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New-onset depression following stable, slow, and rapid rate of prescription opioid dose escalation

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Abstract

Recent studies suggest that longer durations of opioid use, independent of maximum morphine equivalent dose (MED) achieved, is associated with increased risk of new-onset depression (NOD). Conversely, other studies, not accounting for duration, found that higher MED increased probability of depressive symptoms. To determine whether rate of MED increase is associated with NOD, a retrospective cohort analysis of Veterans Health Administration data (2000–2012) was conducted. Eligible patients were new, chronic (>90 days) opioid users, aged 18 to 80, and without depression diagnoses for 2 years before start of follow-up (n = 7051). Mixed regression models of MED across follow-up defined 4 rate of dose change categories: stable, decrease, slow increase, and rapid increase. Cox proportional hazard models assessed the relationship of rate of dose change and NOD, controlling for pain, duration of use, maximum MED, and other

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Conflict of interest statement

The remaining authors have no conflicts of interest to declare.

confounders using inverse probability of treatment-weighted propensity scores. Incidence rate for NOD was 14.1/1000PY (person-years) in stable rate, 13.0/1000PY in decreasing, 19.3/1000PY in slow increasing, and 27.5/1000PY in rapid increasing dose. Compared with stable rate, risk of NOD increased incrementally for slow (hazard ratio = 1.22; 95% confidence interval: 1.05–1.42) and rapid (hazard ratio = 1.58; 95% confidence interval: 1.30–1.93) rate of dose increase. Faster rates of MED escalation contribute to NOD, independent of maximum dose, pain, and total opioid duration. Dose escalation may be a proxy for loss of control or undetected abuse known to be associated with depression. Clinicians should avoid rapid dose increase when possible and discuss risk of depression with patients if dose increase is warranted for pain.

Keywords

Opioids; Depression; Epidemiology; Retrospective cohort

1. Introduction

Longer duration of opioid use is associated with reaching a higher daily dose.⁹ However, even large increases, such as 4 times the starting dose, do not appear to improve long-term pain control.^{2,9} Patients who receive high prescription opioid doses are substantially more likely to die than those whose doses remain stable or decrease.¹⁵ Dose increases to above 100 mg morphine equivalent dose (MED) per day are associated with increased risk of overdose.^{1,8,19} High dose was also associated with high-dose benzodiazepine comedication.¹¹ Assuming benzodiazepine comedication was given for anxiety or depression, dose escalation may be influenced by comorbid pain and mood disorder. Compared with patients maintained on a stable dose, those that increased dose over 1 year were also more likely to report mood disorder and substance use disorder.¹⁴ The literature on dose escalation and dangers of high daily dose has not disentangled the effect of the rate of dose escalation vs high daily dose on morbidity and mortality. One goal of this report is to overcome this limitation and provide clarity as to whether the greater rates of dose escalation or high achieved daily dose is accounting for new-onset depression (NOD).

In a longitudinal cohort without information on duration of use, we observed that patients who increased MED over a 2-year period had greater probability of increased depression symptoms over time compared with those who did not increase dose.²⁴ We have shown duration of opioid use, but not maximum dose, is associated with both NOD²² and transition to treatment-resistant depression.²⁵ It is unclear why maximum opioid dose (controlling for duration) was not a risk factor for depression. One possibility is that previous work has not accounted for variation in the rate of dose increase after starting an opioid.

This study determined if rate of opioid dose change is associated with risk of NOD independent of maximum pain and MED over the same observation period. Specifically, we computed the association between average rate of dose change and NOD in patients who had a rapid increase, slow increase, or decreased rate of dose change vs patients who had a stable rate after controlling for pain, maximum MED per day, total duration of use, and other confounders.

2. Methods

For this retrospective cohort analysis, deidentified patient data were extracted from the Veterans Health Administration (VA) electronic medical record. Data included ICD-9-CM diagnostic codes, inpatient and outpatient clinic stops, prescription fill records, vital signs, and demographic information.

2.1. Cohort identification

A random sample of 500,000 patients was taken from a preliminary cohort of 2,910,335 patients identified with at least one outpatient visit in both Fiscal Years 1999 and 2000 and aged 18 to 80 years. From this sample of 500,000 patients, a sample of cancer and HIV-free patients with at least one yearly visit in the “washout” years (calendar years 2000 and 2001) and at least one visit in follow-up (January 1, 2002 to December 31, 2012) were chosen ($n = 287,909$). As this was a new opioid user design with the outcome of NOD, patients with any opioid use or a diagnosis of depression in the “washout period” were excluded. Thus, at the start of follow-up on January 1, 2002, eligible patients were free of any medical record depression diagnosis and without any opioid prescription fills for 2 years before follow-up ($n = 212,328$). Among new opioid users in follow-up ($n = 79,513$), patients whose use started on/after NOD ($n = 6420$) or last VA encounter ($n = 411$) for those without NOD were excluded. Patients must have also had complete covariate data ($n = 70,997$). Finally, from this original cohort, a subset of new, chronic opioid users, defined as initial use > 90 days,²² was identified for analysis ($n = 7051$). We restricted the sample to patients with > 90 days initial use to remove the confounding associated with increasing risk of depression associated with longer duration of initial opioid use.²² Additional control for total duration of use is described below. The creation of the cohort of new opioid users, free of depression at start of follow-up, has been previously described, see Scherrer et al.²²

2.2. Follow-up time

Follow-up time was defined as months from January 1, 2002 to either date of NOD or censor date. Censor date was defined as date of the last VA encounter in follow-up for those without NOD diagnosis in 2002 to 2012.

