Increasing availability of benzodiazepines among people who inject drugs in a Canadian setting

Final version published as Walton G, Dong H, Milloy M-J, DeBeck K, Kerr T, Wood E, Hayashi K. Increasing availability of benzodiazepines among people who inject drugs in a Canadian setting. *Substance Abuse*. 2018. 39(1): 69-76 (online first June 2017). https://doi.org/10.1080/08897077.2017.1356798

ABSTRACT

Background: Benzodiazepine misuse is associated with mortality and is common among people who inject drugs (PWID). This study aimed to examine the temporal trends in the availability of benzodiazepines among PWID in a Canadian setting, and to identify factors associated with more immediate access to benzodiazepines.

Methods: Data were derived from three prospective cohorts of PWID in Vancouver, Canada, between June 2012 and May 2015. The primary outcome was the perceived availability of benzodiazepines, measured in three levels: not available, delayed availability (available in ≥10 min), and immediate availability (available in <10 min). We used multivariable generalized estimating equations to identify factors associated with availability of benzodiazepines.

Results: In total, 1641 individuals were included in these analyses. In multivariable analyses, factors associated with immediate benzodiazepine availability included incarceration (adjusted odds ratio (AOR): 1.42, 95% CI 1.06, 1.89) and participation in methadone maintenance therapy (MMT) (AOR: 1.35, 95% CI 1.14, 1.60). Factors associated with delayed benzodiazepine availability included incarceration (AOR: 1.45, 95% CI 1.02, 2.07) and MMT (AOR: 1.77, 95% CI 1.48, 2.12). Benzodiazepine availability increased throughout the study period for both immediate (AOR: 1.14, 95% CI 1.10, 1.18 per 6-month follow-up period) and delayed availability (AOR: 1.17, 95% CI 1.12, 1.22 per 6-month follow-up period).

Conclusions: Among our sample of PWID, benzodiazepine availability is increasing and was associated with health and criminal justice system characteristics. Our findings indicate a need to examine prescribing practices and educate both PWID and healthcare providers about the risks associated with benzodiazepine use.

Abstract word count: 248 words (max. 300 words)

KEYWORDS

Benzodiazepines, mortality, people who inject drugs, healthcare providers, risks

1. INTRODUCTION

It is increasingly recognized that there are high rates of misuse and diversion of benzodiazepines and other sedatives.[1-3] In the United States, 5.2% of the population filled at least one prescription for benzodiazepines in 2008.[2] Rates of use are generally higher among older individuals and among females.[2] In British Columbia, Canada, levels of benzodiazepine use have been reported to be as high as 8.4% in the general population, with up to 3.5% of the population filling prescriptions in excess of a 100-day supply.[1]Additionally, among people who inject drugs (PWID), it has been shown in Canada that up to 35% report some benzodiazepine use within the previous six months.[4] Studies looking at benzodiazepine use in the general population have found that most benzodiazepine prescriptions are coming from primary care physicians.[5]

Benzodiazepine use has been associated with an array of harm in the general population including an increased risk of falls, fractures, motor vehicle accidents, and a variety of serious neuropsychiatric side effects.[6-8] Additionally, there is concern for problems with withdrawal, symptom rebound (e.g. increased panic attacks) and abuse after long-term use.[9] At a national level, benzodiazepines were responsible for 426,000 emergency visits in the United States in 2011.[2] Among PWID, benzodiazepine use has been correlated with more intensive drug use, higher risk of overdose, more psychiatric co-morbidities, poorer health and HIV/HCV seroconversion.[10-14] However, even more troubling is that there is an association between benzodiazepines and mortality in PWID. This association has been studied in population-based registries.[15-20] and prospective cohort studies,[21] and these studies highlight overdose mortality in particular. There is evidence that benzodiazepines are associated with overdose mortality among those receiving methadone therapy.[20] Recently a study involving PWID in Vancouver reported an increase

in all-cause mortality associated with benzodiazepine use.[22] It has been postulated that benzodiazepine-related psychomotor side effects leading to improper and unsafe preparation, dosing and injection of drugs could be one of the reasons for this association.[23,24] Also, it has been hypothesized that PWID may be more susceptible to some of the more traditional risks of benzodiazepine use such as falls, motor vehicle accidents and fractures while under the influence of other substances.[22] The harms described above are particularly concerning given that current evidence does not support the use of benzodiazepines for the treatment of chronic anxiety or insomnia disorders.[25]

