Sociodemographic and clinical correlates of gabapentin receipt with and without opioids among a national cohort of patients with HIV

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Abstract

Gabapentin is commonly prescribed for chronic pain, including to patients with HIV (PWH). There is growing concern regarding gabapentin's potential for harm, particularly in combination with opioids. Among PWH, we examined factors associated with higher doses of gabapentin receipt and determined if receipt varied by opioid use. We examined data from the Veterans Aging Cohort Study, a national prospective cohort including PWH, from 2002 through 2017; data were analyzed in 2020. Gabapentin receipt was categorized as none, low dose (<1,469 mg/day), and high dose (≥1,469mg/day). Covariates included prescribed opioid dose, self-reported past year opioid use, and other sociodemographic and clinical variables. We used multinomial logistic regression to determine the independent association between gabapentin receipt and prescribed opioids and other sociodemographic and clinical characteristics. In secondary analyses, we replaced prescribed opioids with self-reported opioid use. Among 3,702 PWH, 902 (24%) received any gabapentin during the study period at a mean daily dose of 1,469 mg. There were no observed differences in gabapentin receipt over the study period. In the multinomial model, high-dose gabapentin receipt was associated with high-dose benzodiazepine receipt (adjusted odds ratio [aOR], 95% confidence interval [CI]= 1.53, [1.03-2.27]), pain interference (1.65 [1.39-1.95]), and hand or foot pain (1.81, [1.45-2.26]). High-dose gabapentin receipt was associated with prescribed high-dose opioids receipt (2.66 [1.95-3.62]) but not self-reported opioid use (1.03 [0.89-1.21]). PWH prescribed gabapentin at higher doses are more likely to receive high-dose opioids and high-dose benzodiazepines, raising safety concerns.

Keywords: Opioid-related disorders, HIV, pain, pharmacoepidemiology, cohort studies

Introduction

The pharmacologic management of chronic pain is challenging. Since the United States (US) Centers for Disease Control and Prevention (CDC) released updated guidelines for opioid therapy for chronic pain in 2016 (Dowell, Haegerich, & Chou, 2016), clinicians are turning to non-opioid medications for the treatment of chronic pain, including to the gabapentinoid drugs (gabapentin and pregabalin) (Goodman & Brett, 2017; Johansen, 2018). Gabapentin, the more commonly prescribed gabapentinoid, is approved by the Food and Drug Administration (FDA) for treatment of only a limited number of pain syndromes. A substantial proportion of gabapentin use is off-label, and prescriptions for gabapentin in the US have tripled in the last 15 years (Goodman & Brett, 2019). Despite initial conjectures that gabapentin did not have potential for misuse (Bonnet et al., 1999; Lavigne et al., 2012; Nunes, 2014), numerous reports have documented gabapentin misuse, particularly among individuals with substance use disorders (Cantrell, Mena, Gary, & McIntyre, 2015; Fischer, Barr, Rogers, Fischer, & Trudeau, 1994; Kruszewski, Paczynski, & Kahn, 2009; Markowitz, Finkenbine, Myrick, King, & Carson, 1997; Reccoppa, Malcolm, & Ware, 2004; Reeves & Ladner, 2014). Individuals who use gabapentin recreationally describe relaxation, pain reduction, and "high" feeling that may manage withdrawal syndromes from other substances (Smith, Havens, & Walsh, 2016; Vickers Smith et al., 2018). Gabapentin use is more common among patients prescribed opioids; European data suggests that 22% to 50% of those newly prescribed gabapentin were concurrently prescribed opioids (Montastruc, Loo, & Renoux, 2018; Torrance et al., 2020). Over the last 15 years, US national poison data have demonstrated an increase in gabapentinoid-related poisonings by 4% per quarter (Dart, Bartelson, Severtson, Bau, & Green, 2017), and over 25% of overdose deaths that involve opioids also involve gabapentin (Mariottini, Kriikku, & Ojanpera, 2020; Slavova et

al., 2018). As a result, in December 2019 the FDA mandated updates of labels for gabapentinoids regarding their risk for respiratory depression and required drug manufacturers to conduct studies on gabapentinoids' safety in combination with opioids (U.S. Food & Drug Administration, 2019). Greater understanding of the correlates of gabapentin use is needed.

Patients with HIV (PWH) represent an important population to study gabapentin receipt because they have a high prevalence of painful conditions (Hewitt et al., 1997; Miaskowski et al., 2011) and yet there is a lack of high-quality observational or controlled interventional studies to inform the management of chronic pain in PWH (Merlin, Bulls, Vucovich, Edelman, & Starrels, 2016). Gabapentin is independently associated with adverse effects, including falls, fractures, and altered mental status (Rentsch et al., 2020). Among PWH, gabapentinoid receipt has been shown to be more common among those with escalating opioid use trajectories than those with stable or infrequent trajectories (Edelman et al., 2020). Despite these risks, PWH are commonly prescribed gabapentin with and without opioids (Becker et al., 2016; Rentsch et al., 2020). There are limited data assessing changes in gabapentin receipt over time and factors that contribute to prescribed gabapentin receipt alone and in combination with opioids.

Therefore, using data from a national cohort of PWH containing self-reported and linked pharmacy data, we sought to: (1) describe trends in gabapentin dose receipt over time, (2) examine factors associated with higher doses of gabapentin receipt, and (3) determine if receipt varied by opioid use.

