Trajectories of self-reported opioid use among patients with HIV engaged in care: Results from a national cohort study

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ABSTRACT

Background: No prior studies have characterized long-term patterns of opioid use regardless of source or reason for use among patients with HIV (PWH). We sought to identify trajectories of self-reported opioid use and their correlates among a national sample of PWH engaged in care.

Setting: Veterans Aging Cohort Study, a prospective cohort including PWH receiving care at eight US Veterans Health Administration (VA) sites.

Methods: Between 2002 and 2018, we assessed past year opioid use frequency based on self-reported "prescription painkillers" and/or heroin use at baseline and follow-up. We used group-based trajectory models to identify opioid use trajectories and multinomial logistic regression to determine baseline factors independently associated with escalating opioid use compared to stable, infrequent use.

Results: Among 3,702 PWH, we identified four opioid use trajectories: 1) no lifetime use (25%); 2) stable, infrequent use (58%); 3) escalating use (7%); and 4) de-escalating use 11%).
In bivariate analysis, anxiety; pain interference; prescribed opioids, benzodiazepines and gabapentinoids; and marijuana use were associated with escalating opioid group membership compared to stable, infrequent use. In multivariable analysis, illness severity, pain interference, receipt of prescribed benzodiazepine medications and marijuana use were associated with escalating opioid group membership compared to stable, infrequent use.

Conclusion: Among PWH engaged in VA care, one in 15 reported escalating opioid use. Future research is needed to understand the impact of psychoactive medications and marijuana use on opioid use and whether enhanced uptake of evidence-based treatment of pain and psychiatric symptoms can prevent escalating use among PWH.

Key phrases (3-6): HIV, opioid, benzodiazepine, antidepressants, gabapentin

INTRODUCTION

The opioid epidemic continues unabated with risk for global spread.[1-4] Among patients with HIV (PWH), the opioid epidemic is threatening improved survival seen in recent decades. Between 2011 and 2015, while the overall death rate for PWH in the United States decreased by 13%, the opioid overdose death rate increased concurrently by 42%.[5] This trend may be driven, in part, by the fact that PWH are commonly prescribed opioids for pain,[6] which increases risk of overdose[6-8] and *extra-medical prescription opioid use*.[9] Defined as use of prescription opioids for indications other than those medically prescribed, in a manner other than prescribed (e.g. higher dose than prescribed), or without a prescription,[9,10] extra-medical prescription opioid use, in turn, is a strong, independent predictor of heroin initation.[11]

Despite these concerns, until recently, there have been insufficient efforts to promote more judicious opioid prescribing for chronic pain and attention to addressing unsafe patterns of opioid use in HIV clinical settings.[12-20] Prior studies of opioid use among PWH lack comprehensive assessment of self-reported opioid use regardless of source of opioid and reason for use; they generally focused on prescribed opioid use (i.e., based on pharmacy data),[6,8,21] self-reported extra-medical opioid use ,[22-26] or the relationship between prescribed opioids and extra-medical opioid use.[9,27] Moreover, these prior studies did not have self-reported data linked with pharmacy data to robustly evaluate the impact of prescribed opioids or psychoactive medications for common comorbidities associated with opioid use (i.e., prescribed benzodiazepines, gabapentinoids, and antidepressants).[28-30] Importantly, psychoactive medications may reinforce[31,32] or diminish opioid effects,[33] and ultimately impact opioid-related risks, including death.[26,34,35]

Thus, using data on a national cohort of PWH engaged in care and containing self-reported and linked pharmacy data, we sought to characterize patterns of self-reported opioid (including

prescription opioid and heroin) use, regardless of reason and source, over time and the associated sociodemographic, clinical, and behavioral correlates.

METHODS

Study Overview

The Veterans Aging Cohort Study (VACS) survey study, is a longitudinal, multi-site study of patients with and without HIV receiving care within the Veterans Health Administration (VA) in Manhattan/Brooklyn, New York; Bronx, New York; Pittsburgh, Pennsylvania; Atlanta, Georgia; Houston, Texas; Baltimore, Maryland; Washington, D.C.; and Los Angeles, California.[36] Data sources include approximately annual patient surveys linked to VA electronic health record data including diagnoses, laboratory, and pharmacy data, as well as administrative data. The Institutional Review Boards at Yale University, VA Connecticut Healthcare System and each participating site approved the study.

Study Population

For this analysis, we used data from seven survey waves completed between 2002 and 2018. We included patients with a HIV diagnosis and excluded those who were missing all self-reported items on opioid use during the study period.

Self-reported Opioid Use

We defined opioid use based on self-reported prescription opioid and heroin use as assessed during the baseline 2002 and follow-up surveys initially launched in 2003, 2004, 2008, 2009, 2011, and 2012 (**Supplementary Figure 1**).[11] Participants were provided a list of substances (e.g., cocaine, marijuana) and asked: *For each of the following drugs, please fill in the oval that best indicates how often in the past 12 months you have used each drug*. Response options include the following: *have never tried; no use in the last year; less than once a month; 1-3 times a month; 1-3 times a week; 4-6 times a week; every day*. Opioid use was considered to be present if either prescription opioid and/or heroin

use was endorsed. In the baseline 2002, frequency of prescription opioid and heroin use was assessed with a single item, while in subsequent surveys, use was assessed separately. Frequency of opioid use was defined based on whichever opioid was most frequently used.

Covariates

Based on existing literature, we examined sociodemographic, clinical and behavioral correlates of opioid use.[23,28,29] Variables were assessed based on self-report and clinical/administrative data, including pharmacy fill/refill data, billing (diagnostic codes documented in the year prior to or day of baseline survey data completion as applicable) and registry data.

Sociodemographic variables included age, gender, race and ethnicity, education, marital status, housing instability, location of residence (based on rural urban commuting codes[37]), and annual household income.

Clinical and behavioral variables included HIV-related factors: antiretroviral therapy receipt, (by receipt of ≥3 antiretroviral agents excluding boosters using pharmacy fill/refill data); CD4 cell count; HIV viral load; and VACS Index Score 2.0. HIV viral load was considered undetectable if <500 copies/mL consistent with standards during the start of the observation period. VACS Index 2.0 is a validated measure of morbidity and mortality based on age, HIV viral load, CD4 cell count, white blood cell count, aspartate aminotransferase, alanine aminotransferase, platelets, creatinine, hepatitis C status, albumin, and body-mass index[38,39] VACS Index 2.0 scores typically range from 20 to 100, although extremes of 0 to 160 are possible. Each 5 point increment is associated with 30% increased risk of death.[38] Cancer was defined as history of any cancer, excluding non-melanoma skin cancers, based on data available in the national VA Cancer Registry.[40]

