



Published in final edited form as:

J Pain. 2016 April ; 17(4): 473–482. doi:10.1016/j.jpain.2015.12.012.

Increased Risk of Depression Recurrence after Initiation of Prescription Opioids in Non-Cancer Pain Patients

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Abstract

Several studies have demonstrated chronic opioid analgesic use is associated with increased risk of new onset depression. It is not known if patients with remitted depression are at increased risk of relapse following exposure to opioid analgesics. A retrospective cohort design using patient data from the Veterans Health Administration (VHA; n=5,400), and Baylor Scott & White Health (BSWH; n=842) was performed with an observation period 2002–2012 in VHA and 2003–2012 in BSWH. Eligible patients had a diagnosis of depression at baseline and experienced a period of remission. Risk of depression recurrence was modeled in patients that either started an opioid or remained without opioid prescriptions before or during remission. Cox-proportional hazard models measured the association between opioid use and depression recurrence controlling for pain, and other confounders. Patients exposed to an opioid compared to those unexposed had a

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Conflict of interest: none

Disclosures: none

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significantly greater risk of depression recurrence in both patient populations (VHA: HR=2.17; 95% CI:2.01–2.34; BSWH: HR=1.77; 95% CI:1.42–2.21). These results suggest opioid use doubles the risk of depression recurrence even after controlling for pain, psychiatric disorders and opioid misuse. Further work is needed to determine if risk increases with duration of use. Repeated screening for depression after opioid initiation may be warranted.

Keywords

opioids; depression recurrence; pain; retrospective; epidemiology

INTRODUCTION

Pain and depression are highly comorbid, and this association is likely bi-directional.^[5] A large community survey study found that persons with major depression, compared to those without, reported more severe and frequent pain and more pain sites.^[15] In a prospective cohort study of remitted depression and anxiety, Gerrits and colleagues^[8] found neck, back, head, orofacial, chest, abdominal and joint pain, and number of pain conditions, measured during remission, were significantly associated with increased risk of depression recurrence. Because pain and depression have been shown to be closely linked and pain is a predictor of depression recurrence, evaluating the independent contribution of opioid analgesic use (OAU) to risk of depression recurrence must be done with rigorous control for confounding by pain.

Depression and opioid use are known to be associated. Patients with depression are more likely to use opioids even when functioning is good.^[9] A well-established literature supports the conclusion that patients with chronic pain and comorbid depression are more likely to be prescribed opioids, receive higher doses, use for a longer duration and at higher doses, and misuse or abuse opioids compared to patients without depression.^[1; 10; 11; 14; 26] A growing body of literature demonstrates the reverse pattern of association exists; patients with chronic non-cancer pain, prescribed opioids are more likely to develop depression. Specifically, we have previously reported that Veterans Health Administration (VHA) patients receiving opioids for >180 days were 51% more likely to have an incident depression diagnosis, compared to patients exposed for <90 days.^[22] More recently, we found that the duration of opioid use, but not morphine equivalent dose (MED) was associated with a two-fold increased risk of incident depression. We found no association between maximum MED, modeled as 1–50 mg, 51–100 mg and >100 mg, and incident depression after controlling for duration of use and pain. We observed up to a two-fold increased risk of incident depression among patients who used for 90 days or longer compared to those who used for 1–30 days. This risk remained after controlling for MED and pain.^[20] Our findings were consistent across three separate patient populations drawn from health care systems with large differences in demographics and comorbidity. Importantly our studies demonstrated chronic OAU leads to depression independent of pain, opioid misuse, and psychiatric and physical comorbidity. These studies were conducted with patients selected to be free of a depression diagnosis for two years prior to baseline. Therefore we do not know if opioid use among patients with a recent history of depression

promotes depression recurrence. If opioid use is associated with increased risk of depression recurrence, the benefits vs. risks of opioids in chronic, non-cancer pain patients with recent depression will need to be carefully and frequently re-evaluated.

This current study, specifically sought to determine whether: 1) in a cohort of VHA patients in depression remission, initiation of an opioid prescription for non-cancer pain increases risk of recurrence after controlling for confounding from pain and other sources of confounding, and 2) results generalize to a patient cohort derived from a private-sector health care system.

METHODS

Patients

Patient data were obtained from VHA and Baylor Scott & White Health (BSWH) System electronic medical record files. BSWH data is part of the Health Care Systems Research Network (HCSRN; formerly HMORN) Virtual Data Warehouse.^[18] VHA medical records included clinic encounters from January 1, 2000 through December 31, 2012, and BSWH data included encounters from January 1, 2003 through December 31, 2012. Patient data used in the present study included ICD-9-CM diagnostic codes, prescription records, vital signs and demographic data.

Eligibility criteria

In both patient cohorts, we restricted the cohort to patients 18–80 years of age at baseline and free of a diagnosis for cancer or HIV. Baseline was January 1, 2002 in the VA data and January 1, 2005 in the Baylor Scott & White data. Further, as shown in Figure 1a and 1b, patients must have been regular users, i.e. have a visit at least once each year, of their healthcare system in the two years prior to baseline. These two years prior to baseline are called the “washout period” and were used to exclude patients with existing opioid use and those with remitted depression (e.g., diagnosed with depression in year 1 of washout and remitted in year 2 of washout). Last, patients initiating opioid use on or after the date of depression recurrence were excluded because they were not informative to the temporal order of the research question; that is, to determine if opioid use in remitted patients increases risk of depression recurrence. Eligibility criteria resulted in 5,400 VHA and 842 BSWH patients free of opioid use for at least 2 years and with a depression diagnosis. All patients must have experienced depression remission during follow-up. As shown in Figure 2, some patients could have experienced the beginning of a period of remission at the end of washout and others had yet to enter a period of remission.

