Prescription Opioid Analgesics Increase the Risk of Depression

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BACKGROUND: Prescription opioid analgesic use has quintupled recently. Evidence linking opioid use with depression emanates from animal models and studies of persons with co-occurring substance use and major depression. Little is known about depressogenic effects of opioid use in other populations.

OBJECTIVE: The purpose of this study was to determine whether prescription opioids are associated with increased risk of diagnosed depression.

DESIGN: Retrospective cohort study, new user design.

PATIENTS: Medical record data from 49,770 US Department of Veterans Affairs (VA) health care system patients with no recent (24-month) history of opioid use or a diagnosis of depression in 1999 and 2000.

MAIN MEASURES: Propensity scores were used to control for bias by indication, and the data were weighted to balance the distribution of covariates by duration of incident opioid exposure. Cox proportional hazard models with adjustment for painful conditions were used to estimate the association between duration of prescription opioid use and the subsequent risk of development of depression between 2001 and 2007.

KEY RESULTS: Of 49,770 patients who were prescribed an opioid analgesic, 91 % had a prescription for < 90 days, 4 % for 90–180 days, and 5 % for > 180 days. Compared to patients whose prescription was for < 90 days, the risk of depression increased significantly as the duration of opioid prescription increased (HR=1.25; 95 % CI: 1.05–1.46 for 90–180 days, and HR=1.51; 95 % CI:1.31–1.74 for > 180 days).

CONCLUSIONS: In this sample of veterans with no recent (24-month) history of depression or opioid analgesic use, the risk of development of depression increased as the duration of opioid analgesic exposure increased. The potential for depressogenic effect should be considered in risk-benefit discussions, and patients initiating opioid treatment should be monitored for development of depression.

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INTRODUCTION

The use of prescription opioid analgesics has quintupled over the past two decades,[1] while the number of outpatient visits for conditions associated with chronic pain has remained relatively stable[2] and evidence that opioids are efficacious for chronic pain has remained equivocal.[3] With use projected to double again in the next 4 years,[4,5] debate over the risks and benefits of prescription opioids has intensified. Some authorities argue that fears of addiction are inflated and have contributed to underutilization of opioids and unnecessary suffering of many chronic pain patients.[6,7] Others are alarmed by estimates that there are nearly 9,000 new cases of opioid abuse per day, and by reports that poisoning (90 % of which is drug-related) has become the leading cause of accidental death in the United States.[7–10]

Enlightened opioid prescribing practices depend upon full understanding of the risks and benefits of treatment. Opioids have long been known to allay pain and suffering, but reports of adverse effects are abundant and continue to emerge.[3,8,11] Chronic use has been linked with functional and neurohormonal deficits, immunosuppression, aberrations in natural reward processes, and paradoxically, with hyperalgesia.[3,12]

Opioid analgesic use also has been associated with symptoms of depression in numerous cross-sectional studies of noncancer pain patients.[13–15] Whether depression is a cause or a consequence of opioid use is less clear. Some data support the former hypothesis. In a 9-year retrospective cohort study, patients with depression were more often prescribed opioids and more likely to be chronic opioid users.[16] In an analysis of longitudinal data from telephone surveys of the general population, Sullivan et al.[15] found

that persons with depression at index (i.e., the baseline evaluation) were more than three times as likely as nondepressed persons to initiate and continue opioid use over the subsequent 3 years of observation.

The hypothesis that depression develops as a consequence of routine opioid analgesic exposure has not been systematically studied in human subjects. Findings from research on animal models of addiction prompted Volkow to suggest that in persons with opioid dependence disorder, depression may develop as an epigenetic or neurobiological consequence of chronic opioid exposure.[17–19]

