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FACTORS INFLUENCING LONG-TERM OPIOID USE AMONG OPIOID NAÏVE PATIENTS: AN EXAMINATION OF INITIAL PRESCRIPTION CHARACTERISTICS AND PAIN ETIOLOGIES

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Abstract

The relationships of characteristics of the initial opioid prescription and pain etiology with the probability of opioid discontinuation were explored in this retrospective cohort study using health insurance claims data from a nationally representative database of commercially insured patients in the U.S. We identified 1,353,902 persons aged ≥14 with no history of cancer or substance abuse, with new opioid use episodes and categorized them into 11 mutually exclusive pain etiologies. Cox Proportional Hazards models were estimated to identify factors associated with time to opioid discontinuation. After accounting for losses to follow-up, the probability of continued opioid use at one year was 5.3% across all subjects. Patients with chronic pain had the highest probability for continued opioid use followed by patients with inpatient admissions. Patients prescribed doses above 90 morphine milligram equivalents (HR=0.91, CI: 0.91–0.92); initiated on tramadol (HR=0.90, CI: 0.89–0.91) or long-acting opioids (HR=0.78, CI: 0.75–0.80); were less likely to discontinue opioids. Increasing days' supply of the first prescription was consistently associated with a lower likelihood of opioid discontinuation (HRs, CIs: 3–4 days' supply = 0.70, 0.70–0.71; 5–7 days' supply = 0.48, 0.47–0.48; 8–10 days' supply = 0.37, 0.37–0.38; 11–14 days' supply = 0.32, 0.31–0.33; 15–21 days' supply = 0.29, 0.28– 0.29; ≥22 days supplied = 0.20, 0.19–0.20). The direction of this relationship was consistent across all pain etiologies. Clinicians should initiate patients with the lowest supply of opioids to mitigate unintentional long term opioid use.

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Keywords

Chronic pain; Opioids; Long-term; Discontinuation; First prescription

INTRODUCTION

In 2012, approximately 126 million US adults suffered from pain with nearly 50 million of them reporting chronic pain.[24] Opioids are one of the most commonly prescribed drugs for alleviating or controlling pain with almost 20% of the patients presenting in a physician's office with noncancer pain being prescribed an opioid.[7] Insufficient evidence exists demonstrating the benefits of chronic opioid therapy for pain management, but several studies show greater risks of abuse, overdose, and fracture with chronic opioid use.[5] Despite these risks, the overall per capita opioid prescribing rate increased by 7.3% from 2007 – 2012, and in 2012 alone, almost 259 million opioid prescriptions were dispensed.[20,26] Similarly, opioid-related overdoses have increased over the last two decades.[33]

U.S. state and national governments, along with other stake holders, have taken active measures to curtail the 'opioid epidemic'. In May 2016 the House passed package bills to prevent opioid overdose, increase availability of naloxone and improve substance abuse disorder treatments.[19] The Centers for Disease Control and Prevention (CDC) published a guideline in March 2016 aimed at improving opioid prescribing practices by establishing standards for prescribing opioids to patients with non-cancer pain conditions.[9] Because chronic opioid use often begins with opioid prescriptions for acute conditions, this guideline offers recommendations about duration of initial opioid therapy, type of opioid with which to initiate therapy (long acting vs short acting) and daily dosing thresholds.[9,13] However, these recommendations were based on clinical impressions that lacked empirical support. Recently, two studies examined the influences of the initial prescribing characteristics on long term opioid use, however both of these studies lacked measures of pain etiology which would almost certainly influence the likelihood of long term opioid use.[8,30] The present study attempts to overcome this limitation and explores the association between characteristics of the first opioid prescription and the probability of opioid discontinuation among opioid naïve patients, controlling for patient level factors and the pain etiology for which an opioid was prescribed.

METHODS

DATA SOURCE

We used a random 10% sample of patients from the Intercontinental Marketing Services (IMS) Lifelink+ database from 2006–2015. IMS Lifelink+ is a nationally representative health insurance claims database of commercially insured patients in U.S. and includes their enrollment information and inpatient, outpatient and pharmacy claims. The demographic variables in the enrollment file include age, sex, geographic region and type of payer (Medicare, Medicaid, commercial insurance, etc). The inpatient and outpatient file contain diagnosis information, procedure codes and the date of service for all insurance claims. The prescription file includes retail as well as mail order prescription records.

STUDY SUBJECTS

All patients with the following characteristics were included: (i) at least one opioid prescription between June 1st 2006 and December 31st 2014, (ii) at least 6 months of continuous pharmacy and medical enrollment without an opioid prescription prior to their first opioid prescription, (iii) be at least 14 years of age when dispensed their first opioid.

Patients who had an inpatient or outpatient claim with any cancer (except non-melanoma skin cancer) or substance abuse disorder diagnosis in the 6 months preceding their first opioid prescription were excluded. Patients whose first prescription was Suboxone (buprenorphine-naloxone combination), which is indicated for substance abuse disorder treatment, were also excluded. We excluded all patients whose demographic information including type of payer, age, sex, and geographic region were missing or invalid.

PATIENT FOLLOWUP AND OPIOID DISCOUNTINUATION

Patients were followed from the date of their first prescription until they either lost enrollment, the study end date (July 1st 2015), or they discontinued opioids, whichever came first. Opioid discontinuation was defined as at least 180 continuous days without opioid use from the end date of the last opioid prescription. The date of discontinuation was defined as the end date of the last opioid prescription prior to 180 opioid-free days. Previous studies have used this definition and show that modification of this definition does not have any impact on the relation between characteristics of the first opioid prescription and likelihood of opioid continuation.[21,30] Patients who continued opioid use for ≥12 months were those who did not meet our definition of opioid discontinuation prior to the 12 month period following their first opioid prescription.

INDICATION FOR OPIOID PRESCRIPTION

The inpatient and outpatient claims preceding the opioid prescription were analyzed to determine the most likely pain etiology for receiving the opioid. All patients were categorized into 11 mutually exclusive categories based on their pain etiology resulting in the opioid prescriptions. In cases where a patient had more than one pain etiology the following hierarchy was used: a. Trauma and Surgery b. Trauma c. Surgery d. Burn e. Childbirth f. Dental procedure g. Chronic pain conditions (headache, back/neck pain, arthritis/joint pain, neuropathic pain, and fibromyalgia) h. Other pain conditions (chest pain, abdominal pain, others) i. Other inpatient admission j. Other Emergency Department visit (not resulting in a hospitalization). Chronic pain conditions were assessed in the prior six months and all other etiologies were assessed in the week prior including the date they received an opioid. If a patient did not fall into any of these categories they were categorized as “Unknown Etiology”. The diagnosis and procedure codes used to identify each indication are listed in Supplementary Appendix Table 1.