Opioid exposure variable

Patients were considered opioid-exposed if they received a prescription for any of the following medications: codeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, oxycodone, oxymorphone, morphine and pentazocine, for any number of days and any daily dose. We created a binary variable indicating ever receiving an opioid vs. remaining opioid-free during follow-up. We did not have sufficient sample size to estimate the duration of exposure or groups defined by dose.

Outcome variable – depression recurrence

Patients were defined as having depression if they had two or more visits in the same 12-month period and/or 1 hospital discharge diagnosis with an ICD-9-CM code for depression (i.e., 296.2, 296.3 and 311). This algorithm, commonly used in studies of depression in administrative data, has excellent concordance when compared to written medical record^[25] and self-report.^[6]

The lack of consistently recorded depression severity (e.g. administrations of the PHQ-9) in administrative medical record data precludes defining the course of depression, including onset of remission, relapse and recurrence with the precision outlined in treatment trials.^[13] Within the limits of our data we are able to determine when patients were no longer being treated for depression but less able to distinguish remission from recovery, and distinguish relapse, which occurs early in the process of recovery, from recurrence which occurs after many months of remission. In the present study, we acknowledge recurrence may better reflect relapse in some cases and remission may be partial or complete. With this caveat, and in the interest of using a consistent terminology, we defined periods of “remission” and “recurrence” using an algorithm previously reported in studies based on administrative medical record data.^[7]

First, a period without depression was defined by at least 120 consecutive days with no record of a depression diagnosis including at least 90 days with no prescription for antidepressants. That is, patients were visiting the medical center but the medical record data indicated four months of care without a diagnosis and three months without pharmacotherapy for depression. Patients meeting this criteria were considered in remission. Depression recurrence was then defined as a new diagnosis for depression after a period of remission. The date of recurrence was the date of an inpatient diagnosis or the date of the first diagnosis when two diagnosis in the same 12-month period defined depression.

Covariates

Both patient data sets contained the same covariate measures with the exception of pain scores and marital status which were only available in VHA data. We selected covariates that might confound the association between opioid initiation and depression recurrence.^[14, 16, 24, 26, 27] Importantly, the combination of covariates had to be a good predictor of opioid initiation to compute a propensity score that could be used to balance covariates between opioid users and never users as described in more detail below. Covariates included demographics; psychiatric and substance use disorders, the latter including opioid abuse/dependence; chronic physical conditions associated with depression; painful conditions; self-reported pain scores; and volume of health services use.

Demographics included age, race, gender, and marital status. A measure of insurance coverage was included to control for access to care outside of VHA, and in the private sector data, Medicare served as a proxy for low cost medication coverage. Psychiatric disorders, measured by ICD-9-CM codes, included posttraumatic stress disorder and a composite anxiety disorder variable which included panic disorder, generalized anxiety disorder, social phobia, obsessive-compulsive disorder and anxiety disorder not otherwise specified.

Substance use disorder included ICD-9-CM codes for nicotine dependence or a code indicating any history of smoking, alcohol abuse/dependence and any drug abuse/dependence. Physical conditions identified by ICD-9-CM codes included type II diabetes, hypertension, cardiovascular and cerebrovascular disease, obesity, low testosterone and sleep apnea (the latter two variables may be confounders or may be in the causal pathway in that opioids lead to low testosterone and sleep apnea which in turn lead to depression recurrence). Volume of health services utilization defined by the quartile of mean clinic visits per month was used to adjust for detection bias which is the potential for finding a condition or other patient variable due to greater contact with healthcare providers.

Pain was measured by ICD-9-CM diagnosis for over 900 conditions for which an opioid may be prescribed.^[23] These conditions were collapsed into five categories: arthritis, back pain, headache, musculoskeletal pain and neuropathic pain. Pain scores, available in VHA data, were measured on a 10-point scale with higher scores designating worse pain. We adjusted for the maximum pain score, i.e. worst pain, reported any time prior to end of follow-up.

Propensity scores (PS) were computed to control for confounding by indication, i.e. pain diagnoses, and to control for other confounders. In this study, the PS is a measure of the probability of a patient being prescribed an opioid. The PS was calculated by a multivariate logistic regression model containing covariates and interaction terms. The model selected for weighting data was determined by optimization of AIC with a c-statistic greater than 0.80. The PS was used to balance covariates in the opioid-treated and untreated groups via conventional Inverse Probability of Treatment Weighting (IPTW) methods.^[2; 4; 12; 17] Patient data were weighted by the inverse probability of receiving opioid treatment. IPTW retains all patients and thus was chosen over matching techniques which often results in many lost observations. The model terms used to compute the PS and IPTW in VHA data were the same as those applied in BSWH data. In the VA data the mean weight was 0.98, SD=0.80, minimum=0.48 and maximum=9.59 and in BSWH data the mean weight was 1.01, SD=0.49, minimum=0.50 and maximum=9.34.

Analytic approach

Bivariate analysis included t-tests and chi-square tests computed to measure the associations among opioid use, covariates and depression recurrence. Bivariate associations were computed first in unweighted data and then in weighted data. Results of bivariate analysis using weighted data were evaluated to determine if the PS model and IPTW were successful in balancing potential confounders in opioid-exposed and unexposed patients. This was determined by showing covariates were similarly distributed and not significantly associated with opioid treatment after applying IPTW.