While the literature describes many harms associated with benzodiazepine use among PWID, there remain significant gaps in knowledge regarding benzodiazepine use in this population. To our knowledge, no study has looked at trends and factors associated with the availability of benzodiazepines among PWID. While many PWID who use benzodiazepines reportedly access them from health care providers,[1,26,27] it is also known that diversion on the street is responsible for a large proportion of benzodiazepine availability.[28] Identifying factors associated with a higher availability of benzodiazepines could inform strategies to reduce drug-related harms and decrease the availability and use of benzodiazepines. Therefore, our study objective was to assess the trend in benzodiazepine availability over time, and to identify factors associated with benzodiazepine availability among PWID in a Canadian setting.

2. METHODS

2.1 Study design and participants

The Vancouver Injection Drug Users Study (VIDUS), AIDS Care Cohort to Evaluate exposure to Survival Services (ACCESS) and At-Risk Youth Study (ARYS) are

open prospective cohorts of people who use illicit drugs in Vancouver, Canada. Detailed sampling and recruitment procedures for these cohorts have been described elsewhere.[29-31] In brief, VIDUS enrolls HIV-negative adults (≥18 years of age) who injected drugs in the month prior to enrolment; ACCESS enrolls HIV-positive adults (≥18 years of age) who used illicit drugs (other than or in addiction to cannabis) in the month prior to enrolment; and ARYS enrolls street-involved youth aged 14-26 years who used illicit drugs other than or in addition to cannabis in the month prior to enrolment. In all studies the primary modes of recruitment were self-referral, word of mouth, and street outreach, and residence in the Greater Vancouver region and written informed consent were required.

The follow-up procedures for these studies, including the questionnaires, were harmonized to permit for analyses of merged data. Specifically, at baseline and semiannually thereafter, participants completed an interviewer-administered questionnaire that elicits a range of data, including demographic characteristics, drug use patterns, availability of drugs, and healthcare access. In addition, venous blood samples were drawn at each visit and used in serologic analyses, including testing for HIV and HCV antibodies and HIV clinical monitoring. Referral for free HIV/AIDS care was provided to participants in the VIDUS and ARYS cohorts found to be HIV positive, and these individuals were subsequently followed in the ACCESS cohort. Participants were given a stipend ($30 CDN) at each study visit for their time. The cohort studies receive annual approval from the University of British Columbia/Providence Healthcare Research Ethics Board.

The present analysis included individuals who completed at least one study interview between June 1, 2012 and May 31, 2015, reported a history of injection drug use at baseline, and provided at least one valid answer to the question regarding the availability

of benzodiazepines during the study period. ARYS participants who initiated injecting drugs during the study period were included in the present study from the time point when they first reported injection drug use.

2.2 Measures

The outcome of interest in this analysis was benzodiazepine availability. At each study visit, participants were asked "How difficult would it be for you to get the following drugs right now in the area where you typically obtain your drugs? – Benzos/Valium/Ativan" and this was reported as either immediate availability ("score within 10 minutes"), delayed availability ("score within 90 minutes", "score within 1 day", or "score within > 1 day") or no availability ("could not score"). Interviews in which individuals did not answer this question were not included in the GEE analysis. Participants were also asked to indicate the current (street) price of benzodiazepines per pill.

We considered a number of explanatory variables including demographic, behavioural, clinical and other exposure characteristics as potential factors associated with benzodiazepine availability, based on prior studies in our setting.[32-34] Socio-demographic variables included; gender (male vs. female); age, (per 10 years older); ethnicity/ancestry (Caucasian vs. other); homelessness (yes vs. no); Downtown Eastside (DTES) residency (yes vs. no); dealing drugs (yes vs. no); sex work (yes vs. no); and incarceration (yes vs. no), all in the previous six months. Vancouver's Downtown Eastside is a neighbourhood with an open drug scene.[35,36] Substance use behaviours included self-report of at least daily cocaine injection (yes vs. no), at least daily heroin injection (yes vs. no), at least daily crack cocaine smoking (yes vs. no), and any history of overdose (yes vs. no), all in the previous six months. In addition we included benzodiazepine use ever since study

