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Characteristics of New Depression Diagnoses in Patients with and without Prior Chronic Opioid Use

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Abstract

Chronic use (>90 Days) of opioid analgesics significantly increases the risk of development of new depression episodes (NDE). It is unclear whether depression that develops in this manner is similar to or different from NDE in persons not exposed to opioid analgesics.

METHODS—VA patients were classified into two groups, those who did not receive an opioid and developed depression (non-OAU+NDE, n=4,314) and those that had >90 days OAU and developed NDE (OAU+NDE, n=444). OAU+NDE patients were compared to non-OAU+NDE in terms of depression severity (PHQ-9 scores), incidence of PTSD, other anxiety disorders and substance use disorders after NDE, receipt of acute phase antidepressant treatment, dual

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antidepressant treatment, mood stabilizers and atypical antipsychotics. Prior to computing bivariate analysis, the prevalence of pain conditions and average maximum pain scores were equalized between the two groups using propensity scores and inverse probability of treatment weighting.

RESULTS—Controlling for pain, OAU+NDE patients had more depression symptoms (p=0.012), more incident PTSD (p=0.04) and opioid abuse/dependence and were more likely to receive 12 weeks of antidepressant treatment (p<0.0001). Last, non-OAU+NDE were more likely to have incident diagnoses for any other anxiety disorder (p=0.014).

CONCLUSIONS—Within the limitations of electronic medical record data, results indicate OAU +NDE patients have more depression symptoms, greater treatment adherence and different comorbid psychiatric conditions compared to non-OAU+NDE, independent of pain. Overall OAU related depression is as severe as non-OAU related depression and repeated depression screening in chronic opioid therapy may be warranted for pain patients, regardless of pain severity.

Keywords

opioids; depression; retrospective cohort; epidemiology

INTRODUCTION

Evidence from studies with disparate patient cohorts from U.S. and Australia support the conclusion that prescription opioid analgesic use is associated with risk of new-depression episodes (NDE) (Scherrer et al., 2016a; Scherrer et al., 2016b; Scherrer et al., 2015; Scherrer et al., 2014; Smith et al., 2015). Among Veterans Health Administration (VA) patients who were free of depression and opioids for two years, compared to patients who used opioids for <90 days, the risk of new-onset depression (NDE) increased among patients who used for 91–180 days (HR=1.25; 95% CI, 1.05–1.46) and further increased among patients who used for >180 days (HR=1.51; 95%CI:1.31–1.74)(Scherrer et al., 2014). These findings were replicated in 3 separate samples of patients, one comprised of VA patients and two private sector patient samples (Scherrer et al., 2016b). Results revealed that longer use of prescription opioids, but not higher maximum morphine equivalent dose (MED), was associated with NDE in all three patient samples (Scherrer et al., 2016b). These effects remained after rigorous control for pain and comorbid physical and psychiatric disorders. In a separate analysis, codeine and oxycodone use of >30 days were associated with greater risk of NDE compared to patients taking only hydrocodone for >30 days (Scherrer et al., 2016a). In our studies of chronic opioid use and depression outcomes we used propensity scores and inverse probability of treatment weighting to balance factors associated with receipt of opioids thereby controlling for bias by indication. Thus this body of research on prescription opioid use and depression outcomes equated the distribution of pain conditions, pain scores and other confounding factors across different levels of opioid exposure.

Opioid-related NDE is characterized by onset in middle age (Scherrer et al., 2016b). Its etiology is likely multifactorial involving contributions from opioid related neuroanatomical changes (Upadhyay et al., 2010), opioid misuse (Howe and M.D., 2013), poor sleep (Onen et al., 2005), physical inactivity and social isolation and androgen deficiency (Kidner et al.,

2009). The characteristics of opioid-related NDE may be different from NDE occurring after stressful life events, following illicit drug abuse or familial NDE with early age of onset.

Whether opioid-associated NDE is similar to or different from NDE that occurs in the absence of OAU is unclear. Addressing gaps in the knowledge base is needed to inform clinical practice and public health policy. Establishing that the clinical features of NDE are similar in patients with and without prior long-term OAU contributes to the validity of studies demonstrating opioids lead to NDE and informs the importance of detecting and treating NDE in chronic OAU. Therefore, in the present study we sought to determine if psychiatric comorbidities, types of prescribed pharmacotherapies and severity of NDE differed between patients with >90 days of opioid use versus those without.

