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Factors predicting development of opioid use disorders among individuals who receive an initial opioid prescription: Mathematical modeling using a database of commercially-insured individuals

Bryan N. Cochran[a,*], Annesa Flentje[b], Nicholas C. Heck[a], Jill Van Den Bos[c], Dan Perlman[c], Jorge Torres[c], Robert Valuck[d], Jean Carter[e]

[a] Department of Psychology, Skaggs Building Room 143, The University of Montana, Missoula, MT 59812, United States
[b] University of California, San Francisco, San Francisco General Hospital, 1001 Potrero Avenue, Suite 7 M, San Francisco, CA 94110, United States
[c] Milliman, Inc., 1400 Wewatta St, Suite 300, Denver, CO 80202, United States
[d] University of Colorado, Skaggs School of Pharmacy and Pharmaceutical Sciences, Mail Stop C238, 12850 E. Montview Blvd. V20-1201, Aurora, CO 80045, United States
[e] Department of Pharmacy Practice, 32 Campus Drive, The University of Montana, Missoula, MT 59812, United States

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ABSTRACT

Background: Prescription drug abuse in the United States and elsewhere in the world is increasing at an alarming rate with non-medical opioid use, in particular, increasing to epidemic proportions over the past two decades. It is imperative to identify individuals most likely to develop opioid abuse or dependence to inform large-scale, targeted prevention efforts.
Methods: The present investigation utilized a large commercial insurance claims database to identify demographic, mental health, physical health, and healthcare service utilization variables that differentiate persons who receive an opioid abuse or dependence diagnosis within two years of filling an opioid prescription (OUDs) from those who do not receive such a diagnosis within the same time frame (non-OUDs).
Results: When compared to non-OUDs, OUDs were more likely to: (1) be male (59.9% vs. 44.2% for non-OUDs) and younger ($M = 37.9$ vs. 47.7); (2) have a prescription history of more opioids (1.7 vs. 1.2), and more days supply of opioids ($M = 272.5$, vs. $M = 33.2$; (3) have prescriptions filled at more pharmacies ($M = 3.3$ per year vs. $M = 1.3$); (4) have greater rates of psychiatric disorders; (5) utilize more medical and psychiatric services; and (6) be prescribed more concomitant medications. A predictive model incorporating these findings was 79.5% concordant with actual OUDs in the data set.
Conclusions: Understanding correlates of OUD development can help to predict risk and inform prevention efforts.

1. Introduction

North America comprises the world's largest drug market and evidences the highest drug-related mortality rate in the world (International Narcotics Control Board, 2012). Within the United States the problem of prescription drug misuse and opioid misuse (broadly defined as using the medication in a manner different than prescribed) in particular, has reached epidemic proportions. Pain relievers were the most commonly misused drug in the psychotherapeutics category from 2002 to 2011 (Substance Abuse and Mental Health Services Administration (SAMHSA), 2012) and from 2004 to 2011, the number of medical emergencies involving opioids increased by 183% (SAMHSA, 2013).

Abuse of prescription drugs is a significant public health problem, associated with high costs both to the health care system and to the individuals who use them. From an economic perspective, it is estimated that opioid misusers' medical care costs are eight times greater than those of non-misusers (White et al., 2005). Mortality due to prescription drug use is a significant cause of death in the United States, accounting for 36% of all poisoning deaths in 2007, a number that tripled from 1999 to 2007 (Warner et al., 2011). It is estimated that 0.04% of individuals receiving a prescription opioid have a fatal overdose, with the odds of mortality higher among those receiving an opioid for pain (Bohnert et al., 2011).

* Corresponding author. Tel.: +1 4062432391; fax: +1 4062436366.
E-mail address: bryan.cochran@umontana.edu (B.N. Cochran).

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Identifying patients who misuse these substances is often difficult, since clinicians must disentangle legitimate pain management needs from possible abuse. When opioid abuse or dependence develops, patients' medical treatment is complicated by tolerance, withdrawal, or potential overdose. Little is known about factors that may place individuals at risk for the development of prescription drug use disorders. As a recent editorial indicates, these individuals may differ significantly from those who are typically studied in substance use disorder research; specifically, many at risk for opioid use disorders may not have a history of illicit drug use prior to developing a problem with opioids (Darke, 2011). Since the rates of prescribing opioids, state by state, are linked to mortality due to overdose, it is clear that a prescription of an opioid places individuals at risk for eventual misuse (Paulozzi et al., 2011).

