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Sex differences in benzodiazepine use in the HIV-infected population

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Abstract

In the HIV-infected population there is a high prevalence of psychiatric disorders, conditions that often coexist with drug and alcohol dependence. Symptoms associated with psychiatric disorders are frequently managed with benzodiazepines, a class of medication often abused. We examined whether HIV-infected patients were more likely to fill a benzodiazepine prescription than their uninfected counterparts using a privately insured, nationally representative sample receiving clinical care between January 2007 and December 2009. Odds ratios (OR) and 95% confidence intervals (CI) to quantify the likelihood of receiving a benzodiazepine were calculated using multivariate logistic regression models. We examined the presence of interaction between HIV infection and sex using backward elimination and by comparing stratum specific odds ratios to identify clinically meaningful differences. Overall, 323,796 beneficiaries were included in the sample, of which 723 were HIV-infected. Bivariate analyses showed that compared to the uninfected sample, HIV-infected patients were more likely to have filled a benzodiazepine prescription (24% vs. 19%) during the study period. HIV-infected patients were also more likely to be male (80% vs. 44%), black (21% vs. 7%), and have a diagnosis of depression (12% vs. 8%) or insomnia (6% vs. 3%) than were uninfected patients. Adjusted for other covariates, HIV infection was associated with an increase (OR): 1.68, 95% CI: 1.39, 2.02) in the likelihood of filling a benzodiazepine prescription. When stratified by sex, HIV-infected males were more likely (OR: 1.68, 95% CI: 1.05, 2.67) than uninfected males to fill a benzodiazepine prescription while there was no observed difference in the likelihood of filling a benzodiazepine prescription between HIV-infected and uninfected females (OR: 1.12, 95% CI: 0.73, 1.70). Our findings suggest that HIV-infected patients, particularly HIV-infected males, are more likely to fill benzodiazepine prescriptions than their uninfected counterparts, highlighting the need for further research to investigate reasons for these observed differences.

Keywords

HIV; benzodiazepine; sex differences; psychiatric disorders; drug utilization

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INTRODUCTION

The burden of psychiatric disorders in the HIV-infected population exceeds that of the general US population (Bing et al., 2001; Pence, Miller, Whetten, Eron, & Gaynes, 2006) and the 12-month prevalence of psychiatric disorders is estimated at 48% (Bing et al., 2001). This estimate is nearly two times greater than the 26% prevalence rate estimated in the general population (Kessler et al., 2005). The most commonly detected psychiatric disorders in the HIV-infected population include major depression, dysthymia, and generalized anxiety disorder (Bing et al., 2001). Additionally, patients who suffer from psychiatric disorders are likely afflicted with symptoms of insomnia (Karaz, 2010). The estimated prevalence rate for anxiety disorders may be as high as 38% (Elliott, 1998), 32% for depression (Bing et al., 2001) and 78% for insomnia (Rubinstein & Selwyn, 1998), in the HIV-infected population. Each of these estimates exceeds those of the general population: 18% for anxiety (Kessler et al., 2005), 7% for depression (Kessler et al., 2003), and 30% for insomnia (Roth, 2007). Managing symptoms of these comorbidities is especially important in HIV-infected patients as they are associated with suboptimal adherence to antiretrovirals (Ammassari et al., 2001; Pence, Miller, Whetten, Eron, & Gaynes, 2006). High levels of adherence are necessary to achieve optimal viral load suppression and mitigate the development of drug-resistant HIV infection (Bangsberg et al., 2000; Paterson et al., 2000).

Benzodiazepines are the most frequently used psychotropic drug class (Paulose-Ram et al., 2004), and are widely prescribed for the management of symptoms related to anxiety, insomnia, and depression (Shader, Greenblatt, & Balter, 1991; Valenstein et al., 2004). Concerns exist regarding benzodiazepine use in the HIV-infected population due to potential interactions with antiretroviral therapy (Ferrando & Wapenyi, 2002; Greenblatt et al., 2000). Moreover, due to their abuse/misuse potential, benzodiazepines are not recommended for patients with a substance abuse history, a common problem among the HIV-infected population (Bing et al., 2001). To date, few studies have compared the prevalence of benzodiazepine use in the HIV-infected and uninfected populations. Furthermore, no studies have examined benzodiazepine usage by sex despite evidence suggesting prevalence rates of psychiatric disorders differ between males and females in the general and HIV-infected populations (Kessler et al., 2003; Lopes et al., 2012; Vesga-Lopez et al., 2008). The current study uses insurance claims data to examine whether HIV-infected patients are more likely to fill a benzodiazepine prescription than uninfected patients and, investigate sex differences in the likelihood of filling a benzodiazepine prescription among HIV-infected and uninfected patients.

