Do Primary Care Clinicians Incorporate Comorbidities and Concurrent Medications When Prescribing Opioids for Low Back Pain? A Retrospective Cross-Sectional Analysis

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Abstract

Background Given the risks of opioid therapy, clinicians are under growing pressure to treat pain with non-opioid medications. Yet non-opioid analgesics such as non-steroidal anti-inflammatory drugs have their own risks; patients with kidney disease or gastrointestinal diseases can experience serious adverse events. We examined how primary care clinicians balance patient comorbidities and concurrent medications when prescribing opioids.

Methods We used a retrospective cross-sectional study design and data from one health system. We identified office visits for low back pain from 2012-2017 and sampled the first visit per patient per year (N= 24,543 visits). We created indicators reflecting contraindications for NSAIDs (kidney, liver, cardiovascular/cerebrovascular, and gastrointestinal diseases; concurrent use of anticoagulants/antiplatelets) and opioids (depression, anxiety, substance use and bipolar disorders, chronic corticosteroid use, and concurrent benzodiazepines) and estimated four logistic regression models, with the first model including all patient visits and then stratifying for previous opioid use.

Results Patients received an opioid prescription at 4% of visits. Among all patients, kidney disease (marginal effect [ME]: 3%; 95%CI: 1%-4%) or chronic/concurrent anticoagulant/antiplatelet prescriptions (ME: 2%, 95%CI: 1%-3%) were associated with a higher probability of receiving an opioid prescription. Concurrent benzodiazepines (ME: 7%, 95%CI: 5%-9%) and substance use diagnoses (ME: 1%, 95%CI: 0%-3%) were also associated with a higher probability of opioid prescription receipt. Among patients with long-term opioid use, contraindications for NSAIDs were not associated with a higher probability of opioid prescription receipt, while the probability of opioid receipt among those with concurrent benzodiazepines was substantially higher (ME: 10%, 95%CI: 14%-53%).

Conclusions Among our entire sample, patients with kidney disease were 75% more likely to receive an opioid prescription for low back pain. Among patients with long-term opioid use, we did not find the same association. Patients with long-term use were likely started on opioids when opioid prescribing was more liberal; discussions regarding non-opioid options would be worthwhile for this population. Patients with concurrent benzodiazepines were 175% more likely to receive an opioid prescription; among patients with long-term opioid use, they were 250% more likely to receive opioids. These findings are troubling, as this combination is dangerous and can lead to overdose.

Background

Given the well-reported risks of opioid therapy,[1] primary care clinicians are under growing pressure to treat pain with non-opioid medications. Comorbidities such behavioral health disorders may place patients taking opioids at greater risk for opioid-related overdose or addiction.[2] Yet non-opioid medications have their own risks, particularly among individuals with certain comorbidities and older adults.[3, 4] Many individuals are unable to use opioid alternatives such as non-steroidal anti-inflammatory drugs (NSAIDs) or other analgesics due to comorbidities such as kidney disease or

gastrointestinal conditions or due to potential drug-drug interactions from concurrently prescribed medications.[4]

To date, however, it is not well understood how clinicians factor in patients' comorbidities and concurrent prescriptions when prescribing opioids. Most studies examining opioid use have focused on risk factors associated with long-term opioid use, opioid overdose, or addiction such as behavioral health diagnoses; few have examined patient comorbidities associated with contraindications of non-opioid analgesics.[5, 6] Understanding how clinicians incorporate clinical comorbidities into decision-making around opioid prescribing can highlight potentially appropriate or inappropriate prescribing, focusing quality improvement efforts and improving the development of more nuanced quality measures.[3]

Our objective was to examine whether patients with contraindications for non-opioid analgesics such as NSAIDs had a higher predicted probability of receiving an opioid prescription during an office visit for low back pain. We were also interested in whether patients with comorbidities or concurrent prescriptions that place them at higher risk for overdose or addiction – relative contraindications for opioids – had lower predicted probabilities of receiving an opioid prescription. We selected to study patients with a low back diagnosis given that there is extensive literature documenting that opioids are often not recommended for this condition.[7] We hypothesized that individuals with comorbidities or concurrent medication use contraindicated with NSAIDs would result in the individual having a higher predicted probability of receiving an opioid prescription, compared to individuals without these comorbidities/concurrent prescriptions, and that individuals with comorbidities and medication use associated with higher risk of overdose or opioid use disorder would have lower predicted probabilities of receiving an opioid prescription.