1.1. Prediction of misuse of opioids/opioid use disorders

Researchers have attempted to identify factors that may predict later drug abuse and dependence. Earlier age of nonmedical use of prescription drugs, earlier initiation of alcohol use, family history of alcoholism, and polydrug abuse are predictive of greater risk for developing prescription drug abuse or dependence (McCabe et al., 2007). Previous research has found that there are particular demographic variables that place individuals at higher risk for the development of a diagnosis of opioid abuse and dependence. Specifically, individuals who are younger (Edlund et al., 2007, 2010) and male (Edlund et al., 2007) were more likely to develop abuse and dependence. Additionally, receiving a larger number of days' supply of prescription opioids was a predictor of an opioid use disorder diagnosis (Edlund et al., 2007), as was having a higher average daily dose (Edlund et al., 2010).

In addition to demographic and other markers, behaviorally-based criteria have been successfully used to identify problematic cases of prescription drug misuse (Smith et al., 2010). In a recent study, clinical expert raters identified key indicators of misuse, including interpersonal problems, arrest history, multiple opioid use, use for no identifiable reason, and comorbid other substance misuse, and used these indicators along with known indicators of misuse to improve accuracy in identifying misuse. This study indicates that multiple sources of data, particularly those regarding different domains of functioning, may best identify those at risk for opioid abuse and dependence.

1.2. Prescription drug use and mental health disorders

Previous studies have also linked problematic use of prescription drugs and mental health diagnoses. Nonmedical use of opioids has been associated with panic, depressive, social phobic or agoraphobic symptoms, and the overall number of psychiatric symptoms endorsed (Becker et al., 2007a,b). Development of opioid abuse and dependence has also been associated with non-opioid substance use and mental health disorders (Edlund et al., 2007, 2010). Recent prospective research has indicated that non-medical use of prescription medications, including opioids, places individuals at risk for unipolar depressive, bipolar, and anxiety disorders (Schepis and Hakes, 2011). The converse relationship may also be true: other mental health conditions may predispose individuals to misuse opioids. In a recent review of the known factors predicting opioid misuse, the authors caution that although many mental health diagnoses may be risk factors for opioid misuse, these conditions are likely to be concealed due to stigma, and some individuals may choose to take prescription opioids to treat undiagnosed co-occurring disorders rather than the appropriate psychiatric medication (Pergolizzi et al., 2012).

1.3. Purpose of this study

This study seeks to identify demographic and healthcare related variables that predict the development of opioid abuse or dependence, utilizing data obtained from the Thomson Reuters MarketScan Commercial Claims and Encounters (CCAE) database, which contains information about commercially insured and Medicare eligible patients. The use of a large sample, physician-diagnosed disorders, and comprehensive demographic and health care utilization data enable detailed analysis of individuals at risk for the development for opioid abuse or dependence. First, individuals diagnosed with opioid use disorders will be compared with those who are not given opioid use diagnoses on a variety of domains. Second, the use of mathematical modeling techniques will aid in identifying people who are at risk for the development of opioid abuse or dependence.

2. Methods and analytic strategy

Patients within the CCAE database who had at least one opioid prescription claim between January 1, 2000 and December 31, 2008 were identified. Patients were included if they maintained continuous insurance eligibility for 6 months prior to, and 2 years beyond, this initial prescription claim ($N = 2{,}841{,}793$). Individuals who subsequently received an ICD-9 CM diagnosis (304.0× or 305.5×) of opioid abuse or dependence were classified as those with opioid use disorders, hereafter referred to as OUDs, ($n = 2913$), and individuals who did not receive a subsequent opioid abuse or dependence diagnosis were classified as those without opioid use disorders, hereafter referred to as non-OUDs ($n = 2{,}838{,}880$).

Of the OUDs, 266 received a diagnosis of opioid abuse, and the remaining 2647 received a diagnosis of opioid dependence. Abuse and dependence cases were therefore grouped together for the purpose of analyses from this point for the following reasons: (1) over 90% of the cases fell into the more serious category of dependence, (2) an abuse diagnosis is often a precursor to dependence, and (3) the clinical distinction between abuse and dependence is less important than the presence or absence of an addictive condition. Furthermore, the distinction between abuse and dependence has been eliminated in the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013), and replaced with opioid use disorders.

