CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

A Tool to Assess Risk of De Novo Opioid Abuse or Dependence

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ABSTRACT

BACKGROUND: Determining risk factors for opioid abuse or dependence will help clinicians practice informed prescribing and may help mitigate opioid abuse or dependence. The purpose of this study is to identify variables predicting opioid abuse or dependence.

METHODS: A retrospective cohort study using de-identified integrated pharmacy and medical claims was performed between October 2009 and September 2013. Patients with at least 1 opioid prescription claim during the index period (index claim) were identified. We ascertained risk factors using data from 12 months before the index claim (pre-period) and captured abuse or dependency diagnosis using data from 12 months after the index claim (postperiod). We included continuously eligible (pre- and postperiod) commercially insured patients aged 18 years or older. We excluded patients with cancer, residence in a long-term care facility, or a previous diagnosis of opioid abuse or dependence (identified by International Classification of Diseases 9th revision code or buprenorphine/naloxone claim in the pre-period). The outcome was a diagnosis of opioid abuse (International Classification of Diseases 9th revision code 304.0x) or dependence (305.5).

RESULTS: The final sample consisted of 694,851 patients. Opioid abuse or dependence was observed in 2067 patients (0.3%). Several factors predicted opioid abuse or dependence: younger age (per decade [older] odds ratio [OR], 0.68); being a chronic opioid user (OR, 4.39); history of mental illness (OR, 3.45); nonopioid substance abuse (OR, 2.82); alcohol abuse (OR, 2.37); high morphine equivalent dose per day user (OR, 1.98); tobacco use (OR, 1.80); obtaining opioids from multiple prescribers (OR, 1.71); residing in the South (OR, 1.65), West (OR, 1.49), or Midwest (OR, 1.24); using multiple pharmacies (OR, 1.59); male gender (OR, 1.43); and increased 30-day adjusted opioid prescriptions (OR, 1.05).

CONCLUSIONS: Readily available demographic, clinical, behavioral, pharmacy, and geographic information can be used to predict the likelihood of opioid abuse or dependence.

 • The American Journal of Medicine (2016) 129, 699-705

KEYWORDS: Demographic factors; Opioid abuse; Opioid dependence; Pharmacy claims-based factors; Predictive model; Prescription drug monitoring program

The United States has seen a dramatic increase in opioid prescriptions in the past decade with a concomitant increase in abuse of opioid medications.[1] There has been a tripling in the rate of opioid-related overdose deaths from 2000 to 2014, with more than 28,000 deaths in 2014.[2] This epidemic creates a dilemma for prescribers who seek to provide adequate pain

Funding: TC receives support from an unrestricted grant from the Foundation for Barnes-Jewish Hospital. RI and AB receive salary support from Express Scripts, an independent pharmacy benefits manager. DT also received salary support from Express Scripts at the time the study was conducted. BFG receives support from Washington University Institute of Clinical and Translational Sciences Grant UL1 TR000448 from the National Institutes of Health.

Conflict of Interest: None.

Authorship: All authors had access to the data and played a role in writing this manuscript.

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0002-9343/$ -see front matter
http://dx.doi.org/10.1016/j.amjmed.2016.02.014

relief while minimizing risks of abuse and dependence. Abuse is defined as the intentional self-administration of a medication for a nonmedical reason,[3] whereas dependence is a maladaptive pattern of substance use.[4,5]

Guidelines exist for using opioids in noncancer pain,[6] but prescribers face challenging situations when prescribing opioids and need tools to aid their decisions. Prescription drug monitoring programs can help reveal aberrant behavior. Forty-nine states have enacted these programs; however, monitoring alone does not prevent abuse.[7-10] Currently, there are limited tools that help predict which patients may develop opioid abuse or dependence. The Opioid Risk Tool identifies at-risk patients on the basis of medical, family, and social history.[11] However, the Opioid Risk Tool does not combine patient and prescription drug monitoring program information to assess risk. Clinicians need to know how risk factors ascertained at the time of prescribing opioids predict subsequent abuse or dependence.

CLINICAL SIGNIFICANCE

- Readily available variables can help quantify the risk of developing opioid abuse.
- Chronic opioid use and history of mental illness are the strongest predictors of abuse.

The objective of this study is to identify demographic characteristics, clinical and behavioral factors obtained from prescription drug monitoring programs, and pharmacy and geographic factors that quantify the risk of developing opioid abuse or dependence. These factors are immediately available to a prescriber by patient interview and by accessing a prescription drug monitoring program and could help assess the risk of prescribing opioids. Once at-risk patients are identified, additional screening tests could be used by the prescriber[12,13] and treatment of abuse and dependence could be pursued.