Methods

Study Setting, Population, and Retrospective Cohort Design

Using administrative data, we created a retrospective cohort of patients with outpatient visits at a large, tertiary care academic health system and its associated primary care clinics. The health system is located in a metropolitan, urban area. Our population sample is primarily insured; most patients have private insurance or Medicare. In 2017, 42% of the entire population of patients seen at primary and specialty care clinic visits at the medical center had Medicare as their primary payor, 5% had Medicaid, 49% had private insurance, and 3% had a payor classified as "other."[8]

We included all patients with lower back pain diagnoses that had at least one office visit in any year between 2012-2017 and then extracted a year's worth of retrospective data to identify factors associated with receipt of an opioid prescription made during the single primary care office visit. Our unit of analysis was the visit.

To construct the cohort, we first identified all outpatient office visits for low back pain from 2012-2017 for all patients seen by clinicians affiliated with the health system and sampled the first office visit per

patient per year. The office visit was defined as the first time that a patient had a non-emergency, non-perioperative office visit with one of the selected ICD-9 codes identified for low back pain during each calendar year (Appendix 1). We then restricted our sample to visits to primary care clinicians. For this visit, we extracted diagnoses, prescribed medications, and demographic data. We also extracted the following data from all visits during the 365 days prior to the visit: opioid prescriptions; prescriptions of anticoagulants, antiplatelets, systemic steroids, NSAIDs; diagnoses where NSAIDs are contraindicated; and diagnoses where opioids are contraindicated (see Appendices 2 and 3 for a list of specific diagnoses and ICD-9 codes). All data were extracted from a database (Clarity) with electronic health record (EHR) data of the academic medical center.

We excluded patients under age 18 at the time of office visit, patients with a cancer diagnosis during the study period, patients pregnant during the sampled office visit, patients receiving palliative care, and individuals with vertebral fractures. These patients have specialized analgesic needs and we felt they fell outside the scope of this study. Our final sample size was 24,543 visits of patients with a low back pain diagnosis among 147 providers.

Measures

Primary Outcome: Receipt of Opioid During Index Visit for Low Back Pain

The primary outcome was defined as receipt of an opioid prescription during the primary care office visit for low back pain (yes/no).

Comorbidities and Medication Use for Which Use of NSAIDs or Opioids are Contraindicated

We created separate indicators for the presence of comorbidities that have contraindications for NSAIDs, including kidney, liver, gastrointestinal, cardiovascular, and cerebrovascular diseases during the office visit or in the previous 365 days using ICD-9 codes (See Appendix 2 for a list of all of the codes used in this analysis).

Individuals may also be taking certain medications which may interact with NSAIDs or should not be prescribed concurrently due to gastrointestinal adverse effects. [9-11] For these individuals, opioid medications may be the more appropriate choice for analgesia. These medications include long-term aspirin use, anticoagulant use, antiplatelet use, and long-term systemic steroid use.[12-14] We used medications prescribed and ICD-9 codes for long-term use of these medications in the previous 365 days before the office visit to create indicators for each of these medications (Appendix 3). We constructed categories of chronic use of these medications by counting the number of prescriptions before the office visit; if the patient had five or more prescriptions for one of these medication classes, we defined that individual as having a chronic prescription. We created one combined indicator for chronic and concurrent anticoagulant and antiplatelet use. We created one indicator each for chronic NSAID use and systemic steroid use.

We created indicators for behavioral health diagnoses, including depression, anxiety, bipolar, and substance use disorders, during the office visit and in encounters 365 days prior. [15, 16] We considered a benzodiazepine to be concurrently prescribed if it was prescribed at the same office visit as the opioid. We also controlled for age, sex, race, ethnicity, employment status, tobacco use, and marital status.

