High-dose prescribed opioids are associated with increased risk of heroin use among US military veterans

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1. Introduction

The proliferation of prescription opioids for the treatment of chronic pain has been associated with significant increases in the non-medical use of prescription opioids, opioid use disorder, and opioid overdose deaths [5, 13, 58]. The prescription of high dose opioids, typically defined as morphine equivalent daily doses (MEDD) of 90 or more milligrams, is specifically associated with adverse drug events [9, 19, 21, 37, 52], morbidity and mortality [23]. Long-term opioid therapy (LTOT) has also been associated with the development of opioid use disorder (OUD); [23] the risk of incident OUD is greater with higher dose and longer duration of LTOT [9, 21, 47]. Despite the substantial body of evidence linking an increased risk of OUD with specific prescription opioid use patterns [41], the association between receipt of prescription opioids and subsequent heroin use is less understood. The use of heroin increases the risk of opioid-attributable overdose, the exposure to potential contaminants such as illicitly manufactured fentanyl, and an increased likelihood of acquisition and transmission of blood borne diseases such as HIV and hepatitis C virus [8, 34, 46].

Understanding the relationship between prescription opioid use and initiation of heroin use among veterans is particularly important. Clinicians may prescribe opioids to men and women during military service or soon after discharge to address injuries sustained during combat, chronic pain, and/or psychological and physical ailments that can arise while readjusting to civilian life [27]. Prior studies conducted by our research team have shown that hydrocodone, codeine, and oxycodone are the three most common opioids prescribed to US veterans engaged in care [20]. A recent report from the Department of Veterans' Affairs (VA) notes that more than one million US veterans engaged in care in the VA health system receive prescription opioids for pain, and nearly half of them continue beyond 90 days [22, 53]. Appropriate prescribing of opioids to this population, with a higher underlying prevalence both of substance use disorders and of pain conditions than the general population, is particularly nuanced and challenging [3, 5, 28].

The impact of prescription opioid receipt on subsequent heroin use is a phenomenon that has been described in the US mainstream media and among particular subpopulations [10, 33, 38, 49, 55], but the scope of this issue among veterans is still largely unexplored. In the current era, regular heroin use among the treatment-seeking general population is often preceded by non-medical use of prescription opioids [14]. We recently demonstrated that non-medical use of prescription opioids (NMUPO) was a strong and independent predictor of heroin initiation among veterans receiving care in the VA [4]. However, it is less clear how receipt of prescription opioids from a VA provider is associated with later heroin use. A better understanding of the relationship between specific opioid prescribing practices and the subsequent use of heroin could assist in creating strategies that mitigate such risk in veterans.

2. Material and methods

2.1 Data

This study used longitudinal behavioral and pharmacy fill/refill data from the Veterans Aging Cohort Study (VACS); detailed data collection and survey methodology for VACS are previously described [35, 36]. In brief, the VACS is a prospective cohort study of military veterans living with HIV and uninfected veterans receiving medical care at eight US VA sites. Since June of 2002, VACS has enrolled more than 7,000 patients from the Infectious Disease or General Medical clinics in Atlanta, Baltimore, Houston, Los Angeles, Pittsburgh, Washington DC and multiple sites in New York City. This longitudinal study contains variables from six follow-up behavioral surveys, completed approximately every 18 months, from 2002 to 2012. The survey data are linked to robust VA electronic medical records (EMR) containing data on prescribed medications based on pharmacy dispensing, medical diagnoses, and laboratory results for each patient. The VACS was approved by the institutional review boards at each participating VA Medical Center and affiliated academic institutions.

2.2 Participant eligibility

Of the 7,502 VACS participants who were potentially eligible for inclusion in our study because they had completed at least one survey, we excluded 689 (9.2%) of participants who reported any illicit opioid use (including heroin and non-medical use of prescription opioids) in the year prior to the first survey the patient completed (baseline survey). We also excluded participants who were never prescribed opioids from the VA during the 10 years of follow-up, n=2980 (39.7%), as well as participants who did not complete at least one additional follow-up survey, n=263 (3.5%). The final analytic sample consisted of 3,570 veterans. In all analyses, dropout was defined as a failure to complete any additional surveys after the baseline survey, while having been enrolled in the VACS study for greater than or equal to 2 years.

2.3 Primary exposures

Consistent with the methods outlined in previous VACS analyses using prescription opioid data from pharmacy records [20, 24, 58], we determined receipt of all outpatient opioids, including codeine, hydrocodone, oxycodone, oxycodone, morphine, fentanyl, hydromorphone, methadone for the treatment of pain, tramadol and propoxyphene. We then determined: 1) the average MEDD supplied in the year prior to each follow-up survey; and 2) number of days supplied in the year prior to each follow-up survey, starting with the baseline survey. Average MEDD was dichotomized into high dose (90 mg) and low dose (<90mg). This definition of high-dose prescription opioid receipt was based on VA and CDC opioid prescribing guidelines [2, 18]. The number of days supplied in the year prior was used to create a dichotomous indicator variable for long-term opioid therapy, defined as 90 days of continuous use, allowing for a 30 day gap between fill/refill in a given year [44]. We also categorized opioids into short-acting (i.e., with a duration of action generally less than 12 hours) versus long-acting medications (including sustained- and extended-release products), according to Drug Enforcement Administration classifications [56].