2.3. Opioid use—duration, dose, and dose change

The new onset opioid use period began with date of initial prescription fill during follow-up (2002–2012) for any of the following opioids: codeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, oxycodone, oxymorphone, morphine, and pentazocine. Short acting and long acting formulations of agents with both forms of release were included. Information included number of pills dispensed or liquid volume, unit dose (mg), and days supply. The “days supply” variable measures the days required to exhaust the medication if taken as prescribed. Using this information, we created a “total opioid days” variable to define total number of opioid supplied days, accounting for overlap and early refills, from initial opioid fill date to NOD or censor date. This variable was divided into tertiles based on the 33rd and 67th percentiles: 284 days, > 284 to 1034 days, and > 1034 days.

Morphine equivalent dose was calculated using standard conversion tables providing the amount of morphine equivalent given type of drug and dose. For an example of a conversion table, see the State of Washington Agency Medical Directors Group website opioid dose calculator, <http://agencymeddirectors.wa.gov/mobile.html>. Daily dose in follow-up was computed from days supply and total amount dispensed, assuming medication was taken at maximum dose allowed. For every month of follow-up that a patient was taking an opioid, we averaged daily MED so that we had monthly opioid dose for each patient from the time of opioid initiation to NOD or censor date.

To classify patients and define categories of rate of dose change, we used SAS Proc Mixed to conduct a mixed effects regression analysis to model individual level longitudinal monthly change in MED from opioid initiation to either date of NOD or censor date. All opioid MED information was included from date of opioid initiation to NOD or censor date. The model included a fixed effect for time, measured as months since opioid initiation, and a random intercept and slope effect. This approach yielded subject-specific slope estimates of MED change per month after opioid initiation. Individual specific slope estimates were multiplied by 12 for ease of interpretation of rate of change over a 1-year period for each patient. This approach has been used in other studies as an efficient classification method.^{13,14} For each patient, we divided this estimated yearly rate by his or her initial average MED in the first month of opioid use, yielding an estimated percent change. Preliminary analysis revealed a non-linear relationship of rate of change and risk of NOD and supported cutoffs at 25% and 75% for slow and rapid rate increases, respectively, as this was where risk of NOD significantly increased and stayed stable over the course of an interval. Thus, we created a 4-group variable: (1) stable rate, referred to as “stable”, 0% to < 25% change; (2) negative rate, referred to as “decreasing”; (3) slow rate increase, referred to as “slow increase”, 25 to <75% change; and (4) rapid rate increase, referred to as “rapid increase”, at least a 75% change.

2.4. Outcome—new-onset depression

New-onset depression was defined by the presence of a primary diagnosis (ICD-9-CM = 296.2, 296.3, 311) of depression in at least 1 inpatient stay or 2 outpatient visits within the same 12-month period in the follow-up period (2002–2012). This algorithm has been shown to be a valid and reliable measure of depression when using medical record information.^{10,28}

2.5. Covariates

To account for largest dose achieved per patient, we adjusted for maximum daily MED reached in the period from opioid initiation to NOD or censor date (1–50 mg, 51–100 mg, 101–180 mg, and > 180 mg).

Demographics included age, sex, race (white vs other), marital status (married vs other), and insurance coverage (VA only vs other sources). We created a health care utilization variable defined by quartiles of the average number of outpatient clinic visits per month. This variable was dichotomized to high (>75th percentile) and low (< 75th percentile) utilization and used as a control for detection bias.

ICD-9-CM codes were used to define psychiatric comorbidities: posttraumatic stress disorder; any other anxiety disorder (eg, a composite of panic disorder, generalized anxiety disorder, social phobia, obsessive compulsive disorder, and anxiety disorder not otherwise specified); alcohol abuse or dependence; any illicit drug abuse or dependence; and nicotine abuse or dependence. Cardiometabolic conditions, also defined by ICD-9-CM code, included type 2 diabetes mellitus, hypertension, cerebrovascular disease, obesity, and cardiovascular disease (eg, a composite of hyperlipidemia, ischemic heart disease, disease of pulmonary circulation, other heart disease, hypertensive heart disease, and myocardial infarction). Other conditions included low testosterone and sleep apnea.