enrolment (yes vs. no). We also considered access to any health services (i.e., a doctor, clinic, specialist, emergency room or hospital) in the previous six months as a potential explanatory variable for access to benzodiazepines. Other health-related variables included; involvement in methadone maintenance therapy (MMT) (yes vs. no); experiencing pain/discomfort (extreme or moderate vs. no); experiencing anxiety (extreme or moderate vs. no); mobility (limited vs. no problem); and ability to perform usual activities (limited vs. no problem) at the time of interview, as assessed by EQ-5D. The EQ-5D tool has been shown to be a valid assessment of general health outcomes in a population of heroin users.[37] We also included 6-month follow-up periods (per period later) to examine the temporal trends of benzodiazepine availability, and the current cohort designation (ARYS vs. ACCESS vs. VIDUS) to account for any potential differences among the cohorts in the sample characteristics.

2.3 Statistical analyses

As an initial analysis we calculated the proportion of each benzodiazepine availability category stratified by each categorical explanatory variable at the baseline. The categorical values were compared using the Cochran-Armitage trend test. For continuous explanatory variables, we calculated the median and inter-quartile range (IQR) and compared using the Kruskal-Wallis test. We also plotted the percentage of participants reporting immediate availability, delayed availability, and no availability on a line graph against the follow up period to illustrate the temporal trend in benzodiazepine availability.

Next, generalized estimating equation (GEE) was used to examine the bivariable relationships between benzodiazepine availability and each explanatory variable. Two separate analyses were conducted to examine the factors associated with immediate

availability and delayed availability, respectively. All behavioural variables were treated as time-varying variables. To determine the independent correlates of benzodiazepine availability, we fit a multivariable GEE, using a *priori*-defined backward stepwise procedure that has been used extensively in several earlier studies.[38,39] Starting with a full model containing all variables associated with the outcome at $p<0.10$ in bivariable analyses, the quasi-likelihood under the independence model criterion (QIC) was noted, and the variable with the largest p-value was dropped to fit a reduced model. This iterative process was continued until the model had the best overall fit as indicated by the lowest QIC value.

As a sub-analysis, we examined changes in the price of benzodiazepines during the study period. Because the reported prices had highly skewed distributions, we presented the modal price, as well as the percentage of the study sample that reported the modal price, as in a previous study.[40] All statistical analyses were performed using SAS version 9.4 (SAS Institute, USA). All tests of significance were two sided, and a $p<0.05$ was selected for defining statistical significance.

3. RESULTS

3.1 Sample characteristics

A total of 1,641 individuals were eligible for the present study and were followed between June 2012 and May 2015. There were 6695 observations with answers about benzodiazepine availability, of which 1306 (19.5%) were for no availability, 1841 (27.5%) were for delayed availability and 3548 (53.0%) were for immediate availability. A total of 15 participants were excluded from the analysis because they did not provide a response to the benzodiazepine availability question during the study period. The participants completed a median of 5 study visits (interquartile range [IQR]: 3 - 6). As shown in Table

1, among the study sample, 65.4 % (1,074/1,641) were men and 59.0 % (967/1,641) were Caucasian. The median age was 45.0 (IQR: 33.8 – 51.8). In total, 152 (9.3 %) reported benzodiazepine use since the study enrolment. Of note, 127 (7.7 %) reported experiencing an overdose within the previous 6 months, and the rates of reporting recent overdose were not significantly different among the three categories of benzodiazepine availability. Benzodiazepine availability was highly prevalent, with 44.9 % to 54.9 % of participants reporting immediate availability throughout the six follow-up periods and 20.4 % to 30.1 % reporting delayed availability. Throughout the study period, the percentage of people reporting immediate and delayed availability as a combined outcome increased from 65.3 % to 79.4 % ($p<0.001$). (See Figure 1 for a graphical representation of these trends.)

