Research Paper

PAIN®

Change in opioid dose and change in depression in a longitudinal primary care patient cohort

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Abstract

Depression is associated with receipt of higher doses of prescription opioids. It is not known whether the reverse association exists in that an increased opioid dose is associated with increased depression. Questionnaires were administered to 355 patients with chronic low back pain at baseline and 1-year and 2-year follow-up. Depression, pain, anxiety, health-related quality of life, and social support or stress were obtained by survey. Opioid type and dose and comorbid conditions were derived from chart abstraction. Random intercept, generalized linear mixed models were computed to estimate the association between change in opioid morphine equivalent dose (MED) thresholds (0, 1-50, >50 mg) and probability of depression over time. Second, we computed the association between change in depression and odds of an increasing MED over time. After adjusting for covariates, an increase to >50 mg MED from nonuse increased a participant's probability of depression over time (odds ratio [OR] = 2.65; 95% confidence interval [CI], 1.17-5.98). An increase to 1 to 50 mg MED did not increase an individual's probability of depression over time (OR = 1.08; 95% CI, 0.65-1.79). In unadjusted analysis, developing depression was associated with a 2.13 (95% CI, 1.36-3.36) increased odds of a higher MED. This association decreased after adjusting for all covariates (OR = 1.65; 95% CI, 0.97-2.81). Post hoc analysis revealed that depression was significantly associated with a 10.1-mg MED increase in fully adjusted models. Change to a higher MED leads to an increased risk of depression, and developing depression increases the likelihood of a higher MED. We speculate that treating depression or lowering MED may mitigate a bidirectional association and ultimately improve pain management.

Keywords: Opioids, Depression, Cohort, Epidemiology

1. Introduction

For decades, research literature has supported a correlation between pain and depression.[9] Persons with depression report greater sensitivity to painful stimuli, report more severe pain scores, and are vulnerable to catastrophizing in response to pain.[5,9,12] Numerous reports have established that patients with chronic noncancer pain with depression, compared with those without, are more likely to receive opioids,[21] use opioids for longer periods of time,[2,15] use higher daily morphine equivalent doses (MED),[11] and misuse and/or abuse prescription opioids.[6,16] Longitudinal data suggest that depression is a risk factor for opioid use. Sullivan et al.[21] reported that subjects in a community cohort who had a psychiatric illness, including depression, compared with subjects free of a diagnosis at baseline, were twice as likely to be opioid users 3 years later. Whether opioid use leads to depression is less well understood. At this time, we are aware of only 1 study designed to determine whether the reverse pattern of association exists, that is, do patients who use opioids in larger amounts or for longer durations have an increased risk of new-onset depression. After controlling for bias by indication in a retrospective cohort design, increasing duration of opioid use was associated with increasing risk of depression in analysis of data from Veterans Administration (VA) medical records.[17]

Better understanding of temporal relationship between opioids and depression and the dose of opioids that places patients at risk for depression may inform prescribing and pain management and improve outcomes for patients with chronic, noncancer pain. In addition to improving pain management, elucidating the nature of the opioid–depression association has public health implications. In 2010, hydrocodone (with acetaminophen),[22] was the most prescribed medication in the United States, and the rate of prescribing opioids increased dramatically in the past 30 years and was not accompanied by parallel increases in painful conditions.[4] Because the prevalence of opioid use is so large, the opioid–depression association is likely a serious, yet poorly understood, public health problem. In particular, if opioids lead to depression and increased severity of depression is associated with more opioid use, it is critical to understand what MED places users at risk to begin identifying where to intervene to break the opioid–depression association.

To determine whether patients who increase MED are at risk for increased depression and whether patients with increased depression experience increased MED, we analyzed data obtained from a cohort of treatment-seeking primary care patients with chronic low back pain (CLBP), from whom 3 waves of data were collected prospectively over a 2-year period. Our first objective was

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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PAIN 156 (2015) 348–355

http://dx.doi.org/10.1097/01.j.pain.0000460316.58110.a0

to determine whether increases to a higher MED (0 mg, 1-50 mg, >50 mg) over time increased the individual probability of depression over time. Our second objective was to determine whether developing depression over time increased the individual probability of higher MED over time. For both objectives, we computed associations before and after adjusting for pertinent covariates, including pain and health-related quality of life (HRQL).

