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Long-term prescription opioid users' risk for new-onset depression increases with frequency of use

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Research Paper

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Long-term prescription opioid users' risk for new-onset depression increases with frequency of use

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Abstract

Long-term opioid therapy (LTOT) is associated with increased risk for depression. It is not known if the frequency of opioid use during LTOT is associated with new-onset depression. We used Optum's de-identified Integrated Claims-Clinical dataset (2010-2018) to create a cohort of 5146 patients, 18 to 80 years of age, with an encounter or claims in the year before new LTOT. New LTOT was defined by >90-day opioid use after remaining opioid free for 6 months. Opioid use frequency during the first 90 days of LTOT was categorized into occasional use (<50% days covered), intermittent use (50% to <80% days covered), frequent use (80% to <90% days covered), and daily use (≥90% days covered). Propensity scores and inverse probability of exposure weighting controlled for confounding in models estimating risk for new-onset depression. Patients were on average 54.5 (SD ± 13.6) years of age, 55.7% were female, 72.5% were White, and 9.5% were African American. After controlling for confounding, daily users (hazard ratio = 1.40; 95% confidence interval: 1.14-1.73) and frequent users (hazard ratio = 1.34; 95% confidence interval: 1.05-1.71) were significantly more likely to develop new-onset depression compared with occasional users. This association remained after accounting for the contribution of post-index pain diagnoses and opioid use disorder. In LTOT, risk for new depression episodes is up to 40% greater in near-daily users compared with occasional users. Patients could reduce depression risk by avoiding opioid use on as many low pain days as possible. Repeated screening for depression during LTOT is warranted.

Keywords: Cohort, Epidemiology, Pain, Opioid, Depression

1. Introduction

Since 2012, the number of new opioid prescriptions in the United States has steadily declined.[4,11] However, between 2006 and 2017, the proportion of 30-day opioid prescriptions and the average duration of prescriptions increased.[26] This is a concern because long-term opioid therapy (LTOT) is associated with numerous adverse outcomes, including increased risk for depression.[9,22,25,34] Among patients with noncancer pain, and in multiple patient cohorts, LTOT (>90 days) compared with short-term use (<30 days) is associated with an increased risk for new-onset depression[22,25] and development of treatment-resistant depression.[24] These associations were independent of pain and comorbid psychiatric disorders. Recently, Rosoff et al. used a Mendelian randomization approach (in which genetic predisposition to opioid use is used as an instrumental variable) to demonstrate a possible causal link between opioid use and risk for depression.[18] However, not all patients receiving LTOT develop depression, and further work is needed to determine the characteristics of LTOT that are associated with risk for new-onset depression.

Most existing literature in this field is based on retrospective cohort designs, and 2 prospective cohort studies have failed to identify a significant association between LTOT and new-onset depression or worsening depression after controlling for confounding factors. In the Pain and Opioids IN Treatment study,[6] longer duration of opioid use was not significantly associated with developing depression after adjusting for duration of pain and comorbid psychiatric disorders.[28] In a prospective cohort of patients starting LTOT for noncancer pain, Von Korff et al.[33] observed no difference in depression symptoms between patients with regular, high-dose use compared with intermittent, low-dose use.[33] However, the authors suggest that the low dose (<50 morphine milligram equivalent [MME]) among regular and intermittent users diminished the chance of detecting a difference in depression between regular and intermittent users. We have observed that higher MME doses, specifically 51 to 100 MME and >100 MME vs 1 to 50 MME, were not associated with risk for depression when controlling for duration of opioid use.[22] This finding in the context of Von Korff et al.[33] results leaves the

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potential that intermittent use vs more frequent use is a key reason long-term opioid use is associated with depression. However, there are no studies that have evaluated the association between frequency of use in LTOT and risk for new-onset depression.

It is possible that using opioids a few days a week, as compared with daily, avoids opioid tolerance and dependence, allowing opioid receptors to recover and perform their role in generating hedonic capacity. Another possibility is that continuous LTOT leads to opioid dependence that is equivalent to the withdrawal and negative affect stage of addiction. This stage is preceded by a period in which euphoric, positive reward drives use.[3] Intermittent opioid users may experience less or no psychological reward from opioids, whereas euphoria is likely more common among frequent users. With more frequent use, risk of physiological dependence increases, and patients will experience negative affect that could worsen to clinically meaningful depression.

If daily or near-daily opioid use impairs the ability to experience pleasure and/or generates repeated short-term withdrawal/negative affect, then daily compared with intermittent opioid use in patients receiving LTOT should be associated with greater risk for new-onset depression. This study compared patients with a new period of >90-day prescription opioid use who used opioids occasionally, intermittently, frequently, and daily. We hypothesized that increasing opioid use frequency would be associated with escalating probability of new-onset depression. We then determined if this association remained after adjusting for pain diagnoses made after the start of opioid use. We also assessed whether opioid use disorder diagnoses after opioid initiation could be a possible mechanism through which frequency of opioid use could affect the risk of new-onset depression.