Materials and methods

Study overview

The Veterans Aging Cohort Study is a longitudinal, multisite study of patients with and without HIV receiving care within the Veterans Health Administration of the Department of Veterans Affairs (VA) in Manhattan/Brooklyn, New York; Bronx, New York; Pittsburgh, Pennsylvania; Atlanta, Georgia; Houston, Texas; Baltimore, Maryland; Washington, DC; and Los Angeles, California (Justice et al., 2006). Data sources include: (1) self-administered patient surveys completed approximately on an annual basis; (2) VA electronic health record data including diagnoses, laboratory and pharmacy data; and (3) administrative data. The institutional review boards at Yale University, VA Connecticut Healthcare System, and each participating site approved the study.

Study population

We used data from seven survey waves completed between 2002 and 2017. We included patients with an HIV diagnosis and excluded those who were missing all self-reported items on opioid use during the study period.

Outcome of interest: gabapentin use

Gabapentin use was defined based on VA outpatient pharmacy fill/refill data. A daily dose was calculated for the 12 months prior to each survey date according to the dose prescribed and the number of days supplied, assuming that doses were taken as prescribed. Given the variation in doses indicated for various conditions (Wang & Zhu, 2017) and the variation in dose threshold for the emergence of adverse effects (Meng et al., 2014; Rentsch et al., 2020), we defined low-dose gabapentin use as below the mean dose and high-dose gabapentin use as above or equal to the mean dose. We did not include pregabalin prescriptions given its limited use during the study period; only 2% of participants were prescribed pregabalin during the study period. Gabapentin receipt was time-updated based on responses at each survey wave.

Independent variable of interest: opioid use

Consistent with our prior work (Edelman et al., 2013; Edelman et al., 2020), we defined opioid use in two ways. First, prescribed opioid receipt was calculated for the 12 months prior to each survey and characterized based on the dose prescribed and the number of days supplied, assuming that doses were taken as prescribed. Doses were converted into morphine equivalent daily-doses (MEDD). Second, self-reported opioid use was assessed based on self-reported prescription opioid and heroin use as assessed during the baseline and follow-up surveys. Participants were provided a list of substances (e.g. cocaine, marijuana) and asked to identify use in the past 12 months as: *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 defined as present if any frequency of prescription opioid and/or heroin use was endorsed. Similar to gabapentin receipt, prescribed opioid receipt and self-reported opioid receipt were time-updated by survey wave.

Covariates

We selected sociodemographic, clinical, and behavioral correlates *a priori* that were plausibly related to gabapentin use and chronic pain management based on published literature and our clinical experiences (Merlin et al., 2014). Variables were assessed based on self-report and clinical/administrative data, including pharmacy fill/refill data, billing (International Classification of Diseases – 9th edition [ICD-9]) diagnostic codes documented in the year before or day of baseline survey data completion as applicable) and registry data.

We assessed calendar year as a categorical variable because survey waves did not occur each year, using the following mutually exclusive groups: 2002-2006, 2007-2011, and 2012-2017. Sociodemographic variables included age, sex, race and ethnicity, education, marital

status, housing instability, urbanicity of residence (based on rural/urban commuting codes (Hart, Larson, & Lishner, 2005)), and annual household income. To explore prescribing variation by facility, we included site of care (eight VA sites) at baseline as a categorical variable.

Clinical and behavioral variables included opioid use disorder diagnoses based on inpatient or outpatient ICD-9 codes for opioid abuse and/or opioid dependence in the year prior to survey administration. Tobacco use was based on self-report of current cigarette smoking. Unhealthy alcohol use was assessed with the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) questionnaire: a score of ≥3 for women and ≥4 for men was categorized as unhealthy alcohol use (Bush, Kivlahan, McDonell, Fihn, & Bradley, 1998). Given concerns for increased overdose risk with concomitant use of gabapentin and benzodiazepines (Peckham, Evoy, et al., 2018; Smith et al., 2016), we assessed benzodiazepine dose receipt by pharmacy fill/refill data.

Anxiety was assessed by the HIV Symptoms Index item (Justice et al., 2001), which asks whether the respondent felt nervous or anxious during the past four 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*). Depressive symptoms were defined as present based on a Patient Health Questionnaire 9 (PHQ-9) score of ≥10 (Kroenke, Spitzer, & Williams, 2001). Pain interference was assessed with one item from the 12-item short-form self-report scale (SF-12) of health-related quality of life: *During the past four weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?* Response options were dichotomized as *not at all* or *a little bit* versus *moderately, quite a bit, or extremely*.

HIV-related covariates included: antiretroviral therapy receipt (defined as receipt of ≥ three antiretroviral agents excluding boosters using pharmacy fill/refill data) consistent with standards during the study period; absolute CD4 cell count; HIV viral load, where undetectable was defined as <500 copies/mL; and VACS Index Score 2.0. VACS Index 2.0 is a validated measure of morbidity and mortality based on age, HIV viral load, absolute CD4 cell count, white blood cell count, aspartate aminotransferase, alanine aminotransferase, platelet count, creatinine, hepatitis C status, albumin, and body mass index (Tate, Sterne, Justice, Veterans Aging Cohort, & the Antiretroviral Therapy Cohort, 2019; Williams et al., 2019).

Covariates time-updated at each survey included age, VACS Index 2.0 scores, benzodiazepine receipt, depressive symptoms, and pain interference; other covariates were assessed at baseline only.

Statistical analyses

We grouped the population into three exclusive categories based on baseline data: no prescribed gabapentin, low dose gabapentin receipt, and high dose gabapentin receipt; we then characterized these groups using descriptive statistics. We used *t*-tests for continuous variables or a nonparametric counterpart for non-normally distributed continuous variables, and chi-square for categorical variables to compare characteristics by gabapentin receipt, considering $p < 0.05$ as statistically significant. We also examined baseline patterns of prescribed gabapentin by prescribed opioid receipt (i.e., none, less than 50mg MEDD, and greater than or equal to 50mg MEDD given increasing risks for adverse events above this threshold (Dowell et al., 2016)).