2. Methods

2.1. Subjects

Patients were eligible for the study if they had a diagnosis of noncancer chronic low back pain on their problem list, and they were regular users of family medicine clinics, defined as 2 or more visits in the past 24 months.

2.2. Procedure

Medical students recruited subjects during routine outpatient visits from 9 practices of the Residency Research Network of Texas. The Residency Research Network of Texas is a collaboration between the Accreditation Council for Graduate Medical Education (AGME)-accredited family medicine residency programs in Texas (http://iims.uthscsa.edu/RRNeT/home) and serves as a productive resource for primary care research.[3,23–26] Students invited potential subjects to participate in a study to examine how pain and health change over time and how pain medicines are used to manage changes in low back pain. Baseline (wave 1) was assessed in 2008 and 2009 with follow-up data collection performed at 12 months (wave 2) and 24 months (wave 3) after enrollment. At baseline, informed consent was obtained, and participants completed a patient survey, addressing pain, health, and function; then, the medical students completed chart abstractions addressing diagnoses, comorbidities, and prescriptions. At Waves 2 and 3, students gathered survey data in person if patients had a scheduled appointment, or by telephone if patients did not have an appointment at the time of their scheduled follow-up assessments. Details of data collection and subject recruitment have been previously reported.[26] Among 362 patients enrolled at baseline, 337 participated in wave 2 and 199 in wave 3. Only 7 subjects had missing data on baseline measures, resulting in 355 eligible subjects at baseline, 330 at wave 2, and 194 at wave 3. We investigated potential nonresponse bias by computing the distribution of covariates (ie, demographics, social support/stress, and pain duration) across wave and observed no significant difference in the distribution of these variables from baseline, wave 2, and wave 3.

As described below, missing data are accounted for in the analytic design. The institutional review boards of all participating institutions approved the study procedures and consent form.

2.3. Measures

2.3.1. Opioid use

Specific opioid medications and dose were abstracted from medical charts at baseline and each follow-up wave. If an opioid prescription was managed by a provider other than the primary care clinic, this information was in the patient chart because study clinic providers obtained the patient's current medication list. Chart abstraction obtained the current average daily MED for the patient's current opioid prescription based on the prescribed type and amount of the following 9 opioids: codeine fentanyl, hydrocodone, hydromorphone, meperidine, methadone, morphine, oxycodone, and propoxyphene. The MED was modeled as none, low (1-50 mg/d), and high dose (>50 mg/d) based on previous studies of the association between depression and MED, which used the 50 mg and similar thresholds.[1,17,26]

2.3.2. Depression

The PHQ-2[8] was administered at each wave to measure depression over the past 30 days. A score of 3 or more indicates probable depression with sensitivity = 82.9% and specificity = 90.0%. The PHQ-2 has been shown to accurately detect worsening, improving, and unchanged depression in outpatients.[10] For all analysis, depression was modeled as a binary variable (yes vs no).

Covariates were selected based on the theoretical and empirical evidence that each is correlated with opioid use and depression. Covariates included characteristics of pain, social support/stress, HRQL, physical comorbidities, obesity, and anxiety. Pain characteristics included the pain level on an average day in the 30 days before survey. Pain level was measured on a 10-point Likert scale with 0 equal to none and 10 equal to severe pain.

Duration of pain in years was assessed with subjects' self-report. Participants addressed social support/stress by reporting the number of persons who are sources of stress and sources of support (possible range: 0-10). Health-related quality of life was measured by the RAND, SF-36 subscales for physical functioning, role physical, and general health, as well as the SF-36 question for pain interference.[13] Comorbidities were obtained from chart abstraction of the patient's problem list containing up to 20 conditions. Obesity was derived from chart-abstracted height and weight. Last, anxiety was considered to be present if subjects reported feeling anxious on several or more days in the past 30 days or having a panic attack in the past 2 weeks. Sociodemographic variables included age, race, gender, disability status, and education.

2.4. Analytic approach

Sociodemographic variables, pain duration, and social support/stress were modeled as time-independent covariates from baseline status. The MED, pain severity, PHQ-2 scores, HRQL, comorbidities, anxiety, and body mass index were measured at all 3 waves and were treated as time-dependent covariates. The longitudinal nature of the data and analyses only excluded missing waves of data per participant. For example, if a subject did not participate at wave 3, his or her wave 1 and wave 2 data were still used in analyses. Thus, all 355 original participants contributed data to the analysis, with 21 (5.9%) contributing 1 wave of data, 144 (40.6%) contributing 2 waves, and 190 (53.5%) contributing all 3 waves of data. Covariate differences by depression status were assessed separately for baseline, wave 2, and wave 3. Differences were examined using a χ^2 test or a 2-sample independent t test.