METHODS

Variables were created from VA electronic medical record data including ICD–9–CM diagnosis codes, prescription fill records, vital signs and demographic information. The source file was a random sample of 500,000 VA patients, age 18–80 that used the VA from 2000–2012. Patients were followed from Jan 1, 2002 to date of last outpatient VA encounter.

Eligible patients were cancer-free, HIV-free, had a visit in each of the two years prior to start of follow-up and were free of any opioid fills and depression diagnoses in that period (i.e. 2000 to 2001), and had at least one visit in the follow-up period (2002 to 2012). Because we were interested in characterizing severity of new-onset NDE and not predictors of NDE, we measured incident substance use and psychiatric comorbidities that occurred at the same time or after NDE. Therefore, eligible patients were free of psychiatric and substance use disorders before NDE. Patients whose opioid use began after NDE and patients without NDE in follow-up were excluded. Lastly, as previous work has shown that a new period of opioid use lasting >90 days is associated with the greatest risk of NDE, only the subset of opioid users whose initial use was >90 days were included in analysis, leaving a final analytic sample size of 4,758.

Measures

Opioid medications included a fill at any dose and duration for codeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, oxycodone, oxymorphone, morphine and pentazocine. Duration was computed by summing the “days’ supply” variable that measures the days required to exhaust the medication if taken at the maximum dose prescribed. Continuous use in days was defined as use from initial opioid fill to the first occurrence of either a gap in fills >30 days or NDE. Maximum daily morphine equivalent dose (MED) was defined as <50 mg, 50–100 mg, and >100 mg and calculated based on the maximum dose available on any given day from the date of initiation to end of continuous use. These doses were selected because they have been reported in our studies of incident depression and too few doses >100 mg were available for additional morphine thresholds.

Depression was defined by two or more outpatient diagnoses (ICD-9-CM codes = 296.2, 296.3 and 311) within the same 12-month period or at least one inpatient diagnosis for

depression. Previous studies support the high positive predictive value of the algorithm. (Frayne et al., 2010; Solberg et al., 2006)

For this study we created two exposure groups: 1) Patients who did not receive an opioid and developed depression (non-OAU+NDE) and 2) Patients who were >90 day opioid users and subsequently developed depression (OAU+NDE).

Outcomes

Outcomes included incident psychiatric and substance use comorbidities (e.g. PTSD, other anxiety, alcohol abuse/dependence, and other drug abuse/dependence) occurring on/after NDE. A summary variable (none, one, multiple) for number of comorbidities was also created.

Other outcomes included depression characteristics. Antidepressant medications included SSRI, SNRI, TCA, MAOI, and an "other" class. Acute phase antidepressant treatment (i.e. ≥12 weeks/84 days must have occurred 30 days before to 14 days after NDE, and duration was calculated until >30-day gap or last VA outpatient visit. Dual antidepressant treatment must have occurred on/after NDE and was positive if fills for two different classes of antidepressants overlapped by >30 days. Other characteristics included treatment with a mood stabilizer or atypical antipsychotic. Routine PHQ-9 administration for patients positive on the PHQ-2 was implemented in 2008 in the VA so maximum PHQ-9 score on or after NDE was available only for a subset (16%) of eligible patients.

Patient Characteristics

Detailed definitions of cohort characteristics have been reported in our prior studies of opioid use and depression (Scherrer et al., 2016b). Volume of healthcare utilization was defined as high if patients were in the top quartile of average number of clinic visits per month. We also included obesity, pain-related conditions, maximum pain score, and nicotine dependence defined as presence at any time from 2000 to 2012. Available baseline demographic variables included age, gender, race, marital status and access to private insurance vs. access to only VA insurance as a proxy for income and detection bias.

Analytic Approach

All analyses were computed using SAS v9.4 (SAS Institute, Cary, NC). Incident psychiatric comorbidities, depression characteristics, and other patient characteristics were compared between non-OAU+NDE and OAU+NDE groups using chi-square tests for categorical variables and independent samples t-tests for continuous variables. To assess whether differences between the groups were irrespective of pain-related variables, we balanced pain-related covariates across OAU and NDE groups using propensity scores. Propensity scores were computed using a binary logistic regression model predicting exposure group by pain-related conditions, with an optimal model selected for weighting data determined by optimizing model fit based on AIC value with a c-statistic of greater than 0.80. Using propensity scores, stabilized weights were calculated using inverse probability of treatment weighting (IPTW) approaches (Cole and Hernan, 2008; Curtis et al., 2007; Kilpatrick RD, 2013; Rosenbaum and Rubin, 1983). The stabilized weight is the marginal probability of

exposure divided by the propensity score. Chi-square tests and independent samples t-tests assessing the relationships of exposure group and outcomes controlling for pain-related conditions were repeated using IPTW.