Previous Opioid Use

We created three categories of previous opioid use documented in the EHR:

(1) no known opioid use prior to the office visit or no opioid use in the 45 days prior to the office visit;

(2) intermittent opioid use, defined as use 45 days or fewer prior to the office visit but not on long-term opioids, and

(3) long-term opioid use, defined as 60 or more opioid days in the 90 days prior to the office visit. [17]

Analyses

We used frequencies to examine univariate statistics and chi-square tests to examine associations between our independent and outcome variables. For our main analysis, we estimated several logistic regressions. First, we estimated a model controlling for previous opioid use, using the three categories constructed above (no opioid use in the previous 45 days, intermittent opioid use, and long-term opioid use) (Model 1). We then estimated three models (Models 2-4) stratified by previous opioid use. [17] We controlled for the year of the prescription in all models. We used a generalized estimating equations approach to account for multiple visits for each patient over the years and included robust standard errors to control for clustering of patients within physicians. We assumed an independent correlation matrix. We used the Stata *margins* command to estimate predicted probabilities.

Results

Patient Demographics

Patients received an opioid prescription at 4.08% of office visits for low back pain (1,002 of 21,020 visits) (Table 1). We found significant associations between sex, race, marital status, and employment status and receipt of an opioid prescription during the visit for low back pain in our unadjusted analyses. A larger proportion of Black patients and lower proportions of Asian/Pacific Islander and patients with Other/Unknown races received an opioid prescription during the visit. A lower proportion of Hispanic patients received an opioid prescription. We did not find an association between age and receipt of an opioid prescription.

Prior Opioid Use

The majority of patients in our sample (93.4%) had no opioid use 45 days prior to the visit. Approximately 4.9% were intermittent opioid users and 1.8% were long-term opioid users prior to the visit.

Prevalence of Comorbidities and Concurrent Medication Use for Which Use of NSAIDs are Contraindicated

33.88% patient-visits had at least one comorbidity or long-term and/or concurrent prescription where NSAIDs were contraindicated. Relatively small proportions of our sample had kidney disease (5.4%), liver disease (1.8%), or inflammatory bowel disease (0.80%) (Table 2). Higher proportions had cardiovascular or cerebrovascular disease (9.9%) and gastrointestinal disorders (10.7%). A small proportion (0.4%) had chronic systemic steroid use in the previous 365 days prior to the visit. In contrast, anticoagulant or antiplatelet use was higher: 17% of individuals were chronic users in the previous 365 days prior.

Among the comorbidities, the only notable associations between a contraindication for NSAIDs and receipt of an opioid prescription during the visit were for kidney disease (9.6% who received an opioid versus 5.2% who did not), cardiovascular or cerebrovascular disease (11.1% versus 9.8%), and concurrent or long-term antiplatelet or anticoagulant use (28.8% versus 16.5%).

Comorbidities and Medication Use Associated with Higher Risk of Opioid Use Disorder or Opioid Misuse

Nearly one third of our sample (25.01%) had at least one comorbidity or concurrent medication considered a relative contraindication for opioids (Table 3): 10.0% of patients had a depression disorder diagnosis, 13.8.0% had an anxiety disorder diagnosis, and 6.1% had a substance use diagnosis. 2.6% of patients were prescribed a benzodiazepine at the office visit.

A higher proportion of those who received an opioid during the visit had depression disorders (12.6% who received an opioid vs 9.9% who did not), anxiety disorders (17.5% vs 13.9%), substance use disorders (12.7% vs 5.8%), bipolar disorder (2.7% or 1.1%) or received a prescription for a benzodiazepine during the visit (8.0% vs 2.3%).

Adjusted Odds Ratios Between Contraindications for NSAIDs and Receipt of Opioid Prescription

We estimated four separate logistic regression models (Table 4): Model 1 included the full sample of visits for low back pain, adjusting for previous opioid use (N = 24,543), models 2-4 were stratified according to opioid use prior to the office visit: no opioid use 45 days prior to the visit (N = 22,912), intermittent opioid use (N=1,165), or long-term opioid use (N=437).

Adjusted Odds of Opioid Prescription and Comorbidities and Concurrent Medication Use Associated with Contraindications for NSAIDs

Having kidney disease was associated with a three-percentage-point higher probability of receiving an opioid prescription during the primary care visit for low back pain, compared to patients with no kidney disease, after controlling for previous opioid use and other covariates (Model 1, marginal effect [ME]: 3%; 95% CI: 1%, 4%) (Table 3). This translates to 75% greater predicted probability (PP) of receiving an opioid prescription comparing individuals with kidney disease and individuals without kidney disease (7% vs.

4%). The same positive association and similar magnitude held for those who were opioid naïve (Model 2, ME: 2%, 95%CI: 1%, 4%).