Longitudinal analysis conditioned the probability of depression at each wave on covariates and MED. Random intercept, generalized linear mixed model analyses (Proc Glimmix, Adaptive Quadrature Method, SAS v9.3, SAS Institute Inc., Cary, NC) examined changes in probability of depression based on changes in opioid use over time, controlling for the effects of different covariate groupings. Model fit and quality were assessed using Akaike's Information Criterion and Pseudo R-squared estimates. Pseudo R-squared estimates were derived using methods described by Snijders and Bosker.[18]

Unadjusted models measured the association between changes in MED and changes in depression over time. Models were expanded by adding: (1) pain characteristics, (2) HRQL measures, (3) comorbidities, obesity and anxiety, (4) social support, social

stress, and (5) demographics. All models included a "time" variable, modeled as time since baseline in years (0, 1, or 2), which controls for each participant's natural course of depression over the study period.

For objective 2, analyses were repeated, except that change in depression was used to predict change in MED over time. Objective 2 analyses used mixed ordinal logistic regression models because of the ordinal nature of the MED variable (none, 1-50 mg, >50 mg) and the proportional odds assumption was met. Results are interpreted as an individual's odds of higher opioid dose vs all lower categories of doses based on changes in probability of depression over time. All analyses were computed using SAS v. 9.3.[7]

3. Results

As shown in **Table 1**, respondents were mostly female (72.4%), older than 46 years (75.2%), mostly of minority race (57.5%), and the majority had a high school education or greater (78.6%). Distribution of sociodemographic variables did not significantly change across baseline, wave 2, and wave 3.

The association between depression and patient characteristics at baseline, wave 2, and wave 3 is shown in **Table 2**. Baseline depression was significantly associated with baseline MED. Subjects with depression were significantly ($P < 0.05$) more likely to be on 1 to 50 mg and >50 mg MED per day and less likely to be nonopioid users. At baseline, subjects with depression, compared with those without, had lower educational achievement ($P < 0.01$) and were significantly more likely to be in the "applying for or on disability group" ($P < 0.001$). Subjects with depression reported more stressful relationships and fewer socially supportive relationships ($P < 0.01$), higher pain severity ($P < 0.001$), more comorbid conditions ($P < 0.001$), worse functioning for each SF-36 subscale ($P < 0.001$), and were more likely to have anxiety at baseline ($P < 0.001$).

Subjects with depression at wave 2 remained more likely to be high-dose opioid users in wave 2. In wave 2, 14.9% of the depressed subjects used >50 mg MED compared with 7.3% of the nondepressed; however, this association was not statistically significant. Associations between subjects with depression at wave 2 and their pain level, SF-36 subscale scores, and anxiety at wave 2 were significant and followed a pattern similar to the one observed at baseline. Although not significant at baseline, age and race were significantly associated with depression in wave 2. Subjects with depression at wave 2 were more 46 to 59 years of age ($P < 0.05$) and non-white ($P < 0.01$). At wave 2, the number of comorbid conditions increased overall and was no longer significantly greater among depressed subjects.

Subjects with depression at wave 3 were also more likely ($P < 0.05$) to be high-dose (>50 mg MED) opioid users and less likely to be nonusers. The covariates significantly associated with depression at wave 3 were the same as those at baseline. As in previous waves, greater pain severity ($P < 0.01$), lower SF-36 subscale scores ($P < 0.001$), and anxiety ($P < 0.001$) at wave 3 remained significantly associated with wave 3 depression. Subjects with depression in wave 3 were still more likely to be non-whites and seeking or applying for disability. In wave 3, depression was no longer significantly associated with age and education. Last, the mean number of comorbid conditions in depressed patients was significantly ($P < 0.01$) larger than in nondepressed wave 3 respondents.

To better illustrate the longitudinal association of MED and depression, the first 3 rows of **Table 2** were plotted in **Figure 1**. As shown, there is a clear increase from wave 1 to wave 3 in the proportion of patients with depression receiving 50 mg MED per day.

