The Impact of Benzodiazepine Use on Mortality Among Polysubstance Users in Vancouver, Canada

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ABSTRACT

Objective. Illicit drug use is a well-established risk factor for increased morbidity and mortality. However, little is known about the impact of benzodiazepine use on mortality among populations of polysubstance users. This study aimed to identify the effect of benzodiazepine use on mortality among a prospective cohort of people in Canada who inject drugs (PWID).

Methods. A cohort of PWID in Vancouver, Canada, was prospectively followed from May 1996 through November 2013. Data on participants were linked to the provincial vital statistics registry to ascertain mortality rates and causes of death. Multivariable extended Cox regression with time-dependent variables was used to investigate the relationship between benzodiazepine use and time to all-cause mortality.

Results. During the study period, 2,802 participants were followed for a median of 67 months (interquartile range: 25–107). In total, 527 (18.8%) participants died, for an incidence density of mortality of 2.9 (95% confidence interval [CI] 2.7, 3.2) deaths per 100 person-years. After adjusting for HIV infection and other potential confounders, benzodiazepine use was independently associated with increased all-cause mortality (adjusted hazard ratio = 1.86, 95% CI 1.38, 2.51) and had a higher risk for mortality than all other traditional substances of abuse among this population. Results were consistent when non-overdose mortality was considered.

Conclusion. In this setting, benzodiazepine use was more strongly associated with mortality than any other substance of abuse. Greater recognition of the safety concerns related to benzodiazepines and strategies to prevent diversion to illicit use are needed.

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Substance abuse is a growing burden on health worldwide, even as its prevalence and contribution to morbidity and mortality is increasingly recognized and studied.[1] However, an accurate estimate of the prevalence and harms of patterns of drug use is difficult to ascertain. The problem is widespread, with recent United Nations estimates of 15–39 million problem drug users and 11–21 million intravenous drug users globally.[2] A 2013 review estimated a pooled crude mortality ratio associated with intravenous drug use of 2.35 per 100 person-years globally and 2.64 per 100 person-years in North America.[3] Although illicit drug use is associated with many preventable adverse health effects, including premature mortality, most research has focused on traditional illegal drugs of abuse, such as heroin, cocaine, and amphetamine-type stimulants.[4–6]

In recent years, however, concern about prescription drug abuse has increased. Studies examining data from large U.S. surveys have described the burden of disease from illicit drug use, including prescription drugs.[7,8] These data demonstrated that, in 2010, almost 3% of the U.S. household population reported nonmedical prescription drug use in the previous month, and that more than 15% of 12th graders reported misusing prescription drugs in the previous year.[7,8] Canadian studies published in 2009 and 2012 highlighted emerging concerns about the harms of prescription opioid misuse, including an epidemic of prescription opioid-related overdose deaths.[9,10] Nonmedical prescription opioid use has surpassed heroin use among street drug users in some settings.[9]

Benzodiazepines have been used since chlordiazepoxide was approved in 1960.[11] Side effects of benzodiazepine use include psychomotor retardation, memory impairment, and development of physiologic dependence.[11,12] In Canada, concern is rising about the diversion and misuse of sedatives, including benzodiazepines.[13] Sedatives and hypnotic drugs are among the most common causes of visits to the emergency department for adverse drug events.[14] An examination of Canadian data to determine the relationship between benzodiazepines and opioid use found that most opioid-related deaths were associated with non-opioid central nervous depressants, including benzodiazepines.[10] Benzodiazepines were also recently associated with opioid-related death during methadone therapy in Canada.[15] Studies on benzodiazepine use among people who inject drugs (PWID) in Canada demonstrated that approximately 35% of PWID reported benzodiazepine use in the previous six months[16] and that benzodiazepine use was associated with an increased risk of self-reported nonfatal overdose.[17] We examined the prevalence of benzodiazepine use among a prospective cohort of PWID in Vancouver, British Columbia, Canada, to determine its association with mortality.

