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Research Paper

Correlates of opioid and benzodiazepine co-prescription among people living with HIV in British Columbia, Canada: A population-level cohort study

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ABSTRACT

Background:Co-prescribing benzodiazepines and opioids is relatively contraindicated due to the possible overdose risk. However, people living with HIV (PLWH) may have concurrent psychiatric and/or chronic pain diagnoses that may lead to the use of opioids and/or benzodiazepines for symptomatic treatment. Consequently, some PLWH may be at-risk for the health harms associated with the co-prescribing of these medications. Given this, the objectives of this study were to first examine the prevalence of opioids and benzodiazepines co-prescribing, and second, to characterize patient factors associated with the co-prescribing of opioids and benzodiazepines among PLWH in British Columbia (BC), Canada.

Methods:Using data derived from a longitudinal BC cohort, we used bivariable and multivariable generalized estimating equation models to establish the prevalence of a benzodiazepine and opioid co-prescription and determine factors associated with this practice.

Results:Between 1996 and 2015, 14 484 PLWH were included in the study and were followed for the entire study period. At baseline, 548 people (4%) were co-prescribed opioids and benzodiazepines, 6593 (46%) were prescribed opioids only, 2887 (20%) were prescribed benzodiazepines only, and 4456 (31%) were prescribed neither medication. A total of 3835 (27%) participants were prescribed both medications at least once during the study period. Factors positively associated with concurrent opioid and benzodiazepine prescribing included: depression/mood disorder [adjusted odds ratio (AOR) = 1.32; 95% confidence interval (CI) = 1.22–1.43] and anxiety disorder (AOR = 1.45; 95% CI = 1.27–1.66), whereas female sex (AOR = 0.76; 95% CI = 0.64-0.91) and substance use disorder (SUD) (AOR = 0.82; 95% CI = 0.74–0.90) were negatively associated with the outcome.

Conclusion:Our findings indicate that co-prescription of opioids and benzodiazepines was seen at some point during study follow-up in over a quarter of PLWH. Given the known risks associated with this prescribing practice, future research can focus on the outcomes of co-prescribing among this patient population and the development of strategies to reduce the co-prescribing of opioids and benzodiazepines.

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Introduction

The co-prescription of opioids and benzodiazepines is relatively contraindicated due to possible overdose risk (Centres for disease control & prevention, 2016). However, opioid and benzodiazepine co-prescription remains an issue of concern globally, as it remains common and in recent years, showed no downward trend (Jann, Kennedy, & Lopez, 2014). For example, in the United States (US), incidence of co-prescription of opioids and benzodiazepines increased by about 80% between 2001–2013 (Sun et al., 2017). In a population of 337 095 people with a substance use disorder (SUD), receiving benzodiazepines for more than seven days was a predictor of also receiving long-term opioids (O'Brien et al., 2017). Moreover, in 144 535 patients from a drug monitoring database undergoing drug testing, up to 25% were using opioids and benzodiazepines concurrently (McClure, Niles, Kaufman, & Gudin, 2017).

The harms of co-prescribing opioids and benzodiazepines have been well-established in the literature, including possible overdose risk through dangerous synergistic effects that can lead to respiratory depression and mortality (Jones, Mogali, & Comer, 2012). For example, studies have demonstrated that the co-prescription of opioids and sedative medications results in a 2.54 increased risk of non-fatal overdose and a 1.56 increased risk of mortality (Kim et al., 2017; Weisberg et al., 2015). Falls, fractures, and car accidents can also be increased with the use of opioids and/or benzodiazepines (Huang et al., 2012; Leung, 2011).

In addition to the health harms to individuals, co-prescription of opioids and benzodiazepines has been shown to strain healthcare resources in developed settings: in the general population, people who were co-prescribed opioids and benzodiazepines had over two times a greater risk of emergency room visits compared to opioid users who did not use benzodiazepines (Jann et al., 2014; Sun et al., 2017). Furthermore, people living with HIV (PLWH) from the Seek and Treat for Optimal Prevention (STOP) HIV in BC cohort who were co-prescribed opioids and benzodiazepines had a 58% higher risk of hospitalization compared to those not being prescribed either medication (Ti et al., 2017).

Despite the risks associated with the co-prescription of these medications, PLWH often have concurrent psychiatric and/or chronic pain diagnoses that may lead to the use of opioids and/or benzodiazepines for symptomatic treatment. For example, an evidence-based review reported that up to 38% of PLWH had an underlying anxiety disorder (Kemppainen, MacKain, & Reyes, 2013), a condition often treated with benzodiazepines (Wu, Wang, Katz, & Farley, 2013). Moreover, studies have indicated that PLWH have a high prevalence of chronic pain (Bruce et al., 2017) and are often prescribed opioid medications. Specifically, a study in the US showed that opioids were prescribed to up to 50% of PLWH (Kim et al., 2017). Additionally, people aging with HIV are more likely to experience polypharmacy and be physiologically compromised, and as such may be particularly at-risk for the health harms associated with co-prescription (Edelman et al., 2013). Indeed, this population experiences an excess risk of mortality from opioids and benzodiazepines (Hazard Ratio [HR] = 1.82) compared to people living without HIV (HR = 1.43) (Weisberg et al., 2015).