The results of generalized linear mixed models predicting changes in depression from changes in opioid use are shown in **Table 3**. In model 1, the unadjusted probability of having depression was significantly greater when a subject was on >50 mg MED as opposed to when he or she was taking no opioids (odds ratio [OR] = 3.32; 95% confidence interval [CI], 1.43-7.69). Similarly, relative to when a subject was not using opioids, if that subject increased his or her dose to 1 to 50 mg per day they had a higher probability of depression, but at a lower magnitude (OR = 1.99; 95% CI, 1.19-3.31) than if they had increased to >50 mg per day.

As shown in model 2, pain severity over the study period, but not the duration of pain at baseline, was significantly associated with an increased probability of depression (OR = 1.40; 95% CI, 1.25-1.56). After adjusting for pain severity and pain duration, the probability of a subject who used ≤50 mg MED per day having depression over the study period was no longer statistically significant. However, if a subject increased from no use to using >50 mg/d, they had a significantly greater probability of depression (OR = 2.95; 95% CI, 1.30-6.68).

In model 3, the probability of depression in a subject who used 1 to 50 mg MED per day, and the probability of depression in a subject who used >50 mg MED per day, both decreased after adjusting for SF-36 subscales. In model 3, higher SF-Pain and SF-General Health scores, indicating better HRQL, were significantly associated with a lower probability of depression (OR = 0.97; 95% CI, 0.96-0.99 and OR = 0.97; 95% CI, 0.96-0.98, respectively). After adjusting for SF-36 subscales, an increase from no use to 1 to 50 mg MED and to >50 mg MED per day was no longer significantly associated with increased odds of depression (OR = 1.12; 95% CI, 0.67-1.85 and OR = 1.81; 95% CI, 0.81-4.04, respectively). This effect did not remain in the full model 7.

The OR measuring the association between opioid MED and depression was similar for the unadjusted model 1, model 4 (adjusting for number of comorbidities, anxiety, and body mass index), and model 5 (adjusting for the number of stressful and supportive social relationships). After adjusting for demographic variables in model 6, the associations between an increase from no use to 1 to 50 mg MED and to >50 mg MED remained significantly associated with depression (OR = 1.71; 95% CI,

Table 1

Cohort characteristics and sample size for baseline, wave 2, and wave 3 follow-up.

Variable	Baseline (n = 355), %	Wave 2 (n = 330), %	Wave 3 (n = 194), %	P
Age				0.96
18-45	24.8	23.9	24.2	
46-59	44.2	44.2	46.9	
60 and over	31.0	31.8	28.9	
Race				0.68
White, non-Hispanic	42.5	42.1	45.9	
Other	57.5	57.9	54.1	
Gender				0.63
Male	27.6	27.3	30.9	
Female	72.4	72.7	69.1	
Education				0.79
<High school	21.4	21.2	19.1	
≥High school	78.6	78.8	80.9	
Applying for/on disability	49.3	47.9	58.8	0.93

Table 2

Association between patient characteristics and depression at baseline, wave 2, and wave 3 follow-up.#