MATERIALS AND METHODS

We used de-identified (in accordance with Health Insurance Portability and Accountability Act requirements) pharmacy and medical claims data from a pharmacy benefit manager (Express Scripts) from October 1, 2009, to September 30, 2013. These data include health insurance claims (inpatient/outpatient medical and outpatient pharmacy) and enrollment data from large employers and health plans across the United States. This study included patients aged 18 years or older as of the index opioid claim date.

International Classification of Diseases, Ninth Revision (ICD−9) codes were used to identify medical diagnoses. First Data Bank "Smart Key" classifications were used to identify opioids on the basis of pharmacy claims.[14] Smart Key Specific Therapeutic Class designations (4-digit codes describing therapeutic drug classes) and Generic Code Numbers (5-digit numbers that group equivalent products based on active ingredients) were used to classify pharmacy claims (**Appendix 1**, available online). Dosage strengths for Specific Therapeutic Class were used in calculating daily morphine equivalent dosing and to classify immediate- vs extended-release opioids.

Exclusion criteria included patients with a cancer diagnosis (**Appendix 2**, available online), with claims for chemotherapy or antiemetics (**Appendix 3**, available online), in residence in long-term care facilities (residence code of 03 from the National Council of Prescription Drug Programs 384-4x classification), in convalescence after chemotherapy (ICD-9 V66.2), or in hospice/palliative/end-of-life care (ICD-9 V66.7). Patients with a prior opioid dependency diagnosis (within 365 days before the index claim) or who were taking buprenorphine/naloxone (typically used to treat opioid dependence) also were excluded (**Appendix 4**, available online).

To predict the likelihood of opioid abuse or dependency, we conducted a retrospective claims analysis. Derivation and validation models were developed. For the derivation model (Figure), we identified patients on the basis of 1 or

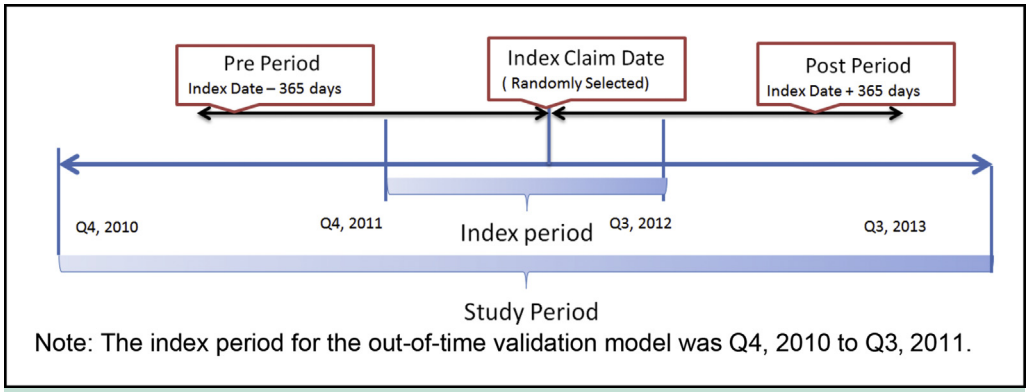

Figure Study timeline for the derivation model.

more claims for opioids in the index period (October 1, 2011, to September 30, 2012); the index claim was a randomly selected opioid claim. For the validation model, we identified patients on the basis of 1 or more claims for opioids in the index period (October 1, 2010, to September 30, 2011), again randomly selected. For both models, we ascertained risk factors using data from 12 months before the index claim (pre-period) and captured abuse or dependency diagnosis by ICD-9 code using data from 12 months postindex claim (postperiod). All patients were continuously eligible during pre- and postperiods.

The primary outcome measure was an ICD-9 diagnosis of nondependent opioid abuse (304.0x) or dependence (305.5x) in the postperiod. Patient characteristics based on pharmacy and medical claims were included as independent variables, including demographic, clinical, behavioral, pharmacy claims, and geographic factors. All factors were measured before the index date.

Variables included age[15] (calculated at the index claim) and the chronic use of opioids[16] (defined as claims for >90 days of opioids in the 6 months before and including the index date). Clinical variables of history of mental illness,[17,18] nonopioid substance abuse,[17] and nondependent alcohol abuse[17-19] were identified by ICD-9 codes (**Appendix 5**, available online). We identified high morphine equivalent dose users (≥120 mg morphine equivalent dosing daily)[20-22] by using pharmacy claims. The other clinical variable, tobacco use disorder,[18,23] also was identified by ICD-9 code.