2. Methods

Saint Louis University provided funding to the author (J.F.S.) to lease an Optum analytics database that contained de-identified electronic health records (EHRs) from a random sample of 5 million adult (≥18 years of age) patients. These patients had medical encounters in health systems across the United States between 2010 and 2018, and about 39% were from the Midwest, 14% from the Northeast, 27% from the South, and 11% from the West. Of the 5 million patients, approximately 18% were part of Optum's de-identified Integrated Claims-Clinical dataset (n = 897,513), which included data from EHR and medical claims. All study variables were created from data elements in the integrated EHR-claim files. The EHR and claims data includes outpatient and inpatient encounters from academic and nonacademic healthcare systems between 2010 and 2018. The data include patients with private, government, or no health insurance. International Classification of Diseases, Ninth Revision (ICD-9) Clinical Modification and International Classification of Diseases, Tenth Revision (ICD-10) Clinical Modification codes, pharmacy claims, prescriptions, vital signs, laboratory results, demographics, and geographic region were used to create study variables.

We created a retrospective cohort of patients starting a new period of opioid therapy by first requiring patients to have one or more prescription opioid fills in 2011 to 2016. This allowed for a 1-year look-back period and a minimum of 2-year follow-up for onset of depression. The maximum possible follow-up was 7.75 years. Patients could enter the cohort at anytime during this observation period once they met eligibility criteria. Patients entered the cohort at the start of a new opioid use period meeting eligibility and only the first eligible LTOT period was included in the analysis (ie, patients only counted once in the analysis). The index date (start of follow-up) was day 91 after the first 90 days of a new opioid use period. This allowed for sampling patients with LTOT (>90 days use). In the 1 year before the start of a new opioid use period, we required a claim or encounter to identify current health care users. Patients with cancer or HIV in the 1 year before start of opioid use or in the first 90 days of LTOT were excluded. To identify new prescription opioid use, we excluded patients with any opioid prescription in the EHR or opioid fill in claims data in the 6 months before the start of new opioid use. The new period of opioid use was limited to those starting a new period of >90 days of continuous opioid use (ie, LTOT). Continuous opioid use was measured using days supply, accounting for overlapping fills, and allowing for no gap between fills >30 days. Once a gap of >30 days occurred, the new period of opioid use ended. Using the first and last opioid fills in the new opioid use period, duration was calculated as the difference in days between the last fill date and the start date of the first fill. Opioid use frequency was calculated within the first 90 days of the new LTOT period. Patients were required to be free of depression diagnoses for 1 year before the start of the new opioid use period and throughout the new 90-day opioid use period. The index date was day 91 of the new LTOT. This eligibility criteria led to excluding patients without health insurance. All patients must have had one or more encounters or claims after index date and had to be between 18 and 80 years of age at start of the new period of opioid use. Patients with missing demographic data were excluded (n = 4 missing gender), leaving 5146 patients in the analytic sample. The sample selection process is illustrated in **Figure 1** and the retrospective cohort design is visualized in e-Figure 1 (supplemental digital content, http://links.lww.com/PAIN/B546).

2.1. Outcome variable

Detailed definitions for all variables are listed in e-table 1 (supplemental digital content, http://links.lww.com/PAIN/B546). New-onset depression was defined by the presence of ICD-9 codes 296.2x, 296.3x, and 311 and ICD-10 codes F32.0-F32.5, F32.9, F33.0-F33.3, F33.4x, and F33.9. A new case of depression was defined by ICD-9 and ICD-10 codes for depression on 1 inpatient visit or 2 outpatient visits within the same 12 months of follow-up. This diagnostic algorithm has excellent agreement with chart abstraction and patient report.[10,31]

3. Exposure

The following prescription opioids, in both immediate- and extended-release formulations, were used to measure opioid use: codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, oxycodone, oxymorphone, pentazocine, tapentadol, and tramadol. Due to a lack of precision in linking buprenorphine to a pain condition, we did not include it as an opioid exposure. Buprenorphine is predominately prescribed for opioid use disorder, and patients with problem opioid use are sometimes switched from another opioid to buprenorphine. Following the concept of Smolina et al.,[29,30] we used the proportion of days that an opioid supply was available in the first 90 days of use to create categories for frequency of opioid use. We computed the distribution of days covered in the first 90 days[29,30] (e-table 2, supplemental digital content, http://links.lww.com/PAIN/B546) and the distribution of hazard ratios (HRs) for the risk of depression for every 10% (9 day) increase in frequency of use (e-table 3, supplemental digital content, http://links.lww.com/PAIN/B546). Balancing confounding factors across 10