3.2 GEE analyses

The results of the bivariable and multivariable GEE analyses are presented in Table 2. In multivariable analyses, variables independently associated with immediate benzodiazepine availability included Caucasian ethnicity (adjusted odds ratio [AOR]: 1.25, 95% CI 1.04, 1.49), benzodiazepine use ever during study enrollment (AOR: 3.04, 95% CI 2.13, 4.32), living in the DTES (AOR: 1.73, 95% CI 1.48, 2.03), drug dealing (AOR: 1.78, 95% CI 1.45, 2.17), recent incarceration (AOR: 1.42, 95% CI 1.06, 1.89) and involvement in a methadone maintenance therapy program (AOR: 1.35, 95% CI 1.14, 1.60). Factors independently associated with delayed availability of benzodiazepines included Caucasian ethnicity (AOR: 1.58, 95% CI 1.32, 1.90), benzodiazepine use ever during study enrolment (AOR: 3.02, 95% CI 2.11, 4.32), drug dealing (AOR: 1.72, 95% CI 1.37, 2.16), recent incarceration (AOR: 1.45, 95% CI 1.02, 2.07) and involvement in a methadone maintenance therapy program (AOR: 1.77, 95% CI 1.48, 2.12). There was a trend toward

a positive association between access to any health services and immediate availability of benzodiazepines (AOR: 1.20, 95% CI 0.97, 1.48); however, this result was not significant. Lastly, per period later in the follow-up, participants were more likely to report both immediate availability (AOR: 1.14, 95% CI 1.10, 1.18) and delayed availability of benzodiazepines (AOR: 1.17, 95% CI 1.12, 1.22).

3.3 Pill Price

In the sub-analysis, the modal price of benzodiazepines reported by the participants remained the same throughout the study period at $1 CDN per pill, reported by 42.5-54.0% of participants at each study visit.

4. DISCUSSION

The present study demonstrated increasing availability of benzodiazepines over time among cohorts of PWID in Vancouver between 2012 and 2015, while the self-reported price of benzodiazepines remained constant. Participants who reported a history of benzodiazepine use during the study period reported higher perceived availability. In addition, we found that the perceived availability of benzodiazepines was higher among people reporting residence in the DTES, drug dealing, incarceration and participation in methadone maintenance therapy.

The increasing trend of perceived availability of benzodiazepines throughout our study period was concerning, and persisted after adjusting for key potential confounders including a history of benzodiazepine use, residence in the DTES, and engagement in drug dealing. These patterns may reflect a change in the culture of the increasing use of prescription drugs in society, both from the health care system and illegally.[1,28] Consistent

with our findings, Canadian studies also suggest that while the dangers of benzodiazepine use are becoming increasingly recognized in the scientific community, clinical practice is lagging and benzodiazepine prescribing among middle aged populations appears stable or even slightly increasing.[1,27]

Participants who reported recent incarceration were significantly more likely to report increased availability of benzodiazepines. It is possible that this association exists because those with higher use of benzodiazepines had more severe addiction and related problems and were more likely to engage in criminal activities that could result in law enforcement interactions. Another possible interpretation is that through the course of incarceration individuals are commonly prescribed benzodiazepine to address mental health related issues,[12] which leads to increased use (and hence increased perceived availability) post incarceration. If benzodiazepine prescriptions are commonly initiated in correctional facilities, the potential contribution of benzodiazepine use to the elevated risk of fatal overdose post incarceration[41] warrants examination. It has been shown that combined opioid and sedative use is a risk factor for overdose mortality after release from prison.[42] In this context, the association between incarceration and increased availability of benzodiazepines found in the present study is concerning. Additional research in this area should be a public health priority.

Another troubling finding of this study is the independent association between engagement in MMT and easier access to benzodiazepines. Studies have shown that people engaged in methadone therapy have high levels of benzodiazepine use, with one study reporting the prevalence of past-year use at 66%.[20] This might reflect the fact that those enrolled in MMT are more engaged with the health care system. Notably, while we did not

find a significant association between health care utilization and benzodiazepine availability, there was a positive trend observed that did approach statistical significance. It is clear that MMT leads to many positive health and social outcomes;[43-46] however, MMT can also be associated with drug related death, especially during times of induction into and cessation of therapy.[47] Benzodiazepine use has also been associated with an increase in the risk of opioid-related death.[20,47,48] The increased availability of benzodiazepines among patients in MMT, along with the well-studied harms in this population, highlights the need to intervene, through physician and patient education and public health interventions, to decrease inappropriate benzodiazepine prescribing and prevent these unintended consequences. Importantly, successful discontinuation of benzodiazepine use in patients engaged in methadone maintenance therapy does predict improvement in health outcomes including retention in treatment.[49]

Increased perceived availability of benzodiazepines was independently associated with DTES residence and drug dealing. The DTES is a setting with an open drug market and public drug use[35,36] and is close to a number of health care providers. In an environment so dense in potential sources of benzodiazepines, through both legitimately prescribed and illegally obtained avenues, it is expected that participants who reported residence here also reported relatively high availability of benzodiazepines. The independent association of drug dealing with perceived availability of benzodiazepines may be linked to these participants having direct access to personal stores of many substances of abuse, or through extensive personal networks throughout the drug market. More research is needed to investigate whether PWID are obtaining their benzodiazepines from legal or illegal sources.

