AIDS and Behavior (2019) 23:3340–3349
https://doi.org/10.1007/s10461-019-02608-3

ORIGINAL PAPER

Patterns and Correlates of Prescription Opioid Receipt Among US Veterans: A National, 18-Year Observational Cohort Study

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Published online: 17 July 2019

Abstract

A better understanding of predisposition to transition to high-dose, long-term opioid therapy after initial opioid receipt could facilitate efforts to prevent opioid use disorder (OUD). We extracted data on 69,268 patients in the Veterans Aging Cohort Study who received any opioid prescription between 1998 and 2015. Using latent growth mixture modelling, we identified four distinguishable dose trajectories: low (53%), moderate (29%), escalating (13%), and rapidly escalating (5%). Compared to low dose trajectory, those in the rapidly escalating dose trajectory were proportionately more European-American (59% rapidly escalating vs. 38% low); had a higher prevalence of HIV (31% vs. 29%) and hepatitis C (18% vs. 12%); and during follow-up, had a higher incidence of OUD diagnoses (13% vs. 3%); were hospitalised more often [18.1/100 person-years (PYs) vs. 12.5/100 PY]; and had higher all-cause mortality (4.7/100 PY vs. 1.8/100 PY, all $p < 0.0001$). These measures can potentially be used in future prevention research, including genetic discovery.

Keywords Opioids · Pharmacoepidemiology · Pharmacy fill data · Phenotype · Electronic health records

Introduction

Globally, pain is highly prevalent and a major contributor to poor quality of life [1–3]. Compounding the deleterious impact of pain per se, long-term opioid therapy—a mainstay of pain treatment for the past 25 years—carries a risk of opioid use disorder (OUD) and a variety of short- and long-term adverse effects and dose-dependent excess mortality [4–6]. These risks, coupled with findings of modest or minimal benefit, have spurred efforts to shift chronic pain treatment to non-opioid and non-pharmacologic approaches [7, 8]. Current opioid prescribing guidelines recommend weighing likely benefit against risk before initiating treatment and re-weighing that balance at frequent intervals during treatment. Recognizing the dose-dependent nature of most opioid therapy-related harms, the 2016 Guideline for Prescribing Opioids for Chronic Pain from the U.S. Centers for Disease Control and Prevention recommended extra caution when exceeding 50 milligrams (mg) morphine equivalent daily dose (MEDD) and to avoid exceeding 90 mg MEDD [9]. In the UK and Germany, prescribing guidelines recommend caution exceeding doses higher than 120 mg MEDD [10, 11]. Despite these guidelines, little is known about patterns of prescription opioid use over the course of therapy, including dose and duration, and which factors distinguish patients across clinically distinct categories of exposure.

Prior studies of moderate- and high-dose opioid therapy have identified history of mental health and substance use disorder diagnoses as important risk factors for OUD, and have shown that African-Americans (AA) were consistently less likely to be prescribed high-dose opioid therapy than European-Americans (EA) [12, 13]. Another striking and consistent finding is a relatively small proportion of patients consuming a high proportion of all prescribed opioids. For example, Edlund et al. found that 5% of a cohort of privately-insured patients received 70% of the opioids prescribed [14], suggesting the presence of a distinct predisposition

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10461-019-02608-3) contains supplementary material, which is available to authorized users.

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for high-dose, long-term opioid use among some individuals. While risk gene identification is a critical step towards understanding the biology of inter-individual differences in drug response, only a few genome-wide association studies reporting significant results for opioid dependence [15–18] or dosing [19] have been published to date, all of which had relatively small sample sizes and varying definitions of opioid exposure. Better opioid exposure metrics could enhance efforts to identify patients with distinct patterns of prescription opioid exposure (i.e. a phenotype) that place them at increased risk of developing OUD and other harms. Electronic health record (EHR) data are an underutilised source of information to develop such metrics of prescription opioid receipt.

Understanding patterns of and risk factors for long-term opioid therapy is particularly important among patients with HIV. Prior studies have shown persons with HIV are more likely to receive both any [20] and long-term opioid therapy [21] and are at higher risk of death on long-term opioid therapy than individuals without HIV [22]. Mounting evidence that long-term opioid therapy adversely impacts immune function leading to increased risk of pneumonia [23, 24] adds to the importance of this topic for patients with HIV and the physicians who treat them. Using a large, population-based sample, we sought to develop empirical, clinically-meaningful phenotypes of prescription opioid receipt among patients with and without HIV. Because high-dose, long-term prescription opioid use is a complex trait manifested through various interacting pharmacokinetic (e.g., metabolic), pharmacodynamic (e.g., receptor-mediated), and environmental factors, we explored a variety of measures that may ultimately be useful in elucidating different aspects of the pathophysiology of OUD.