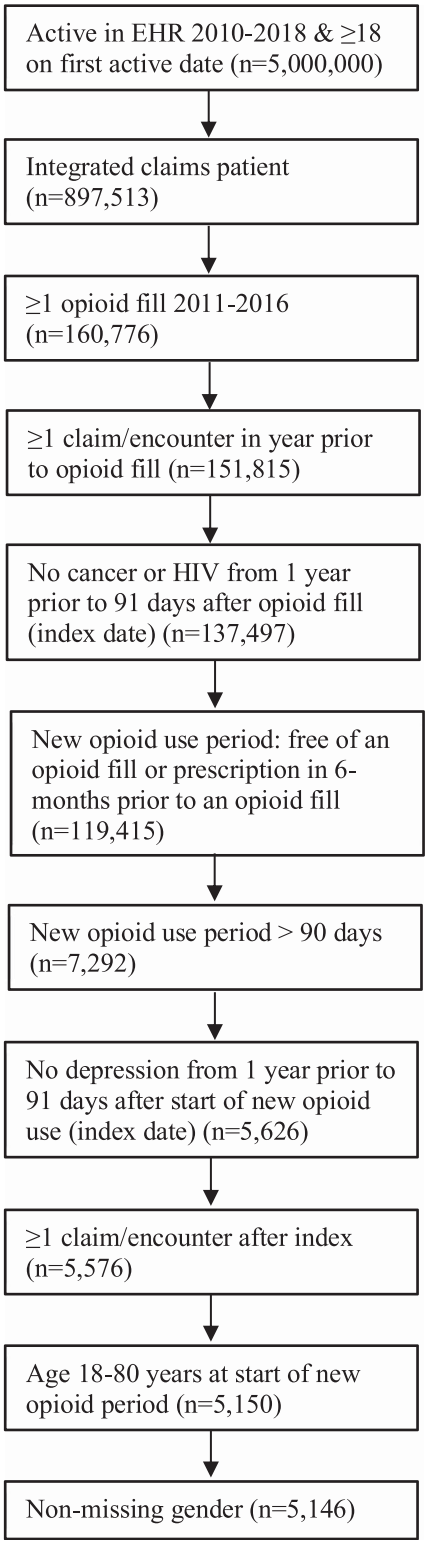

Figure 1. Sampling approach. EHR, electronic health record.

categories was not feasible; therefore, we used the distribution of HRs to create 4 categories that permitted control for confounding. Compared with <50% of days covered (<45 days), risk for new-onset depression did not increase until 80% (72 days) of days covered, with another increase at 90% (81 days). Thus, occasional use was defined by <50% days covered, which equates to <45 days of opioid use during the first 90-day use period. Intermittent use was defined by 50% to <80% days covered, which equates to 45 to 71 days of opioid use. Frequent use was defined as 80% to <90% days covered, which equates to 72 to 80 days of opioid use. Daily use was defined as ≥90% days covered, which equates to ≥81 days of opioid use during the first 90-day use period.

3.1. Follow-up time

Follow-up time was defined as months from index date to new-onset depression or censoring. Among patients not developing new-onset depression in follow-up, censoring was defined as the last available claim or encounter. Follow-up time for these patients was the difference in months from index to censor date. So, for example, if index date was January 1, 2012 and a patient was censored at April 20, 2012, follow-up time was 4 months. For someone developing depression, follow-up time was calculated similarly as the difference in months from index to new-onset depression date.

3.2. Potential confounders

We selected potential confounding factors that theoretically could be associated with opioid prescribing or with risk for depression and based on our previous studies of prescription opioid use and new-onset depression.[22] Covariates included demographics, geographic region, health care use, maximum MME dose, and comorbid physical and psychiatric conditions. See e-table 1 for detailed variable definitions (supplemental digital content, http://links.lww.com/PAIN/B546).

Demographic variables included age, gender, and race. Census-based geographic regions were defined as Midwest, Northeast, South, West, and Other/unknown. To control for detection bias, we computed the distribution of the mean number of clinical encounters per month. The top 25th percentile was defined as high utilization.

Maximum MME achieved during the first 90 days of opioid use was calculated using standard equianalgesic conversion tables. We assumed patients took the maximum dose prescribed per day based on days supply and quantity dispensed. MME was classified into 1 to 50, 51 to 90, 91 to 180, and >180 mg.

Following the approach used in previous studies of opioid use and depression,[19,21–24] we created separate variables for pain conditions derived from >900 conditions for which an opioid may be prescribed.[27] Pain conditions were arthritis, back pain, musculoskeletal pain, neuropathy, and headache. ICD-9 and ICD-10 codes were used to define type 2 diabetes, ischemic heart disease, stroke, low testosterone, and sleep apnea. Obesity was defined by ICD-9/10 diagnostic code or body mass index of ≥30 kg/m^2.

ICD-9 and ICD-10 codes were used to measure psychiatric covariates, including alcohol abuse/dependence, any form of drug abuse/dependence, including opioid abuse/dependence and nicotine dependence, and any anxiety disorder, and prescription data were used to measure benzodiazepine co-medication. Any anxiety disorder was a diagnosis for post-traumatic stress disorder, panic disorder, obsessive compulsive disorder, social phobia, generalized anxiety disorder, or anxiety not otherwise specified. Benzodiazepine co-medication was defined as a prescription or fill for any benzodiazepine that overlapped with the first 90 days of the new LTOT period. Pain, physical and psychiatric comorbidities were measured from January 1, 2010 to index date.