Having long-term or concurrent anticoagulant/antiplatelet prescription was associated with a two-percentage-point higher probability of receiving an opioid prescription during the visit, compared to patients with no such medication use, all else equal (Model 1, ME: 2%, 95% CI: 1%, 3%). This translates to a 50% higher probability of receiving an opioid prescription between those with long-term or concurrent anticoagulant/antiplatelet use versus those without this type of medication use (6% vs. 4%). We found a similar positive association and magnitude for patients who had no prior opioid use 45 days to the visit and those with intermittent opioid use. Among intermittent and long-term users, we did not find an association between kidney disease and receipt of an opioid prescription.

Adjusted Odds of Opioid Prescription and Comorbidities and Medication Use Associated with Relative Contraindications for Opioids

Having a substance use disorder diagnosis was associated with a one-percentage-point increase in receipt of an opioid prescription at the office visit in the full sample after controlling for previous opioid use (Model 1, ME: 1%, 95% CI: 0%, 3%) and a two-percentage-point increase in the opioid naïve model (Model 2, ME: 2%, 95% CI: 1%, 3%).

The probability of being co-prescribed a benzodiazepine was positively associated with receiving an opioid prescription during the visit across nearly all models (Model 1, ME: 7%, 95% CI: 5%, 9%. This translates to a 175% greater probability of receiving an opioid prescription between those with a concurrent benzodiazepine prescription versus those without (11% PP vs. 4.0% PP). We had similar findings among patients with no opioid use 45 days prior to the office visit (Model 2, ME: 6%, 95% CI: 4%, 8%) and previous long-term use (Model 4, ME: 10%, 95% CI: 14%, 53%).

Interestingly, we found bipolar disorder was associated with a higher predicted probability of receipt of an opioid prescription among patients with intermittent opioid use (Model 3: ME: 15%, 95% CI: 0%-30%) but a significantly lower probability of receipt among patients with long-term opioid use (Model 4: ME: -15%, 95% CI: -25%- -5%).

Discussion

In this retrospective cohort study of primary care visits of patients with low back pain, we examined comorbidities and concurrent prescriptions associated with both appropriate and inappropriate opioid prescribing, finding that clinicians incorporated important clinical factors and prescriptions when prescribing opioids for patients with little to no previous opioid use, including kidney disease and chronic or concurrent anticoagulant or antiplatelet use. Interestingly, we found no association between age and receipt of an opioid prescription in our adjusted or unadjusted analyses; however, given that age-related medication contraindications are often kidney-related, controlling for kidney disease may have lessened the strength of that association. We also found higher predicted probabilities of receipt of an opioid

prescription among patients with relative contraindications for opioids, including substance use disorder and patients concurrently prescribed benzodiazepines. Prescribing behavior was mixed among patient-visits with bipolar disorder, potentially reflecting decision-making among different populations of patients.

Our findings illustrate that clinicians are using some patient comorbidities to make appropriate prescribing decisions. However, we found that potentially appropriate prescribing decisions incorporating comorbidities such as kidney disease and concurrent anticoagulants or antiplatelets were more likely to be observed for opioid-naïve patients compared to patients who have been on chronic opioid therapy. This likely reflects more recent cautious prescribing. For patients on long-term opioid therapy who do not have contraindications to other medications, clinicians may consider whether other pharmacological or non-pharmacological options are a better fit and might consider patient-centered tapering opioid plans.

Various organizations and federal agencies are developing quality measures to examine prescribing at the system, facility, and provider levels. [17–19] These measures are aimed at assisting health system leaders in identifying variation in prescribing levels among clinicians in an effort to ultimately decrease initial opioid prescribing and long-term opioid use. [17] However, an important limitation of these measures is that they do not distinguish between potentially inappropriate and potentially appropriate opioid prescribing. These quality measures may penalize clinicians, such as geriatricians, who treat a higher proportion of older patients with kidney disease or who are on anticoagulants or antiplatelet medications. Developing quality measures that incorporate patient comorbidities will more accurately capture appropriate and inappropriate prescribing.

That patients with a concurrent benzodiazepine prescription had a substantially higher probability of receiving an opioid is concerning findings because they illustrate that patients at higher risk for overdose or addiction might be receiving inappropriate opioid prescriptions. [20, 21] Similarly, we found that patients with diagnosed substance use disorders had higher probabilities of receiving opioid prescriptions, although these were smaller in magnitude. While patients with a history of substance use can still be prescribed opioids if followed closely, [22] some patients can develop opioid use disorders when prescribed opioid medications. [23] Health systems and provider groups might consider additional training in opioid prescribing and academic detailing to help clinicians identify patients at highest risk for Opioid Use Disorder and opioid misuse.