Symptoms hypothesized to be associated with opioid use were assessed by self-report.[23] Anxiety was assessed by the HIV Symptoms Index item,[41] which asks whether the respondent felt *nervous or anxious* during the past 4 weeks and how much they were bothered by these feelings;

responses were categorized as absent (*I do not have this symptom or I have this symptom and it doesn't bother me*] or present (*It bothers me a little, it bothers me,* or *it bothers me a lot*).[42] Depressive symptoms was defined as present based on a Patient Health Questionnaire-9 (PHQ-9) score of ≥10.[43,44] Pain interference was assessed with one item from the 12-item short-form self-report scale (SF-12) of health-related quality of life that asked: *During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?* Response options were categorized as binary variable (*not at all* or *a little bit vs. moderately, quite a bit,* or *extremely*).[45]

To capture patient receipt of medically prescribed opioids, based on outpatient VA pharmacy fill and refill dates in the year prior to the baseline survey date, we determined receipt of prescribed oral and transdermal opioids (i.e., excluding buprenorphine and methadone for opioid use disorder) consistent with our prior methods.[9,46] Prescribed opioid receipt was characterized based morphine equivalent daily dose (low dose: <50mg, high dose: ≥50mg[47]) and duration (short-term: <90 days supplied, long-term: ≥90 days supplied) to create a composite, mutually exclusive 5-level variable. We additionally examined duration of receipt of other prescribed psychoactive medications, including benzodiazepines, gabapentinoids and antidepressants, given they are commonly prescribed for conditions associated with opioid use, may alter opioid effects, and may be used extra-medically (see **Supplementary Table 1**).[30-33,48,49]

Self-reported substance use variables included tobacco use based on current cigarette smoking and unhealthy alcohol use assessed with the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) questionnaire score of ≥3 for women and ≥4 for men.[50] Non-opioid drug use, including marijuana (*marijuana or hashish*) and stimulant use *(cocaine or crack* and *stimulants [amphetamines, uppers, speed, crank, crystal, meth, bam])* was assessed similarly to opioid use. Participants were categorized as reporting non-opioid past year drug use if they endorsed at least

monthly use. Opioid use disorder (OUD) was assessed based on the presence of inpatient or outpatient International Classification of Diseases, Ninth Revision (ICD-9) codes for opioid abuse and/or opioid dependence in the year prior to the baseline survey

Statistical Analysis

We examined patterns of responses to the survey items. For opioid and non-opioid drug use, if a participant responded that they *have never tried* the given substance on a survey following a survey on which they reported use, they were recoded as having *no use in the last year* (i.e. since the last survey). We then used descriptive characteristics to examine patterns of frequency of prescription opioid and heroin use by survey wave and determine the baseline characteristics of our sample, using Chi-square and Wilcoxon rank sum test as appropriate.

Consistent with our prior work,[51-53] we next used a semi-parametric, group-based method to fit opioid use trajectories.[54,55] Models were implemented using Proc TRAJ,[54,55] a procedure that first sorts each participant's set of reported opioid use frequency responses into longitudinal patterns. Then, group-based trajectories are estimated based on the number and shape of groups provided *a priori*, and by using a maximum likelihood procedure. The procedure then calculates each individual's probability of belonging to each trajectory and assigns them to the trajectory with the highest probability of membership. The strengths of this approach are that all available data from each individual are used to estimate participants' trajectories and that the individuals with missing data are also included.[55] We used an enhanced modeling approach where attrition is modeled simultaneously with the trajectory group as a function of time before drop out.[56] This approach has been increasingly applied to address non-random attrition, including missing data due to death.[57-59] Specifically, the DROPOUT option in Proc TRAJ was used to model the probability of dropout for each group as a function of measurement before dropout. To determine the number of groups and trajectory shapes, we examined model fit statistics (i.e., the Bayesian information criterion [BIC],

with BIC values closer to zero indicating a better fit), significance of polynomial terms, and aimed for models in which each group membership was greater than 5% of the modeled sample.[52,54] We also examined the distribution of posterior group membership probabilities to ensure adequate model fit with a median probability greater than 0.70. Based on these criteria, the model fit was best when we used a zero-inflated Poisson outcome distribution allowing for trajectories to take a quadratic form. Estimated trajectories and observed mean frequency of opioid use at each assessment for each trajectory group were then computed and plotted using TRAJPLOT.[60] The time scale was based on years since baseline, with each survey being administered on an approximately annual basis.

We then examined bivariate associations between baseline participant characteristics and trajectory group membership, examining global *p*-values for comparisons across all four groups and separate comparisons between the escalating vs. stable, infrequent group given our specific interest to understand characteristics associated with escalating patterns of use compared to lower and more stable use patterns.

Lastly, we created a series of multinomial models using block-wise sequential regression to identify independent predictors associated with group membership, including only independent variables with a $p<0.05$ for the global comparisons in bivariate analyses. The first model (a.) included sociodemographic characteristics; we then sequentially added (b.) clinical characteristics, then (c.) prescribed opioid and non-opioid psychoactive medications, and finally (d.) other substance use. We examined model statistics using Akaike information criterion (AIC) and evaluated for collinearity using the variance inflation factor (VIF). All statistical analyses were conducted in SAS (version 9.4) and p values <0.05 were considered statistically significant.

RESULTS

Baseline participant characteristics

Among VACS survey participants with HIV (N=3,728), we excluded those missing all self-reported items on opioid use during the study period (n=26), yielding a final analytic sample of 3,702 participants. Over the 16-year study, the mean years of follow-up was 6 (standard deviation [SD]=4.2), ranging from 5.5 to 10.0 across trajectory groups and 38% died (**Table 1**). Across follow-up survey waves, 13-18% reported past year prescription opioid use and 2-4% reported past year heroin use (**Figures 1a-1b**).

The mean age was 50 years old (SD=9) and the sample was nearly all men (97%), and predominantly Black (67%). Sixty percent had completed some college, 41% were married or living with a partner, 42% had experienced housing instability, 95% lived in urban settings, and 51% had an annual household income less than $11,999. Most had received antiretroviral therapy (77%), had a median CD4 cell count of 378 cells/mm^3 (interquartile range [IQR]=227, 562]), 58% had an undetectable HIV viral load, and the median VACS Index 2.0 score was 58 (IQR=48, 70). Thirty-eight percent had HCV co-infection and 19% received a diagnosis of cancer.

Psychiatric and pain symptoms, psychoactive medication receipt, and substance use were common. Thirty-eight percent reported bothersome levels of anxiety, 23% reported at least moderate levels of depression, and 34% had at least moderate pain interference. The proportion of participants with psychoactive medication receipt was: opioids 28%; benzodiazepines 14%; gabapentinoids 11%; and antidepressants 37% (**supplementary Table 2**). Seventy-seven percent reported smoking cigarettes, 37% screened positive for unhealthy alcohol use, 28% reported marijuana use, and 24% reported stimulant use in the past year. Nine percent had received a diagnosis of opioid use disorder.

Group-Based Opioid Use Trajectory Models

The final four-group solution generated opioid use trajectories with distinct patterns: 1) no lifetime use (25%); 2) stable, infrequent use (58%); 3) escalating use (7%); and 4) de-escalating use (11%)

(**Figure 2**). The first two trajectories were best characterized with intercept and linear terms; the second two groups also included quadratic forms. The median probability of group membership in each group was 0.93, 0.96, 0.76, and 0.93, respectively, indicating good model fit.