2.4 Primary outcome

Self-reported heroin use during the follow-up surveys was ascertained starting with a participant's first follow-up survey and was based on the time-updated survey item: "How often in the past year you used each drug – Heroin?" Past year heroin use was defined as any change in respondent's answer to the previous survey question from "Never" or "No use in the last year", to indicating any frequency of heroin use in the previous year. We used the date of the corresponding survey to approximate the date of past year heroin use.

2.5 Confounders and other covariates

Selection of independent variables and potential confounders that were included in the analysis was based on a review of prior literature [17, 32, 40, 43, 45]. Baseline VACS survey demographics included age, sex, race/ethnicity, marital status, employment status, and gross annual income. HIV status was identified using VA Immunology Case Registry and Hepatitis C virus status was determined using International Classification of Disease (ICD)-9 codes and laboratory data. Level of social isolation was ascertained from responses to the following baseline survey items: "How often do you see or hear from relatives or close friends? Would you say less than once a month, about once a month, a few times a month, a few times a week, every day?" and "How many close friends or family do you have with whom you feel at ease, can talk about private matters, or can call on for help?" We determined whether the participant had ever been homeless or stayed at a homeless shelter from the following questions on the baseline survey: "Have you ever been without a permanent address that you call home?" and "Have you ever stayed one or more nights in a shelter, on the street, in a park or an abandoned building?" Additionally, we included time-updated survey variables for: other drug use (including marijuana, cocaine, and methamphetamines); unhealthy alcohol use; and diagnoses of post-traumatic stress disorder (PTSD) and major depression. Any past-year use of marijuana, cocaine and methamphetamines was dichotomized as yes/no. Unhealthy alcohol use was characterized using the Alcohol Use Disorders Identification Test (AUDIT)-C; a score of 4 and above indicated unhealthy alcohol use for men, and a threshold of 3 for women [16, 42]. Diagnoses of PTSD, major depression, and opioid use disorder were ascertained from ICD-9 codes and updated at every survey wave. Pain interference in daily life was ascertained from responses to the following time-updated survey item: "During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?" We dichotomized participants' responses into "some amount of pain interference in daily life" vs. "no pain interference in daily life".

2.6 Analysis

We analyzed patterns of opioid prescribing over time for each of the six follow-up waves using the Cochran-Armitage test for trend. We used χ^2 or Fisher's exact tests to examine the baseline correlates of receipt of high dose prescription opioids, as well as past year heroin use at any time over the follow-up period. Unadjusted Kaplan–Meier analysis and the log-rank test were then used to calculate the incidence of past year heroin use and compare time to first report of heroin use during follow-up, stratifying by the past year receipt of high-dose opioid prescription at baseline and past year receipt of long-term opioid therapy,

respectively. Next, we used Cox proportional hazards regression to estimate crude hazard ratios (CHRs) and 95% confidence intervals (CIs) related to factors associated with heroin use. We then constructed a separate multivariable Cox model, including all variables assessed in bivariable analyses, for the two main exposure variables: prior receipt of high-dose opioid prescription and prior receipt of long-term opioid therapy. All variables were found to meet the proportional hazards assumption for the Cox regression models (i.e. none exhibited significant deviance from this assumption at $p < 0.05$) [12]. Since employment status was highly correlated with education ($p<0.001$) and income ($p<0.001$), we did not include it in the fully adjusted final model.

We created inverse probability of censoring weights (IPCW) to account for potential biases arising from differential dropout. Weights were obtained through fitting a weighted pooled logistic regression model for dropout, including baseline and time-varying predictors of dropping out, defined as not completing all six follow-up surveys. We included a robust sandwich estimator in all Cox regression models to account for potential clustering heterogeneity by study site, and the estimation required to create the weights [29, 31]. Analyses were conducted using SAS version 9.4.

2.7   Sensitivity Analyses

To address the potential for confounding and selection bias due to the inclusion of time-updated covariates affected by prior exposure using a standard regression approach, we conducted a sensitivity analysis using inverse probability of treatment and censoring weights [15]. In brief, we used weighting to create a pseudo-population in which exposure and dropout were independent of measured confounders. We used pooled logistic models to estimate the inverse of the probability of each participant's probability of receiving a high-dose prescription opioid and receiving long-term opioid therapy, respectively. The numerator of the stabilized weights included baseline covariates that predicted the probability of the exposure, and the denominator included baseline and time-updated covariates that were included in the main analysis. We examined the weights for means, standard deviations, and extreme minimum and maximum values. Finally, we conducted a sensitivity analysis in which opioid dose was categorized as a three-level variable: low (0–49 MME), medium (50–89 MME), and high (90 MME).