Methods

Study Design and Sample

We used data from the Veterans Aging Cohort Study (VACS), described in detail elsewhere [25, 26]. In brief, the VACS is a large, observational cohort based on data from the U.S. Department of Veterans Affairs (VA) EHR that includes all HIV-infected patients in VA care (> 50,000 HIV+ subjects) and uninfected patients (> 100,000), 1:2 matched on region, age, race/ethnicity, and sex. The development of VACS was approved by the Institutional Review Boards of the VA Connecticut Healthcare System and Yale School of Medicine, granted a waiver of informed consent, and deemed Health Insurance Portability and Accountability Act (HIPAA) compliant.

We included all patients who were dispensed any opioid prescription of at least seven consecutive days between 1 January 1998 and 30 September 2015. We defined baseline date as the first dispensed opioid prescription during the study period. So as to accurately assess changes in dosing over time, we limited the sample to new prescription opioid users by excluding individuals with baseline opioid receipt > 90 mg MEDD. A dose of this magnitude suggests a high likelihood of transfer into the VA system with previous opioid use (i.e., unlikely to be true opioid initiation), Further, we excluded individuals unlikely to have sufficient data to establish longitudinal exposure patterns such as those with less than 6 months of VA follow-up after baseline or high risk for mortality at baseline. Thus, we excluded those with a cancer diagnosis (except non-melanoma skin cancers) before or during follow-up, or a VACS Index score > 100 at baseline, which indicates a 20% 1-year mortality risk and is a proxy for severe illness [27]. The VACS Index is a measure of physiologic injury incorporating age, CD4 count, HIV-1 RNA, haemoglobin, a marker of liver fibrosis (FIB-4), estimated glomerular filtration rate, and hepatitis C virus (HCV) status, and has been shown to predict AIDS and non-AIDS morbidity and mortality in multiple settings [28–33]. Finally, we excluded individuals with diagnosis of OUD or evidence of OUD treatment at baseline recognising that prescription opioid usage patterns may differ in this subgroup. Thus, we excluded individuals with a past OUD diagnosis [defined by International Classification of Diseases, Ninth Revision (ICD-9) codes: 304.0, 304.7, or 305.5], opioid treatment program attendance (defined by VA stop code: 523), or buprenorphine receipt prior to baseline.

Opioid Metrics

We followed patients from baseline to the end of their last opioid prescription fill (allowing for any gap length between fills), death, or last VA visit, up to 30 September 2015. All outpatient opioids in all formulationsprescribed for any indication during follow-up were considered in the analysis. We transformed each opioid prescription dose into MEDD by multiplying the daily quantity by the strength of the prescription using standard procedures [20]. We then constructed five continuous measures based on MEDD for each patient for the duration of their follow-up: mean, median, mode, maximum, and cumulative dose. Because hospitalised patients are likely to receive an opioid that replaces a concurrent outpatient prescription, any opioids dispensed during inpatient stays and days of inpatient stays were removed from the calculation of all measures as a way to avoid double count of exposure. We capped each of the five continuous measures at their raw distribution's 99th percentile to remove undue influence by extreme outliers.

Next, we used latent growth mixture modelling to identify major classes of opioid dose trajectories [34]. Models were implemented in SAS using PROC TRAJ [35, 36]. The

procedure calculates each individual's probability of belonging to each trajectory and assigns them to the trajectory with the highest probability of membership. We used censored normal models and evaluated 1- to 7-group models. The optimal number of classes was determined by balancing three criteria: changes in the Bayesian information criterion (BIC, where smaller indicates a better fit), a sufficient average group membership probability (> 70%), and a sufficient proportion of patients in each group to permit meaningful analysis (i.e., > 1% or n > 700) [37]. We used number of 90-day intervals elapsed since baseline as the time scale (presented in figures as years since baseline for readability) and mean MEDD per interval as the dependent variable. Models were stratified by HIV status to look for potential differences in opioid dose trajectories. As a sensitivity analysis, we compared trajectory group assignment between the final model from the full sample with the same model limited to those with complete data at 4, 8, and 12 years.