3.3. Analytic approach

All primary analyses were performed with SAS v9.4 (SAS Institute, Cary, NC) at a 2-tailed alpha = 0.05. Distributions of variables are presented as mean values (±SD) or frequency and percent.

3.3.1. Weighting

Bias by indication may confound the association between frequency of opioid use and new-onset depression. Thus, we balanced all potential confounders across categories of frequency of opioid use using propensity scores (PS) and inverse probability of exposure weighting (IPEW). Successful balancing of covariates allows for unbiased estimates of exposure effects.[7,17] Propensity scores were calculated using generalized boosted modeling.[14,15] Generalized boosted modeling often outperforms traditional regression techniques for PS analysis (eg, logistic, multinomial), especially with multiple exposure groups. Generalized boosted modeling is a nonparametric, iterative regression technique that assesses and incorporates multiple interaction and higher order terms, which reduces the risk of model misspecification, and allows for deviations in additivity and linearity. Generalized boosted modeling estimation of the PS for multiple exposure groups was conducted using the "twang" package in R v4.0.3.[5]

After obtaining PS scores, stabilized weights (observed exposure probability × 1/PS) were calculated to retain original sample size in weighted analysis and reduce bias associated with extreme weights (large variance).[35] Standardized mean difference percent, a common effect size measure (SMD% = 100 × SMD), assessed covariate balance between frequency groups, with a threshold of ≥10% defining imbalance.[2] The SMD compares differences in mean values in units of SD. Although originally created for comparing continuous variables, it has been shown that it can be used for binary/dichotomous variables.[1] Because there are 4 exposure categories, the maximum SMD% of all pairwise comparisons was reported. Also, for multicategory confounders (race, region, and maximum daily MME), a binary indicator was created for each level and SMD% for each level was calculated. Standardized mean difference % formulas are shown in e-Table 4 (supplemental digital content, http://links.lww.com/PAIN/B546).

3.3.2. Primary analysis

Bivariate comparisons between covariates and opioid use frequency group were performed using χ^2 tests for categorical variables and 1-way analysis of variance for continuous variables. Standardized mean difference % before and after weighting assessed covariate balance. Cox proportional hazard models before and after weighting were used to calculate HRs and 95% confidence intervals (CIs) for the association between frequency of opioid use and new-onset depression. Weighted models used robust, sandwich-type variance estimators for CIs and *P*-values.[2] The proportional hazard assumption was tested in unweighted and weighted models by including a time-dependent interaction term of opioid use frequency and log (follow-up time); the assumption was met for all models ($P > 0.05$).

The e-value for the HR point estimates was calculated to determine if unmeasured confounding could explain significant results.[12] The e-value is the minimum strength of association (for this analysis, the minimum HR) needed for any unmeasured confounder to have with both the exposure and the outcome to completely explain observed associations. Because there were 4 exposure groups, the minimum calculated e-value for any significant pairwise point estimate was given.

3.3.3. Secondary analyses

To determine whether pain conditions that could occur after index and before new-onset depression (or censoring) could explain the relationship between frequency of opioid use and new-onset depression, we extended the weighted Cox model by adding time-dependent pain covariates in follow-up. More frequent opioid use may increase risk for opioid use disorder that may subsequently lead to depression. Thus, a separate extended weighted model was calculated that included a time-dependent indicator for opioid use disorder in follow-up.

4. Results

As shown in **Table 1**, the cohort was on average 54.5 (SD ± 13.6) years of age, 55.7% were female, 72.5% were White, and 9.5% were African American. Most patients were from the Midwest or Southern United States. Most patients had a maximum MME ≤90 mg. Back pain, arthritis, and musculoskeletal pain were the most common pain conditions. Alcohol and drug abuse/dependence were present in <7% of the sample and nearly one-third had nicotine dependence. Approximately 15% had a diagnosis for an anxiety disorder and 23.8% had a benzodiazepine co-medication.

The covariate distributions by categories of opioid use frequency are shown in **Table 2**. Patients with maximum MME of 1 to 50 mg were most common among intermittent users (SMD % = 36.6) and those with maximum MME of 51 to 90 mg were more prevalent among occasional users (SMD% = 18.9). There were more patients with 91 to 180 MME in the frequent and daily user groups (SMD% = 10.2). The prevalence of patients with a maximum MME >180 mg increased with each category of more frequent opioid use (SMD% = 45.0).

Arthritis was least prevalent, whereas back pain was most prevalent among daily users (SMD% = 15.2 and 22.3, respectively). Musculoskeletal pain was most common among occasional users (SMD% = 32.6), and headache was most common among occasional and intermittent users (SMD% = 12.4%). The prevalence of drug abuse/dependence increased with each category of more frequent opioid use (SMD% = 21.8%). Benzodiazepine co-medication was most prevalent among daily users (SMD% = 17.2).