From 1 to 5 % of patients who initiate opioid analgesics report dysphoria as an acute side effect of treatment,[20] suggesting adverse effects on mood could contribute to depression. In the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV-TR*),[21] depression that occurs as a result of opioid intoxication or withdrawal is denoted as an opioid-induced mood disorder. Whether routine medical use of opioid analgesics is associated with incident depression has not been studied. In the present study, we used national US Department of Veterans Affairs (VA) medical record data to determine whether the duration of incident prescription opioid analgesic use for non-cancer, non-HIV pain was associated with an increased risk of developing depression within 7 years after baseline in a new user design that corrected for bias by indication. Opioid analgesics are prescribed for acute and chronic pain; chronic pain increases the risk of development of depression, and depression is thought to increase sensitivity to painful stimuli.[22] Consequently, propensity score analyses were used that controlled for potential confounding effects of pain and other factors that affect exposure to opioid analgesics and the occurrence of depression.[23]

METHODS

Data Source

Electronic medical record data are extracted to administrative databases maintained by the Veterans Health Administration Office of Information at the Austin Information Technology Center. These databases include all inpatient and outpatient ICD–9–CM diagnosis codes, prescription records, and sociodemographic information.

Cohort Eligibility

Medical record data were obtained for the period from 1999, the first year for which complete national data were available, to 2007, which was the last year of available data when the cohort was created. Data were initially obtained for analyses of the association between substance use (including opioids), depression and incident heart disease; therefore, records from the years 1999 to 2000 inclusive were used to identify all patients with ICD-9-CM codes for depression in both years and exclude patients with ICD-9-CM codes for cardiovascular disease in either year. For the present study of incident depression, we excluded all patients from the total cohort who had a diagnosis of depression or drug-induced mood disorder in 1999 or 2000. This being a new user study design, we excluded all patients who were prescribed an opioid analgesic in 1999 or 2000 (n=52,140). After applying exclusions, 175,852 patients, age 18–80, who were regular users (annual users in 1999 and 2000) of VA healthcare without a history of prescription opioid use and without a history of depression remained at baseline, 2001. Of these, 49,770 initiated an opioid prescription during follow-up. Exclusion criteria are shown in Figure 1.

Predictor Variables

Incident opioid use was defined as a prescription at any dose and duration after baseline (1/1/2001) for the following medications: codeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, oxycodone, oxymorphone and pentazocine. Prescriptions were defined by the "days supply" variable which measures the days required to exhaust the medication if taken as prescribed. The total duration of opioid use was defined as the sum of days supplied without a gap of 30 days or more. Patients were classified into three levels (1–89 days, 90–180 days and > 180 days total days continuous supply). We used the 90-day duration threshold because it indicates chronic use as employed in prior studies. Patients could only contribute to one exposure group. Duration of use was computed until the end of continuous use or until onset of depression. Use of opioids after incident depression was not considered in assigning patients to an exposure level. Thus, if a patient used opioids for 200 days and had an incident depression on day 100, they were classified in the 90–180 day exposure group. If the patient, for example, remained on opioids for 200 days without a record indicating incident depression, they were assigned to the > 180 day group.

Outcome Variable

Diagnoses were determined by ICD-9-CM codes shown in e-Table 1. Incident depression was defined by the presence of a primary diagnosis of depression in at least one inpatient stay or two outpatient visits within a 12-month period that occurred after the baseline date. In VA patients, the presence in the medical record of two or more depression diagnoses has an 88 % positive predictive value and 71 % negative predictive value compared to self-reported lifetime