Sample Characteristics

We extracted demographic and clinical characteristics from the VA EHR. Demographic variables included age at baseline, sex, and self-reported race/ethnicity. Clinical characteristics included HIV status (defined by ICD-9 codes 042, 044 or V08), HCV infection ever (determined by any confirmatory HCV RNA test before or during the study period), VACS Index in the year prior to baseline, pain-related diagnoses (abdominal, back, chest, extremity, fractures, headaches, kidney stones, menstrual, neck, neuropathic, osteoarthritis, rheumatoid arthritis, temporomandibular, and other), and comorbid conditions (anxiety disorder, bipolar disorder, coronary artery disease, congestive heart failure, cirrhosis, chronic obstructive pulmonary disease, diabetes, drug-related diagnoses, hypertension, major depression, post-traumatic stress disorder, renal insufficiency, schizophrenia, and other psychoses). Pain-related diagnoses and comorbid conditions were defined by the presence of one inpatient or two outpatient ICD-9 codes (Supplementary Table 1) assessed prior to baseline allowing for a 180-day lag after baseline [20]. These characteristics were assessed at baseline to support future predictive models that would identify patients potentially at risk of transitioning to high-dose, long-term opioid therapy. We extracted substance use and pain during follow-up because of shared associations across substances (e.g., opioids, alcohol, and nicotine) and their relationship with chronic pain [38]. Smoking status (never vs. ever) was based on self-report. ICD-9 codes were used for alcohol use disorder (AUD) (303.X or 305-305.03) and incident OUD (304.0, 304.7, and 305.5), The numeric rating scale (NRS) pain score is a widely used screening instrument that queries patients on their pain intensity on a scale from 0 ("no pain") to 10 ("worst pain") [39, 40]. Median NRS pain scores were used to identify moderate or severe pain (scores ≥ 4). Hospitalisation and all-cause mortality rates per 100 person-years (PYs) were estimated to provide construct validity for the opioid metrics.

Statistical Analyses

We compared patients in each of the identified trajectory groups by all extracted demographic and clinical characteristics at baseline and during follow-up using Chi square (χ^2) tests for categorical variables and non-parametric Kruskal–Wallis χ^2 tests for continuous variables. Given the large sample size effect on statistical significance, we considered an absolute difference of 5% in prevalence of pain-related diagnoses or comorbid conditions between any two trajectory groups clinically important. We also characterised all opioid prescriptions dispensed to patients in each of the trajectory groups by formulation and type of opioid. For each patient, we calculated the proportion of follow-up time exposed to prescription opioids as the total number of days prescribed opioids divided by the total number of days of follow-up during the study period. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Sample Characteristics

Of the 163,743 patients in VACS, 105,812 (65%) received an opioid prescription for ≥ 7 consecutive days during the study period. At baseline, 9857 (9%) of the 105,812 opioid-exposed patients had a cancer diagnosis, 301 (0.3%) had a VACS Index score > 100, 7684 (7%) had an OUD diagnosis, 1474 (1%) had attended an opioid treatment programme, 80 (0.1%) had received buprenorphine, 1822 (2%) had an initial opioid prescription > 90 mg MEDD, and 21,680 (20%) had less than 6 months of follow-up. In total, 36,544 (35%) of the 105,812 patients who received an opioid prescription were excluded from this analysis (Fig. 1).

The 69,268 remaining patients had a mean baseline age of 49 years [standard deviation (SD) = 10 years] and were predominately male (97%); 47% were AA and 42% were EA; and 28% were HIV+. Mean follow-up time was 8 years (SD = 4 years). Baseline date ranged from April 1998 to August 2015 (median August 2003). Among the 2.3 million opioid prescriptions captured in this analysis, the vast majority (96%) were of tablet formulation with the remaining other oral or transdermal formulations (e.g., elixirs, patches). The most commonly prescribed opioids were hydrocodone (34%), oxycodone (20%), tramadol (17%), codeine (11%), and morphine (9%).

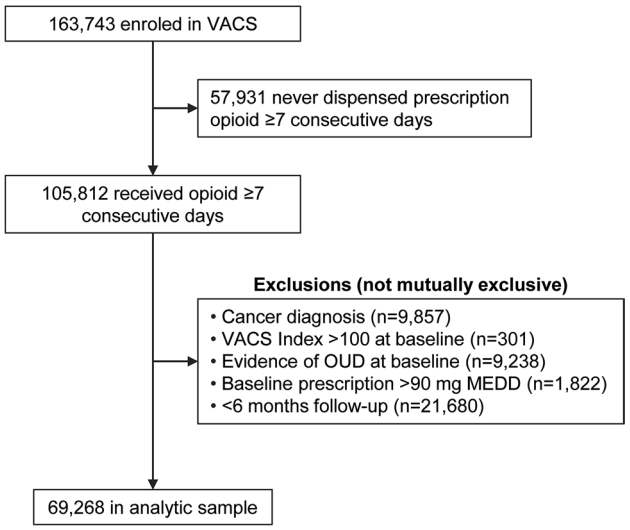

Fig. 1 Study flow diagram

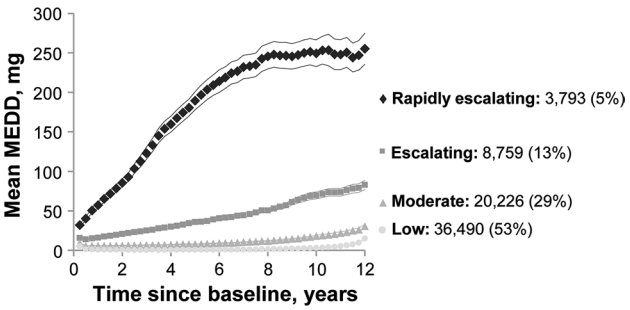

Fig. 2 Prescription opioid dose trajectories among 69,268 opioid-exposed patients in the US Veterans Aging Cohort Study 1998–2015