Median follow-up time was 32 months (interquartile range [IQR] = 16-55). Median follow-up time by opioid use frequency group was: (1) occasional = 40 months (IQR = 21-64); (2) intermittent = 36 months (IQR = 19-57); (3) frequent = 33 months (IQR = 16-55); and (4) daily = 30 months (IQR = 15-50). Among patients who developed depression, median follow-up time was 15 months (IQR = 6-28).

The median follow-up time to depression was 18 months (IQR = 5-34) among occasional users, 14 months (IQR = 6-30) among intermittent users, 16 months (IQR = 7-27) among frequent users, and 15 months (IQR = 6-26) among daily users.

Among the entire sample, 26.7% developed depression in follow-up. The overall unadjusted incidence rate of new-onset depression per 1000 person-years (PY) was 88.7/1,000 PY. The new-onset depression incidence rate increased from 68.1/1,000 PY among occasional users to 69.9/1,000 PY among intermittent users to 93.7/1000 PY for frequent users to 110.0/1000 PY among daily users (**Table 3**).

Table 1

Demographic and baseline characteristics (%) of new long-term prescription opioid users aged 18 to 80 years (n = 5146).

Covariates, n (%) or mean (±SD)	Overall (n = 5146)
Sociodemographic related	
Age, mean (±SD), y	54.5 (±13.6)
Female gender	2869 (55.7)
Race	
White	3732 (72.5)
Black	488 (9.5)
Other/unknown	926 (18.0)
Region	
Midwest	1639 (31.8)
Northeast	498 (9.7)
South	2262 (44.0)
West	559 (10.9)
Other/unknown	188 (3.6)
High healthcare utilization	1287 (25.0)
Opioid related	
Maximum daily MME (mg)*	
1-50	2491 (48.4)
51-90	1264 (24.6)
91-180	853 (16.6)
>180	538 (10.4)
Comorbidities†	
Arthritis	3426 (66.6)
Back pain	3629 (70.5)
Muscle pain	3335 (64.8)
Neuropathy	1046 (20.3)
Headache	1129 (21.9)
Type II diabetes	1323 (25.7)
Obesity	1502 (29.2)
Ischemic heart disease	861 (16.7)
Stroke	168 (3.3)
Low testosterone	190 (3.7)
Sleep apnea	604 (11.7)
Alcohol abuse/dependence	173 (3.4)
Drug abuse/dependence	336 (6.5)
Nicotine dependence	1521 (29.6)
Any anxiety disorder‡	781 (15.2)
Benzodiazepine co-medication§	1226 (23.8)

* MME—measured in first 90 days of new long-term opioid use (opioid start to index date).
† Comorbidities measured from start of data (January 1, 2010) to index date.
‡ Anxiety disorders = posttraumatic stress disorder, panic disorder, obsessive compulsive disorder, social phobia, generalized anxiety disorder, anxiety not otherwise specified.
§ Benzodiazepine co-med = fill or prescription during the first 90 days of new long-term opioid use (opioid start to index date).
MME, morphine milligram equivalent.

Results in e-Table 5 show SMD% estimates for each covariate after IPEW, which weights analyses using stabilized weights, to assess balance between groups. As shown in the supplementary e-Table 5 (supplemental digital content, http://links.lww.com/PAIN/B546), IPEW balanced all baseline covariates across opioid use frequency groups (all maximum pairwise SMD% <10%). The stabilized weights obtained from PS models ranged from 0.31 to 4.73, with a mean = 0.99 (SD ± 0.34) (results not shown).

Cox proportional hazard models estimating the association between frequency of opioid use and new-onset depression are shown in **Table 4**. After controlling for confounding by using weighted data (see model 2), we observed daily prescription opioid use compared with occasional use was associated with increased risk for new-onset depression (HR = 1.40; 95% CI: 1.14-1.73). Frequent use compared with occasional use was significantly associated with increased risk for new-onset depression (HR = 1.34; 95% CI: 1.05-1.71). The risk for new-onset depression did not differ between intermittent compared with occasional users. After extending the model by allowing for pain conditions that could occur after 90 days of opioid use, there were only small changes in the associations between frequency of opioid use and new-onset depression (see model 3). There was little change in the association between frequency of prescription opioid use and new-onset depression after accounting for the contribution of opioid use disorder that could occur after 90 days of opioid use (see model 4). Among the entire sample, 8.3% had opioid use disorder after 90 days of opioid use, and the prevalence of opioid use disorder increased with each category of opioid duration ($P < 0.0001$): occasional, 3.1%; intermittent, 5.3%; frequent, 8.3%; and daily, 11.9%.

As shown in the footnote to **Table 4**, post-hoc comparisons between each category of opioid use duration revealed a significantly greater risk for depression in daily users vs intermittent users (HR = 1.40; 95% CI: 1.23-1.61) and in frequent vs intermittent users (HR = 1.35; 95% CI: 1.12-1.61). There was no significant difference in depression risk between daily and frequent users. These comparisons remained largely unchanged after extending models by adding post 90-day opioid use pain conditions or opioid abuse/dependence.