Using unweighted and weighted data, we computed Cox proportional hazard models to estimate the association between opioid treatment and time to depression recurrence. Cox models using weighted data controlled for confounding via weighting and we computed a final model that allowed for further adjustment for each pain condition and maximum pain score that could occur any-time prior to end of follow-up. This additional adjustment controlled for pain after initiation of opioid use. The unit of follow-up time was in months,

and the end of follow-up was defined by depression recurrence, last patient encounter or end of the observation period. Cox proportional hazard models were computed using the PHREG procedure in SAS version 9.4 (SAS Institute, Cary, NC) with α set at 0.05. Two-tailed tests were used in all analysis. The proportional hazard assumption was violated in BSWH at the early part of follow-up, however use of time dependent covariates overcomes concerns about violating the assumption. This study was reviewed and approved by the Institutional Review Boards of participating institutions.

RESULTS

Patient characteristics in the VHA and BSWH cohorts are shown in Table 1. On average, compared to BSWH, VHA patients were older (mean=50.4±12.4 vs 42.1±15.2) and predominantly male (86.8% vs. 23.9%). Both patient groups were mostly white (>79%).

During the follow-up period, 52.0% of VHA and 46.9% of BSWH patients received at least one opioid prescription. Comorbid psychiatric disorders were more common among VHA patients as were physical health conditions with the exception of sleep apnea which was diagnosed in roughly 8% of both patient groups.

Over 50% of both patient groups had at least one painful condition. Arthritis, back pain and neuropathic pain were more common in VHA patients while headaches and musculoskeletal conditions more often diagnosed in BSWH patients. The average maximum pain score reported by VHA patients was 8.0±2.6, on a ten point scale.

The unweighted distributions of depression recurrence and covariates by opioid exposure are shown in Table 2. The cumulative incidence of depression in exposed and unexposed was similar (57.7% and 60.1%, respectively, $p=.08$). However, this is an artefact of not accounting for how fast depression onsets in the two groups.. For instance, when examining incidence rate in VA data, results showed that opioid exposed had a higher rate of depression recurrence (IR=130.1/1000 person-years, CI: 123.9–136.6) than non- exposed (IR=114.4/1000 person-years, CI: 108.8–120.2).

In VHA patients, opioid exposure was significantly associated with younger age ($p<0.0001$), and significantly fewer opioid exposed patients were male and white ($p<0.05$ and $p<0.0001$, respectively). All psychiatric comorbidities were more common among opioid-exposed compared to non-exposed patients ($p<0.0001$). Physical health conditions, painful conditions, pain score and health services utilization were all more prevalent among patients receiving at least one opioid prescription compared to those who were not opioid-exposed ($p<0.0001$). Among BSWH patients, patients prescribed at least one opioid were significantly more likely to have a comorbid health diagnosis ($p<0.5$ to $p<0.0001$) with the exception of cerebrovascular disease and sleep apnea. The only psychiatric disorder significantly associated with opioid exposure was nicotine dependence/history of smoking ($p<0.05$). Last, contrary to the VHA patient sample, opioid-exposed BSWH patients had a significantly lower volume of health care utilization compared to non-exposed ($p<0.0001$).

After weighting data, covariates were no longer significantly associated with opioid exposure in both VHA and BSWH patients (see Table 3). Mean pain scores among VHA

opioid-exposed and unexposed patients were nearly identical (mean=8.0 non-exposed vs. mean=8.2 exposed). Overall, IPTW successfully balanced the distribution of covariates and, importantly, the percentage of painful conditions was nearly the same in opioid-exposed and non-exposed persons in both patient populations.

Results of Cox proportional hazard models are shown in Table 4. Prior to weighting data in Model 1, VHA and BSWH patients who initiated an opioid, compared to those that did not, were significantly more likely to have a depression recurrence (HR=1.87; 95% CI:1.74–2.02 and HR=1.50; 95% CI:1.19–1.88, respectively) in this univariate model. In Model 2, after correcting for confounding via data weighting, but without additional covariate adjustment, the association between opioid initiation and depression recurrence increased and remained significant in VHA and BSWH patient samples. The magnitude of association between opioid exposure and depression recurrence remained similar in Model 3 which included additional adjustment for painful conditions, and pain scores in VHA data, that may have occurred between initiation of an opioid and depression recurrence. In this model, we observed both VHA and BSWH opioid-exposed patients had up to a two-fold increased risk of depression recurrence relative to unexposed counterparts (HR=2.17; 95% CI:2.01–2.34 in VHA and HR=1.77; 95% CI:1.42–2.21 in BSWH). Survival curves illustrating the association between opioid exposure and time to depression recurrence are shown in Figure 3a (VA patients) and 3b (BSWH patients).

Supplemental analysis

We computed post-hoc analysis in the VHA patient cohort to determine if risk of recurrence differed in patients who began opioids before entering a period of remission versus initiating while in a period of remission. Among 2,809 opioid starts in VHA patients, 30.8% occurred before remission (n=865) and 69.2% occurred during the remission period (n=1,944). We computed an unadjusted survival model comparing risk of depression recurrence among patients who started opioids before remission versus those who started while in remission. Results indicated starting opioids while depressed was associated with a significant risk of depression recurrence compared to starting opioids during remission (HR=1.87; 95% CI: 1.70–2.07). This finding is preliminary as confounders were not balanced between these two groups. Although sample size prohibited computing survival models with an exposure variable for the duration of opioid use, we observed that the distribution of VHA patients who used for 1–30 days, 31–90 days and >90 days was similar in those who did and did not experience recurrence. Among the VHA patients who experienced a depression recurrence, 75.5% used opioids for 1–30 days, 12.7% used for 31–90 days and 11.8% used opioids for >90 days. Among VHA patients that did not experience a depression recurrence, 75.6% used opioids for 1–30 days, 13.6% for 31–90 days and 10.8% for > 90 days. We also found morphine equivalent dose was similarly distributed in patients with and without depression recurrence.