Prescriber shopping was hypothesized to be a risk factor,[15,24,25] and patients were identified as prescriber shoppers if they received opioid prescriptions from ≥2 prescribers[15] within 60 days before and inclusive of the index date. Geographic region is associated with opioid abuse or dependence.[17] Patients were classified into geographic regions (Northeast, South, West, or Midwest as defined by US Census Bureau[26]) according to their index claim state of residence.

Pharmacy shopping also was considered as a risk factor,[15,24,27] and patients were considered pharmacy shoppers if they filled opioid prescriptions at 3 or more pharmacies[15,24] within 60 days before and inclusive of the index date. Prior research indicates that men are more likely to be opioid abusers than women.[17,28] We hypothesized that the same relationship would be observed for opioid abuse or dependence.

Pharmacy claims were used to determine the number of opioid prescriptions in the pre-period.[17] To capture prior use of opioids, the number of 30-day adjusted opioid prescriptions in the pre-period was used. Day's supply of all opioid prescriptions was divided by 30.4 days/month to convert to months and address the day's supply differential between dispensing channels. Pharmacy claims also identified long-term use of immediate-release opioids. For patients who were taking opioids for at least 6 months of the pre-period, we computed a ratio of immediate release to total opioids being taken. Patients were considered chronic immediate-release users if this ratio exceeded 0.5.

We computed a binary distance variable of less than and greater than 50 miles from patient to index opioid prescriber based on centroids of the respective ZIP codes. We hypothesized that potential opioid abusers or dependents would travel farther to receive an opioid prescription.

From a population of approximately 1.4 million patients with at least 1 opioid claim during the index period for the derivation model, 694,851 patients constituted the final analytic sample (**Table 1**). Datasets were created and statistical analyses were conducted using SAS version 9.3 and SAS Enterprise Guide version 5.1 (SAS Institute Inc, Cary, NC). Descriptive statistics included comparison of bivariate differences in risk factors between opioid abusers or dependents and nonabusers or nondependents using analysis of variance for continuous variables and chi-square tests for categoric variables. All comparisons were 2-tailed. Variance inflation factor was analyzed to ascertain multicollinearity among independent variables.

Multivariate logistic regression analyses were performed to predict the likelihood of opioid abuse or dependence. To address potential bias in the estimated coefficient and to test the robustness of the findings, 2 sensitivity analyses were conducted (**Appendix 6**, available online).

Validation was conducted to assess performance of the predictive model in an independent sample. The validation model design was identical to the derivation model with the exception of index period. The index period for the validation model was 1 year earlier, from October 1, 2010, to September 30, 2011, which resulted in a cohort of 634,588 patients.

This research was exempt from institutional review board approval on the basis of the Code of Federal Regulation, §46.101b, from the US Department of Health and Human Resources,[29] and exempted from the Washington University Institutional Review Board.

Table 1 Sample Selection Methodology and Description of Sample Size

	Derivation Model	Validation Model
Study Selection Criteria	N	N
Total patients with opioid prescription claims during index period*	1,428,137	1,453,996
No cancer diagnosis or medication	1,348,793	1,376,236
Not in long-term care facilities	1,345,908	1,376,210
Not in hospice care facilities	1,345,720	1,376,052
No diagnosis for prior drug dependency	1,339,418	1,370,631
Continuously eligible during pre- and postperiod	751,937	689,519
Aged ≥18 y as of the index date	696,922	636,620
No missing values for key covariates	694,851	634,588

*Derivation model: index period Q4 2011 to Q3 2012; validation model: index period Q4 2010 to Q3 2011.

RESULTS

The derivation cohort included 694,851 patients, of whom 2067 (0.3%) were opioid abusers/dependents. They were significantly younger (Table 2). There were more chronic opioid users (55.8% vs 10.4%) in the group that developed abuse or dependence.

Clinical factors significantly varied between the 2 groups of patients. Opioid abusers/dependents had a higher proportion of mental illness (52.1% vs 14.9%) and nonopioid substance abuse (4.1% vs 0.2%), and nondependent alcohol abuse (4.0% vs 0.5%) compared with nonabusers/nondependents. Furthermore, opioid abuse/dependence was associated with high morphine equivalent dose users (19.3% vs 1.9%) and tobacco use disorder (19.4% vs 4.4%).

Opioid abuser/dependents were more likely to be prescriber shoppers (35.6% vs 11.6%). There were also significant regional differences among the 2 groups, with the South, West, and Midwest having a higher percentage of abusers or dependents compared with the Northeast.