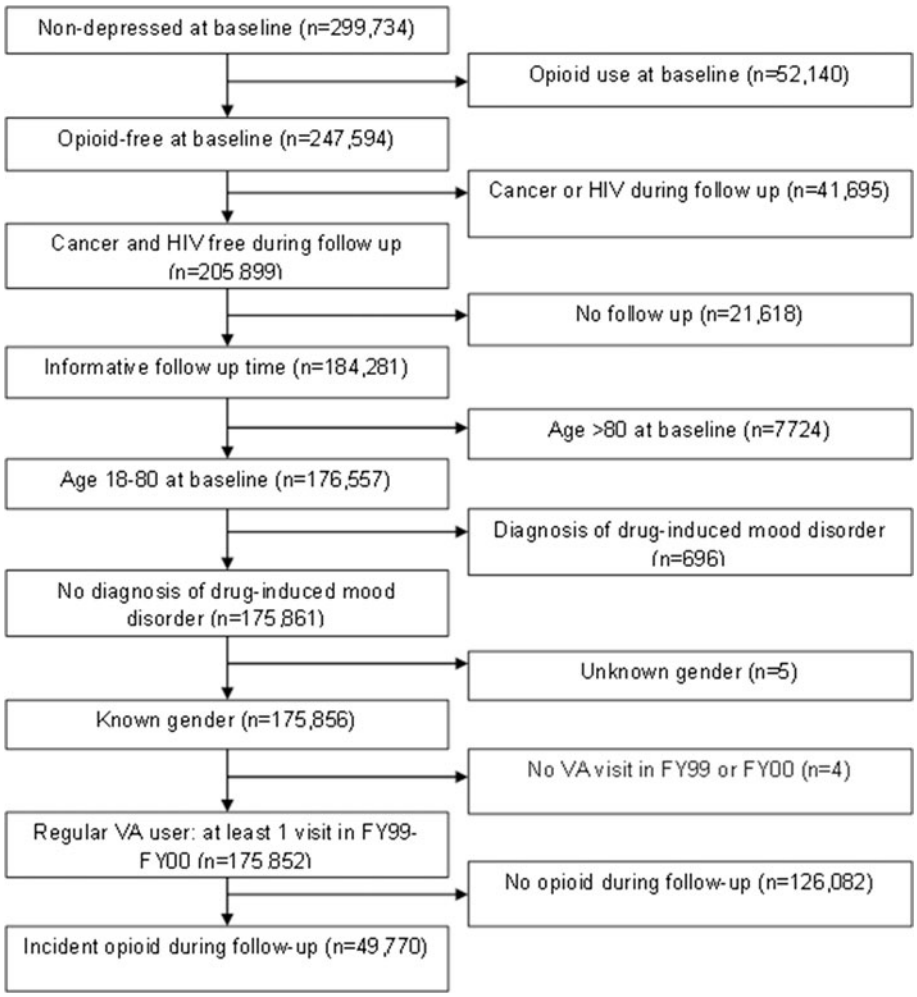

Figure 1. Selection of study participants.

history of depression.[24] This approach has a 99 % positive predictive value when compared to chart review.[25]

Propensity Score and Covariate Definitions

Because chronic pain is associated with depression, bias by indication may confound the association between opioid use and incident depression. To control for this potential bias, we computed propensity scores to estimate the probability of 1–89 days, 90–180 days and > 180 day use. Propensity scores control for imbalance in patient characteristics associated with treatment and are being increasingly applied in observational cohort studies.[26] Propensity models are particularly powerful when built from administrative medical record data because the large number of variables available allow for robust adjustment.[26,27] Following methods described by others,[28–30] we used an Inverse Probability of Treatment Weighting (IPTW) approach to correct for bias and confounding. In the present analysis, the probability of receiving an opioid is not random and a main predictor of opioid receipt, pain, is confounded with the outcome of interest, incident depression. A PS is the conditional probability (i.e. propensity) of a particular treatment (i.e. duration of opioid) given measured covariates (e.g. painful conditions). We computed the PS using a multivariable, multinomial logistic regression model to predict exposure to each opioid duration group as a function of the covariates shown in Table 1.

The covariates were then balanced across opioid exposure groups by using inverse probability weighting. The data is weighted by the inverse probability of being a 1–89 day, 90–180 day and > 180 day opioid recipient. The inverse probability of treatment weighting was computed for the probability of 90–180 day exposure and probability of > 180 day exposure relative to the probability of 1–90 day exposure. This results in a "pseudo-population" in which each patient's duration of opioid exposure is independent of the covariates that predicted exposure. Survival models using the pseudo-population are not biased

Table 1. Percentile Mean Daily Morphine Dose (mg), Overall and by Duration of Opioid Use

	Percentile								
	10th	20th	30th	40th	50th	60th	70th	80th	90th
Total (n=49770)	7.5	12.9	15	20	22.5	30	32.1	42.9	60
1–89 days (n=45,478)	7.5	12.5	15	20	22.5	30	30	40	60
90–180 days (n=2,053)	9.0	13.5	15	20	27.0	30	40	56.3	75
> 180 days (n=2,239)	13.5	18.0	21.4	40	36	40	60	75	110

by indication (painful conditions), nor by confound due to factors correlated with opioids and depression (substance abuse). We chose this approach over matching because the latter results in excluding large portions of the cohort.