Last, to overcome immortal time bias, we computed the association between duration of opioid use in VA data and risk of recurrence. by restricting opioid use to start at least one year after remission. In balanced data, compared to patients who used for 1–30 days, we found 31–90 days of continuous use and >90 days of continuous opioid use were not

significantly associated with increased risk of recurrence but point estimates were in the direction of increasing risk with longer duration of use (HR=1.04; 95% CI:0.80–1.35 and HR=1.17; 95% CI:0.88–1.58).

DISCUSSION

In two large patient cohorts with large differences in demographics and comorbidity burden, we observed that patients who were in a period of depression remission had an approximately two-fold greater risk of depression recurrence if they initiated an opioid medication compared to patients who remained unexposed to opioids. While a growing body of evidence supports the association between longer duration of opioid use and increasing risk of new-onset depression^[21; 22], to our knowledge, this study is novel in demonstrating that opioid therapy increases the risk of depression recurrence among patients with remitted depression.

Additional research is necessary to determine the mechanisms underlying our findings. However, one potential explanation is that opioid exposure acts to prevent full remission and then opioids worsen partly remitted depression which leads to recurrence. Patients who start opioid medication prior to a period of remission may experience partial remission and be more vulnerable to worsening depression and recurrence. While limited, supplemental analysis indicated opioid initiation while depressed compared to when in remission was associated with increased risk of recurrence (HR=1.87). This provides limited evidence that risk of recurrence may be driven by opioid use leading to incomplete remission which in turn places patients at risk for recurrence.

In this study, we did not find evidence for an association between longer duration or higher dose of opioids and increased risk of depression recurrence. This contrasts with our studies of incident depression in which longer duration was associated with increasing risk ^[19; 20]. We speculate that the role of opioid dose and duration in risk of incident depression may not apply to risk of depression recurrence for which risk may not be increased as a function of dose or longer duration. As suggested by supplementary data analysis, there is very limited evidence that duration is associated with risk of recurrence.

Limitations

Opioid exposure was based on prescription fills and it is impossible to know whether patients took their medications as prescribed. If patients did not use their prescription, and were misclassified as opioid exposed, the error would bias results to the null and our hazard ratios may actually under-estimate risk of recurrence.

The algorithms for remission and recurrence are imperfect indicators of the course of disease. If consistently available for all patients, repeated, monthly assessments of depression symptoms would have allowed for more precise measures of remission and recurrence; however, such data are rarely available in retrospective medical record databases. In the VA patient sample, 638 had PHQ-9 scores during remission and recurrence. Of these, 259 were not exposed to opioids and 379 did initiate an opioid. On average PHQ-9 scores among opioid free patients were 10.9 ± 7.6 during remission and 10.9 ± 7.6 at recurrence

compared to 11.5 ± 7.1 during remission and 11.4 ± 7.3 during recurrence in opioid exposed patients. A PHQ-9 score of 10 is the cut-point for moderate depression and these values may point to re-initiating treatment for those who did not experience full remission. These data are limited to a small subsample of the VHA patients and do not include pre-remission depression severity measures. While these PHQ-9 scores raise the possibility that opioid exposure is not associated with limited remission, they could also indicate that patients with more persistent symptoms are also the patients receiving multiple PHQ-9 measures. In sum, these data were insufficient to determine if opioids limit depression remission. Further research with prospective data collection is needed to understand how opioid use impacts the course of depression.

Conclusions

Prescription opioid use among patients with a recent history of depression increases the chance of recurrence and this effect is independent of pain diagnoses and pain intensity scores. In addition to monitoring pain patients for new onset depression, clinicians should be aware and discuss the probability of depression recurrence with patients considering opioid therapy.

As of 2013, in the developed world, back pain and depression were ranked number 1 and 2 in the top ten causes of years lived with disability.^[3] The burden of disease due to these conditions may be increased if opioid treatment for chronic pain, especially back pain, leads to persistent depression. The present findings highlight a particularly challenging situation faced by clinicians and pain patients and point to the need for careful consideration of depression in the assessment of benefit and risk. To improve clinical outcomes and for public health, the current study highlights the need to develop effective non-opioid pain medication and non-pharmacological therapies for chronic pain.

Acknowledgments

Funding: This study was supported by the National Institute of Mental Health, Prescription Opioid Analgesics and Risk of Depression, R21MH101389.

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Perspective

In two large patient cohorts with large differences in demographics and comorbidity, patients with remitted depression, exposed to opioid analgesics were 77% to 117% more likely to experience a recurrence of depression than those who remained opioid free. Routine, not just at initiation of treatment, screening for depression is warranted.