The minimum e-value for any significant pairwise HR comparison in the weighted model was 1.58. A covariate would need at least this association with both the exposure and the outcome to completely explain significant findings.

5. Discussion

In a large, nationally distributed cohort of patients with LTOT, we observed that increasing frequency of prescription opioid use is associated with greater risk for new-onset depression. In patients with >90-day opioid use, daily users and frequent users, compared with intermittent users, had a 40% and a 34% increased risk, respectively, for new depression episodes. This association was independent of maximum daily MME, pain conditions, comorbid psychiatric disorders, physical conditions, benzodiazepine co-medication, and demographics. The relationship between greater frequency of opioid use and new-onset depression remained significant after accounting for the contribution of pain diagnoses and opioid use disorder that could occur after the new 90-day opioid use period and before depression onset.

There was evidence of a threshold for risk because patients who used an opioid ≥90% (ie, daily) and those who used ≥80% (ie, frequently) did not differ in risk for depression. Those who used 50% to <80% of the time did not differ in risk from those who used <50% of the time. Therefore, the prior evidence that >90-day prescription opioid use is associated with new-onset depression[22,25] is possibly due to the subgroup of LTOT who use daily or near daily. In addition, this finding supports the concept that nearly continuously occupied opioid receptors may prevent normal hedonic capacity leading to anhedonia and/or depression.[3,8,13] Some have suggested that depression develops in frequent LTOT because of the negative affect associated with withdrawal.[16] Our results do not directly address this issue but we observed that opioid use disorder after 90 days of opioid use did not modify the association between more frequent opioid use and new-onset depression. To the degree that opioid use disorder is diagnosed by providers, this finding suggests that opioid use disorder does not explain the relationship between frequent LTOT and new-onset depression. It is also possible that intermittent users were able to limit their opioid use because they had better overall mental health. Symptoms of depression, not reaching criteria for a diagnosis, may have been lower in those with intermittent use and that could

Table 2

Demographic and baseline characteristics by prescription opioid use frequency* (n = 5146).

Covariates, n (%) or mean (±SD)	Occasional (n = 582)	Intermittent (n = 1661)	Frequent (n = 664)	Daily (n = 2239)	*P*	Max SMD%†
Age, mean (±SD), y	52.8 (±13.8)	55.2 (±14.1)	53.7 (±14.0)	54.7 (±13.0)	0.001	17.5
Female gender	344 (59.1)	935 (56.3)	359 (54.1)	1231 (55.0)	0.245	10.2
Race						
White	434 (74.6)	1205 (72.6)	484 (72.9)	1609 (71.9)		6.1
Black	45 (7.7)	147 (8.8)	60 (9.0)	236 (10.5)	0.378	9.8
Other/unknown	103 (17.7)	309 (18.6)	120 (18.1)	394 (17.6)		2.6
Region						
Midwest	210 (36.1)	532 (32.0)	197 (29.7)	700 (31.3)		13.7
Northeast	60 (10.3)	180 (10.8)	63 (9.5)	195 (8.7)	0.020	7.2
South	223 (38.3)	715 (43.1)	300 (45.2)	1024 (45.7)		15.1
West	57 (9.8)	182 (11.0)	76 (11.5)	244 (10.9)		5.4
Other/unknown	32 (5.5)	52 (3.1)	28 (4.2)	76 (3.4)		11.7
High healthcare utilization	158 (27.2)	432 (26.0)	158 (23.8)	539 (24.1)	0.276	7.7
Maximum daily MME (mg)						
1-50	293 (50.3)	961 (57.9)	344 (51.8)	893 (39.9)		36.6
51-90	178 (30.6)	384 (23.1)	148 (22.3)	554 (24.7)	<0.0001	18.9
91-180	89 (15.3)	239 (14.4)	119 (17.9)	406 (18.1)		10.2
>180	22 (3.8)	77 (4.6)	53 (8.0)	386 (17.2)		45.0
Arthritis	405 (69.6)	1164 (70.1)	448 (67.5)	1409 (62.9)	<0.0001	15.2
Back pain	363 (62.4)	1160 (69.8)	477 (71.8)	1629 (72.8)	<0.0001	22.3
Muscle pain	434 (74.6)	1148 (69.1)	422 (63.6)	1331 (59.5)	<0.0001	32.6
Neuropathy	117 (20.1)	355 (21.4)	146 (22.0)	428 (19.1)	0.231	7.1
Headache	135 (23.2)	413 (24.9)	131 (19.7)	450 (20.1)	0.002	12.4
Type II diabetes	129 (22.2)	433 (26.1)	169 (25.5)	592 (26.4)	0.204	10.0
Obesity	169 (29.0)	520 (31.3)	204 (30.7)	609 (27.2)	0.034	9.0
Ischemic heart disease	97 (16.7)	288 (17.3)	123 (18.5)	353 (15.8)	0.325	7.3
Stroke	15 (2.6)	66 (4.0)	16 (2.4)	71 (3.2)	0.164	8.9
Low testosterone	15 (2.6)	64 (3.9)	18 (2.7)	93 (4.2)	0.152	8.8
Sleep apnea	83 (14.3)	198 (11.9)	83 (12.5)	240 (10.7)	0.100	10.7
Alcohol abuse/dependence	30 (5.2)	53 (3.2)	22 (3.3)	68 (3.0)	0.084	10.7
Drug abuse/dependence	21 (3.6)	71 (4.3)	46 (6.9)	198 (8.8)	<0.0001	21.8
Nicotine dependence	184 (31.6)	483 (29.1)	188 (28.3)	666 (29.8)	0.594	7.2
Any anxiety disorder	93 (16.0)	246 (14.8)	91 (13.7)	351 (15.7)	0.569	6.4
Benzodiazepine co-medication	117 (20.1)	339 (20.4)	157 (23.6)	613 (27.4)	<0.0001	17.2