RESULTS

Of eligible patients, 90.7% had non-OAU+NDE (n=4,314) and 9.3% had >90 days OAU +NDE (n=444). Among OAU+NDE patients, 12.6% reached a maximum MED of >100 mg. Unadjusted associations prior to IPTW to control for odds of pain diagnoses and pain score values are shown in Table 1. Prior to applying IPTW, we observed the OAU+NDE group had a higher cumulative incidence of PTSD (17.3% vs. 11.9%), opioid (4.3% vs. 0.5%) and other drug abuse/dependence (11.3% vs. 4.8%) compared to non-OAU+NDE. Also, OAU +NDE compared to non-OAU+NDE had a higher proportion of patients with at least 84 days of acute antidepressant treatment, dual antidepressant treatment, and mood stabilizer treatment as well as a higher maximum PHQ-9 score. Other anxiety, alcohol abuse/ dependence, and atypical antipsychotic treatment were unrelated to OAU-NDE group. All pain-related conditions, obesity, and nicotine abuse/dependence were also more prevalent among OAU+NDE compared to non-OAU+NDE. Finally, OAU+NDE compared to non-OAU+NDE were more likely to be younger, insured only by VA, and not married.

Table 2 shows IPTW-adjusted associations of substance use and other psychiatric disorders, and depression characteristics by OAU-NDE group, balanced across pain-related conditions and pain scores. All pain-related conditions balanced across groups with no significant difference in the prevalence of pain conditions and average maximum pain score between groups. The c-statistic for the PS model was 0.836 indicating the model predicted the likelihood of pain-related conditions well.

Weighted associations showed that 12.4% of the non-OAU+NDE and 15.8% of the OAU +NDE group developed PTSD at or after NDE (p=.040); however, onset of any other type of anxiety disorder was significantly more likely in the non-OAU+NDE vs. OAU+NDE group (p=0.014). Among substance use disorders, only opioid abuse/dependence was significantly associated with the two OAU groups and was significantly more common among the OAU +NDE group (1.5% vs. 0.6%).

Several depression characteristics significantly differed between groups. Compared to the non-OAU+NDE group, the OAU+NDE group had a higher prevalence of acute antidepressant treatment for at least 12 weeks, i.e. 84 days (62.4% v 50.1% p<0.0001) and higher maximum PHQ-9 score (12.9 v 10.7 p=0.012). Atypical antipsychotic use was more common among the non-OAU+NDE group (21.4% vs. 15.1%; p=0.002). Higher prevalence of nicotine dependence, high health services use, younger age, male gender, white race, access to VA healthcare coverage only and lower prevalence of currently married patients were significantly associated with being an OAU+NOD patient (p-value range: <0.005 to <0.0001). Dual antidepressant use and receipt of a mood stabilizer did not differ between groups.

DISCUSSION

In this large VA patient sample (n=4,758), NDE during chronic OAU, compared to NDE in the absence of opioid use, was significantly associated with more incident PTSD, significantly higher PHQ total scores, and greater likelihood of receiving adequate duration of antidepressant medication. Compared to NDE during chronic opioid treatment, developing depression in the absence of OAUs during our observation period was significantly associated with a greater incidence of a non-PTSD anxiety disorder and receipt of an atypical antipsychotic Our results are not due to pain-related conditions or maximum pain score as IPTW approaches balanced these covariates across the two groups.

Both substance induced depression vs. non-substance induced depression are risk factors for future depressive episodes (Nunes et al. 2006) and the present study extends this literature to prescription opioids and is consistent with prior literature in that both drug and non-drug related depression are, at a minimum, equally severe. Our results are consistent with a heroin treatment study which revealed persistent heroin use during methadone treatment predicted more severe depression symptoms (Wang et al., 2012), which is consistent with our prior study demonstrating longer OAU increased risk of transitioning from depression to treatment resistant depression (Scherrer et al., 2016c). Atypical antipsychotic prescriptions were significantly more prevalent among non-OAU+NDE patients. Post-hoc analysis revealed similar prevalence of bipolar in both OUA and non-OAU depression groups but schizophrenia was significantly more common among the non-OAU depression group (6.7% vs. 2.9%; $p<0.002$) in unadjusted analysis. Physician concerns about adherence among patients with schizophrenia may explain the observation that antipsychotics were more common in non-OAU+NDE patients.