Pain included 6 separate variables. Five variables for painful chronic conditions were defined from over 900 ICD-9-CM codes^{26,27}: arthritis, back pain, headaches, musculoskeletal pain, and neuropathic pain. Pain scores, collected during routine care in the VA, were on a numerical rating scale ranging from 0 to 10, with higher scores indicating greater current pain intensity. Pain score was defined and used in 2 separate ways: (1) a time invariant, maximum pain score before the end of follow-up and (2) a time varying pain score for each month of follow-up, as variability of pain scores in the VA have been previously reported.⁶ For the time varying pain score assessment, pain score was assumed to be consistent across subsequent months until a new monthly assessment was available. For example, if a patient had a pain score of 5 in month 10 of follow-up and the next pain score available was 6 in month 15 of follow-up, pain score in months 10 through 14 of follow-up was 5.

Comedication with benzodiazepines was defined as at least one benzodiazepine fill occurring sometime in the period of opioid use. Benzodiazepines included alprazolam, clonazepam, diazepam, lorazepam, chlordiazepoxide, and clorazepate. All measures of comorbidity, benzodiazepine use, and pain antedated the occurrence of NOD.

2.6. Propensity scores and inverse probability of treatment weighting

Because bias by indication may confound the association between rate of dose change and NOD, we balanced all potential confounders listed in Table 1's covariate section across categories of rate of dose change using propensity scores. A propensity score is the probability that a patient will be in a rate of change group (ie, stable, decreasing, slow increase, and rapid increase), given covariates. The propensity score was computed using a multivariable, multinomial logistic regression model, predicting exposure to rate of dose change group given the covariates listed in Table 1. After obtaining the propensity score, we applied inverse probability of treatment weighting (IPTW) approaches to create stabilized weights.^{4,5,12,16,20,21,31} The stabilized weight is the marginal probability of exposure, or exposure to dose change group given no covariates, divided by the propensity score. Inverse probability of treatment weighting results in pseudopopulations for each dose change group such that covariates listed in Table 1 balance across groups. Propensity models perform well if covariates achieve balance across groups and stabilized weights have a mean near 1 and do not fall outside a maximum of 10.²⁹

2.7. Statistical analysis

All analyses were performed with SAS v9.4 (SAS Institute, Cary, NC) at an alpha of 0.05. Before weighting data, bivariate analyses using analysis of variance for continuous variables and χ^2 for categorical variables assessed the relationship of covariates with dose change group. Bivariate analyses were repeated after IPTW to ensure covariates balanced across dose change groups. A χ^2 test and Poisson regression model were used to compare crude cumulative incidence proportion and incidence rate (in person-years), respectively, across rate of dose change groups. Average follow-up time was also compared across groups using an analysis of variance. Hazard ratios (HRs) and 95% confidence intervals (CIs) for time to NOD were estimated using Cox proportional hazard models, where rate of dose change group was treated as a time-dependent covariate. Fully adjusted models included additional time-dependent variables to control for pain diagnosis after opioid initiation and for changing monthly pain score in follow-up. Time-dependent variables allow ascertainment of exposure status changes (eg, a new diagnosis of pain or a changing pain score) and time under exposure. Evaluation of hazard trends for dose change and covariates, tested using the SAS PROC PHREG model including interactions of each covariate with follow-up time, confirmed that the proportional hazard assumption was met for rate dose change ($P = 0.104$) and all other covariates included ($P > 0.05$). This project was approved by the institutional review boards of participating institutions.

3. Results

Distributions of covariates and outcomes overall and by rate of dose change group are shown in Table 1. Among this sample of chronic opioid users, average rate of dose change was stable for 47.0% of participants, decreasing for 19.0%, slowly increasing for 24.8%, and rapidly increasing for 9.2% from start of opioid use to NOD or censor date. Overall cumulative incidence of depression from 2002 to 2012 was 14.4%, whereas incidence rate was 16.3 per 1000 person-years. Mean follow-up time was 106.8 months (SD = 34.7 months). Approximately 7.0% of the sample reached a maximum dose of 101 to 180 mg and 4.1% reached a maximum dose of >180 mg. Figure 1 shows fitted overall mixed regression lines and average rate of yearly MED change for each rate of dose change group.

Comparisons between rate of dose change groups showed that 12.7% of the stable group, 12.4% of the decreasing group, 16.3% of the slow increase group, and 22.7% of the rapid increase group developed depression during follow-up ($P < 0.0001$). Incidence rate followed a similar pattern with highest rate in the rapid increase group (27.5/1000 person-years) and smallest in the decreasing group (13.0/1000 person-years).

Total opioid days was also related to rate of dose change group such that the rapid increase and decrease groups had more opioid days (>284: 72.3% and 80.3%, respectively) followed by the stable group (65.4%, >284) and the slow increase group (57.5%, >284). The rapid group had a greater proportion of patients with a maximum dose achieved in follow-up of >100 mg, followed by the decreasing group and the slow increase group.

