Patterns and correlates of prescription opioid receipt among US Veterans: a national, 18-year observational cohort study

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Running head (65/80 characters including spaces): Prescription opioid receipt among HIV+ and uninfected US Veterans

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ABSTRACT (149/150 words)

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 1998-2015. 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 [PY] 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 (5): 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 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 (GWAS) 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 six 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% one-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 (eGFR), 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 formulations prescribed 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 99^{th} percentile to remove undue influence by extreme outliers.

Next, we used latent growth mixture modelling (LGMM) 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), hepatitis C virus (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 I**) 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 (PY) 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, 9,857 (9%) of the 105,812 opioid-exposed patients had a cancer diagnosis, 301 (0.3%) had a VACS Index score >100, 7,684 (7%) had an OUD diagnosis, 1,474 (1%) had attended an opioid treatment programme, 80 (0.1%) had received buprenorphine, 1,822 (2%) had an initial opioid prescription >90 mg MEDD, and 21,680 (20%) had

less than six months of follow-up. In total, 36,544 (35%) of the 105,812 patients who received an opioid prescription were excluded from this analysis (**Figure 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%).

Trajectory modelling

In all models, all groups had an average group membership probability >80% and contained >3% (n~2,000) 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 Figure 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=8,759, 13%), and rapidly escalating dose (n=3,793, 5%) (**Figure 2**). Trajectory models were largely similar when stratified by HIV status (**Supplemental Figure 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 II**). Compared to models limited to individuals with complete data at 4, 8, and 12 years, agreement of trajectory group assignment was 75.9% at four years, 88.0% at eight years, and 96.7% at 12 years **(Supplemental Table III)**. 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

241 Bivariate comparisons of demographic and clinical characteristics by trajectory groups were
242 all statistically significant (p<0.001), except for temporomandibular pain (p=0.18) (**Table I**). While
243 statistically significant, the differences in some baseline pain-related diagnoses (i.e., abdominal,
244 fractures, headaches, kidney stones, menstrual, rheumatoid arthritis, and temporomandibular) and
245 comorbid conditions (anxiety disorder, bipolar disorder, coronary artery disease, congestive heart
246 failure, cirrhosis, chronic obstructive pulmonary disease, drug-related diagnoses, major depression,
247 post-traumatic stress disorder, renal insufficiency, schizophrenia, and other psychoses) were not
248 >5% between any two trajectory groups and thus the data are not otherwise shown.
249 Compared to individuals in the low dose trajectory, those in the rapidly escalating dose
250 trajectory were more likely to be EA (59% of rapidly escalating patients vs. 38% of low; χ^2=1059,
251 p<0.0001), to have HIV (31% vs. 29%; χ^2=145, p<0.0001), and hepatitis C infection (18% vs.12%;
252 χ^2=155, p<0.0001), and less likely to be AA (32% vs. 50%; χ^2=1059, p<0.0001) and to have
253 diabetes at baseline (12% vs. 15%; χ^2=121, p<0.0001). All reported statistical tests in this and
254 subsequent paragraphs are for the analyses of all four trajectory groups rather than directly
255 comparing the two extreme trajectory groups. It should be noted the lowest or highest prevalence of
256 demographic or clinical characteristics were not always found in the extreme trajectory groups. For
257 example, prevalence of HIV infection was lowest in the moderate dose trajectory (25%). Full details
258 can be found in **Table I**.
259 The most common pain-related diagnoses were extremity (53%), back (50%), osteoarthritis
260 (38%), and other pain (38%). Compared to individuals in the low dose trajectory, those in the rapidly
261 escalating dose trajectory had higher baseline prevalence of back pain (62% of rapidly escalating
262 patients vs. 43% of low; χ^2=1379, p<0.0001), neck pain (19% vs. 12%; χ^2=353, p<0.0001),
263 neuropathic pain (17% vs. 9%; χ^2=349, p<0.0001), and osteoarthritis (44% vs 37%; χ^2=841,
264 p<0.0001). Conversely, those in the highest dose trajectory had proportionately fewer chest pain
265 diagnoses (21% of rapidly escalating patients vs. 24% of low; χ^2=64, p<0.0001) and other pain
266 diagnoses (39% vs. 49%; χ^2=259, p<0.0001) at baseline than those in the low dose trajectory.
267 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 (χ^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 (χ^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 (χ^2=50855, p<0.0001, **Table II**). 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; χ^2=22161, 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; χ^2=520, p<0.0001) and had higher all-cause mortality (4.7/100 PY vs. 1.8/100 PY; χ^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 (**Figure 3**). Compared to individuals in the low dose trajectory, those in the rapidly escalating trajectory were more likely to have an incident OUD diagnosis (13% of rapidly escalating patients vs. 3% of low; χ^2=917, p<0.0001), report smoking (76% vs. 68%; χ^2=671, p<0.0001), and report moderate (43% vs. 20%; χ^2=2644, p<0.0001) or severe pain (27% vs. 7%; χ^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%; χ^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, 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 cohort received an outpatient opioid prescription for seven 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 five 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 more prevalent 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, U.S. 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 Veterans Aging Cohort Study (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.

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References

1. Dobscha SK, Corson K, Flores JA, Tansill EC, Gerrity MS. Veterans Affairs Primary Care Clinicians' Attitudes toward Chronic Pain and Correlates of Opioid Prescribing Rates. Pain Medicine. 2008;9(5):564-71.

2. Gironda RJ, Clark ME, Massengale JP, Walker RL. Pain among veterans of Operations Enduring Freedom and Iraqi Freedom. Pain Medicine. 2006;7(4):339-43.

3. Fayaz A, Croft P, Langford RM, Donaldson LJ, Jones GT. Prevalence of chronic pain in the UK: a systematic review and meta-analysis of population studies. BMJ Open. 2016;6(6):e010364.

4. Solomon DH, Rassen JA, Glynn RJ, Lee J, Levin R, Schneeweiss S. The Comparative Safety of Analgesics in Older Adults with Arthritis. Archives of Internal Medicine. 2010.

