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Risk factors Associated with Benzodiazepine Use among People who Inject Drugs in an Urban Canadian Setting

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Abstract

Background—Though known to have abuse potential, benzodiazepine medications remain widely prescribed. Furthermore, issues related to benzodiazepine use by people who inject drugs (PWID) remain to be fully characterized. We therefore sought to examine the prevalence of and risk factors associated with benzodiazepine use in a street-involved urban population.

Methods—Between May 1996 and November 2013, data were derived from two open prospective cohort studies in Vancouver, Canada, restricted to PWID. Multivariable logistic regression with generalized estimating equations (GEE) was used to determine factors independently associated with benzodiazepine use.

Results—Over the study period, 2806 individuals were recruited, including 949 (34%) women. Of these, 1080 (38.5%) participants reported benzodiazepine use at least once during the study period. In the multivariable analysis, Caucasian ethnicity, daily heroin injection, daily cocaine injection, non-fatal overdose, incarceration, syringe sharing, and unsafe sex were all independently associated with benzodiazepine use. Conversely, older age, homelessness, and daily crack smoking were negatively associated with benzodiazepine use.

Conclusions—Use of benzodiazepines was common in this urban setting and was associated with several markers of addiction severity and significant health and social vulnerabilities including syringe sharing and unsafe sex. These findings underscore the need to promote treatment for benzodiazepine use, safer benzodiazepine prescribing, including greater recognition of the limited indications for evidence-based use of this medication class.

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Conflict of Interest None

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Keywords

benzodiazepine; diversion; prescription drug misuse; overdose

1. INTRODUCTION

The diversion and illicit misuse of physician-prescribed medicines constitutes a significant and growing health problem (Paulozzi 2012). Indeed, the U.S. Centers for Disease Control and Prevention (CDC) estimates that hospital emergency room visits for misused opioid and benzodiazepine (BZD) prescriptions increased by 111% and 89%, respectively, between 2004 and 2008 (Centers for Disease and Prevention 2010).

The misuse and abuse of BZD medication has been previously documented to be widespread, particularly among people who use drugs recreationally (Jones, Mogali et al. 2012). Non-medical prescription of BZDs in a Baltimore cohort of PWID was reported to be 12% (Khosla, Juon et al. 2011), while lifetime illicit and prescription tranquilizer misuse was 11% in people who had ever injected drugs in two large US centres (Lankenau, Schrager et al. 2012). Moreover, risks associated with the combination of opioids and BZDs were recently raised as a public health concern by the U.S. Substance Abuse and Mental Health Services Administration (SAMHSA) (Substance Abuse and Mental Health Services Administration 2014). Co-administration of methadone or buprenorphine with BZDs by patients receiving opioid replacement therapy has also been shown to be associated with marked increases in death by overdose (Reynaud, Petit et al. 1998, Ernst, Bartu et al. 2002). Additional data from SAMHSA demonstrate that treatment admissions for co-abuse of BZDs and narcotic pain relievers has risen by over 500% between 2000 and 2010 (2012).

While several studies investigating the abuse of BZDs by recreational drug users and patients receiving opioid replacement therapy were conducted in the 1980's and 1990's, data regarding BZD use (whether prescription or non-prescription) among PWID is lacking, and risk factors associated with BZD use among street-involved populations has not yet been fully described (Jones, Mogali et al. 2012). We therefore undertook the present study to examine the prevalence and factors associated with BZD use among PWID in a major Canadian city, looking at a number of markers reflective of drug use severity and social vulnerability.