CHARACTERISITCS OF THE FIRST OPIOID PRESCRIPTION

We calculated the days’ supply and average daily dose of the first opioid prescription for each patient. The days’ supply of the first prescription was categorized into the following 7 categories: 1.) 1–2 days; 2.) 3–4 days; 3.) 5–7 days; 4.) 8–10 days; 5.) 11–14 days; 6.) 15–21 days 7.) ≥22 days. Categories were chosen based on the most likely days’ supply increments

a physician was expected to prescribe. Average daily dose was calculated as total strength of the prescription expressed in morphine milligram equivalents (MME) divided by the days' supply of the first prescription. If a patient had multiple prescriptions on the first day, the daily dose in MME for all the prescriptions on the index date were summed and divided by the days' supply of the longest lasting prescription. We then categorized the average daily dose into four categories: 0–24 MME, 25–49 MME, 50–89 MME and ≥90 MME, with the higher dosing cut points being derived from the CDC guidelines on opioid use in chronic pain.[9]

We categorized patients into 6 mutually exclusive categories based on the choice of their first opioid prescription: 1) Long-Acting (Buprenorphine, Fentanyl, Morphine, Oxycodone, Oxymorphone and Tapentadol); 2) Other Schedule II Short Acting (Fentanyl, Hydromorphone, Levorphanol, Meperidine, Methadone, Morphine, Oxymorphone and Tapentadol); 3) Oxycodone Short-Acting; 4) Hydrocodone Short-Acting; 5) Schedule III–IV and Nalbuphine (Codeine, Dihydrocodeine, Butorphanol, Nalbuphine, Pentazocine and Propoxyphene); 6) Tramadol. If multiple opioid prescriptions were filled on the index date, the following hierarchy was used to assign subjects: 1) Long-Acting; 2) Other Schedule II Short Acting; 3) Oxycodone Short-Acting; 4) Hydrocodone Short-Acting; 5) Schedule III–IV and Nalbuphine; 6) Tramadol.

COVARIATES

We gathered data on patient level factors which might influence duration of opioid use. The covariates included: age-group (14–17, 18–21, 22–30, 31–44, 45–54, 55–64 and ≥65), gender, region of residence (Midwest, South, East and West), payer type (Commercial, Medicaid, Medicare and Self-insured), whether they had a muscle relaxant or hypnotic (benzodiazepine or non[15] benzodiazepine GABA receptor modulator) prescription or a diagnosis for a mental health condition (mood disorder, personality disorder, adjustment disorder, anxiety disorder and miscellaneous disorders) in the 6 months preceding their first opioid prescription and the year in which they initiated opioid use (2006–2014). The Clinical Classification Software and Generic Product Identifier codes used to define each mental health condition and prescriptions for hypnotics and muscle relaxants are listed in Supplementary Appendix Table 2.

ANALYSIS

We characterized patients who continued opioid use for ≥365 days versus those who discontinued before 365 days by comparing the covariates described earlier, pain etiologies for the first opioid prescription and characteristics of the first opioid prescription between the two groups. Kaplan Meier curves were used to calculate the median time to discontinuation and the probability of continued opioid use at one and three years for each of the pain etiologies separately. We visually depicted the curves for the first one year of opioid use for 5 indications: Surgery, Trauma, Other pain, Chronic Pain and Childbirth.

We then developed multivariate cox-proportional hazards regressions to determine the influence of the first opioid prescription characteristics (days' supply, average daily dose and

choice of first prescription) on the likelihood of opioid discontinuation. We controlled for all the other patient level covariates as well as the pain etiology for the first opioid prescription.

We interacted the pain etiology with days' supply to determine the effect of days' supply on likelihood of opioid discontinuation by pain etiology. Since prescribers are most likely to intend long-term opioid use among patients with a chronic pain condition, we stratified the population based on whether or not they had any chronic pain diagnosis in the six months prior to their first opioid prescription, irrespective of any other pain etiology. Persons without a diagnosis for chronic pain in the 6 month prior period were assumed to be treating acute pain. We then determined the influence of the first opioid prescription characteristics on the likelihood of opioid discontinuation (controlling for all the factors previously mentioned) in the two sub-groups separately. As a sensitivity analysis to ensure these patients were new opioid users, we modified our inclusion criteria by defining an opioid naïve patient as one who had at least 12 months of continuous pharmacy and medical enrollment without an opioid prescription prior to their first opioid prescription. All the analysis were performed using SAS 9.3. The study was reviewed by the University of Arkansas for Medical Sciences Institutional Review Board (protocol #205743) and was determined to not be human subjects' research.

RESULTS

We identified a total of 1,353,902 cancer-free opioid naïve patients aged ≥14 years who filled an opioid prescription between June 1st, 2006 and 31st December, 2014 and were cumulatively followed for 782,400.6 years (mean = 210.9 days and standard deviation = 144.7 days). The application of the inclusion and exclusion criteria are described in Figure 1. A total of 1,119,345 patients met our criteria for opioid discontinuation and the rest (234,557) were censored either due to loss of enrollment or study end. Of the 1.3 million persons, 993,935 subjects were enrolled for at least one year after their first opioid prescription and of those enrolled for at least one year, 33,019 (3.32%) continued opioid use for ≥365 days. Based on the Kaplan Meier estimate (accounting for patient censoring) the probability of continuing opioid use for ≥365 days in the overall sample was 5.3%. Patients who continued opioids for at least one year were more likely to be older, female, residing in the south, receive prescription(s) for hypnotics or muscle relaxants or have a diagnosis for mood, anxiety or miscellaneous mental health disorders in the 6 months preceding the first opioid prescription (Table 1.). Patients who continued opioid use for ≥365 days were also more likely to be prescribed longer, higher dose prescriptions and had a higher likelihood of being initiated with long-acting opioids or tramadol.

In our population, the most common indication for receiving an opioid was a chronic pain condition (25.14%) followed by, surgery (13.26%), trauma (12.50%) and other pain conditions (6.41%) (Table 2.). We were unable to identify a pain etiology for approximately one-third of the patients with a new opioid prescription (34.95%). The probability of continued long-term use from the Kaplan Meier statistic (≥365 days or ≥1095 days) was the highest for chronic non-cancer pain (10.07% and 5.11%) followed by other inpatient admission (6.60% and 2.91%) and trauma (3.96% and 1.71%) and lowest for childbirth (1.33% and 0.45%) (Figure 2, Table 2.).

The hazard ratios controlling for pain etiology and other patient level factors are found in Table 3. Hazard ratios less than 1 indicate a lower likelihood of opioid discontinuation or stated another way, higher likelihood of continued opioid use. We found that patients who were prescribed higher average daily dosewere less likely to discontinue opioids; 25–49 MME (HR: 0.97, CI: 0.96–0.97), 50–89MME (HR: 0.95, CI: 0.94–0.95), and ≥90 MME (HR: 0.91, CI: 0.91–0.92) compared to patients prescribed 0–24 MME. Patients initiated with long-acting opioids (HR=0.79, CI: 0.77–0.82) or tramadol (HR=0.89, CI: 0.89–0.90) had a lower likelihood of opioid discontinuation compared to those initiated with schedule III or IV opioids or nalbuphine. Increases in the days supplied of the initial opioid prescription consistently increased the time to opioid discontinuation. Compared to opioids prescribed for 2 days or less, being prescribed 3–4 days (HR=0.70, CI: 0.70–0.71) decreased the chances of opioid discontinuation by 30% while being prescribed 22 or more days had the greatest impact on likelihood of opioid discontinuation (HR=0.20, CI: 0.19–0.20) (Table 3. And Supplementary Appendix Table 3.).