Limitations

It is not possible to know whether opioids were taken as prescribed. Unmeasured confounding could be present and lifetime histories of depression and opioid use are not available. Therefore it is unknown if the two depression groups had different risk factors for depression prior to the start of the observation period. We balanced groups on only pain variables therefore it is possible that unbalanced variables such as younger age, lower prevalence of married patients and higher prevalence of nicotine dependence contributed to greater depression severity in the OAU+NOD group. The VA sample is predominately male and differs in socioeconomic status and clinical characteristics when compared to private sector patients; however, our prior studies in VA patients were replicated in private sector patient groups. Medical record data limits characterizing depression, and we are unable to determine if more comorbidity and higher PHQ-9 scores equated to impaired functioning and health-related quality of life.

Conclusions

Within the limits of available medical record data, the majority of evidence indicates NDE after >90 OAU is at least as severe, if not more severe, than NDE unrelated to OAU. This adds validity to prior conclusions that OAU is associated with new onset, clinically significant depression. Suicidality in chronic pain is likely explained by comorbid mental

illness (Cambell et al. 2016). Screening and treatment of depression in non-cancer pain patients may limit risk of persistent mood disorder and subsequent suicidal ideation. (e Opioid prescribing for pain management should be coupled with careful screening and treatment of emerging depression. Screening tools such as the PHQ-2 and PHQ-9 are readily available for routine use in pain management and can be programmed in electronic medical record systems to prompt screening prior to prescribing an opioid.

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Highlights

- Chronic prescription opioid use is associated with new depression episodes
- The etiology of depression following chronic opioid use likely differs from depression in non-opioid users
- We compared new depression episodes in patients with and without prior history of >90 days prescription opioid use
- New depression episodes following opioid use were characterized by more depression symptoms, greater PTSD comorbidity and greater 12 week acute phase antidepressant treatment

Table 1

Association of incident psychiatric comorbidity outcomes, depression severity indicators, and covariates with opioid and depression exposure groups (2002–2012) (n=4,758)

Outcomes /covariates, n(%)	Total (N=4,758)	Non-OAU + NDE (n=4,314)	OAU + NDE (n=444)	p-value
Incident Psychiatric Outcomes [a]				
PTSD	590 (12.4)	513 (11.9)	77 (17.3)	.001
Other anxiety [b]	732 (15.4)	654 (15.2)	78 (17.6)	.181
Alcohol abuse/dependence	504 (10.6)	449 (10.4)	55 (12.4)	.197
Opioid abuse/dependence	42 (0.9)	23 (0.5)	19 (4.3)	<.0001
Other drug abuse/dependence	255 (5.4)	205 (4.8)	50 (11.3)	<.0001
Number of outcomes				
None	3212 (67.5)	2948 (68.3)	264 (59.5)	
One	1108 (23.3)	998 (23.1)	110 (24.8)	<.0001
Multiple	438 (9.2)	368 (8.5)	70 (15.8)	
Depression characteristics				
Acute ADM treatment length (days) [c]				
None	1405 (29.5)	1314 (30.5)	91 (20.5)	
1–83	910 (19.1)	831 (19.3)	79 (17.8)	<.0001
84 +	2443 (51.4)	2169 (50.3)	274 (61.7)	
Dual ADM treatment [a, d]	594 (12.5)	505 (11.7)	89 (20.1)	<.0001
Atypical antipsychotic [a]	1013 (21.3)	912 (21.1)	101 (22.8)	.431
Mood stabilizer [a]	1487 (31.3)	1242 (28.8)	245 (55.2)	<.0001
Maximum PHQ-9 score, mean (sd) [a, e]	11.0 (7.5)	10.6 (7.4)	13.4 (7.5)	.001
PHQ-9 score available [a, e]	743 (15.6)	644 (14.9)	99 (22.3)	<.0001
OAU characteristics				
Maximum MED (mg) [f]				n/a
1–50	-	-	312 (70.3)	
51–100	-	-	76 (17.1)	
> 100	-	-	56 (12.6)	
Other Covariates [g]				
Obesity	1829 (38.4)	1615 (37.4)	214 (48.2)	<.0001
Nicotine abuse/dependence	1550 (23.6)	1317 (30.5)	233 (52.5)	<.0001
Arthritis	3460 (72.7)	3053 (70.8)	407 (91.7)	<.0001
Back pain	2566 (53.9)	2182 (50.6)	384 (86.5)	<.0001
Headaches	888 (18.7)	762 (17.7)	126 (28.4)	<.0001
Musculoskeletal pain	2303 (48.4)	1964 (45.5)	339 (76.4)	<.0001
Neuropathic pain	1273 (26.8)	1052 (24.4)	221 (49.8)	<.0001
Maximum pain score, mean (sd)	6.9 (2.9)	6.7 (2.9)	9.2 (1.3)	<.0001
High healthcare utilization	736 (15.5)	567 (13.1)	169 (38.1)	<.0001