Trajectory Modelling

In all models, all groups had an average group membership probability > 80% and contained > 3% (n ~ 2000) patients. We chose a 4-group trajectory model because there was little marginal benefit when increasing to a 5-, 6-, or 7-group model compared to when increasing from a 2- to 3- or 3- to 4-group model, as measured by BIC (Supplemental Fig. 1). The four opioid dose trajectory groups were designated as low dose (n = 36,490, 53%), moderate dose (n = 20,226, 29%), escalating dose (n = 8759, 13%), and rapidly escalating dose (n = 3793, 5%, Fig. 2). Trajectory models were largely similar when stratified by HIV status (Supplemental Fig. 2). Patients with HIV in the rapidly escalating dose trajectory reached higher doses than uninfected patients; however, the estimates had more variance than uninfected patients in the same dose trajectory. To maximize precision in dose trajectory estimates, we combined HIV+ and uninfected patients into a single model for the primary analysis and calculated HIV prevalence in each trajectory group. Agreement between trajectory group assignment using a combined model compared to models stratified by HIV status was high (98.2% for HIV+ and 99.4% for uninfected, Supplemental Table 2). Compared to models limited to individuals with complete data at 4, 8, and 12 years, agreement of trajectory group assignment was 75.9% at 4 years, 88.0% at 8 years, and 96.7% at 12 years (Supplemental Table 3). These findings suggest there may be fewer than four distinct trajectory groups when models are limited to shorter follow-up times.

Characteristics by Trajectory Group

Bivariate comparisons of demographic and clinical characteristics by trajectory groups were all statistically significant ($p < 0.001$), except for temporomandibular pain ($p = 0.18$, Table 1). While statistically significant,the differences in some baseline pain-related diagnoses (i.e., abdominal, fractures, headaches, kidney stones, menstrual, rheumatoid arthritis, and temporomandibular) and comorbid conditions (anxiety disorder, bipolar disorder, coronary artery disease, congestive heart failure, cirrhosis, chronic obstructive pulmonary disease, drug-related diagnoses, major depression, post-traumatic stress disorder, renal insufficiency, schizophrenia, and other psychoses) were not > 5% between any two trajectory groups and thus the data are not otherwise shown.

Compared to individuals in the low dose trajectory, those in the rapidly escalating dose trajectory were more likely to be EA (59% of rapidly escalating patients vs. 38% of low; $\chi^2 = 1059$, $p < 0.0001$), to have HIV (31% vs. 29%; $\chi^2 = 145$, $p < 0.0001$), and hepatitis C infection (18% vs. 12%; $\chi^2 = 155$, $p < 0.0001$), and less likely to be AA (32% vs. 50%; $\chi^2 = 1059$, $p < 0.0001$) and to have diabetes at baseline (12% vs. 15%; $\chi^2 = 121$, $p < 0.0001$). All reported statistical tests in this and subsequent paragraphs are for the analyses of all four trajectory groups rather than directly comparing the two extreme trajectory groups. It should be noted the lowest or highest prevalence of demographic or clinical characteristics were not always found in the extreme trajectory groups. For example, prevalence of HIV infection was lowest in the moderate dose trajectory (25%). Full details can be found in Table 1.

The most common pain-related diagnoses were extremity (53%), back (50%), osteoarthritis (38%), and other pain (38%). Compared to individuals in the low dose trajectory, those in the rapidly escalating dose trajectory had higher baseline prevalence of back pain (62% of rapidly escalating patients vs. 43% of low; $\chi^2 = 1379$, $p < 0.0001$), neck pain (19% vs. 12%; $\chi^2 = 353$, $p < 0.0001$), neuropathic pain (17% vs. 9%; $\chi^2 = 349$, $p < 0.0001$), and osteoarthritis (44% vs. 37%; $\chi^2 = 841$, $p < 0.0001$). Conversely, those in the

Table 1 Baseline characteristics of 69,268 opioid-exposed patients in the Veterans Aging Cohort Study between 1998 and 2015, by opioid dose trajectory group