When stratified by those with and without chronic pain, similar relationships between characteristics of first opioid prescription and likelihood of opioid discontinuation were observed. (Table 3 and Supplementary Appendix Tables 4 and 5). The interaction between days' supply categories and pain etiologies yielded similar results as our base case analysis, with the days' supply having a stepwise impact on the likelihood of opioid discontinuation irrespective of pain etiology for the first opioid prescription (Figure 3.). A 3–4 days' supply (compared to 1–2 days' supply) reduced the likelihood of opioid discontinuation by 41% to 23%, and 22 or more days supplied reduced the likelihood of discontinuation by 67% to 80% (Figure 3.).

When we required patients to be opioid naïve for 12 months the sample decreased to 955,371. The relationships between the characteristics of the first opioid prescription and the likelihood of opioid discontinuation were similar using this sample compared to the original definition of an opioid naïve patient (Table 3. and Supplementary Appendix Table 6.).

DISCUSSION

This is the first study to examine the characteristics of initial opioid prescribing among opioid-naïve patients while controlling for the pain etiology resulting in the opioid use. Similar to our previous report, we found that the days' supply of the first prescription is a major prognostic factor for continued opioid use after controlling for pain types, patient demographics, and mental disorders.[30] The days' supply demonstrated a clear "dose-response" relationship with the likelihood of opioid discontinuation. Persons initially prescribed 5–7 days of opioids are twice as likely and persons prescribed 11–14 days are three times as likely to continue opioids compared to persons prescribed 2 days or less. This dose response relationship between initial days supplied and was consistently found when we conducted subgroup analyses of chronic and acute pain groups. Prior to these multivariate and subgroup analyses, it was unclear the extent to which persons with chronic pain were more likely to be prescribed higher quantities with more days supplied of opioids and thus confound previously reported relationships between days supplied and duration.[8,30] The results of the multivariate models and in particular the models including the interaction

between pain etiology and days' supply indicate that the days supplied independently contributes to the longer durations of opioids and this effect is not meaningfully modified by pain etiology (Figure 3.). For this reason, clinicians need to be aware that the days supplied of an initial opioid prescription may be the single most modifiable factor prognostic for continued opioid use when prescribing opioids.

There are also policy implications with our findings. Eight states, primarily in the northeast U.S., have enacted legislation limiting the supply of initial opioid prescriptions.[32] Most of these policies limit the days' supply of an initial opioid to 7 days or less. We are not aware of specific policy analyses looking at the effect of implementing these opioid limits on long term use and other opioid related outcomes, however these data along with our previous analyses[30] suggest that these policies may have the potential to decrease long term opioid use. Until policy analyses of these opioid limits are conducted, our data could cautiously be used by other states to support implementing similar opioid limit policies.

This paper hypothesized that the pain etiology is a major predictor of long-term opioid use because the pain etiology is a major contributor to the treatment plan. For example, patients newly diagnosed with chronic, non-cancer pain are more likely to begin opioid therapy with the understanding that the goal may be long-term use whereas those prescribed opioids for a dental procedure or trauma are unlikely to have long-term opioid use in the treatment plan. Clinically, back pain has been found to be strongly associated with long-term opioid use in different patient populations.[16–18] Several other chronic pain conditions have also been found to be associated with long-term opioid use including neck pain, arthritis, and headaches.[12] As expected, our data show that chronic pain diagnosis had the highest probability for continued opioid use at 1 and 3 years and has the longest median time to discontinuation. Initial opioid use after an inpatient admission had the next highest probability for continued opioid use at 1 and 3 years. Previous studies have found that opioid prescribing upon discharge from an inpatient admission is strongly associated with opioid use either 6 months or 1 year post discharge, even among opioid-naïve patients.[3,14] The data also show that for other conditions such as trauma, surgery, and dental procedures, long term opioid use is not common. According to the unadjusted Kaplan Meier estimates, on average, fewer than 6% of persons with these pain etiologies were on opioids one year later.

Persons with mood, anxiety, and other mental disorders, hypnotic (benzodiazepines and non-benzodiazepine GABA receptor modulators) use, or musculoskeletal relaxant use in the 6 months prior to initial opioid use used opioids longer (Table 3.). This is a similar finding to previous reports in many patient populations including Medicaid, VA, and other commercially insured patients.[2,10,11] Also, the majority of opioid users are between the ages of 31–64 years of age with the highest percentage being from the South (Table 3.).

Consistent with previous literature, increasing age, being female, being from the South or the West, or having public insurance (especially Medicaid) was associated with a lower likelihood of opioid discontinuation.[4,22,23] We also found that patients with mental health disorders are more likely to be long-term opioid users as compared to those without mental health disorders which is corroborated by other studies.[10,11,28,29] and we found that hypnotics and skeletal muscle relaxants were also associated with longer opioid durations

and co-prescribing these drugs have also been shown to be associated with opioid use.[6,15,25] Our analyses show that the likelihood of opioid discontinuation is slowly increasing with time (HR=1.02 in 2007 vs HR=1.11 in 2014) which suggests that prescribers may be becoming more aware of the harms of long-term opioid use.

Regardless of indication, patients with initial use of long-acting opioid formulations or tramadol had the lowest probability of opioid discontinuation. These findings suggest that prescribers may be using tramadol for long-term pain management since it is thought to be a safer alternative to other opioids due to its more selective affinity for μ-opioid receptors. With sparse data on long-term safety and efficacy of tramadol available and recent studies showing tramadol might not be as benign in abuse potential as previously thought[1,31] it is unclear if and to what extent it confers a lower risk than other opioids. Though the risks of long term use were lowest for Schedule III/IV opioids or nalbuphine, only subtle differences existed between schedule III/IV opioids and short acting hydrocodone (HR=0.95, CI: 0.95–0.96) and oxycodone formulations (HR=0.97, CI: 0.96–0.98) and it appears that either of these opioid products confer similar, though not identical, risks of long term use.

These results must be interpreted in light of several limitations. Inpatient, outpatient, and prescription claims paid for out of pockets are not collected in our claims database; however, our inclusion criteria require patients to have at least 6 months of continuous medical and pharmacy enrollment prior to their initial opioid. This criteria assures that patients had financial incentives to utilize their pharmacy benefits and have their prescriptions recorded. Secondly, this analysis does not incorporate the effect titration of opioid dose might have on predicting opioid discontinuation. Third, it is not possible to know which long term use is an outgrowth of acute use or intentional chronic opioid use. This analysis did control for pain etiology which at least partially addresses intentional versus unintentional use as a larger proportion of chronic pain patients might be intentionally initiating chronic use. Fourth, pain intensity is not captured in this database, which is likely also to be a predictor of chronic opioid use as are factors like smoking status and alcohol use which were also not available in this data source. We attempted to study individuals that did not have a substance use disorder by excluding those with a prior diagnosis or used suboxone, however, we recognize that these criteria may not have excluded all such individuals and these subjects would likely have a different opioid use trajectory than those without substance use disorders. Lastly, this study did not evaluate the risks of long term opioid use such as dependence, addiction, misuse, or overdose.