Additionally, more research is needed to examine how to restrict access to benzodiazepines from legal and illegal sources.

Our study has limitations. First, as our sample was not randomly recruited, the generalizability of the results may be limited. Second, given the potential heterogeneity of drug-using populations between different communities, the results may not generalizable to other settings. Lastly, self-report data may be subjected to reporting biases.

5. CONCLUSION

We found that perceived availability of benzodiazepines has increased over the study period among this sample of PWID. We also found several high-risk groups of PWID reporting more immediate availability of benzodiazepines. These included those residing in the DTES, those recently incarcerated, those engaged in drug dealing, and those enrolled in MMT. The implications of the findings related to recent incarceration or involvement in MMT are particularly troubling given that these sub-populations of PWID are already identified as being at heightened risk of fatal overdose in certain circumstances (such as during induction of MMT). Given the known limited clinical benefits and serious health harms associated with benzodiazepines, these findings indicate a need for education at the level of both users and prescribers, and to examine benzodiazepine prescribing practices in community and prison settings. As part of this, further research is needed to explore the exact mechanisms behind the increased availability reported in these groups and how they are securing their benzodiazepines, as well as to examine why availability is increasing over time.

REFERENCES

1. Cunningham CM, Hanley GE, Morgan S. Patterns in the use of benzodiazepines in British Columbia: examining the impact of increasing research and guideline cautions against long-term use. *Health policy (Amsterdam, Netherlands).* 2010;97(2-3):122-129.

2. Olfson M, King M, Schoenbaum M. Benzodiazepine use in the United States. *JAMA psychiatry.* 2015;72(2):136-142.

3. *First Do No Harm: Responding to Canada's Prescription Drug Crisis.* Ottawa, Ontario: National Advisory Council of Prescription Drug Misuse. Canadian Centre on Substance Abuse;2013.

4. *I-Track: Enhanced Surveillance of HIV, Hepatitis C and Associated Risk Behaviours Among Pople Who Inject Drugs in Canada. Phase 2 Report. .* Ottawa, ON: Center for Communicable Disease and Infection Control, Infectious Disease Prevention and Control Branch, Public Health Agency of Canada;2013.

5. Cascade E, Kalali AH. Use of benzodiazepines in the treatment of anxiety. *Psychiatry (Edgmont (Pa : Township)).* 2008;5(9):21-22.

6. Barker MJ, Greenwood KM, Jackson M, Crowe SF. Persistence of cognitive effects after withdrawal from long-term benzodiazepine use: a meta-analysis. *Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists.* 2004;19(3):437-454.

7. Smink BE, Egberts AC, Lusthof KJ, Uges DR, de Gier JJ. The relationship between benzodiazepine use and traffic accidents: A systematic literature review. *CNS drugs.* 2010;24(8):639-653.

8. Cumming RG, Le Couteur DG. Benzodiazepines and risk of hip fractures in older people: a review of the evidence. *CNS drugs.* 2003;17(11):825-837.

9. Licata SC, Rowlett JK. Abuse and dependence liability of benzodiazepine-type drugs: GABA(A) receptor modulation and beyond. *Pharmacology, biochemistry, and behavior.* 2008;90(1):74-89.

10. Bach P, Walton G, Hayashi K, et al. Benzodiazepine Use and Hepatitis C Seroconversion in a Cohort of Persons Who Inject Drugs. *American journal of public health.* 2016;106(6):1067-1072.

11. Ickowicz S, Hayashi K, Dong H, et al. Benzodiazepine use as an independent risk factor for HIV infection in a Canadian setting. *Drug and alcohol dependence.* 2015;155:190-194.

12. Bleich A, Gelkopf M, Schmidt V, Hayward R, Bodner G, Adelson M. Correlates of benzodiazepine abuse in methadone maintenance treatment. A 1 year prospective study in an Israeli clinic. *Addiction.* 1999;94(10):1533-1540.