Given the intersection between HIV, mental health, chronic pain, and substance use disorders, identifying factors associated with the co-prescription of opioids and benzodiazepines is critical for future development of interventions to prevent the harms associated with this prescribing practice. Some cross-sectional studies point to the role that mental health and other factors may play in being co-prescribed opioids and benzodiazepines (Merlin et al., 2016; Saunders et al., 2012). For example, a US study found that depression and anxiety, having public or no medical insurance (vs private insurance), and age > 50 were associated with chronic co-prescription of opioids and sedatives (Merlin et al., 2016). However, in BC, essential healthcare, including HIV care and medication, are provided free of charge; thus, factors associated with co-prescription may differ from the US setting. Additionally, there are few studies on this topic among PLWH specifically, Merlin and colleagues' study being one in the current literature. As such, there may be additional factors that may be associated with co-prescription that were not captured previously (e.g., comorbidities, viral load and CD4). Our study will thus add to the literature of co-prescription among PLWH by examining the prevalence and correlates of co-prescription longitudinally and in a Canadian context, as there is a paucity of data originating from outside the US on this topic.

Methods

Study cohort design

Data were derived from the Seek and Treat for Optimal Prevention (STOP) HIV/AIDS in BC cohort, which includes all people diagnosed with HIV in BC between January 1996 and March 2015. The cohort is comprised of the following linked databases: 1) the BC Centre for Excellence in HIV/AIDS, which provides data on antiretroviral distribution, viral load and resistance testing, and CD4 cell count measurement (BC Centre for Excellence in HIV/AIDS, 2014); 2) The BC Centre for Disease Control, which provides data on HIV testing and new HIV diagnosis (British Columbia Centre for Disease Control Public Health Laboratory, 2016; British Columbia Centre for Disease Control, 2016); 3) Medical Service Plan (MSP) physician billing database, which provides data on HIV and non-HIV physician services (British Columbia Ministry of Health, 2016); 4) Discharge Abstract Database (DAD), which provides data on hospital admissions and discharges (Canadian Institute of Health Information, 2016); 5) the BC PharmaNet database, which provides data on non-ART drug dispensations (British Columbia Ministry of Health, 2014); and 6) BC Vital Statistics database, which provides data on deaths (British Columbia Vital Statistics Agency, 2016). BC provides a government-funded universal healthcare system, and each British Columbian is assigned a Personal Health Number (PHN). Use of healthcare services can be tracked through PHNs, and study participants were linked through each database via their PHN. Participants were followed retrospectively from baseline until the end of the study period. More details on this cohort can be found elsewhere (Heath et al., 2014). This study has been approved by the University of British Columbia/Providence Health Care research ethics board.

Measures

The main outcome variable was prescription of an opioid or benzodiazepine, alone or together, derived from the PharmaNet database. We defined co-prescription as the overlapping prescribing of opioids and benzodiazepines for at least one day. Medications prescribed for opioid agonist therapy (e.g., buprenorphine, methadone) were excluded from the outcome definition given that the inclusion of these medications for the treatment of opioid use disorder may skew the results (see below). Similar to other studies investigating opioid and benzodiazepine co-prescription (Ti et al., 2017), we categorized the main outcome variable into four mutually exclusive levels: 1) opioid and benzodiazepine co-prescription; 2) opioid use only; 3) benzodiazepine use only; 4) use of neither medication.

The main explanatory variables of interest were: sex (female vs male); age (per 10-year increase); calendar year (per year increase); depression diagnosis based on ICD-9/10 codes derived from MSP and

DAD; anxiety diagnosis based on ICD-9/10 codes derived from MSP and DAD; substance use disorder based on ICD-9/10 codes derived from MSP and DAD, a prescription of methadone or buprenorphine/naloxone derived from Pharmanet, or identification as a high-risk group derived from the BC Centre for Disease Control or BC Centre for Excellence in HIV/AIDS databases (Closson et al., 2017); Charlson comorbidity index (CCI; per unit increase) derived from MSP and DAD; CD4 cell count (per 100 cells/mL increase) derived from the BC Centre for Excellence in HIV/AIDS database; and viral load (per log 10 increase) derived from the BC Centre for Excellence in HIV/AIDS database.

Explanatory variables were assessed as the closest measurement prior to or on the start date for each prescription interval. For time-varying variables, specifically CCI, CD4, and VL, if there was no measure captured within the six-month time window, the variable was treated as missing. If a single patient had multiple discrete instances of opioids and/or benzodiazepines prescriptions, explanatory variables were measured for each prescription interval. If a person had no opioid or benzodiazepine prescription, we considered their baseline to end of follow-up to be one interval.