Factors associated with Opioid Use Trajectory Group

In bivariate analyses, education, marital status, housing instability, annual household income, CD4 cell count, VACS Index 2.0 score and hepatitis c virus co-infection varied across groups (all global *p*-values <0.05, **Table 1**). In addition, symptoms; receipt of prescribed opioids and other psychoactive medications (**Figures 3a-2d, supplementary Table 2**); and substance use all varied across groups (all global *p*-values <0.05). In pair-wise comparisons, anxiety symptoms, pain interference, prescribed opioids, benzodiazepines and gabapentinoid receipt, and marijuana use were more common among those with escalating opioid use than those with stable, infrequent use (*p*-values <0.05).

In sequential, multivariable analyses, the AIC values improved with each subsequent model and the VIF was <2 for each variable; we, therefore, present results for the final model (**Table 2).** Our findings suggested that education, and housing instability were independently associated with group membership. Additionally, VACS Index 2.0 score; pain interference; receipt of prescribed opioids and antidepressants; and evidence of tobacco, unhealthy alcohol, marijuana, and stimulant use also varied by opioid use trajectory group membership (all global *p*-values <0.05). For example, cigarette use was more common in the de-escalating group (adjusted odds ratio [AOR] = 1.61, 95%CI: 1.07-2.41) and less common in those with no lifetime use (AOR = 0.50, 95%CI: 0.41-0.60) compared to those with stable, infrequent use. Further, measures of illness severity, pain interference, prescribed benzodiazepine medication duration and marijuana use varied among those with escalating opioid use compared to those with stable, infrequent use (*p*-values for pair-wise comparison <0.05). For instance, receipt of short-term and long-term prescribed benzodiazepines were more common in the

escalating group (AOR = 1.58, 95%CI: 0.84 – 2.98 & AOR = 1.89, 95%CI: 1.09 – 3.29, respectively) compared to the stable, infrequent use.

DISCUSSION

To our knowledge, this is the first study to examine longitudinal patterns of self-reported l opioid use among PWH and with linked outpatient pharmacy data, including both prescribed opioids and other psychoactive medications commonly prescribed to PWH. Our study reveals several important findings. First, in this sample of patients engaged in care, up to nearly 1 in 5 patients reported past year opioid use and 1 in 15 patients had evidence of escalating opioid use. Second, escalating opioid use was associated with potentially modifiable factors, including physical and emotional symptoms, psychoactive medication receipt, and substance use, as well as key sociodemographic characteristics that highlight potentially vulnerable subpopulations. In a series of multivariable analyses, illness severity, pain interference, receipt of prescribed benzodiazepines and marijuana use were independently associated with escalating opioid use. HIV-related variables were not consistently associated with patterns of opioid use.

Our finding that up to nearly 20% of patients reported past year opioid use and 7% of patients had a pattern consistent with escalating opioid use is concerning. While some of this opioid use may reflect use of prescribed opioids (i.e., provided by a clinician) for treatment of pain, findings from the Medical Monitoring Project (MMP), a national surveillance study of PWH, demonstrated that 3% of the sample had extra-medical opioid use largely driven by extra-medical prescription opioids use.[26] Given these data from the MMP combined with those from other studies[24,25,48,61] and a clinical context where opioid prescribing practices have been slowly changing,[62] our data raise concern that a substantial number of individuals are exposed to opioids and at risk for escalating opioid use. This is concerning as opioid use, and particularly a pattern of escalating use, is likely associated with greater potential harms, including falls,[63] infectious complications,[46] addiction, and overdose. Our study

results reinforce the importance of the US Preventive Services Task Force new recommendations for screening and identification of extra-medical opioid use,[64] promotion of harm reduction services, and use of evidence-based OUD treatment, such as buprenorphine or methadone,[13,18,65] among PWH engaged in care.

That escalating opioid use was more common among those with physical and emotional symptoms, and substance use is supported by prior work.[26,29,61] These associations may be explained by common reasons driving opioid use, including a motivation to seek euphoria, treat pain and its associated negative affective responses, or self-medication of anxiety and depressive symptoms.[23,66-68] Accordingly, efforts to prevent escalating opioid use might focus on comprehensive evidenced-based treatment of pain, mental health and substance use.[69] While the VA as well as the Ryan White-funded infrastructure facilitate access to mental health and substance use treatment for PWH, these conditions often go under-recognized and undertreated.[70] Furthermore, the existence of and access to evidence-based treatments to address pain among PWH is generally lacking.[71,72] Efforts to develop novel interventions for PWH with pain are actively underway and will likely be an essential part of the solution to help prevent development of escalating opioid use among PWH.[73]

It is notable that, compared to those with stable, infrequent opioid use, PWH with escalating opioid use tended to receive psychoactive prescribed medications, including opioids, benzodiazepines, gabapentinoids and antidepressants again suggesting the influence of pain and other psychological symptoms and/or the potential synergistic euphorigenic effect of multiple CNS-acting medications. Further, based on multivariable analyses, findings indicate that receipt of prescribed benzodiazepine medications were independently associated with escalating opioid use. In the time period of this study, prescribed opioids were often dispensed liberally in HIV treatment settings[51] with limited adherence to guidelines for opioid prescribing, such as urine toxicology testing, opioid treatment agreements, limiting co-prescribing of other psychoactive medications

(e.g., benzodiazepines) and optimal use of non-pharmacologic pain treatments.[12,14] Release of guidelines for opioid prescribing by the Centers for Disease Control and Prevention and Infectious Diseases Society of America[17,74] have stimulated more careful opioid prescribing.[62] Whether non-opioid psychoactive medication duration is a marker of symptom severity, treatment initiation or lack of response, or itself serves to promote escalating opioid use warrants further investigation. Regardless, these findings are concerning given that these medications may also be used extra-medically to promote euphoria and/or recover from opioid use,[48,49] and in combination with opioids these drugs may contribute to risk of adverse events, particularly overdose.[32,74-77]

Nearly 80% had received antiretroviral medications in the year prior to baseline and this, nor HIV viral suppression varied by opioid use trajectory. CD4 cell count and overall illness severity by VACS Index 2.0 score, in contrast, were associated with opioid use trajectory. These findings may be explained by the fact that PWH receiving prescribed opioids may be more likely to be engaged in clinical care.[15,16] To guide clinical practices and policies, future studies that further explore the interaction between prescribed opioid receipt, self-reported opioid use, and HIV-related outcomes over time are needed. In particular, studies are needed to determine the degree to which biological (e.g., gut homeostasis, immunosuppression)[78-81] or behavioral (e.g., antiretroviral therapy non-adherence) mechanisms drive associations between opioid exposure and HIV outcomes. We additionally found that marijuana use was consistently associated with opioid use over time and an independent predictor of escalating opioid use. Given expanding access to marijuana and suggestion that marijuana use may help decrease opioid use, it will be critical to further investigate longitudinal associations.[82]