5. Bohnert ASB, Valenstein M, Bair MJ, Ganoczy D, McCarthy JF, Ilgen MA, et al. Association Between Opioid Prescribing Patterns and Opioid Overdose-Related Deaths. JAMA: The Journal of the American Medical Association.305(13):1315-21.

6. Dunn KM, Saunders KW, Rutter CM, Banta-Green CJ, Merrill JO, Sullivan MD, et al. Opioid Prescriptions for Chronic Pain and Overdose. Annals of Internal Medicine. 2010;152:85-92.

7. Dowell D, Haegerich T, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain -- United States, 2016. MMWR Recomm Rep. 2016;epub.

8. The Opioid Therapy for Chronic Pain Work Group. VA/DoD Clinical Practice Guideline for Opioid Therapy for Chronic Pain. In: Department of Veterans Affairs, Department of Defense, editors. 2017.

9. Dowell D, Haegerich T, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. MMWR Recomm Rep. 2016;65(No. RR-1):1-49.

10. Faculty of Pain Medicine. Opioids aware: a resource for patients and healthcare professionals to support prescribing of opioid medicines for pain [Available from: http://www.fpm.ac.uk/faculty-of-pain-medicine/opioids-aware.

11. Hauser W, Bock F, Engeser P, Hege-Scheuing G, Huppe M, Lindena G, et al. Recommendations of the updated LONTS guidelines. Long-term opioid therapy for chronic noncancer pain. Schmerz. 2015;29(1):109-30.

12. Morasco BJ, Duckart JP, Carr TP, Deyo RA, Dobscha SK. Clinical characteristics of veterans prescribed high doses of opioid medications for chronic non-cancer pain. PAIN®. 2010;151(3):625-32.

13. Sullivan MD, Edlund MJ, Fan M-Y, DeVries A, Braden JB, Martin BC. Trends in use of opioids for non-cancer pain conditions 2000–2005 in commercial and Medicaid insurance plans: the TROUP study. Pain. 2008;138(2):440-9.

14. Edlund MJ, Martin BC, Fan M-Y, Braden JB, Devries A, Sullivan MD. An Analysis of Heavy Utilizers of Opioids for Chronic Noncancer Pain in the TROUP Study. Journal of Pain and Symptom Management. 2010;40(2):279-89.

15. Gelernter J, Kranzler HR, Sherva R, Koesterer R, Almasy L, Zhao H, et al. Genome-wide association study of opioid dependence: multiple associations mapped to calcium and potassium pathways. Biol Psychiatry. 2014;76(1):66-74.

16. Cheng Z, Zhou H, Sherva R, Farrer LA, Kranzler HR, Gelernter J. Genome-wide Association Study Identifies a Regulatory Variant of RGMA Associated With Opioid Dependence in European Americans. Biol Psychiatry. 2018.

17. Nelson EC, Agrawal A, Heath AC, Bogdan R, Sherva R, Zhang B, et al. Evidence of CNIH3 involvement in opioid dependence. Mol Psychiatry. 2015.

18. Li D, Zhao H, Kranzler HR, Li MD, Jensen KP, Zayats T, et al. Genome-wide association study of copy number variations (CNVs) with opioid dependence. Neuropsychopharmacology. 2015;40(4):1016-26.

19. Smith AH, Jensen KP, Li J, Nunez Y, Farrer LA, Hakonarson H, et al. Genome-wide association study of therapeutic opioid dosing identifies a novel locus upstream of OPRM1. Mol Psychiatry. 2017;22(3):346-52.

20. Edelman EJ, Gordon K, Becker WC, Goulet JL, Skanderson M, Gaither JR, et al. Receipt of opioid analgesics by HIV-infected and uninfected patients. J Gen Intern Med. 2013;28(1):82-90.

21. Becker WC, Gordon K, Edelman EJ, Kerns RD, Crystal S, Dziura JD, et al. Trends in Any and High-Dose Opioid Analgesic Receipt Among Aging Patients With and Without HIV. AIDS and behavior. 2016;20(3):679-86.

22. Weisberg DF, Gordon KS, Barry DT, Becker WC, Crystal S, Edelman EJ, et al. Long-term Prescription of Opioids and/or Benzodiazepines and Mortality Among HIV-Infected and Uninfected Patients. J Acquir Immune Defic Syndr. 2015;69(2):223-33.

23. Edelman EJ, Gordon KS, Crothers K, Akgun K, Bryant KJ, Becker WC, et al. Association of Prescribed Opioids With Increased Risk of Community-Acquired Pneumonia Among Patients With and Without HIV. JAMA Intern Med. 2019.

24. Wiese AD, Griffin MR, Schaffner W, Stein CM, Greevy RA, Mitchel EF, Jr., et al. Opioid Analgesic Use and Risk for Invasive Pneumococcal Diseases: A Nested Case-Control Study. Ann Intern Med. 2018;168(6):396-404.

25. Fultz SL, Skanderson M, Mole L, Gandhi N, Bryant K, Crystal S, et al. Development and verification of a "virtual" cohort using the national VA Health Information System. Medical Care. 2006;44(8):S25-S30.

26. Justice AC, Dombrowski E, Conigliaro J, Fultz SL, Gibson D, Madenwald T, et al. Veterans Aging Cohort Study (VACS): Overview and description. Med Care. 2006;44(8):S13-S24.

27. Justice AC, Modur S, Tate J, Althoff K, Jacobson LP, Gebo KA, et al. Predictive Accuracy of the Veterans Aging Cohort Study Index for Mortality With HIV Infection: A North American Cross Cohort Analysis. J Acquir Immune Defic Syndr. 2013;62(2):149-63.

28. Akgun KM, Gordon K, Pisani M, Fried T, McGinnis KA, Tate JP, et al. Risk factors for hospitalization and medical intensive care unit (MICU) admission among HIV-infected Veterans. J Acquir Immune Defic Syndr. 2013;62(1):52-9.