2. MATERIAL AND METHODS**2.1. Study Sample**

Data from two open prospective cohorts of persons who use drugs in Vancouver, Canada, were used for this study: the Vancouver Injection Drug Users Study (VIDUS), and the AIDS Care Cohort to Evaluate access to Survival Services (ACCESS). With the exception of recruitment related to HIV status, recruitment and follow-up procedures for VIDUS and ACCESS are identical, allowing for combined analysis. The ACCESS cohort includes HIV-positive individuals who have used illicit drugs other than cannabis in the previous month, whereas HIV-negative individuals who report having injected drugs in the month prior to

enrollment are followed in VIDUS. The present study was restricted to individuals from the VIDUS and ACCESS cohorts with a history of drug injecting and who were recruited between May 1996 and November 2013. The VIDUS and ACCESS sampling and recruitment procedures have been described previously (Strathdee, Palepu et al. 1998, Tyndall, Currie et al. 2003). Briefly, enrollment in the cohorts is through self-referral, word of mouth, and street outreach; participants must be 18 years of age or older and reside in the greater Vancouver region. All participants provided written informed consent; a stipend (\$20 CDN) was given at each study visit to compensate time and transportation. VIDUS and ACCESS have received ethics approval from the University of British Columbia/Providence Healthcare Research Ethics Board.

2.2. Measures

Participants completed an interviewer-administered questionnaire at baseline and at six-month intervals that elicited data concerning demographic characteristics, injection and non-injection drug use patterns, and various risk behaviors. In addition, HIV and hepatitis C virus (HCV) antibody testing was performed at baseline and at each follow-up visit for individuals with negative test results to date. Interviews were conducted in private and included comprehensive pre- and post-test counseling by trained nurses.

The primary outcome of interest was self-reported BZD use in the previous six months (yes vs. no). The following demographic characteristics, drug use patterns, social and structural-level risk factors were considered to be potentially associated with the outcome: age (per year older), gender (female vs. male), ethnicity (Caucasian vs. non-Caucasian), homelessness (yes vs. no), daily heroin injection (yes vs. no), daily crack smoking (yes vs. no), daily cocaine injection (yes vs. no), overdose (yes vs. no), sex work (yes vs. no), incarceration (yes vs. no), syringe sharing (yes vs. no), unprotected vaginal and anal sex (yes vs. no). Except for gender and ethnicity, all variables were treated as time-updated and referred to behaviors and activities in the six months predating the interview.

2.3. Statistical Analysis

We first summarized the baseline characteristics of participants, stratified by baseline BZD use in the past six months. Comparisons were made by using Pearson's Chi-square test (or Fisher's exact test) for categorical variables and the Wilcoxon rank-sum test for continuous variables.

Next, variables potentially associated with active BZD use during follow-up were evaluated using generalized estimating equations (GEE) with a logit-link function and exchangeable working correlation structure, since serial measures for cohort participants were available. This approach serves to examine behaviors and characteristics that correlated with BZD use at each follow-up period throughout the study. First, using GEE, we examined the bivariable associations between each explanatory variable and BZD use. Next, we fitted a multivariable model, considering all variables with $p < 0.10$ in bivariable GEE analyses as the full model. A backward model selection procedure was used to construct the final model, as indicated by the lowest quasi-likelihood under the independence model criterion (QIC)

value (Cui 2007). All statistical analyses were performed using the SAS software version 9.3 (SAS, Cary, NC, USA). All p -values are two-sided.

3. RESULTS

Between May 1996 and November 2013, 2806 persons who inject drugs (PWID) met criteria for inclusion in the present study from the VIDUS ($n = 2020$) and ACCESS cohorts ($n = 786$). Over time, the median number of study visits per participant was 9 (interquartile range [IQR]: 4 - 15). These participants generated 31,961 observations for this analysis. There were 1080 (38%) participants who reported BZD use at least once during the study period.

The median age of the cohort at baseline was 37 years (IQR: 29 – 44), 1713 (61%) of respondents were Caucasian, and 949 (34%) were female. Table 1 shows the sample characteristics stratified by BZD use in the previous six months at baseline. As shown, at baseline, those reporting BZD use were younger, more likely to be female, HIV positive, and homeless. Additionally they injected heroin or cocaine at least daily, smoked crack as least daily, had experienced a non-fatal overdose and reported incarceration, syringe sharing, sex work, and unprotected sex in the preceding six months (all $p < 0.05$).