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Figure 1.a

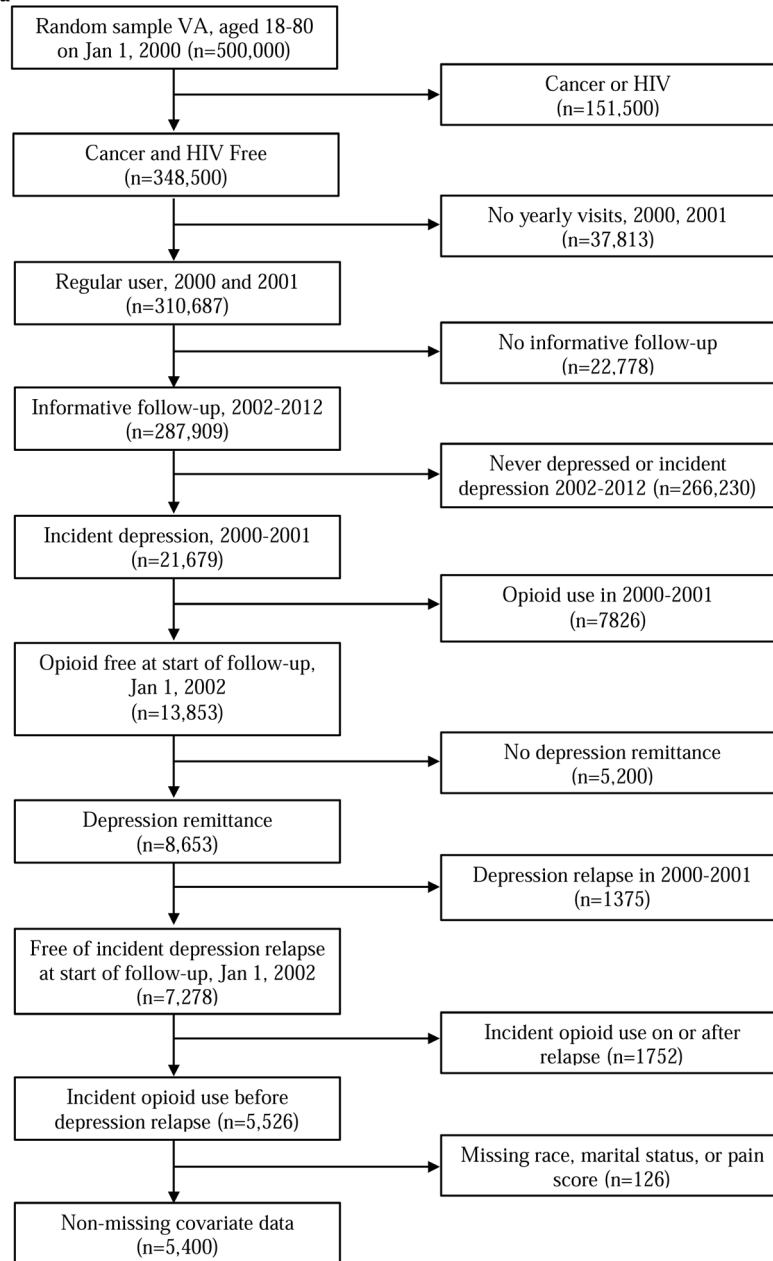


Figure 1a

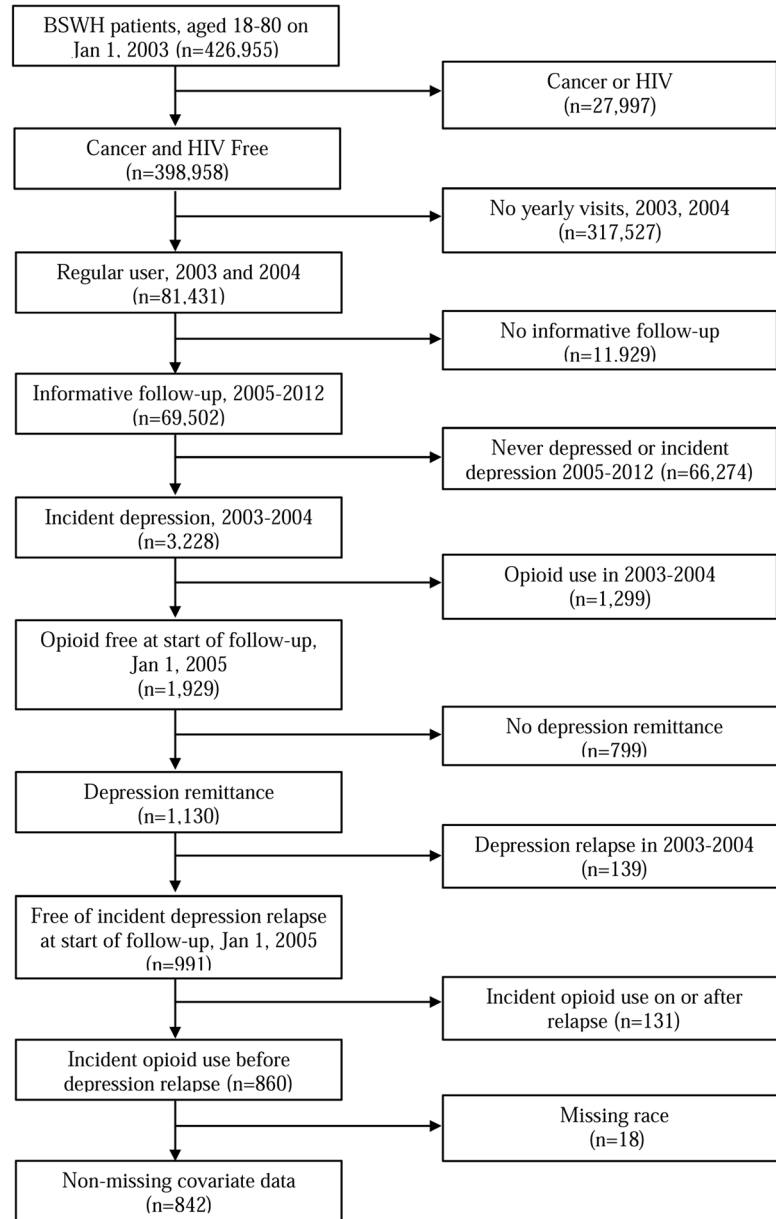
Figure 1b**Figure 1b****Figure 1.**

Figure 1a. VA patient eligibility