3.   Results

3.1   Sample Composition

The mean age of VACS members in the final analytic sample was 49.8 (SD = 9.0 years); 2302 (65.1%) participants were black, 324 (9.2%) were Hispanic, and 764 (21.6%) were white. The majority of participants were male (94.5%); approximately half of them were living with HIV and 32.9% were positive for hepatitis C virus infection. At baseline, 235 (6.6%) participants reported ever having engaged in injection drug use, and 38.6% reported having ever spending the night in a homeless shelter, street, or abandoned building. At baseline, 28.0% of participants reported that they were currently working for wages, 9.9% reported that were currently seeking employment and unemployed for less than one year, 33.4% reported that they were currently unable to work, 7.6% reported being self-employed,

and 16.2% reported being retired. Of the 3,570 participants who were in the analytic sample, 1160 (32.5%) were lost to follow-up over the study period.

3.2 Trends in prescription opioid receipt from the VA

Of the 3,570 eligible participants, the proportion of study participants who were receiving high-dose prescription opioids (≥ 90 mg MEDD) did not change over the follow-up period and ranged from 4.4% to 5.9% (Cochran-Armitage test for trend $p = 0.222$). The proportion receiving long-term opioid therapy (≥ 90 consecutive days) steadily increased from 23.3%, in 2002 to 39.9%, in 2012 (Cochran-Armitage test for trend $p<0.001$). A vast majority of participants received only short-acting opioids from the VA (see Table 1).

3.3 Risk factors for past year heroin use

Over the 10-year follow-up period, 174 (4.9%) participants reported past year heroin use. At baseline, study participants who reported past year heroin use were more likely to be Black, report a lower gross annual income, report past year cocaine and methamphetamine use, and have experienced homelessness and social isolation. (Table 2)

The ten-year unadjusted incidence rate of past year heroin use was 8.15 events per 1,000 person-years. Time to past year heroin use differed significantly between participants who had prior receipt of a high-dose prescription opioid at baseline and participants who had no prior receipt of high-dose opioids; the log-rank test was significant at $p<0.001$. (Figure 1)

In contrast, the rate of past year heroin use did not differ significantly between participants who had long-term prior receipt of prescription opioids and participants who had short-term prior receipt of prescription opioids ($p=0.469$, figure not shown). The rate of past year heroin use did not vary significantly between participants receiving short-acting opioids, long-acting opioids, or both (data not shown).

Prior receipt of a high-dose opioid prescription opioid, having HCV infection, fewer years of education, diagnosis with PTSD, diagnosis with depression, and self-reported pain interference were all significantly associated with an increased risk of past year heroin use in unadjusted Cox regression analyses (Table 3). In the first fully adjusted and weighted multivariable Cox regression analysis, prior receipt of high-dose prescription opioids from the VA was positively and significantly associated with past year heroin use (adjusted hazard ratio [AHR] = 2.54, 95% CI = 1.26–5.10, see Table 4). In the second fully adjusted Cox regression model, prior receipt of long-term opioid therapy from the VA was not significantly associated with past year heroin use (AHR =1.09, 95% CI = 0.75–1.57). Being age 50–56 years, compared to participants younger than 42 years of age, having HCV infection, past year cocaine use, and past year stimulant use all significantly increased the hazard of past year heroin use in both models. In addition, participants reporting pain interference in daily life had an increased risk of heroin use.

3.4 Sensitivity Analyses

The Cox regression with prescription opioid dose categorized into low, medium, and high revealed that participants receiving a medium dose versus a low dose did not have a

significantly increased CHR of past year heroin use. In the fully adjusted model, high dose compared to low dose was positively and significantly associated with past year heroin use (AHR = 3.16, 95% CI = 1.75–5.68).

The stabilized inverse probability of exposure weights were statistically well-behaved for both primary exposures of interest. The mean of the weights for receipt of high-dose prescription opioids was 0.99 (SD= 0.23) and they ranged from 0.25 to 4.51. The mean of the weights for receipt of a long-term prescription opioid was 1.00 (SD= 0.30) and they ranged from 0.18 to 3.61. In the sensitivity analysis with treatment and censoring weights, participants who received high-dose prescription opioids from the VA had 2.11 the hazard of past year heroin use compared to participants who received prescription opioids in doses less than 90 mg MEDD (95%CI: 1.30–3.43). The receipt of long-term opioid therapy from the VA was not significantly associated with past year heroin use in the sensitivity analysis.

4. Discussion

In this study, we examined the relationship between specific opioid prescribing patterns and subsequent heroin use in a population of US military veterans receiving medical care in the VA system. Our results indicate that, among veterans who reported no past year illicit opioid use at baseline and who received prescription opioids from the VA, prior receipt of high-dose prescription opioids increased the risk of subsequent heroin use.