* Occasional use = <50% days covered/<45 days of opioid use during the first 90-day use period. Intermittent use = 50% to <80% days covered/45 to 71 days of opioid use during the first 90-day use period. Frequent use = 80% to <90% of days covered/72 to 80 days of opioid use during the first 90-day use period. Daily use = ≥90% days covered/≥81 days of opioid use during the first 90-day use period.

† Maximum SMD percent (SMD% = 100 × SMD) of all group pairwise comparisons.

MME, morphine milligram equivalent; SMD, standardized mean difference.

reduce the number of new-onset depression diagnoses in those who used less often.

Another explanation for our results could be development of hyperalgesia and negative reward in more frequent users.[13,15] As initial euphoria associated with opioid use is replaced by increased pain sensitivity and acute withdrawal, negative reward may contribute to more frequent use and low mood. Another mechanism could be opioid-induced testosterone deficiency, which has been associated with LTOT and depression.[6] Yet, our results remained after controlling for low testosterone. In addition to more frequent use leading to opioid dependence and withdrawal and subsequent worsening of negative affect, LTOT in humans has been associated with changes in brain regions (ie, nucleus accumbens and amygdala) involved in motivation, reward, and mood regulation.[32,36] These changes last long after opioid cessation.[36] We speculate that frequent LTOT limits the brain's ability to generate natural reward and maintain normal hedonic tone, leading to low mood and depression.

Our results are inconsistent with 2 prospective cohort studies. The Pain and Opioids IN Treatment study reported that the association between opioid use and risk for depression was largely explained by comorbid psychiatric disorders and duration of pain.[28] While we lacked measures on the duration of pain conditions, we used robust methods to control for acute and chronic pain diagnoses before and after the 90-day opioid use exposure. As shown in several previous studies, controlling for psychiatric disorders, including substance use disorder, and opioid abuse/dependence did not change the association between LTOT and new-onset depression.[22,25] In a separate study, Von Korff et al.[33] suggested that a lack of increase in depression symptoms with long-term opioid use could be due to older study participants not exceeding <50 MME. Higher MME

Table 3

New onset depression events—cumulative incidence % and incidence rate per 10,000 person-years.

Group	Total n	NOD events	Cumulative incidence %	Incidence rate per 1000 PY
Overall	5146	1376	26.7	88.7/1000 PY
Opioid use intensity*				
Occasional	582	135	23.2	68.1/1000 PY
Intermittent	1661	372	22.4	69.9/1000 PY
Frequent	664	189	28.5	93.7/1000 PY
Daily	2239	680	30.4	110.0/1000 PY

* Occasional use = <50% days covered/<45 days of opioid use during the first 90-day use period. Intermittent use = 50% to <80% days covered/45 to 71 days of opioid use during the first 90-day use period. Frequent use = 80% to <90% of days covered/72 to 80 days of opioid use during the first 90-day use period. Daily use = ≥90% days covered/≥81 days of opioid use during the first 90-day use period.
NOD, new-onset depression; PY, person-years.

was positively correlated with more frequent opioid use in our study. However, we balanced the difference in MME across opioid use frequency groups, which suggests that our findings are not explained by opioid dose. Nonetheless, we have found that rapid increases in MME vs stable MME are associated with new-onset depression.[19] Therefore, we computed post-hoc analysis to compare the difference in daily MME between the first and last dose in the 90-day opioid use period. Occasional and intermittent users had no significant change in dose (41.2 MME to 40.7 MME and 36.4 MME to 37.9 MME, respectively). Frequent and daily users had significant dose increases (41.5 MME to 46.1 MME and 64.7 MME to 77.8 MME, respectively). It is possible that rapid increases in dose is a contributing factor to the association between more frequent use and new-onset depression.

Future research is needed to model the risk of depression using variables that are measured prospectively and map onto the measures applied in retrospective cohort studies that demonstrate a strong association between duration and intensity of prescription opioid use and risk for depression. We are currently collecting data in such a prospective design[20] to establish if there is a causal association between frequent prescription opioid use and new-onset depression among patients receiving LTOT.

