Preventive Medicine 91 (2016) 110–116

Contents lists available at ScienceDirect

Preventive Medicine

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

The influence of prescription opioid use duration and dose on development of treatment resistant depression

Jeffrey F. Scherrer PhD [a,b,*], Joanne Salas MPH [a,b], Mark D. Sullivan MD [c], F. David Schneider MD, MSPH [a], Kathleen K. Bucholz PhD [d], Thomas Burroughs PhD [e], Laurel Copeland PhD [f,g,h], Brian Ahmedani PhD [i], Patrick J. Lustman PhD [d,j]

[a] Department of Family and Community Medicine, Saint Louis University School of Medicine, St. Louis, MO 63104, United States
[b] Harry S. Truman Veterans Administration Medical Center, Columbia, MO, United States
[c] Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle, WA, United States
[d] Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, United States
[e] Saint Louis University Center for Outcomes Research, St. Louis, MO, United States
[f] Center for Applied Health Research, Baylor Scott & White Health, Central Texas Veterans Health Care System, United States
[g] Texas A&M Health Science Center, Bryan, TX, United States
[h] UT Health Science Center, San Antonio, TX, United States
[i] Henry Ford Health System, Center for Health Policy and Health Services Research, Department of Psychiatry, United States
[j] The Bell Street Clinic, VA St. Louis Health Care System – John Cochran Division, St. Louis, MO, United States

ARTICLE INFO

Article history:
Received 2 March 2016
Received in revised form 1 June 2016
Accepted 1 August 2016
Available online 3 August 2016

Keywords:
Opioids
Pain
Depression
Epidemiology

ABSTRACT

Long-term prescription opioid use is associated both with new-onset and recurrence of depression. Whether chronic opioid use interferes with depression management has not been reported, therefore we determined whether patients' longer duration of opioid use and higher opioid dose are associated with new-onset treatment resistant depression (TRD) after controlling for confounding from pain and other variables.

Data was obtained from Veteran Health Administration (VHA) de-identified patient medical records. We used a retrospective cohort design from 2000–2012. Eligible subjects (n = 6169) were 18–80 years of age, free of cancer and HIV, diagnosed with depression and opioid-free for the 24-month interval prior to the observation period. Duration of a new prescription for opioid analgesic was categorized as 1–30 days, 31–90 days and >90 days. Morphine-equivalent dose (MED) during follow-up categorized as ≤50 mg versus >50 mg per day. Pain and other sources of confounding were controlled by propensity scores and inverse probability of treatment weighting. Cox proportional hazard models were computed to estimate the association between duration and dose of opioid and onset of TRD.

After controlling for confounding by weighting data, opioid use for 31–90 days and for >90 days, compared to 1–30 days, was significantly associated with new onset TRD (HR = 1.25; 95% CI: 1.09-1.45 and HR = 1.52; 95% CI: 1.32-1.74, respectively). MED was not associated with new onset TRD.

The risk of developing TRD increased as time spent on opioid analgesics increased. Long-term opioid treatment of chronic pain may interfere with treatment of depression.

1. Introduction

The opioid epidemic in the United States remains unmitigated with annual prescriptions of opioid medications exceeding 240 million in each of years 2009–2013 (Dart et al., 2015). Most research on the opioid epidemic is focused on risk of abuse, overdose and death (Dart et al., 2015). An emerging literature now indicates risk of new onset and recurrent depression to be among the adverse effects of opioids (Scherrer et al., 2014, 2015, 2016a; Smith et al., 2015). This is particularly concerning because short term improvements in depression and pain following opioid therapy may lead to dose increases or continued opioid use which increases risk of adverse outcomes, including depression (Howe and S, 2014). However, the possibility that long-term opioid use leads to depression complicates pain management in unforeseen ways. Widespread exposure to long-term opioid therapy in the U.S. (Informatics IIfH, 2011) portends a potential increase in what may have been an otherwise avoidable depression.

Patients with pain and depression, versus those without depression, are at increased risk for receiving opioid prescriptions, using for longer periods and at higher doses, and abusing these medications (Grattan

* Corresponding author at: Family and Community Medicine, Saint Louis University School of Medicine, 1402 N. Grand Blvd, St. Louis, MO 63104, United States.
E-mail address: scherrjf@slu.edu (J.F. Scherrer).

http://dx.doi.org/10.1016/j.ypmed.2016.08.003
0091-7435/

et al., 2012; Sullivan, 2010; Sullivan et al., 2006). Over the past 2 years, we have shown that opioid therapy is not only predicted by depression but independently increases the risk of new onset depression (Scherrer et al., 2014, 2016a). Longer term use, but not higher dose, is associated with 35–100% increased risk of new-onset depression (Scherrer et al., 2016a), and opioid exposure is related to a 100% increased risk of depression recurrence (Scherrer et al., in review).

Prescription opioids and pain may also contribute to treatment resistant depression (TRD). The literature on pain and TRD is sparse. In a study designed to characterize comorbidity in TRD and non-TRD claims data, muscle pain, joint pain, headache/migraine and back pain were twice as prevalent among patients with TRD than those without TRD (Kubitz et al., 2013). Past studies provide evidence for a pain, opioid, and TRD association, but to our knowledge, no studies have investigated whether longer term use or higher opioid dose leads to TRD among patients with depression and non-cancer pain.