Our findings are broadly consistent with the literature, which shows that veterans who use heroin are also more likely to engage in polysubstance use, including use of non-opioid illicit drugs [50, 51]. The proportion of participants who reported past year heroin use at each year of follow-up was slightly higher than the percent of individuals who reported past year heroin use in the 2013 National Survey of Drug Use and Health [38]. However, we suggest caution when comparing our study results to those of a national survey of the general population, since by design, all study participants received opioid analgesics at least once during the study period, and approximately half were persons living with HIV. Both of these eligibility criteria likely elevated the probability of heroin use over the study period. However, by identifying a population with a higher prevalence of risk factors for future heroin use, clinicians can more appropriately direct these patients to overdose education and naloxone distribution [48] in hopes of reducing the risk of potential heroin attributable overdoses.

At baseline, study participants who reported past year heroin use were more likely to be Black. Additionally, Black participants were at an increased risk of past year heroin use in the unadjusted Cox regression analyses. However, in multivariable models, the adjusted rate of past year heroin use did not differ significantly between Black participants and participants of other races. It is possible that variables serving as proxies for structural inequalities and included in the final model (e.g. education, income), confounded the association between race and past year heroin use. As greater levels of education and a higher number of close friends/family were protective against past year heroin use in our study, involvement with support groups and improved access to opioid safety and overdose prevention programs may mitigate the risk of future heroin use. Additionally, peer

engagement and outreach programs have proven to be an effective intervention in encouraging treatment-seeking for opioid use disorders, as well as for connecting veterans to evidence-based approaches to addiction treatment (e.g., opioid agonist treatment with methadone or buprenorphine, non-pharmacologic treatments) [7].

Our findings suggest that diagnosis and treatment of psychiatric disorders are important considerations when prescribing opioid therapy, though existing guidelines concerning the use of opioids vary widely in their recommendations regarding patients with co-morbid depression and other psychiatric disorders [54]. Lower household wealth is associated with chronic pain that substantially limits participation in daily activities [30]. Therefore, the fact that work-related pain interference in daily life remained associated with an increased risk of past year heroin use in the fully adjusted model suggests that patients may be engaging in heroin use to alleviate pain that has not been adequately addressed by prescription opioid therapy and that efforts to reduce the burden of disabling chronic pain should prioritize socioeconomically vulnerable groups

More than half of VA primary care patients report pain, with many reporting chronic pain; however, current VA/Department of Defense opioid therapy guidelines recommend use of long-acting opioids only for persistent pain, and prescription of opioid therapy for chronic pain only after other non-opioid analgesic pharmacotherapies and non-pharmacologic pain treatments have insufficiently improved pain-related function [39]. Though our results further substantiate current VA and CDC opioid prescribing guidelines, which recommended prescribing opioids for short durations and recommend against prescribing opioids in doses greater than 90 mg MEDD [1], Gaither and colleagues found that, from 1998 to 2010, the majority of VA patients initiating long-term opioid therapy did not receive opioid therapy guideline-concordant care (although older guidelines were in effect when this study was published.) [24] Future research is needed to determine the extent to which opioid prescribing is consistent with current guidelines.

We posit that prior receipt of long-term opioid prescriptions was not associated with past year heroin use because our data were collected prior to the enactment of recent CDC and VA/DOD guidelines regarding the tapering of prescription opioids, and it is unlikely that opioid tapering and/or abrupt discontinuation of opioid therapy drove patients to engage in heroin use during this time period [18]. Nonetheless, future studies should examine whether abrupt discontinuation or inappropriate tapering of opioid therapy is associated with an increased risk of transitioning to heroin use among veterans and high-risk populations. This is particularly important in the context of the VA's Opioid Safety Initiative, which strongly encourages opioid tapering, if not discontinuation, without explicit examination of unintended harms of this initiative [60]. It is essential to continue addressing unmet pain management needs of veterans, as is also recommended by guidelines from the American College of Physicians, which specifically recommends increased use of non-opioid pharmacological and non-pharmacological approaches [11].

Our study had a number of limitations. First, there is a potential for confounding by indication, whereby patients at higher risk of heroin use were also more likely to receive high-dose prescription opioids. We addressed this by using inverse probability weighting

methods, and creating weights based on patients' probability of receiving high dose opioids, conditioned on a comprehensive list of potential, time-updated confounders [59]. Second, our exposure data was based on pharmacy fill/refill records from the VA, and we were not able to account for opioid prescriptions filled outside of the VA [25, 26]. One recent study demonstrated that 18% of veterans receive opioids both inside and outside of the VA [6]. In that vein, receipt of a prescription opioid prescription may not have accurately captured the true amount of opioids actually being taken by VACS participants. There is also some likelihood of measurement error and bias in our outcome variable: past year heroin use. While this variable captures self-report of any heroin use in the ten-year follow-up period, we were not able to discern whether this is truly lifetime incident heroin use or represents re-initiation of heroin use. We only used a single domain (e.g. work-related interference) to measure pain interference in daily life. The complexity of chronic pain and its interference in daily activities is likely not fully captured by this question. Additionally, almost 50% of participants reported being retired or unable to work at baseline, which may have affected the validity and measurement of this item. Moreover, as we did not measure employment status over time, we are unable to examine whether daily pain interfered in employment status, or loss of employment related to chronic pain increased the risk of heroin use. Despite these limitations, our study has important implications for clinical care, policy and future research. The finding that prior receipt of a high-dose prescription opioid may increase the risk of past year heroin use among veterans receiving care at the VA supports the current CDC and VA guidelines that recommend prescribing opioid at lower doses. Our results indicate that further efforts are needed to develop effective screening strategies to identify heroin use among those prescribed high dose opioids.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