Statistical analyses

First, we calculated descriptive statistics on the study sample at baseline, stratified by the four levels of the outcome described above. For quantitative variables, we calculated the median, as well as the first (Q1) and third (Q3) quartile. To estimate the unadjusted and adjusted effect of demographic and clinical factors on opioid and benzodiazepine co-prescription, we used generalized estimating equation models (GEE) for binary outcomes with logit link for the analysis of correlated data, using "not co-prescribed opioids and benzodiazepines" as the reference group. Specifically, we first fitted each selected explanatory variable to a bivariable GEE model with the main outcome of interest to obtain unadjusted odds ratios (OR) and 95% confidence intervals (CI). Then, a multivariable GEE model was fit using a statistical protocol based on examination of the quasi-likelihood under the independence model criterion (QIC) for GEE and p-values. First, a preliminary model was constructed including all variables significantly associated with the outcome in bivariable analyses at $p < 0.10$. Following this, each variable with the highest p-value was removed sequentially, which resulted in a final multivariable GEE model that included the set of variables associated with the lowest QIC. We also tested collinearity using variance inflation factor. All statistical analyses were computed using SAS software version 9.4 (SAS Institute, Cary, NC) and all p-values were two-sided.

Results

A total of 14 484 individuals diagnosed with HIV were included in the study between 1996 and 2015. At baseline, participants had a median age of 38 years (Q1-Q3 = 31–45 years), and 11 671 (80.6%) were male. Table 1 outlines demographic and clinical characteristics of the study sample at baseline. At baseline, 548 (4%) were co-prescribed opioids and benzodiazepines, 6593 (46%) were prescribed opioids only, 2887 (20%) were prescribed benzodiazepines only, and 4456 (31%) of participants were prescribed neither opioids nor benzodiazepines. Throughout the study period, a total of 3835 (27%) participants were co-prescribed both medications at least once. Participants were co-prescribed both medications for a median of 11 days (Q1-Q3 = 6–26 days), were prescribed opioids only for a median of 6 days (Q1-Q3 = 4–11 days), and were prescribed benzodiazepines for a median of 19 days (Q1-Q3 = 9–31 days).

Table 2 presents the results from the bivariable and multivariable GEE analyses for the main outcome variable (concurrent opioid and benzodiazepine prescription). In bivariable analyses, a concurrent opioid and benzodiazepine co-prescription was independently and positively associated with: presence of a depression/mood disorder (OR = 1.47; 95% CI = 1.37–1.57), presence of an anxiety disorder (OR = 1.48; 95% CI = 1.33–1.66), age (OR = 1.16, 95% CI = 1.11–1.22), and CCI (OR = 1.08, 95% CI = 1.06–1.10), whereas being female (OR = 0.78, 95% CI = 0.67-0.90) and calendar year (OR = 0.73, 95%CI = 0.68-0.79) were negatively associated with co-prescription of opioids and benzodiazepines. In a multivariable GEE model, factors that remained positively associated with the outcome included: depression/mood disorder (adjusted OR [AOR] = 1.32; 95% CI = 1.22–1.43), age (AOR = 1.11, 95% CI = 1.04–1.18), CCI (AOR = 1.09, 95% CI = 1.07–1.11), and anxiety disorder (AOR =

Table 1
Baseline characteristics of 14 484 people living with HIV in British Columbia, Canada.

Characteristic	Total (%) or median	Co-prescription of opioids and benzodiazepines		*p* - value
		Yes (%) (*n* = 548)	No (%) (*n* = 13 936)	
Drug prescribed (at baseline)				
Overlap use for both medications	548 (3.8)	548 (100.0)	0	
Opioids only	6593 (45.5)	0 (0)	6593 (47.3)	
Benzodiazepines only	2887 (19.9)	0 (0)	2887 (20.7)	
Neither medication	4456 (30.8)	0 (0)	4456 (32.0)	
Sex				< 0.001
Female	2813 (19.4)	138 (25.2)	2675 (19.2)	
Male	11 671 (80.6)	410 (74.8)	11 261 (80.8)	
Age (median, Q1-Q3)	38 (31,45)	39 (33,45)	38 (31,45)	0.003
Calendar year (median, Q1-Q3)	2003 (1998, 2009)	1998 (1996, 2003)	2003 (1998,2009)	< 0.001
Depression/mood disorder				< 0.001
Yes	1823 (12.6)	111 (20.3)	1712 (12.3)	
No	12 661 (87.4)	437 (79.7)	12 224 (87.7)	
Anxiety disorder				< 0.001
Yes	777 (5.4)	60 (11.0)	717 (5.1)	
No	13 707 (94.6)	488 (89.1)	13 219 (94.9)	
Substance use disorder				< 0.001
Yes	3214 (22.2)	248 (45.3)	2966 (21.3)	
No	11 270 (77.8)	300 (54.7)	10 970 (78.7)	
Charlson comorbidity index (median, Q1-Q3)	4 (4,6)	5 (4,6)	4 (4,6)	< 0.001
Viral load (log10 copies/ml) (median, Q1-Q3)	3.7 (1.7,4.8)	4.3 (3.0,5.0)	3.7 (1.7, 4.8)	< 0.001
CD4 cell count (cells/mm3) (median, Q1-Q3)	360 (200,540)	320 (130, 510)	360 (200, 542)	0.008

Q: quartile

Table 2
Bivariable and multivariable generalized estimating equation analyses of factors associated with opioids and benzodiazepines co-prescription.