Figure 1b BSWH patient eligibility

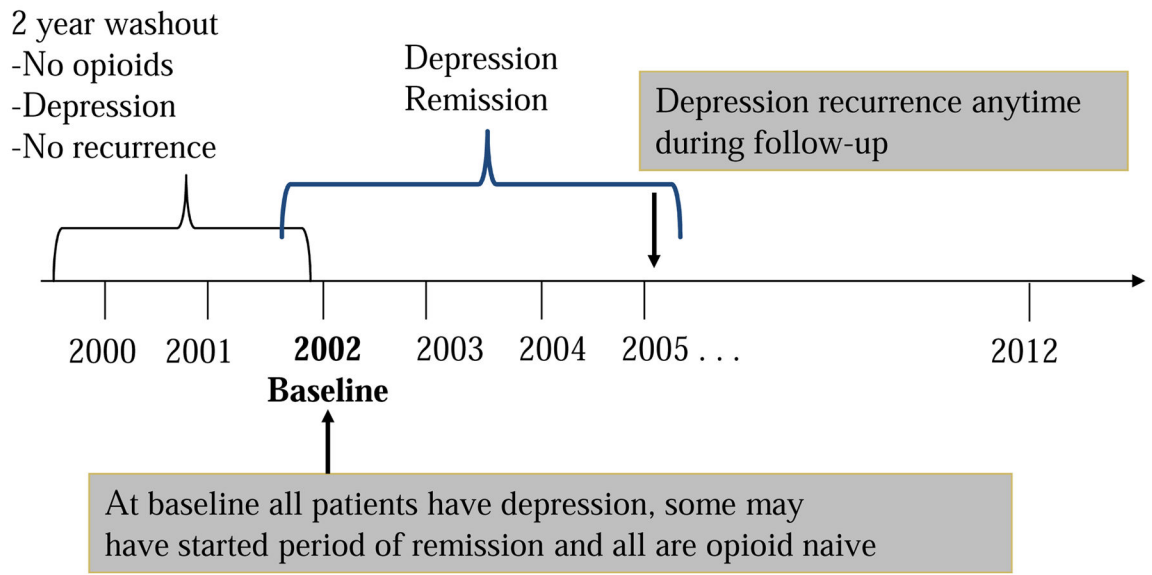


Figure 2.

Figure 3a

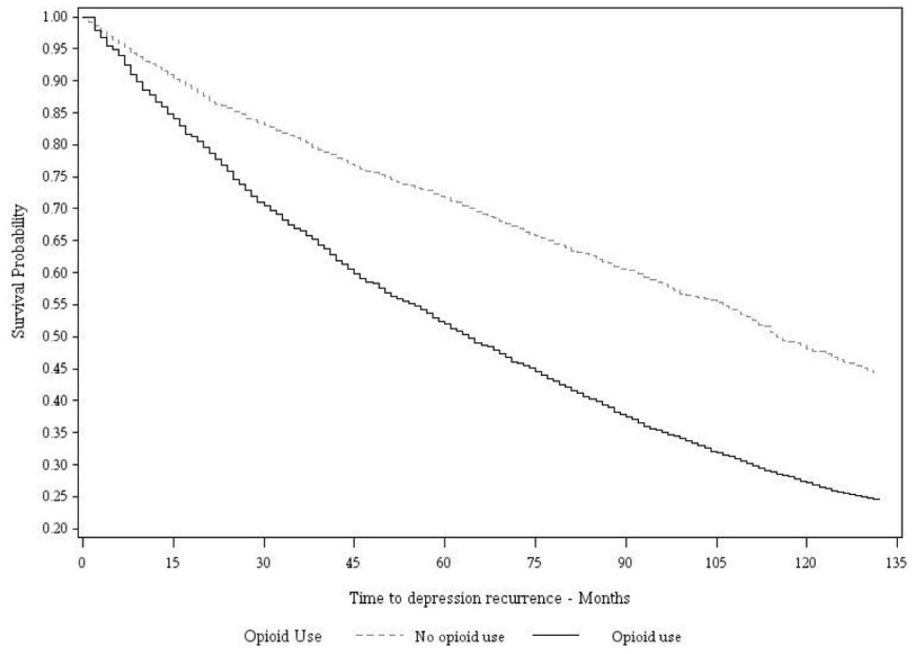


Figure 3a

Figure 3b

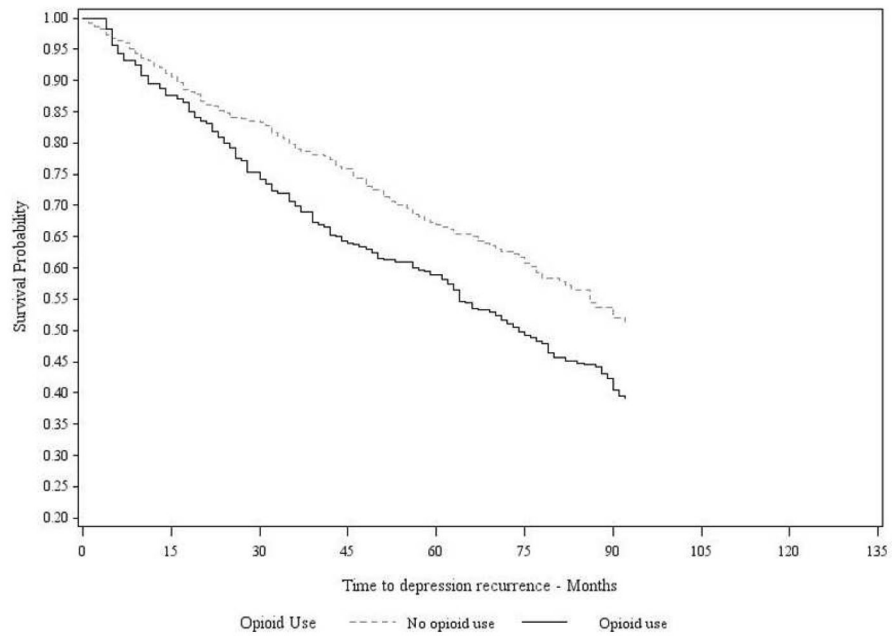


Figure 3b

Figure 3.