7. References

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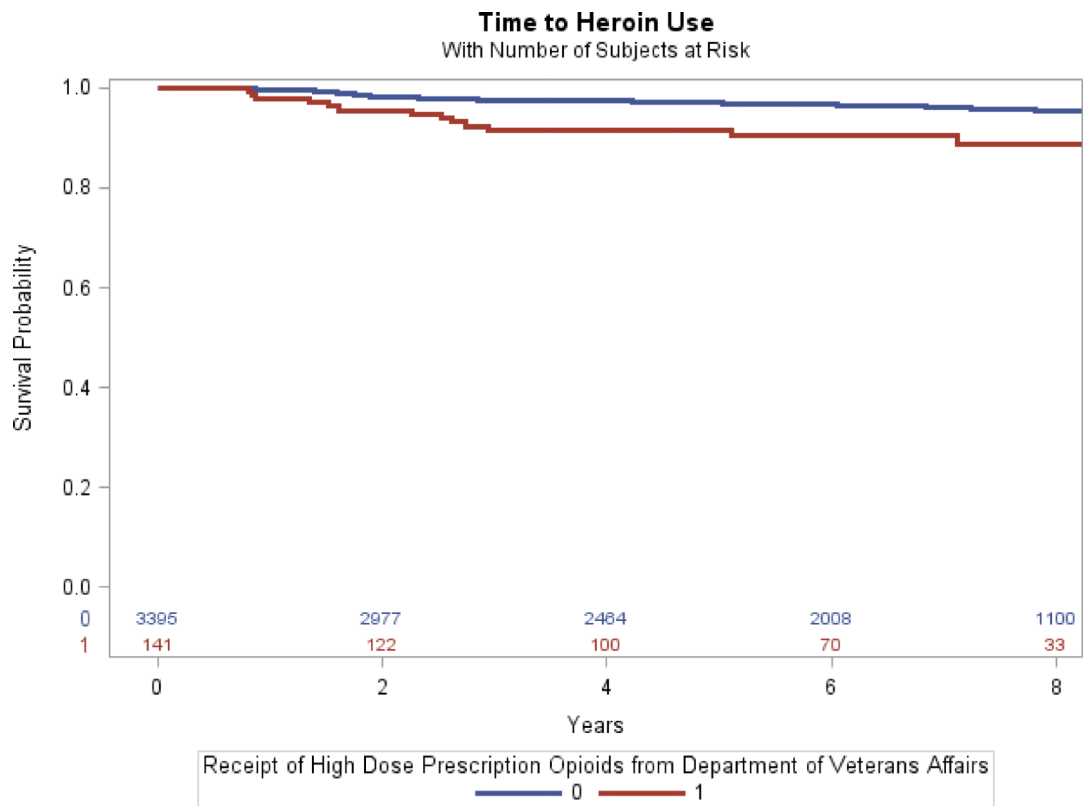
Time to Heroin Use
With Number of Subjects at Risk

Figure 1.
Relationship between receipt of high-dose prescription opioids and past year heroin use among VACS participants 2002–2012

Note: 0=No prior receipt of high dose prescription opioids; 1=Prior receipt of high dose prescription opioids

Table 1.

Characteristics of prescription opioid dose and duration dispensed to VACS participants, 2002–2012

Survey	BL	1	2	3	4	5	6
Days of Consecutive Opioid Rx Use, Previous Year							
Short-Term Use (≥1 day & <90 days)	1188 (76.7%)	511 (67.1%)	754 (67.4%)	767 (66.0%)	807 (61.1%)	789 (62.0%)	745 (60.1%)
Long-Term Use (≥90 days)	361 (23.3%)	251 (32.9%)	365 (32.6%)	395 (34.0%)	514 (38.9%)	483 (38.0%)	494 (39.9%)
Opioid Rx MEDD, Previous Year							
1–50mg	1353 (88.7%)	665 (88.0%)	977 (88.5%)	1011 (87.7%)	1156 (88.6%)	1123 (88.8%)	1108 (89.6%)
51–90mg	104 (6.8%)	49 (6.5%)	69 (6.2%)	74 (6.4%)	86 (6.6%)	84 (6.6%)	74 (6.0%)
90mg	68 (4.5%)	42 (5.5%)	58 (5.2%)	68 (5.9%)	62 (4.7%)	58 (4.6%)	54 (4.4%)
Median MEDD in mg (IQR)	31.1 (13.4–48.8)	32.0 (13.2–50.7)	34.5 (16.0–53.0)	39.1 (21.4–56.8)	40.6 (23.5–57.7)	40.3 (24.6–56.0)	37.1 (21.2–53.0)
Opioid Formulation							
Short-Acting Only	1113 (81.7%)	386 (78.1%)	626 (79.6%)	602 (77.6%)	752 (81.2%)	775 (82.3%)	807 (84.7%)
Long-Acting Only	54 (4.0%)	33 (6.7%)	41 (5.2%)	67 (8.6%)	59 (6.4%)	45 (4.8%)	45 (4.7%)
Both	195 (14.3%)	75 (15.2%)	119 (15.1%)	107 (13.8%)	115 (12.4%)	122 (13.0%)	101 (10.6%)