Our study has some limitations. First, we defined frequency of opioid use based on the highest frequency of reported prescription opioid or heroin use over the prior 12 months, rather than summing these frequencies, with the assumption that individuals are typically using one form of

opioid in a given day. Second, our findings may not be generalizable to non-Veteran populations or women. Third, these data may not reflect current shifting trends in opioid prescribing or the impact of the wider availability of illicitly manufactured fentanyl for extra-medical opioid use. Fourth, as surveys were self-administered, there may have been variability in interpretation of the items among participants and over time with regards to what type of opioid use (i.e., medically prescribed or otherwise) was being ascertained. In particular, a relatively large proportion (34%) of participants endorsed no lifetime use following a report of some use in a prior survey. We chose to re-code these responses as *no use in the last year*. As such, there is likely some misclassification of participants grouped into the *no lifetime use* and *stable, infrequent use* categories. However, we expect the degree of misclassification to be low and nondifferential, since membership in the *no lifetime use* trajectory was strongly associated with no use of other substances (including tobacco and cocaine). Fifth, the de-escalating group had a higher proportion of participants who had died and shorter period of follow-up. However, a strength of our trajectory-based analysis is that individuals with missing data are included, and our approach accounts for non-random missing data, including from death and other reasons for dropout. Sixth, participants were assigned to the trajectory to which they had the highest posterior probability of membership. Although the posterior probabilities were generally high (above 0.90, indicating good model fit), there is likely some misclassification across trajectories, particularly for persons with lower probabilities of membership in one group over others. Lastly, our measures of psychoactive medication receipt were based on VA pharmacy data and thus do not capture non-VA medication.

Conclusions

To help mitigate the impact of the opioid epidemic among PWH, future efforts to limit escalating opioid use should focus on optimizing care of individuals with pain, mental health symptoms and other substance use. As opioid prescribing practices shift, future research is needed

to elucidate the longitudinal associations between psychoactive medication receipt, marijuana use and opioid use trajectories and the associated impact on HIV-related outcomes.

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Table 1

Table 1. Sociodemographic and clinical characteristics associated with membership in group-based extra-medical opioid use trajectories among patients with HIV

Characteristic	Overall （N=3702）	No lifetime use (N=903)	Stable, infrequent use (N=2297)	Escalating use (N=145)	De-escalating use (N=357)	Global p value	p value for stable infrequent use vs. escalating use
Demographics							
Age, mean (SD)	49.8 (8.9)	49.5 (10.8)	49.8 (8.4)	49.4 (7.1)	50.6 (6.8)	0.109	0.501
Gender, n (%)						0.780	0.784
Male	3604 (97.4)	875 (96.9)	2239 (97.5)	141 (97.2)	349 (97.8)		
Female	98 (2.7)	28 (3.1)	58 (2.5)	4 (2.8)	8 (2.2)		
Race/ethnicity, n (%)						0.373	0.642
White	716 (19.3)	153 (16.9)	459 (20.0)	35 (24.1)	69 (19.3)		
Black	2478 (66.9)	621 (68.8)	1525 (66.4)	92 (63.5)	240 (67.2)		
Hispanic	355 (9.6)	98 (10.9)	210 (9.1)	13 (9.0)	34 (9.5)		
Other	153 (4.1)	31 (3.4)	103 (4.5)	5 (3.5)	14 (3.9)		
Education, n (%)						0.0002	0.053
High school or Less	1476 (40.3)	347 (38.9)	905 (39.8)	46 (31.7)	178 (50.1)		
Some college or More	2190 (59.7)	546 (61.1)	1368 (60.2)	99 (68.3)	177 (49.9)		
Marital status, n (%)						0.005	0.224
Never married	832 (22.8)	187 (21.1)	546 (24.1)	29 (20.3)	70 (19.8)		
Married/living with Partner	1499 (41.1)	346 (39.1)	913 (40.3)	68 (47.6)	172 (48.7)		
Divorced/ widowed	1315 (36.1)	353 (39.8)	805 (35.6)	46 (32.2)	111 (31.4)		
Housing instability ever[a], n (%)	1562 (42.4)	243 (27.1)	1043 (45.7)	73 (50.3)	203 (57.0)	<0.0001	0.273
Location of residence, n (%)						0.390	0.206
Urban	3479 (95.0)	853 (95.2)	2155 (94.9)	134 (93.1)	337 (96.0)		
Suburban	103 (2.8)	20 (2.2)	71 (3.1)	4 (2.8)	8 (2.3)		
Rural	80 (2.2)	23 (2.6)	45 (2.0)	6 (4.2)	6 (1.7)		
Annual income, n (%)						<0.0001	0.195
<$11,999	1822 (50.9)	359 (41.5)	1164 (52.2)	73 (51.4)	226 (65.3)		
$12,000 - $49,999	1494 (41.7)	437 (50.5)	885 (39.7)	63 (44.4)	109 (31.5)		
>=$50,000	266 (7.4)	69 (8.0)	180 (8.1)	6 (4.2)	11 (3.2)		
HIV-related factors							
Antiretroviral therapy receipt, n (%)	2855 (77.1)	721 (79.8)	1753 (76.3)	114 (78.6)	267 (74.8)	0.115	0.526
CD4 cell count, cells/mm3, median (IQR)	378 (227, 562)	392 (242, 578)	376 (228, 559)	405 (254, 575)	341 (171, 540)	0.002	0.231
HIV viral load <500 copies/mL,	2113 (57.9)	547 (61.3)	1295 (57.2)	80 (55.2)	191 (54.7)	0.091	0.633

n (%)							
VACS Index 2.0 score,[b] median (IQR)	58 (48, 70)	55 (45, 64)	58 (48, 70)	56 (47, 65)	64 (54, 78)	<0.0001	0.110
Other health conditions and status, n (%)							
HCV positive	1415 (38.2)	147 (16.3)	987 (43.0)	70 (48.3)	211 (59.1)	<0.0001	0.211
Any cancer	701 (18.9)	169 (18.7)	424 (18.5)	31 (21.4)	77 (21.6)	0.467	0.381
Anxiety Symptoms[c]	1349 (37.5)	258 (29.4)	850 (38.0)	66 (47.8)	175 (50.6)	<0.0001	0.022
Depressive Symptoms[d]	828 (22.6)	141 (15.8)	513 (22.5)	41 (28.5)	133 (37.5)	<0.0001	0.099
Pain Interference[e]	1244 (33.9)	222 (24.8)	746 (32.8)	70 (48.3)	206 (58.2)	<0.0001	0.0001
Other substance use, n (%)							
Smokes Cigarettes	2839 (76.7)	560 (62.0)	1835 (79.9)	125 (86.2)	319 (89.4)	<0.0001	0.064
Unhealthy alcohol use[f]	1352 (36.5)	257 (28.5)	896 (39.0)	61 (42.1)	138 (38.7)	<0.0001	0.464
Marijuana[g]	1021 (27.6)	228 (25.3)	618 (26.9)	54 (37.2)	121 (33.9)	0.0007	0.007
Stimulants or Cocaine[g]	891 (24.1)	138 (15.3)	567 (24.7)	40 (27.6)	146 (40.9)	<0.0001	0.433
Opioid use Disorder	337 (9.1)	5 (0.6)	197 (8.6)	18 (12.4)	117 (32.8)	<0.0001	0.113
Average follow-up years, mean (SD)	6.2 (4.2)	6.5 (3.7)	5.9 (4.3)	10.0 (1.9)	5.5 (4.0)	<0.0001	<0.0001
Died during study period, n (%)	1422 (38.4)	301 (33.3)	898 (39.1)	34 (23.5)	189 (52.9)	<0.0001	0.0002