METHODS

The Vancouver Injection Drug Users Study (VIDUS) and AIDS Care Cohort to Evaluate Access to Survival Services (ACCESS) are open prospective cohorts of drug users in Vancouver. The recruitment and follow-up procedures for the two studies are identical to allow for analyses of merged data; the only substantive differences are (*1*) human immunodeficiency virus (HIV)-positive participants are followed in ACCESS, whereas HIV-negative participants are followed in VIDUS and (*2*) ACCESS includes non-injecting (e.g., crack cocaine) drug users, whereas VIDUS only enrolls people who inject drugs in the month prior to enrollment. In both studies, the primary modes of enrollment are self-referral, word of mouth, and street outreach. Detailed sampling and recruitment procedures for these two cohorts are described elsewhere.[18,19] To be eligible, participants must be ≥18 years of age, reside in the greater Vancouver region, and have injected drugs in the month prior to enrollment. All participants provide written informed consent. Participants are given a stipend ($30 Canadian) at each study visit for their time and transportation.

At baseline and semianually thereafter, participants complete an interviewer-administered questionnaire on a range of topics, including demographic characteristics, injection and non-injection drug use, and sexual risk behaviors. Venous blood samples drawn at each visit are used for serologic analyses, including testing for HIV and hepatitis C virus (HCV) antibodies. All participants have private interviews and are offered pretest and posttest counseling with trained nurses. Referral for free HIV/acquired immunodeficiency syndrome care is provided to those found to be HIV positive, and these participants are subsequently followed in ACCESS.

Our study included individuals who were recruited from May 1996 through November 2013 and who reported a history of injection drug use at baseline. Fifty-two of 2,854 (1.8%) participants who did not report a history of injection drug use at baseline were excluded; these participants were part of the ACCESS cohort. We collected mortality data, including data on underlying cause of death among participants, through a confidential record linkage with the British Columbia Vital Statistics Agency and ongoing follow-up with contacts (e.g., friends) provided by participants. The Vital Statistics database records cause of death

according to the International Classification of Diseases, 10th Revision.

The primary endpoint in this analysis was all-cause mortality, with overdose and non-overdose mortality considered in subanalyses. The primary explanatory variable was any benzodiazepine use in the previous six months. We also considered demographic, behavioral, clinical, and other exposure characteristics as potential confounders of the association between benzodiazepine use and mortality, based on prior studies of health and social harms among PWID in our setting.[20–22] These confounders were substance-using behaviors in the previous six months, including at least daily cocaine injection, at least daily heroin injection, at least daily amphetamine injection, at least daily crack cocaine smoking, at least daily speedball (cocaine and heroin) injection, and at least daily alcohol use. Other variables were age, sex (male and female), time since first injection, race (white and nonwhite), HIV serostatus (positive and negative), HCV antibody serostatus (positive and negative), methadone maintenance therapy, sex work, and living in unstable housing in the previous six months. We defined unstable housing as living in one of the city's Downtown Eastside single-room-occupancy hotels, shelters, or other transitional housing, or living on the street. All variables were identical to prior reports on injection drug users in Vancouver.[23]

As an initial analysis, we calculated the frequency and prevalence of benzodiazepine use at baseline, stratified by each binary explanatory variable. We compared the prevalences using the Wald χ^2 test. For continuous explanatory variables, we calculated the median and interquartile range (IQR) and compared them using the Wilcoxon rank sum test. We then calculated all-cause mortality rates and overdose mortality rates, including 95% confidence intervals (CIs), using the Poisson distribution.

Next, we used extended Cox regression to examine the bivariable relationship between each explanatory variable and time to all-cause mortality.[24] We treated all behavioral variables as time-varying variables. To fit the multivariable model, we used a conservative stepwise backward selection approach. We included all variables found to be significantly associated with time to all-cause mortality in bivariable analyses at $p<0.10$ in a multivariable model, and we used a stepwise approach to fit a series of reduced models. After comparing the value of the coefficient associated with benzodiazepine use in the full model with the value of the coefficient in each of the reduced models, we dropped the secondary variable associated with the smallest relative change. We continued this iterative process until the minimum change exceeded 5%. We considered remaining variables as potential confounders in a final multivariable model. We used this procedure previously to estimate the effect of a primary explanatory variable on an outcome of interest after adjusting for secondary variables.[25]

We also conducted subanalyses in which we restricted the dependent variable to deaths resulting from overdose and non-overdose to examine whether benzodiazepine use was independently associated with overdose deaths or non-overdose deaths or both. We performed all statistical analyses using SAS® version 9.3.[26] All *p*-values were two-sided.

