary or unstable, or homeless. Opioid use type was defined as “Heroin use and not on OAT” or “Prescription opioid use only or currently on OAT.” The “Prescription opioid use only or currently on OAT” category includes heroin use while on OAT, prescription opioid use, or enrollment in OAT and not currently using heroin. Questions pertaining to poly drug use (categorized as depressants or uppers) were defined as “No” if they did not use the substance within two hours before or after opioid use, or “Yes” if they self-reported use within two hours before or after opioid use. Depressants included either alcohol or downers, with downers defined as “drugs like Valium, Xanax, Klonopin, and Ativan.” Uppers were defined as “drugs like crack, cocaine, crystal/meth, Adderall, Concerta, or Ritalin.”

Overdose history was ascertained by asking the participant whether they ever had a serious opioid overdose either in the past 30 days, past year, or in their lifetime. A serious opioid overdose was defined as an incident in which “a person’s skin, lips, or fingers turn blue, or they stop breathing or breathe really slowly, or they cannot be woken up without help (for example CPR, opiate antidote Narcan).” Quality of life indicators were identified from the physical health domain of the WHOQOL-BREF questionnaire and split into tertiles of low, medium, or high.

Participants’ frequency of opioid use was collected by asking how many days opioids were used in the last 30 days. Participants were also asked how many times in the last 30 days they had used opioids when nobody else was around. Using these two variables, a proportion of days of opioid use while alone was created by dividing the number of days opioids were used alone in the past 30 days (numerator) by the number of days opioids were used in the last 30 days (denominator).

Outcome Measures from UW/HMC, CHARS, or Vital Records

An opioid-related overdose or fatality was captured and identified if ICD-10 codes matched any of the following: X40, X41, X42, X43, X44, X60, X61, X62, X63, X64, X85, Y10, Y11, Y12, Y13, or Y14. These ICD-10 codes correspond with an opioid poisoning (both illicit and prescription) as the underlying cause of the medical visit (inpatient or ER) or death. Records were matched based on social security number, date of birth, and full legal name. These data were administratively censored on December 31, 2015.

Data Analysis

Because data were utilized from an RCT, a variable indicating enrollment in the study intervention arm was incorporated into all models. Separate Cox proportional hazards models were used to test the hazard

of drug use patterns including opioid use type, poly drug use, overdose history, psychological measures of well-being, and proportion of days of opioid use while alone. The outcome of interest was time to first opioid-related overdose or opioid-related fatality (whichever occurred first). All models were adjusted for the following covariates: intervention status, age, sex, race, and housing status. The main predictor of interest was opioid use type. As opioid use type was hypothesized to be a significant confounder, further analyses also adjusted for opioid use type status. These analyses tested the predictors of interest separately for the following models (adjusting for all previous covariates including opioid use type) which included poly drug use, overdose history in the last 30 days, overdose history in the last year, overdose history in one's lifetime, QOL indicators, and proportion of days of opioid use while alone.

The secondary aim examined all-cause mortality as the outcome, and used the same models as described above.

Each of the models were tested for proportionality of hazards using Schoenfeld residuals. A global test was used to determine whether there was a difference in the proportionality of hazards. The analysis was conducted using STATA 14.2.

Statistical Power

The study is powered to detect a hazard ratio of at least 2.1, or 0.48, assuming 80% power, alpha of 0.05, sample size of 241 and failure probability of 23.6% (as observed for time to first opioid-related overdose or opioid-related fatality). The secondary aim of all-cause mortality is powered to detect a hazard ratio of at least 3.0, or 0.33, assuming 80% power, alpha of 0.05, sample size of 241, and failure probability of 10.8% (as observed for all-cause mortality).

Results

Opioid-related overdose or fatality

The study recorded 373.24 person-years of data for 241 participants from 2013-2015. The median follow-up time was 589 days, with a range of 6 to 1,064 days using time to opioid-overdose or death as the outcome of interest. Participants had a mean age of 41.2 years, were mostly male (71.4%), white (52.7%), heroin users not on OAT (58.5%), and homeless (52.5%). There were 57 opioid overdoses (23.7%), with 49 non-fatal overdoses, and 8 fatal overdoses (Table 1). There were 15 non opioid-related fatalities, which were not counted as an event outcome. A complete description of the characteristics of the study population is presented in Table 1.

Demographic covariates (intervention, age, sex, race, and housing status) were not significantly associated with opioid overdose (Table 1). In a Cox regression analysis using demographic variables and heroin use without opioid agonist therapy as the main predictor of interest (Model 1), heroin use without OAT was associated with an 95% increase in hazard of future opioid overdose or fatality when compared to those using prescription opioids or enrolled in OAT (adjusted Hazard Ratio (aHR), 1.95; 95% CI 1.07, 3.53) as shown in Table 2.