Variables were included in the regression model because they predict receipt of opioids and are potential confounders between opioid exposure and depression. The predictors of duration of opioid use included in the propensity score incorporated the domains of sociodemographics, health care use, health behaviors, anxiety and substance use disorders, and painful conditions. These factors antedated the occurrence of incident depression. Sociodemographics included age, gender, race and marital status. Health care use was defined as number of clinic visits per month. Health behaviors were obesity, defined as body mass index ≥ 30, and personal history of smoking and or nicotine dependence. Psychiatric disorders included alcohol and/or drug abuse/dependence, posttraumatic stress disorder (PTSD), generalized anxiety disorder, panic disorder, social phobia, obsessive compulsive disorder and anxiety not otherwise specified (NOS). Painful conditions included neuropathies, headaches, musculoskeletal conditions, back pain and arthritis; their presence was based on the ICD-9-CM codes previously reported as indications for opioid analgesics in VA patients.[31] Smoking and or nicotine dependence, substance use disorders, psychiatric disorders and painful conditions were considered present if a patient had at least one ICD-9-CM code for a primary or for up to ten secondary diagnoses. ICD-9-CM codes used to define lifetime diagnoses are available on-line.

Analytic Design

The retrospective cohort design employed is shown in Figure 2. Opioid exposure was treated as a time dependent covariate and variables used in the propensity score could occur anytime before depression. As shown, covariates used in the propensity score could occur anytime before incident depression, including during the period of opioid use.

Bivariate analyses included t tests for continuous variables and chi–square tests for categorical variables. Hazard ratios for incident depression were estimated using Cox proportional hazards models in which opioid use was a time dependent variable with month as the unit of time and follow-up beginning in 2001. Data weighting balances pain diagnoses across opioid exposure groups, but continued treatment seeking for chronic pain may be an indicator of persistent pain. Thus, Cox models were computed using weighted data and separate models were estimated before and after adjusting for pain diagnoses that were modeled as time-dependent covariates. Follow-up continued until onset of depression, last date of available data, death, or the last documented use of the VA healthcare system. The Proc PHREG procedure in SAS version 9.1.3 (SAS Institute, Cary, NC) with α set at 0.05 was used for the Cox regression models. Two-tailed tests were conducted to allow for both risk factors and protective effects. This project was approved by the Institutional Review Boards of the St. Louis VAMC and Washington University.

RESULTS

At baseline, the mean age of patients was 54.6 years (SD, 12.9); 92.6 % were male, 69.5 % were white, 24.7 % African-American, and 51.4 % were married. Among the 49,770 prescribed an opioid, 91.4 % (n=45,478) had 1–89 days of continuous use, 4.1 % (n=2,053) had 90–180 days and 4.5 % (n=2,239) had 180 days or more. Hydrocodone accounted for 41.2 % of incident prescriptions followed by codeine (33 %), oxycodone (23.6 %), morphine (0.9 %), fentanyl (0.6 %), meperidine (0.4 %), hydromorphone (0.2 %) and pentazocine (0.04 %). The distribution of mean daily morphine equivalent dose (milligrams) is shown in Table 1. The greatest difference in daily morphine exposure by duration of use begins at the 60–70th percentile. Within each percentile of daily morphine, longer use is associated with a higher daily morphine dose.

In the entire cohort, 46.8 % were in the top 75th percentile of health care visits, 31.9 % were obese, 37.8 % had a diagnosis of nicotine dependence and/or personal history of smoking; 20.1 % had a diagnosis of alcohol and or drug abuse/dependence, 10.3 % had PTSD and 7.7 % had a non-PTSD anxiety disorder. The most common painful condition was arthritis (77.5 %) followed by back pain (60.2 %), musculoskeletal pain (59.3 %), neuropathy (26.0 %) and headache (17.3 %).