Notes:

a. reported "yes" to "Have you ever been without a permanent address that you call home?"

b. VACS Index 2.0 score, validated measure of morbidity and mortality, based on HIV biomarkers (CD4 cell count, HIV viral load), hemoglobin, white blood cell count, liver fibrosis by FIB-4, hepatitis C status (HCV, based on antibody status and HCV RNA and diagnostic codes), albumin, kidney function by estimated glomerular filtration rate, and body mass index

c. anxiety symptoms considered present if response included any of the following: "bothers me a little," "it bothers me," "it bothers me a lot"

d. depressive symptoms, defined as present based on PHQ-9 score >9

e. self-reported pain interference in daily life, defined as present based if response included any of the following: "moderately," "quite a bit" or "extremely"

f. alcohol use disorder identification test-consumption (AUDIT-C) – defined as score of ≥3 for women, ≥4 for men

g. substance use considered present if response consistent with any use over the past 12 months

Table 2

Table 2. Factors associated with group-based extra-medical opioid use trajectories among patients with HIV engaged in care, final multinomial logistic regression model

Characteristic	No use (N=903)	Stable, infrequent use (N=2297)	Escalating use (N=145)	De-escalating use (N=357)	Global p value	p value for stable, infrequent use vs. escalating use
Demographics						
Education					0.0125	0.061
High school or less	Ref	Ref	Ref	Ref		
Some college or more	0.89 (0.74, 1.06)	Ref	1.47 (0.99, 2.17)	0.75 (0.58, 0.97)		
Marital status					0.0811	0.316
Never married	Ref	Ref	Ref	Ref		
Married/living with Partner	1.39 (1.10, 1.75)	Ref	1.33 (0.83, 2.12)	1.14 (0.81, 1.62)		
Divorced/widowed	1.35 (1.07, 1.70)	Ref	0.96 (0.58, 1.59)	1.08 (0.75, 1.56)		
Housing instability ever	0.54 (0.45, 0.66)	Ref	1.10 (0.75, 1.60)	1.14 (0.87, 1.50)	<0.0001	0.576
Annual income					0.1142	0.416
<$11,999	Ref	Ref	Ref	Ref		
$12,000 - $49,999	1.14 (0.94, 1.38)	Ref	1.14 (0.77, 1.68)	0.91 (0.68, 1.22)		
>=$50,000	0.73 (0.52, 1.04)	Ref	0.64 (0.26, 1.57)	0.68 (0.33, 1.39)		
Health conditions and symptoms						
VACS Index 2.0 in 10 point increments	0.91 (0.86, 0.96)	Ref	0.88 (0.78, 0.98)	1.14 (1.06, 1.23)	<0.0001	0.031
Anxiety symptoms	0.97 (0.79, 1.19)	Ref	1.07 (0.71, 1.61)	1.06 (0.79, 1.42)	0.9495	0.905
Depressive symptoms	0.89 (0.69, 1.14)	Ref	1.01 (0.64, 1.58)	1.28 (0.94, 1.75)	0.2905	0.959
Pain interference	0.95 (0.77, 1.17)	Ref	1.56 (1.05, 2.33)	1.42 (1.07, 1.89)	0.0121	0.025
Prescribed medications						
Opioid duration and dose					<0.0001	0.750
None	Ref	Ref	Ref	Ref		
Short-term + low dose	0.82 (0.65, 1.02)	Ref	1.14 (0.74, 1.76)	1.39 (1.00, 1.93)		
Shot-term + high dose	0.48 (0.20, 1.18)	Ref	1.36 (0.40, 4.61)	1.78 (0.76, 4.16)		
Long-term + low dose	0.56 (0.32, 0.98)	Ref	0.87 (0.38, 2.03)	7.60 (5.08, 11.36)		
Long-term + high Dose	0.24 (0.07, 0.81)	Ref	1.95 (0.74, 5.14)	12.66 (7.25, 22.10)		
Benzodiazepine Duration					0.1150	0.049
None	Ref	Ref	Ref	Ref		
Short-term	0.84 (0.55, 1.28)	Ref	1.58 (0.84, 2.98)	0.87 (0.53, 1.41)		
Long-term	0.81 (0.56, 1.17)	Ref	1.89 (1.09, 3.29)	0.79 (0.50, 1.26)		
Antidepressant duration					0.0134	0.281
None	Ref	Ref	Ref	Ref		
Short-term	0.68 (0.51, 0.92)	Ref	1.28 (0.77, 2.12)	1.29 (0.90, 1.84)		
Long-term	0.72 (0.57, 0.92)	Ref	0.84 (0.53, 1.34)	1.03 (0.75, 1.42)		
Gabapentinoid duration					0.0714	0.245
None	Ref	Ref	Ref	Ref		
Short-term	0.59 (0.34, 1.02)	Ref	1.14 (0.54, 2.42)	1.30 (0.78, 2.16)		

Long-term	1.28 (0.85, 1.93)	Ref	1.77 (0.95, 3.32)	1.58 (1.01, 2.46)		
Substance use						
smokes cigarettes	0.50 (0.41, 0.60)	Ref	1.40 (0.84, 2.35)	1.61 (1.07, 2.41)	<0.0001	0.210
unhealthy alcohol use	0.71 (0.59, 0.86)	Ref	1.05 (0.73, 1.51)	0.87 (0.67, 1.14)	0.0039	0.776
marijuana, any in past year	1.23 (1.00, 1.51)	Ref	1.52 (1.03, 2.25)	0.93 (0.70, 1.25)	0.0425	0.035
cocaine or stimulant use, any in past year	0.73 (0.57, 0.94)	Ref	1.09 (0.70, 1.68)	2.08 (1.55, 2.79)	<0.0001	0.838

Notes: AIC for overall model: 6118.74; AIC for group 2 and 3 only: 1016.06

Supplementary Table 1. Benzodiazepine, gabapentinoids, and antidepressant medication receipt