	Full sample	Trajectory group				χ^2
		Low	Moderate	Escalating	Rapidly escalating	
Sample size, n (%)	69,268	36,490 (53)	20,226 (29)	8759 (13)	3793 (5)	
Age, mean (SD)	49 (10)	48 (10)	50 (10)	49 (10)	48 (9)	394
Male	66,972 (97)	35,084 (96)	19,588 (97)	8584 (98)	3716 (98)	102
Race						
African American	32,448 (47)	18,238 (50)	9510 (47)	3479 (40)	1221 (32)	1059
European American	29,299 (42)	13,997 (38)	8519 (42)	4527 (52)	2256 (59)	
Hispanic	5593 (8)	3279 (9)	1604 (8)	504 (6)	206 (5)	
Other	1928 (3)	976 (3)	593 (3)	249 (3)	110 (3)	
HIV+	19,308 (28)	10,709 (29)	5099 (25)	2307 (26)	1193 (31)	145
HCV+	9407 (14)	4503 (12)	2814 (14)	1420 (16)	670 (18)	155
VACS Index, mean (SD)	17.6 (18)	17.2 (17)	18.1 (18)	17.8 (18)	18.6 (19)	45
NRS pain score, mean (SD)	3.1 (3)	2.7 (3)	3.3 (3)	3.8 (3)	4.4 (3)	1281
Pain-related diagnoses						
Back	34,583 (50)	15,818 (43)	11,330 (56)	5099 (58)	2336 (62)	1379
Chest	16,934 (24)	8820 (24)	5277 (26)	2050 (23)	787 (21)	64
Extremity	42,186 (61)	21,248 (58)	13,309 (66)	5413 (62)	2216 (58)	326
Neck	10,238 (15)	4530 (12)	3478 (17)	1504 (17)	726 (19)	353
Neuropathic	7819 (11)	3426 (9)	2575 (13)	1156 (13)	662 (17)	349
Osteoarthritis	28,843 (42)	13,337 (37)	9630 (48)	4205 (48)	1671 (44)	841
Other	32,595 (47)	17,915 (49)	9535 (47)	3674 (42)	1471 (39)	257
Comorbid conditions						
Diabetes	10,712 (15)	5362 (15)	3567 (18)	1320 (15)	463 (12)	121
Hypertension	23,020 (33)	11,249 (31)	7530 (37)	3058 (35)	1183 (31)	259

Categorical reported as n (%), continuous reported as mean (SD); significance tested using Chi square (χ^2) or non-parametric Kruskal–Wallis χ^2 tests comparing all four trajectory groups; mean probability of trajectory group membership was 0.94, 0.88, 0.92, and 0.97 for the low, moderate, escalating, and rapidly escalating group, respectively; all $p < 0.0001$

HIV human immunodeficiency virus, *HCV* hepatitis C virus, *VACS* Veterans Aging Cohort Study, *NRS* numeric rating scale, *SD* standard deviation

highest dose trajectory had proportionately fewer chest pain diagnoses (21% of rapidly escalating patients vs. 24% of low; $\chi^2 = 64$, $p < 0.0001$) and other pain diagnoses (39% vs. 49%; $\chi^2 = 259$, $p < 0.0001$) at baseline than those in the low dose trajectory. Average baseline NRS pain scores increased linearly from 2.7 (SD = 3) in the low opioid dose trajectory to 4.4 (SD = 3) in the rapidly escalating dose trajectory ($\chi^2 = 1281$, $p < 0.0001$). Similar averages were found when looking at average NRS pain scores during follow-up, with a more pronounced linear trend ($\chi^2 = 7602$, $p < 0.0001$).

The proportion of follow-up time exposed to prescription opioids differed by dose trajectory group, increasing from 6% in the low dose trajectory to 32% in the moderate trajectory, 65% in the escalating trajectory, and 82% in the rapidly escalating trajectory ($\chi^2 = 50{,}855$, $p < 0.0001$, Table 2). Individuals in the low trajectory group had an average mean exposure of 20 mg MEDD (SD = 11 mg), while those in the rapidly escalating trajectory group had an average mean exposure of 107 mg MEDD (SD = 52 mg; $\chi^2 = 22{,}161$, $p < 0.0001$). Median, mode, maximum, and cumulative measures were strongly correlated with increasing trajectory group. The most commonly prescribed type of opioids were hydrocodone (35%) and tramadol (24%) in the low dose trajectory compared with oxycodone (31%) and morphine (26%) in the rapidly escalating trajectory group. Compared to individuals in the low dose trajectory, those in the rapidly escalating dose trajectory were hospitalised more often (18.1/100 PY vs. 12.5/100 PY; $\chi^2 = 520$, $p < 0.0001$) and had higher all-cause mortality (4.7/100 PY vs. 1.8/100 PY; $\chi^2 = 1300$, $p < 0.0001$).