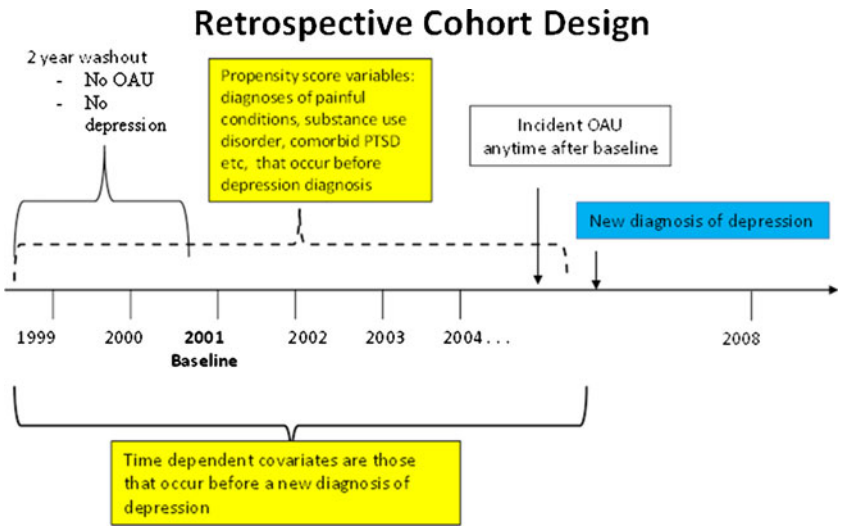

Figure 2. Study design. OAU=Opioid Analgesic Use.

In unweighted data, all sociodemographic variables were significantly associated with duration of opioid use. Male, white and married patients were disproportionately longer-term opioid users (Table 2). Greater health services utilization, obesity and history of smoking and or nicotine dependence, alcohol and or drug abuse/dependence, PTSD and other anxiety disorders were positively associated with longer duration of opioid use. With the exception of headache, chronic pain diagnoses were more prevalent among patients with 90–180 day and > 180 days use. After weighting the data by the inverse probability of treatment duration, the distributions of covariates were balanced. With the exception of mean age, there were no significant differences in the prevalence of covariates between patients with 1–89 days, 90–180 days and > 180 days opioid use.

In weighted data, the incidence of depression increased with duration of opioid use. During the follow-up interval, the cumulative incidence of depression for the entire cohort was 6.4 %. As shown in Figure 2, patients exposed to > 180 days of opioids has a shorter time to depression diagnosis as compared to patients with 90–180 days and 1–89 days exposure. In patients with 1–89 days of opioid use, the incidence of depression was 17.7/1000 PY; among patients with 90–180 days, the incidence of depression was 23.8/1000 PY; and in patients with > 180 days of opioid use, the incidence was 27.8/1000 PY. The results of Cox-proportional hazard models using weighted data indicated that longer opioid use was associated with increasing risk of depression (Table 3 and Figure 3). Compared to patients using opioids for 1–89 days, the risk of diagnosed depression was significantly greater in patients who used for 90–180 days (HR= 1.25; 95 % CI:1.06–1.47) and in patients who used > 180 days (HR=1.53; 95 %CI:1.33–1.76). The association between duration of opioid use and incident of depression remained unchanged after adjusting for painful conditions. In adjusted analysis, the risk of depression was 1.24 (95 % CI: 1.05–1.46) and 1.51 (95 % CI: 1.31–1.74) in 90–180 day users and > 180 days users, respectively. Sensitivity analysis, treating covariates as non-time dependent, produced nearly identical results for the association between 90 and 180 day users and risk of depression (HR=1.24; 95 % CI:1.04–1.47) and between > 180 day users and risk of depression (HR=1.56; 95 % CI:1.34–1.80).

DISCUSSION

We examined the impact of the duration of new opioid prescriptions on risk of depression in a large sample of veterans (*N*=49,770) with no recent (24-month) history of opioid use or depression. After balancing the distribution of covariates in patients prescribed opioid analgesics for 1–89, 90–180, and > 180 days, respectively, we observed that longer duration of opioid prescription was associated with increased risk of development of depression. Patients using for 90–180 days had a 25 % increased risk of depression, and those using for more than 180 days had a more than a 50 % increased risk. The effects remained significant after additional adjustment for chronic pain due to neuropathies, headaches, musculoskeletal diseases, back pain, and arthritis.