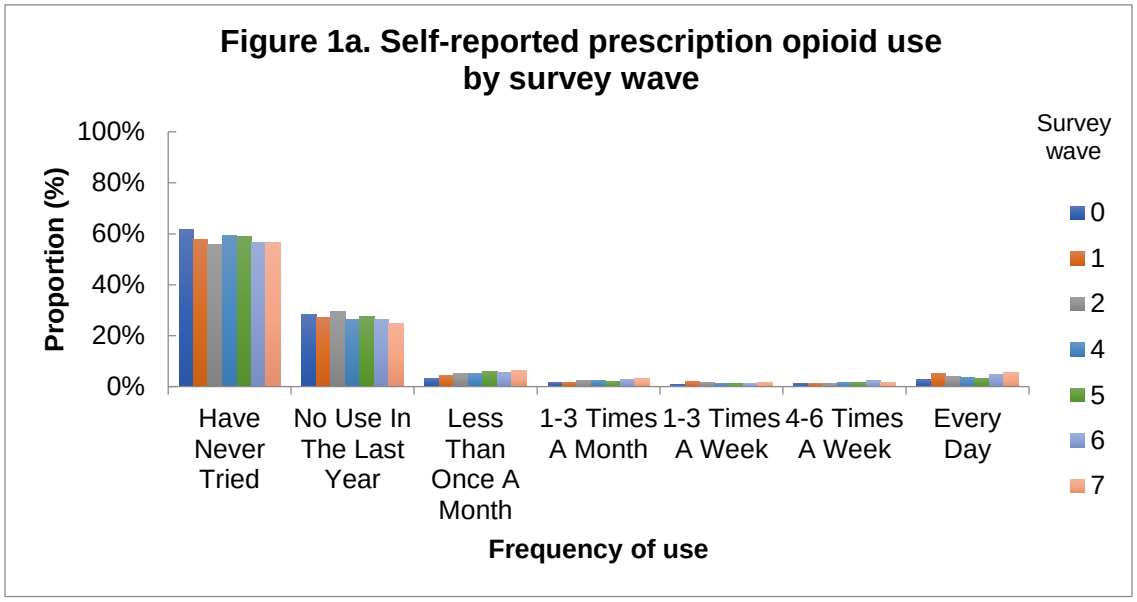
Medication Class	Specific Medications
Benzodiazepines	alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, eszopiclone, flurazepam, lorazepam, midazolam, oxazepam, temazepam, triazolam, zaleplon and zolpidem
Gabapentinoids	gabapentin, pregabalin
Antidepressants	amitriptyline, amoxapine, bupropion, citalopram, clomipramine, desipramine, desvenlafaxine, doxepin, duloxetine, escitalopram, fluoxetine, fluvoxamine, imipramine, isocarboxazid, levomilnacipran, maprotiline, milnacipran, mirtazapine, nefazodone, nortriptyline, paroxetine, phenelzine sulfate, protriptyline, selegiline, sertraline, tranylcypromine, trazodone, trimipramine, venlafaxine, vilazodone, and vortioxetine.

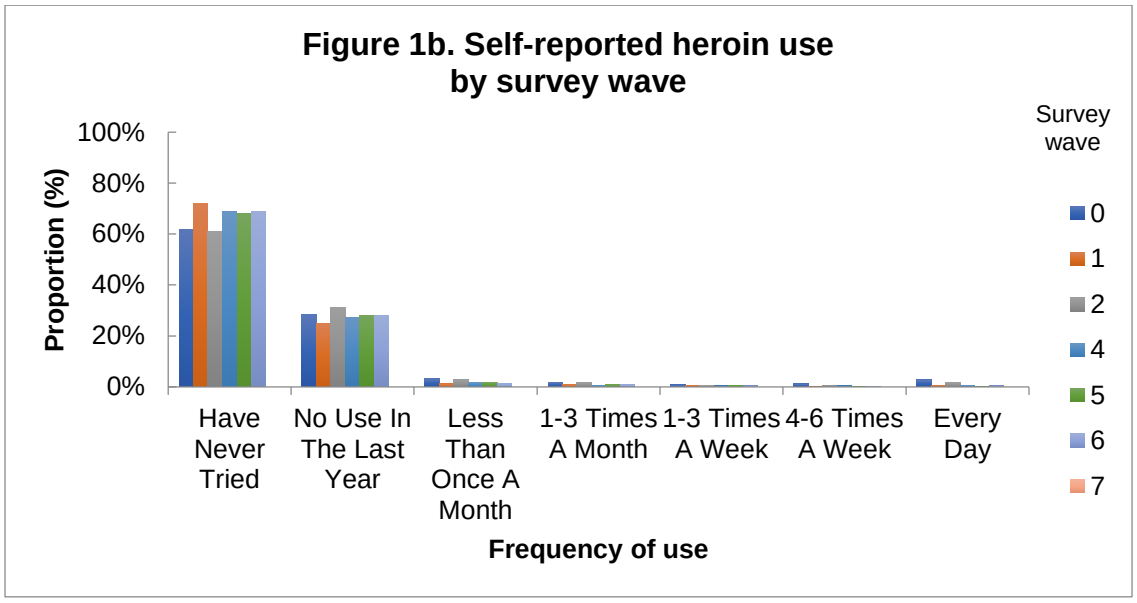
Supplementary Table 2. Prescribed medications and associations with membership in group-based self-reported opioid use trajectories among patients with HIV

Medication, n (%)	Overall (N=3702)	No lifetime use (N=903)	Stable, infrequent use (N=2297)	Escalating use (N=145)	De-escalating use (N=357)	Global p value	p value for stable infrequent use vs. escalating use
Prescribed opioids						<0.0001	0.010
None	2674 (72.2)	741 (82.1)	1682 (73.2)	93 (64.1)	158 (44.3)		
Short-term + low dose	682 (18.4)	133 (14.7)	449 (19.6)	33 (22.8)	67 (18.8)		
Shot-term + high dose	60 (1.6)	6 (0.7)	41 (1.8)	4 (2.8)	9 (2.5)		
Long-term + low dose	198 (5.4)	18 (2.0)	92 (4.0)	8 (5.5)	80 (22.4)		
Long-term + high dose	88 (2.4)	5 (0.6)	33 (1.4)	7 (4.8)	13 (12.0)		
Prescribed benzodiazepine duration						<0.0001	0.001
None	3194 (86.3)	818 (90.6)	1985 (86.4)	110 (75.9)	281 (78.7)		
Short-term	217 (5.9)	35 (3.9)	136 (5.9)	13 (9.0)	33 (9.2)		
Long-term	291 (7.9)	50 (5.5)	176 (7.7)	22 (15.2)	43 (12.0)		
Prescribed gabapentinoid duration						<0.0001	0.001
None	3309 (89.4)	840 (93.0)	2073 (90.3)	118 (81.4)	278 (77.9)		
Short-term	164 (4.4)	19 (2.1)	106 (4.6)	10 (6.9)	29 (8.1)		
Long-term	229 (6.2)	44 (4.9)	118 (5.1)	17 (11.7)	50 (14.0)		
Prescribed antidepressant duration						<0.0001	0.062
None	2333 (63.0)	669 (74.1)	1421 (61.9)	76 (52.4)	167 (46.8)		
Short-term	487 (13.2)	76 (8.4)	312 (13.6)	27 (18.6)	72 (20.2)		
Long-term	882 (23.8)	158 (17.5)	564 (24.6)	42 (29.0)	118 (33.1)		

Note: Duration of medications defined based on days supplied in the year prior to baseline survey as either none: zero days supplied; short-term: <90 days supplied; or long-term: ≥90 days supplied.