Pharmacy shopping differed between the 2 groups. There was a higher percentage of pharmacy shoppers (6.8% vs 0.6%) in the opioid abuse/dependence group than in the nonopioid abusers/dependence group. There was a higher proportion of men in the abuse/dependence group than in the nonabuser/nondependent group. Patients who developed abuse or dependency averaged higher numbers of 30-day adjusted opioid prescriptions in the pre-period (9.3 vs 1.8) and more chronic immediate-release users (32.2% vs 6.8%).

The derivation and validation data set found similar effects for all variables, except that a long (>50 miles) distance between patient and index opioid prescriber was significantly more common among opioid abusers/dependents in the derivation dataset but not in the validation data.

As indicated by a variance inflation factor of less than 10 for all variables, independent variables in the model did not have a high level of collinearity. Thus, all variables were retained in the model. The c-statistic was 0.852 for the derivation model and 0.847 for the validation model, indicating that the 2 models (Table 3) successfully discriminate between opioid abusers/dependents and nonabusers or nondependent patients.

Younger age (odds ratio [OR], 0.68 per decade older; 95% confidence interval [CI], 0.65-0.70) significantly predicated opioid abuse or dependence. Chronic use of opioids (OR, 4.39; 95% CI, 3.71-5.19) and history of mental illness (OR, 3.45; 95% CI, 3.13-3.79) were strong predictors of developing opioid abuse/dependence. Histories of other substance abuse (OR, 2.82; 95%, CI, 2.18-3.64) and alcohol abuse (OR, 2.37; 95% CI, 1.84-3.05), and doses of opioids

Table 2 Baseline Characteristics*

	Derivation Model		Validation Model	
Measure	Dependent	Nondependent	Dependent	Nondependent
No.	2067	692,784	1580	633,008
Age, mean (SD)	44.1 (15.5)	48.8 (15.6)	43.6 (15.1)	49.1 (15.6)
Chronic users, N (%)	1154 (55.8)	72,072 (10.4)	869 (55.0)	62,597 (9.9)
Mental illness, N (%)	1076 (52.1)	103,398 (14.9)	781 (49.4)	86,546 (13.7)
Nonopioid substance abuse, N (%)	84 (4.1)	1696 (0.2)	59 (3.7)	1280 (0.2)
Nondependent alcohol abuse, N (%)	82 (4.0)	3191 (0.5)	55 (3.5)	2623 (0.4)
Daily MED ≥120 mg/d, N (%)	398 (19.3)	13,075 (1.9)	301 (19.1)	15,663 (2.5)
Tobacco use disorder, N (%)	401 (19.4)	30,584 (4.4)	290 (18.4)	23,663 (3.7)
Prescriber shoppers, N (%)	735 (35.6)	80,354 (11.6)	575 (36.4)	72,373 (11.4)
Region, N (%)				
Northeast	386 (18.7)	218,291 (31.5)	313 (19.8)	206,560 (32.6)
South	772 (37.4)	198,229 (28.6)	489 (31.0)	172,457 (27.2)
West	409 (19.8)	111,168 (16.1)	368 (23.3)	104,301 (16.5)
Midwest	500 (24.2)	165,096 (23.8)	410 (26.0)	149,690 (23.7)
Pharmacy shoppers, N (%)	141 (6.8)	3855 (0.6)	125 (7.9)	3406 (0.5)
Percent male, N (%)	994 (48.1)	298,126 (43.0)	780 (49.4)	271,038 (42.8)
Prior opioid 30-d adjusted prescriptions, mean (SD)	9.3 (9.3)	1.8 (4.1)	9.1 (9.2)	1.7 (4.0)
Chronic immediate-release users, N (%)	665 (32.2)	46,839 (6.8)	536 (33.9)	40,069 (6.3)
Distance from patient to prescriber, N (%)				
≤50 miles	1747 (84.5)	600,035 (86.6)	1343 (85.0)†	539,518 (85.2)†
>50 miles	320 (15.5)	92,749 (13.4)	237 (15.0)†	93,490 (14.8)†

MED = morphine equivalent dose; SD = standard deviation.

*All data were significantly different at $P < .05$ between opioid dependents and nondependents, except for cells marked with a note indicating otherwise.

†Not significantly different between opioid dependents and nondependents at $P < .05$.