RESULTS

A total of 2,802 individuals were eligible for the present study and were followed for a median of 67.0 months (IQR: 24.8–107.0). Among the study sample, 1,855 (66.2%) participants were men, 1,699 (60.6%) participants were white, and 862 (30.8%) participants were HIV positive at baseline. The median age was 37.1 years (IQR: 29.2–43.8), and the median time since first injection was 14.0 years (IQR: 5.8–23.6). At baseline, 734 (26.2%) participants reported benzodiazepine use in the previous six months, 1,028 (36.7%) injected heroin daily, 802 (28.6%) injected cocaine daily, 683 (24.4%) smoked crack cocaine daily, 524 (18.7%) consumed alcohol daily, and 80 (2.9%) injected amphetamines daily (Table 1).

Benzodiazepine use was significantly more prevalent among participants who reported daily heroin injection (prevalence ratio [PR] = 1.36, 95% CI 1.20, 1.54; $p<0.001$) and daily cocaine injection (PR=1.94, 95% CI 1.72, 2.19, $p<0.001$) than among those who did not report daily heroin or cocaine injection (Table 1).

During the study period, 527 (18.8%) participants died, yielding an incidence density of 2.9 (95% CI 2.7, 3.2) deaths per 100 person-years. In the bivariable analyses, benzodiazepine use was significantly and positively associated with time to all-cause mortality; the unadjusted hazard ratio (HR) was 1.74 (95% CI 1.29, 2.33; $p<0.001$). Daily cocaine injection (HR=1.46, 95% CI 1.17, 1.82; $p<0.001$) and daily alcohol use (HR=1.27, 95% CI 1.00, 1.61; $p=0.047$) were also significantly and positively associated with all-cause mortality. In the multivariable analysis, after adjusting for potential confounders, including HIV serostatus and daily cocaine injection, benzodiazepine use remained independently and positively associated with time to all-cause mortality (adjusted hazard ratio [AHR] = 1.86, 95% CI 1.38, 2.51; $p<0.001$) (Table 2).

The subanalysis on non-overdose mortality showed that benzodiazepine use had an HR of 1.87 (95% CI

Table 1. Characteristics of people who inject drugs enrolled in the VIDUS and ACCESS cohorts, stratified by any benzodiazepine use in the past 6 months, Vancouver, Canada, November 1996 to May 2013