Dramatic increases in opioid prescription use have occurred in tandem with drug overdose becoming a leading cause of accidental death in the US. The term “Pharmageddon” was coined to capture the epidemic nature and adverse public health consequences of opioid analgesics.[5,32] Our findings add to such concerns by showing that opioid use for more than 90 days significantly increases the risk of developing

Table 2. Baseline Characteristics of Subjects Before and After Propensity Score Weighting by Opioid Analgesic Use (OAU) Duration

	Unweighted data				Weighted by inverse probability of treatment			
	Duration of OAU				Duration of OAU			
	1–89 days (n=45,478)	90–180 days (n=2,053)	> 180 days (n=2,239)	Chi-sq p value	1–89 days	90–180 days	> 180 days	Chi-sq p value
Sociodemographics								
Age group:								
18–50 years of age	38.0	34.8	37.6		37.8	37.3	36.2	
51–62 years of age	32.6	33.8	36.2	< 0.0001	32.8	33.0	32.5	0.35
63–80 years of age	29.4	31.4	26.2		29.3	29.7	31.3	
Gender:								
Male	92.3	94.5	96.0	< 0.0001	92.6	92.8	92.6	0.92
Race:								
White	68.6	76.6	80.4		69.5	69.8	69.9	
Non-White	25.3	19.8	15.9	< 0.0001	24.7	24.7	24.7	0.90
Unknown	6.1	3.6	3.7		5.9	5.5	5.4	
Marital status:								
Married	51.1	55.2	54.5		51.3	53.1	52.2	
Not Married*	45.8	42.5	43.6	< 0.0001	45.6	43.9	45.2	0.34
Unknown	3.2	2.3	1.9		3.0	3.0	2.6	
Health behaviors								
Health care utilization:†								
< 25th percentile	6.5	5.5	5.7		6.4	5.9	5.3	
25th–50th percentile	16.3	14.7	15.5	< 0.0001	16.2	15.1	16.3	0.28
50th–75th percentile	30.9	27.5	30.0		30.7	31.2	30.6	
> 75th percentile	46.4	52.3	48.8		46.8	47.9	47.8	
Obesity (BMI≥30)	31.8	33.4	32.0	0.32	31.9	32.3	33.9	0.13
History of smoking and or nicotine dependence	37.2	41.8	45.9	< 0.0001	37.8	37.6	37.1	0.76
Psychiatric comorbidity								
Alcohol and or drug abuse/dependence	19.8	22.2	25.2	< 0.0001	20.1	20.4	19.4	0.86
PTSD	10.0	12.8	14.7	< 0.0001	10.3	10.6	10.0	0.80
Other anxiety disorders‡	7.4	9.5	12.3	< 0.0001	7.7	7.8	7.7	0.99
Painful conditions								
Neuropathy§	25.5	32.3	30.6	< 0.0001	26.1	26.3	27.5	0.31
Headaches§	17.3	17.2	17.7	0.87	17.3	17.7	17.7	0.80
Musculoskeletal§	59.1	63.0	59.6	< 0.01	59.3	59.6	60.7	0.38
Back pain§	59.0	70.2	74.2	< 0.0001	60.2	60.9	60.3	0.82
Arthritis§	76.8	83.8	85.5	< 0.0001	77.5	78.2	79.0	0.17

Divorced/widowed/separated/single/never married
† *mean health care encounters per month*
‡ *generalized anxiety disorder, panic disorder, obsessive compulsive disorder, social phobia, anxiety disorder unspecified*
§ *chronic painful diagnoses for which opioids may be prescribed in VA patients, according to Seal et al.*[31]

depression. The mechanisms by which opioids may contribute to the development of depression are unclear but likely multifactorial. The possibilities include opioid-induced resetting of the brain "reward pathway" to a higher threshold, resulting in the inability of natural rewards to generate pleasure and/or relief;[33–35] kappa receptor overactivity associated with opiate discontinuation, with dysphoria and body aches occurring months and years after opioids are stopped;[35] and via medical abnormalities associated with opiate use (e.g., adrenal, testosterone, and vitamin D deficiencies, glucose dysregulation)[35,36] that may present as physical correlates of major depression. Whether collateral treatments can help to prevent or delay opioid-associated depression is a subject that merits further study.