Note: mg=milligrams; Rx=prescription; MEDD=morphine-equivalent daily dose; IQR=Interquartile Range

Table 2.

Baseline characteristics associated with recent heroin use among veterans participating in VACS, 2002–2012

| Characteristic | Total (%) (*N* = 3,570) | Reported Recent Heroin Use | | *p* – value* |
		Yes (%) (*N* = 174)	No (%) (*N* =3,396)	
Sex				0.025
Male	3373 (94.5)	171 (98.3)	3202 (94.3)	
Age				0.005
42 years	708 (19.8)	32 (18.4)	676 (19.9)	
43–49 years	1043 (29.2)	61 (35.1)	982 (28.9)	
50–56 years	1146 (32.1)	65 (37.4)	1081 (31.8)	
57 years	673 (18.8)	16 (9.2)	657 (19.3)	
HIV Infection				<0.001
Yes	1830 (51.3)	116 (66.7)	1714 (50.5)	
HCV Infection				<0.001
Yes	1117 (32.9)	126 (74.1)	991 (30.8)	
Race				<0.001
White	764 (21.6)	14 (8.2)	750 (22.3)	
Black	2302 (65.1)	133 (77.8)	2169 (64.5)	
Hispanic	324 (9.2)	14 (8.2)	310 (9.2)	
Other	144 (4.1)	10 (5.8)	134 (4.0)	
Education				<0.001
High School or Less	1409 (39.9)	93 (54.7)	1316 (39.2)	
Some College or Greater	2119 (60.1)	77 (45.3)	2042 (60.8)	
Currently Employed				<0.018
Yes	997 (28.0)	35 (20.1)	962 (28.4)	
Gross Annual Income				<0.001
<$6,000	713 (20.7)	59 (35.3)	654 (20.0)	
$6,000 - $11,999	896 (26.1)	54 (32.3)	842 (25.7)	
$12,000 - $24,999	880 (25.6)	28 (16.8)	852 (26.0)	
$25,000 - $49,999	684 (19.9)	25 (14.9)	659 (20.1)	
$50,000	265 (7.7)	1 (0.6)	264 (8.1)	
Marital Status				0.024
Married/Living with Partner	1064 (30.1)	38 (22.2)	1026 (30.5)	
Divorced/Separated/Widowed	1491 (42.2)	88 (51.5)	1403 (41.8)	
Never Married	975 (27.6)	45 (26.3)	930 (27.7)	
Smoke Cigarettes				<0.001
Never	860 (24.4)	21 (12.4)	839 (25.0)	
Current	1734 (49.1)	122 (72.2)	1612 (48.0)	
Former	936 (26.5)	26 (15.4)	910 (27.1)	
Marijuana use, Past Year				0.497

| Characteristic | Total (%) (N = 3,570) | Reported Recent Heroin Use | | p – value* |
		Yes (%) (N = 174)	No (%) (N = 3,396)	
Yes	793 (23.0)	42 (25.1)	751 (22.9)	
Stimulant use, Past Year				0.001
Yes	92 (2.7)	12 (7.3)	80 (2.5)	
Cocaine use, Past Year				<0.001
Yes	599 (17.4)	54 (32.5)	545 (16.6)	
Any Injection Drug Use, Lifetime				<0.001
Yes	235 (6.6)	46 (26.4)	189 (5.6)	
Diagnosed Opioid Use Disorder, Past Year				<0.001
Yes	205 (5.7)	54 (31.0)	151 (4.4)	
Unhealthy alcohol use, Past Year (AUDIT-C score 3 or 4)				0.196
Yes	1393 (39.0)	76 (43.7)	1317 (38.8)	
Ever without a permanent address to call home				<0.001
Yes	1496 (42.1)	101 (58.0)	1395 (41.2)	
Ever stayed one or more nights in homeless shelter				<0.001
Yes	1373 (38.6)	101 (58.0)	1272 (37.7)	
Diagnosed PTSD, Past Year				0.135
Yes	408 (11.4)	26 (14.9)	382 (11.2)	
Diagnosed Major Depressive Disorder, Past Year				0.010
Yes	467 (13.1)	34 (19.5)	433 (12.7)	
Pain Interference in Daily Life, Past Year				0.342
Yes	1122 (69.4)	33 (63.5)	1089 (69.6)	
# Close Friends/Family				<0.001
None	400 (11.3)	34 (19.6)	366 (10.8)	
1–4	2297 (64.7)	110 (63.6)	2187 (64.8)	
5	853 (24.0)	29 (16.8)	824 (24.4)	
How often you see friends/family				0.039
< once a month	687 (19.6)	45 (26.2)	642 (19.2)	
Monthly	1008 (28.7)	52 (30.2)	956 (28.6)	
Weekly/Daily	1816 (51.7)	75 (43.6)	1741 (52.1)	
Receipt of High-Dose Opioid Rx from the VA				0.754
Yes	68 (4.5)	3 (4.8)	65 (4.4)	
Receipt of Long-term Opioid Rx from the VA				0.878
Yes	361 (23.3)	15 (24.2)	346 (23.3)	