29. Akgun KM, Tate JP, Crothers K, Crystal S, Leaf DA, Womack J, et al. An adapted frailty-related phenotype and the VACS index as predictors of hospitalization and mortality in HIV-infected and uninfected individuals. J Acquir Immune Defic Syndr. 2014;67(4):397-404.

30. Escota GV, Patel P, Brooks JT, Bush T, Conley L, Baker J, et al. Short communication: The Veterans Aging Cohort Study Index is an effective tool to assess baseline frailty status in a contemporary cohort of HIV-infected persons. AIDS Res Hum Retroviruses. 2015;31(3):313-7.

476 31. Marquine MJ, Umlauf A, Rooney AS, Fazeli PL, Gouaux BD, Paul Woods S, et al. The
477 veterans aging cohort study index is associated with concurrent risk for neurocognitive impairment.
478 J Acquir Immune Defic Syndr. 2014;65(2):190-7.
479 32. Tate JP, Justice AC, Hughes MD, Bonnet F, Reiss P, Mocroft A, et al. An internationally
480 generalizable risk index for mortality after one year of antiretroviral therapy. AIDS. 2013;27(4):563-
481 72.
482 33. Womack JA, Goulet JL, Gibert C, Brandt CA, Skanderson M, Gulanski B, et al. Physiologic
483 frailty and fragility fracture in HIV-infected male veterans. Clinical infectious diseases : an official
484 publication of the Infectious Diseases Society of America. 2013;56(10):1498-504.
485 34. Altman M, Lewis-Beck M, Bryman AE, Liao TF. Encyclopedia of Social Science Research
486 Methods. 2004.
487 35. Jones BL, Nagin DS. Advances in group-based trajectory modeling and an SAS procedure
488 for estimating them. Sociological Methods & Research. 2007;35(4):542-71.
489 36. Jones BL, Nagin DS, Roeder K. A SAS procedure based on mixture models for estimating
490 developmental trajectories. Sociological Methods & Research. 2001;29(3):374-93.
491 37. Nagin D. Group-based modeling of development: Harvard University Press; 2005.
492 38. Palmer RH, Brick L, Nugent NR, Bidwell LC, McGeary JE, Knopik VS, et al. Examining the
493 role of common genetic variants on alcohol, tobacco, cannabis and illicit drug dependence: genetics
494 of vulnerability to drug dependence. Addiction. 2015;110(3):530-7.
495 39. Goulet JL, Brandt C, Crystal S, Fiellin DA, Gibert C, Gordon AJ, et al. Agreement between
496 electronic medical record-based and self-administered pain numeric rating scale: clinical and
497 research implications. Med Care. 2013;51(3):245-50.
498 40. Breivik H, Borchgrevink PC, Allen SM, Rosseland LA, Romundstad L, Hals EK, et al.
499 Assessment of pain. Br J Anaesth. 2008;101(1):17-24.
500 41. Banta-Green CJ, Merrill JO, Doyle SR, Boudreau DM, Calsyn DA. Opioid use behaviors,
501 mental health and pain--development of a typology of chronic pain patients. Drug Alcohol Depend.
502 2009;104(1-2):34-42.

503 42. Gagnon B, Scott S, Nadeau L, Lawlor PG. Patterns of community-based opioid prescriptions
504 in people dying of cancer. J Pain Symptom Manage. 2015;49(1):36-44 e1.
505 43. Guarino H, Marsch LA, Deren S, Straussner SL, Teper A. Opioid Use Trajectories, Injection
506 Drug Use, and Hepatitis C Virus Risk Among Young Adult Immigrants from the Former Soviet Union
507 Living in New York City. J Addict Dis. 2015;34(2-3):162-77.
508 44. Hser YI, Huang D, Saxon AJ, Woody G, Moskowitz AL, Matthews AG, et al. Distinctive
509 Trajectories of Opioid Use Over an Extended Follow-up of Patients in a Multisite Trial on
510 Buprenorphine + Naloxone and Methadone. J Addict Med. 2017;11(1):63-9.
511 45. Monga N, Rehm J, Fischer B, Brissette S, Bruneau J, El-Guebaly N, et al. Using latent class
512 analysis (LCA) to analyze patterns of drug use in a population of illegal opioid users. Drug Alcohol
513 Depend. 2007;88(1):1-8.
514 46. Naumann RB, Marshall SW, Gottfredson NC, Lund JL, Ringwalt CL, Skinner AC.
515 Trajectories of dispensed prescription opioids among beneficiaries enrolled in a Medicaid controlled
516 substance "lock-in" program. Pharmacoepidemiol Drug Saf. 2018.
517 47. Barnett ML, Olenksi AR, Jena AB. Opioid Prescribing by Emergency Physicians and Risk of
518 Long-Term Use. N Engl J Med. 2017;376(19):1896.
519 48. Burgess DJ, Nelson DB, Gravely AA, Bair MJ, Kerns RD, Higgins DM, et al. Racial
520 differences in prescription of opioid analgesics for chronic noncancer pain in a national sample of
521 veterans. J Pain. 2014;15(4):447-55.
522 49. Hoffman KM, Trawalter S, Axt JR, Oliver MN. Racial bias in pain assessment and treatment
523 recommendations, and false beliefs about biological differences between blacks and whites. Proc
524 Natl Acad Sci U S A. 2016;113(16):4296-301.
525 50. Altice FL, Kamarulzaman A, Soriano VV, Schechter M, Friedland GH. Treatment of medical,
526 psychiatric, and substance-use comorbidities in people infected with HIV who use drugs. Lancet.
527 2010;376(9738):367-87.
528 51. Schranz AJ, Barrett J, Hurt CB, Malvestutto C, Miller WC. Challenges Facing a Rural Opioid
529 Epidemic: Treatment and Prevention of HIV and Hepatitis C. Curr HIV/AIDS Rep. 2018;15(3):245-
530 54.