After adding use of depressants or uppers in Model 2, we found that depressants were associated with a 2.99 times higher hazard of opioid overdose compared to those which did not use depressants within two hours of opioid use (aHR, 2.99; 95% CI 1.47, 6.08) adjusting for use of uppers, intervention status, age, sex, race, housing status, and opioid use type. Use of uppers with opioids was not associated with opioid overdose, adjusting for depressant use, intervention status, age, sex, race, housing status, and opioid use type (aHR, 0.64; 95% CI 0.36, 1.12).

Each measure of overdose history was modeled separately. History of overdose within the last thirty days was not associated with opioid overdose, adjusting for intervention status, age, sex, race, housing status, and opioid use type (aHR, 1.83; 95% CI 0.99, 3.39). History of overdose within the last year was associated with a 2.95 times higher hazard of opioid overdose when compared to those who had not overdosed in the last year, adjusting for intervention status, age, sex, race, housing status, and opioid use type (aHR, 2.95; 95% CI 1.67, 5.22). History of overdose in one's lifetime was associated with a 3.55 times higher hazard of opioid overdose when compared to those who had never overdosed,

adjusting for intervention status, age, sex, race, housing status, and opioid use type (aHR, 3.55; 95% CI 1.71, 6.08).

Quality of life indicators were not associated with opioid overdose, adjusting for intervention status, age, sex, race, housing status, and opioid use type (Model 6).

The proportion of days of opioid use while alone (days used opioids alone in past 30 days/days used opioids in last 30 days) was significant when comparing those who did not usually use alone (0-32%) versus those who usually used alone (67-100%) when adjusting for intervention status, age, sex, race, housing status, and opioid use type (Model 7). Usually using alone was associated with a 93.7% higher hazard of opioid overdose than those who usually did not use alone (aHR 1.96; 95% CI 1.03, 3.71). When comparing the 33-66% group versus the group that did not usually use alone, the results were not statistically significant when adjusting for intervention status, age, sex, race, housing status, and opioid use type (aHR, 1.74; 95% CI 0.77, 3.96). Three participants were excluded from this model, as their proportion of days of using opioids alone was greater than 1.

All-cause mortality

There were 441.84 person-years of data when examining all-cause mortality as the outcome of interest as our secondary aim. Twenty-six deaths were recorded, resulting in an all-cause mortality rate of 58.85 deaths per 1,000 person-years (95% CI 40.07, 86.42). Opioid use type was not significantly associated with all-cause mortality, adjusting for intervention status, age, sex, race, housing status, with an adjusted hazard ratio of 0.68 and 95% confidence interval of 0.30, 1.52. Use of depressants and opioids within two hours of each other was not significantly associated with all-cause mortality compared to those who did not use depressants, adjusting for uppers, intervention status, age, sex, race, housing status, and opioid use type (aHR, 0.45; 95% CI 0.19, 1.05). Use of uppers and opioids within two hours of each other was associated with a 3.15 times higher hazard of all-cause mortality when compared to those who did not use uppers, adjusting for downers, intervention status, age, sex, race, housing status, and opioid use type (aHR, 3.15; 95% CI 1.31, 7.59). Overdose history (30 days, past year, and lifetime), QOL indicators, and proportion of days of opioid use while alone were not significantly associated with all-cause mortality (Table 2). A ten year increase in age was associated with a 55% increase in hazard of all-cause mortality when adjusting for intervention status, age, sex, race, housing status, and opioid use type (aHR, 1.55;

95% CI 1.08, 2.21). Other/unknown race was associated with all-cause mortality when compared to those who identified as White, adjusting for intervention status, age, sex, race, housing status, and opioid use type (aHR, 3.06; 95% CI 1.29, 7.27). The full results of the adjusted analyses are shown in Table 2.

Proportionality of Hazards

For each of the models, Schoenfeld residuals were created to test the global proportionality of hazards, and all of the models failed to reject the null hypothesis that there was no violation of the proportionality of hazards.