Multi-substance use and self-reported pain were common in this sample of opioid-exposed patients. Overall, 70% of the sample reported smoking, 32% received an AUD diagnosis during follow-up, and 40% reported moderate to severe pain during follow-up (Fig. 3). Compared to individuals in the low dose trajectory, those in the rapidly escalating trajectory were

Table 2 Follow-up characteristics of 69,268 opioid-exposed patients in the Veterans Aging Cohort Study between 1998 and 2015, by opioid dose trajectory group

	Full sample	Trajectory group				χ^2
		Low	Moderate	Escalating	Rapidly escalating	
Sample size, n (%)	69,268	36,490 (53)	20,226 (29)	8759 (13)	3793 (5)	
OUD	3475 (5)	1256 (3)	992 (5)	728 (8)	499 (13)	917
AUD	22,283 (32)	11,472 (31)	6629 (33)	3033 (35)	1149 (30)	43
Smoking status						
Ever	48,794 (70)	24,784 (68)	14,365 (71)	6747 (77)	2898 (76)	671
Never	19,292 (28)	11,317 (31)	5530 (27)	1794 (20)	651 (17)	
NRS pain score, mean (SD)	2.9 (3)	2.1 (3)	3.4 (3)	4.2 (3)	4.8 (3)	7602
NRS pain score category						
Moderate pain, 4–6	19,220 (28)	7264 (20)	6809 (34)	3527 (40)	1620 (43)	2644
Severe pain, 7–10	8628 (12)	2719 (7)	3031 (15)	1856 (21)	1022 (27)	2346
Hospitalization rate, per 100 PY (95% CI)	13.8 (13.6–13.9)	12.5 (12.4–12.7)	14.7 (14.4–15.0)	15.8 (15.3–16.2)	18.1 (17.4–18.8)	520
Mortality rate, per 100 PY (95% CI)	2.45 (2.41–2.49)	1.84 (1.79–1.88)	2.74 (2.66–2.82)	3.44 (3.31–3.58)	4.70 (4.46–4.95)	1300
Years of follow-up, mean (SD)	7.6 (4)	7.8 (4)	7.3 (4)	7.6 (4)	7.6 (4)	215
Proportion of exposed follow-up time	0.25	0.06	0.32	0.65	0.82	50,855
Continuous MEDD measures, mg (SD)						
Mean	29 (30)	20 (11)	25 (18)	47 (34)	107 (52)	22,161
Median	26 (28)	18 (12)	22 (17)	41 (32)	98 (55)	20,162
Mode	25 (30)	16 (13)	22 (19)	40 (35)	95 (58)	18,087
Maximum	81 (85)	46 (39)	79 (67)	148 (103)	271 (103)	23,401
Cumulative	26,796 (49,041)	3501 (5491)	23,319 (25,366)	81,088 (62,324)	144,066 (73,402)	38,191
Number of outpatient opioid prescriptions	2,297,421	332,937	763,197	709,161	492,126	
Hydrocodone	34%	35%	40%	39%	16%	85,302
Oxycodone	20%	15%	14%	22%	31%	59,313
Tramadol	17%	24%	25%	13%	4%	117,800
Codeine	11%	20%	13%	8%	4%	69,919
Morphine	9%	1%	3%	9%	26%	219,588
Propoxyphene	4%	3%	4%	4%	4%	787
Methadone	3%	< 1%	1%	3%	10%	91,739
Fentanyl	1%	< 1%	< 1%	1%	5%	43,154
Other[a]	< 1%	< 1%	< 1%	1%	1%	5150

Categorical reported as n (%), continuous reported as mean (SD); significance tested using Chi square (χ^2) or non-parametric Kruskal–Wallis χ^2 tests comparing all four trajectory groups; mean probability of trajectory group membership was 0.94, 0.88, 0.92, and 0.97 for the low, moderate, escalating, and rapidly escalating group, respectively; all $p < 0.0001$

OUD opioid use disorder, *AUD* alcohol use disorder, *NRS* numeric rating scale, *SD* standard deviation, *PY* person-years, *CI* confidence interval, *MEDD* morphine equivalent daily dose

[a]Includes hydromorphone, meperidine, pentazocine, tapentadol, levorphanol, buprenorphine, oxymorphone

more likely to have an incident OUD diagnosis (13% of rapidly escalating patients vs. 3% of low; $\chi^2 = 917$, $p < 0.0001$), report smoking (76% vs. 68%; $\chi^2 = 671$, $p < 0.0001$), and report moderate (43% vs. 20%; $\chi^2 = 2644$, $p < 0.0001$) or severe pain (27% vs. 7%; $\chi^2 = 2346$, $p < 0.0001$) during follow-up. Patients were more likely to have an AUD diagnosis during follow-up in the moderate dose trajectory (33%) and escalating dose trajectory (35%) when compared to those in the low dose trajectory (31%; $\chi^2 = 43$, $p < 0.0001$). However, those in the rapidly escalating dose trajectory had proportionately fewer AUD diagnoses during follow-up (30%).

