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Benzodiazepine Use as an Independent Risk Factor for HIV Infection in a Canadian Setting

Sarah Ickowicz¹, Kanna Hayashi^{1,2}, Huiru Dong¹, MJ Milloy^{1,2}, Thomas Kerr^{1,2}, Julio S. G. Montaner^{1,2}, and Evan Wood^{1,2}

¹British Columbia Centre for Excellence in HIV/AIDS, St. Paul's Hospital

²Department of Medicine, University of British Columbia

Abstract

Background—Although the harms of prescription drug diversion are of growing international concern, the potential impact of prescription drug use on HIV infection has not been well assessed. We evaluated whether benzodiazepine use was associated with HIV seroconversion among a cohort of persons who inject drugs (PWID) in a Canadian setting.

Methods—Between May, 1996 and November, 2013, data were derived through a prospective cohort study of PWID in Vancouver, Canada. A total of 1,682 baseline HIV negative participants were followed for a median of 79.5 months (interquartile range: 32.1 – 119.1), among whom 501 (29.8%) reported benzodiazepine use at baseline, and 176 seroconverted during follow-up, equal to an incidence density of 1.5 (95% Confidence Interval [CI]: 1.3 – 1.7) cases per 100 person-years. Poisson regression with time-dependent variables was used to assess whether benzodiazepine use was associated with the time to HIV seroconversion.

Results—After adjustment for potential confounders, benzodiazepine use (Adjusted Rate Ratio: 1.50; 95% CI: 1.01 – 2.24) was independently associated with a higher rate of HIV seroconversion.

Conclusions—Benzodiazepine use was an independent risk factor for HIV seroconversion among PWID in this setting. Greater recognition of the safety concerns related to benzodiazepine medications including diversion are needed.

Keywords

benzodiazepine; HIV infection; injection drug use

Send correspondence to: Evan Wood, Professor of Medicine, University of BC, BC Centre for Excellence in HIV/AIDS, 608 - 1081 Burrard Street, Vancouver BC V6Z 1Y6, Canada, **Tel:** 604-806-9692, **Fax:** 604-806-9044, uhri-ew@cfnenet.ubc.ca.

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Conflicts of interest: None

1. INTRODUCTION

The Joint United Nations Programme on HIV/AIDS estimates that of 12.7 million people who inject drugs (PWID) worldwide, 13% are living with HIV/AIDS (Joint United Nations Programme on HIV/AIDS, 2014). PWID represent 30% of incident HIV infections outside of sub-Saharan Africa, and in areas of Europe and Central Asia where HIV incidence rates are rising most rapidly in recent years, the epidemic is being driven largely by injection drug use with more than 80% of cases occurring among PWID (Joint United Nations Programme on HIV/AIDS, 2014). Of an estimated 2.1 million PWID in North America, over 320,000 are living with HIV/AIDS (Mathers et al., 2008). It is estimated that PWID account for 13.7% of incident HIV cases in Canada (Public Health Agency of Canada, 2011), and 6.9% in the United States (Centers for Disease Control and Prevention, 2010). This has led to the development of multiple harm reduction strategies to mitigate HIV risk among PWID.

Although intravenous cocaine and heroin use are now well-established risk factors for HIV infection (Tyndall et al., 2003; Vlahov et al., 1997), use of non-injection drugs, particularly methamphetamine and crack cocaine, have also been linked with high risk sexual behavior and elevated rates of HIV infection (DeBeck et al., 2009; Parry et al., 2011; Roth et al., 2014). Recently, there has been increased concern over abuse and diversion of prescription medications, particularly opioids and benzodiazepines, though these concerns have particularly focused on misuse potential and accidental overdose rather than the potential relationship to infectious disease risk (National Advisory Council on Prescription Drug Misuse, 2013). Though benzodiazepine use is an established risk factor for HIV risk behavior among injection drug users (Darke, 1994), a direct association between benzodiazepine use and HIV infection has not been previously described.

Vancouver's Downtown Eastside (DTES) neighborhood is home to a well-described HIV epidemic among PWID (Maas et al., 2007) with past reports demonstrating that intravenous cocaine and crack cocaine smoking are important risk factors for HIV seroconversion (DeBeck et al., 2009; Tyndall et al., 2003). However, past HIV incidence analyses have not focused on benzodiazepine use as an important risk factor. To our knowledge, the effect of benzodiazepine use on HIV infection risk in PWID has not been explored in detail previously. Therefore, the objective of the present study was to evaluate whether benzodiazepine use was associated with HIV incidence among a cohort of PWID in Vancouver.