The results of the bivariable and multivariable GEE analyses of factors associated with BZD use are shown in Table 2.

In the multivariable GEE analysis, Caucasian ethnicity, daily heroin injection, daily cocaine injection, non-fatal overdose, sex work, incarceration, syringe sharing, and unprotected sex remained independently and positively associated with BZD use. Conversely, age, HIV status, homelessness, and daily crack smoking were negatively associated with BZD use.

A separate analysis stratified by HIV status was also performed. When analyses were restricted to HIV positive participants, Caucasian ethnicity, daily heroin injection, daily cocaine injection, non-fatal overdose, sex work, incarceration, syringe sharing, and unprotected sex were positively associated with BZD, use whereas age, homelessness, and daily crack smoking were negatively associated. When analyses were restricted to HIV negative participants, the results were common, although sex work was no longer associated with BZD use.

4. DISCUSSION

The present study demonstrated that approximately 40% of our sample of PWID in Vancouver, Canada, reported BZD use throughout the study period. In addition, the present study found that BZD use was associated with several markers of addiction severity and significant health and social vulnerabilities, including syringe sharing and unsafe sex.

Our study did not attempt to differentiate between BZDs taken as prescribed, misused prescription BZDs, or non-prescription (diverted or illicit) BZDs, as we sought to quantify and characterize BZD use from all sources in the high-risk population of PWID in whom

any concomitant use of additional sedative substances, particularly opioids or alcohol, may lead to increased morbidity and mortality.

Earlier research has explored the prevalence of BZD use in populations receiving opioid replacement therapy. More specifically, a study conducted in two US cities in 1981 reported 65-70% of patients receiving opioid replacement therapy (who were not prescribed BZD) were found to have a BZD-positive urine drug test result during a single month of testing (Stitzer, Griffiths et al. 1981). Furthermore, Iguchi *et al.* reported six-month prevalence rates for illicit sedative drug use (largely BZD but also some barbiturates) among a similar population of patients on opioid replacement therapy in New York City, Philadelphia, and Baltimore as being 44%, 53% and 66% respectively; lifetime prevalence ranged between 78 - 94% in these three cities (Iguchi, Handelsman et al. 1993). A more recent European study reported BZD use (prescribed and illicit) among patients entering opioid replacement therapy patients to be 70% (Specka, Bonnet et al. 2011). Finally, a US report published in 2011 found that 39% of opioid replacement therapy patients used BZDs without a prescription (Chen, Berger et al. 2011).

Our study provides over 10 years of data and explores street-based drug users, not all of whom are on opioid replacement therapy. Here, we found that BZD use was associated with several markers of addiction severity (daily heroin and daily cocaine injection), and also with behaviors linked to additional health risks, including syringe sharing, unsafe sex practices, and non-fatal overdose. Others have documented significant risks associated with BZD use in numerous contexts, including fatal motor vehicle accidents (Thomas 1998, Krikkku, Hurme et al. 2014), falls in the elderly (Pariante, Dartigues et al. 2008, Olfson, King et al. 2014), accidental overdose with prescribed narcotic pain relievers (Paulozzi 2012, Paulozzi, Mack et al. 2014), and concomitant use by patients enrolled in opioid replacement therapy (Reynaud, Petit et al. 1998, Ernst, Bartu et al. 2002). Thus the present study provides further evidence that BZD use is likely associated both with increased addiction severity in PWID and also with increased risk to personal health.

In response to mounting concerns regarding harms associated with BZD use, a re-alignment of the indications for the prescription of BZDs is urgently needed. Specifically, given the clinical evidence for safety and cognitive harms associated with long-term BZD use (Wu, Wang et al. 2009, Billioti de Gage, Moride et al. 2014), the known limitations of BZDs for existing clinical indications and safer existing alternatives (Furukawa, Streiner et al. 2002, Watanabe, Churchill et al. 2009, Dold, Li et al. 2012, Dell'osso and Lader 2013, Dold, Li et al. 2013), and recent reports of high rates of diversion (McCabe, West et al. 2011, Johnston 2014), these findings highlight the importance of physician education aimed at reducing inappropriate and unsafe prescribing of BZDs. To this end, inappropriate prescriptions for BZDs were reportedly decreased by 50% following implementation of legislation to identify problematic prescribing in Ontario, Canada, in 2011 and 2012 (Gomes, Juurlink et al. 2014).