To determine whether long-term opioid use and/or higher opioid dose contributes to transitioning from depression to TRD, we used medical record data from a retrospective cohort of Veterans Health Administration (VA) patients. After controlling for confounding due to pain, we computed the association between increasing duration of opioid use and TRD, controlling for dose; and modeled the association between higher dose and TRD, controlling for duration.

2. Methods

Patient data were obtained from administrative extracts of the VA electronic medical record. Medical record data contain all diagnoses, medications, laboratory results, type of clinics utilized, provider type, and vital signs that are collected during routine care. The data is complete in terms of capturing elements recorded during routine care. Care received outside the VA may not be included in data. We adjust for access to non-VA healthcare to account this potential bias. Our records contained clinic encounters from January 1, 2000 through December 31, 2012, ICD-9-CM diagnoses, prescription records, vital signs and demographics. This project was approved by the VA and Saint Louis University Institutional Review Boards.

2.1. Eligibility criteria

As shown in Fig. 1, a random sample of 500,000 patients aged 18-80 years of age at baseline was restricted to patients free of ICD-9-CM codes for cancer or HIV. Patients were required to be regular users of VA care defined by having annual visits in 2000 and 2001. To be informative for this study, eligible patients must have had at least one visit during the follow-up period 2002–2012. All patients had a diagnosis of depression and were free of opioid prescriptions in the two years prior to the start of follow-up, 01/01/2002. We required patients to have depression at start of follow-up because this study is designed to determine if opioid use in patients with depression leads to TRD. At the start of follow-up, 47% had a current prescription for an antidepressant and 93% had filled an antidepressant prescription at some point in the prior two years. During the follow-up period, incident opioid use could occur any time prior to onset of TRD, defined below. A total of 6,223 patients met all eligibility criteria; after removing 54 patients with missing covariate data, our final analytic sample consisted of 6169 patients.

2.2. Opioid exposure

A prescription for any dose and duration of the following medications were included: codeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, morphine, oxycodone, oxymorphone, and pentazocine. The duration of continuous use was counted by summing the days-supply of pills required to exhaust the medication if taken at the maximum dose prescribed between the end of one prescription and the start of another. Use was considered continuous if there was no gap of >30 days between fills. Duration of use was computed from date of initial opioid fill until end of follow-up or the start of a >30 day gap.

We used the same duration and dose exposure categories from our previous study of opioids and new onset depression (Scherrer et al., 2016a) to allow us to compare results with the present study. We classified patients into three mutually exclusive categories: 1–30 days, 31–90 and >90 days continuous supply starting from their incident prescription.

Morphine equivalent dose (MED) was computed using standard morphine equivalent conversion tables that express the specific opioid medication in terms of equivalent morphine content (Hygiene NYCDoHaM). For example, 1 mg of oral oxycodone is equal to 1.5 mg of morphine. We assigned patients to a binary variable indicating a daily MED >50 mg or ≤50 mg using the total opioid available to patients on the last day before the end of follow-up or before a >30-day gap.

2.3. Treatment-resistant depression (TRD)

Depression was defined by the presence of two outpatient or one inpatient ICD-9-CM code for depression in the same 12 months, an algorithm for prevalent depression that has excellent agreement compared to written medical records (Solberg et al., 2006). Definitions for TRD vary. These include a failure to respond to one antidepressant trial at adequate dose and duration (Fava and Davidson, 1996), simultaneous prescription of more than one antidepressant, augmentation with atypical antipsychotics or MAOIs and electroconvulsive therapy (Thase and Rush, 1997). We followed a definition previously employed in retrospective cohort studies involving medical records (Corey-Lisle et al., 2002; Scherrer et al., 2012). Patients were defined as having TRD if any of the following were recorded in the medical record: a) electroconvulsive therapy, b) MAOI prescription, c) two or more antidepressants (any SSRI, SNRI, TCA or "other" non-MAOI antidepressant) at the same time overlapping by at least 31 days, or d) augmentation therapy (i.e. prescription of a mood stabilizing or atypical antipsychotic after antidepressant treatment).

2.4. Confounders

Variables associated with pain, opioid exposure and depression were selected as potential confounders to be used in propensity score models described below. Variables included measures of pain, psychiatric and physical comorbidities, other prescription medication, health care utilization and demographics. Non-cancer pain was measured by 900 conditions for which pain could be severe enough to call for an opioid prescription (Seal et al., 2012), and diagnoses were collapsed into five pain categories: arthritis pain, back pain, headache, musculoskeletal and neuropathic pain. The ICD-9-CM codes used for each category are reported in the supplementary material of a previous study (Scherrer et al., 2014). The average maximum pain score reported any time prior to end of follow-up was obtained from patient-reported pain on a scale from 0-10. Pain scores are routinely obtained in VA care during collection of vital signs.

Psychiatric disorders were included as confounders due to evidence that they are often comorbid with depression, pain, and opioid use (Howe and S, 2014). We used ICD-9-CM codes to identify attention deficit disorder, antisocial personality disorder, posttraumatic stress disorder and any other anxiety disorder as a composite indicator of any diagnoses for panic disorder, generalized anxiety disorder, social phobia, obsessive compulsive disorder or anxiety disorder NOS. Substance use disorder included alcohol abuse/dependence and illicit drug abuse/dependence, including opioid abuse/dependence. Data on substance use disorders and psychiatric disorders are obtained from ICD-9-CM codes which could have been assigned in specialty mental health service lines or in primary care and other settings. Tobacco use is obtained from either record indicator of smoking history or diagnoses of