Other comorbidities related to dose change group were comedication with benzodiazepines, nicotine, alcohol, and drug dependence; hypertension, cardiovascular disease, obesity, and

all pain conditions, including maximum pain score. Age was the only sociodemographic variable related to dose change group. After applying IPTW, all covariates balanced across dose change groups, as shown in Table 2. Inverse probability of treatment weighting stabilized weights ranged from 0.16 to 5.76, with a mean of 1.00 (SD = 0.44) and median of 0.89.

Table 3 shows results of unweighted and weighted Cox proportional hazards models assessing the association between dose change group and time to NOD. In unweighted data, slow (HR = 1.40, 95% CI: 1.20–1.62) and rapid (HR = 2.00, 95% CI: 1.66–2.42) increases in MED were associated with 40% and 100% increases in risk of depression ($P < 0.0001$), respectively, compared with stable dose. See Figure 2 for unweighted survival curves. After weighting data and adjusting for changes in pain comorbidities and changing monthly pain score during follow-up, both slow and rapid increases in MED, compared with stable MED, were associated with a 22% and 58% increased risk of depression, respectively. Other contrasts also showed that the rapid increase group had a 30% increased risk of depression compared with the slow increase group ($P = 0.02$). Both the rapid ($P < 0.0001$) and slow increase ($P = 0.002$) groups had an increased risk of depression when compared with the decreasing group.

4. Discussion

In a large sample of VA patients with chronic opioid use, we observed a significant association between the rate of opioid dose change and risk of NOD independent of maximum pain and MED, adding to the existing knowledge base that certain characteristics of opioid use increase risk for depression.^{14,22,24,25} Of note, our previous study, demonstrating risk of NOD increases with longer duration of initial opioid use, found no relationship between dose and NOD after controlling for duration of use.²² Combining this previous finding with the current results, suggests that greater rate of MED escalation, not high achieved daily MED, contributes to NOD in chronic opioid users.

Our sample in this study was limited to patients who remained without NOD despite > 90 days of initial opioid use, which is the period of opioid use associated with a 35% increased risk of NOD in VA patients.²² The current results indicate that these patients who used for >90 days without developing NOD remained at risk because of rate of MED escalation. Thus, risk of opioid-related NOD may be due to multiple characteristics of opioid use. Patients who are chronic, opioid users without depression should be informed by providers that both slow and rapid rates of dose increase may put them at greater risk of NOD.

Numerous studies have studied dose escalation in the context of the dangers associated with reaching high MED.^{1,8,19} Our finding that rate of dose escalation, independent of maximum dose reached, is a risk for NOD points to the need to investigate rate of dose escalation and maximum achieved dose as risk factors for overdose and abuse. Studies should be conducted to determine whether simply increasing dose is a risk factor for abuse and overdose even when daily MED remains at levels (ie, <100 mg/day) thought to be more safe in regard to abuse and overdose.

Dose escalation may be occurring in response to increased pain reports known to be more frequent in patients with substance use and mental health disorders.^{18,30} This is suggested by the association of dose escalation with substance use disorders before weighting (Table 1). Patients with one or more of these characteristics may increase the amount of medication on their own, seek out providers who have a low threshold for prescribing increasing doses, or may persist in requests for a dose increase until it is obtained. These patient characteristics are not available in administrative medical record data nor are data on self-escalation. We speculate that current results could be explained by patient characteristics that are linked to high risk for both new occurrence of depression and to increased need for a higher opioid dose.¹⁷ It is also possible that loss of control over opioid use and misuse is driving dose escalation and contributing to depression. Clinical guidelines for opioid therapy also warn that repeated dose increases can be indicators of abuse or diversion.³ Undetected opioid misuse or subclinical symptoms would not necessarily be captured by our adjustment for opioid abuse/dependence.

Limitations of this study include the veteran sample that is predominantly male and burdened with more physical and psychiatric comorbidity than a private-sector sample of similar age.²² Despite this threat to generalizability, we have previously shown analyses of opioid duration and NOD as well as opioid use and depression recurrence generated very similar results in VA and private-sector patient samples.^{22,23} Because this is a retrospective cohort design, our data concern opioid prescription fills rather than actual opioid use, so we do not know which patients took their opioids or did not adhere to the prescription, which may result in misclassifying dose and duration of opioid use. However, medications are free or highly discounted in the VA, limiting the possibility that opioid use was misclassified. Also, the diagnostic algorithm used for depression minimizes false positives. However, false negatives are possible, though these should occur at the same rate in those with and without opioid dose escalation. This risk is minimized in the VA because patients receive annual depression screening. Finally, the retrospective study design has limitations including unmeasured confounding. Patient level measures such as pain-related impairment and lack of lifetime medical histories that could influence the associations observed in our results were not available in the medical record.

Rate of dose escalation should be an indicator to providers that the patient is at risk for depression. If the psychological characteristics of impulsivity, catastrophizing, and self-destructiveness accurately describe patients who escalate dose, it is possible that these traits could also contribute to depression, opioid abuse, and overdose.

