Journal of Affective Disorders 210 (2017) 125–129

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Brief report

Characteristics of new depression diagnoses in patients with and without prior chronic opioid use

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ARTICLE INFO

Keywords:
Opioids
Depression
Retrospective cohort
Epidemiology

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 analgesic use (OAU).

Methods: VA patients were classified into two groups, those who did not receive an opioid and developed depression (non-OAU+NDE, n=4314) 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 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=.012), more incident PTSD (p=.04) and opioid abuse/dependence and were more likely to receive 12 weeks of antidepressant treatment (p < .0001). Last, non-OAU+NDE were more likely to have incident diagnoses for any other anxiety disorder (p=.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.

1. 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., 2014, 2015, 2016a, 2016b; 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 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

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http://dx.doi.org/10.1016/j.jad.2016.12.027
Received 12 August 2016; Received in revised form 28 October 2016; Accepted 17 December 2016
Available online 21 December 2016

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 analgesic use (OAU) and NDE 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, 2013), poor sleep (Onen et al., 2005), physical inactivity and social isolation and androgen deficiency (Kidner et al., 2009; Smith and Elliot, 2012). 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 OAU versus those without.

2. 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 to 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. 2000–2001), and had at least one visit in the follow-up period 2002–2012). 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 OAU 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 4758.

2.1. 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 d opioid users and subsequently developed depression (OAU+NDE).

2.2. 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.

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.

2.3. 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 .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 et al., 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.