52. Ogdie A, Pang WG, Forde KA, Samir BD, Mulugeta L, Chang KM, et al. Prevalence and risk factors for patient-reported joint pain among patients with HIV/hepatitis C coinfection, hepatitis C monoinfection, and HIV monoinfection. BMC Musculoskelet Disord. 2015;16:93.

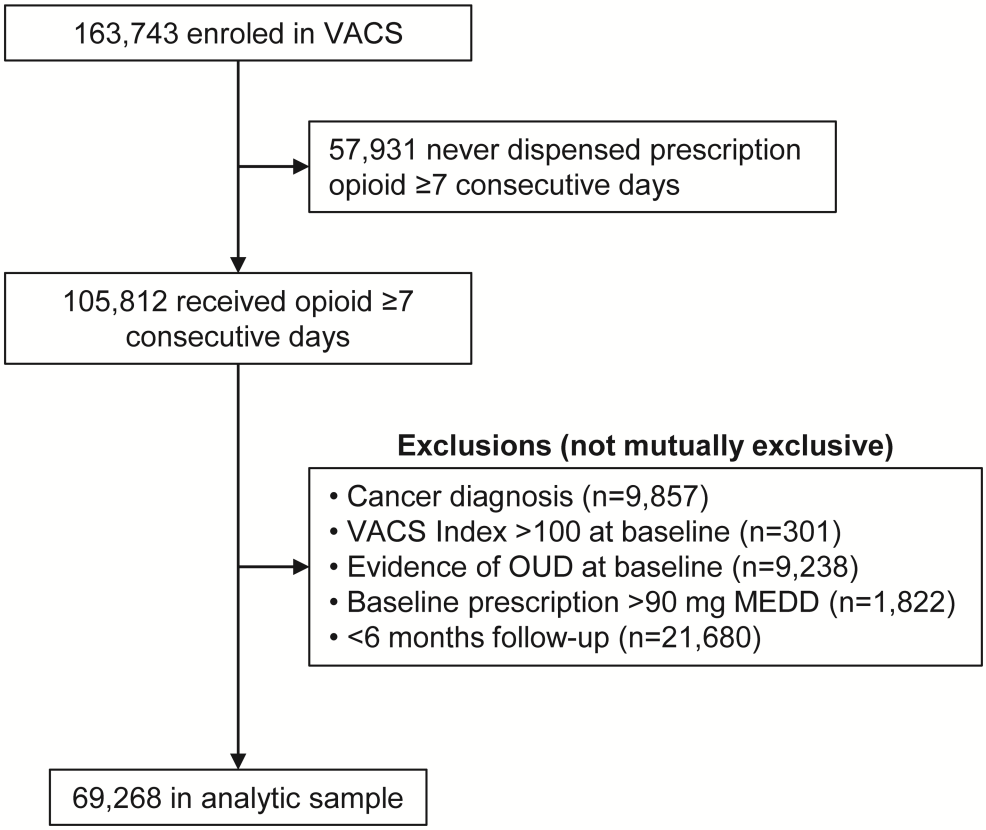
53. Association AP. Diagnostic and statistical manual of mental disorders (DSM-5®): American Psychiatric Pub; 2013.

54. Dowell D, Haegerich T, Chou R. No Shortcuts to Safer Opioid Prescribing. N Engl J Med. 2019.

55. Krebs EE, Gravely A, Nugent S, Jensen AC, DeRonne B, Goldsmith ES, et al. Effect of Opioid vs Nonopioid Medications on Pain-Related Function in Patients With Chronic Back Pain or Hip or Knee Osteoarthritis Pain: The SPACE Randomized Clinical Trial. JAMA. 2018;319(9):872-82.