The first set of planned comparisons involved conducting either *t*-tests (for continuous variables) or chi-square analyses (for categorical data) to test for statistically significant differences between cases and controls on a variety of variables present in the database. These analyses also served the purpose of identifying variables of interest for the mathematical modeling to be conducted in the next step. With regard to mental health diagnoses and co-occurring substance use disorders, the predictor variables were not time-dependent (i.e., any lifetime diagnosis was counted as positive in the use of these predictor variables).

Once the variables that statistically discriminated cases from controls were identified, significant interactions between these variables were identified using CHAID (Chi-Square Automatic Interaction Detection) analyses. The goal of a CHAID analysis is to find homogeneous clusters of a response variable where clusters are defined by the levels in a set of predictor variables. Particular emphasis is placed on the interaction of the predictor variables. The algorithm splits the population according to levels in the predictor variable, which make the responses within the resultant groups as similar as possible and the average between groups as different as possible (Biggs et al., 1991; Kass, 1980).

Significant interactions detected through CHAID were reviewed by the research team and included in the subsequent logistic

Table 1
Characteristics of a commercially insured opioid-using population (n = 2,841,793) with comparisons of non-OUDs (n = 2,838,880), and OUDs (n = 2913).

Demographics				
Variable	Entire Sample	Non-OUDs	OUDs	Comparison of non-OUDs and OUDs
Age	Mean (SD)	Mean (SD)	Mean (SD)	t-Value
	47.7 (18.2)	47.7 (18.2)	37.9 (14.8)	35.55*
	n (%)	n (%)	n (%)	X^2
Gender				291.77*
Female	1,586,335 (55.8)	1,585,167 (55.8)	1,168 (40.1)	
Male	1,255,458 (44.2)	1,253,713 (44.2)	1,745 (59.9)	
Region				218.60*
Northeast	267,379 (9.4)	266,915 (9.4)	464 (15.9)	
North Central	816,325 (28.7)	815,376 (28.7)	949 (32.6)	
South	1,255,249 (44.2)	1,254,255 (44.2)	994 (34.1)	
West	497,865 (17.5)	497,359 (17.5)	506 (17.4)	
Other/unknown	4,975 (0.2)	4,975 (0.2)	0.0 (0.0)	
Dependent status				653.65*
Dependent	341,637 (12.0)	340,865 (12.0)	772 (26.5)	
Employee	1,706,933 (60.1)	1,705,676 (60.1)	1,257 (43.2)	
Spouse	793,223 (27.9)	792,339 (27.9)	884 (30.3)	

* $p < 0.0001$.

regression model if the following conditions were met: (1) the levels in the predictor variable split the groups such that there was at least a 10% difference between the resultant groupings, and (2) a minimum of 10 participants per cell would need to result from the interaction split in order to be meaningful for future modeling.

Once the significant variables identified through the bivariate analyses were selected and the CHAID analyses performed, we divided the sample into a build set comprised of 70% of the participants and a validation set comprised of the remaining 30%. The research team devised and tested a series of 18 logistic regression models to fit the data, with variables selected on the basis of several criteria: (1) varying degrees of parsimony, from the simplest demographic variables only to the all-inclusive model using every significant variable and interaction; (2) clinical setting, with models comprised of all mental health variables, or all pharmacy data, for example; and (3) all models were tested both with and without the interaction variables found through the CHAID analyses.

Each model was tested using the validation set. Global null hypothesis tests (i.e., log likelihood ratio, Wald, and Lagrange multiplier "Score" tests) were used to determine presence of one or more significant predictor variables. Model fit was then explored using the Akaike Information Criterion (AIC) model fit index. This index was selected a priori over other fit indices because the models were not nested, built from the same database, and based on a large sample size. In considering fit indices, we did not want to eliminate variables that could be of potential use in future models, which the BIC is prone to do, particularly with large sample sizes (Kass and Raftery, 1995). We wanted to produce a model that favored sensitivity over parsimony, as the AIC does (Dziak et al., 2012). The choice of the best fitting model was based on the AIC, the relative overall parsimony of the model, and the predictive ability of the model to identify OUDs in the validation set.

3. Results

3.1. Bivariate comparisons between OUDs and non-OUDs

For the first series of analyses, bivariate comparisons of OUDs and non-OUDs were completed on variables related to demographics, medical service utilization, co-occurring conditions, and concomitant medication usage. The exact variables of interest were chosen by a team of researchers with expertise in pharmacoeconomics, public health, substance misuse, and mental health.