Outcomes /covariates, n(%)	Total (N=4,758)	Non-OAU + NDE (n=4,314)	OAU + NDE (n=444)	p-value
Demographic Information				
Age, mean (sd)	55.4 (14.6)	55.9 (14.6)	50.4 (12.4)	<.0001
Gender: male	4264 (89.6)	3862 (89.5)	402 (90.5)	.503
Race: White	3929 (82.6)	3556 (82.4)	373 (84.0)	.403
Insurance: VA only	2817 (59.2)	2511 (58.2)	306 (68.9)	<.0001
Marital status: Married	2968 (62.4)	2717 (63.0)	251 (56.5)	.008

Note: OAU = Opioid analgesic use; NDE = New onset depression

[a]Must occur on or after date of new onset depression diagnosis

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

[c]Acute ADM Treatment positive if within 30 days before and 14 days after depression diagnosis

[d]Dual ADM is positive if have two or more antidepressants overlapping by at least 31 days

[e]PHQ-9 scores available only on a subsample of patients. Availability distribution compared between groups.

[f]For opioid use patients only

[g]Covariates could have occurred at any point from 2000–2012

Table 2

Adjusted associations of incident psychiatric outcomes and depression severity indicators across opioid depression groups. Balanced on pain-related variables using inverse probability of OAU treatment weighting. (2002–2012) (n=4,758)

Outcome /covariates, weighted %	Non-OAU + NOD (n=4,314)	OAU + NOD (n=444)	p-value
Incident Psychiatric Outcomes [a]			
PTSD	12.4	15.8	.040
Other anxiety [b]	15.5	11.1	.014
Alcohol abuse/dependence	10.6	8.9	.265
Opioid abuse/dependence	0.6	1.5	.023
Other drug abuse/dependence	5.0	4.8	.821
Number of outcomes			
None	67.5	70.0	
One	23.6	20.3	.264
Multiple	8.9	9.7	
Depression characteristics			
Acute ADM treatment length (days) [c]			
None	30.6	15.0	
1–83	19.4	22.7	<.0001
84 +	50.1	62.4	
Dual ADM treatment [a, d]	11.9	11.7	.894
Atypical antipsychotic [a]	21.4	15.1	.002
Mood stabilizer [a]	30.2	34.5	.063
Maximum PHQ-9 score, mean (sd) [a, e]	10.7 (7.5)	12.9 (6.4)	.012
Other Covariates [g]			
Obesity	38.2	40.2	.417
Nicotine abuse/dependence	31.0	49.1	<.0001
High healthcare utilization	14.0	21.8	<.0001
Demographic Information			
Age, mean (sd)	55.6 (14.60	52.6 (12.1)	<.0001
Gender: male	89.2	93.2	.009
Race: White	81.8	89.0	.0001
Insurance: VA only	58.7	69.6	<.0001
Marital status: Married	37.2	30.6	.006
Balanced variables included in PS model [f]			
Arthritis	72.8	74.2	.505
Back pain	53.9	54.3	.889
Headaches	18.7	18.5	.938

Outcome /covariates, weighted %	Non-OAU + NOD (n=4,314)	OAU + NOD (n=444)	p-value
Musculoskeletal pain	48.4	49.5	.660
Neuropathic pain	26.7	27.6	.702
Maximum pain score, mean (sd)	6.9 (2.9)	7.1 (2.6)	.240

Note: OAU = Opioid analgesic use; NOD = New onset depression; PS=Propensity score

[a] Must occur on or after date of new onset depression diagnosis

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

[c] Acute ADM Treatment positive if within 30 days before and 14 days after depression diagnosis

[d] Dual ADM is positive if have two or more antidepressants overlapping by at least 31 days

[e] PHQ-9 scores available only on a subsample of patients. Availability distribution compared between groups.

[f] Assessment of balance for covariates included in PS model. Propensity model c-stat=0.836

[g] Covariates could have occurred at any point from 2000–2012