After adjusting for potential confounders including pain etiology, the opioid type, dose, and days' supply of the initial opioid prescription are significant predictors of continued opioid use. Days' supply of the initial opioid prescription is the strongest predictor of long-term opioid use and was consistently found to be prognostic across all pain etiologies we examined. For this reason, clinicians should be particularly conscientious when initially prescribing opioids in ensuring that the days' supply is no longer than necessary to mitigate the risk of unintentional long term use. States, particularly those where chronic opioid use is high, should consider policies that limit the initial supply of opioids.

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Bibliography

1. Babalonis S, Lofwall MR, Nuzzo PA, Siegel AJ, Walsh SL. Abuse liability and reinforcing efficacy of oral tramadol in humans. Drug Alcohol Depend. 2013; 129:116–24. [PubMed: 23098678]
2. Braden JB, Fan M-Y, Edlund MJ, Martin BC, DeVries A, Sullivan MD. Trends in use of opioids by noncancer pain type 2000–2005 among Arkansas Medicaid and HealthCore enrollees: results from the TROUP study. J Pain [Internet]. 2008; 9:1026–35. [cited 2016 Jun 7]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18676205.
3. Calcaterra SL, Yamashita TE, Min S-J, Keniston A, Frank JW, Binswanger IA. Opioid Prescribing at Hospital Discharge Contributes to Chronic Opioid Use. J Gen Intern Med. 2016; 31:478–85. [PubMed: 26553336]
4. Campbell CI, Weisner C, Leresche L, Ray GT, Saunders K, Sullivan MD, Banta-Green CJ, Merrill JO, Silverberg MJ, Boudreau D, Satre DD, Von Korff M. Age and gender trends in long-term opioid analgesic use for noncancer pain. Am J Public Health American Public Health Association. 2010; 100:2541–7.
5. Chou R, Turner JA, Devine EB, Hansen RN, Sullivan SD, Blazina I, Dana T, Bougatsos C, Deyo RA. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. Ann Intern Med [Internet]. 2015; 162:276–86. [cited 2016 Jun 22]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25581257.
6. Cunningham J, Craner J, Evans M, Hooten WM. Benzodiazepine use in patients with chronic pain in an interdisciplinary pain rehabilitation program. J Pain Res Volume. 2017; 10:311–7.
7. Daubresse M, Chang H-Y, Yu Y, Viswanathan S, Shah ND, Stafford RS, Kruszewski SP, Alexander GC. Ambulatory Diagnosis and Treatment of Nonmalignant Pain in the United States, 2000–2010. Med Care [Internet]. 2013; 51:870–8. [cited 2017 Mar 1]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24025657.
8. Deyo RA, Hallvik SE, Hildebran C, Marino M, Dexter E, Irvine JM, Van Otterloo J, Wright D, Leichtling AG, Millet LM. Association Between Initial Opioid Prescribing Patterns and Subsequent Long-Term Use Among Opioid-Naïve Patients: A Statewide Retrospective Cohort Study. J Gen Intern Med.
9. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. MMWR Recomm Reports [Internet]. 2016; 65:1–49. [cited 2017 Mar 1]. Available from: http://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1er.htm.
10. Edlund MJ, Austen MA, Sullivan MD, Martin BC, Williams JS, Fortney JC, Hudson TJ. Patterns of opioid use for chronic noncancer pain in the Veterans Health Administration from 2009 to 2011. Pain. 2014; 155:2337–43. [PubMed: 25180008]
11. Edlund MJ, Martin BC, Devries A, Fan M-Y, Braden JB, Sullivan MD. Trends in use of opioids for chronic noncancer pain among individuals with mental health and substance use disorders: the TROUP study. Clin J Pain [Internet]. 2010; 26:1–8. [cited 2015 Dec 8]. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2917238&tool=pmcentrez&rendertype=abstract.
12. Edlund MJ, Martin BC, Fan M-Y, Braden JB, Devries A, Sullivan MD. An analysis of heavy utilizers of opioids for chronic noncancer pain in the TROUP study. J Pain Symptom Manage [Internet]. 2010; 40:279–89. [cited 2015 Dec 8]. Available from: http://www.sciencedirect.com/science/article/pii/S0885392410003234.
13. Edlund MJ, Martin BC, Russo JE, Devries A, Braden JB, Sullivan MD. The Role of Opioid Prescription in Incident Opioid Abuse and Dependence Among Individuals with Chronic Non-cancer Pain. Clin J Pain [Internet]. 2013; 30:1. [cited 2017 Mar 1]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24281273.