Table 3 Multivariate Adjusted Odds Ratio for Opioid Dependency Models

		Derivation Model‡		Validation Model‡	
	Reference	OR*	95% CI	OR*	95% CI
Age (per decade of life)	NA	0.68	0.65-0.70	0.65	0.63-0.68
Chronic users	Absent	4.39	3.71-5.19	4.29	3.53-5.22
Mental illness	Absent	3.45	3.13-3.79	3.37	3.02-3.76
Nonopioid substance abuse	Absent	2.82	2.18-3.64	2.87	2.11-3.89
Nondependent alcohol abuse	Absent	2.37	1.84-3.05	2.10	1.55-2.85
Daily MED ≥120 mg/d	Absent	1.98	1.68-2.34	1.93	1.61-2.32
Tobacco use disorder	Absent	1.80	1.60-2.04	2.09	1.81-2.40
Prescriber shoppers	Absent	1.71	1.55-1.89	1.74	1.55-1.95
South region	Northeast	1.65	1.45-1.87	1.44	1.25-1.67
West region	Northeast	1.49	1.29-1.72	1.70	1.46-1.99
Midwest region	Northeast	1.24	1.08-1.42	1.31	1.13-1.53
Pharmacy shoppers	Absent	1.59	1.31-1.92	1.98	1.61-2.43
Male	Female	1.43	1.31-1.57	1.52	1.37-1.68
Prior opioid 30-d adjusted prescriptions	NA	1.05	1.04-1.06	1.04	1.03-1.05
Chronic immediate-release user	Absent	1.07†	0.93-1.22	1.27	1.09-1.48
Distance from patient to prescriber	≤50 miles	1.12†	0.99-1.27	0.95†	0.83-1.10

CI = confidence interval; MED = morphine equivalent dose; NA = not applicable (for continuous variables); OR = odds ratio.
*All data were significant at $P < .05$ unless marked with a note indicating otherwise.
†Not significant at $P < .05$.
‡The c-statistics were 0.852 for the derivation model and 0.847 for the validation model.

≥120 mg or morphine equivalents per day (OR, 1.98; 95% CI, 1.68-2.34) elevated the risk of developing opioid abuse or dependence. Tobacco use (OR, 1.80; 95% CI, 1.60-2.04); prescriber shoppers (OR, 1.71; 95% CI, 1.55-1.89); and residing in the South (OR, 1.65; 95% CI, 1.45-1.87), West (OR, 1.49; 95% CI, 1.29-1.72), and Midwest (OR, 1.24; 95% CI, 1.08-1.42) compared with the Northeast also were significant predictors of developing opioid abuse/dependence.

Finally, pharmacy shoppers (OR, 1.59; 95% CI, 1.31-1.92), male gender (OR, 1.43; 95% CI, 1.31-1.57), and each additional 30-day adjusted opioid prescription (OR, 1.05; 95% CI, 1.04-1.06) were predictive of developing opioid abuse/dependence.

Distance from patient to prescriber was not statistically significant in either model. Being a chronic immediate-release user was insignificant in the derivation model.

With only 1 exception (chronic immediate-release opioid), the predictors of opioid abuse or dependence that were significant in the derivation model also were significant in the validation model. Additional sensitivity analyses (**Appendix 6**, available online) corroborated the associations in the derivation and validation models.

DISCUSSION

This study identified 12 patient characteristics that predict increased risk of de novo abuse or dependence in opioid users. The strongest predictors were chronic use, mental illness, nonopioid substance use, alcohol abuse, high morphine equivalent dose per day, younger age, and male gender. These effects were in the direction as hypothesized. In this study, the relationships between the distance from patient to prescriber and being a chronic immediate-release user to the odds of developing opioid abuse or dependence were not consistently significant. All identified risk factors are available through patient history or a prescription drug monitoring program. Thus, our study provides useful risk factors for prescribers to be able to determine a patient's risk of developing opioid abuse or dependence in the next 12 months. These factors can help prescribers weigh the risks and benefits of prescribing opioids.

Our findings are consistent with prior research. Dufour et al[30] developed a predictive model using data from 1 commercial insurer with 3500 cases of opioid abuse or dependence. They also found a lower risk with advanced age and high risks among men.

Our results also are consistent with those of Edlund et al,[31] who evaluated 46,000 patients in Arkansas. They reported that opioid abuse or dependence was associated with mental health disorders, prior opioid abuse, younger age (18-30 years), prior nonopioid substance abuse, and higher morphine equivalent dose per day. White et al[27] developed an abuse prediction model based on 116,382 patients in Maine who used opioids. One of their main findings was that ≥4 opioid prescriptions (OR, 7.34) and early refills (OR, 3.39) predicted abuse. Dose escalation also was a significant risk factor (OR, 1.88). We did not assess early refills or dose escalation because they cannot be assessed at the time of first prescription. Compared with

these seminal studies, our study is larger and more representative of the US population.