Our study teased apart risk due to dose escalation from high daily MED and we believe guidelines⁷ and prior studies showing MED thresholds^{1,8,19} associated with abuse and overdose should be revisited. It is possible that the rate of dose escalation is a better predictor of opioid abuse and overdose than high daily MED.

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References

- [1]. Bohnert AS, Valenstein M, Bair MJ, Ganoczy D, McCarthy JF, Ilgen MA, Blow FC. Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA* 2011;305:1513–21.
- [2]. Chen L, Vo T, Seefeld L, Malarick C, Houghton M, Ahmed S, Zhang Y, Cohen A, Retamozo C, St. Hilaire K, Zhang V, Mao J. Lack of correlation between opioid dose adjustment and pain score change in a group of chronic pain patients. *J Pain* 2013;14:384–92. [PubMed: 23452826]
- [3]. Chou R, Gilbert JF, Fine PG, Adler JA, Ballantyne JC, Davies P, Donovan MI, Fishbain DA, Foley KM, Fudin J, Gilson AM, Kelter A, Mauskop A, O'Connor PG, Passik SD, Pasternak GW, Portenoy RK, Rich BA, Roberts RG, Todd KH, Miaskowski C. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain* 2009;10:113–30. [PubMed: 19187889]
- [4]. Cole SR, Hernan MA. Constructing inverse probability weights for marginal structural models. *Am J Epidemiol* 2008;168:656–64. [PubMed: 18682488]
- [5]. Curtis LH, Hammill BG, Eisenstein EL, Kramer JM, Anstrom KJ. Using inverse probability-weighted estimators in comparative effectiveness analysis with observational databases. *Med Care* 2007;45:S103–7. [PubMed: 17909367]
- [6]. Dobscha SK, Morasco BJ, Kavas AE, Peters DM, Hart K, McFarland BH. Short-term variability in outpatient pain intensity scores in a national sample of older veterans with chronic pain. *Pain Med* 2015;16:855–65. [PubMed: 25545398]
- [7]. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic Pain—United States, 2016. *JAMA* 2016;315:1624–45. [PubMed: 26977696]
- [8]. Dunn KM, Saunders JD, Rutter CM, Banta-Green CJ, Merrill JO, Sullivan MD, Weisner CM, Silverberg MJ, Campbell CI, Psaty BM, Von Korff M. Opioid prescriptions for chronic pain and overdose. A cohort study. *Ann Intern Med* 2010;152: 85–92. [PubMed: 20083827]
- [9]. Franklin GM, Enass AR, Turner JA, Daniell WE, Fulton-Kehoe D. Opioid use for chronic low back pain: a prospective, population-based study among injured workers in Washington state, 2002–2005. *Clin J Pain* 2009;25:743–51. [PubMed: 19851153]
- [10]. Frayne SM, Miller DR, Sharkansky EJ, Jackson VW, Wang F, Halanych JH, Berlowitz DR, Kader B, Rosen CS, Keane TM. Using administrative data to identify mental illness: what approach is best? *Am J Med Qual* 2010;25:42–50. [PubMed: 19855046]
- [11]. Fredheim OM, Borchgrevink PC, Mahic M, Skurtveit S. A pharmacoepidemiological cohort study of subjects starting strong opioids for nonmalignant pain: a study from the Norwegian Prescription Database. *PAIN* 2013;154:2487–93. [PubMed: 24075311]
- [12]. Harder VS, Stuart EA, Anthony JC. Propensity score techniques and the assessment of measured covariate balance to test causal associations in psychological research. *Psychol Methods* 2010;15:234–49. [PubMed: 20822250]
- [13]. Hayward RA, Heisler M, Adams J, Dudley RA, Hofer TP. Overestimating outcome rates: statistical estimation when reliability is suboptimal. *Health Serv Res* 2007;42:1718–38. [PubMed: 17610445]
- [14]. Henry SG, Wilsey BL, Melnikow J, Iosif AM. Dose escalation during the first year of long-term opioid therapy for chronic pain. *Pain Med* 2015;16: 733–44. [PubMed: 25529548]
- [15]. Kaplovitch E, Gomes T, Camacho X, Dhalla IA, Mamdani MM, Juurlink DN. Sex differences in dose escalation and overdose death during chronic opioid therapy: a population-based cohort study. *PLoS One* 2015;10:e0134550.
- [16]. Kilpatrick RD, Gilbertson D, Brookhart MA, Polley E, Rothman KJ, Bradbury BD. Exploring large weight deletion and the ability to balance confounders when using inverse probability of treatment weighting in the presence of rare treatment decisions. *Pharmacoepidem Drug Saf* 2013; 22:111–21.
- [17]. Klein DN, Kotov R, Bufferd SJ. Personality and depression: explanatory models and review of the evidence. *Annu Rev Clin Psycho* 2011;7: 269–95.