Table 3. Association Between Duration (days) of Incident Opioid Analgesic Use (OAU) and Incident Depression in Data Weighted by the Inverse Probability of Opioid Exposure Duration

	Model 1	Model 2
OAU 1–89 days	1.0	1.0
OAU 90–180 days	1.25 (1.06–1.47)	1.24 (1.05–1.46)
OAU>180 days	1.53 (1.33–1.76)	1.51 (1.31–1.74)
Neuropathy*		1.23 (1.13–1.33)
Headaches*		1.69 (1.56–1.84)
Musculoskeletal*		1.40 (1.30–1.52)
Back pain*		1.69 (1.56–1.82)
Arthritis*		1.24 (1.13–1.35)

* *Chronic painful diagnoses for which opioids may be prescribed in VA patients, according to Seal et al.* [31]

There are case reports that support opioid treatment of refractory depression.[37] Euphoria is a reliable but typically transient effect of opioids that may occur even in the face of ongoing depression. Our data indicate that medical use of opioids for > 90 days is more likely to promote than to relieve depression. That an opioid-associated risk of depression could be demonstrated in a sample at low risk of depression (given their advanced age and having no

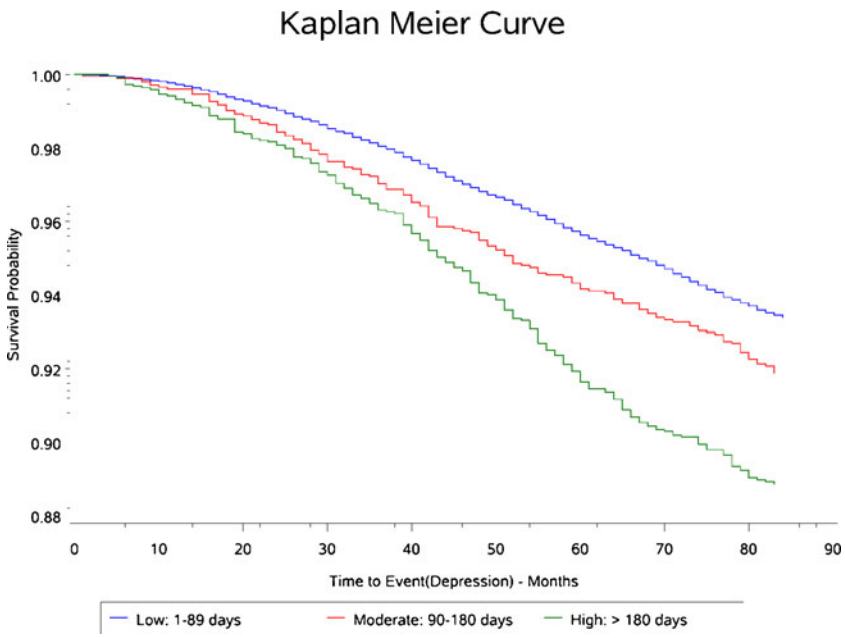

Figure 3. Survival curve showing time to incident depression by duration of incident opioid use: 1–89 days, 90–180 days and > 180 days.

recent (24-month) history of depression) is noteworthy, and raises the possibility that some depression episodes may have been avoided had opioid therapy not been initiated or limited to less than 90 days.