Gabapentin receipt was modeled longitudinally using generalized estimating equations across all survey waves. Specifically, we used multinomial logistic regression with generalized

estimating equations to determine the unadjusted and adjusted odds ratios for receipt of gabapentin, with no prescribed gabapentin as the referent category. Next, we performed sensitivity analyses in which we re-constructed the logistic regression models without the prescribed opioid variable (and including only the self-reported opioid use variable), and without the self-reported opioid use variable (and including only the prescribed opioid variable). Lastly, in *post-hoc* analysis, we included site of care as a variable in the multinomial model. In these analyses, we removed patient race/ethnicity from the model due to collinearity with site of care. We performed all descriptive statistics and models using SAS 9.4 (Cary, North Carolina, USA) in 2020.

Results

Baseline participant characteristics

Among VACS survey participants with HIV (N = 3,728), we excluded all 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 15-year study, the mean years of follow-up was 6 (standard deviation [SD] 4.2), and 38% died (**Table 1**). At baseline, the mean age for the sample was 50 years and nearly all identified as male (97%) and most identified as black (67%). Sixty percent had completed some college, 41% were married or living with a partner, 42% had experienced housing instability recently, 95% lived in urban settings, and 51% had an annual household income less than $12,000. Most were receiving antiretroviral therapy (77%), 58% had an undetectable viral load (<50 copies/uL), and the median absolute CD4 cell count was 378 cells/mm^3.

At baseline, 38% percent reported being bothered by anxiety, 23% reported at least moderate depressive symptoms, and 34% had at least moderate pain interference. 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 been previously diagnosed with OUD.

Among the analytic sample, 391 (11%) had received gabapentin in the 12 months prior to baseline and 902 (24%) received any gabapentin (i.e., at least one prescription) during the study period. The mean gabapentin dose was 1,469 mg/day. Regarding our two measures of opioid use, 1,028 (28%) had received prescribed opioids; 1,356 (37%) self-reported any opioid use. Regarding other medication classes, 508 (14%) were prescribed benzodiazepines. Among those prescribed gabapentin, the mean daily dose was 1,469mg (SD 1,114) and the mean days supplied was 114 (SD 103). Gabapentin daily dose receipt by category (none, low-dose [<1,469mg], and high-dose [≥1,469mg]) are shown over time in **Figure 1**. For each time period, approximately half of those PWH prescribed gabapentin were also prescribed opioids within the last 12 months, with little variation by time period.

Bivariate analyses

In bivariate analyses comparing gabapentin dose receipt categories, compared to those not prescribed opioids, those prescribed opioids at low (n = 880, 24% overall) or high doses (148, 4% overall) were more commonly prescribed low or high dose-gabapentin ($p < 0.01$). Self-reported opioid use (n = 1,356, 37% overall) was also more common in patients prescribed gabapentin ($p < 0.01$). Anxiety, depression, sleep problems, and painful symptoms were more common in patients prescribed gabapentin (**Table 1**). Neither gabapentin dose nor days supplied varied by opioid dose prescribed (**Table 2**).

Multivariable analyses

Longitudinal, multinomial logistic regression models demonstrated that high-dose prescribed benzodiazepines were associated with increased odds of receiving high-dose gabapentin (adjusted odds ratio [aOR], 95% confidence interval [CI] = 1.53 [1.03-2.27]), as was pain interference (1.65 [1.39-1.95]) and hand or foot pain (1.81 [1.45-2.26], **Table 3**). High-dose prescribed opioids were strongly associated with increased odds of high dose gabapentin receipt (2.66 [1.95-3.62]), but self-reported opioid use was not (1.03 [0.89-1.21]). In a *post-hoc* analysis, gabapentin receipt varied by site of care with greater odds of high-dose gabapentin receipt (compared to Atlanta as reference) in New York (1.75 [1.22-2.52]) and lesser odds in Washington, DC (0.51 [0.28-0.90]) and Pittsburgh (0.63 [0.39-1.00]; **Supplemental Table 1**).

Sensitivity analyses, in which the models were constructed without the self-reported opioid use variable and again without the prescribed opioid use variable, did not change the significance or directionality of predictors of gabapentin receipt (data not otherwise shown).

Discussion

In this national study of over 3,500 PWH engaged in care, about half of gabapentin prescriptions occurred with opioid prescriptions having also been dispensed within the last 12 months, and high-dose opioid prescription was an independent predictor of high-dose gabapentin prescription. This is of concern given increasing evidence that gabapentin may be harmful, particularly in combination with opioids, given their similar central nervous systems effects (Vickers Smith et al., 2018). The recent rise in the presence of gabapentin in opioid-related overdoses is also a reason for concern (Slavova et al., 2018), which are 60% more likely in patients who use opioids concurrently with gabapentin than those who do not take gabapentin

(Gomes et al., 2017). Co-prescribed benzodiazepines, self-report of at least moderate pain interference, site-of-care, and self-report of hand or foot pain were also independent predictors of gabapentin receipt. Self-reported opioid use, such as non-prescribed opioids including heroin, was not. Across the sample, prescribed gabapentin did not significantly increase in frequency or dose over time during our study period.