Variable	Baseline		Wave 2		Wave 3	
	Not depressed (n = 147)	Depressed (n = 201)	Not depressed (n = 127)	Depressed (n = 104)	Not depressed (n = 75)	Depressed (n = 68)
Opioid use§						
No use	61.2%	45.8%*	53.7%	40.6%	59.5%	37.9%*
50 mg or lower	32.7%	45.8%	39.0%	44.5%	23.0%	36.4%
> 50 mg	6.1%	8.5%	7.3%	14.9%	17.6%	25.8%
Sociodemographics						
Age						
18-45	25.8%	24.4%	22.8%	19.2%*	28.0%	23.5%
46-59	38.1%	49.7%	35.4%	53.9%	34.7%	47.1%
60 and over	36.1%	25.9%	41.7%	26.9%	37.3%	29.4%
Race						
White, non-Hispanic	47.6%	39.8%	53.5%	35.6%†	58.7%	39.7%*
Other	52.4%	60.2%	46.5%	64.4%	41.3%	60.3%
Gender						
Male	25.2%	29.8%	21.3%	26.9%	26.7%	27.9%
Female	74.8%	70.2%	78.7%	73.1%	73.3%	72.1%
Education						
<High school	14.3%	27.4%†	14.2%	27.9%†	13.3%	20.6%
≥High school	85.7%	72.6%	85.8%	72.1%	86.7%	79.4%
Applying for/on disability	33.3%	61.2%‡	36.2%	55.8%†	30.7%	58.8%‡
Psychosocial characteristics						
Number of close stressful people (mean ± SD)	.09 ± 1.1	1.3 ± 1.2†	1.0 ± 1.2	1.2 ± 1.1	0.9 ± 1.2	1.3 ± 1.2
Number of close supportive people (mean ± SD)	3.0 ± 1.9	2.4 ± 1.7†	2.9 ± 1.9	2.5 ± 1.7	3.3 ± 2.0	2.6 ± 1.7*
Pain characteristics						
Pain severity (mean ± SD)	6.0 ± 2.3	7.3 ± 2.0‡	5.6 ± 2.9	7.4 ± 2.1‡	5.4 ± 2.6	6.8 ± 2.3†
Pain duration (y; mean ± SD)	13.5 ± 13.4	13.7 ± 13.3	13.4 ± 12.6	15.9 ± 14.9	15.3 ± 16.1	15.4 ± 12.2
HRQL‖						
SF–pain interference (mean ± SD)	44.3 ± 26.8	22.5 ± 22.3‡	46.6 ± 22.6	25.2 ± 22.4‡	49.3 ± 28.1	25.4 ± 22.2‡
SF–physical functioning (mean ± SD)	43.4 ± 28.7	25.0 ± 23.0‡	47.6 ± 29.4	23.5 ± 22.1‡	49.7 ± 31.4	31.8 ± 26.8‡
SF–role physical (mean ± SD)	19.7 ± 31.4	6.5 ± 17.2‡	22.8 ± 33.7	4.6 ± 14.4‡	23.1 ± 36.5	8.5 ± 21.0‡
SF–general health (mean ± SD)	53.0 ± 23.7	32.4 ± 21.4‡	48.9 ± 23.8	30.8 ± 22.0‡	50.9 ± 24.9	35.3 ± 20.9‡
Comorbidities						
Number of comorbidities (mean ± SD)¶	2.4 ± 1.7	3.1 ± 1.8‡	3.3 ± 2.1	3.6 ± 2.1	2.8 ± 1.8	4.0 ± 2.1†
Anxiety—yes	59.9%	96.0%‡	58.3%	84.6%‡	38.7%	89.7%‡
Obese/overweight	79.9%	82.7%	84.1%	89.5%	78.5%	85.3%

* $P < 0.05$.
† $P < 0.01$.
‡ $P < 0.001$.
§ Morphine equivalent dose.
‖ RAND SF-36 subscales, higher scores indicate better functioning.
¶ Comorbid conditions from patient chart.
# Of the 330 patients who completed wave 2, there were 234 patients who completed the survey and 322 who had chart data; of the 194 patients in wave 3, 144 patients completed the survey and 191 patients had chart data.
HRQL, health-related quality of life.

1.03-2.82 and OR = 2.96; 95% CI, 1.30-6.78, respectively). Last, after simultaneous adjustment for all covariates in model 7, pain was no longer significantly associated with depression (OR = 1.05; 95% CI, 0.93-1.19), and relative higher functioning for a subject in SF-Pain remained associated with lower risk of depression (OR = 0.98; 95% CI, 0.96-0.99). In model 7, a subject had a statistically significant increased probability of depression when they changed MED from no use to >50 mg MED per day (OR = 2.65; 95% CI, 1.17-5.98), but not if change was from no use to 1 to 50 mg MED per day (OR = 1.08; 95% CI, 0.65-1.79).

The results of the ordinal logistic mixed models are shown in **Table 4**. In the unadjusted model (model 1), developing depression was associated with more than a 2-fold increased probability of changing to a higher MED as opposed to a lower MED (OR = 2.13; 95% CI, 1.36-3.36). When adjusting for pain characteristics in model 2, a subject was still at greater risk for increasing to a higher MED as opposed to lower MED when depressed, but the effect was attenuated (OR = 1.85; 95% CI, 1.17-2.92). Model 2 also showed that with each 1 unit increase of pain severity, a subject had a 14% increased probability of changing to a higher MED as opposed to lower MED (OR = 1.14; 95% CI, 1.03-1.25). The greatest attenuation of association between change in depression and change to a higher MED was observed after adjusting for HRQL (SF-36 subscales) in model 3 (OR = 1.38; 95% CI, 0.86-2.22). When simultaneously adjusting for all covariates in model 7, a subject who changed from nondepressed to depressed had a 65% increased odds of having a higher as opposed to lower MED, although this effect was not significant (OR = 1.65; 95% CI, 0.97-2.81; $P = 0.06$).