Figure 3a. Survival Curve Veterans Health Administration Patient Data

Figure 3b. Survival Curve Baylor Scott & White Patient Data

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Table 1

Distribution of opioid exposure and covariates by healthcare organization

Exposure/covariates, n(%)	VA (n=5,400)	BSWH (n=842)	p-value
Age, mean(sd)	50.4 (\pm 12.4)	42.1 (\pm 15.2)	<.0001
Gender: male	4687 (86.8)	201 (23.9)	<.0001
Race: White	4292 (79.5)	676 (80.3)	.591
Insurance			
VA only	3860 (71.5)	--	n/a
Medicare	--	104 (12.4)	
Marital status: Married	2318 (42.9)	--	n/a
Opioid use: Yes	2809 (52.0)	395 (46.9)	.006
Psychiatric comorbidities #			
PTSD	1525 (28.2)	<6 (<1.0)	<.0001
Other anxiety *	1465 (27.1)	131 (15.6)	<.0001
Nicotine dependence/history of smoking	2415 (44.7)	72 (8.6)	<.0001
Alcohol abuse/dependence	1917 (35.5)	36 (4.3)	<.0001
Any illicit drug abuse/dependence	1470 (27.2)	19 (2.3)	<.0001
Metabolic/Cardiovasc comorbidities #			
Diabetes Type II	1587 (29.4)	122 (14.5)	<.0001
Hypertension	3530 (65.4)	314 (37.3)	<.0001
Cardiovascular disease @	3854 (71.4)	424 (50.4)	<.0001
Cerebrovascular disease	726 (13.4)	83 (9.9)	.004
Obesity diagnosis	1882 (34.8)	164 (19.5)	<.0001
Other comorbidities #			
Low T	137 (2.5)	11 (1.3)	.029
Sleep apnea	440 (8.2)	73 (8.7)	.608
Painful conditions #			
Arthritis	3654 (67.7)	442 (52.5)	<.0001
Back pain	3049 (56.5)	419 (49.8)	<.001
Headaches	1311 (24.3)	242 (28.7)	.005
Musculoskeletal pain	2729 (50.5)	491 (58.3)	<.0001
Neuropathic pain	1323 (24.5)	138 (16.4)	<.0001
Maximum pain score, mean (sd)	8.0 (\pm 2.6)	--	n/a
Healthcare utilization: Top 25 th percentile	1813 (33.6)	239 (28.4)	.003

[^] Opioid morphine equivalent dose (MED) at end of follow-up defined by incident depression, end or incident opioid prescription or last available observation,

[#] Comorbidities occurring before incident depression

^{*} Other anxiety disorders = panic disorder, OCD, social phobia, GAD, Anxiety NOS

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

Table 2
Unweighted association of opioid use exposure (OAU) with outcome and covariates, by healthcare organization

Outcome/covariates, n(%)	VA (n=5,400)			BSWH (n=842)		
	No OAU (n=2591)	OAU (n=2809)	p-value	No OAU (n=447)	OAU (n=395)	p-value
Incident depression recurrence (yes)	1557 (60.1)	1621 (57.7)	.075	200 (44.7)	152 (38.5)	0.066
Age, mean(sd)	52.2 (±13.5)	48.7 (±11.1)	<.0001	42.0 (±16.2)	42.3 (±14.0)	0.776
Gender: male	2275 (87.8)	2412 (85.9)	.036	111 (24.8)	90 (22.8)	0.487
Race: White	2126 (82.1)	2166 (77.7)	<.0001	355 (79.4)	321 (81.3)	0.501
Insurance						
VA only	1773 (68.4)	2087 (74.3)	<.0001	--	--	--
Medicare	--	--	--	65 (14.5)	39 (9.9)	0.040
Marital status: Married	1138 (43.9)	1180 (42.0)	.156	--	--	--
Psychiatric comorbidities ^a						
PTSD	529 (20.4)	996 (35.5)	<.0001	< 5	< 5	0.670
Other anxiety ^b	599 (23.1)	866 (30.8)	<.0001	63 (14.1)	68 (17.2)	0.212
Nicotine dependence/history of smoking	967 (37.3)	1448 (51.6)	<.0001	29 (6.5)	43 (10.9)	0.023
Alcohol abuse/dependence	806 (31.1)	1111 (39.6)	<.0001	17 (3.8)	19 (4.8)	0.471
Any illicit drug abuse/dependence	568 (21.9)	902 (32.1)	<.0001	7 (1.6)	12 (3.0)	0.151
Metabolic/Cardiovasc comorbidities ^a						
Diabetes Type II	636 (24.6)	951 (33.9)	<.0001	54 (12.1)	68 (17.2)	0.035
Hypertension	1541 (59.5)	1989 (70.8)	<.0001	152 (34.0)	162 (41.0)	0.036
Cardiovascular disease ^c	1664 (64.2)	2190 (78.0)	<.0001	205 (45.9)	219 (55.4)	0.006
Cerebrovascular disease	279 (10.8)	447 (15.9)	<.0001	47 (10.5)	36 (9.1)	0.496
Obesity diagnosis	725 (28.0)	1157 (41.2)	<.0001	69 (15.4)	95 (24.1)	0.002
Other comorbidities ^a						
Low T	41 (1.6)	96 (3.4)	<.0001	< 5	< 5	0.020
Sleep apnea	111 (4.3)	329 (11.7)	<.0001	31 (6.9)	42 (10.6)	0.057
Painful conditions ^a						
Arthritis	1357 (52.4)	2297 (81.8)	<.0001	202 (45.2)	240 (60.8)	<.0001
Back pain	1024 (39.5)	2025 (72.1)	<.0001	186 (41.6)	233 (59.0)	<.0001