Our findings add to the growing literature characterizing the harmful co-prescribing of gabapentin and opioids among PWH and uninfected individuals (Buttram, Kurtz, Cicero, & Havens, 2019; Edelman et al., 2020; Gomes et al., 2017; Peckham, Evoy, et al., 2018; Peckham, Fairman, & Sclar, 2018a; Peckham & Sclar, 2019; Slavova et al., 2018; Smith et al., 2016). It has been suggested that clinicians, seeking alternatives to opioids and concerned about long-term adverse effects from non-steroidal anti-inflammatory drugs, may more readily prescribe gabapentinoids either instead of these other classes or in efforts to taper them (Goodman & Brett, 2017; Mahase, 2020), and there may be considerable variation in practice across providers or sites of care, as we observed (Green, Cooke O'Dowd, Watt, Majeed, & Pinder, 2019).In a national study of visits to office-based physicians in 2015, 11.8% of medical encounters involved an opioid prescription, and, among these, 16.2% had a gabapentinoid prescription (St Clair et al., 2020). In that study, predictors of opioid-gabapentinoid co-receipt included patient age, peaking at age 55-64 years, as well as number of other medications, peaking at 10 or more. Among PWH, a prior study using VACS showed that gabapentinoid receipt is more common among PWH with escalating opioid use trajectories than those with stable or infrequent trajectories (Edelman et al., 2020). Our study adds to these findings by demonstrating that prescribed opioids at higher doses are associated with prescribed gabapentin at higher doses. Additionally, our finding that prescribed benzodiazepines also correlates with gabapentin use raises concern for gabapentin co-

prescribing with other psychoactive medications in addition to opioids, including benzodiazepines, antidepressants, and other anticonvulsants.

Our finding that self-reported opioid use was not associated with gabapentin prescription, but prescribed opioid use was, warrants comment. Prior studies involving individuals not infected with HIV have demonstrated that, among a cohort of over 500 adults reporting nonmedical use of diverted prescription opioids, 15% report using gabapentin specifically "to get high." In that study, gabapentin use was assessed by self-report, and the most common source of gabapentin was physicians (52%); however, drug dealers were also a prominent source (36%) (Smith, Lofwall, & Havens, 2015). Because our assessment of gabapentin use was by prescription fill/refill data, we may have seen a stronger association between self-reported opioid use and gabapentin use if we also assessed self-reported (and therefore non-prescribed) gabapentin. However, our finding suggests that provider behavior plays an important role in the co-occurrence of gabapentin and opioid use in PWH. In a 2019 qualitative study that involved 12 key informant substance use disorder treatment providers in Florida, US, all informants reported the benefits of prescribing gabapentin to clients to manage problems related to withdrawal symptoms, mental distress, and pain, but there was lack of clarity about how gabapentin may be misused and its harms in conjunction with other opioids (Buttram, Kurtz, Ellis, & Cicero, 2019).

Our study has several limitations. First, our findings may not be generalizable to non-Veteran populations or women, since our participants represented a mostly male population with a high prevalence of comorbid medical and psychiatric conditions. However, the VA is the largest provider of HIV care in the US, with over 31,000 veterans receiving HIV care in 2019 (U.S. Department of Veterans Affairs, 2021), so our findings are directly relevant to a large and vulnerable population. In addition, our sample was from the U.S.; while prescribing patterns in

other settings likely differ, there is growing guidance internationally regarding co-prescribing of opioids and gabapentin (Krcevski Skvarc et al., 2021). Second, because surveys were self-administered, there may have been variability in the interpretation of the items among participants and over time, particularly regarding what type of opioid use was being queried. Third, our measures of medication receipt were based on VA pharmacy data and therefore did not capture non-VA medication. Fourth, we did not assess self-reported gabapentin use or prescriptions of pregabalin, which is also a gabapentinoid and has central nervous system effects similar to gabapentin (Schifano, 2014; Schifano et al., 2011). However, the low count of participants prescribed pregabalin (n=67, 2%) precluded the inclusion of pregabalin in our analyses. Finally, the number of survey respondents changed by year, with less respondents in later years. This may have impacted our calculations of gabapentin dose receipt for later years, as the individuals continuing to participate in survey completion may be more likely to be healthier than those who exit care.

Two key implications emerge from this study's findings. First, health systems should closely monitor for the co-prescription of gabapentin and opioids. Calls for increased pharmacovigilance of gabapentin have been made (Peckham, Fairman, & Sclar, 2017; Peckham & Sclar, 2018), and some US jurisdictions have increased regulatory oversight of gabapentin by either changing its status to schedule V or mandating reports of dispensing (Peckham, Fairman, & Sclar, 2018b). Providers and health systems that care for PWH in particular may benefit from these efforts. Second, our data suggest the need for site-specific, active interventions to promote safe prescribing of psychoactive medications for PWH. Academic detailing, an educational approach based on behavioral science that promotes rational prescribing, has shown promise in

encouraging the evidence-based use of medications for other disorders (Soumerai & Avorn, 1990) and has been successfully implemented in the VA health care system (Harris et al., 2016).

In summary, this national study of PWH engaged in care highlights a concerning phenomenon of co-prescribed opioids and gabapentin among this population. As providers seek to use non-opioid medications for the management of painful conditions by turning to gabapentin, they may be inadvertently introducing new harms. Supporting health systems and providers in the monitoring or gabapentin prescriptions and in safe management of painful conditions using evidence-based interventions is warranted. Further studies are needed to understand the relationship between other psychoactive substances (including benzodiazepines) and gabapentinoids and characterize the non-prescribed use of gabapentin in PWH and other populations.

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Declaration of interests:

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Table 1. Baseline sociodemographic and clinical characteristics by prescribed gabapentin dose among individuals with HIV participating in the Veterans Aging Cohort Study (N=3,702).