Characteristic	Odds Ratio (OR)	
	Unadjusted OR (95% Confidence Interval)	Adjusted OR (95% Confidence Interval)
Sex (female vs male)	0.78 (0.67–0.90)	0.76 (0.64–0.91)
Age at baseline (per 10-year increase)	1.16 (1.11–1.22)	1.11 (1.04–1.18)
Calendar year (per 10-year increase)	0.73 (0.68–0.79)	0.65 (0.59–0.72)
Depression/mood disorder (yes vs no)	1.47 (1.37–1.57)	1.32 (1.22–1.43)
Anxiety (yes vs no)	1.48 (1.33–1.66)	1.45 (1.27–1.66)
Substance use disorder (yes vs no)	0.95 (0.88–1.03)	0.82 (0.74–0.90)
Charlson comorbidity index (per unit increase)	1.08 (1.06–1.10)	1.09 (1.07–1.11)
CD4 cell count (per 100 cells/mm3)	1.00 (0.98–1.03)	1.02 (1.00–1.05)
Viral load (per log10 copies/ml)	1.04 (1.02–1.07)	1.03 (1.00–1.07)

1.45; 95% CI = 1.27–1.66). Substance use disorder (AOR = 0.82; 95% CI = 0.74-0.90), calendar year (AOR = 0.65, 95% CI = 0.59-0.72) and female sex (AOR = 0.76; 95% CI = 0.64-0.91) were negatively associated with opioid and benzodiazepine co-prescription.

Discussion

Our findings indicate that co-prescription of opioids and benzodiazepines was frequent in this setting, seen in over a quarter of participants throughout the study period. The mean duration of use for both opioids and benzodiazepines was 11 days. Since most guidelines caution against prescribing altogether (Centres for disease control & prevention, 2016; College of Physicians & Surgeons British Columbia, 2016), there is a paucity of evidence on the impact of fairly short co-prescription duration such as the one described in our study.

Our findings indicate that co-prescription of opioids and benzodiazepines was seen in over a quarter of participants throughout the study period. In the only other study on co-prescription in PLWH we are aware of, 24% (n = 61) of people who were chronically prescribed opioids (n = 253) were also co-prescribed sedatives (Merlin et al., 2016). This accounts for only 4.1% of the total cohort (N = 1474) in this study (Merlin et al., 2016). The high prevalence of co-prescribing in the present analysis contrast with the provincial opioid prescribing guidelines, in which the BC College of Physicians and Surgeons cautions that “Physicians MUST NOT prescribe combinations of opioids with benzodiazepines” (College of Physicians & Surgeons British Columbia, 2016). However, PLWH may have co-morbidities that may necessitate the use of both medications (Bruce et al., 2017; Kemppainen et al., 2013). As such, the complex health needs of PLWH may partially explain the high level of co-prescription reported in our study. Of note, in our study, there was a significant downward trend of co-prescribing over the study period. This is in contrast with other settings in the US, where for example, in a population of patients prescribed opioids, the co-prescription of benzodiazepine increased from 9% to 17% between 2001 and 2013 (Sun et al., 2017). Our finding may be due to a number of reasons, including strict prescribing guidelines and risk of disciplinary action (Busse, Juurlink, & Guyatt, 2017). It is noteworthy that the study period ended in March 2015; since then, Canada has seen a significant increase in number of opioid prescriptions (i.e., increased by 6.8% between 2012 and 2016), thus potentially impacting co-prescribing in the BC setting (Canadian Institute for Health Information, 2018). Future research should seek to explore co-prescribing in the context of the ongoing opioid crisis.