METHODS

We established a four state nationally representative, population-based cohort using data from a large private insurance claims database from January 2007 to December 2009. This claims database includes patient socio-demographics and codes related to interactions with the healthcare system. Beneficiaries were included if they resided in Kentucky, Maryland, North Carolina, or Washington, were between 19 and 64 years of age, and had at least one healthcare claim in 2007 followed by a subsequent claim in either 2008 or 2009. Beneficiaries were identified as HIV-positive if they had at least one healthcare claim in

2007 with the ICD-9 code '042' (Human Immunodeficiency Virus (HIV) disease). The outcome of interest was filling a benzodiazepine prescription. Benzodiazepine fills during the study period were represented by a claim for any benzodiazepine identified using national drug codes. We considered the following covariates assessed in the year 2007: sex, age, race, education, state of residence, continuous insurance enrollment, substance abuse treatment (e.g. residential or non-residential treatment facility), and psychiatric disorders. Bivariate analysis examined the association between HIV-infection and benzodiazepine use. Multivariate logistic regression models adjusted for covariates identified above were used to estimate the adjusted odds ratio (AOR) of filling a benzodiazepine prescription for HIV-infected patients. We examined the presence of interaction between HIV-infection and the covariates using backwards elimination. Statistical significance was considered using the Wald χ^2 p-value associated with the interaction term as well as clinically meaningful differences by comparing stratum specific odds ratios. Data use was approved by the XXXXX Institutional Review Board. Statistical analysis was conducted using Stata 12.0 (StataCorp., College Station, TX).

RESULTS

A total of 323,902 beneficiaries met the inclusion criteria for this study. Of these beneficiaries 106 were excluded due to duplicate or conflicting information. Overall, our study cohort consisted of 323,796 beneficiaries, 723 were identified as HIV-infected. Baseline characteristics and benzodiazepine utilization for HIV-infected and uninfected patients are shown in Table 1. Compared to the uninfected population the HIV-infected population had a greater proportion of men (80% versus 44%) and blacks (21% versus 7%). The HIV-infected population also had a greater proportion of patients with a diagnosis of depression (12% versus 8%) or insomnia (6% versus 3%). We observed a greater proportion of HIV-infected patients filled a benzodiazepine prescription during the study period (24% versus 19%) with alprazolam, diazepam, and lorazepam being the most commonly filled benzodiazepines.

Figure 1 shows the AOR of filling a benzodiazepine prescription for HIV-infected patients stratified by sex relative to the overall estimate of HIV-infected patients. The overall AOR demonstrates that without stratifying by sex, HIV-infected patients have 1.68 times greater odds of filling a benzodiazepine prescription than uninfected patients (95% CI: 1.39, 2.02). When stratified by sex, results from the multivariate regression showed HIV-infected males are 1.68 times more likely to fill a benzodiazepine prescription than uninfected males, adjusting for covariates (95% CI: 1.05, 2.67), while no statistical difference was observed between HIV-infected and uninfected females (AOR: 1.12, 95% CI: 0.73, 1.70). Interaction between HIV-infection and age, race, education, substance abuse treatment, and psychiatric disorders was considered but statistical significance was not achieved at the 0.05 level nor were there any clinically meaningful differences between the strata.

In the overall population the likelihood of filing a benzodiazepine prescription is influenced by the patient's age, sex, and race, along with treatment for substance abuse and psychiatric disorder diagnosis. With each additional ten years patients age, their odds of filling a benzodiazepine prescription increase 21% (AOR: 1.21, 95% CI: 1.20, 1.22). Additionally,

males are less likely than females (AOR: 0.62, 95% CI: 0.61, 0.63) and nonwhite patients are less likely than white patients to fill a benzodiazepine prescription (AOR: 0.72, 95% CI: 0.70, 0.74). Furthermore, treatment for substance abuse (AOR: 1.27, 95% CI: 1.14, 1.42), or having a diagnosis of anxiety (AOR: 5.99, 95% CI: 5.81, 6.18), depression (AOR: 2.48, 95% CI: 2.42, 2.56), or insomnia (AOR: 2.78, 95% CI: 2.65, 2.90) increase the odds of filling a benzodiazepine prescription.