Characteristic	Overall (N=3702)	No gabapentin (N=3311, 90%)	Low-dose† gabapentin (N=196, 5%)	High-dose† gabapentin (N=195, 5%)	Overall *p* value
Average follow-up years, mean (SD)	7.0 (3.7)	7.0 (3.7)	6.8 (4.0)	7.0 (4.0)	0.75
Average number of completed surveys, mean (SD)	4.6 (2.2)	4.6 (2.2)	4.5 (2.3)	4.8 (2.4)	0.55
Demographics					
Age, mean (SD)	49.8 (8.9)	49.6 (9.0)	50.4 (7.8)	51.3 (8.3)	0.02
<45, n (%)	1040 (28.1)	947 (28.6)	49 (25.0)	44 (22.6)	0.30
45-65, n (%)	2478 (66.9)	2199 (66.4)	139 (70.9)	140 (71.8)	
>65, n (%)	184 (5.0)	165 (5.0)	8 (4.1)	11 (5.6)	
Gender, n (%)					0.64
Male	3604 (97.4)	3226 (97.4)	190 (96.9)	188 (96.4)	
Female	98 (2.7)	85 (2.6)	6 (3.1)	7 (3.6)	
Race/ethnicity, n (%)					<0.01
White	716 (19.3)	621 (18.8)	39 (19.9)	56 (28.7)	
Black	2478 (66.9)	2235 (67.5)	129 (65.8)	114 (58.5)	
Hispanic	355 (9.6)	311 (9.4)	22 (11.2)	22 (11.3)	
Other	153 (4.1)	144 (4.4)	6 (3.1)	3 (1.5)	
Education, n (%)					0.25
High school or less	1476 (40.3)	1310 (40.0)	90 (45.9)	76 (39.6)	
Some college or More	2190 (59.7)	1968 (60.0)	106 (54.1)	116 (60.4)	
Marital status, n (%)					0.89
Never married	832 (22.8)	746 (22.9)	42 (21.8)	44 (23.0)	
Married/living with Partner	1499 (41.1)	1337 (41.0)	86 (44.6)	76 (39.8)	
Divorced/widowed	1315 (36.1)	1179 (36.1)	65 (33.7)	71 (37.2)	
Housing instability ever	1562 (42.4)	1367 (41.5)	98 (50.3)	97 (50.8)	<0.01
Location of residence					0.52
Urban	3479 (95.0)	3116 (95.1)	180 (93.3)	183 (94.8)	
Suburban	103 (2.8)	91 (2.8)	8 (4.2)	4 (2.1)	
Rural	80 (2.2)	69 (2.1)	5 (2.6)	6 (3.1)	
Annual income					<0.01
<$11,999	1822 (50.9)	1599 (49.9)	128 (67.0)	95 (50.3)	
$12,000 - $49,999	1494 (41.7)	1357 (42.4)	55 (28.8)	82 (43.4)	
>=$50,000	266 (7.4)	246 (7.7)	8 (4.2)	12 (6.4)	
HIV-related factors					
Antiretroviral therapy receipt, n (%)	2855 (77.1)	2538 (76.7)	151 (77.0)	166 (85.1)	0.02
CD4 cell count, cells/mm3, median (IQR)	378 (227, 562)	377 (227, 561)	350 (210, 564)	402 (248, 589)	0.25
HIV viral load <500 copies/mL, n (%)	2113 (57.9)	1881 (57.6)	107 (55.4)	125 (64.8)	0.12
VACS Index 2.0 score, median (IQR)	57 (47, 69)	57 (47, 68)	62 (52, 75)	57 (47, 69)	<0.01
Other substance use, n (%)					
Smokes cigarettes	2839 (76.7)	2519 (76.1)	163 (83.2)	157 (80.5)	0.03
Unhealthy alcohol use	1352 (36.5)	1215 (36.7)	59 (30.1)	78 (40.0)	0.10

Marijuana	1021 (27.6)	906 (27.4)	57 (29.1)	58 (29.7)	0.69
Stimulants or Cocaine	164 (4.4)	147 (4.4)	4 (2.0)	13 (6.7)	0.08
Prescribed benzodiazepines, n (%)					<0.01
None	3194 (86.3)	2923 (88.3)	140 (71.4)	131 (67.2)	
Low-dose§	370 (10.0)	286 (8.6)	38 (19.4)	46 (23.6)	
High-dose§	138 (3.7)	102 (3.1)	18 (9.2)	18 (9.2)	
Prescribed opioids, n (%)					<0.01
None	2674 (72.2)	2472 (74.7)	100 (51.0)	102 (52.3)	
Low-dose‡	880 (23.8)	744 (22.5)	78 (39.8)	58 (29.7)	
High-dose‡	148 (4.0)	95 (2.9)	18 (9.2)	35 (18.0)	
Other health conditions and symptoms, n (%)					
HCV antibody positive	1415 (38.2)	1238 (37.4)	96 (49.0)	81 (41.5)	<0.01
Cancer	701 (18.9)	624 (18.9)	44 (22.5)	33 (16.9)	0.35
Anxiety symptoms	1349 (37.5)	1158 (35.9)	94 (50.5)	97 (52.4)	<0.01
Depressive symptoms	828 (22.6)	686 (20.9)	72 (37.5)	70 (36.1)	<0.01
Pain interference	1244 (33.9)	1003 (30.6)	115 (58.7)	126 (65.6)	<0.01
Hand/foot pain	1814 (49.0)	1531 (46.2)	134 (68.4)	149 (76.4)	<0.01
Sleep problems	2186 (59.1)	1902 (57.4)	145 (74.0)	139 (71.3)	<0.01
Muscle/joint pain	1941 (52.4)	1675 (50.6)	129 (65.8)	137 (70.3)	<0.01
Reported opioid use					<0.01
No use in last year	2346 (63.4)	2132 (64.4)	104 (53.1)	110 (56.4)	
Any use in last year	1356 (36.6)	1179 (35.6)	92 (46.9)	85 (43.6)	
Died during study period, n (%)	1422 (38.4)	1246 (37.6)	107 (54.6)	69 (35.4)	<0.01
Site					<0.01
Atlanta	567 (15.3)	513 (15.5)	29 (14.8)	25 (12.8)	
Bronx	378 (10.2)	329 (9.9)	24 (12.2)	25 (12.8)	
Houston	511 (13.8)	466 (14.1)	24 (12.2)	21 (10.8)	
Los Angeles	506 (13.7)	429 (13.0)	35 (17.9)	42 (21.5)	
NY	540 (14.6)	463 (14.0)	45 (23.0)	32 (16.4)	
Baltimore	487 (13.2)	461 (13.9)	12 (6.1)	14 (7.2)	
Washington DC	596 (16.1)	551 (16.6)	22 (11.2)	23 (11.8)	
Pittsburgh	117 (3.2)	99 (3.0)	5 (2.6)	13 (6.7)	