Table 1. Characteristics of the study population

	Total		No Opioid Overdose or Fatality		Opioid Overdose or Fatality	
	N	%	N	%	N	%
	241	100.0	184	76.4	57	23.7
Intervention	115	47.7	91	49.5	24	42.1
Age* (Mean, SD)	241	41.2, 11.5	184	40.8, 10.9	57	42.8, 13.2
Female	69	28.6	52	28.3	17	29.8
Race						
White	127	52.7	96	52.2	31	54.4
Black	31	12.9	25	13.6	6	10.5
Other/Unknown	83	34.4	63	34.2	20	35.1
Housing Status**						
Permanent Housing	73	30.4	57	31.0	16	28.1
Temporary Housing	41	17.1	29	15.8	12	21.1
Homeless	126	52.5	97	52.7	29	50.9
Opioid Use Type						
Heroin without OAT	141	58.5	100	54.4	41	71.9
Rx only or OAT	100	41.5	84	45.7	16	28.1
Poly drug use within two hours of opioid use in the last 30 days						
Depressants (any)	153	63.5	106	57.6	47	82.5
Alcohol	90	37.3	61	33.2	29	50.9
Downers	109	45.2	78	42.4	31	54.4
Uppers	129	53.5	101	54.9	28	49.1
Opioid Overdose History						
*In Past 30 Days***	46	19.2	28	15.2	18	31.6
*In Last Year**	76	31.7	45	24.5	31	54.4
*In Lifetime**	149	62.1	101	54.9	48	84.2
WHOQOL-BREF: Quality of Life Score in Tertiles**						
Lowest (Range 7-16)	88	38.3	69	37.5	19	33.33
Middle (Range 17-22)	77	33.5	58	31.5	19	33.33
Highest (Range 23-35)	65	28.3	48	26.1	17	29.82
Days of Opioid Use in Past 30 Days**						
<10 Days	27	11.2	22	12.0	5	8.8
10-26 Days	46	19.1	31	16.9	15	26.3
27-30 Days	166	68.9	129	70.1	37	64.9
Days of opioid use when no one else was around**						
<10 Days	111	46.1	90	48.9	21	36.8
10-26 Days	69	28.6	51	27.7	18	31.6
27-30 Days	60	24.9	43	23.4	17	29.8
Proportion of days of opioid use while alone**						
Used alone 0% to 32%	91	37.8	76	41.3	15	26.3
Used alone 33% to 66%	35	14.5	25	13.6	10	17.5
Used alone 67% to 100%	109	45.2	78	42.4	31	54.4

*Age presented via mean and standard deviation rather than percentage. **Incomplete and less than 5% missingness

Table 2. Adjusted hazard ratios and 95% confidence intervals for the association between patient demographic and drug use characteristics and opioid overdose or fatality and all-cause mortality.

	Opioid overdose or fatality		All-cause mortality	
	Adj. Hazard	95% Confidence Interval	Adj. Hazard	95% Confidence Interval
Model 1				
Intervention	0.87	0.51, 1.47	1.01	0.46, 2.24
Age (10 year increments)	1.19	0.94, 1.50	***1.55***	***1.08, 2.21***
Female	1.19	0.67, 2.13	0.56	0.20, 1.55
Race				
White	Ref	Ref	Ref	Ref
Black	0.68	0.28, 1.67	1.06	0.28, 4.06
Other/Unknown	1.08	0.61, 1.90	***3.06***	***1.29, 7.27***
Housing Status				
Permanent	Ref	Ref	Ref	Ref
Temporary	1.35	0.63, 2.90	0.32	0.07, 1.43
Homeless	1.03	0.55, 1.95	0.50	0.21, 1.18
Opioid Use Type				
Rx only or OAT	Ref	Ref	Ref	Ref
Heroin – Not on OAT[1]	***1.95***	***1.07, 3.53***	0.68	0.30, 1.52
Model 2				
Poly drug use in two hours of opioid use within the last 30 days[2]				
Depressants	***2.99***	***1.47, 6.08***	0.45	0.19, 1.05
Uppers	0.64	0.36, 1.12	***3.15***	***1.31, 7.59***
Model 3				
Overdose History In Last 30 Days[2]	1.83	0.99, 3.39	0.61	0.17, 2.16
Model 4				
Overdose History In Last year[2]	***2.95***	***1.67, 5.22***	0.75	0.28, 1.97
Model 5				
Overdose History In Lifetime[2]	***3.55***	***1.71, 6.08***	1.74	0.71, 4.24
Model 6				
WHOQOL-BREF: Quality of Life Score in Tertiles[2]				
Lowest (Range 7-16)	Ref	Ref	Ref	Ref
Middle (Range 17-22)	1.17	0.60, 2.25	0.84	0.33, 2.09
Highest (Range 23-35)	1.35	0.68, 2.66	0.67	0.29, 1.85
Model 7				
Proportion of days of opioid use while alone[2]				
Used alone 0% to 32%	Ref	Ref	Ref	Ref
Used alone 33% to 66%	1.74	0.77, 3.96	2.07	0.67, 6.42
Used alone 67% to 100%	***1.96***	***1.03, 3.71***	0.81	0.33, 2.01

Each model is separated by a double bar.