14. Furlan AD, Hassan S, Famiyeh I-M, Wang W, Dhanju J. Long-term opioid use after discharge from inpatient musculoskeletal rehabilitation. J Rehabil Med. 2016; 48:464–8. [PubMed: 27008591]
15. Horsfall JT, Sprague JE. The Pharmacology and Toxicology of the "Holy Trinity. Basic Clin Pharmacol Toxicol. 2017; 120:115–9. [PubMed: 27550152]
16. Hudson TJ, Edlund MJ, Steffick DE, Tripathi SP, Sullivan MD. Epidemiology of regular prescribed opioid use: results from a national, population-based survey. J Pain Symptom Manage. 2008; 36:280–8. [PubMed: 18619768]
17. Hudson TJ, Painter JT, Martin B, Austen MA, Williams JS, Fortney J, Sullivan MD, Edlund ME. Pharmacoepidemiologic analyses of opioid use among OEF/OIF/OND veterans. Pain. 2017:1. [PubMed: 27780180]
18. Ivanova JI, Birnbaum HG, Schiller M, Kantor E, Johnstone BM, Swindle RW. Real-world practice patterns, health-care utilization, and costs in patients with low back pain: the long road to guideline-concordant care. Spine J. 2011; 11:622–32. [PubMed: 21601533]
19. Kelly, Erin Groppe M. House passing bills to fight opioid addiction [Internet]. USA Today. 2016. [cited 2016 Jun 7]. Available from: http://www.indystar.com/story/news/politics/2016/05/11/house-passing-bills-fight-opioid-addiction/84250820/
20. Levy B, Paulozzi L, Mack KA, Jones CM. Trends in Opioid Analgesic–Prescribing Rates by Specialty, U.S., 2007–2012. Am J Prev Med [Internet]. 2015; 49:409–13. [cited 2017 Mar 1]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25896191.
21. Martin BC, Fan M-Y, Edlund MJ, Devries A, Braden JB, Sullivan MD. Long-term chronic opioid therapy discontinuation rates from the TROUP study. J Gen Intern Med [Internet]. 2011; 26:1450–7. [cited 2016 Jun 7]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21751058.
22. McDonald DC, Carlson K, Izrael D. Geographic variation in opioid prescribing in the U.S. J Pain. 2012; 13:988–96. [PubMed: 23031398]
23. Morden NE, Munson JC, Colla CH, Skinner JS, Bynum JPW, Zhou W, Meara E. Prescription opioid use among disabled Medicare beneficiaries: intensity, trends, and regional variation. Med Care [Internet]. 2014; 52:852–9. [cited 2016 Jun 7]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25119955.
24. Nahin RL. Estimates of Pain Prevalence and Severity in Adults: United States, 2012. J Pain. 2015; 16:769–80. [PubMed: 26028573]
25. Nielsen S, Lintzeris N, Bruno R, Campbell G, Larance B, Hall W, Hoban B, Cohen ML, Degenhardt L. Benzodiazepine Use among Chronic Pain Patients Prescribed Opioids: Associations with Pain, Physical and Mental Health, and Health Service Utilization. Pain Med. 2015; 16:356–66. [PubMed: 25279706]
26. Paulozzi LJ, Mack KA, Hockenberry JM. Division of Unintentional Injury Prevention, National Center for Injury Prevention and Control, CDC. Vital signs: variation among States in prescribing of opioid pain relievers and benzodiazepines - United States, 2012. MMWR Morb Mortal Wkly Rep [Internet]. 2014; 63:563–8. [cited 2017 Mar 1]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24990489.
27. Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Prescription of Long-Acting Opioids and Mortality in Patients With Chronic Noncancer Pain. JAMA. 2016; 315:2415. [PubMed: 27299617]
28. Richardson LP, Russo JE, Katon W, McCarty CA, DeVries A, Edlund MJ, Martin BC, Sullivan M. Mental health disorders and long-term opioid use among adolescents and young adults with chronic pain. J Adolesc Health NIH Public Access. 2012; 50:553–8.
29. Seal KH, Shi Y, Cohen G, Cohen BE, Maguen S, Krebs EE, Neylan TC. Association of mental health disorders with prescription opioids and high-risk opioid use in US veterans of Iraq and Afghanistan. JAMA. 2012; 307:940–7. [PubMed: 22396516]
30. Shah A, Hayes CJ, Martin BC. Characteristics of Initial Prescription Episodes and Likelihood of Long-Term Opioid Use — United States, 2006–2015. MMWR Morb Mortal Wkly Rep [Internet]. 2017; 66:265–9. [cited 2017 Mar 26]. Available from: http://www.cdc.gov/mmwr/volumes/66/wr/mm6610a1.htm.
31. "Weak" opioid analgesics. Codeine, dihydrocodeine and tramadol: no less risky than morphine. Prescrire Int. 2016; 25:45–50. [PubMed: 27042732]

32. Preventing Opioid Misuse: Legislative Trends and Predictions > National Conference of State Legislatures [Internet]. [cited 2017 Apr 26]. Available from: http://www.ncsl.org/blog/2017/01/31/preventing-opioid-misuse-legislative-trends-and-predictions.aspx

33. Vital signs: overdoses of prescription opioid pain relievers---United States, 1999--2008. MMWR Morb Mortal Wkly Rep [Internet]. 2011; 60:1487–92. [cited 2016 Jun 1]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22048730.

PERSPECTIVE

This study shows that characteristics of the first opioid prescription, particularly duration of the prescription, are significant predictors of continued opioid use irrespective of the indication for an opioid prescription. These data should encourage prescribers to initiate patients on the minimum effective opioid dose and duration to reduce unintended long-term use and could motivate policies that restrict the initial supply of opioids.

Highlights

- Patients with chronic pain had the highest probability of continued opioid use.
- Long-term opioid use was uncommon for other conditions (<5% at one year).
- Initiation with tramadol or long-acting opioids increases likelihood of continued use.
- The day supplied of the first opioid prescription is the strongest predictor of continued opioid use.

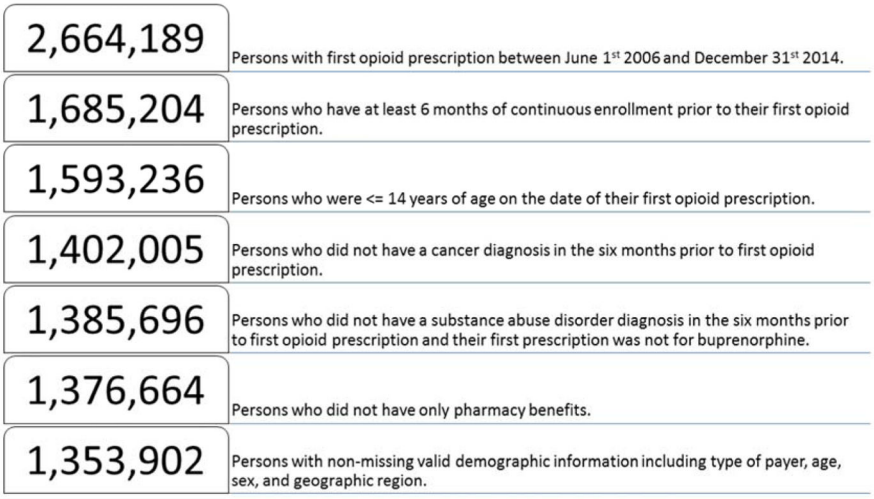

FIGURE 1.
Inclusion/exclusion criteria and patient flow diagram

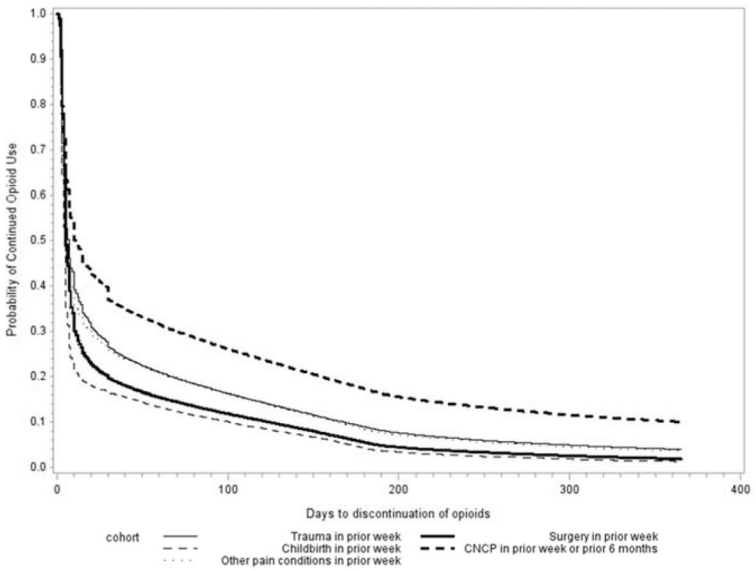

FIGURE 2.