§ Benzodiazepine dose was dichotomized as low-dose (0 through 20mg diazepam-equivalent daily dose) and high-dose (greater than 20mg diazepam-equivalent daily dose)

‡ Opioid dose was dichotomized as low-dose (0 through 50mg morphine-equivalent daily dose) and high-dose (greater than 50mg morphine equivalent daily dose).

†High-dose gabapentin was defined as greater than or equal to the mean daily dose across the sample (1,469mg/day); low-dose gabapentin was defined as less than the mean daily dose.

Table 2. Baseline patterns of prescribed gabapentin among those prescribed gabapentin and stratified by no prescribed opioids, low-dose, and high dose opioid receipt among patients with HIV(N=3,702).

Characteristic	Overall sample (N=3702)	No prescribed opioid (N=2674)	Low-dose* prescribed opioid (N=880)	High-dose* prescribed opioid (N=148)	*p* value
Days supplied gabapentin					
Median, IQR	128 (47, 232)	120 (44, 233)	129 (44, 249)	163 (67, 214)	0.76
Mean (SD)	144.7 (103.6)	141.8 (105.2)	146.9 (107.6)	149.9 (87.3)	0.82
Gabapentin daily dose, mg					
Median, IQR	1126.2 (656.8, 2052.6)	1152.7 (686.2, 2080.0)	929.5 (600.0, 1854.3)	1334.9 (910.2, 2206.7)	0.08
Mean (SD)	1468.5 (1113.7)	1513.5 (1139.5)	1358.4 (1119.7)	1583.9 (987.2)	0.33

* Opioid dose was dichotomized as low-dose (0 through 50mg morphine-equivalent daily dose) and high-dose (greater than 50mg morphine equivalent daily dose).

Table 3. Multinomial regression using generalized estimating equations of factors associated with gabapentin dose receipt among patients with HIV (N = 3,702).

Characteristic	Any gabapentin AOR (95%CI) (N=391)	Low-dose† gabapentin AOR (95%CI) (N=196)	*p* value for groups low versus none	High-dose† gabapentin AOR (95%CI) (N=195)	*p* value for groups high versus none	Overall p value
Demographics						
Age			0.10		0.43	0.39
<45	Ref	Ref		Ref		
45-65	0.89 (0.67, 1.19)	0.68 (0.48, 0.98)		1.09 (0.74, 1.61)		
>65	1.27 (0.72, 2.25)	1.10 (0.52, 2.30)		1.81 (0.83, 3.96)		
Race/ethnicity, n (%)			0.50		0.12	0.12
White	Ref	Ref		Ref		
Black	1.20 (0.96, 1.51)	1.19 (0.90, 1.57)		1.32 (0.92, 1.89)		
Hispanic	1.07 (0.77, 1.49)	1.14 (0.76, 1.70)		1.06 (0.64, 1.76)		
Other	0.63 (0.38, 1.05)	0.81 (0.45, 1.44)		0.52 (0.22, 1.20)		
Housing instability ever	1.11 (0.97, 1.26)	1.09 (0.92, 1.29)	0.30	1.13 (0.95, 1.35)	0.17	0.13
Annual income			0.38		0.53	0.84
<$11,999	Ref	Ref		Ref		
$12,000 - $49,999	0.96 (0.78, 1.18)	0.91 (0.68, 1.21)		0.98 (0.74, 1.29)		
>=$50,000	1.11 (0.79, 1.58)	0.96 (0.59, 1.56)		1.23 (0.78, 1.94)		
HIV-related factors						
Antiretroviral therapy receipt, n (%)	1.05 (0.91, 1.22)	1.00 (0.82, 1.21)	0.96	1.12 (0.91, 1.38)	0.27	0.50
VACS Index 2.0 score, median (IQR)*	1.00 (0.99, 1.01)	1.01 (1.00, 1.03)	0.01	0.99 (0.98, 1.00)	0.02	0.98
Other substance use						
Smokes cigarettes, n (%)	1.04 (0.89, 1.22)	1.11 (0.90, 1.37)	0.31	1.03 (0.83, 1.28)	0.77	0.61
Prescribed benzodiazepines*			<0.01		0.03	<0.01
None, n (%)	Ref	Ref		Ref		
Low-dose§	1.13 (0.90, 1.43)	1.21 (0.91, 1.60)		1.02 (0.73, 1.40)		
High-dose§	1.35 (1.00, 1.83)	1.47 (1.03, 2.10)		1.53 (1.03, 2.27)		
Prescribed			<0.01		<0.01	<0.01