5.1. Limitations

We did not have data on whether patients used their prescription opioid. We lacked data to identify pro re nata (PRN) opioid prescriptions. It is possible that PRN prescriptions were more common among intermittent users, and future studies should investigate risk for new-onset depression in patients with PRN vs opioid prescriptions written for daily use. The relatively large percent of patients with unknown race limited conclusions about differences by race within those classified as unknown. Uninsured patients did not meet eligibility criteria and results may not generalize to this patient group. Misclassification is a risk. Even though our depression algorithm has been validated, there is chance that we misclassified some patients as nondepressed when they actually had undiagnosed depression. This would tend to bias our estimates to the null, and our point estimates could be conservative. Unmeasured confounding is a potential limitation. Based on our e-value, an unmeasured confounder would have to have a HR of 1.58 with both opioid use frequency and new-onset depression to completely explain our results.[12] We are unable to conceive of such a variable. For instance, our previous studies of LTOT and depression revealed that greater pain severity scores were associated with only a 24% increased risk for depression.[22]

Table 4

Results from Cox proportional hazard models estimating the association of prescription opioid use frequency and new-onset depression (n = 5146)*.

Opioid use intensity†	Model 1—crude/unweighted	Model 2—weighted‡	Model 3—weighted + time-dependent post-index pain§	Model 4—weighted + time-dependent post-index OUD‖
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Occasional	1.00	1.00	1.00	1.00
Intermittent	1.01 (0.83-1.22)	1.00 (0.80-1.24)	0.98 (0.78-1.22)	0.98 (0.79-1.23)
Frequent	1.33 (1.07-1.66)	1.34 (1.05-1.71)	1.29 (1.01-1.64)	1.31 (1.03-1.67)
Daily	1.52 (1.26-1.82)	1.40 (1.14-1.73)	1.32 (1.07-1.63)	1.35 (1.09-1.67)
Arthritis			1.17 (1.03-1.33)	
Back pain			1.20 (1.06-1.36)	
Muscle pain			1.15 (1.01-1.32)	
Neuropathy			1.34 (1.16-1.55)	
Headache			1.42 (1.23-1.64)	
Opioid abuse/dependence				1.95 (1.54-2.47)

Weighted models use propensity scores and inverse probability of exposure weighting to control for confounders by balancing confounder distributions between exposure groups.
* *P* values for test of proportional hazards assumption: unweighted ($P = 0.99$); weighted ($P = 0.92$)—all $P > 0.05$, therefore assumption is met for models.
† Occasional use = <50% days covered/<45 days of opioid use during the first 90-day use period. Intermittent use = 50% to <80% days covered/45 to 71 days of opioid use during the first 90-day use period. Frequent use = 80% to <90% of days covered/72 to 80 days of opioid use during the first 90-day use period. Daily use = ≥90% days covered/≥81 days of opioid use during the first 90-day use period.
‡ Other weighted comparisons (model 2): frequent vs intermittent, HR = 1.35 (1.12-1.61); daily vs intermittent, HR = 1.40 (1.23-1.61); daily vs frequent, HR = 1.04 (0.88-1.23).
§ Other weighted comparisons (model 3): frequent vs intermittent, HR = 1.31 (1.10-1.58); daily vs intermittent, HR = 1.35 (1.18-1.55); daily vs frequent, HR = 1.03 (0.87-1.22).
‖ Other weighted comparisons (model 4): frequent vs intermittent, HR = 1.33 (1.12-1.60); daily vs intermittent, HR = 1.37 (1.20-1.57); daily vs frequent, HR = 1.03 (0.87-1.22).
CI, confidence interval; HR, hazard ratio; OUD, opioid use disorder.

We did not have pain scores in our data. However, our previous studies in Veteran Health Administration cohorts indicate that the association between LTOT and new-onset depression is independent of pain score severity.[21,23] Finally, we do not have adequate measurement of lifetime measures of depression; the association between more frequent opioid use and new-onset depression may be more common in patients who had a lifetime history of depression that preceded our observation period. However, there were only 47 patients with a new-onset depression episode defined by diagnostic codes for recurring depression. Because these patients could have had a depressive episode before our observation period, we conducted post-hoc sensitivity analysis by excluding these patients and results remained unchanged.

6. Conclusions

In a cohort of EHR data with integrated claims data, patients receiving LTOT had an increased risk for depression if they are using an opioid at least 80% of the time. There is no increased risk for new-onset depression in patients with LTOT who use opioids less frequently. The association may be explained by continual occupation of opioid receptors that blocks natural reward processes. Longitudinal cohort studies are needed to confirm the mechanisms behind LTOT and increased risk for new-onset depression. Clinicians need to repeatedly screen for depression in patients receiving LTOT who are daily or near-daily users and encourage nonpharmacological pain management for this patient population.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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J. F. Scherrer and J. Salas had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/B546.

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