Probability of continued opioid use for <=365 days for Patients with Childbirth, Surgery, Trauma or Other Pain diagnosis in week prior to their first opioid prescription or Chronic Pain diagnosis in 6 months prior to their first opioid prescription.

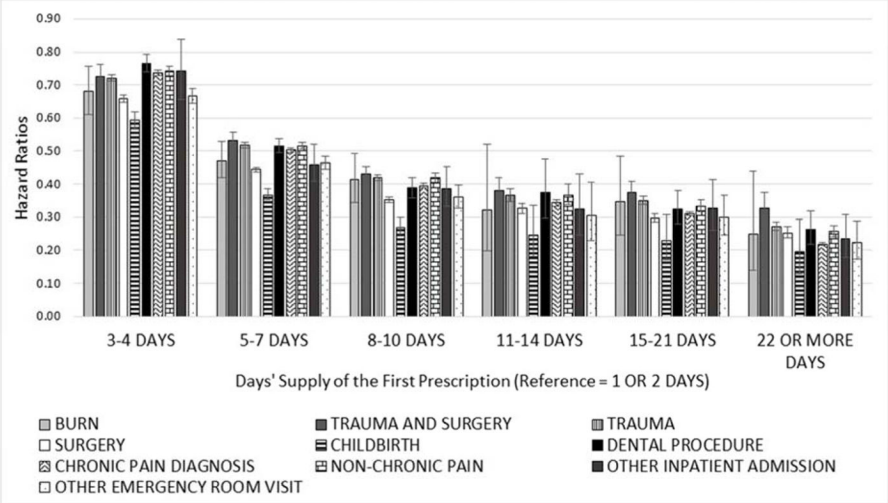

FIGURE 3.

Hazard Ratios for each days' supply category (reference = 1 or 2 days) by the pain etiology resulting in opioid prescription, derived by interacting days' supply with each etiology.

TABLE 1

Characteristics of patients who used opioids ≥365 days and <365 days. N: Number of Patients; MME: Morphine Milligram Equivalents. The number of persons using opioids for more or less than 365 days is for the entire sample and the 359,967 subjects who were not enrolled for at least 365 days were classified as having less than 365 days of opioid use. If a patient qualified for more than one indication the following hierarchy was used: Trauma and Surgery; Trauma; Surgery; Burn; Childbirth; Dental procedure; Chronic non-cancer pain; Other pain; Other inpatient admission; Other Emergency Department visit. Average daily dose was calculated as total strength of the prescription expressed in MME divided by the days' supply of the first prescription. If a patient had multiple prescriptions on the first day the daily dose in MME for all the prescriptions on the index date were summed and divided by the days' supply of the longest lasting prescription. The first prescription was categorized into 6 mutually exclusive categories and in case of multiple prescriptions on the index date using the following hierarchy to assign category: 1) Long-Acting; 2) Other Schedule II Short Acting; 3) Oxycodone Short-Acting; 4) Hydrocodone Short-Acting; 5) Schedule III–IV and Nalbuphine; 6) Tramadol.

	PATIENTS WHO USED OPIOID <365 DAYS (N = 1,320,883; 97.56%)*	**PATIENTS WHO USED OPIOID ≥365 DAYS (N = 33,019; 2.44%)***
CHARACTERISTIC	**N (%)**	**N (%)**
AGE IN YEARS AT THE TIME OF FIRST OPIOID PRESCRIPTION		
A. 14–17	85,176 (6.45%)	254 (0.77%)
B. 18–21	106,626 (8.07%)	519 (1.57%)
C. 22–30	202,016 (15.29%)	2,685 (8.13%)
D. 31–44	352,056 (26.65%)	7,946 (24.06%)
E. 45–54	277,909 (21.04%)	9,584 (29.03%)
F. 55–64	221,938 (16.80%)	8,399 (25.44%)
G. ≥65	75,162 (5.69)	3,632 (11.00%)
FEMALE GENDER	708,925 (53.67%)	18,484 (55.98)
REGION OF RESIDENCE		
A. EAST	288,890 (21.88%)	6,098 (18.47%)
B. MIDWEST	393,006 (29.75%)	9,656 (29.24%)
C. SOUTH	486,699 (36.85%)	13,552 (41.04%)
D. WEST	152,198 (11.52%)	3,713 (11.25%)
PAYER TYPE		
A. COMMERCIAL	888,034 (67.23%)	20,568 (62.29%)
B. MEDICAID	400,451 (30.32%)	10,503 (31.81%)
C. MEDICARE	16,584 (1.26%)	788 (2.39%)
D. SELF-INSURED	15,184 (1.20%)	1,160 (3.51%)
MENTAL HEALTH CONDITIONS		
A. MOOD DISORDER	72,379 (5.48%)	3,138 (9.50%)
B. PERSONALITY DISORDER	1,052 (0.08%)	32 (0.10%)

	PATIENTS WHO USED OPIOID <365 DAYS (N = 1,320,883; 97.56%)*	PATIENTS WHO USED OPIOID ≥365 DAYS (N = 33,019; 2.44%)*
CHARACTERISTIC	**N (%)**	**N (%)**
C. ADJUSTMENT DISORDER	19,717 (1.49%)	473 (1.43%)
D. ANXIETY DISORDER	57,160 (4.33%)	2,472 (7.49%)
E. MISCELLANEOUS DISORDER	13,382 (1.01%)	512 (1.55%)
YEAR OF OPIOID INITIATION		
A. 2006	41,037 (3.11%)	1,715 (5.19%)
B. 2007	194,712 (14.74%)	6,352 (19.24%)
C. 2008	200,111 (15.15%)	5,690 (17.23%)
D. 2009	180,871 (13.69%)	4,587 (13.89%)
E. 2010	164,211 (12.43%)	4,040 (12.24%)
F. 2011	154,023 (11.66%)	3,646 (11.04%)
G. 2012	143,602 (10.87%)	3,131 (9.48%)
H. 2013	141,279 (10.70%)	3,387 (10.26%)
I. 2014	101,037 (7.65%)	471 (1.43%)
BEZODIAZEPINE PRESCRIPTION IN PRIOR 6 MONTHS	144,234 (10.92%)	8,065 (24.43%)
MUSCLE RELAXANT PRESCRIPTION IN PRIOR 6 MONTHS	131,733 (9.97%)	6,538 (19.80%)
INDICATION FOR OPIOID PRESCRIPTION‡		
A. TRAUMA AND SURGERY	36,676 (2.78%)	299 (0.91%)
B. TRAUMA	166,331 (12.59%)	2,907 (8.80%)
C. SURGERY	178,126 (13.49%)	1,356 (4.11%)
D. BURN	2,539 (0.19%)	20 (0.06%)
E. CHILDBIRTH	18,059 (1.37%)	58 (0.18%)
F. DENTAL PROCEDURE	22,732 (1.72%)	197 (0.60%)
G. CHRONIC NON-CANCER PAIN	323,058 (24.46%)	17,340 (52.52%)
H. OTHER PAIN CONDTIONS	85,527 (6.47%)	1,319 (3.99%)
I. OTHER INPATIENT ADMISSION	3,489 (0.26%)	92 (0.28%)
J. OTHER EMERGENCY DEPARTMENT VISIT	20,372 (1.54%)	180 (0.55%)
K. UNKNOWN INDICIATION	463,974 (35.13)	9,251 (28.02%)
CHOICE OF FIRST OPIOID PRESCRIPTION^		
A. LONG-ACTING OPIOID	5,675 (0.43%)	871 (2.64%)
B. SCHEDULE TWO SHORT ACTING OPIOID	14,801 (1.12%)	525 (1.59%)
C. SHORT ACTING OXYCODONE	224,814 (17.02%)	3,839 (11.63%)
D. SHORT ACTING HYDROCODONE	768,447 (58.18%)	16,446 (49.81%)
E. SCHEDULE III OR IV OR NALBUPHINE	198,943 (15.06%)	4,384 (13.28%)
F. TRAMADOL	108,203 (8.19%)	6,954 (21.06%)
DAYS' SUPPLY OF FIRST PRESCRIPTION		
A. 1–2	274,601 (20.79%)	2,580 (7.81%)