Note:

*
From Chi-square tests or Fisher's exact tests

HIV=Human Immunodeficiency Virus; HCV=Hepatitis C Virus; PTSD=Post Traumatic Stress Disorder

Table 3.

Inverse probability of censoring weighted unadjusted Cox proportional hazard model of factors associated with time to self-reported past year heroin use among veterans receiving prescription opioids from the VA, participating in VACS, 2002–2012

Characteristic	CHR[*][†] (95% CI)	P – value
Receipt of High-Dose Opioid Rx from the VA (ref: low dose)	2.52 (1.69–3.76)	<0.001
Receipt of Long-term Opioid Rx From the VA (ref: short-term)	0.87 (0.56–1.35)	0.531
MEDD of Opioid Prescription (ref: low dose (1–50mg))		
Medium Dose (50–90mg)	1.40 (0.83–2.35)	0.211
High Dose (90mg)	2.58 (1.73–3.85)	<0.001
Sex (ref: Female)	2.22 (0.80–6.15)	0.126
Age (ref: 42 years)		
43 – 49 years	1.16 (0.59–2.30)	0.659
50 – 56 years	1.25 (0.84–1.88)	0.273
57 years	0.54 (0.25–1.16)	0.113
HIV (infected versus uninfected)	1.62 (1.12–2.35)	0.010
HCV (infected versus uninfected)	7.81 (6.17–9.88)	<0.001
Race (ref: White)		
Black	3.13 (1.96–4.99)	<0.001
Hispanic	2.38 (0.92–6.18)	0.074
Other	4.54 (2.65–7.78)	<0.001
Education (ref: High School or Less)		
Some College or Greater	0.56 (0.42–0.76)	<0.001
Currently Employed (yes versus no)	0.65 (0.53–0.79)	<0.001
Gross Annual Income (ref: <$6,000)		
$6,000 - $11,999	0.72 (0.57–0.91)	0.006
$12,000 - $24,999	0.41 (0.26–0.65)	<0.001
$25,000	0.30 (0.21–0.43)	<0.001
Marital Status (ref: Married/Living w/Partner)		
Divorced/Separated/Widowed	1.73 (1.35–2.21)	<0.001
Never Married	1.40 (0.90–2.18)	0.130
PTSD (ever diagnosis vs. none)	1.62 (1.22–2.16)	<0.001
Depression (ever diagnosis vs. none)	1.77 (1.11–2.82)	0.017
Pain Interference in Daily Life (any vs. none)	1.57 (1.13–2.17)	0.007
Unhealthy alcohol use, Past Year (AUDIT-C score 3 or 4)	2.17 (1.48–3.20)	<0.001
Smoker (ref: Never)		
Current	4.04 (1.71–9.54)	0.001
Former	1.32 (0.60–2.89)	0.494
Marijuana Use, Past Year (ref: none)	5.55 (3.58–8.61)	<0.001
Cocaine Use, Past Year (ref: none)	31.48 (19.35–51.21)	<0.001

Characteristic	CHR[*][†] (95% CI)	P – value
Stimulant Use, Past Year (ref: none)	18.82 (10.73–33.00)	<0.001
Any Injection Drug Use, Lifetime (ref: none)	5.75 (4.08–8.11)	<0.001
Opioid Use Disorder (diagnosis vs. none)	9.99 (7.03–14.19)	<0.001
Ever stayed in homeless shelter (ref: no)	2.19 (1.58–3.05)	<0.001
Number of close friends/family (ref: none)		
1–4	0.55 (0.34–0.87)	0.012
5	0.38 (0.20–0.72)	0.003

Note:

[*] Crude Hazard Ratio

[†] Using robust sandwich estimator

HIV = human immunodeficiency virus; HCV = hepatitis C virus; PTSD = post-traumatic stress disorder

Time-updated variable; Rx=prescription

Table 4.