- [18]. Larance B, Campbell G, Peacock A, Nielsen S, Bruno R, Hall W, Lintzeris N, Cohen M, Degenhardt L. Pain, alcohol use disorders and risky patterns of drinking among people with chronic non-cancer pain receiving long-term opioid therapy. *Drug Alcohol Depend* 2016;162: 79–87. [PubMed: 27049582]
- [19]. Manchikanti L, Helm S II, Fellows B, Janata JW, Pampati V, Grider JS, Boswell MV. Opioid epidemic in the United States. *Pain Physician* 2012; 15:ES9–ES38. [PubMed: 22786464]
- [20]. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology* 2000;11:550–60. [PubMed: 10955408]
- [21]. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983;70:41–55.
- [22]. Scherrer JF, Salas J, Copeland LA, Stock EM, Ahmedani BK, Sullivan MD, Burroughs T, Schneider FD, Bucholz KK, Lustman PJ. Prescription opioid duration, dose, and increased risk of depression in 3 large patient populations. *Ann Fam Med* 2016;14:54–62. [PubMed: 26755784]
- [23]. Scherrer JF, Salas J, Copeland LA, Stock EM, Schneider FD, Sullivan MD, Bucholz KK, Burroughs T, Lustman PJ. Increased risk of depression recurrence after initiation of prescription opioids in Non-Cancer pain patients. *J Pain* 2016;17:473–82. [PubMed: 26884282]
- [24]. Scherrer JF, Salas J, Lustman PJ, Burge S, Schneider FD; RRNo Texas. Change in opioid dose and change in depression in a longitudinal primary care patient cohort. *PAIN* 2015;156:348–55. [PubMed: 25599457]
- [25]. Scherrer JF, Salas J, Sullivan M, Schneider FD, Bucholz KK, Burroughs T, Copeland LA, Ahmedani BK, Lustman PJ. The influence of prescription opioid use duration and dose on development of treatment resistant depression. *Prev Med* 2016;91:110–16. [PubMed: 27497660]
- [26]. Scherrer JF, Svrakic DM, Freedland KE, Chrusciel T, Balasubramanian S, Bucholz K, Lawler EV, Lustman PJ. Prescription opioid analgesics and risk of depression. *J Gen Intern Med* 2014;29:491–9. [PubMed: 24165926]
- [27]. Seal KH, Shi Y, Cohen G, Cohen BE, Maguen S, Krebs EE, Neylan TC. Association of mental health disorders with prescription opioids and high-risk opioid use in US Veterans of Iraq and Afghanistan. *JAMA* 2012;307:940–7. [PubMed: 22396516]
- [28]. Solberg LI, Engebretson KI, Sperl-Hillen JM, Hroschowski MC, O'Connor PJ. Are claims data accurate enough to identify patients for performance measures or quality improvement? the case of diabetes, heart disease, and depression. *Am J Med Qual* 2006;21:238–45. [PubMed: 16849780]
- [29]. Sturmer T, Wyss R, Glynn RJ, Brookhart MA. Propensity scores for confounder adjustment when assessing the effects of medical interventions using nonexperimental study designs. *J Intern Med* 2014;275:570–80. [PubMed: 24520806]
- [30]. Wasserman RA, Brummett CM, Goesling J, Tsodikov A, Hassett AL. Characteristics of chronic pain patients who take opioids and persistently report high pain intensity. *Reg Anesth Pain Med* 2014;39:13–17. [PubMed: 24310048]
- [31]. Xu S, Ross C, Raebel MA, Shetterly S, Blanchette C, Smith D. Use of stabilized inverse propensity scores as weights to directly estimate relative risk and its confidence intervals. *Value Health* 2010;13: 273–7. [PubMed: 19912596]

Figure 1.
Estimated rate of morphine equivalent dose (mg) change, by dose change group.

Figure 2.
Kaplan Meier curve—depression risk and dose change among chronic opioid users.

Table 1

Association of covariates and new-onset depression with dose change group, chronic opioid users (2002–2012) (n = 7051).