	PATIENTS WHO USED OPIOID <365 DAYS (N = 1,320,883; 97.56%)*	PATIENTS WHO USED OPIOID ≥365 DAYS (N = 33,019; 2.44%)*
CHARACTERISTIC	**N (%)**	**N (%)**
B. 3–4	490,737 (37.15%)	5,266 (15.95%)
C. 5–7	363,181 (27.50%)	7,336 (22.22%)
D. 8–10	99,417 (7.53%)	4,040 (12.24%)
E. 11–14	15,331 (1.16%)	1,056 (3.20%)
F. 15–21	39,205 (2.97%)	3,638 (11.02%)
G. ≥22	38,411 (2.91%)	9,103 (27.57%)
AVERAGE DAILY DOSE OF FIRST PRESCRIPTION IN MME†		
A. 0–24	286,529 (21.69%)	11,862 (35.92%)
B. 25–49	663,512 (51.10%)	13,428 (40.67%)
C. 50–89	255,446 (19.34%)	3,658 (12.94%)
D. ≥90	115,396 (8.74%)	3,457 (9.38%)

N: Number of Patients; MME: Morphine Milligram Equivalents

*The number of persons using opioids for more or less than 365 days is for the entire sample and the 359,967 subjects who were not enrolled for at least 365 days were classified as having less than 365 days of opioid use..

≠If a patients qualified for more than one indication the following hierarchy was used: Trauma and Surgery; Trauma; Surgery; Burn; Childbirth; Dental procedure; Chronic non-cancer pain; Non-chronic pain; Other inpatient admission; Other Emergency Department visit

†Average daily dose was calculated as total strength of the prescription expressed in MME divided by the days' supply of the first prescription. If a patient had multiple prescriptions on the first day the daily dose in MME for all the prescriptions on the index date were summed and divided by the days' supply of the longest lasting prescription.

^The first prescription was categorized into 6 mutually exclusive categories and in case of multiple prescriptions on the index date using the following hierarchy to assign category: 1) Long-Acting; 2) Other Schedule II Short Acting; 3) Oxycodone Short- Acting; 4) Hydrocodone Short-Acting; 5) Schedule III–IV and Nalbuphine; 6) Tramadol

TABLE 2

Probability of continued opioid use at one and three year and the median time to discontinuing opioids by indication for first opioid prescription. Probabilities of continued opioid use and median days to discontinuation are based on Kaplan Meier estimates. If a patients qualified for more than one indication the following hierarchy was used: Trauma and Surgery; Trauma; Surgery; Burn; Childbirth; Dental procedure; Chronic non-cancer pain; Other pain; Other inpatient admission; Other Emergency Department visit.

INDICATION FOR FIRST OPIOID PRESCRIPTION**	NUMBER OF PATIENTS (%)	ONE YEAR PROBABILITY OF CONTINUED OPIOID USE, %	THREE YEAR PROBABILITY OF CONTINUED OPIOID USE, %	MEDIAN DAYS TO DISCONTINUATION
TRAUMA AND SURGERY	36,975 (2.73%)	1.97%	0.74%	7.00
TRAUMA	169,238 (12.50%)	3.96%	1.71%	5.00
SURGERY	179,482 (13.26%)	1.90%	0.64%	5.00
BURN	2,559 (0.19%)	1.98%	0.89%	5.00
CHILDBIRTH	18,117 (1.34%)	1.33%	0.45%	5.00
DENTAL PROCEDURE	22,929 (1.69%)	2.29%	0.77%	5.00
CHRONIC NON-CANCER PAIN	340,398 (25.14%)	10.07%	5.11%	11.00
OTHER PAIN CONDTIONS	86,846 (6.41%)	3.69%	1.48%	5.00
OTHER INPATIENT ADMISSION	3,581 (0.26%)	6.60%	2.91%	8.00
OTHER EMERGENCY DEPARTMENT VISIT	20,552 (1.52%)	2.47%	1.11%4.00	
UNKNOWN ETIOLOGY	473,225 (34.95)	4.47%	2.20%	5.00

*Probabilities of continued opioid use and median days to discontinuation are based on Kaplan Meier estimates

**If a patients qualified for more than one indication the following hierarchy was used: Trauma and Surgery; Trauma; Surgery; Burn; Childbirth; Dental procedure; Chronic non-cancer pain; Non-chronic pain; Other inpatient admission; Other Emergency Department visit

TABLE 3

Multivariate analysis for the impact of pain etiologies and characteristics of first opioid prescription on time to opioid discontinuation. REF: Reference Category for the variable CI: Confidence Intervals. All models controlled for covariates including: Year of opioid initiation; Region of residence; Primary payer; Gender; Age; Mental Health Conditions (Anxiety Disorder, Personality Disorder, Mood Disorder, Adjustment Disorder, and Miscellaneous Disorder) in previous 6 months; Benzodiazepine or Non-benzodiazepine GABA-receptor modulator in previous 6 months; Muscle Relaxant in previous 6 months. If a patients qualified for more than one indication the following hierarchy was used: Trauma and Surgery; Trauma; Surgery; Burn; Childbirth; Dental procedure; Chronic non-cancer pain; Other pain; Other inpatient admission; Other Emergency Department visit. Average daily dose was calculated as total strength of the prescription expressed in MME divided by the days' supply of the first prescription. If a patient had multiple prescriptions on the first day the daily dose in MME for all the prescriptions on the index date were summed and divided by the days' supply of the longest lasting prescription. The first prescription was categorized into 6 mutually exclusive categories and in case of multiple prescriptions on the index date using the following hierarchy to assign category: 1) Long-Acting; 2) Other Schedule II Short Acting; 3) Oxycodone Short-Acting; 4) Hydrocodone Short-Acting; 5) Schedule III–IV and Nalbuphine; 6) Tramadol