Our findings showed a strong correlation between anxiety and mood disorders and the co-prescription of opioids and benzodiazepines. These findings are consistent with other studies. For example, in a US cohort of primary care patients receiving opioids for non-cancer chronic pain, 61% of those who were co-prescribed opioids and benzodiazepines had an anxiety disorder (Park et al., 2016). In another US cohort of PLWH, symptoms of anxiety and depression were associated with almost twice the odds of co-prescription of opioids and benzodiazepines (Merlin et al., 2016). Of note, benzodiazepines and opioids are not recommended as first line or long-term treatment for anxiety and mood disorders or pain, respectively, yet they are still widely prescribed to treat these conditions (Baldwin et al., 2005; Busse & Craigie et al., 2017; O’Brien et al., 2017; Olfson, King, & Schoenbaum, 2015). In light of the possible health harms associated with opioid and benzodiazepine use, and particularly with co-prescription (Jones et al., 2012), expanding the treatment toolbox to treatment modalities that extend beyond pharmacotherapeutic options may be warranted, and alternative methods for pain and anxiety management should be considered. For example, cognitive behavioural therapy, mindfulness-based therapies, and biofeedback have shown to be effective for chronic pain, depression, and anxiety (Gould, Otto, Pollack, & Yap, 1997; Hofmann, Sawyer, Witt, & Oh, 2010; Moore, 2000; Morley, Eccleston, & Williams, 1999; Morone, Greco, & Weiner, 2008; Sudak, 2012; Tsai, Chen, Lai, Lee, & Lin, 2007). While acknowledging that financial coverage for these alternative forms of therapy remains limited, exploring these alternative methods of pain or psychiatric disorder management could lessen the reliance on pharmacotherapies, and lower the harms caused by the use of opioids and psychiatric medication.

Our study reported a negative association with SUD and co-prescription of opioids and benzodiazepines, which may be partially explained by the hesitancy of healthcare providers to prescribe opioids to people with a history of SUD. A study conducted in BC reported that 66% of a cohort of people who inject drugs were denied prescription analgesia for reasons including “accusations of drug seeking” (44% of participants) (Voon et al., 2015). According to a qualitative study conducted in the US, some physicians were reluctant to prescribe opioids for fear of “being deceived” by their SUD patients or “being manipulated into inappropriate prescribing” (Merrill, Rhodes, Deyo, Marlatt, & Bradley, 2002). Another study suggested that other misconceptions such as believing that prescribing opioids can cause addiction relapse may lead to under-prescribing of opioids for this specific population (Alford, Compton, & Samet, 2006). However, people with a history of SUD are a complex patient population with commonly occurring concurrent chronic pain and psychiatric illnesses that may require treatment (Alford et al., 2006; Morasco et al., 2011; Weisner et al., 2009). Therefore, future studies should explore strategies on how to best manage these concurrent illnesses while minimizing the risks associated with co-prescription in this population.

We found that being female was associated with a lower risk of being co-prescribed opioids and benzodiazepines. This finding was inconsistent with the literature, where studies showed that women were prescribed opioids (Campbell et al., 2010; O’Brien et al., 2017), benzodiazepines (Martinez-Cengotitabengoa et al., 2016; O’Brien et al., 2017), or both (Merlin et al., 2016; Saunders et al., 2012), at a higher prevalence than men. However, in the context of HIV, it is known that women across jurisdictions experience barriers to accessing healthcare services (Johnson et al., 2015; Stevens & Keigher, 2009; Tapp et al., 2011), with fear of stigma and disclosure as reasons for not accessing these essential services (Johnson et al., 2015). In BC, where HIV

treatment and care are available without financial barriers, studies have demonstrated that frequent drug use and higher engagement in street-involved survival activities contribute to women's marginalization from the healthcare system (Tapp et al., 2011). Alternatively, the negative association between female sex and co-prescription may reflect women living with HIV receiving better, evidence-based care. There is room for future studies to delineate the factors behind the negative association between co-prescription and female sex.

This present study has limitations. First, administrative data was utilized, and as such, certain diagnoses including psychiatric disorders or SUD may have been undetected, and thus not captured, or been inappropriately coded. However, the definitions we used have been previously used in other published studies (Closson et al., 2017). Second, our study did not capture the illicit use of opioids or benzodiazepines as the PharmaNet database only captures opioids and benzodiazepines that are prescribed (British Columbia Ministry of Health, 2014). Third, as is common with health administrative data, only participants who interacted with the healthcare system will be captured; thus, we may have missed a subgroup of PLWH who have never interacted with the healthcare system. Nevertheless, over a 19-year period, we believe this subgroup to be very minimal. Fourth, since our study ended in March 2015, we failed to capture recent trends in opioid prescriptions. Given the emergence of an opioid overdose epidemic in 2016 (Government of British Columbia, 2016), future research should seek to explore the impact of co-prescribing post 2015. Fifth, a type 1 statistical error is possible due to the large sample size. Lastly, this study was conducted in BC, where HIV treatment and related medical care are free of charge. This may limit the generalizability of these findings to other jurisdictions with different drug dispensation and healthcare systems.

In this study, the prevalence of co-prescribing was found to be high, almost a quarter of a cohort of PLWH. We reported that having anxiety or a mood disorder to be positively associated with opioid and benzodiazepine co-prescription among PLWH, while the presence of a SUD and being female was negatively associated with this outcome. This study adds to the body of knowledge on this topic by reporting data on the issue of PLWH and co-prescription in a universal healthcare setting. Given the known risks associated with this prescribing practice, future research can focus on the outcomes of co-prescribing among this patient population and the development of strategies to reduces the co-prescribing of opioids and benzodiazepines.