2. METHODS

2.1 Population and Data Collection

Data for this study were derived from the Vancouver Injection Drug Users Study (VIDUS), an open prospective cohort study of persons who use injection drugs in Vancouver, Canada. Participants are recruited through self-referral, word-of-mouth and street outreach. VIDUS began in May 1996, with enrollment and follow-up ongoing as of July 2015. The study procedures have also been described in previous publications (Tyndall et al., 2003). Individuals are eligible to be enrolled in VIDUS if they are 18 years of age or older, reside in the Greater Vancouver region, have injected illicit drugs at least once in the past month,

test seronegative for HIV, and provide written informed consent at the time of enrollment. At baseline and at semiannual follow-up visits thereafter, participants complete an interviewer-administered questionnaire that elicits a range of data, including demographic characteristics, information regarding injection and non-injection drug use, and sexual risk behaviors. The questionnaire is continually amended to address emerging themes. In addition, venous blood samples are drawn to test for HIV and hepatitis C virus (HCV) antibodies at each follow-up visit for individuals whose test results were negative at the previous assessment. All participants are offered both pre- and post-test counseling with trained nurses and referral for free healthcare if needed. Participants are given an honorarium (\$30 CDN) at each study visit for their time and transportation. The study has been approved by the University of British Columbia/Providence Healthcare Research Ethics Board. For the present study, participants were eligible if they were recruited between May 1, 1996 and November 30, 2013, were HIV negative at baseline and had had at least one followup visit to assess for HIV incidence.

2.2 Statistical Analysis

The primary endpoint in the analysis was time to HIV seroconversion. The primary explanatory variable of interest was self-reported benzodiazepine use during the previous six months (yes vs. no) and was treated as a time updated covariate based on each participant's semi-annual follow up visit. Potential confounders were selected based on previous studies from this setting and included: gender (male vs. female); age; ancestry (Caucasian vs. non-Caucasian); homelessness; involvement in a methadone maintenance program; daily heroin injection; daily cocaine injection; daily non-injection crack use; unprotected sex, defined as vaginal or anal sex without a condom; and involvement in sex work, defined as exchange of sex for gifts, food, shelter, or clothing. All variable definitions were identical to earlier studies (Miller et al., 2002; Strathdee et al., 1997). All behavioral variables were treated as time-updated covariates and referred to the previous six months.

A statistical protocol was adopted from previous VIDUS studies (Strathdee et al., 1997; Tyndall et al., 2003). First, we compared baseline characteristics of those who did and did not report any benzodiazepine use using the Chi-square test for binary measures and Wilcoxon rank sum test for continuous measures. The cumulative probabilities of remaining HIV negative were estimated using the Kaplan-Meier product limit method, and compared using the two-sample log-rank test.

We then used Poisson regression (Frome, 1983) to examine bivariable associations between each explanatory variable and the time to HIV seroconversion. To fit the multivariable model, we employed a conservative stepwise backward selection approach. We included all variables found to be significantly associated with time to HIV seroconversion in bivariable analyses at $p < 0.10$ in a multivariable model and 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 to the value of the coefficient in each of the reduced models, we dropped the secondary explanatory variable associated with the smallest relative change. We continued this iterative process until the minimum change exceeded 5%. Remaining variables were considered as potential confounders in a final multivariable

model. Analyses were conducted using SAS 9.3 (Cary, NC); the threshold for statistical significance was set at $p < 0.05$. All p -values were two-sided.

3. RESULTS

During the study period, 1,927 baseline HIV-negative participants were recruited. Among this sample, 245 (12.7%) did not return for at least one follow-up and were therefore ineligible for further analysis. Compared to those included in the analyses, these 245 HIV-negative participants who were excluded from the analysis were more likely to be younger (median 32.0 years vs. 36.6 for included participants, $p < 0.001$) and to engage in unprotected sex ($p = 0.012$), whereas there was no significant difference between the two groups in terms of gender, ethnicity, homelessness, involvement in a methadone program, daily cocaine injection, daily heroin injection, daily non-injection crack use, sex work involvement and benzodiazepine use (all $p > 0.05$).

As indicated in Table 1, baseline benzodiazepine users were less likely to be homeless, involved in a methadone program, and daily non-injection crack users, but were more likely to be younger (median 35.7 years vs 36.9 for non benzodiazepine users), daily injection cocaine users, and engaging in unprotected sex (all $p < 0.05$). Among participants who reported benzodiazepine use at baseline, 7 (1.4 %) reported injection use, while 496 (99.0%) reported non-injection use.

Among the study sample of 1,682 participants, there were 176 HIV seroconversions for an incidence density of 1.5 (95% Confidence Interval [CI]: 1.3 – 1.7) cases per 100 person-years. As shown in Figure 1, participants who reported benzodiazepine use at baseline were less likely to remain HIV negative over the course of the study period. At 5 years after recruitment, the cumulative probability of remaining HIV negative was 85.4% among benzodiazepine users and 91.9% among non-benzodiazepine users (log-rank $p < 0.001$).