Weighted, multivariable, Cox proportional hazard model of factors associated with time to self-reported past year heroin use among recipients of prescription opioids from the participating in the VACS, 2002–2012

Variables	Model 1 Main exposure: Receipt of High-Dose Opioid Rx[†]		Model 2 Main exposure: Receipt of Long-term Opioid Rx[†]	
	HR[*] (95% CI)	P-value	HR (95% CI)	P-value
High Dose Opioid Rx (ref: low dose)	2.54 (1.26–5.10)	0.009	N/A	N/A
Long-Term Opioid Rx (ref: short-term)	N/A	N/A	1.09 (0.75–1.57)	0.645
Sex (ref: Female)	1.07 (0.27–4.22)	0.918	1.07 (0.24–4.89)	0.926
Age (ref: 42 years)	--	--	--	--
43 – 49 years	0.66 (0.41–1.06)	0.083	0.69 (0.42–1.14)	0.152
50 – 56 years	0.56 (0.35–0.90)	0.016	0.62 (0.42–0.92)	0.018
57 years	0.61 (0.29–1.28)	0.190	0.74 (0.38–1.45)	0.384
HIV (infected versus uninfected)	0.88 (0.63–1.23)	0.466	0.80 (0.54–1.17)	0.250
HCV (infected versus uninfected)	2.70 (1.83–3.97)	<0.001	3.46 (2.44–4.91)	<0.001
Race (ref: White)	--	--	--	--
Black	1.55 (0.72–3.34)	0.334	1.50 (0.79–2.87)	0.218
Hispanic	0.96 (0.28–3.30)	0.949	1.34 (0.41–4.41)	0.625
Other	1.91 (0.55–6.57)	0.305	1.86 (0.72–4.77)	0.198
Education (ref: High School or Less)	--	--	--	--
Some College or Greater	0.62 (0.40–0.97)	0.036	0.52 (0.35–0.78)	0.001
Gross Annual Income (ref: <$6,000)	--	--	--	--
$6,000 - $11,999	1.04 (0.70–1.55)	0.842	0.93 (0.64–1.34)	0.694
$12,000 - $24,999	1.03 (0.72–1.47)	0.863	1.07 (0.71–1.59)	0.753
$25,000	0.80 (0.38–1.70)	0.567	0.75 (0.41–1.37)	0.350
Marital Status (ref: Married/Living w/ Partner)	--	--	--	--
Divorced/Separated/Widowed	1.40 (1.08–1.80)	0.011	1.18 (0.78–1.78)	0.444
Never Married	0.93 (0.59–1.45)	0.931	0.84 (0.51–1.40)	0.842
PTSD (ever diagnosis vs. none)	0.84 (0.50–1.39)	0.501	0.82 (0.48–1.40)	0.475
Depression (ever diagnosis vs. none)	0.69 (0.41–1.15)	0.155	0.63 (0.30–1.29)	0.206
Pain Interference in Daily Life (any vs. none)	1.41 (1.17–1.69)	<0.001	1.18 (0.89–1.57)	0.241
Unhealthy alcohol use, Past Year	0.96 (0.61–1.49)	0.844	0.79 (0.50–1.24)	0.306
Smoker (ref: Never)	--	--	--	--
Current	1.61 (0.61–4.27)	0.338	1.35 (0.40–4..52)	0.624
Former	1.01 (0.41–2.47)	0.986	0.67 (0.22–2.08)	0.491
Any Injection Drug Use with Heroin, lifetime (yes vs no)	1.78 (1.11–2.86)	0.017	2.66 (1.60–4.41)	<0.001
Opioid Use Disorder (diagnosis vs. none)	4.47 (2.65–7.55)	<0.001	4.67 (2.77–7.88)	<0.001
Marijuana Use, Past Year (ref: none)	1.54 (0.83–2.89)	0.183	1.58 (0.89–2.80)	0.113

Variables	Model 1 Main exposure: Receipt of High-Dose Opioid Rx[†]		Model 2 Main exposure: Receipt of Long-term Opioid Rx[†]	
	HR[*] (95% CI)	P-value	HR (95% CI)	P-value
Cocaine Use, Past Year (ref: none)	13.21 (7.11–24.52)	<0.001	15.94 (8.15–31.15)	<0.001
Stimulant Use, Past Year (ref: none)	4.63 (2.07–10.39)	<0.001	4.06 (1.85–8.92)	<0.001
Ever stayed in homeless shelter (ref: no)	0.92 (0.64–1.34)	0.681	0.88 (0.60–1.30)	0.528
Number of close friends/family (ref: none)	--	--	--	--
1–4	0.70 (0.49–0.99)	0.044	0.75 (0.47–1.20)	0.230
5	0.37 (0.20–0.69)	0.002	0.48 (0.27–0.87)	0.016

Note:

[*] Hazard ratio

Time-updated values

[†] Using robust sandwich estimator

HIV = human immunodeficiency virus; HCV = hepatitis C virus; PTSD = post-traumatic stress disorder; Rx=prescription