opioids*						
None, n (%)	Ref	Ref		Ref		
Low-dose‡	0.91 (0.76, 1.08)	0.98 (0.78, 1.23)		0.84 (0.67, 1.05)		
High-dose‡	2.16 (1.68, 2.78)	1.72 (1.25, 2.37)		2.66 (1.95, 3.62)		
Other health conditions and symptoms, n (%)						
HCV antibody positive	1.06 (0.92, 1.21)	1.04 (0.87, 1.25)	0.65	1.05 (0.87, 1.27)	0.61	0.44
Anxiety symptoms	0.92 (0.80, 1.07)	0.93 (0.78, 1.12)	0.45	0.88 (0.73, 1.07)	0.21	0.28
Depressive symptoms*	1.10 (0.96, 1.25)	1.10 (0.93, 1.31)	0.27	1.09 (0.91, 1.30)	0.38	0.17
Pain interference*	1.49 (1.32, 1.68)	1.37 (1.18, 1.60)	<0.01	1.65 (1.39, 1.95)	<0.01	<0.01
Hand/foot pain	1.60 (1.38, 1.86)	1.44 (1.20, 1.72)	<0.01	1.81 (1.45, 2.26)	<0.01	<0.01
Sleep problems	1.04 (0.89, 1.21)	1.19 (0.98, 1.46)	0.08	0.94 (0.76, 1.17)	0.59	0.64
Muscle/joint pain	1.01 (0.88, 1.16)	0.95 (0.80, 1.14)	0.60	1.06 (0.87, 1.29)	0.58	0.90
***Reported opioid use**			0.52		0.57	0.43
No use in last year	Ref	Ref		Ref		
Any use in last year	1.05 (0.94, 1.17)	1.05 (0.90, 1.23)		1.03 (0.89, 1.21)		
Calendar year of follow-up			0.25		0.66	0.34
2002-2006	Ref	Ref		Ref		
2007-2011	0.93 (0.79, 1.10)	0.91 (0.83,1.12)		0.93 (0.74, 1.17)		
2012-2017	1.14 (0.96, 1.35)	1.22 (0.97, 1.52)		1.12 (0.88, 1.42)		

* Time-updated variable (all others variables measured at baseline only)

§ Benzodiazepine dose was dichotomized as low-dose (0 through 20mg diazepam-equivalent daily dose) and high-dose (greater than 20mg diazepam-equivalent daily dose)

‡ Opioid dose was dichotomized as low-dose (0 through 50mg morphine-equivalent daily dose) and high-dose (greater than 50mg morphine equivalent daily dose).

†High-dose gabapentin was defined as greater than or equal to the mean daily dose across the sample (1,469mg/day); low-dose gabapentin was defined as less than the mean daily dose.

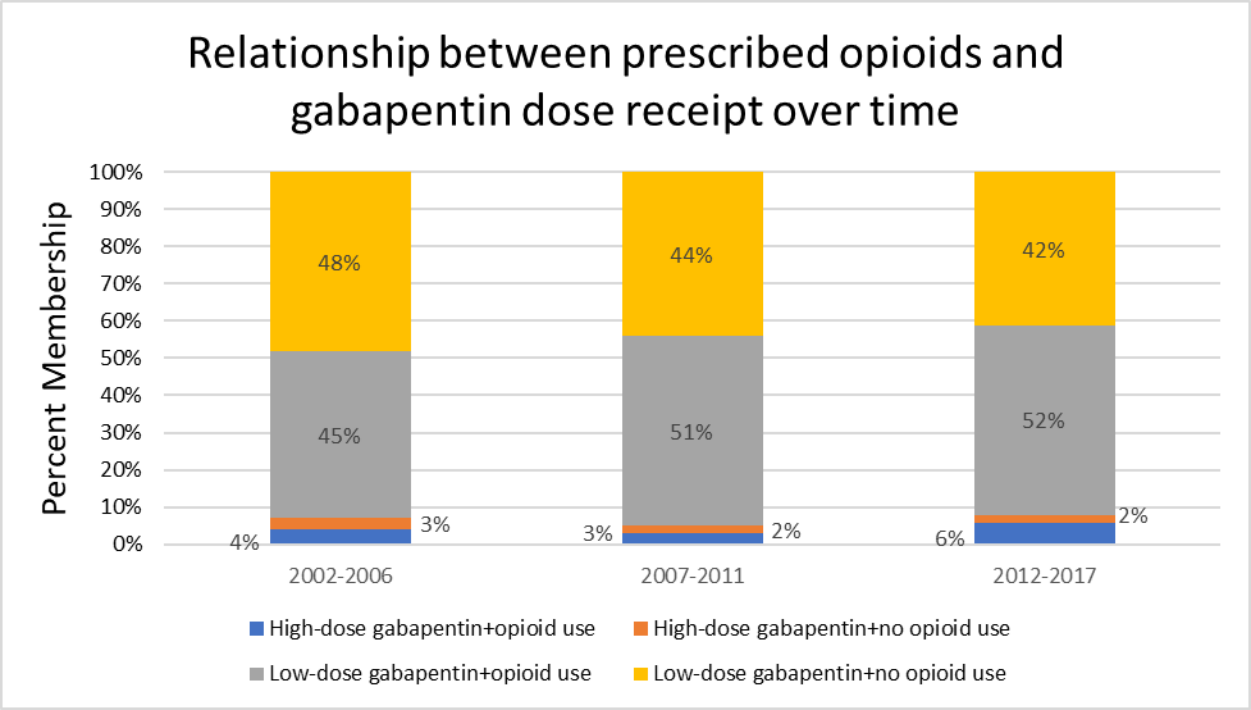

Figure 1. Relationship between opioid prescriptions and gabapentin dose receipt over time among 3,702 patients with HIV.

PWH: People with HIV.