Strategies aimed at limiting misuse or diversion must acknowledge that, at least for adolescents and young adults, the majority of nonmedical users of BZDs obtained these medications from friends or relatives, often at no cost (McCabe and Boyd 2005, McCabe and West 2014). However, strategies implemented to limit diversion of narcotics, such as

daily dispensing requirements, avoidance of high volume pill dispensing, pill count call-backs, urine drug testing, and the frequent prescriber utilization of prescription monitoring programs, may offer some tools (Hahn 2011, Reifler, Droz et al. 2012, McCabe and West 2014). In addition, education of prescribers regarding the harms of BZDs and the safety of alternative medications is urgently needed. Finally, appropriate treatment strategies for BZD users must also be given priority. This might involve a controlled tapering of prescribed BZDs, or a more intensely supervised detoxification for patients with complicated comorbidities (Ashton 1994, Lader, Tylee et al. 2009, Darker, Sweeney et al. 2015).

This study has several limitations. Firstly, cohort participants do not represent a random sample, and therefore our findings may be not entirely generalizable. Secondly, given the observational nature of this study, we are unable to establish any causal relationships. It is also possible that confounders not measured in our study may have influenced our findings. Also, potential reluctance by participants to reveal personal behaviors of a sensitive nature during interviews in addition to possible recall deficiencies may have led to an underreporting of BZD use and associated risks (Perlis, Des Jarlais et al. 2004). As discussed, this study was unable to differentiate prescribed versus non-prescribed BZD use. Finally, our results may be impacted by local BZD prescribing patterns and the availability of addiction services, both of which may vary substantially between different health jurisdictions and/or regions both nationally and internationally.

5. CONCLUSIONS

Illicit use of BZD was prevalent among PWIDs in this urban setting and was associated with several markers of addiction severity and significant health and social vulnerabilities including syringe sharing, non-fatal overdose and unsafe sex. These findings underscore the need to promote safe BZD prescribing, including greater recognition of the limited indications for evidence-based use of this medication class, and greater recognition of how the diversion and misuse of BZDs represents a significant risk in morbidity and mortality for PWID.

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Highlights

- We asked persons who inject drugs about illicit benzodiazepine use
- Almost 40% of our sample reported illicit benzodiazepine use over the study period
- Benzodiazepines use was associated with addiction severity and health/social risks
- Treatment of benzodiazepine misuse and safer prescribing are important priorities.

TABLE 1

Baseline characteristics of PWID participating in the VIDUS and ACCESS cohorts in Vancouver, Canada, stratified by BZD use (n = 2806).