DISCUSSIONS

This study demonstrates that HIV-infected patients are more likely to fill a benzodiazepine prescription than uninfected patients. Furthermore, we show HIV-infected males are more likely than uninfected males to fill a benzodiazepine prescription, with no observed difference between HIV-infected and uninfected females. This difference is notable as concerns exist regarding benzodiazepine use in the HIV-infected population due to their high abuse/misuse potential and the link between substance abuse and poor medication adherence (Arnsten et al., 2002; Singh et al., 1996).

The overall difference in the odds of filling a benzodiazepine prescription between HIV-infected and uninfected patients may be related to the high prevalence of psychiatric disorders in this population (Bing et al., 2001). However, we adjusted for these conditions in our models suggesting additional factors shown to be associated with benzodiazepine use in this population and not captured within claims data, such as exposure to stressful events related to HIV serostatus and disclosure (Roux et al., 2011), may explain the differences in benzodiazepine use between the HIV-infected and uninfected populations. The high prevalence of substance abuse and dependence in the HIV-infected population (Bing et al., 2001) should also be considered as an explanation of the observed differences in benzodiazepine use. Few studies have compared benzodiazepine use in the HIV-infected and uninfected populations and to our knowledge, this study is the first to examine differences in receipt of benzodiazepines by sex. Roux et al. (2011), investigated factors associated with regular benzodiazepine use in HIV-infected patients but as this study included HIV-infected patients only, comparisons to the uninfected population were not made (Roux et al., 2011).

Reasons for observed differences between males and females in our study may be related to underlying differences in the prevalence of psychiatric disorders, differences in stigmatization, as well as differences in overall health care utilization between HIV-infected men and women. Lopes et al. (2012), showed HIV-infected men were more likely than uninfected men to have a specific DSM-IV diagnosis with no observed differences among women. Our results support these findings as we found HIV-infected men more likely than uninfected men to fill a benzodiazepine prescription, with no observable differences between women. Additionally, Roux et al. (2011), found that individuals belonging to the injecting drug use (IDU) and men who have sex with men (MSM) HIV-transmission groups were more likely than their heterosexual HIV-transmission group counterparts to report regular benzodiazepine use. This finding is likely associated with IDUs and MSM group members perceiving and facing greater discrimination and stigmatization (Herek, Capitano, & Widaman, 2003). Evidence exists of differences in healthcare utilization between HIV-

infected men and women. Hellinger and Encinosa (2004) found HIV-infected men were more likely than HIV-infected women to receive antiretroviral therapy and costlier medications.

Limitations to this study exist. First, this study uses data from a private insurance claims database for four states, and may not accurately represent the overall HIV-infected or uninfected populations. Also, this study does not account for the number of benzodiazepine prescriptions filled or the quantity and dosages of those prescriptions. Additionally, we cannot account for prescriptions acquired through family and friends or paid for using cash. Finally, while our results show HIV-infected patients are more likely to fill a benzodiazepine prescription, we did not differentiate between appropriate and inappropriate use.

Despite these limitations, our findings demonstrate HIV-infected patients, especially HIV-infected males, are more likely to use benzodiazepines. Our findings, in combination with evidence demonstrating sex differences in psychiatric disorders, show the need for further research evaluating reasons for observed differences. Furthermore, intervention studies targeting this at-risk population to reduce the risk of substance abuse and improve HIV clinical care are warranted.