Characteristic	*Number of study participants*	*Number of participants indicating benzodiazepine use*	*Percent of participants using benzodiazepines (95% CI)*[a]	*Prevalence ratio (95% CI)*	P-*value*[b]
Total	2,802	734	26.2 (24.6, 27.8)		
Sex					
Male	1,855	462	24.9 (22.9, 26.9)	0.87 (0.76, 0.99)	0.029
Female	947	272	28.7 (25.8, 31.6)	Ref.	
Race					
White	1,699	462	27.2 (25.1, 29.3)	1.10 (0.97, 1.25)	0.138
Nonwhite	1,103	272	24.7 (22.1, 27.2)	Ref.	
Median age, in years (IQR)	37.1 (29.2, 43.8)	35.2 (28.0, 41.1)			<0.001
Unstable housing[c]					
Yes	1,972	493	25.0 (23.1, 26.9)	0.86 (0.75, 0.98)	0.026
No	809	235	29.0 (25.9, 32.2)	Ref.	
Not reported	21	6	NC	NC	
Median time since first injection, in years (IQR)	14.0 (5.8, 23.6)	13.7 (5.3, 24.0)			0.207
Sex work[c]					
Yes	637	197	30.9 (27.3, 34.5)	1.24 (1.08, 1.42)	0.002
No	2,154	537	24.9 (23.1, 26.8)	Ref.	
Not reported	11	0	NC	NC	
Methadone maintenance therapy[c]					
Yes	650	120	18.5 (15.5, 21.5)	0.64 (0.54, 0.77)	<0.001
No	2,142	614	28.7 (26.7, 30.6)	Ref.	
Not reported	10	0	NC	NC	
Daily alcohol use[c]					
Yes	524	234	44.7 (40.4, 48.9)	2.04 (1.80, 2.30)	<0.001
No	2,273	498	21.9 (20.2, 23.6)	Ref.	
Not reported	5	2	NC	NC	
Daily heroin injection[c]					
Yes	1,028	323	31.4 (28.6, 34.3)	1.36 (1.20, 1.54)	<0.001
No	1,768	409	23.1 (21.2, 25.1)	Ref.	
Not reported	6	2	NC	NC	
Daily cocaine injection[c]					
Yes	802	319	39.8 (36.4, 43.2)	1.94 (1.72, 2.19)	<0.001
No	1,983	407	20.5 (18.7, 22.3)	Ref.	
Not reported	17	8	NC	NC	
Daily crack cocaine smoking[c]					
Yes	683	72	10.5 (8.2, 12.9)	0.34 (0.27, 0.42)	<0.001
No	2,115	661	31.3 (29.3, 33.2)	Ref.	
Not reported	4	1	NC	NC	
Daily amphetamine injection[c]					
Yes	80	3	3.8 (0.0, 8.0)	0.14 (0.05, 0.42)	<0.001
No	2,716	731	26.9 (25.2, 28.6)	Ref.	
Not reported	6	0	NC	NC	
Daily speedball injection[c]					
Yes	311	129	41.5 (36.0, 47.0)	1.70 (1.47, 1.98)	<0.001
No	2,486	605	24.3 (22.6, 26.0)	Ref.	
Not reported	5	0	NC	NC	

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Table 1 (continued). Characteristics of people who inject drugs enrolled in the VIDUS and ACCESS cohorts, stratified by any benzodiazepine use in the past 6 months, Vancouver, Canada, November 1996 to May 2013

Characteristic	*Number of study participants*	*Number of participants indicating benzodiazepine use*	*Percent of participants using benzodiazepines (95% CI)*[a]	*Prevalence ratio (95% CI)*	P-*value*[b]
HIV serostatus[c]					
Positive	862	167	19.4 (16.7, 22.0)	0.66 (0.57, 0.77)	<0.001
Negative	1,938	567	29.3 (27.2, 31.3)	Ref.	
Not reported	2	0	NC	NC	
HCV serostatus[c]					
Positive	2,268	597	26.3 (24.5, 28.1)	1.05 (0.89, 1.24)	0.556
Negative	511	128	25.0 (21.3, 28.8)	Ref.	
Not reported	23	9	NC	NC	

[a]Data not reported were excluded from percentage and prevalence ratio calculations.

[b]*P*-values were from the Wald χ^2 test for binary variables, and from the Wilcoxon rank sum test for continuous variables.

[c]Refers to activities and status in the six months prior to interview.

VIDUS = Vancouver Injection Drug Users Study

ACCESS = AIDS Care Cohort to Evaluate Access to Survival Services

CI = confidence interval

Ref. = reference group

IQR = interquartile range

NC = not calculated

HIV = human immunodeficiency virus

HCV = hepatitis C virus

1.34, 2.62) and an AHR of 2.04 (95% CI 1.45, 2.87) (both $p<0.001$). The other substance use variable significantly associated with non-overdose mortality was daily cocaine use (HR=1.56, 95% CI 1.21, 2.00; $p<0.001$) (Table 3). The subanalysis on overdose mortality showed that benzodiazepine use was not significantly associated with overdose mortality (HR=1.40; 95% CI 0.76, 2.57; $p=0.284$; AHR=1.48, 95% CI 0.80,

Table 2. Bivariable and multivariable Cox regression analysis of factors associated with all-cause mortality (*n*=527) among people who inject drugs enrolled in the VIDUS and ACCESS cohorts (*n*=2,802), Vancouver, Canada, November 1996 to May 2013