Table 2 shows the results of bivariable and multivariable Poisson model analyses of time to HIV seroconversion. As shown, in the multivariable analysis, benzodiazepine use was independently and positively associated with time to HIV seroconversion (Adjusted Rate Ratio: 1.50 [95% CI: 1.01–2.24]; $p = 0.044$). Potential confounders adjusted in the model included age, ancestry, and daily cocaine injection.

4. DISCUSSION

In the present study, we found that benzodiazepine use was common among our sample of PWID in Vancouver and that benzodiazepine users represent a subgroup of PWID who were more likely to be younger, and to engage in high intensity drug use and high risk sexual behavior. Over the study period, benzodiazepine use was also independently associated with a 1.5 fold elevated risk of HIV infection even after adjustment for other drug use patterns and socio-demographic risks.

There is currently only limited data available on prescription drug use among PWID with most past studies examining traditional illicit drugs of abuse (e.g., heroin and cocaine). However, several large-scale surveys in the United States have given insight into trends for

illicit prescription drug use over the past several years (Compton et al., 2007; Johnston, 2013; US Department of Health and Human Services, 2011). Reported risk factors for illicit prescription drug use include male gender, younger age, and lower income (Compton et al., 2007; Schulden et al., 2012). Illicit drug use is relatively common among adolescents and young adults, with almost 50% of 12th graders having reported using illicit drugs at least once, and 15.2% having used prescription drugs in the past year (Schulden et al., 2012; US Department of Health and Human Services, 2011). Combined with rising rates of fatal and nonfatal opioid overdose and emergency department visits (McCabe and West, 2014; Schulden et al., 2012), this knowledge has contributed to increased concern over diversion of prescription drugs for nonmedical use. Adolescents have been shown to be a leading source of diversion of controlled medications, and 84% of nonmedical users of prescription benzodiazepines obtained them from friends or peers (Johnston, 2013; McCabe and Boyd, 2005). In a previous study, 70% of adolescents who were prescribed benzodiazepine used them only as directed, while 30% used too much, or used to get high or to increase other drug effects (McCabe et al., 2011). Unfortunately, previously reported data on prescription drug abuse is likely not applicable to our study due to differences in study populations, with our population being adult rather than adolescent and likely of lower socioeconomic status in general given high rates of homelessness and street entrenchment.

Use of benzodiazepines among injection drug users in general, as well as heroin users specifically, has previously been associated with increased rates of injection, needle sharing, polydrug use and hepatitis C positivity (Darke, 1994). Benzodiazepine injectors have also been shown to have higher rates of unemployment and incarceration (Darke et al., 2010). Past research has also demonstrated benzodiazepines to be a known overdose risk factor in heroin users, including those on methadone maintenance therapy (Dietze et al., 2006; Nielsen et al., 2007). This shows a clear association between benzodiazepine use and HIV risk behavior, but not with HIV seroconversion specifically. Although there have been several HIV incidence analyses in this population with focus on traditional drugs of abuse, including heroin and cocaine (Miller et al., 2006, 2007) as well as social and structural factors (Corneil et al., 2006; Marshall et al., 2009), a specific association between HIV incidence and abuse of pharmaceutical medications like benzodiazepines has not been previously investigated.

To our knowledge, this is the first study to demonstrate an independent association between benzodiazepine use and elevated risk of HIV infection. Past reviews have demonstrated that benzodiazepines cause sedation, impaired recall, subjective feelings of euphoria, and heightened effects of co-administered drugs (Lader, 2014; Lintzeris and Nielsen, 2010). Importantly, it is noteworthy that recent reviews have highlighting the lack of clinical evidence for therapeutic indications for the use of benzodiazepines outside of the alcohol withdrawal context (Lader, 2011). In our study, benzodiazepine users were more likely to report high intensity heroin use, a finding that has been previously described in midazolam injectors (Hayashi et al., 2013). The cognitive and psychiatric effects of benzodiazepine use may impair judgment and increase vulnerability to engage in behaviors that independently increase HIV risk, such as unprotected sex, sex work, engaging in higher risk networks (i.e., higher HIV prevalence) and injecting practices. However, to our knowledge, a specific

association between benzodiazepine use and increased risk behavior has not been previously described.

Our study is limited by its observational design, though we note it would not be ethical or possible to examine this question through an interventional study design. Additionally, the data may be subject to reporting biases, including recall bias and socially desirable responding. Of note, our primary endpoint was based on objective laboratory evidence of HIV seroconversion. In addition, self-reported data has been previously used to measure drug use patterns and control for potential confounding in observational studies involving PWID and found to be valid (Darke, 1998). Further, our study was limited by the fact that benzodiazepine use was only available as a dichotomous variable and patterns of use were not collected in detail. We also did not have standardized measures of mental illness and it is likely that BZD use was higher among individuals with certain comorbidities such as anxiety. Nevertheless, we believe the association between benzodiazepine use and HIV infection is an important observation.