13. Ross J, Darke S. The nature of benzodiazepine dependence among heroin users in Sydney, Australia. *Addiction (Abingdon, England).* 2000;95(12):1785-1793.

14. Kerr T, Fairbairn N, Tyndall M, et al. Predictors of non-fatal overdose among a cohort of polysubstance-using injection drug users. *Drug and alcohol dependence.* 2007;87(1):39-45.

15. Fischer B, Brissette S, Brochu S, et al. Determinants of overdose incidents among illicit opioid users in 5 Canadian cities. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne.* 2004;171(3):235-239.

16. Zamparutti G, Schifano F, Corkery JM, Oyefeso A, Ghodse AH. Deaths of opiate/opioid misusers involving dihydrocodeine, UK, 1997-2007. *British journal of clinical pharmacology.* 2011;72(2):330-337.

17. Shah R, Uren Z, Baker A, Majeed A. Trends in deaths from drug overdose and poisoning in England and Wales 1993-1998. *Journal of public health medicine.* 2001;23(3):242-246.

18. Calcaterra S, Glanz J, Binswanger IA. National trends in pharmaceutical opioid related overdose deaths compared to other substance related overdose deaths: 1999-2009. *Drug and alcohol dependence.* 2013;131(3):263-270.

19. Charlson F, Degenhardt L, McLaren J, Hall W, Lynskey M. A systematic review of research examining benzodiazepine-related mortality. *Pharmacoepidemiology and drug safety.* 2009;18(2):93-103.

20. Leece P, Cavacuiti C, Macdonald EM, et al. Predictors of Opioid-Related Death During Methadone Therapy. *Journal of substance abuse treatment.* 2015;57:30-35.

21. Gossop M, Stewart D, Treacy S, Marsden J. A prospective study of mortality among drug misusers during a 4-year period after seeking treatment. *Addiction (Abingdon, England).* 2002;97(1):39-47.

22. Walton GR, Hayashi K, Bach P, et al. The Impact of Benzodiazepine Use on Mortality Among Polysubstance Users in Vancouver, Canada. *Public health reports (Washington, DC : 1974).* 2016;131(3):491-499.

23. Lintzeris N, Mitchell TB, Bond AJ, Nestor L, Strang J. Pharmacodynamics of diazepam co-administered with methadone or buprenorphine under high dose conditions in opioid dependent patients. *Drug and alcohol dependence.* 2007;91(2-3):187-194.

24. Hayashi K, Suwannawong P, Ti L, Kaplan K, Wood E, Kerr T. High rates of midazolam injection and associated harms in Bangkok, Thailand. *Addiction (Abingdon, England).* 2013;108(5):944-952.

25. Dell'osso B, Lader M. Do benzodiazepines still deserve a major role in the treatment of psychiatric disorders? A critical reappraisal. *European psychiatry : the journal of the Association of European Psychiatrists.* 2013;28(1):7-20.

26. Darke S, Ross J, Teesson M, Lynskey M. Health service utilization and benzodiazepine use among heroin users: findings from the Australian Treatment Outcome Study (ATOS). *Addiction (Abingdon, England).* 2003;98(8):1129-1135.

27. Alessi-Severini S, Bolton JM, Enns MW, et al. Use of benzodiazepines and related drugs in Manitoba: a population-based study. *CMAJ open.* 2014;2(4):E208-216.

28. Ross J, Darke S, Hall W. Benzodiazepine use among heroin users in Sydney: patterns of use, availability and procurement. *Drug and alcohol review.* 1996;15(3):237-243.

29. Tyndall MW, Currie S, Spittal P, et al. Intensive injection cocaine use as the primary risk factor in the Vancouver HIV-1 epidemic. *AIDS (London, England).* 2003;17(6):887-893.

30. Milloy MJ, Kerr T, Buxton J, et al. Social and environmental predictors of plasma HIV RNA rebound among injection drug users treated with antiretroviral therapy. *Journal of acquired immune deficiency syndromes (1999).* 2012;59(4):393-399.

31. Wood E, Stoltz JA, Montaner JS, Kerr T. Evaluating methamphetamine use and risks of injection initiation among street youth: the ARYS study. *Harm reduction journal.* 2006;3:18.