Our study has several limitations. Although we aimed to capture prior opioid use as accurately as possible, we may not have captured opioids prescribed outside of the health system. However, many prescribers enter recent or concurrent prescriptions into the EHR during the medication reconciliation portion of the visit, so we were able to capture prescriptions identified by the patient during the visit. We may also have missing diagnoses and medications for patients if they sought care outside of the system. However, we used data from visits 365 days prior to the visit, which improves our ability to identify diagnoses and long-term medication use. We also included an extensive list of comorbidities, many of which had not been explored in papers focused on opioid prescribing. We were also likely underpowered

to detect some associations among patients with long-term opioid use. Finally, our study data was limited to one academic medical system with a predominantly insured population in a large metropolitan area, so findings may not be generalizable to rural settings or low resource settings.

Conclusion

In conclusion, our findings suggest that clinicians are considering some clinical comorbidities to make decisions about opioid prescribing for low back pain, including the presence of kidney disease and concurrent use of anticoagulants and antiplatelet medications, suggesting appropriate opioid prescribing. However, we also found that patients receiving a benzodiazepine or with a history of substance use disorder had higher odds of receiving an opioid, which indicates that some opioid prescriptions may place vulnerable patients at risk for overdose, addiction, or even death. Clinicians, pharmacists, and health system administrators should identify comorbidities and concurrent medication use during quality improvement initiatives to identify potentially appropriate and inappropriate opioid prescribing.

Declarations

Ethics approval and consent to participate

This study was approved by the Cedars-Sinai Medical Center's Institutional Review Board and was granted a waiver of informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

The data that support the findings of this study are available on request from the corresponding author MSK. The data are not publicly available due to federal restrictions as the data contain information that could compromise patient privacy.

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Authors' contributions

MSK designed the study, analyzed the data, and wrote and edited the manuscript.

LT played a critical role in the data extract and assisted with data analysis.

AMM contributed to the study design, data analysis, writing, and editing.

JN contributed to the study design, data analysis, writing, and editing.

MVH contributed to the study design, data analysis, writing, and editing.

TKN contributed to the study design, data analysis, writing, and editing.

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References

1. 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**. *Annals of internal medicine* 2015, **162**(4):276-286.
2. Compton Iii WM, Cottler LB, Jacobs JL, Ben-Abdallah A, Spitznagel EL: **The role of psychiatric disorders in predicting drug dependence treatment outcomes**. *American Journal of Psychiatry* 2003, **160**(5):890-895.
3. American Geriatrics Society Panel on the Pharmacological Management of Persistent Pain in Older P: **Pharmacological Management of Persistent Pain in Older Persons**. *Journal of the American Geriatrics Society* 2009, **57**(8):1331-1346.
4. Smith H, Bruckenthal P: **Implications of Opioid Analgesia for Medically Complicated Patients**. *Drugs & Aging* 2010, **27**(5):417-433.
5. Breckenridge J, Clark JD: **Patient characteristics associated with opioid versus nonsteroidal anti-inflammatory drug management of chronic low back pain**. *The Journal of Pain* 2003, **4**(6):344-350.
6. Turk DC, Okifuji A: **What factors affect physicians' decisions to prescribe opioids for chronic noncancer pain patients?** *Clin J Pain* 1997, **13**.
7. Deyo RA, Von Korff M, Duhrkoop D: **Opioids for low back pain**. *BMJ : British Medical Journal* 2015, **350**.
8. California Office of Statewide Health Planning and Development: **CEDARS SINAI MEDICAL CENTER (106190555) Annual Financials - Audited**. In.; 2017.
9. Hernández-Díaz S, Rodríguez LAG: **Steroids and Risk of Upper Gastrointestinal Complications**. *American Journal of Epidemiology* 2001, **153**(11):1089-1093.