Outcome/covariates, n (%)	Overall (n = 7051)	Stable (n = 3314)	Decreasing (n = 1339)	Slow increase (n = 1749)	Rapid increase (n = 649)	P
Outcome						
Depression, cumulative incidence	1016 (14.4)	420 (12.7)	164 (12.4)	285 (16.3)	147 (22.7)	<0.0001
Depression, incidence rate	16.3/1000 PY	14.1/1000 PY	13.0/1000 PY	19.3/1000 PY	27.5/1000 PY	<0.0001
Follow-up time, mo, mean (SD)	106.8 (34.7)	108.2 (34.3)	113.9 (28.3)	101.6 (37.5)	99.3 (37.1)	<0.0001
Covariates						
Total opioid tertiles, d						
284	2335 (33.1)	1147 (34.6)	264 (19.7)	744 (42.5)	180 (27.7)	
>284–1034	2390 (33.9)	1070 (32.3)	573 (42.8)	515 (29.5)	232 (35.8)	<0.0001
>1034	2326 (33.0)	1097 (33.1)	502 (37.5)	490 (28.0)	237 (36.5)	
Maximum monthly dose, mg						
1–50	4824 (68.4)	2557 (77.2)	784 (58.5)	1194 (68.3)	289 (44.5)	
51–100	1445 (20.5)	559 (16.9)	354 (26.4)	368 (21.0)	164 (25.3)	<0.0001
101–180	496 (7.0)	138 (4.2)	144 (10.7)	119 (6.8)	95 (14.6)	
>180	286 (4.1)	160 (1.8)	57 (4.3)	68 (3.9)	101 (15.6)	
Benzodiazepine (comedication)	2251 (31.9)	1015 (30.6)	449 (33.5)	557 (31.8)	230 (35.4)	0.049
Psychiatric comorbidities*						
PTSD	1222 (17.3)	553 (16.7)	254 (19.0)	315 (18.0)	100 (15.4)	0.127
Other anxiety [†]	1110 (15.7)	488 (14.7)	232 (17.3)	281 (16.1)	109 (16.8)	0.122
Nicotine abuse/dependence	3395 (48.2)	1557 (47.0)	631 (47.1)	854 (48.8)	353 (54.4)	0.005
Alcohol abuse/dependence	1499 (21.3)	662 (20.0)	299 (22.3)	3554 (20.3)	183 (28.2)	<0.0001
Any illicit drug abuse/dependence	988 (14.0)	424 (12.8)	206 (15.4)	231 (13.2)	127 (19.6)	<0.0001
Metabolic/cardiovascular comorbidities*						
Diabetes type II	3116 (44.2)	1493 (45.1)	596 (44.5)	766 (43.8)	261 (40.2)	0.150
Hypertension	6011 (85.3)	2845 (85.8)	1168 (87.2)	1458 (83.4)	540 (83.2)	0.007
Cardiovascular disease [‡]	6201 (87.9)	2944 (88.8)	1196 (89.3)	1504 (86.0)	557 (85.8)	0.003
Cerebrovascular disease	1490 (21.1)	690 (20.8)	289 (21.6)	375 (21.4)	136 (21.0)	0.926

Outcome/covariates, n (%)	Overall (n = 7051)	Stable (n = 3314)	Decreasing (n = 1339)	Slow increase (n = 1749)	Rapid increase (n = 649)	P
Obesity diagnosis	2735 (38.8)	1263 (38.1)	567 (42.4)	646 (36.9)	259 (39.9)	0.014
Other comorbidities [*]						
Low T	284 (4.0)	125 (3.8)	69 (5.2)	58 (3.3)	32 (4.9)	0.035
Sleep apnea	721 (10.2)	329 (9.9)	164 (12.3)	171 (9.8)	57 (8.8)	0.043
Painful conditions [*]						
Arthritis	6120 (86.8)	2850 (86.0)	1202 (89.8)	1482 (84.7)	586 (90.3)	<0.0001
Back pain	5361 (76.0)	2496 (75.3)	1066 (79.6)	1285 (73.5)	514 (79.2)	<0.001
Headaches	1369 (19.4)	622 (18.8)	301 (22.5)	319 (18.2)	127 (19.6)	0.015
Musculoskeletal pain	4329 (61.4)	1929 (58.2)	921 (68.8)	1042 (59.6)	437 (67.3)	<0.0001
Neuropathic pain	2635 (37.4)	1189 (35.9)	532 (39.7)	653 (37.3)	261 (40.2)	0.035
Maximum pain score, mean (SD)	8.7 (1.9)	8.5 (2.0)	8.9 (1.7)	8.6 (2.0)	9.0 (1.6)	<0.0001
High health care utilization	1969 (27.9)	782 (23.6)	408 (30.5)	525 (30.0)	254 (39.1)	<0.0001
Age	56.0 (12.5)	56.6 (12.3)	55.1 (12.4)	56.4 (12.7)	53.6 (12.6)	<0.0001
Sex: male	6740 (95.6)	3188 (96.2)	1272 (95.0)	1669 (95.4)	611 (94.1)	0.062
Race: white	5924 (84.0)	2806 (84.7)	1104 (82.4)	1474 (84.3)	540 (83.2)	0.271
Insurance: VA only	4415 (62.6)	2050 (61.9)	851 (63.6)	1103 (63.1)	411 (63.3)	0.658
Marital status: married	3994 (56.6)	1405 (42.4)	583 (43.5)	758 (43.3)	311 (47.9)	0.080

^{*} Comorbidities occurring before new-onset depression.

[†] Other anxiety disorders = panic disorder, obsessive compulsive disorder, social phobia, generalized anxiety disorder, and anxiety not otherwise specified.

[‡] Cardiovascular disease = hyperlipidemia, ischemic heart disease, diseases of pulmonary circulation, other heart disease, hypertensive heart disease, and myocardial infarction.