The impact of morphine equivalent dose was considered in post-hoc analysis. Using standard morphine equivalent dosing guidelines,[18] we computed the distribution of mean, maximum daily morphine exposure overall and within each opioid duration group (1–89 days, 90–180 days and > 180 days). We computed the distribution of incident depression cases along the continuum of daily morphine and observed an increase in depression cases at 38 mg, which was also approximately the 70th percentile of morphine daily dose (See Table 1). We created a binary variable to indicate high (≥ 39 mg) vs. low (< 39 mg) daily dose. We then computed the proportion of incident depression cases by high vs. low dose stratified on duration of use. As shown in Figure 4, within each duration of use, patients receiving a high daily dose are at significantly increased risk of depression. However, the proportion of subjects with depression remains similar among low dose patients across duration of use. In contrast, in patients receiving a high dose, the proportion of depressed patients increases across duration of use from 9.3 % in 1–89 day users, to 13.1 % in 90–180 day users to 15.0 % in > 180 day users. These post-hoc analyses should be interpreted cautiously,

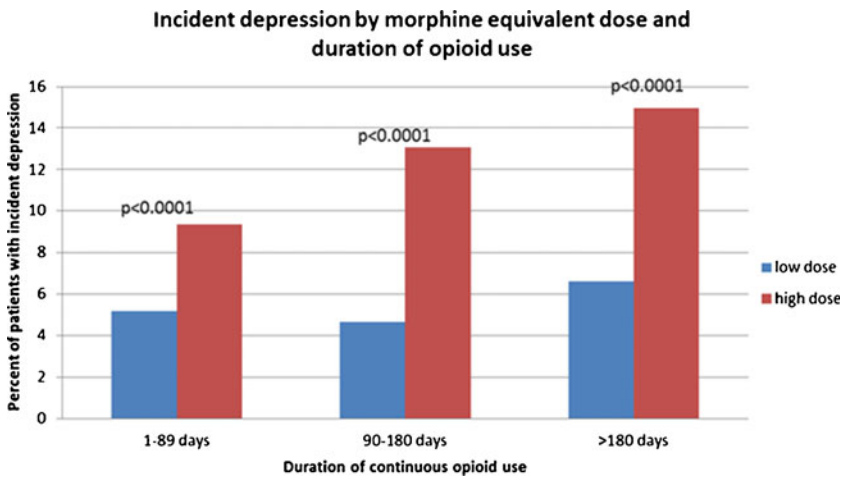

Figure 4. Association of daily morphine equivalent dose, duration and depression.

because propensity scores were utilized to correct for duration of opioid exposure, but not for morphine equivalent dose.

Limitations. We were not able to determine whether the opioids were taken as prescribed, supplemented with illicit opioids, or taken with additional prescriptions obtained outside the VA. However, misclassification is unlikely to explain our findings, because long-term users are also more likely to be obtaining opioids from undocumented sources. If we underestimated the number of long-term users, then the estimate of risk in the present study is conservative. Patients may have subclinical depression that contributed to a longer duration of opioid use and vulnerability to diagnosable depression. Future research is warranted that uses structured diagnostic interviews (e.g., the Diagnostic Interview Schedule) that determine lifetime diagnoses of depression and dates of onset and recovery, to determine if the patients who developed depression had a prior depression diagnosis or prior significant elevations in depressive symptoms. Retrospective cohort study designs have been criticized as being vulnerable to residual confounding. Schneeweiss[38] and Psaty et al.[39] have demonstrated that an unmeasured confounder must be independent of measured confounders and strongly associated with the exposure and outcome in order for residual confounding to explain the observed associations. In the present case, to reduce the observed estimate of risk between opioid use and incident depression (HR =1.50) to the null, an unmeasured confounder would have to be common (20 % prevalence) and would have to increase the risk of depression by five times and opioid analgesic use by over three-fold. Even the largest unmeasured contributor to depression, family history, could not explain our findings because it only confers a three-fold risk, and therefore does not rise to the five-fold magnitude that would be required to explain our findings.[38] Other unmeasured risk factors, such as childhood trauma or past history of depression symptoms, are highly correlated with measured confounders (e.g. nicotine dependence, substance use disorder, anxiety disorders).

Conclusions. The longer one is exposed to opioid analgesics, the greater is their risk of developing depression. Practical strategies must be developed to prevent, detect, and treat iatrogenic depression due to prescription opioid analgesics. The development of safe and effective alternatives to opioids for chronic pain management remains a public health priority.

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