Figure 1. Self-reported frequency of prescription opioid and heroin use by survey wave

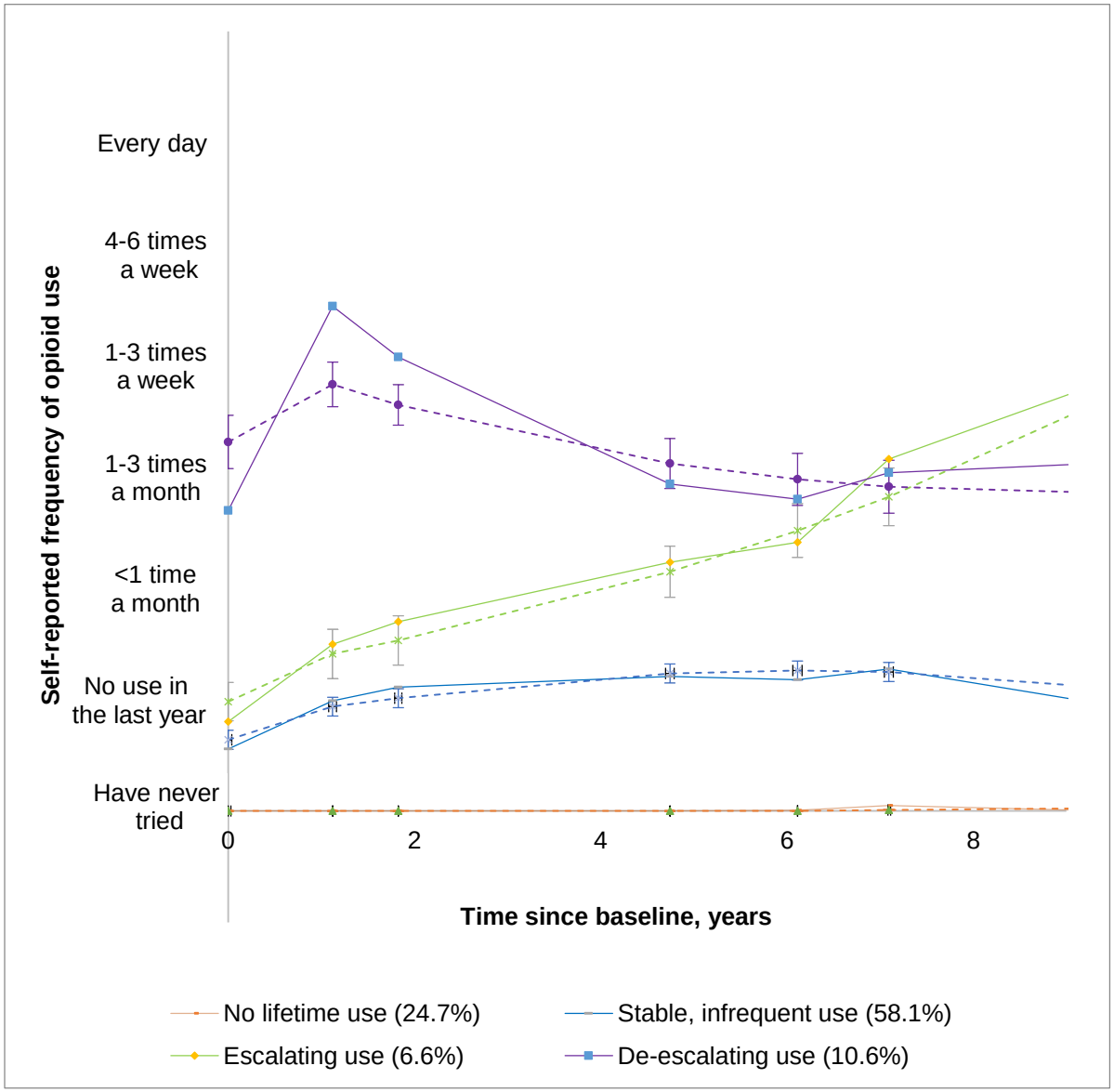




Note: Baseline 2002 survey ("0" in the legend) combined prescription opioid and heroin use into a single item. Follow-up survey 3 did not include this item (as such, data is missing for this wave)

Figure 2

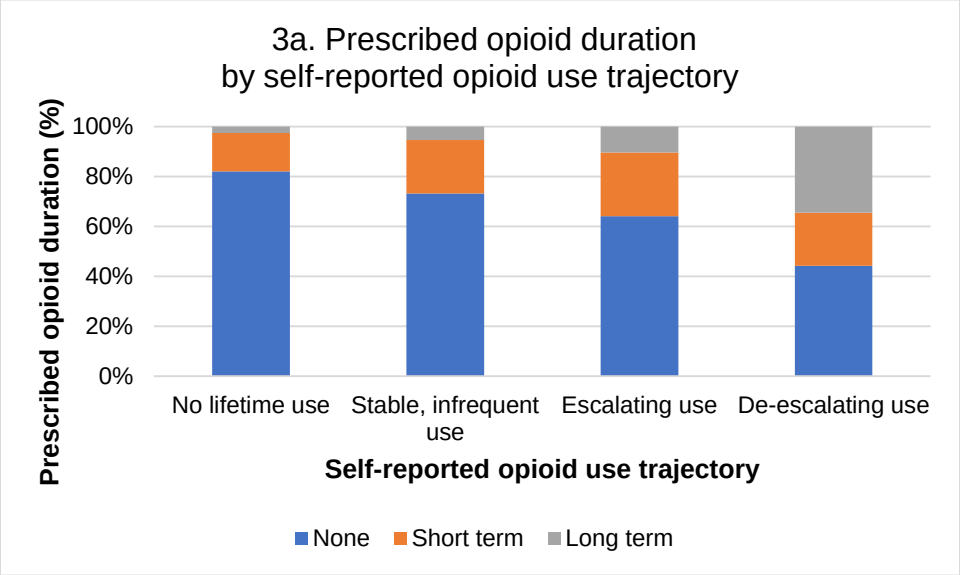
Figure 2. Group-based self-reported opioid use trajectories among patients with HIV (2002-2018)