PY, person-years; VA, Veterans Health Administration.

Weighted association of covariates with dose change group, weighted by inverse probability of exposure, chronic opioid users (2002–2012) (n = 7051).

Table 2

Covariates, %	Stable (n = 3314)	Decreasing (n = 1339)	Slow increase (n = 1749)	Rapid increase (n = 649)	P
Total opioid tertiles, d					0.981
284	33.2	31.9	33.1	33.6	
>284–1034	33.8	33.9	33.7	33.9	
>1034	33.0	34.2	33.2	32.5	
Maximum monthly dose, mg					
1–50	68.5	68.0	68.6	69.1	
51–100	20.5	20.8	20.4	19.9	0.999
101–180	7.1	7.2	6.9	7.2	
>180	4.0	4.0	4.1	3.9	
Benzodiazepine (comedication)	31.8	32.8	31.7	30.7	0.816
Psychiatric comorbidities *					
PTSD	17.7	17.4	17.2	19.0	0.789
Other anxiety †	15.6	15.3	15.3	15.0	0.978
Nicotine abuse/dependence	47.9	49.1	48.8	45.4	0.425
Alcohol abuse/dependence	21.0	21.8	21.4	20.8	0.938
Any illicit drug abuse/dependence	13.8	14.9	14.2	13.7	0.798
Metabolic/cardiovascular comorbidities *					
Diabetes type II	44.3	42.0	44.0	47.4	0.152
Hypertension	85.3	85.2	85.4	86.1	0.958
Cardiovascular disease ‡	88.0	87.5	87.8	88.2	0.960
Cerebrovascular disease	21.2	20.6	20.8	21.4	0.968
Obesity diagnosis	38.8	38.8	39.0	40.1	0.932
Other comorbidities *					
Low T	4.1	4.9	4.2	4.6	0.640
Sleep apnea	10.1	9.8	10.7	11.4	0.636

Covariates, %	Stable (n = 3314)	Decreasing (n = 1339)	Slow increase (n = 1749)	Rapid increase (n = 649)	P
Painful conditions *					
Arthritis	86.7	88.3	86.7	85.8	0.352
Back pain	76.2	78.0	75.6	75.0	0.352
Headaches	19.5	19.8	19.2	19.7	0.982
Musculoskeletal pain	61.4	63.2	61.3	60.6	0.621
Neuropathic pain	37.2	37.3	37.6	37.1	0.991
Maximum pain score, mean (SD)	8.6 (1.9)	8.7 (1.9)	8.6 (1.9)	8.7 (1.9)	0.394
High health care utilization	27.8	28.1	28.1	28.6	0.982
Age	56.0 (12.5)	55.8 (12.3)	55.8 (12.5)	56.0 (12.4)	0.957
Sex: male	95.6	95.6	95.3	95.1	0.916
Race: white	83.8	84.5	84.4	83.4	0.861
Insurance: VA only	62.1	62.8	62.7	62.3	0.959
Marital status: married	56.7	55.8	56.3	55.2	0.870

* Comorbidities occurring before new-onset depression.

[†] Other anxiety disorders = panic disorder, obsessive compulsive disorder, social phobia, generalized anxiety disorder, and anxiety not otherwise specified.

[‡] Cardiovascular disease = hyperlipidemia, ischemic heart disease, diseases of pulmonary circulation, other heart disease, hypertensive heart disease, and myocardial infarction.
VA, Veterans Health Administration.

Cox proportional hazards models, association between dose change group and new-onset depression, unweighted and weighted by inverse probability of exposure, chronic opioid users (2002–2012) (n = 7051). *

Table 3

Variable	Model 1—crude [†] HR (95% CI)	Model 2—weighted [‡] HR (95% CI)	Model 3—weighted + pain [§] HR (95% CI)
Dose change group			
Stable	1.00	1.00	1.00
Decreasing	0.91 (0.76–1.09)	0.90 (0.75–1.07)	0.91 (0.76–1.09)
Slow increase	1.40 (1.20–1.62)	1.20 (1.04–1.40)	1.22 (1.05–1.42)
Rapid increase	2.00 (1.66–2.42)	1.59 (1.31–1.94)	1.58 (1.30–1.93)
Arthritis			1.20 (1.01–1.43)
Back pain			1.71 (1.46–2.00)
Headache			1.57 (1.37–1.81)
Musculoskeletal pain			1.56 (1.36–1.78)
Neuropathy			1.10 (0.96–1.25)
Pain score			1.10 (1.08–1.12)

* Test for proportional hazards assumption, $P = 0.104$.

[†] Significant contrasts: decrease vs slow increase; decrease vs rapid increase; slow increase vs rapid increase.

[‡] Significant contrasts: decrease vs slow increase; decrease vs rapid increase; slow increase vs rapid increase.

[§] Significant contrasts: decrease vs slow increase; decrease vs rapid increase; slow increase vs rapid increase.

CI, confidence interval; HR, hazard ratio.