Rice et al[17] also studied a large, representative dataset. Their findings of nonopioid drug abuse (OR, 9.89) and a history of mental illness (OR, 2.45) increasing the risk for opioid abuse support our findings. Our study differentiates from prior studies in that we quantified how readily available demographic, clinical, behavioral, pharmacy, and geographic information predict opioid abuse or dependence. Prescribers will be able to use these variables in real-time to make a more accurate risk assessment of developing opioid abuse or dependence.

Study Limitations

First, the model is not implementable in states without a prescription drug monitoring program, but 49 states have a program in place or pending. Second, our study did not include Medicare, Medicaid, or Veterans Administration patients and awaits validation in these populations. However, most of the total US population is covered by private insurance.[32] Third, because we used 1 year of ICD-9 codes after the index claim for identifying opioid abuse or dependence, we likely failed to capture some episodes of abuse or dependence. Future studies could include longer follow-up. Finally, the relationship between receiving $\geq$50% of the total dose in the immediate-release form and being diagnosed with opioid abuse or dependence was significant in the validation model, but not in the derivation model.

CONCLUSIONS

In light of the opioid abuse epidemic, the findings of this study warrant updating tools that estimate the risk for abuse or dependence. We recommend incorporating factors found in a prescription drug monitoring program into a patient's risk analysis. We found that risk factors for a patient being diagnosed with opioid abuse or dependence are younger age; being a chronic opioid user; histories of mental illness, nonopioid substance abuse, and alcohol abuse; being a high morphine equivalent dose user; a history of tobacco use; using multiple prescribers; residing in the South, West, or Midwest; using multiple pharmacies; male gender; and an increasing number of opioid prescriptions. Our study quantifies risk factors that are available to prescribers who are considering prescribing opioids. These insights highlight the importance of using readily available demographic, clinical, pharmacy, and geographic information to estimate the risk for opioid abuse or dependence.

ACKNOWLEDGMENTS

H. M. Dinesh, MS, Genpact, contributed to data collection. From Express Scripts, Craig Reno, BS, MBA, provided clinical expertise on the analysis, Ria Westergaard, PharmD, provided clinical expertise on the analysis. In addition to the authors, Ruth Martinez, RPh, contributed to writing and editing the manuscript.

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SUPPLEMENTARY DATA

Supplementary appendices accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.amjmed.2016.02.014.

APPENDICES

Appendix 1 Specific Therapeutic Class and Associated Description for Opioid Claims

STC	STC Description
0268	Analgesics, narcotics
6122	Narcotic antitussive first-generation antihistamine-decongestant combination
7740	Analgesics narcotic, anesthetic adjunct agents
8483	Narcotic antitussive-anticholinergic combination
8485	Narcotic antitussive first-generation antihistamine
8502	Narcotic antitussive-decongestant combinations
8514	Narcotic antitussive-decongestant-expectorant combination
8518	Narcotic antitussive-expectorant combination
8769	Analgesic narcotic agonist NSAID combination
B902	Analgesic narcotics-dietary supplement combination
B947	Narcotic nonsalicylate analgesic-barbiturate-xanthine combination
B955	Narcotic salicylate analgesics-barbiturate-xanthine combination
B974	Narcotic analgesic-nonsalicylate analgesic combination
C423	Narcotic antitussive-decongestant-analgesic-expectorant combination
C431	Narcotic antitussive first-generation antihistamine-analgesic, nonsalicylate combination
C618	Narcotic salicylate analgesic combination

NSAID = nonsteroidal anti-inflammatory drug; STC = Specific Therapeutic Class.

Appendix 2. International Classification of Diseases, 9th Revision Cancer Diagnosis Codes for Patient Exclusion Criteria

ICD-9 codes 140-165, 170-176, 179-209 excluding benign neoplasms under 209.x (209.4*, 209.5*, and 209.6*) were used to identify patients with cancer.

*Denotes all combination codes under the ICD-9.

ICD-9 = International Classification if Diseases, 9th Revision.