10. Shorr RI, Ray WA, Daugherty JR, Griffin MR: **Concurrent use of nonsteroidal anti-inflammatory drugs and oral anticoagulants places elderly persons at high risk for hemorrhagic peptic ulcer disease**. *Archives of internal medicine* 1993, **153**(14):1665-1670.
11. Bhatt DL, Scheiman J, Abraham NS, Antman EM, Chan FKL, Furberg CD, Johnson DA, Mahaffey KW, Quigley EM, Harrington RA: **ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents**. *Journal of the American College of Cardiology* 2008, **52**(18):1502-1517.
12. Navarese EP, Andreotti F, Schulze V, Kołodziejczak M, Buffon A, Brouwer M, Costa F, Kowalewski M, Parati G, Lip GYH *et al*: **Optimal duration of dual antiplatelet therapy after percutaneous coronary intervention with drug eluting stents: meta-analysis of randomised controlled trials**. *BMJ : British Medical Journal* 2015, **350**:h1618.
13. Pithadia AB, Jain S: **Treatment of inflammatory bowel disease (IBD)**. *Pharmacological Reports* 2011, **63**(3):629-642.
14. Ridker PM, Goldhaber SZ, Danielson E, Rosenberg Y, Eby CS, Deitcher SR, Cushman M, Moll S, Kessler CM, Elliott CG: **Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism**. *New England Journal of Medicine* 2003, **348**(15):1425-1434.
15. Kisely S, Lin E, Gilbert C, Smith M, Campbell L-A, Vasiliadis H-M: **Use of administrative data for the surveillance of mood and anxiety disorders**. *Australian & New Zealand Journal of Psychiatry* 2009, **43**(12):1118-1125.
16. Weiss AJ, Barrett ML, Heslin KC, Stocks C: **Trends in Emergency Department visits involving mental and substance use disorders, 2006–2013: statistical brief# 216**. 2006.
17. Centers for Disease Control and Prevention: **Quality Improvement and Care Coordination: Implementing the CDC Guideline for Prescribing Opioids for Chronic Pain**. In. Atlanta, GA: National Center for Injury Prevention and Control, Division of Unintentional Injury Prevention; 2018.
18. **HEDIS Measures** [http://www.ncqa.org/hedis-quality-measurement/hedis-measures]
19. **Measures, Reports & Tools** [https://www.qualityforum.org/Measures_Reports_Tools.aspx]
20. Park TW, Saitz R, Ganoczy D, Ilgen MA, Bohnert ASB: **Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study**. *BMJ : British Medical Journal* 2015, **350**:h2698.
21. Jones CM, McAninch JK: **Emergency department visits and overdose deaths from combined use of opioids and benzodiazepines**. *American journal of preventive medicine* 2015, **49**(4):493-501.
22. Passik SD, Kirsh KL: **Opioid therapy in patients with a history of substance abuse**. *CNS Drugs* 2004, **18**(1):13-25.
23. Boscarino JA, Rukstalis M, Hoffman SN, Han JJ, Erlich PM, Gerhard GS, Stewart WF: **Risk factors for drug dependence among out-patients on opioid therapy in a large US health-care system**. *Addiction* 2010, **105**(10):1776-1782.

Tables

Table 1
Patient demographic and clinical characteristics of patients with a visit for low back pain, 2012–2017

	No opioid prescription at office visit n = 23,541	**Opioid prescription at office visit n = 1,002**	**Total sample n = 24,543**	**P-Value**
	N (%)	N (%)	N (%)	
Total	23,541 (96.9)	1,002 (4.1)	24,543 (100)	
Age				
Under Age 65	17674 (75.1)	739 (73.8)	18413 (75)	
Age 65 and Older	5867 (24.9)	263 (26.2)	6130 (25)	0.45
Sex				
Female	14408 (61.2)	578 (57.7)	14986 (61.1)	
Male	9133 (38.8)	424 (42.3)	9557 (38.9)	0.03
Hispanic Ethnicity				
Non-Hispanic	18463 (78.4)	811 (80.9)	19274 (78.5)	
Hispanic	3762 (16)	137 (13.7)	3899 (15.9)	
Unknown/Refused	1316 (5.6)	54 (5.4)	1370 (5.6)	0.13
Race				
White	13914 (59.1)	585 (58.4)	14499 (59.1)	
Black	4427 (18.8)	274 (27.3)	4701 (19.2)	
Asian/Pacific Islander	2716 (11.5)	57 (5.7)	2773 (11.3)	
Other/Unknown	2484 (10.6)	86 (8.6)	2570 (10.5)	< 0.001
Marital Status				
Single	7399 (31.4)	296 (29.5)	7695 (31.4)	