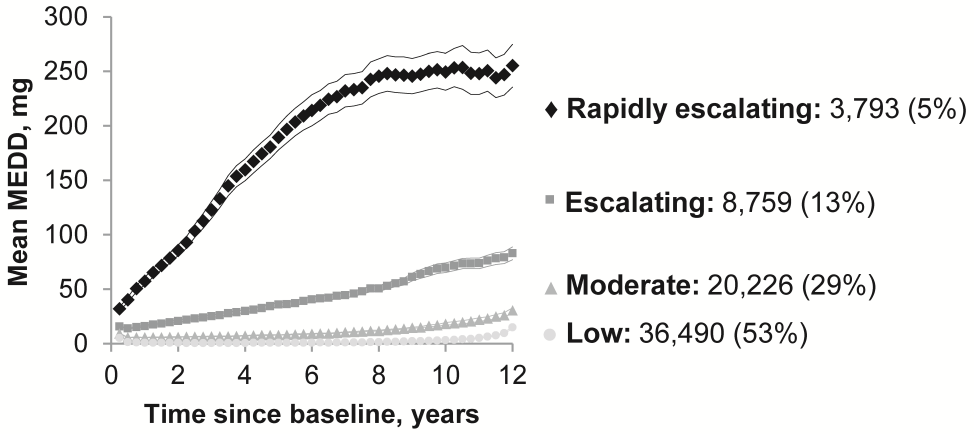
Tables and figures

Figure 1. Study flow diagram



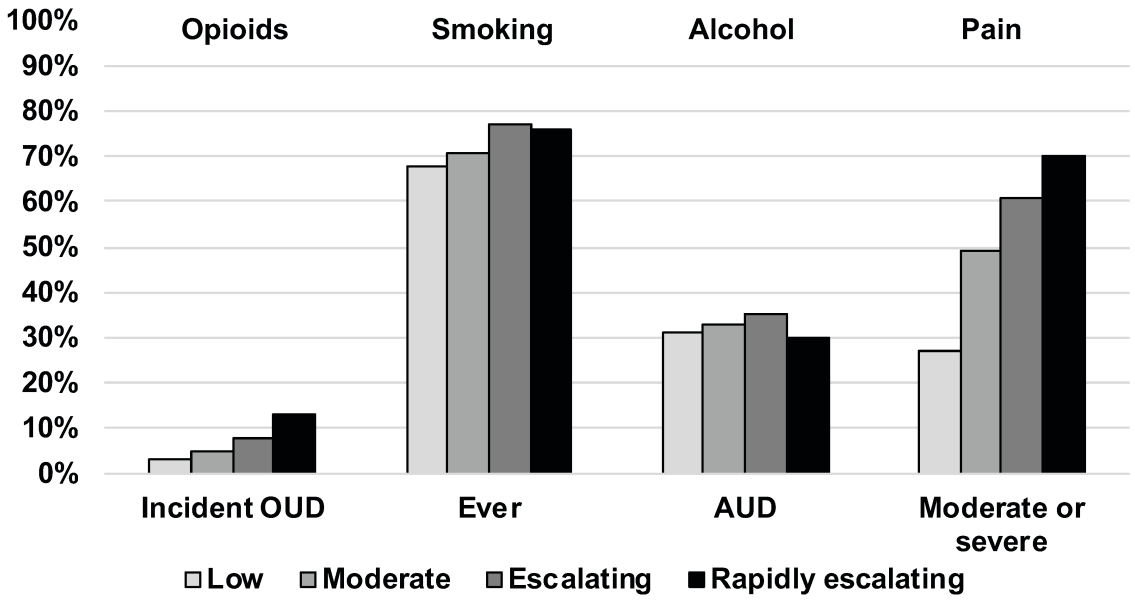
Abbreviations: VACS – U.S. Veterans Aging Cohort Study; OUD – opioid use disorder; mg – milligrams; MEDD – morphine equivalent daily dose
Note: 'Evidence of OUD' included OUD diagnoses, attendance at an opioid treatment programme, or receipt of buprenorphine

Figure 2. Prescription opioid dose trajectories among 69,268 opioid-exposed patients in the U.S. Veterans Aging Cohort Study, 1998-2015



Abbreviations: MEDD – morphine equivalent daily dose; mg – milligrams
Note: major classes (i.e., unobserved latent sub-groups) of opioid dose trajectories were identified using latent growth mixture modelling

Figure 3. Substance use and NRS pain scores during follow-up by opioid dose trajectory, n=69,268



Abbreviations: NRS – numeric rating scale; OUD – opioid use disorder; AUD – alcohol use disorder
Note: all chi-square tests $p<0.0001$

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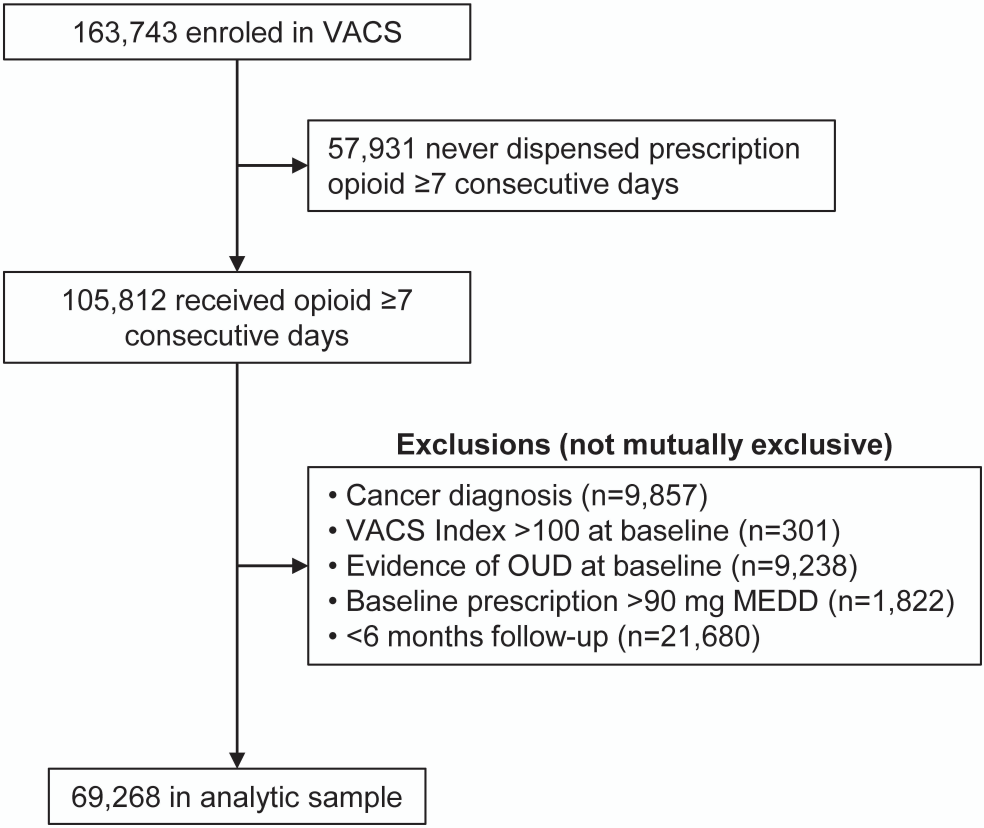

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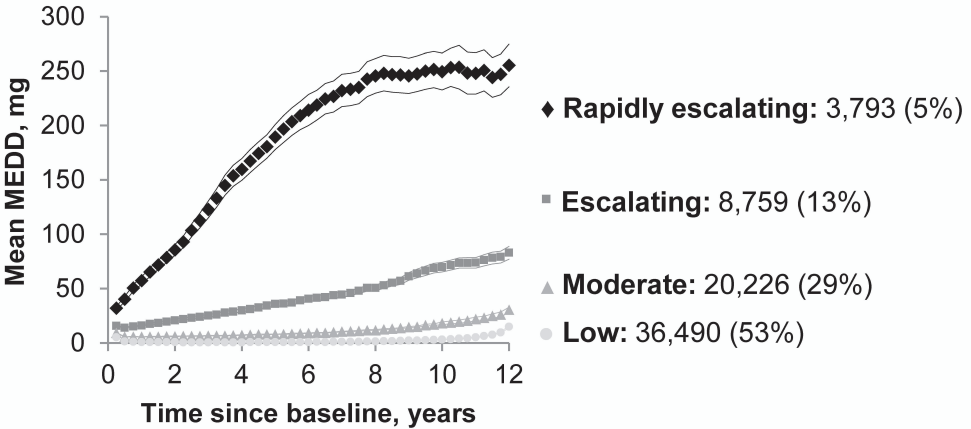