4. Discussion

In a cohort of 355 primary care patients with CLBP assessed for pain severity, depression, and opioid use over 3 waves of data

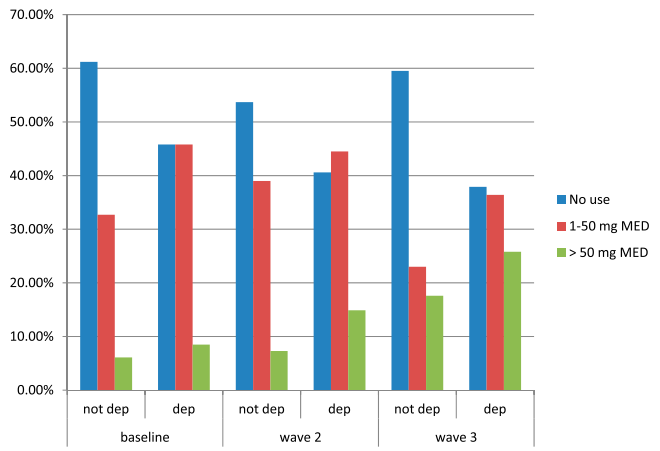

Figure 1. Association between morphine equivalent dose (MED) and depression (dep) over 3 waves of data collection with patients in primary care with chronic low back pain (CLBP).

collection, we observed that increasing to a higher daily MED (>50 mg) also significantly increased individual probability of depression over time. This association remains even after adjusting for repeated measures of pain severity in the month before each survey. Better HRQL partly accounted for this association in submodels. But in the full model, after adjusting for all covariates, an increase to >50 mg MED was significantly associated with a participant's greater probability of depression. This association suggests that HRQL influences only the MED to depression pathway under select combinations of other covariates. Consistent with our previous study,[17] change to a lower daily MED (1-50 mg MED) did not increase individual risk of depression in a full model. In our previous work,[17] low dose <38 mg MED was not associated with increased risk of depression even in the long term, greater than 180-day users. This study replicates our previous findings in a VA patient population. Replication in the present cohort of primary care patients residing in Texas, using different measures of depression and pain, and different analytic approach, provides compelling evidence that high-dose opioid use over time is an independent risk factor for developing depression.

Results of objective 2 indicate there is a significant increased odds (OR = 2.13; 95% CI, 1.36-3.36) of a subject with depression receiving a higher daily MED over the study interval. Adjusting for HRQL greatly attenuated this association (OR = 1.38), suggesting that the relationship between change from

Table 3

Mixed logistic regression models measuring the association (OR [95% CI]) between change in morphine equivalent opioid dose (MED) and change in depression over time before and after adjusting for covariates.

	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)	Model 5 OR (95% CI)	Model 6 OR (95% CI)	Model 7 OR (95% CI)
Opioid use							
No use	1.00	1.00	1.00	1.00	1.00	1.00	1.00
≤50 mg	1.99 (1.19-3.31)	1.45 (0.87-2.41)	1.12 (0.67-1.85)	2.00 (1.24-3.22)	1.84 (1.11-3.06)	1.71 (1.03-2.82)	1.08 (0.65-1.79)
>50 mg	3.32 (1.43-7.69)	2.95 (1.30-6.68)	1.81 (0.81-4.04)	3.25 (1.47-7.20)	3.09 (1.35-7.10)	2.96 (1.30-6.78)	2.65 (1.17-5.98)
Pain characteristics							
Pain severity		1.40 (1.25-1.56)					1.05 (0.93-1.19)
Pain duration, y		1.01 (0.99-1.03)					1.02 (0.99-1.04)
HRQL							
SF–pain interfere			0.97 (0.96-0.99)				0.98 (0.96-0.99)
SF–physical functioning			0.99 (0.98-1.00)				0.99 (0.98-1.01)
SF–physical role			1.00 (0.99-1.01)				1.00 (0.99-1.01)
SF–general health			0.97 (0.96-0.98)				0.99 (0.98-1.00)
Comorbidities							
Number of comorbidities				1.11 (0.99-1.26)			1.04 (0.92-1.19)
Anxiety							
				12.13 (6.50-22.64)			8.33 (4.39-15.81)
Obese/overweight				1.29 (0.68-2.42)			0.87 (0.45-1.69)
Psychosocial characteristics							
Number of stressful people					1.50 (1.17-1.93)		1.32 (1.05-1.65)
Number of support people					0.78 (0.67-0.92)		0.92 (0.81-1.06)
Demographic characteristics							
Age							
≥60						0.80 (0.38-1.70)	0.72 (0.34-1.53)
46-59						1.46 (0.73-2.90)	1.10 (0.59-2.05)
18-45						1.00	1.00
Race							
Non-white						1.73 (0.97-3.10)	1.75 (1.03-2.98)
Education							
<High school						3.03 (1.46-6.27)	1.57 (0.83-2.98)
Gender							
Female						0.82 (0.44-1.52)	0.61 (0.35-1.05)
Disability status							
On/apply						3.28 (1.82-5.92)	1.00 (0.59-1.70)
Model information							
Pseudo R-square	19.25%	25.42%	36.82%	30.60%	21.44%	24.92%	48.28%
AIC	914.40	873.70	781.10	759.56	899.55	879.32	667.30