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Conflict of interest statement

LT is supported by a grant from the Michael Smith Foundation. NF is supported by a grant from the Michael Smith Foundation/St-Paul's foundation. JM's Treatment as Prevention (TasP) research, paid to institution, has received support from the Public Health Agency of Canada, British Columbia Ministry of Health or BC MoH and US NIH (NIDA R01DA036307 and CTN 248). Institutional grants have been provided by J&J, Merck and a Knowledge Translation Award from CIHR. JM has served as an advisor to the federal and BC governments, UNAIDS, WHO in the last year.

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References

Alford, D. P., Compton, P., & Samet, J. H. (2006). Acute pain management for patients receiving maintenance methadone or buprenorphine therapy. *Annals of Internal Medicine, 144*(2), 127–134.

Baldwin, D., Anderson, I., Nutt, D., Bandelow, B., Bond, A., Davidson, J., ... Wittchen, H.-U. (2005). *Evidence-based guidelines for the pharmacological treatment of anxiety disorders: Recommendations from the British association for psychopharmacology, 19*https://doi.org/10.1177/0269881105059253.

BC Centre for Excellence in HIV/AIDS (2014). *Drug treatment program and virology registry. BC Centre for Excellence in HIV/AIDS*.

British Columbia Centre for Disease Control (2016). *HIV/AIDS information system (HAISYS). Clinical prevention services.* Retrieved fromBritish Columbia Centre for Disease Control.http://www.bccdc.ca/about/accountability/data-access-requests/public-health-data.

British Columbia Centre for Disease Control Public Health Laboratory (2016). *HIV laboratory testing datasets (tests: ELISA, Western blot, NAAT, p24, culture). Clinical prevention services.* Retrieved fromBritish Columbia Centre for Disease Controlhttp://www.bccdc.ca/about/accountability/data-access-requests/public-health-data.

British Columbia Ministry of Health (2014). *PharmaCare. British Columbia ministry of health. British Columbia ministry of health.* Retrieved fromhttp://www2.gov.bc.ca/gov/content/health/conducting-health-research-evaluation/data-access-health-data-central.

British Columbia Ministry of Health (2016). *Medical services plan (MSP) payment information file; consolidation file (MSP registration & premium billing); home & community care (continuing care); mental health; PharmaNet.* British Columbia Ministry of Health. Retrieved fromBritish Columbia Ministry of Health [publisher]http://www2.gov.bc.ca/gov/content/health/conducting-health-research-evaluation/data-access-health-data-central.

British Columbia Vital Statistics Agency (2016). *Vital statistics. British Columbia ministry of health.* Retrieved fromhttp://www2.gov.bc.ca/gov/content/health/conducting-health-research-evaluation/data-access-health-data-central.

Bruce, R. D., Merlin, J., Lum, P. J., Ahmed, E., Alexander, C., Corbett, A. H., ... Selwyn, P. (2017). 2017 HIVMA of IDSA clinical practice guideline for the management of chronic pain in patients living with HIV. *Clinical Infectious Diseases, 65*(10), e1–e37. https://doi.org/10.1093/cid/cix636.

Busse, J. W., Craigie, S., Juurlink, D. N., Buckley, D. N., Wang, L., Couban, R. J., ... Cooper, L. (2017). Guideline for opioid therapy and chronic noncancer pain. *Canadian Medical Association Journal, 189*(18), E659–E666.

Busse, J. W., Juurlink, D. N., & Guyatt, G. H. (2017). Response to "Clarification from the College of Physicians and Surgeons of BC on commentary about limitations of the CDC guideline for prescribing opioids,". *CMAJ, 189*(13), E509.

Campbell, C. I., Weisner, C., LeResche, L., Ray, G. T., Saunders, K., Sullivan, M. D., ... Boudreau, D. (2010). Age and gender trends in long-term opioid analgesic use for noncancer pain. *American Journal of Public Health, 100*(12), 2541–2547.

Canadian Institute for Health Information (2018). *Amount of opioids prescribed dropping in Canada; prescriptions on the rise* (2018, December 13), Retrieved fromhttps://www.cihi.ca/en/amount-of-opioids-prescribed-dropping-in-canada-prescriptions-on-the-rise.

Canadian Institute of Health Information (2016). *Discharge abstract database (Hospital separations).* Retrieved fromBritish Columbia Ministry of Health [publisher]http://www2.gov.bc.ca/gov/content/health/conducting-health-research-evaluation/data-access-health-data-central.

Centres for disease control and prevention (2016). CDC guideline for prescribing opioids for chronic pain — United States, 2016. *MMWR Recommendations and Reports, 65*. https://doi.org/10.15585/mmwr.rr6501e1er.

Closson, K., Osborne, C., Smith, D. M., Kesselring, S., Eyawo, O., Card, K., ... Study, for T. C. O. and S. utilization T. (COAST) (2017). Factors associated with mood disorder diagnosis among a population based cohort of men and women living with and without HIV in British Columbia between 1998 and 2012. *AIDS and Behavior,* 1–11. https://doi.org/10.1007/s10461-017-1825-3.