Variable	*Unadjusted hazard ratio (95% CI)*	P-*value*[a]	*Adjusted*[b] *hazard ratio (95% CI)*	P-*value*[a]
Benzodiazepine use[c] (yes vs. no)	1.74 (1.29, 2.33)	<0.001	1.86 (1.38, 2.51)	<0.001
HIV serostatus[c] (positive vs. negative)	2.52 (2.12, 2.99)	<0.001	2.57 (2.15, 3.07)	<0.001
HCV serostatus (positive vs. negative)	1.99 (1.33, 2.98)	<0.001	NA	NA
Daily heroin injection[c] (yes vs. no)	0.81 (0.65, 1.01)	0.064	NA	NA
Daily alcohol use[c] (yes vs. no)	1.27 (1.00, 1.61)	0.047	NA	NA
Daily cocaine injection[c] (yes vs. no)	1.46 (1.17, 1.82)	<0.001	1.32 (1.06, 1.65)	0.015

[a]*P*-values were from the Wald χ^2 test.

[b]HCV serostatus, daily heroin injection, and daily alcohol use were excluded from the multivariable model through the a-priori defined modeling procedure. As such, adjusted hazard ratios are not reported.

[c]Refers to activities and status in the six months prior to interview.

VIDUS = Vancouver Injection Drug Users Study

ACCESS = AIDS Care Cohort to Evaluate Access to Survival Services

CI = confidence interval

HIV = human immunodeficiency virus

HCV = hepatitis C virus

NA = not applicable

Table 3. Bivariable and multivariable Cox regression analyses of factors associated with non-overdose mortality (*n*=403) among people who inject drugs enrolled in the VIDUS and ACCESS cohorts (*n*=2,802), Vancouver, Canada, November 1996 to May 2013

Variable	*Unadjusted hazard ratio (95% CI)*	P-*value*[a]	*Adjusted*[b] *hazard ratio (95% CI)*	P-*value*[a]
Benzodiazepine use[c] (yes vs. no)	1.87 (1.34, 2.62)	<0.001	2.04 (1.45, 2.87)	<0.001
HIV serostatus[c] (positive vs. negative)	2.92 (2.39, 3.57)	<0.001	2.99 (2.44, 3.66)	<0.001
HCV serostatus[c] (positive vs. negative)	2.16 (1.34, 3.50)	0.002	NA[d]	NA
Daily heroin injection[c] (yes vs. no)	0.82 (0.64, 1.06)	0.134	NA[d]	NA
Daily alcohol use[c] (yes vs. no)	1.21 (0.92, 1.59)	0.176	NA[d]	NA
Daily cocaine injection[c] (yes vs. no)	1.56 (1.21, 2.00)	<0.001	1.50 (1.16, 1.94)	0.002

[a]*P*-values were from the Wald χ^2 test.

[b]The multivariable model was adjusted for age.

[c]Refers to activities and status in the six months prior to interview.

[d]HCV serostatus, daily heroin injection, and daily alcohol use were excluded from the multivariable model through the a-priori defined modeling procedure. As such, adjusted hazard ratios are not reported.

VIDUS = Vancouver Injection Drug Users Study

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NA = not applicable

2.72; p=0.210). No other substance examined was significantly associated with overdose mortality (Table 4).

Among participants who reported benzodiazepine use during the study period, 70 of 294 deaths (23.8%) were overdoses, whereas among participants who did not report benzodiazepine use, 54 of 233 deaths (23.2%) were overdoses. HIV-related causes accounted for 70 of 294 deaths (23.8%) among those who reported benzodiazepine use and 54 of 233 deaths (23.2%) among those who did not report benzodiazepine use. Among the 294 deaths of participants who reported benzodiazepine use and the 233 deaths of participants who did not report benzodiazepine use, liver-related causes accounted for 18 (6.1%) and 14 (6.0%) deaths, suicide accounted for 16 (5.4%) and two (0.9%) deaths, homicide accounted for eight (2.7%) and nine (3.9%) deaths, accidental causes accounted for 13 (4.4%) and 13 (5.6%) deaths, other causes accounted for 77 (26.2%) and 45 (19.3%) deaths, and unspecificied causes accounted for 22 (7.5%) and 42 (18.0%) deaths, respectively.