	No opioid prescription at office visit n = 23,541	Opioid prescription at office visit n = 1,002	Total sample n = 24,543	P-Value
Married, Domestic Partnership, or Significant Other	12147 (51.6)	487 (48.6)	12634 (51.5)	
Divorced, Legally Separated, or Widowed	3112 (13.2)	189 (18.9)	3301 (13.4)	
Other/Unknown	883 (3.8)	30 (3)	913 (3.7)	< 0.001
Employment Status				
Full Time, Self-Employed, Part-Time, Full-Time Student	14567 (61.9)	593 (59.2)	15160 (61.8)	
Retired	4304 (18.3)	199 (19.9)	4503 (18.3)	
Disabled or Never Worked	1048 (4.5)	64 (6.4)	1112 (4.5)	
Not Employed, Unknown, or Missing	3622 (15.4)	146 (14.6)	3768 (15.4)	0.01
Chronic NSAID Use				
No	23238 (98.7)	985 (98.3)	24223 (98.7)	
Yes	303 (1.3)	17 (1.7)	320 (1.3)	0.26
Tobacco User				
Never Smoker	16493 (70.1)	609 (60.8)	17102 (69.7)	
Ever Smoker, Quit	4911 (20.9)	251 (25)	5162 (21)	
Ever Smoker, Current	1938 (8.2)	136 (13.6)	2074 (8.5)	
Unknown	199 (0.8)	6 (0.6)	205 (0.8)	< 0.001
Opioid Use Prior to the Index Visit				
No Opioid Use 45 Days Prior to Index Visit	22177 (94.2)	735 (73.4)	22,912 (93.4)	
Intermittent Opioid Use Prior to Index Visit	1036 (4.4)	158 (15.8)	1194 (4.9)	

	No opioid prescription at office visit n = 23,541	Opioid prescription at office visit n = 1,002	Total sample n = 24,543	P-Value
Long-Term Opioid Use Prior to Index Visit	328 (1.4)	109 (10.9)	437 (1.8)	< 0.001

Table 2
Patient clinical diagnoses or medication use which are contraindications for NSAIDs

	No opioid prescription at office visit n = 23,541	Opioid prescription at office visit n = 1,002	Total sample n = 24,543	P-Value
	N (%)	N (%)	N	
Kidney Disease				
None	22307 (94.8)	906 (90.4)	23213 (94.6)	
Diagnosed	1234 (5.2)	96 (9.6)	1330 (5.4)	< 0.001
Liver Disease				
None	23116 (98.2)	983 (98.1)	24099 (98.2)	
Diagnosed	425 (1.8)	19 (1.9)	444 (1.8)	0.83
Inflammatory Bowel Disease				
None	23357 (99.2)	991 (98.9)	24348 (99.2)	
Diagnosed	184 (0.8)	11 (1.1)	195 (0.8)	0.27
Cardiovascular or Cerebrovascular Disease				
None	21233 (90.2)	891 (88.9)	22124 (90.1)	
Diagnosed	2308 (9.8)	111 (11.1)	2419 (9.9)	0.19
Gastrointestinal Disorder, including GERD, Peptic Ulcers, or Bleeding				
None	21021 (89.3)	895 (89.3)	21916 (89.3)	
Diagnosed	2520 (10.7)	107 (10.7)	2627 (10.7)	0.98
Chronic Systemic Steroid Use				
No	23445 (99.6)	584 (67.5)	10917 (51.9)	

	No opioid prescription at office visit n = 23,541	Opioid prescription at office visit n = 1,002	Total sample n = 24,543	P-Value
Yes	96 (0.4)	281 (32.5)	10103 (48.1)	< 0.001
Concurrent of Chronic Anticoagulant or Antiplatelet Use				
No	19662 (83.5)	713 (71.2)	20375 (83)	
Yes	3879 (16.5)	289 (28.8)	4168 (17)	< 0.001
Abbreviations: NSAIDs: Non-steroidal anti-inflammatory drugs				

Table 3
Patient clinical diagnoses or medication use which are relative contraindications for opioids