College of Physicians and Surgeons British Columbia (2016). *Safe prescribing of drugs with potential for misuse/diversion* (2016, October 28), Retrieved fromCollege of Physicians and Surgeons British Columbiahttps://www.cpsbc.ca/files/pdf/PSG-Safe-

Prescribing.pdf.
Edelman, E. J., Gordon, K. S., Glover, J., McNicholl, I. R., Fiellin, D. A., & Justice, A. C. (2013). The next therapeutic challenge in HIV: Polypharmacy. *Drugs & Aging, 30*(8), 613–628. https://doi.org/10.1007/s40266-013-0093-9.
Gould, R. A., Otto, M. W., Pollack, M. H., & Yap, L. (1997). Cognitive behavioral and pharmacological treatment of generalized anxiety disorder: A preliminary meta-analysis. *Behavior Therapy, 28*(2), 285–305.
Government of British Columbia (2016). *Provincial health officer declares public health emergency* (2016, April 14), Retrieved fromhttps://news.gov.bc.ca/releases/2016hlth0026-000568.
Heath, K., Samji, H., Nosyk, Bohdan, Colley, G., Gilbert, M., Hogg, R. S., ... Montaner, J. S. G. (2014). Cohort profile: Seek and treat for the optimal prevention of HIV/AIDS in British Columbia (STOP HIV/AIDS BC). *International Journal of Epidemiology, 43*(4), 1073–1081.
Hofmann, S. G., Sawyer, A. T., Witt, A. A., & Oh, D. (2010). The effect of mindfulness-based therapy on anxiety and depression: A meta-analytic review. *Journal of Consulting and Clinical Psychology, 78*(2), 169.
Huang, A. R., Mallet, L., Rochefort, C. M., Eguale, T., Buckeridge, D. L., & Tamblyn, R. (2012). Medication-related falls in the elderly. *Drugs & Aging, 29*(5), 359–376. https://doi.org/10.2165/11599460-000000000-00000.
Jann, M., Kennedy, W. K., & Lopez, G. (2014). Benzodiazepines: A major component in unintentional prescription drug overdoses with opioid analgesics. *Journal of Pharmacy Practice, 27*(1), 5–16.
Johnson, M., Samarina, A., Xi, H., Ramalho, Valdez, Madruga, J., Hocqueloux, L., Loutfy, M., ... Zachry, W. (2015). Barriers to access to care reported by women living with HIV across 27 countries. *AIDS Care, 27*(10), 1220–1230.
Jones, J. D., Mogali, S., & Comer, S. D. (2012). Polydrug abuse: A review of opioid and benzodiazepine combination use. *Drug and Alcohol Dependence, 125*(1), 8–18.
Kemppainen, J. K., MacKain, S., & Reyes, D. (2013). Anxiety symptoms in HIV-infected individuals. *Journal of the Association of Nurses in AIDS Care, 24*(1), S29–S39.
Kim, T. W., Walley, A. Y., Heeren, T. C., Patts, G. J., Ventura, A. S., Lerner, G. B., ... Saitz, R. (2017). Polypharmacy and risk of non-fatal overdose for patients with HIV infection and substance dependence. *Journal of Substance Abuse Treatment, 81*, 1–10.
Leung, S. Y. (2011). Benzodiazepines, opioids and driving: An overview of the experimental research. *Drug and Alcohol Review, 30*(3), 281–286. https://doi.org/10.1111/j.1465-3362.2011.00311.x.
Martinez-Cengotitabengoa, M., Besga, A., Bermudez-Ampudia, C., Garcia-Alocen, A., Gonzalez-Ortega, I., Lopez, M. P., ... Abrain, A. (2016). Gender differences in benzodiazepines prescription in old age patients. *European Psychiatry, 33*, S336.
McClure, F. L., Niles, J. K., Kaufman, H. W., & Gudin, J. (2017). Concurrent use of opioids and benzodiazepines: Evaluation of prescription drug monitoring by a United States Laboratory. *Journal of Addiction Medicine, 11*(6), 420.
Merlin, J. S., Tamhane, A., Starrels, J. L., Kertesz, S., Saag, M., & Cropsey, K. (2016). Factors associated with prescription of opioids and co-prescription of sedating medications in individuals with HIV. *AIDS and Behavior, 20*(3), 687–698. https://doi.org/10.1007/s10461-015-1178-8.
Merrill, J. O., Rhodes, L. A., Deyo, R. A., Marlatt, G. A., & Bradley, K. A. (2002). Mutual mistrust in the medical care of drug users. *Journal of General Internal Medicine, 17*(5), 327–333.
Moore, N. C. (2000). A review of EEG biofeedback treatment of anxiety disorders. *Clinical Electroencephalography, 31*(1), 1–6.
Morasco, B. J., Gritzner, S., Lewis, L., Oldham, R., Turk, D. C., & Dobscha, S. K. (2011). Systematic review of prevalence, correlates, and treatment outcomes for chronic non-cancer pain in patients with comorbid substance use disorder. *Pain®, 152*(3), 488–497.