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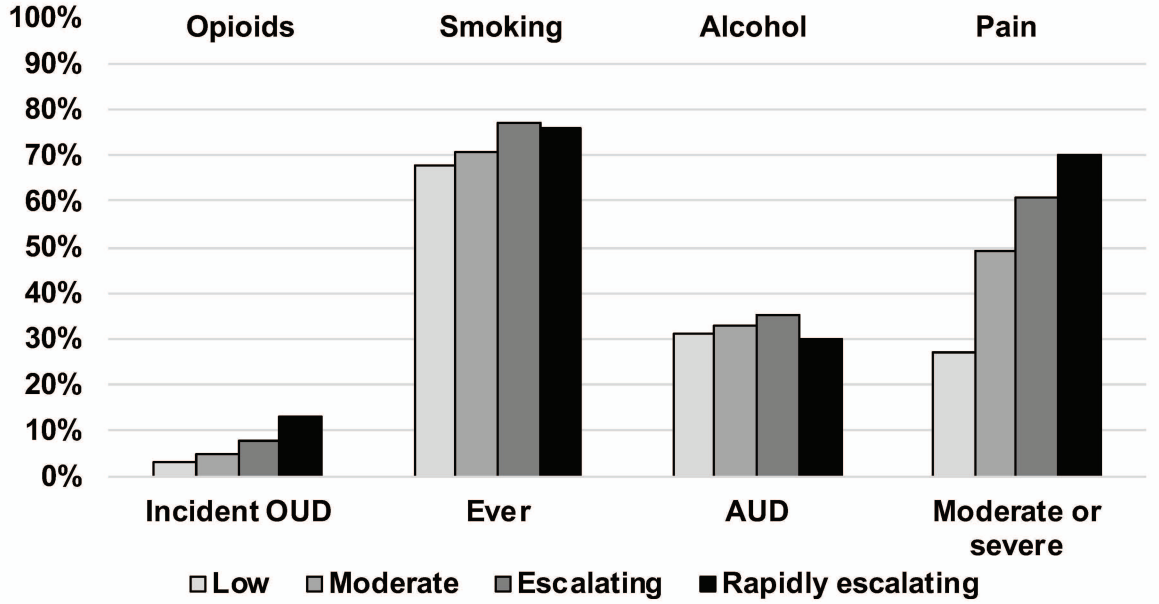


Abbreviations: NRS – numeric rating scale; OUD – opioid use disorder; AUD – alcohol use disorder
Note: all chi-square tests $p<0.0001$

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

		Trajectory group				
	Full sample	**Low**	**Moderate**	**Escalating**	**Rapidly escalating**	**χ^2**
Sample size, n (%)	69,268	36,490 (53)	20,226 (29)	8,759 (13)	3,793 (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)	8,584 (98)	3,716 (98)	102
Race						
African American	32,448 (47)	18,238 (50)	9,510 (47)	3,479 (40)	1,221 (32)	1,059
European American	29,299 (42)	13,997 (38)	8,519 (42)	4,527 (52)	2,256 (59)	
Hispanic	5,593 (8)	3,279 (9)	1,604 (8)	504 (6)	206 (5)	
Other	1,928 (3)	976 (3)	593 (3)	249 (3)	110 (3)	
HIV+	19,308 (28)	10,709 (29)	5,099 (25)	2,307 (26)	1,193 (31)	145
HCV+	9,407 (14)	4,503 (12)	2,814 (14)	1,420 (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)	1,281
Pain-related diagnoses						
Back	34,583 (50)	15,818 (43)	11,330 (56)	5,099 (58)	2,336 (62)	1,379
Chest	16,934 (24)	8,820 (24)	5,277 (26)	2,050 (23)	787 (21)	64
Extremity	42,186 (61)	21,248 (58)	13,309 (66)	5,413 (62)	2,216 (58)	326
Neck	10,238 (15)	4,530 (12)	3,478 (17)	1,504 (17)	726 (19)	353
Neuropathic	7,819 (11)	3,426 (9)	2,575 (13)	1,156 (13)	662 (17)	349
Osteoarthritis	28,843 (42)	13,337 (37)	9,630 (48)	4,205 (48)	1,671 (44)	841
Other	32,595 (47)	17,915 (49)	9,535 (47)	3,674 (42)	1,471 (39)	257
Comorbid conditions						
Diabetes	10,712 (15)	5,362 (15)	3,567 (18)	1,320 (15)	463 (12)	121
Hypertension	23,020 (33)	11,249 (31)	7,530 (37)	3,058 (35)	1,183 (31)	259

Notes: 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 $p<0.0001$

Abbreviations: HIV - human immunodeficiency virus; HCV - hepatitis C virus; VACS - Veterans Aging Cohort Study; NRS - numeric rating scale; SD - standard deviation

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

		Trajectory group				
	Full sample	**Low**	**Moderate**	**Escalating**	**Rapidly escalating**	**χ^2**
Sample size, n (%)	69,268	36,490 (53)	20,226 (29)	8,759 (13)	3,793 (5)	
OUD	3,475 (5)	1,256 (3)	992 (5)	728 (8)	499 (13)	917
AUD	22,283 (32)	11,472 (31)	6,629 (33)	3,033 (35)	1,149 (30)	43
Smoking status						
Ever	48,794 (70)	24,784 (68)	14,365 (71)	6,747 (77)	2,898 (76)	671
Never	19,292 (28)	11,317 (31)	5,530 (27)	1,794 (20)	651 (17)	
NRS pain score, mean (SD)	2.9 (3)	2.1 (3)	3.4 (3)	4.2 (3)	4.8 (3)	7,602
NRS pain score category						
Moderate pain, 4-6	19,220 (28)	7,264 (20)	6,809 (34)	3,527 (40)	1,620 (43)	2,644
Severe pain, 7-10	8,628 (12)	2,719 (7)	3,031 (15)	1,856 (21)	1,022 (27)	2,346
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)	1,300
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)	3,501 (5,491)	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