DISCUSSION

A substantial proportion of PWID in Vancouver reported some benzodiazepine use in the previous six months. We found a strong independent association between benzodiazepine use and mortality in both an analysis on all-cause mortality and a subanalysis on non-overdose mortality. In our cohort of polysubstance-using PWID, benzodiazepine use was more strongly associated with mortality than any other drug of abuse considered.

Previous studies on prescription drug misuse largely focused on opioids, while the nonmedical use of benzodiazepines received relatively little attention.[7–9,13] Examining substance-using (predominantly opioid-using) populations, reviews of coroners' cases[27] and other sources[9,28] showed an association between benzodiazepine use and overdose mortality. One Canadian study found that 92% of opioid-related deaths were associated with the concomitant use of benzodiazepines or alcohol.[9] The evidence associating benzodiazepines with mortality in the polysubstance-using population is limited to a small number of studies focusing on mostly opioid-using populations, and the association was made only with overdose deaths.[9,27–29] The participants in our cohort reported a broad range of primary drugs of abuse, with only 36% reporting daily heroin use at baseline. Yet, we still showed an association between benzodiazepine use and mortality.

Benzodiazepines are often abused concomitantly with other substances because they are perceived to heighten the effects of co-administered drugs such as opioids.[30] A 2012 study examining the pharmacodynamics of co-administering diazepam with either methadone or buprenorphine found increases in the intensity in subjective drug effects and decreases in the

performance on psychological testing.[19] It has been hypothesized that during concomitant use of benzodiazepines and injection drugs, benzodiazepine-induced psychomotor symptoms contribute to harms involved in the preparation and injection of drugs that could lead to infection and overdose.[11] Concerns about these pharmacodynamic interactions that potentially lead to risky behaviors are well founded. A 2012 study on a Thai population showed that daily users of intravenous midazolam reported higher rates of polysubstance use, higher rates of heroin use, higher rates of overdose, and higher rates of binge drug use compared with people who did not use intravenous midazolam daily.[31] Benzodiazepines may also lessen the comedown from stimulants such as cocaine or amphetamines.[32] The cognitive and psychomotor effects of benzodiazepine use could contribute to the mortality shown in other studies associated with benzodiazepine use in polysubstance users, particularly because the effects produce measurable differences in risk-taking substance-abuse behaviors.

Our study did not show a significant association between benzodiazepine use and overdose mortality, although it did indicate a nonsignificant trend toward an association. The reason for the lack of association is unclear, but it may be that participants in our study used fewer opioids than participants in previous studies. It is also possible that rates of death caused by overdose in our cohort were lower than rates in previous studies because participants in our study had greater access to safe places to inject drugs, such as the supervised injection facility Insite. Another possible reason is that our sample size was insufficient to detect a significant effect. Additionally, as with any mortality data, potentially overdose deaths may have been misclassified as non-overdose deaths. The association between benzodiazepine use and non-overdose mortality could be explained by outcomes that were not measured in this study; for example, as a result of falls, motor vehicle accidents, and other factors that may be consequences of benzodiazepine use, all of which could increase the risk of deaths that would not be classified as overdose related.

Aside from the well-documented psychomotor and addiction liability caused by benzodiazepine use,[11,32,33] other concerns about the safety and appropriateness of benzodiazepines exist for many common clinical indications. Evidence points to the association between benzodiazepine use and long-term cognitive effects in multiple cognitive domains,[34] an increased risk of falls and fractures in the elderly, and motor vehicle accidents.[29] In addition to the dangers of benzodiazepine use, research shows that the efficacy of benzodiazepines for common clinical indications (e.g., anxiety, insomnia) is limited, especially for chronic use.[35] Our data suggest clinicians should seek alternative medications when patients, especially polysubstance-using patients, seek benzodiazepines.