32. Hayden A, Hayashi K, Dong H, et al. The impact of drug use patterns on mortality among polysubstance users in a Canadian setting: a prospective cohort study. *BMC public health.* 2014;14:1153.

33. Nolan S, Hayashi K, Milloy MJ, et al. The impact of low-threshold methadone maintenance treatment on mortality in a Canadian setting. *Drug and alcohol dependence.* 2015.

34. Zivanovic R, Milloy MJ, Hayashi K, et al. Impact of unstable housing on all-cause mortality among persons who inject drugs. *BMC public health.* 2015;15:106.

35. Ciccarone D, Bourgois P. Injecting drugs in tight spaces: HIV, cocaine and collinearity in the Downtown Eastside, Vancouver, Canada. *The International journal on drug policy.* 2016.

36. Linden IA, Mar MY, Werker GR, Jang K, Krausz M. Research on a vulnerable neighborhood-the vancouver downtown eastside from 2001 to 2011. *Journal of urban health : bulletin of the New York Academy of Medicine.* 2013;90(3):559-573.

37. van der Zanden BP, Dijkgraaf MG, Blanken P, de Borgie CA, van Ree JM, van den Brink W. Validity of the EQ-5D as a generic health outcome instrument in a heroin-dependent population. *Drug and alcohol dependence.* 2006;82(2):111-118.

38. Ti L, Milloy MJ, Buxton J, et al. Factors Associated with Leaving Hospital against Medical Advice among People Who Use Illicit Drugs in Vancouver, Canada. *PloS one.* 2015;10(10):e0141594.

39. Hayashi K, Dong H, Marshall BD, et al. Sex-Based Differences in Rates, Causes, and Predictors of Death Among Injection Drug Users in Vancouver, Canada. *American journal of epidemiology.* 2016;183(6):544-552.

40. Hayashi K, Nosyk B, Ti L, et al. Increasing availability of illicit drugs among people who inject drugs in Bangkok, Thailand. *Drug and alcohol dependence.* 2013;132(1-2):251-256.

41. Merrall EL, Kariminia A, Binswanger IA, et al. Meta-analysis of drug-related deaths soon after release from prison. *Addiction (Abingdon, England).* 2010;105(9):1545-1554.

42. Binswanger IA, Stern MF, Yamashita TE, Mueller SR, Baggett TP, Blatchford PJ. Clinical risk factors for death after release from prison in Washington State: a nested case-control study. *Addiction (Abingdon, England).* 2016;111(3):499-510.

43. Degenhardt L, Randall D, Hall W, Law M, Butler T, Burns L. Mortality among clients of a state-wide opioid pharmacotherapy program over 20 years: risk factors and lives saved. *Drug and alcohol dependence.* 2009;105(1-2):9-15.

44. Brugal MT, Domingo-Salvany A, Puig R, Barrio G, Garcia de Olalla P, de la Fuente L. Evaluating the impact of methadone maintenance programmes on mortality due to overdose and aids in a cohort of heroin users in Spain. *Addiction (Abingdon, England).* 2005;100(7):981-989.

45. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *The Cochrane database of systematic reviews.* 2009(3):Cd002209.

46. Gowing L, Farrell MF, Bornemann R, Sullivan LE, Ali R. Oral substitution treatment of injecting opioid users for prevention of HIV infection. *The Cochrane database of systematic reviews.* 2011(8):Cd004145.

47. Cousins G, Teljeur C, Motterlini N, McCowan C, Dimitrov BD, Fahey T. Risk of drug-related mortality during periods of transition in methadone maintenance treatment: a cohort study. *Journal of substance abuse treatment.* 2011;41(3):252-260.

48. McCowan C, Kidd B, Fahey T. Factors associated with mortality in Scottish patients receiving methadone in primary care: retrospective cohort study. *BMJ (Clinical research ed).* 2009;338:b2225.

49. Darke S, Ross J, Mills K, Teesson M, Williamson A, Havard A. Benzodiazepine use among heroin users: baseline use, current use and clinical outcome. *Drug and alcohol review.* 2010;29(3):250-255.

[Table 1 Here]

[Table 2 Here]

Figure 1: Trend in availability of benzodiazepines among people who inject drugs in Vancouver, Canada throughout study period: June 2012 – May 2015.