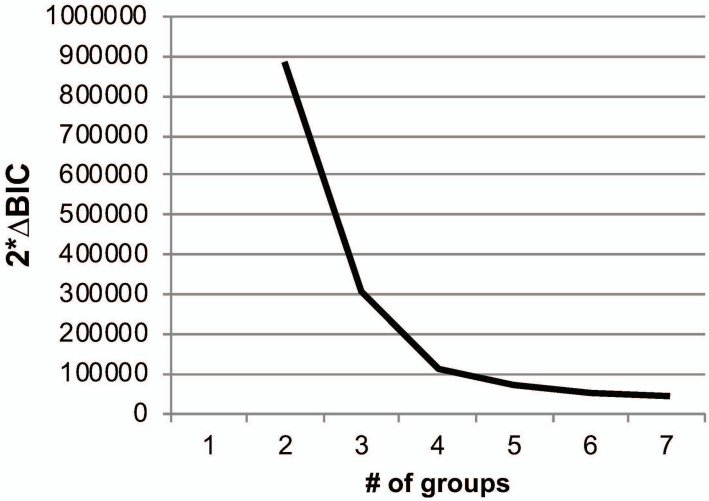
Other[a]	<1%	<1%	<1%	1%	1%	5,150

Notes: 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 $p<0.0001$

Abbreviations: 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

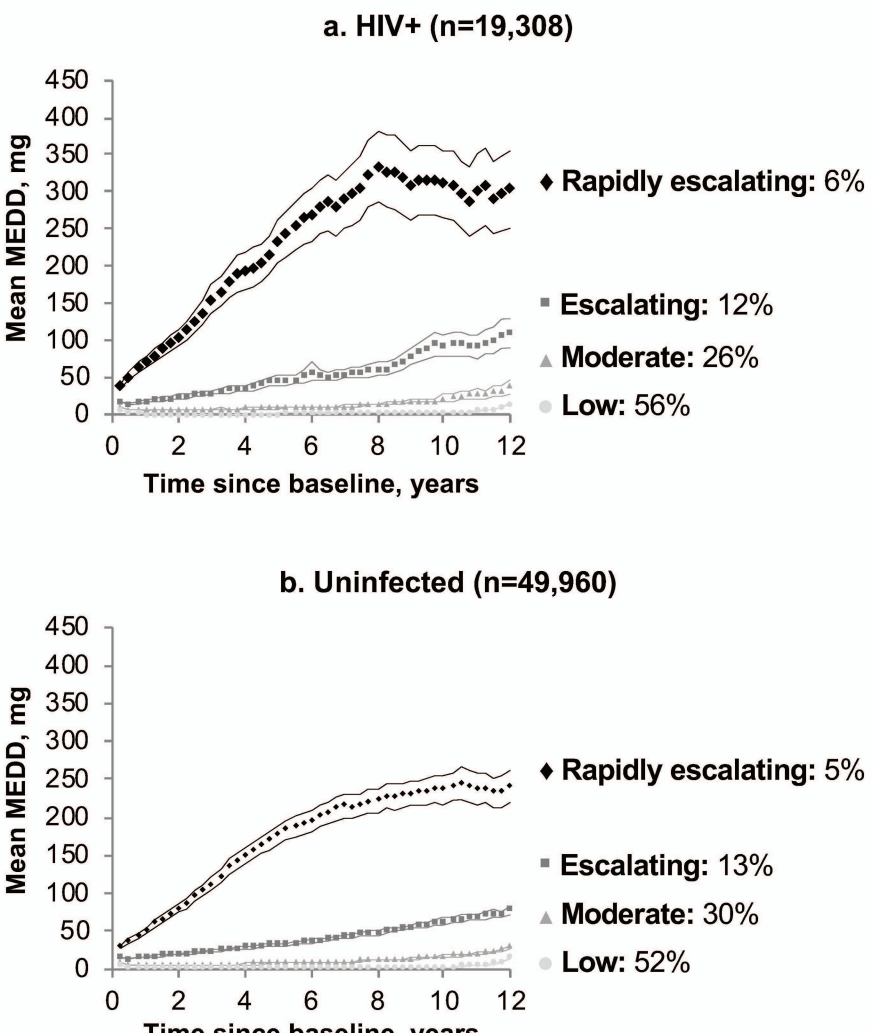
[a]Includes hydromorphone, meperidine, pentazocine, tapentadol, levorphanol, buprenorphine, oxymorphone

Supplemental Figure 1. Change in Bayesian Information Criterion (BIC) to guide selection of number of groups in trajectory model



# of groups	BIC	2*ΔBIC
1	-5181838	-
2	-4742679	878318
3	-4588095	309168
4	-4531178	113834
5	-4493515	75326
6	-4466346	54338
7	-4444203	44286

Supplemental Figure 2. Prescription opioid dose trajectories among 69,268 opioid-exposed patients in the U.S. Veterans Aging Cohort Study, 1998-2015, by HIV status



Abbreviations: MEDD – morphine equivalent daily dose; mg – milligrams
Note: major classes (i.e., unobserved latent sub-groups) of opioid dose trajectories were identified using latent growth mixture modelling

Supplementary Table I. ICD-9 codes for pain-related diagnoses and comorbid conditions