Discussion

In a large, national cohort of US Veterans with and without HIV, we identified and characterised EHR-derived trajectories of longitudinal prescription opioid exposure,

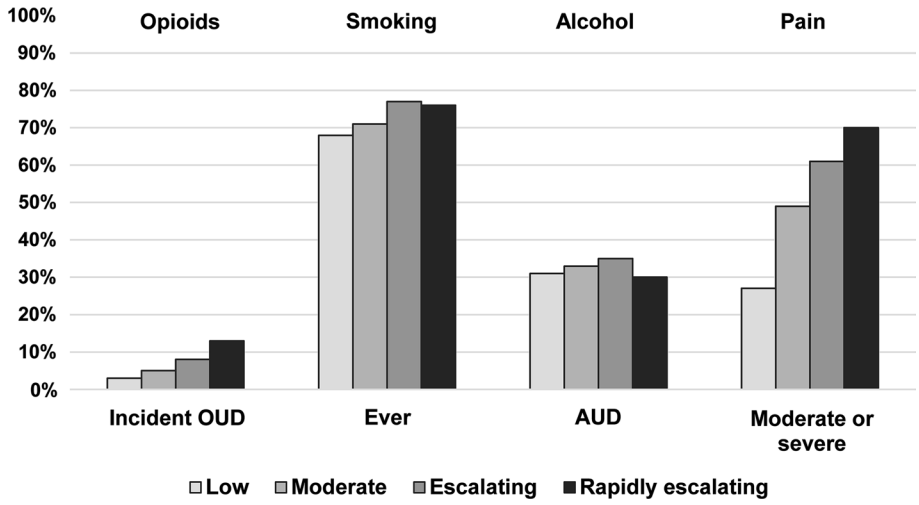

Fig. 3 Frequency of substance use and NRS pain scores by opioid dose trajectory, n = 69,268

wherein four clinically differentiable patterns of opioid receipt emerged and assigned approximately 20% of the sample to an escalating or rapidly escalating dose group. The trajectories were clinically distinguished by different incidences of OUD, types of pain-related diagnoses, pain scores, and prevalence of AUD and smoking, and were associated with distinct rates of hospitalisation and mortality. A key strength of the current analysis was the utilisation of a large, national sample of patients exposed to any prescription opioid. Although several papers have previously identified trajectories of opioid use over time [41–46], these were often obtained in small, sub-national samples, were limited to event- (e.g., post-operation) or disease-specific cohorts, or included only illegal or a few select prescription opioids.

Approximately two-thirds of the VACS received an outpatient opioid prescription for 7 days or longer. While our study encompassed a period of time when increases in opioid prescribing within and outside the VA have been well described, the high prevalence of non-trivial opioid exposure in this sample means that these data can be useful for an exploration of genetic risk. Ideally, such analyses should distinguish between high levels of opioid exposure that result from the prescribing practices of providers versus patients' experiences of pain and prescribing outcomes. Additionally, mean and median doses were higher than previously reported in VACS samples [21], which is likely because the present analysis extended 5 years beyond our prior work. Opioid doses were likely increasing due to cohort and period effects. This is a particularly important finding among patients with HIV as our prior work demonstrated a dose-dependent increased risk of all-cause mortality among individuals with HIV compared to uninfected [22]. We also found that lower potency opioids were more prevalent in lower exposure groups and higher potency opioids were moreprevalent in the rapidly escalating exposure group. While perhaps not surprising, these cross-sectional findings provide a compelling rationale to explore sequencing of opioid types over time or whether early exposure to certain types predicts more rapid escalation as has been shown in emergency department settings [47].

We identified a wide variety of demographic and clinical features associated with differentiable trajectories of prescription opioid receipt, some of which confirm the findings from earlier related studies and provide validation of the identified trajectories, while other findings were novel. The disproportionately high prevalence of EAs in the rapidly escalating trajectory group compared to AAs is consistent with several epidemiologic and clinical studies showing that AAs are less likely than EAs to be prescribed any high-dose, long-term opioid therapy. This finding may be explained by prescriber bias [48] or possibly that AAs are more forthcoming in disclosing opioid risk factors, though there are studies providing evidence for the former hypothesis [49] while the latter deserves more study. That HCV infection was also associated with rapidly escalating trajectory membership is likely explained by its known association with OUD, which we have previously shown is more common among patients receiving high opioid doses [50–52]. Our finding that members of the higher trajectory groups had higher rates of hospitalisation and all-cause mortality than individuals in the lower trajectory groups deserves more detailed, risk-adjusted, time-updated analyses. Accrual of cumulative adverse effects of long-term opioid use may play a causal role or the observed relationships may be due to confounding by indication.