The present study demonstrates that benzodiazepine use was an independent risk factor for HIV infection among a cohort of PWID in a Canadian setting. While future research, potentially using qualitative research methods, will be valuable to disentangle the potential mechanisms through which benzodiazepine use confers an elevated risk of HIV infection, it is likely that benzodiazepine intoxication and potential cognitive effects have an impact upon HIV risk behavior. Given the clinical evidence for cognitive harms associated with long-term benzodiazepines use (Barker et al., 2004) and recent reports of high rates of diversion (Johnston, 2013; McCabe et al., 2011), these findings highlight the importance of physician education aimed at reducing inappropriate and unsafe use of benzodiazepines, and reveal a need for targeted HIV prevention programs for benzodiazepine users.

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Highlights

- 2335 persons who inject drugs (PWID) were followed over a 15 year follow up period
- 511 (21.9%) participants died (mortality ratio of 3.4 deaths per 100 person years)
- enrollment in a methadone maintenance program(MMT) was protective against mortality
- Enrollment in an MMT was also protective against non-overdose mortality
- Our data support the need for universal, unrestricted access to low-threshold MMT

Figure 1.
Probability of remaining HIV negative stratified by baseline benzodiazepine use.

Table 1

Baseline characteristics of PWID stratified by benzodiazepine use.

Demographic Characteristic	BDZ Use n=501	No BDZ Use n=1181	Odds Ratio (95% CI)	P-value
Gender				
Male	327 (65.3)	794 (67.2)	0.92 (0.73, 1.14)	0.435
Female	174 (34.7)	387 (32.8)		
Age				
Median (IQR)	35.7 (27.9–41.2)	36.9 (28.4–43.8)		0.004
Ethnicity				
Caucasian	324 (64.7)	721 (61.0)	1.17 (0.94, 1.45)	0.162
Other	177 (35.3)	460 (39.0)		
Homeless*				
Yes	71 (14.2)	317 (26.8)	0.45 (0.34, 0.60)	<0.001
No	430 (85.8)	864 (73.2)		
Methadone Program*				
Yes	69 (13.8)	274 (23.2)	0.52 (0.39, 0.70)	<0.001
No	432 (86.2)	900 (76.2)		
Daily Heroin Injection*				
Yes	236 (47.1)	496 (42.0)	1.23 (1.00, 1.52)	0.050
No	263 (52.5)	682 (57.7)		
Daily Cocaine Injection*				
Yes	208 (41.5)	304 (25.7)	2.07 (1.66, 2.58)	<0.001
No	288 (57.5)	870 (73.7)		
Daily Non-injection Crack Use*				
Yes	46 (9.2)	356 (30.1)	0.23 (0.17, 0.32)	<0.001
No	455 (90.8)	823 (69.7)		
Unprotected Sex**				
Yes	252 (50.3)	373 (31.6)	2.17 (1.75, 2.69)	<0.001
No	249 (49.7)	801 (67.8)		
Sex Work*				
Yes	117 (23.4)	263 (22.3)	1.06 (0.82, 1.35)	0.670
No	384 (76.6)	911 (77.1)		

Note: PWID=people who inject drugs. BDZ=benzodiazepine.

* Indicates behavior during the six-month period prior to interviews.

** Unprotected sex was defined as vaginal or anal sex without a condom.

Table 2

Univariable and multivariable Poisson regression analyses of the time to HIV infection among 1682 PWID.

Variable Name	Unadjusted Rate		Adjusted Rate	
	Ratio (95% CI)	P-value	Ratio (95% CI)	P-value
BDZ Use[*]	3.06 (2.09, 4.49)	<0.001	1.50 (1.01, 2.24)	0.044
Male gender	0.61 (0.45, 0.82)	0.001		
Age (per 10 years older)	0.55 (0.47, 0.63)	<0.001	0.73 (0.62, 0.85)	<0.001
Caucasian (versus other)	0.74 (0.55, 0.99)	0.044	0.75 (0.56, 1.01)	0.061
Homeless[*]	1.01 (0.70, 1.47)	0.947		
Methadone Program[*]	0.45 (0.32, 0.63)	<0.001		
Daily Heroin Injection[*]	2.54 (1.89, 3.42)	<0.001		
Daily Cocaine Injection[*]	5.79 (4.30, 7.81)	<0.001	3.74 (2.75, 5.08)	<0.001
Daily Non-injection Crack[*]	1.03 (0.74, 1.44)	0.845		
Unprotected Sex^{**}	1.46 (1.05, 2.01)	0.023		
Sex Work[*]	2.41 (1.72, 3.39)	<0.001		

Note: PWID=people who inject drugs. BDZ=benzodiazepine.

^{*} Indicates behavior during the six-month period prior to interviews.

^{**} Unprotected sex was defined as vaginal or anal sex without a condom.