Appendix 3 Generic Code Numbers Associated with Cancer Drug Markers for Patient Exclusion Criteria

STC Description	Generic Code Numbers Used
Antineoplastic — selective retinoid receptor agonists (retinoid X receptor)	92373
Antibiotic antineoplastics	29203, 34241, 34242, 34247, 34248, 35080, 38581, 38590, 38591, 38592, 38593, 38594, 38600, 38601, 38602, 38610, 38613, 38622, 38623, 38630, 47340, 47343, 94175, 96679, 97242, 97271, 97272, 97277, 97278, 97282, 99510, 99835
Anti-CD20 (B lymphocyte) monoclonal antibody	27827, 30137
Antiemetic/antivertigo agents	16007, 16008, 17256, 17258, 20011, 20228, 23756, 29247, 33531, 60548, 99260, 99267, 99335, 99862
Antileprotics	19321, 28301, 95392, 98220
Antineoplast humanized VEGF inhibitor recomb monoclonal antibody	21427
Antineoplast, histone deacetylase inhibitors	28397, 97345
Antineoplast — alkylating agents	6939, 7182, 7196, 9217, 12014, 14401, 17724, 24699, 24701, 34221, 34310, 38232, 38340, 38350, 38351, 38352, 38353, 38357, 38360, 38361, 38370, 38380, 38390, 38410, 38420, 38422, 38431, 38432, 38433, 38440, 38450, 38451, 38910, 38911, 38912, 38920, 48862, 60901, 72722, 72730, 72731, 72732, 72733, 72734, 92893, 92903, 92913, 92933, 97957, 98310, 98311, 98709, 98710, 98813
Antineoplast — antidrogenic agents	450, 22642, 22645, 25740, 29886, 33183
Antineoplast — antimetabolites	880, 10290, 12473, 19901, 21179, 21473, 21485, 21501, 21503, 22663, 23432, 23439, 24037, 25932, 27027, 27365, 27663, 27664, 30776, 30777, 30778, 31611, 31612, 32981, 34230, 34231, 38490, 38500, 38520, 38530, 38531, 38532, 38540, 38541, 38542, 38543, 93472, 97455, 97456, 97457, 97458, 97825, 99268
Antineoplast — Aromatase inhibitors	17300
Antineoplast — epothilones and analogs	98998, 98999
Antineoplast — halichondrin B analogs	29249
Antineoplast — Hedgehog pathway inhibitor	31307
Antineoplast — Janus kinase inhibitors	30892, 30893, 30894, 30895, 30896
Antineoplast — mTOR kinase inhibitors	20784, 20844, 28783, 31396, 34589, 34590, 34592, 98597
Antineoplast — topoisomerase I inhibitors	14254, 14256, 22661, 29519, 97955, 97956, 99056, 99790
Antineoplast — VEGF A and B isoforms, and PLGF inhibitors	32988, 32989
Antineoplast — vinca alkaloids	38560, 38572, 38580, 38820, 38970, 97327, 97630
Antineoplast antibody/radioactive-drug complexes	20159, 20160
Antineoplast epidermal growth factor receptor blocker monoclonal antibody	13632, 13638, 13639, 15979, 15983, 28471, 32343
Antineoplast immunomodulator agents	26314, 26315, 27276, 27277, 29809, 29811, 29812, 31911, 34147, 34148, 34149, 34150, 34743
Antineoplast LHRH and GNRH agonist, pituitary suppressant	13133, 15338, 15344, 16945, 16946, 17377, 18155, 19219, 21004, 23768, 24301, 28506, 28507, 29894, 30083, 84590, 84591, 84592, 84593, 84594, 84596, 84597, 84598, 84601, 84602, 99763, 99764
Antineoplast systemic enzyme inhibitors	13369, 19586, 19656, 19907, 19908, 23793, 23794, 23795, 26263, 26452, 26453, 26454, 27257, 27258, 27259, 27829, 28737, 29405, 29406, 29817, 29818, 30332, 30457, 30458, 31294, 31295, 32722, 33199, 33202, 33363, 33873, 33874, 33903, 33904, 33905, 34723, 34724, 34726, 34727, 98140, 99070, 99867
Antineoplast antibody/antibody-drug complexes	14171, 18373, 18374, 20158, 21050, 24507, 30404, 34234, 34235
Antineoplast — miscellaneous	7480, 7481, 7544, 7550, 7552, 7560, 14103, 24094, 24231, 28663, 28762, 29066, 29591, 29662, 29663, 29664, 30918, 33734, 38710, 38730, 38731, 38732, 38740, 38750, 39000, 39150, 39152, 39153, 39154, 47410, 48480, 48481, 48590, 85410, 85602, 85602, 93610
Chemotherapy rescue/antidote agents	1330, 27236, 31194, 36901, 38950, 38953, 38955, 87552, 87553, 87554, 87555, 87556, 87557, 87558, 87559, 87562, 87563, 89655
CXCR4 chemokine receptor antagonist	16124