High-dose gabapentin: greater than or equal to mean dose (1,469mg/day) receipt.

Low-dose gabapentin: lower than to mean dose (1,469mg/day) receipt.

Supplemental Table 1. Multinomial regression using generalized estimating equations of factors associated with gabapentin dose receipt among patients with HIV (N = 3,702), with site-of-care variable included.

Characteristic	Any gabapentin AOR (95%CI) (N=391)	Low-dose† gabapentin AOR (95%CI) (N=196)	*p* value for groups low versus none	High-dose† gabapentin AOR (95%CI) (N=195)	*p* value for groups high versus none	Overall p value
Demographics						
Age			0.05		0.63	0.40
<45	Ref	Ref		Ref		
45-65	0.84 (0.63, 1.12)	0.61 (0.42, 0.89)		0.86 (0.62, 1.20)		
>65	1.08 (0.61, 1.91)	0.84 (0.39, 1.77)		0.89 (0.66, 1.19)		
Housing instability ever	1.07 (0.94, 1.22)	1.06 (0.90, 1.26)	0.47	1.10 (0.92, 1.32)	0.29	0.32
Annual income			0.39		0.38	0.69
<$11,999	Ref	Ref		Ref		
$12,000 - $49,999	0.94 (0.76, 1.16)	0.89 (0.66, 1.19)		0.97 (0.74, 1.27)		
>=$50,000	1.17 (0.83, 1.65)	1.01 (0.61, 1.65)		1.28 (0.83, 1.99)		
HIV-related factors						
Antiretroviral therapy receipt, n (%)	1.00 (0.86, 1.16)	0.92 (0.75, 1.12)	0.41	1.09 (0.88, 1.35)	0.41	0.99
VACS Index 2.0 score, median (IQR)*	1.00 (0.99, 1.01)	1.02 (1.01, 1.03)	<0.01	0.99 (0.98, 1.00)	0.11	0.49
Other substance use						
Smokes cigarettes, n (%)	1.04 (0.89, 1.22)	1.11 (0.90, 1.37)	0.30	1.04 (0.84, 1.29)	0.71	0.62
Prescribed benzodiazepines*			<0.01		0.03	<0.01
None, n (%)	Ref	Ref		Ref		
Low-dose§	1.16 (0.92, 1.47)	1.23 (0.92, 1.64)		1.03 (0.74, 1.43)		
High-dose§	1.29 (0.94, 1.77)	1.34 (0.92, 1.94)		1.52 (1.00, 2.30)		
Prescribed opioids*			<0.01		<0.01	<0.01
None, n (%)	Ref	Ref		Ref		
Low-dose‡	0.88 (0.74, 1.05)	0.99 (0.78, 1.25)		0.82 (0.65, 1.03)		
High-dose‡	2.26 (1.75, 2.92)	1.76 (1.26, 2.45)		2.76 (2.01, 3.79)		
Other health conditions and symptoms, n (%)						
HCV antibody positive	1.06 (0.92, 1.22)	1.04 (0.87, 1.25)	0.67	1.07 (0.87, 1.30)	0.53	0.67
Anxiety	0.92 (0.80, 1.06)	0.92 (0.77, 1.11)	0.37	0.88 (0.72, 1.08)	0.22	0.37

symptoms						
Depressive symptoms*	1.13 (0.99, 1.28)	1.13 (0.95, 1.34)	0.18	1.11 (0.93, 1.33)	0.27	0.18
Pain interference*	1.48 (1.31, 1.68)	1.39 (1.18, 1.62)	<0.01	1.62 (1.36, 1.93)	<0.01	<0.01
Hand/foot pain	1.62 (1.39, 1.87)	1.42 (1.18, 1.70)	<0.01	3.50 (2.24, 5.46)	<0.01	<0.01
Sleep problems	1.03 (0.88, 1.20)	1.20 (0.98, 1.46)	0.07	0.93 (0.75, 1.15)	0.50	0.73
Muscle/joint pain	0.98 (0.85, 1.13)	0.93 (0.78, 1.11)	0.42	1.03 (0.84, 1.26)	0.78	0.83
***Reported opioid use**			0.57		0.75	0.46
No use in last year	Ref	Ref		Ref		
Any use in last year	1.04 (0.93, 1.17)	1.05 (0.90, 1.22)		1.03 (0.88, 1.20)		
Calendar year of follow-up			0.33		0.57	0.32
2002-2006	Ref	Ref		Ref		
2007-2011	0.96 (0.81, 1.14)	0.95 (0.77, 1.19)		0.95 (0.75, 1.20)		
2012-2017	1.14 (0.96, 1.36)	1.19 (0.95, 1.49)		1.15 (0.89, 1.47)		
Site			<0.01		<0.01	<0.01
Atlanta	Ref	Ref		Ref		
Bronx	0.90 (0.67, 1.23)	0.97 (0.65, 1.47)		0.87 (0.57, 1.33)		
Houston	1.39 (0.99, 1.96)	1.72 (1.10, 2.69)		1.27 (0.79, 2.02)		
Los Angeles	0.79 (0.57, 1.08)	1.01 (0.69, 1.47)		0.66 (0.40, 1.08)		
New York	1.64 (1.23, 2.18)	1.45 (0.96, 2.20)		1.75 (1.22, 2.52)		
Baltimore	1.33 (1.02, 1.74)	2.08 (1.51, 2.89)		1.01 (0.68, 1.52)		
Washington, DC	0.39 (0.25, 0.61)	0.31 (0.16, 0.62)		0.51 (0.28, 0.90)		
Pittsburgh	0.66 (0.47, 0.92)	0.72 (0.45, 1.16)		0.63 (0.39, 1.00)		