Morley, S., Eccleston, C., & Williams, A. (1999). Systematic review and meta-analysis of randomized controlled trials of cognitive behaviour therapy and behaviour therapy for chronic pain in adults, excluding headache. *Pain, 80*(1), 1–13.
Morone, N. E., Greco, C. M., & Weiner, D. K. (2008). Mindfulness meditation for the treatment of chronic low back pain in older adults: A randomized controlled pilot study. *Pain, 134*(3), 310–319. https://doi.org/10.1016/j.pain.2007.04.038.
O'Brien, P. L., Karnell, L. H., Gokhale, M., Pack, B. K., Campopiano, M., & Zur, J. (2017). Prescribing of benzodiazepines and opioids to individuals with substance use disorders. *Drug and Alcohol Dependence, 178*, 223–230.
Olfson, M., King, M., & Schoenbaum, M. (2015). Benzodiazepine use in the United States. *JAMA Psychiatry, 72*(2), 136–142.
Park, T. W., Saitz, R., Nelson, K. P., Xuan, Z., Liebschutz, J. M., & Lasser, K. E. (2016). The association between benzodiazepine prescription and aberrant drug-related behaviors in primary care patients receiving opioids for chronic pain. *Substance Abuse, 37*(4), 516–520. https://doi.org/10.1080/08897077.2016.1179242.
Saunders, K., Von Korff, M., Campbell, C. I., Banta-Green, C. J., Sullivan, M. D., Merrill, J. O., ... Weisner, C. (2012). Concurrent use of alcohol and sedatives among persons prescribed chronic opioid therapy: Prevalence and risk factors. *Journal of Pain, 13*(3), 266–275. https://doi.org/10.1016/j.jpain.2011.11.004.
Stevens, P. E., & Keigher, S. M. (2009). Systemic barriers to health care access for US women with HIV: The role of cost and insurance. *International Journal of Health Services, 39*(2), 225–243.
Sudak, D. M. (2012). Cognitive behavioral therapy for depression. *Psychiatric Clinics, 35*(1), 99–110.
Sun, E. C., Dixit, A., Humphreys, K., Darnall, B. D., Baker, L. C., & Mackey, S. (2017). Association between concurrent use of prescription opioids and benzodiazepines and overdose: Retrospective analysis. *BMJ, 356*, j760.
Tapp, C., Milloy, M.-J., Kerr, T., Zhang, R., Guillemi, S., Hogg, R. S., ... Wood, E. (2011). Female gender predicts lower access and adherence to antiretroviral therapy in a setting of free healthcare. *BMC Infectious Diseases, 11*, 86. https://doi.org/10.1186/1471-2334-11-86.
Ti, Lianping, Nolan, Seonaid, Bohdan, N., Aghajanian, Jaffar, Cui, Zishan, Barrios, Rolando, ... on behalf of the STOP HIV/AIDS study group (2017). *Co-prescription of benzodiazepines and opioids on hospitalization rates among people living with HIV in British Columbia, Canada. Presented at the International AIDS Conference, Paris, France*. Retrieved from http://cfenet.ubc.ca/sites/default/files/uploads/IAS2017/posters/WEPEB0486-LianpingTi.pdf.
Tsai, P.-S., Chen, P.-L., Lai, Y.-L., Lee, M.-B., & Lin, C.-C. (2007). Effects of electromyography biofeedback-assisted relaxation on pain in patients with advanced cancer in a palliative care unit. *Cancer Nursing, 30*(5), 347. https://doi.org/10.1097/01.NCC.0000290805.38335.7b.
Voon, P., Callon, C., Nguyen, P., Dobrer, S., Montaner, J. S., Wood, E., ... Kerr, T. (2015). Denial of prescription analgesia among people who inject drugs in a Canadian setting. *Drug and Alcohol Review, 34*(2), 221–228.
Weisberg, D. F., Gordon, K. S., Barry, D. T., Becker, W. C., Crystal, S., Edelman, E. J., ... Kerns, R. D. (2015). Long-term prescription opioids and/or benzodiazepines and mortality among HIV-infected and uninfected patients. *Journal of Acquired Immune Deficiency Syndromes (1999), 69*(2), 223.
Weisner, C. M., Campbell, C. I., Ray, G. T., Saunders, K., Merrill, J. O., Banta-Green, C., ... Boudreau, D. (2009). Trends in prescribed opioid therapy for non-cancer pain for individuals with prior substance use disorders. *Pain, 145*(3), 287–293.
Wu, C.-H., Wang, C.-C., Katz, A. J., & Farley, J. (2013). National trends of psychotropic medication use among patients diagnosed with anxiety disorders: Results from medical expenditure panel survey 2004–2009. *Journal of Anxiety Disorders, 27*(2), 163–170.