Table 4. Bivariable and multivariable Cox regression analyses of factors associated with overdose mortality (*n*=124) among people who inject drugs enrolled in the VIDUS and ACCESS cohorts (*n*=2,802), Vancouver, Canada, November 1996 to May 2013

Variable	*Unadjusted hazard ratio (95% CI)*	P-*value*[a]	*Adjusted*[b] *hazard ratio (95% CI)*	P-*value*[a]
Benzodiazepine use[c] (yes vs. no)	1.40 (0.76, 2.57)	0.284	1.48 (0.80, 2.72)	0.210
HIV serostatus[c] (positive vs. negative)	1.57 (1.10, 2.24)	0.013	1.59 (1.11, 2.26)	0.011
HCV serostatus[c] (positive vs. negative)	1.60 (0.78, 3.28)	0.198	NA[d]	
Daily heroin injection[c] (yes vs. no)	0.78 (0.50, 1.22)	0.279	NA[d]	
Daily alcohol use[c] (yes vs. no)	1.48 (0.92, 2.37)	0.105	NA[d]	
Daily cocaine injection[c] (yes vs. no)	1.18 (0.73, 1.88)	0.501	NA[d]	

[a]*P*-values were from the Wald χ^2 test.

[b]The multivariable model was adjusted for age.

[c]Refers to activities and status in the six months prior to interview.

[d]HCV serostatus, daily heroin injection, and daily alcohol use were excluded from the multivariable model through the a-priori defined modeling procedure. As such, adjusted hazard ratios are not reported.

VIDUS = Vancouver Injection Drug Users Study

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Limitations

This study had several limitations. First, this study was limited by its observational design, although it would not be ethical or possible to study this population in a controlled fashion. Second, the results of this study may not be generalizable to other PWID populations because of the unique environment of our setting and the unique behaviors of our study participants. Nevertheless, the diversity of drugs used by participants in our study was greater than the diversity of drugs used by participants in previous studies.[28] Third, we did not routinely assess mental illness in this cohort, although individuals with severe mental illness (e.g., psychosis) were not eligible to participate if they could not provide informed consent. Fourth, because of self-reported drug use, our results may have been affected by socially desirable responses, recall bias, or other reporting biases; however, previous studies have shown self-reporting of drug-use behavior to be valid.[36] Finally, our primary endpoint was mortality, an objective measure obtained through the provincial database. Our results did not account for people who died in other provinces; however, it has been shown that migration from the province is low in this population.[37]

CONCLUSION

We found a strong independent association between benzodiazepine use and all-cause mortality in a sample of PWID in Vancouver, demonstrating a greater risk for mortality than all other drugs of abuse considered. This association was robust and persisted when we investigated the subgroup of non-overdose mortality. Our results add to the literature identifying the role of benzodiazepine use in overdose mortality among opioid users. This study was unique in that it was a prospective analysis of polysubstance users, was adjusted for other drugs of abuse as well as HIV-seropositive status, and considered the effect of benzodiazepine use on overdose and non-overdose mortality. Future studies should further examine mortality risk of more specific drug-use patterns in the PWID population, including potentially the co-usage of prescription drugs with other traditional substances of abuse. Given the known harms of benzodiazepines,[9,11,12,27–33] these findings highlight the importance of physician education aimed at promoting alternative medications to benzodiazepines and safer prescription strategies to avoid diversion to the street.

The authors thank the study participants for their contributions to the research, as well as current and past researchers and staff members. This study was supported by the U.S. National Institutes of Health (NIH) (Vancouver Injection Drug Users Study: U01DA038886; AIDS Care Cohort to Evaluate Access to Survival Services: R01DA021525) and the Canadian Institutes of Health Research through the Canadian Research Initiative on Substance Misuse (SMN-139148). Dr. Milloy is supported in part by NIH (R01-DA051525). Dr. Hayashi is supported by the Canadian Institutes of Health Research Fellowship. This research was undertaken, in part, with funding from a Tier 1 Canada Research Chair in Inner City Medicine, which supports Dr. Wood. Dr. Montaner is supported with grants paid to his institution by the British Columbia Ministry of Health and by NIH (R01DA036307). He has also received limited unrestricted funding, paid to his institution, from Abbvie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck, and ViiV Healthcare. Dr. Ahamad is supported by the National Institute on Drug Abuse (R25DA037756).

The viewpoints in this article are those of the authors and do not represent those of the funding agencies. The two cohort studies have been approved by the University of British Columbia/Providence Healthcare Research Ethics Board.

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