All models adjusted for years since baseline assessment.

AIC, Akaike's Information Criterion; CI, confidence interval; HRQL, health-related quality of life; OR, odds ratio.

Table 4

Mixed ordinal logistic regression models measuring the association (OR [95% CI]) between change in depression and change in morphine equivalent opioid dose (MED) over time before and after adjusting for covariates.

	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)	Model 5 OR (95% CI)	Model 6 OR (95% CI)	Model 7 OR (95% CI)
Depression	2.13 (1.36-3.36)	1.85 (1.17-2.92)	1.38 (0.86-2.22)	2.38 (1.43-3.97)	2.03 (1.28-3.21)	1.95 (1.23-3.10)	1.65 (0.97-2.81)
Pain characteristics							
Pain severity		1.14 (1.03-1.25)					1.03 (0.91-1.18)
Pain duration, y		1.00 (0.98-1.02)					1.00 (0.97-1.02)
HRQL							
SF–pain interfere			0.99 (0.98-1.00)				0.99 (0.98-1.01)
SF–physical functioning			0.99 (0.98-1.00)				0.99 (0.98-1.00)
SF–physical role			0.99 (0.98-1.00)				0.99 (0.98-1.01)
SF–general health			1.00 (0.99-1.01)				1.01 (1.00-1.02)
Comorbidities							
Number of comorbidities				1.17 (1.01-1.34)			1.12 (0.97-1.29)
Anxiety				0.76 (0.42-1.39)			0.75 (0.41-1.38)
Obese/overweight				0.46 (0.22-0.94)			0.74 (0.35-1.52)
Psychosocial characteristics							
Number of stressful people					1.03 (0.81-1.32)		1.01 (0.78-1.31)
Number of support people					0.86 (0.74-1.01)		0.88 (0.75-1.04)
Demographic characteristics							
Age							
≥ 60						0.99 (0.46-2.13)	0.66 (0.27-1.63)
46-59						0.99 (0.49-1.98)	0.80 (0.38-1.68)
18-45						1.00	1.00
Race							
Non-white						0.57 (0.31-1.02)	0.55 (0.30-1.03)
Education							
<High school						0.58 (0.28-1.18)	0.59 (0.27-1.26)
Gender							
Female						0.69 (0.37-1.28)	0.61 (0.33-1.16)
Disability status							
On/apply						3.64 (2.01-6.59)	2.51 (1.31-4.82)
Model information							
Pseudo R-square	42.41%	42.89%	45.33%	44.46%	42.69%	44.94%	48.09%
AIC	1250.03	1245.4	1205.24	1140.85	1250.51	1232.73	1104.16

All models adjusted for years since baseline assessment.

AIC, Akaike's Information Criterion; CI, confidence interval; HRQL, health-related quality of life; OR, odds ratio.

nondepressed to depressed and change to larger MED is partly explained by lower HRQL. However, simultaneous adjustment for all covariates leads us to conclude that there is evidence, albeit marginally nonsignificant, that developing depression leads to a participant's increased likelihood of change to a higher MED (OR = 1.65; 95% CI, 0.97-2.81). The present categorization of MED into 3 ordinal groups reduced statistical power. At baseline, only 6.1% of nondepressed and 8.5% of depressed subjects had >50 mg MED. Thus, to increase statistical power, we re-evaluated treating MED as a continuous variable in post hoc analysis. In the post hoc general linear mixed model regression, we observed that a patient who becomes depressed over time has a corresponding MED increase of 10.1 mg, which remained significant after adjusting for all covariates shown in model 7 ($P < 0.01$). Thus, depression is significantly associated with patients' increasing opioid dose. Although our observation that depression is associated with greater opioid use has been previously reported,[2,11,15,19–21] the present finding is novel in identifying the association between an increase in opioid use and increase in depression.