Outcome/covariates, n(%)	VA (n=5,400)			BSWH (n=842)		
	No OAU (n=2591)	OAU (n=2809)	p-value	No OAU (n=447)	OAU (n=395)	p-value
Headaches	407 (15.7)	904 (32.2)	<.0001	112 (25.1)	130 (32.9)	0.012
Musculoskeletal pain	833 (32.2)	1896 (67.5)	<.0001	222 (49.7)	269 (68.1)	<.0001
Neuropathic pain	396 (15.3)	927 (33.0)	<.0001	54 (12.1)	84 (21.3)	0.0003
Maximum pain score, mean (sd)	6.9 (±3.0)	9.0 (±1.5)	<.0001	--	--	--
Healthcare utilization ^d : Top 25 th percentile	528 (20.4)	1285 (45.8)	<.0001	164 (36.7)	75 (19.0)	<.0001

^d Comorbidities occurring before incident depression relapse

^b Other anxiety disorders = panic disorder, OCD, social phobia, GAD, Anxiety NOS

^c Cardiovascular disease = hyperlipidemia, ischemic heart disease, diseases of pulmonary circulation, other heart disease, hypertensive heart disease, myocardial infarction

^d top 25th percentile of the distribution of average health care encounters per month

Table 3

Weighted by inverse probability of opioid use exposure, association (%) of opioid use exposure (OAU) with covariates, by healthcare organization

Covariates, (%)	VA (n=5,400)			BSWH (n=842)		
	No OAU (n=2591)	OAU (n=2809)	p-value	No OAU (n=447)	OAU (n=395)	p-value
Age, mean(sd)	50.5(±12.4)	50.2(±12.2)	.406	42.1(±15.4)	42.0(±14.8)	0.932
Gender: male	86.5	86.5	.964	24.4	22.9	0.624
Race: White	79.3	78.6	.531	78.9	79.7	0.764
Insurance						
VA only	70.3	72.0	.179	--	--	--
Medicare	--	--	--	12.1	12.6	0.805
Marital status: Married	42.7	51.6	.429	--	--	--
Psychiatric comorbidities ^a						
PTSD	28.6	29.4	.506	< 5	< 5	0.948
Other anxiety ^b	26.7	27.5	.528	15.8	16.2	0.847
Nicotine dependence/history of smoking	44.4	45.8	.324	8.3	8.9	0.779
Alcohol abuse/dependence	35.0	35.7	.593	4.0	4.4	0.781
Any illicit drug abuse/dependence	26.7	27.2	.697	1.7	2.1	0.669
Metabolic/Cardiovasc comorbidities ^a						
Diabetes Type II	28.4	29.7	.283	15.7	14.6	0.661
Hypertension	64.7	66.0	.307	37.7	36.3	0.672
Cardiovascular disease ^c	72.1	73.7	.199	51.2	50.3	0.800
Cerebrovascular disease	14.1	14.6	.618	9.8	8.9	0.688
Obesity diagnosis	35.6	35.9	.814	19.0	19.5	0.866
Other comorbidities ^a						
Low T	2.7	2.6	.760	< 5	< 5	0.110
Sleep apnea	7.8	8.3	.508	7.2	7.9	0.724
Painful conditions ^a						
Arthritis	67.6	69.8	.089	53.7	53.7	0.995
Back pain	56.4	58.3	.170	51.4	51.0	0.912
Headaches	24.4	25.8	.274	29.0	28.8	0.931

Covariates, (%)	VA (n=5,400)			BSWH (n=842)		
	No OAU (n=2591)	OAU (n=2809)	p-value	No OAU (n=447)	OAU (n=395)	p-value
Musculoskeletal pain	50.0	52.2	.109	59.6	58.9	0.840
Neuropathic pain	23.8	24.9	.347	17.2	16.2	0.709
Maximum pain score, mean (sd)	8.0 (2.6)	8.2 (2.2)	.0003	--	--	--
Healthcare utilization ^d : Top 25 th percentile	32.8	34.8	.109	27.6	28.0	0.900

^a Comorbidities occurring before incident depression relapse

^b Other anxiety disorders = panic disorder, OCD, social phobia, GAD, Anxiety NOS

^c Cardiovascular disease = hyperlipidemia, ischemic heart disease, diseases of pulmonary circulation, other heart disease, hypertensive heart disease, myocardial infarction

^d top 25th percentile of the distribution of average health care encounters per month

Table 4

Association (HR (95% CI))[†] between opioid use and incident depression relapse, unweighted and weighted by inverse probability of opioid use exposure

	VA patients (n=5,400)			BSWH patients (n=842)		
	Model 1 Unweighted data	Model 2 Weighted data	Model 3 Weighted data + pain	Model 1 Unweighted data	Model 2 Weighted data	Model 3 Weighted data + pain
Opioid use: yes	1.87 (1.74–2.02)	2.20 (2.04–2.37)	2.17 (2.01–2.34)	1.50 (1.19–1.88)	1.81 (1.46–2.26)	1.77 (1.42–2.21)
Arthritis	--	--	0.95 (0.88–1.04)	--	--	1.01 (0.80–1.29)
Back pain	--	--	1.30 (1.20–1.41)	--	--	1.09 (0.87–1.36)
Headache	--	--	1.09 (1.00–1.18)	--	--	1.44 (1.14–1.80)
Musculoskeletal pain	--	--	1.12 (0.92–1.11)	--	--	1.16 (0.92–1.48)
Neuropathy	--	--	1.01 (0.92–1.11)	--	--	1.04 (0.75–1.44)
Pain Score	--	--	0.98 (0.97–1.00)	--	--	--

[†]HR=hazard ratio; CI=confidence interval