CHARACTERISTIC	HAZARD RATIO (95% CI)			
	ALL OPIOID NAiVE PATIENTS MEETING INCLUSION/EXCLUSION CRITERIA (N=1,353,902)	NO CHRONIC PAIN CONDITION DIAGNOSIS IN SIX MONTHS PRIOR TO FIRST OPIOID PRESCRIPTION (N=810,035)	AT LEAST ONE CHRONIC PAIN CONDITION DIAGNOSIS IN SIX MONTHS PRIOR TO FIRST OPIOID PRESCRIPTION (N=543,867)	NO OPIOID PRESCRIPTION FOR AT LEAST ONE YEAR PRIOR TO FIRST OPIOID PRESCRIPTION (N=955,371).
INDICATION FOR OPIOID PRESCRIPTION (REF=SURGERY)‡				
A. TRAUMA AND SURGERY	0.91 (0.90–0.92)	0.84 (0.82–0.86)	-	0.91 (0.89–0.92)
B. TRAUMA	0.84 (0.83–0.84)	0.85 (0.84–0.86)	-	0.84 (0.83–0.84)
C. BURN	0.96 (0.92–1.00)	0.94 (0.90–0.99)	-	0.96 (0.92–1.01)
D. CHILDBIRTH	1.11 (1.10–1.13)	1.08 (1.06–1.10)	-	1.14 (1.12–1.17)
E. DENTAL PROCEDURE	0.90 (0.88–0.91)	0.88 (0.87–0.90)	-	0.91 (0.89–0.93)
F. CHRONIC NON-CANCER PAIN	0.77 (0.77–0.78)	-	-	0.78 (0.78–0.79)
G. OTHER PAIN CONDTIONS	0.85 (0.84–0.86)	0.83 (0.82–0.84)	-	0.85 (0.85–0.86)
H. OTHER INPATIENT ADMISSION	0.82 (0.79–0.85)	0.80 (0.77–0.83)	-	0.82 (0.78–0.86)
I. OTHER EMERGENCY DEPARTMENT VISIT	0.92 (0.91–0.94)	0.89 (0.88–0.91)	-	0.93 (0.91–0.95)
J. UNKNOWN ETIOLOGY	0.92 (0.92–0.93)	0.90 (0.89–0.91)	-	0.93 (0.93–0.94)
CHOICE OF FIRST OPIOID PRESCRIPTION (REF= SCHEDULE III OR IV OR NALBUPHINE)†				
A. LONG-ACTING OPIOID	0.79 (0.77–0.82)	0.74 (0.70–0.78)	0.86 (0.83–0.89)	0.80 (0.77–0.83)
B. SCHEDULE TWO SHORT ACTING OPIOID	0.93 (0.92–0.95)	0.98 (0.96–1.00)	0.91 (0.88–0.93)	0.92 (0.90–0.94)
C. SHORT ACTING OXYCODONE	0.97 (0.96–0.98)	1.00 (0.99–1.01	0.97 (0.96–0.99)	0.97 (0.96–0.98)

CHARACTERISTIC	HAZARD RATIO (95% CI)			
	ALL OPIOID NAïVE PATIENTS MEETING INCLUSION/EXCLUSION CRITERIA (N=1,353,902)	NO CHRONIC PAIN CONDITION DIAGNOSIS IN SIX MONTHS PRIOR TO FIRST OPIOID PRESCRIPTION (N=810,035)	AT LEAST ONE CHRONIC PAIN CONDITION DIAGNOSIS IN SIX MONTHS PRIOR TO FIRST OPIOID PRESCRIPTION (N=543,867)	NO OPIOID PRESCRIPTION FOR AT LEAST ONE YEAR PRIOR TO FIRST OPIOID PRESCRIPTION (N=955,371).
D. SHORT ACTING HYDROCODONE	0.95 (0.95–0.96)	0.97 (0.96–0.98)	0.94 (0.93–0.95)	0.95 (0.95–0.96)
E. TRAMADOL	0.89 (0.89–0.90)	0.92 (0.91–0.93)	0.86 (0.85–0.87)	0.90 (0.89–0.91)
DAYS' SUPPLY OF FIRST PRESCRIPTION (REF=1–2)				
A. 3–4	0.70 (0.70–0.71)	0.68 (0.67–0.68)	0.77 (0.76–0.78)	0.69 (0.69–0.70)
B. 5–7	0.48 (0.47–0.48)	0.45 (0.45–0.46)	0.54 (0.54–0.55)	0.46 (0.46–0.47)
C. 8–10	0.37 (0.37–0.38)	0.35 (0.35–0.36)	0.42 (0.41–0.42)	0.36 (0.36–0.37)
D. 11–14	0.32 (0.31–0.33)	0.30 (0.29–0.30)	0.36 (0.35–0.37)	0.31 (0.31–0.32)
E. 15–21	0.29 (0.28–0.29)	0.27 (0.26–0.27)	0.32 (0.31–0.32)	0.28 (0.28–0.29)
F. ≥22	0.20 (0.19–0.20)	0.17 (0.17–0.18)	0.22 (0.21–0.22)	0.19 (0.18–0.19)
AVERAGE DAILY DOSE OF FIRST PRESCRIPTION IN MME (REF=0–24 MME)[^]				
A. 25–49	0.97 (0.96–0.97)	0.98 (0.97–0.98)	0.97 (0.96–0.97)	0.97 (0.96–0.98)
B. 50–89	0.95 (0.94–0.95)	0.98 (0.97–0.99)	0.95 (0.94–0.96)	0.95 (0.94–0.96)
C. ≥ 90	0.91 (0.91–0.92)	0.96 (0.95–0.97)	0.92 (0.90–0.93)	0.92 (0.91–0.92)

REF: Reference Category for the variable CI: Confidence Intervals. All models controlled for covariates including: Year of opioid initiation; Region of residence; Primary payer; Gender; Age; Mental Health Conditions (Anxiety Disorder, Personality Disorder, Mood Disorder, Adjustment Disorder, and Miscellaneous Disorder) in previous 6 months; Benzodiazepine or Nonbenzodiazepine GABA-receptor modulator in previous 6 months; Muscle Relaxant in previous 6 months

[‡]If a patients qualified for more than one indication the following hierarchy was used: Trauma and Surgery; Trauma; Surgery; Burn; Childbirth; Dental procedure; Chronic non-cancer pain; Non-chronic pain; Other inpatient admission; Other Emergency Department visit

[^]Average daily dose was calculated as total strength of the prescription expressed in MME divided by the days' supply of the first prescription. If a patient had multiple prescriptions on the first day the daily dose in MME for all the prescriptions on the index date were summed and divided by the days' supply of the longest lasting prescription.

[†]The first prescription was categorized into 6 mutually exclusive categories and in case of multiple prescriptions on the index date using the following hierarchy to assign category: 1) Long-Acting; 2) Other Schedule II Short Acting; 3) Oxycodone Short- Acting; 4) Hydrocodone Short-Acting; 5) Schedule III–IV and Nalbuphine; 6) Tramadol