This study and our previous research[17] point to the amount of daily morphine exposure, and not just the duration of exposure, as the contributing factor for new-onset depression. Additional data collection is needed to determine whether patients are at risk due to past depressive episodes or recent depression symptoms. Another plausible pathway to incident depression due to high-dose MED is opioid abuse. High-dose opioid use is associated with the risk of opioid misuse and abuse,[11,14] and prospective data are needed to determine whether relationship dysfunction, job loss, family disruption, and additional life consequences associated with opioid abuse are in the pathway from high-dose MED to new-onset depression. Last, determining the covariate combinations for which HRQL partly mediates the opioid to depression association could identify subjects for whom high-dose opioid use leads to depression independent of changes in quality of life and functioning.

Depression may be associated with greater sensitivity to pain and higher MED required to control pain symptoms. Others[26] have offered explanations for why depressed patients receive more opioid prescriptions, which include patients using opioids for emotional regulation resulting in using more often than pain symptoms warrant and thereby requesting and receiving larger doses. We speculate that greater pain sensitivity leads to a higher MED that in turns precipitates or worsens depression leading to continued or worsened pain sensitivity and the patient requests for more opioids. Last, depression may contribute to opioid misuse,[26] and we speculate that a bidirectional relationship could be mediated by substance abuse.

4.1. Limitations

This study is limited by geographic region and may not generalize beyond ambulatory care patients, but as described above, our primary results replicated our previous study in a national VA patient cohort. Depression was assessed by self-report using the PHQ-2. This instrument is a good screener to detect probable depression in the past month but is not the gold standard for psychiatric diagnosis, and it does not measure lifetime history of depression. Thus, we are unable to account for the effect of depression before baseline. Dates of depression onset were not collected, thus the onset of depression could have been a few months after exposure or up to a year after increasing dose. Longitudinal studies that include diagnostic interviews are warranted to determine which depression symptoms onset first, symptom duration, and the characteristics of depression (cognitive vs somatic) associated with opioid exposure.

Pain severity was reported for CLBP. Results may not generalize to other painful conditions (eg, fibromyalgia). It is possible that changes in depression and MED occurred between assessments. This possibility may limit our ability to identify how quickly a change in MED or depression occurs and prevents assessment of the lag time between change in value of the exposure variable and change in value of the outcome variable. Our categories of MED do not provide information on other levels of high-dose use. Therefore, we computed a fully adjusted model with MED categories being none, 1 to 50 mg, 51 to 100 mg, and >100 mg. After adjusting for all covariates shown in **Table 3**, model 7, increasing to >100 mg was associated with 3.66 (95% CI, 1.13-11.89) odds of developing depression, which suggests a dose–response relationship. Last, we are not able to determine whether this study has identified a bidirectional relationship or a cyclical one due to insufficient sample size and insufficient waves of follow-up data.

5. Conclusions

Results support the conclusion that use of opioids at a dose equal to or greater than 50 mg MED per day is associated with increasing depression, and worsening depression is associated with increased MED. These associations remain after accounting for the influence of worsening pain severity and HRQL. Providers should consider current opioid dose when patients with pain present with depression. Both providers and patients should be aware and discuss the risk of depression when considering opioid medications that equate to more than 50 mg MED per day. Providers should routinely screen for depression in patients receiving more than 50 mg of opioid per day and have frank and open discussions with patients before increasing dose beyond 50 mg.

This study does not establish causation, but results do support evidence for both directions of association, morphine dose to depression and depression to morphine dose, and suggest the possibility that a bidirectional relationship does exist. Additional prospective cohort studies may help identify which patients, such as those with a history of major depression, are most vulnerable to developing depression when using prescription opioids.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Supported by Health Resources and Services Administration (Award #D54HP16444); Texas Academy of Family Physicians Foundation; the Office of the Medical Dean of the University of Texas Health Science Center at San Antonio; and the National Center for Research Resources (Award #UL 1RR025767).

Article history:
Received 5 September 2014
Received in revised form 30 October 2014
Accepted 24 November 2014

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