Characteristic	Total (%) (n = 2806)	Illicit BZD use		p - value
		Yes (%) (n = 734)	No (%) (n = 2072)	
Age				
Median (IQR)	37 (29 – 44)	35 (28 – 41)	38 (30 – 45)	<0.001
Gender				
Female	949 (33.82)	272 (37.06)	677 (32.67)	0.031
Male	1857 (66.17)	462 (62.94)	1395 (67.33)	
Caucasian ethnicity				
Yes	1713 (61.00)	463 (63.07)	1250 (60.33)	0.189
No	1093 (38.95)	271 (36.92)	822 (39.67)	
HIV status				
Seropositive	861 (30.68)	167 (22.75)	694 (33.49)	<0.001
Seronegative	1942 (69.21)	566 (77.11)	1376 (66.41)	
Homeless [†]				
Yes	679 (24.19)	99 (13.49)	580 (27.99)	<0.001
No	2122 (75.62)	634 (86.38)	1488 (71.81)	
Daily heroin injection [†]				
Yes	1030 (36.71)	323 (44.00)	707 (34.12)	<0.001
No	1769 (63.04)	409 (55.72)	1360 (65.64)	
Daily crack smoking [†]				
Yes	685 (24.41)	72 (9.80)	613 (29.58)	<0.001
No	2117 (75.45)	661 (90.05)	1456 (70.27)	
Daily cocaine injection [†]				
Yes	803 (28.08)	319 (43.46)	484 (23.36)	<0.001
No	1985 (70.74)	407 (55.45)	1578 (76.16)	
Overdose [†]				
Yes	377 (13.44)	147 (20.02)	230 (11.10)	<0.001
No	2418 (86.17)	584 (79.56)	1834 (88.51)	
Sex work [†]				
Yes	637 (22.70)	197 (26.83)	440 (21.24)	0.002
No	2158 (76.91)	537 (73.16)	1621 (78.23)	
Jail/detention [†]				
Yes	372 (13.26)	81 (11.04)	291 (14.04)	0.037
No	2428 (86.53)	653 (88.96)	1775 (85.66)	
Syringe sharing [†]				
Yes	955 (34.03)	432 (58.86)	523 (25.24)	<0.001
No	1835 (65.40)	302 (41.14)	1533 (73.99)	

Characteristic	Total (%) (<i>n</i> = 2806)	Illicit BZD use		<i>p</i> - value
		Yes (%) (<i>n</i> = 734)	No (%) (<i>n</i> = 2072)	
Unprotected sex [†]				
Yes	920 (32.79)	357 (48.64)	563 (27.17)	<0.001
No	1875 (66.82)	377 (51.36)	1498 (72.30)	

NOTE: Percentages may not necessarily sum to 100% due to missing data or rounding error

PWID = Persons Who Inject Drugs

VIDUS = Vancouver Injection Drug Users Study

ACCESS = AIDS Care Cohort to Evaluate Access to Survival Services

IQR = Interquartile Range.

[†] Denotes activities in last 6 months

TABLE 2

Bivariable and multivariable generalized estimating equation (GEE) analyses of factors associated with BZD use in Vancouver, Canada, 2005 - 2013.

Characteristic	Odds Ratio (OR)	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age		
Per year older	0.92 (0.91 – 0.93)	0.96 (0.95 – 0.97)
Gender		
Female vs. male	1.04 (0.91 – 1.20)	
Caucasian ethnicity		
Yes vs. no	1.36 (1.19 – 1.57)	1.41 (1.21 – 1.64)
HIV status		
Seropositive vs. seronegative	0.58 (0.49 – 0.68)	0.85 (0.73 – 0.99)
Homeless [†]		
Yes vs. no	0.76 (0.68 – 0.86)	0.58 (0.51 – 0.66)
Daily heroin injection [†]		
Yes vs. no	2.20 (1.99 – 2.44)	1.33 (1.18 – 1.49)
Daily crack smoking [†]		
Yes vs. no	0.32 (0.28 – 0.37)	0.33 (0.29 – 0.38)
Daily cocaine injection [†]		
Yes vs. no	3.04 (2.74 – 3.37)	1.96 (1.75 – 2.20)
Overdose [†]		
Yes vs. no	2.70 (2.40 – 3.05)	1.66 (1.46 – 1.90)
Sex work [†]		
Yes vs. no	2.19 (1.93 – 2.50)	1.26 (1.08 – 1.46)
Incarcerated/detention [†]		
Yes vs. no	1.72 (1.55 – 1.91)	1.28 (1.15 – 1.44)
Syringe sharing [†]		
Yes vs. no	4.91 (4.44 – 5.43)	2.71 (2.43 – 3.02)
Unprotected sex [†]		
Yes vs. no	2.51 (2.26 – 2.80)	1.57 (1.41 – 1.75)

CI = Confidence Interval.

[†] Denotes activities in last 6 months