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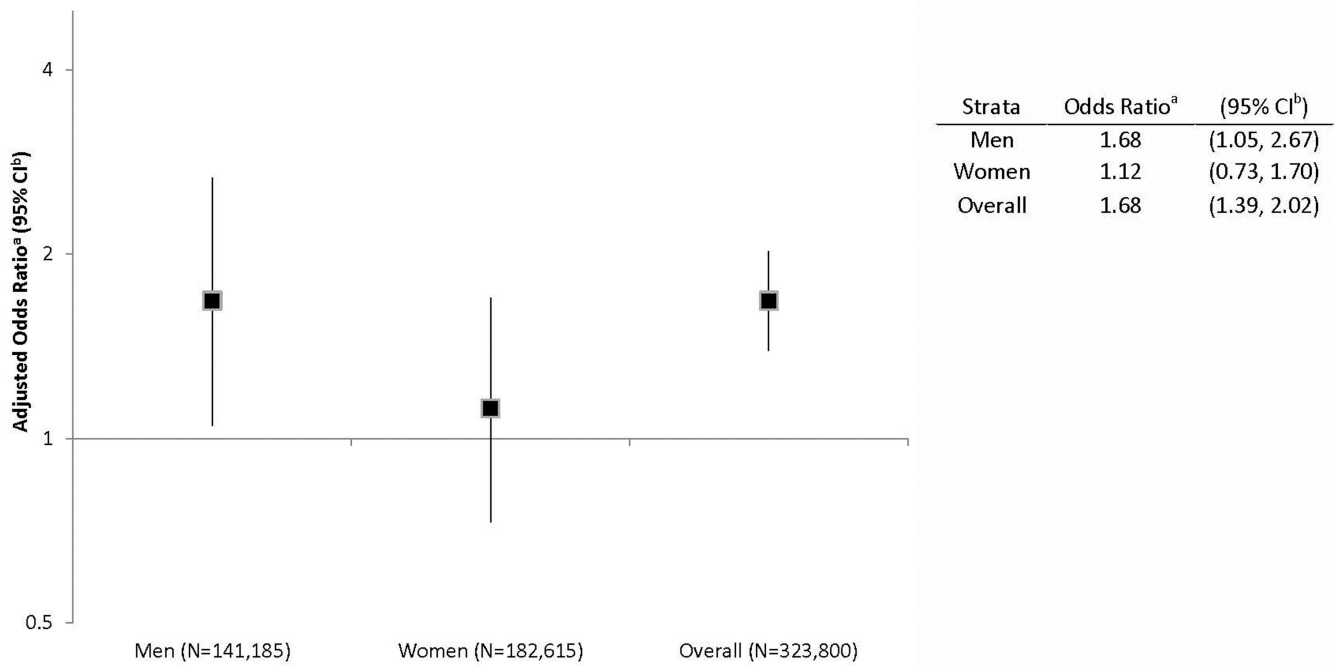


Figure 1. Likelihood of filling a benzodiazepine prescription among HIV-infected individuals compared to HIV-uninfected individuals stratified by sex. ^aAdjusted for state of residence, age, race, education, and enrollment eligibility (e.g., continuous insurance coverage, gaps in insurance coverage). ^bCI: Confidence Interval.

Table 1

Comparison of demographics of HIV-infected and HIV-uninfected patients.

Variables	HIV N = 723		HIV-uninfected N = 323,073		p-value
	N	%	N	%	
Benzodiazepine Usage					
Filled Benzodiazepine Prescription	174	24%	60,420	19%	< 0.001
State of Residence					
Kentucky	67	9%	36,698	11%	0.077
Maryland	193	27%	59,635	18%	< 0.001
North Carolina	339	47%	177,680	55%	< 0.001
Washington	124	17%	49,060	15%	0.141
Sex					
Male	578	80%	140,605	44%	< 0.001
Age					
Mean Age (for year 2007), SD ^a	43.02	8.83	41.98	11.46	0.015
Race					
White	483	67%	255,735	79%	< 0.001
Black	155	21%	23,085	7%	< 0.001
Hispanic	32	4%	11,501	4%	0.209
Other	49	7%	29,917	9%	0.021
Education					
Less than High School	6	1%	2,023	1%	0.488
High School Graduate	237	33%	112,330	35%	0.262
Some College	345	48%	139,963	43%	0.017
College Graduate	118	16%	60,340	19%	0.104
Psychiatric Diagnosis					
Anxiety	47	7%	21,386	7%	0.989
Depression	84	12%	26,026	8%	< 0.001
Insomnia	44	6%	9,973	3%	< 0.001
Substance Abuse Treatment					

<i>Variables</i>	<i>HIV</i> N=723		<i>HIV-uninfected</i> N = 323,073		<i>p-value</i>
	N	%	N	%	
Receiving Substance Abuse Treatment	5	1%	1,941	1%	0.752
Enrollment Eligibility					
Continuously Eligible	284	39%	145,518	45%	0.002
Gaps in Coverage	439	61%	177,555	55%	0.002

^aSD: Standard Deviation