While we excluded individuals who were likely to have initiated opioid therapy outside the VA Healthcare System (i.e., those with initial exposure of > 90 mg MEDD or evidence of OUD at baseline), we found that incidence of OUD diagnoses increased with increasing dose trajectory group. We hypothesise that access to and use of high-dose opioid therapy may lead to OUD more than low-dose exposures,

or that individuals with initially unrecognized OUD may be more likely to seek and receive higher-dose therapy, or both. In addition, there could be a tendency towards misclassification by clinicians who may be more likely to assign a diagnosis of OUD to a patient on high-dose opioid therapy when they may actually mean "physiologic dependence." Of note, specific OUD criteria of tolerance and withdrawal are "not considered to be met for those individuals taking opioids solely under appropriate medical supervision" [53]. Moreover, the implementation of arbitrary or excessively rigid opioid control policies may result in withdrawal and other symptoms that could be characterized by other OUD diagnostic criteria (e.g., unsuccessful efforts to taper, or craving) [54]. Further research is warranted to explore these hypotheses.

Other substance use during exposure to prescription opioids was common in this cohort. We observed an increased prevalence of baseline smoking and AUD with increasing prescription opioid dose trajectory except in the rapidly escalating group. Prevalence of smoking was lower in the rapidly escalating dose trajectory compared to the escalating dose trajectory. Prevalence of AUD was lower in the rapidly escalating dose trajectory compared to all other trajectory groups. While we can only speculate on the role of clinicians' behaviour, it is possible that clinicians may have been less likely to continue prescribing high-dose therapy to patients with diagnosed AUD due to safety concerns. Alternatively, patients on sustained high-dose exposure observed in the rapidly escalating group may have greater difficulty tolerating alcohol in addition to opioids than those in lower dose trajectories. Moderate and severe self-reported pain was also common in this cohort. Approximately 70% of patients in the rapidly escalating dose trajectory and 27% of those in the low dose trajectory reported moderate to severe pain during follow-up. Average baseline NRS pain scores linearly increased from 2.7 in the low opioid dose trajectory group to 4.4 in the rapidly escalating dose trajectory group. These averages were similar to those found during follow-up in a recent randomised trial [55].

Our study had limitations. First, we assumed that dispensed opioid prescriptions were taken as directed, but we have no direct measure of MEDD actually consumed. Second, we could not account for opioids prescribed outside the VA, and thus some patients' exposure to prescription opioids may have been underestimated. Third, VACS and therefore our sample was predominantly male military Veterans, so our findings may not generalize to women or a more general population. Despite these limitations, the study supports the utility of EHR data and provides important insights into the predominant patterns of opioid use in a large, US national cohort. Future work should identify opioid dose trajectories using EHR data in other national samples, including North American and European cohorts.

Conclusions

We identified and characterised clinically differentiable, longitudinal, EHR-derived patterns of prescription opioid receipt in the VACS, wherein approximately 20% of all opioid-exposed patients had potentially deleterious escalating or rapidly escalating trajectories. High-dose, long-term opioid exposure may play a causal role in the observed relationships between trajectory groups, or they may be due to confounding by indication. These empirically-validated measures deserve more detailed, risk-adjusted, time-updated epidemiologic analyses and genetic research to inform prevention interventions.

Acknowledgements This work was supported by US National Institutes of Health, including Grants from National Institute on Alcohol Abuse and Alcoholism (U24-AA020794, U01-AA020790, U10-AA013566-completed to ACJ) and National Institute on Drug Abuse (NIDA R01-DA040471, R01-DA12690). Additional support was provided by the US Department of Veterans Affairs (i01-BX003341), Yale School of Medicine Drug Use, Addiction, and HIV Research Scholars Program (DAHRS K12-DA033312), and Agency for Healthcare Research and Quality (AHRQ U19-HS021112 and R18-HS023258). The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The views presented in this paper are the authors' and not necessarily those of the Department of Veterans Affairs or the United States Government.

Compliance with Ethical Standards

Conflict of interest Dr. Kranzler is a Member of the American Society of Clinical Psychopharmacology's Alcohol Clinical Trials Initiative, which was supported in the last 3 years by AbbVie, Alkermes, Ethypharm, Indivior, Lilly, Lundbeck, Otsuka, Pfizer, and XenoPort. Drs. Kranzler, Gelernter, and A. Smith are also named as Inventors on PCT Patent Application #15/878,640 entitled: "Genotype-guided dosing of opioid agonists," filed January 24, 2018. The remaining authors have no conflicts of interest.

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