	No opioid prescription at office visit n = 23,541	Opioid prescription at office visit n = 1,002	Total sample n = 24,543	P-Value
	N (%)	N (%)	N (%)	
Depression Disorder				
No	21206 (90.1)	876 (87.4)	22082 (90)	
Yes	2335 (9.9)	126 (12.6)	2461 (10)	< 0.01
Anxiety Disorder				
No	20333 (86.4)	830 (82.8)	21163 (86.2)	
Yes	3208 (13.6)	172 (17.2)	3380 (13.8)	< 0.01
Substance Use Disorder				
No	22168 (94.2)	875 (87.3)	23043 (93.9)	
Yes	1373 (5.8)	127 (12.7)	1500 (6.1)	< 0.001
Bipolar Disorder				
No	23275 (98.9)	975 (97.3)	24250 (98.8)	
Yes	266 (1.1)	27 (2.7)	293 (1.2)	< 0.001
Benzodiazepine Prescribed at Index Visit				
No	22989 (97.7)	925 (92.3)	23914 (97.4)	
Yes	552 (2.3)	77 (7.7)	629 (2.6)	< 0.001

Table 4
Marginal effects of clinical comorbidities and concurrent or chronic prescriptions on the probability of receiving an opioid prescription during a primary care visit for low back pain (2012–2017)

	Model 1	Model 2	Model 3	Model 4
	Full Sample n = 24,543	No Opioid Use 45 Days Prior to Index Visit n = 22,912	Intermittent Opioid Use Prior to Index Visit n = 1,165	Long-Term Opioid Use Prior to Index Visit n = 437
Contraindications to NSAIDS				
Kidney Disease	0.03*** (0.01, 0.04)	0.02** (0.01, 0.04)	0.09 (0, 0.18)	-0.01 (-0.18, 0.16)
Liver Disease	-0.01 (-0.02, 0.01)	-0.01 (-0.03, 0.01)	-0.05 (-0.15, 0.05)	-0.01 (-0.22, 0.2)
Inflammatory Bowel Disease	0.01 (-0.02, 0.04)	0.01 (-0.02, 0.03)	0.08 (-0.19, 0.35)	-0.03 (-0.32, 0.25)
Cardiovascular or Cerebrovascular Disease	-0.01 (-0.01, 0)	0 (-0.01, 0)	-0.06* (-0.11, -0.01)	0.01 (-0.08, 0.1)
Gastrointestinal Disorder, including GERD, Peptic Ulcers, or Bleeding	-0.01 (-0.01, 0)	-0.01 (-0.01, 0)	-0.03 (-0.08, 0.02)	-0.06 (-0.16, 0.05)
Index or Chronic Anticoagulant or Antiplatelet Use	0.02*** (0.01, 0.03)	0.02*** (0.01, 0.03)	0.02 (-0.03, 0.07)	0.07 (-0.02, 0.16)
Relative contraindications to opioids				
	Full Sample	No Opioid Use 45 Days Prior to Index Visit	Intermittent Opioid Use Prior to Index Visit	Long-Term Opioid Use Prior to Index Visit
Depression Disorder	0 (-0.01, 0.01)	0 (-0.01, 0.01)	0 (-0.06, 0.06)	0.01 (-0.12, 0.13)

	Model 1	Model 2	Model 3	Model 4
Anxiety Disorder	-0.01 (-0.01, 0)	0 (-0.01, 0)	-0.07** (-0.11, -0.03)	0.02 (-0.05, 0.1)
Substance Use Disorder	0.01* (0, 0.03)	0.02** (0.01, 0.03)	0.01 (-0.07, 0.09)	0.03 (-0.08, 0.15)
Bipolar Disorder	0.02 (-0.01, 0.05)	0.03 (0, 0.05)	0.15* (0, 0.3)	-0.15** (-0.25, -0.05)
Chronic Systemic Steroid Use	-0.02* (-0.04, 0)	-0.01 (-0.04, 0.01)	–	-0.15 (-0.32, 0.03)
Benzodiazepine Prescribed at Index Visit	0.07*** (0.05, 0.09)	0.06*** (0.04, 0.08)	0.15 (-0.03, 0.33)	0.10** (0.14, 0.53)
Note: In all models, we also controlled for age, race, ethnicity, sex, marital status, employment status, tobacco use, year of the prescription, and chronic use of Non-steroidal anti-inflammatory drugs. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$				

Supplementary Files

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- AppendixTableofContents.docx
- 2020.08.20AppropriateOpioidPrescribingKellerFINAL.docx