[1] Denotes the adjusted model including intervention, age, sex, race, housing status.

[2] Denotes the adjusted model including intervention, age, sex, race, housing status, and opioid use type.

Discussion

The study identified history of prior overdose, poly drug use with depressants, proportion of days of opioid use while alone, and heroin use without OAT enrollment as strong predictors of future medically attended opioid overdose or fatality. Self-reported measures of quality of life was not found to be associated with risk of future non-fatal or fatal opioid overdose. Poly drug use with uppers was identified as a strong predictor of all-cause mortality.

History of overdose at any point in one's lifetime was found to be a stronger predictor of future overdose than history of an overdose in the last year, while overdose history in the past thirty days was not associated with opioid overdose. History of overdose may be associated with years of use, and those with a longer period of use may be exposed to longer period of risk of overdose than more recent users, but it does not fully explain the relationship to future overdose event. Perhaps those who had more recently overdosed are more cognitively aware of the apparent risks, although recent overdose was not seen as a protective factor. The relationship should be explored further in future studies.

Housing status was not found to be associated with future opioid overdose, contrasting with O'Driscoll et al.'s study of Seattle injection drug users which found homelessness associated with a 2.3 times higher relative risk of fatal overdose [10]. This could be due in part to their study including non-opiate users such as cocaine users. Alternatively as their study was conducted in 2001, the access and availability of housing and healthcare-related services for those who are homeless or temporarily housed is likely to have changed. This is also a relatively acute population in that they were recruited at the safety net hospital for the region and only 30% reported permanent housing (Table 1).

The proportion of days of opioid use while alone is a unique finding. Although a majority of opioid fatalities involve a victim who was reportedly alone [8], there are scant studies identifying a hazard or risk of using alone. These findings further support recommendations to strongly discourage using alone. Conversely, these data support efforts to encourage use around others (rather than alone) as a means to reduce opioid overdoses. Safe Injection Facilities would be a viable option to give opioid users a place to use under medical supervision, as implemented in British Columbia and many countries around the world [25].

The secondary aim of all-cause mortality identified poly drug use with uppers as a risk factor, when adjusting for poly drug use of depressants. It is interesting to note that poly drug use with uppers was not associated with opioid overdose while adjusting for depressants. Interventions to educate and reduce poly drug use of uppers should be explored for this high-risk group.

Limitations

The medical records data were acquired from UW Medical Center and CHARS, with death records acquired from Washington State Vital Records. Although UW Medical Center data included in-patient care along with hospitalization data, the CHARS data was limited only to hospitalizations. All non-medically attended overdose events would have been missed, along with any hospitalizations or deaths which occurred out of state. The number of overdose events is likely conservative in this sample, but it is unclear how this may have affected the relationship with individual risk factors. The study attempted to mitigate this by asking participants whether they were planning on moving outside of the study area within a year of entering the study and excluding those who planned to move.

The study was limited by sample size, and there may be some concerns for type II error, as the study was powered at 80% with a hazard ratio of 2.1, or 0.48. As drug use history and participant demographics were captured at baseline, it is possible that one's drug use history demographics such as housing status could have changed over the course of the study. Additionally, the binary categorization of opioid use type is crude, however, this compromise was made to account for the small sample size. Given a larger sample size, the study would have utilized four categories: 1) heroin user not enrolled in OAT, 2) heroin user enrolled in OAT, 3) prescription opioid user, and 4) OAT only (no heroin use).

Strengths

The analysis improved upon previous studies which were limited by their cross-sectional design. The prospective cohort design collected extensive information regarding drug use history and demographic characteristics for 241 participants, accumulating 373.24 person-years of data in a population that is difficult to identify. The study also draws strength from an outcome based upon identifying non-fatal overdose in addition to fatal opioid overdoses.

Conclusions

The findings are consistent with previous studies identifying opioid use type, drug use history, poly drug use, and using alone as risk factors for opioid-related overdoses, and helps to strengthen those findings through the use of a prospective cohort design [5, 6, 8, 12]. These findings are especially relevant to clinicians in an acute care setting, where there is an opportunity to educate and inform opioid patients of their apparent risks and prioritize interventions. As Coffin et al. and Pierce et al. have noted, medical professionals should discuss and identify known risk factors with opioid patients in an effort to reduce future opioid overdose events [5, 12]. Future interventions should be aimed at reducing poly drug use, discouraging use alone, and enrolling patients in an opiate agonist treatment program.

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