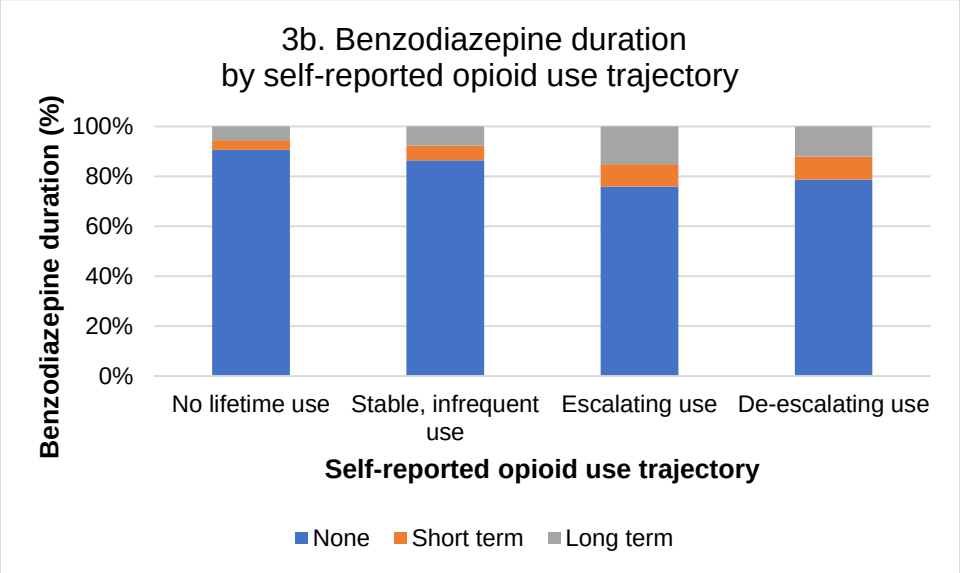


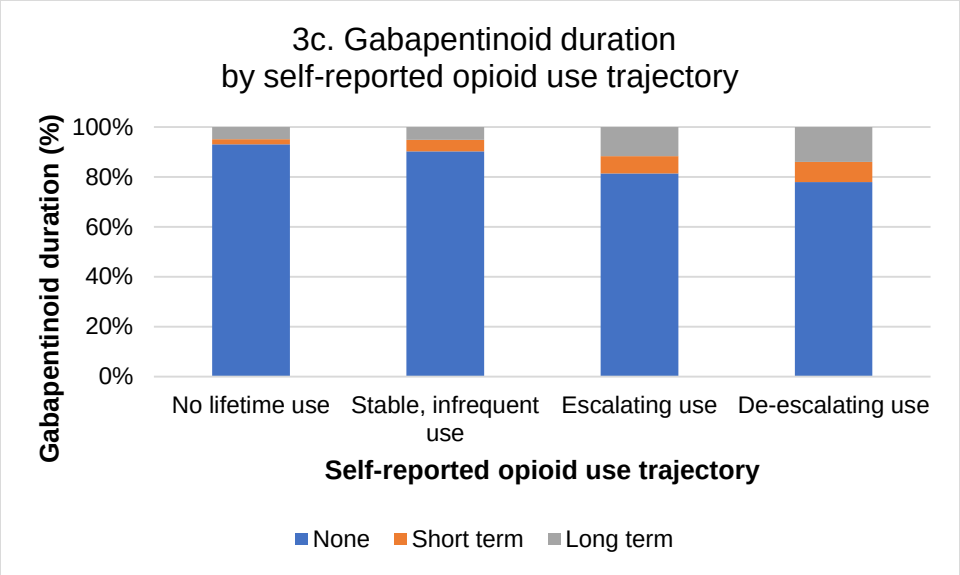
Note: Dashed lines represent estimated trajectories; solid lines represent observed frequency of extra-medical opioid use for each trajectory group.

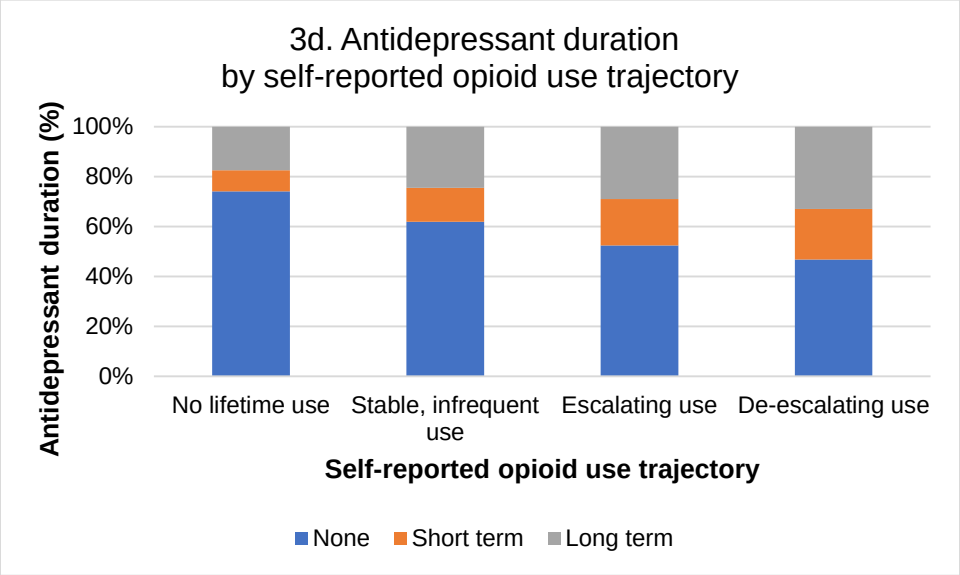
Figure 3

Figure 3. Duration of medication receipt of a) prescribed opioids, b) benzodiazepines, c) gabapentinoids, and d) antidepressants by self-reported opioid use trajectory









Note: Duration of medications defined based on days supplied in the year prior to baseline survey as either none: zero days supplied; short-term: <90 days supplied; or long-term: ≥90 days supplied.

Supplementary Figure 1. Survey items to assess self-reported opioid use

OTHER DRUG USE

41. For each of the following drugs, please fill in the circle that best indicates how often in the past 12 months you used each drug.

		IN THE LAST 12 MONTHS					
	HAVE NEVER TRIED	NO USE IN THE LAST YEAR	LESS THAN ONCE A MONTH	1 - 3 TIMES A MONTH	1 - 3 TIMES A WEEK	4 - 6 TIMES A WEEK	EVERY DAY
a. Marijuana or Hashish	0	0	0	0	0	0	0
b. Cocaine or Crack	0	0	0	0	0	0	0
c. Stimulants (amphetamines, uppers, speed, crank, crystal meth, bam)	0	0	0	0	0	0	0
d. Heroin	0	0	0	0	0	0	0
e. Prescription painkillers (such as Oxycontin, Vicodin, Percocet)	0	0	0	0	0	0	0
f. Prescription benzodiazepines (Valium,Deastat, Ativan)	0	0	0	0	0	0	0
g. Other	0	0	0	0	0	0	0

Notes: Example above taken from survey administered at follow-up 5 (www.vacohort.org). Opioid use was listed as *opioids (heroin, morphine, codeine, opium)* in the baseline survey and separately as *heroin* and *prescription opioids (morphine, codeine, Vicodin, Percocet, OxyContin)* in follow-up surveys. Opioid use was not assessed in this manner in the follow-up 3 survey.