Appendix 3 Continued

STC Description	Generic Code Numbers Used
Cytotoxic T-lymphocyte antigen recombinant monoclonal antibody	29688, 29689
Immunomodulators	26405, 46471, 46472, 47511, 47512, 47513, 47520, 47521, 47522, 47523, 47524, 47525, 47526, 47527, 47528, 47529, 47530, 47600, 47601, 47602, 47603, 47604, 47605, 47661, 47662, 47663, 48891, 48931, 48941, 49031, 90823, 90833
Keratinocyte growth factor	23928
Leukocyte (WBC) stimulants	13206, 13308, 13309, 15666, 26001, 26220, 26221, 26222
LHRH (GNRH) agonist analog pituitary suppressants	23768, 80254, 84350
Selective estrogen receptor modulators	17307, 17308, 38720, 38721, 50377
Steroid antineoplastics	38640, 38661, 38700
Tissue protective treatment of chemotherapy extravasation	30562
Topical antineoplastic and premalignant lesion agents	89921

GNRH = gonadotropin-releasing hormone; LHRH = luteinizing hormone; MTOR = mammalian target of rapamycin; PLGF = placental growth factor; STC = specific therapeutic class; VEGF = vascular endothelial growth factor; WBC = white blood cell.

Appendix 4 Generic Code Numbers Associated with Suboxone for Patient Exclusion Criteria

STC Description	Generic Code Numbers Used
Narcotic withdrawal therapy agents	18973, 18974, 28958, 28959, 33741, 33744, 34904, 34905, 36677, 36678, 36679

STC = specific therapeutic class.

Appendix 5 International Classification of Diseases, Ninth Revision Codes Associated with Independent Variables

Description	ICD-9 Code
Nonopioid substance abuse	304.1-304.9 and 305.2-305.9, excluding 305.5x
Tobacco use disorder	305.1
Nondependent alcohol abuse	303.9 and 305.0x
Mental illness	290-302 and 306-316

ICD-9 = International Classification of Diseases, Ninth Revision.

APPENDIX 6. SENSITIVITY ANALYSES TO TEST THE ROBUSTNESS OF THE FINDINGS

The first sensitivity analysis was "Firth's bias-adjusted estimation," which maximizes a penalized likelihood function and provides finite parameter estimates. Second was "oversampling" to increase the target rate by 10 times. This helps address the bias resulting from the margin of sampling error being related to the outcome sample size.

Sensitivity Analysis Using Firth Bias-Adjusted Estimation Method and Oversampling Method

		Firth's Bias-Adjusted Estimation Model‡		Oversampling Method Model‡	
	Reference	OR*	95% CI	OR*	95% CI
Age	NA	0.96	0.96-0.97	0.96	0.96-0.96
Chronic users	Absent	4.39	3.71-5.19	3.98	3.28-4.83
History of mental illness	Absent	3.45	3.13-3.79	3.63	3.28-4.03
History of nonopioid substance abuse	Absent	2.83	2.18-3.63	3.93	2.84-5.44
History of nondependent alcohol abuse	Absent	2.38	1.84-3.04	2.64	1.93-3.60
Daily MED ≥120 mg/d	Absent	1.98	1.67-2.34	1.83	1.50-2.24
History of tobacco use disorder	Absent	1.80	1.59-2.04	2.04	1.77-2.34
Prescriber shoppers	Absent	1.71	1.55-1.89	1.71	1.53-1.91
Region					
South	Northeast	1.65	1.45-1.87	1.79	1.56-2.05
West	Northeast	1.49	1.29-1.72	1.52	1.30-1.78
Midwest	Northeast	1.24	1.08-1.42	1.29	1.12-1.50
Pharmacy shoppers	No	1.59	1.31-1.92	2.03	1.58-2.61
Male	Female	1.43	1.31-1.57	1.52	1.37-1.68
Prior opioid 30-d adjusted prescriptions	NA	1.05	1.04-1.06	1.06	1.05-1.07
Chronic immediate-release users	Absent	1.06†	0.93-1.22	1.03†	0.88-1.21
Distance from patient to prescriber	≤50 miles	1.12†	0.99-1.27	1.12†	0.98-1.28

CI = confidence interval; MED = morphine equivalent dosing; NA = not applicable (for continuous variables); OR = odds ratio.
*All data were significant at $P < .05$ unless marked with a note indicating otherwise.
†Not significant at $P < .05$.
‡The c-statistics for the Firth's bias-adjusted estimation model was 0.853, and oversampling method model was 0.876.