Category	ICD-9 codes
Pain-related diagnoses	
Abdominal	533.90; 535.00/.50; 540.9; 541; 550.90/.92; 553.1/.3/.20/.21/.29; 564.1; 577.0; 590.80; 789.0X
Back	721.3/.42; 721.5-721.91; 722.1/.10/.2/.30/.32/.52/.6/.70/.80/.83/.90/.93; 724; 724.0/.00/.02/.09; 724.1-724.6; 724.8; 737.10/.30; 738.4/.5; 739.2-739.4; 756.10/.11/.12/.13/.19; 805.4/.8; 839.2X/.42; 846.X; 847.1/.2/.3/.9
Chest	413.9; 786.50/.59
Extremity	274.0/.9; 354.0; 707.15; 717.2/.3/.4/.6/.9; 718.31; 719.40-719.47; 719.49; 726.0/.10/.12/.19/.2/.31/.32/.33/.5/.60/.64/.65/.70/.71; 727.03-727.06; 727.3/.41/.61; 728.71; 729.5/.82; 735.0/.4/.5; 831.00; 836.0/.1/.2; 840.0/.4/.8/.9; 841.9; 842.00/.10; 843.8/.9; 844.1/.2/.8/.9; 845.00/.09/.10; 848.5
Fractures	733.13; 802.0; 805.2; 807.00/.01/.20; 808.8; 810.00; 812.00/.09/.20/.40; 813.01/.05/.41/.81; 814.00/.01; 815.00; 816.00/.02/.10; 820.8; 822.0; 823.00/.80/.81; 824.0/.2/.4/.6/.8; 825.0/.20/.25; 826.0; 829.0; 831.04; 850.9; 873.0/.43; 879.8; 881.00/.01; 882.0; 883.2; 886.0; 891.0; 892.0; 893.0; 910.0; 913.0; 914.0; 916.0; 919.0; 920; 922.1/.2/.3/.31/.32; 923.00/.10/.11/.20/.21/.3/.9; 924.00/.01/.10/.11/.20/.21/.3/.5/.8/.9; 927.3; 959.01/.1/.2/.7/.9; E885.9; E887; E888; E888.9; E906.0/.3
Headaches	307.81; 346/.00/.01/.1/.10/.11/.2/.20/.21/.8/.80/.81/.9/.90/.91; 784/.0
Kidney stones	574.10/.20; 575.10; 592.0/.1/.9; 594.1
Menstrual	625.3/.9; 626.6/.8; 627.1/.2
Neck	721.0; 722.0/.4; 723.0/.1; 847.0
Neuropathic	053.13; 072.72; 337.0; 356.0/.2/.4/.9; 357/.2/.3; 723.4
Osteoarthritis	711.XX; 712.0; 715.XX; 716.1X/.2X/.3X/.4X/.5X/.6X/.9X; 727.0X
Rheumatoid arthritis	714.0X/.2X/.9X; 719.30; 720.0X
Temporomandibular	524.6/.60./61/.62/.63/.69
Other pain	379.91; 380.22/.23; 381.81; 382.9; 388.70; 470; 522.4/.5; 525.9; 565.1; 569.42; 604.90; 611.71/.79; 703.0; 706.2; 725; 728.85; 729.1; 786.52; 848.3/.8/.9; 873.63; 996.4
Comorbid conditions	
Anxiety disorder	300; 300.01; 300.02; 300.09; 799.2
Bipolar disorder	296.0X/.1X/.4X/.5X/.6X/.7X; 296.8-296.82; 296.89; 296.9; 296.90; 296.99; V11.1
Coronary artery disease	410.X-413.X; 414.00-414.01; 414.8/.9; 429.7; V45.81/.82
Congestive heart failure	402.01; 402.11/.91; 404.01/.03/.11/.13/.91/.93; 428.X
Cirrhosis	571.2/571.5/571.6
COPD	490-492.8; 496
Diabetes	250.X; 357.2
Drug-related diagnoses	292-292.2; 304.X; 305.2-305.9X
Hypertension	401.X-405.X; 437.2
Major depression	296.2X;296.3X
Other psychoses	293.X; 294.X; 298.X; 299.X
PTSD	309.81

Renal insufficiency	403.1/.11/.91; 404.02/.03/.12/.13/.92/.93; 580.X-581.89; 582.X-583.89; 584.X-588.X; 792.5; V42.0; V45.1; V56.X
Schizophrenia	295-295.6X; 295.8-295.9X; V11.0

Abbreviations: ICD-9 - The International Classification of Diseases, Ninth Revision; COPD - chronic obstructive pulmonary disorder; PTSD - post-traumatic stress disorder

Supplementary Table II. Agreement in trajectory group assignment by HIV status

(a) HIV+

		Stratified model by HIV status			
		Group 1	Group 2	Group 3	Group 4
Full model	Group 1	10,692	17	0	0
	Group 2	89	4,982	28	0
	Group 3	0	91	2,216	0
	Group 4	0	0	122	1,071

Agreement: 18,961/19,308 = 98.2%

(b) Uninfected

		Stratified model by HIV status			
		Group 1	Group 2	Group 3	Group 4
Full model	Group 1	25,716	65	0	0
	Group 2	54	15,004	69	0
	Group 3	0	26	6,348	78
	Group 4	0	0	0	2,600

Agreement: 49,668/49,960 = 99.4%

Supplementary Table III. Agreement in trajectory group assignment by level of completeness of data

(a) Complete data at 4 years

Full sample	Group 1	Group 2	Group 3	Group 4
Group 1	26,493	2,075	16	-
Group 2	5,078	8,527	996	61
Group 3	671	2,278	3,295	311
Group 4	21	140	1,028	1,573

Agreement: 39,888/52,563 = 75.9%

(b) Complete data at 8 years

Full sample	Group 1	Group 2	Group 3	Group 4
Group 1	17,240	1,118	-	-
Group 2	1,125	7,814	683	-
Group 3	36	702	3,488	205
Group 4	-	-	272	1,702

Agreement: 30,244/34,385 = 88.0%

(c) Complete data at 12 years

Full sample	Group 1	Group 2	Group 3	Group 4
Group 1	4,236	-	-	-
Group 2	199	3,691	-	-
Group 3	-	173	2,139	-
Group 4	-	-	10	1,205

Agreement: 11,271/11,653 = 96.7%