Table 1 presents demographic metrics for OUDs and non-OUDs. As expected, OUDs were more likely than non-OUDs to be younger (37.9 vs. 47.7 years, respectively) and male (59.9% vs. 44.2% male, respectively). OUDs were also more likely to be a spouse or dependent, rather than the primary insured individual in the plan; 60.1% of non-OUDs were the primary insured person, whereas 43.2% of OUDs were the primary insured.

Table 2
Opioid use and medical service utilization among a commercially insured opioid-using population (N = 2,841,793), with comparisons of non-OUDs (n = 2,838,880), and OUDs (n = 2,913).

Variable	Non-OUDs Mean (SD)	OUDs Mean (SD)	Comparison of non-OUDs and OUDs (t-value)
Rx copayment	$5.84 ($5.13)	$8.69 ($9.70)	15.83*
Number of opioid classes	1.2 (0.4)	1.7 (0.7)	33.35*
Short acting opioid: count of different medications	1.4 (0.7)	2.4 (0.7)	37.04*
Long acting opioid: count of different medications	1.1 (0.4)	1.4 (0.7)	10.31*
Opioid days supply	33.2 (104.9)	272.5 (367.7)	35.11*
Opioid units dispensed	160.0 (890.1)	1,082.1 (2,112.3)	23.56*
Pharmacies visited for opioid claims	1.3 (0.8)	3.3 (3.5)	29.57*
Outpatient physician visits	6.5 (6.8)	10.3 (10.5)	19.76*
Outpatient mental health visits	0.7 (3.1)	9.0 (11.0)	40.96*
Inpatient hospital admissions	0.1 (0.4)	0.8 (1.2)	28.99*
Inpatient mental health admissions	0.0 (0.1)	0.4 (0.7)	322.36*
Hospitalization days	0.5 (2.6)	4.8 (11.1)	89.84*
Mental health hospitalization days	0.0 (0.7)	3.2 (7.2)	232.08*
Emergency room visits	0.3 (0.8)	1.7 (4.0)	18.46*
Hospital days	0.5 (2.6)	4.8 (11.1)	21.14*

* $p < 0.0001$.

Table 3
Mental health diagnoses of a commercially insured opioid-using population (N = 2,841,793), with comparisons of non-OUDs (n = 2,838,880), and OUDs (n = 2,913).

Variable	Non-OUDs n (%)	OUDs n (%)	Comparison of non-OUDs and OUDs X^2
Any anxiety disorder	156,110 (5.5)	842 (28.9)	3050.76*
Any mood disorder	259,375 (9.1)	1,588 (54.5)	7179.6*
Any pain disorder	2,534 (0.1)	59 (2.0)	1174.98*
Any personality disorder	825 (0.0)	23 (0.8)	538.30*
Somatoform disorders	1,805 (0.1)	22 (0.8)	206.08*
Psychotic disorders	4,930 (0.2)	56 (1.9)	498.05*
Any other substance use disorder	96,539 (3.4)	1,681 (57.7)	25,703.25*

* $p < 0.0001$.

Data regarding participants' opioid utilization is presented in Table 2. The number of opioid classes differed significantly between OUDs and non-OUDs (1.7 vs. 1.2, respectively). OUDs also had a higher mean count of both short acting (M = 2.4 vs. M = 1.4 for non-OUDs) and long acting opioids (M = 1.4 vs. M = 1.1 for non-OUDs). Similarly, the number of days of opioid supply that individuals were prescribed during the study period was also different between groups, with OUDs receiving an average of 272.5 days' supply of opioids, and non-OUDs an average of 33.2 days' supply of opioids. Identified OUDs also had a higher number of opioid units dispensed (M = 1082.1 for OUDs vs. M = 160.0 for non-OUDs). Notably, the number of pharmacies visited to fill opioid prescriptions differed significantly between groups, with OUDs visiting an average of 3.3 pharmacies per year, compared to 1.3 for non-OUDs.

Annual medical service utilization rates also differed significantly between groups, as shown in Table 2. OUDs had significantly more physician visits (10.3 vs. 6.5, respectively), outpatient mental health visits (9.0 vs. 0.7), inpatient admissions (0.8 vs. 0.1, respectively), inpatient mental health admissions (0.4 vs. 0.0, respectively), hospitalization days (4.8 vs. 0.5, respectively), mental health hospitalization days (3.2 vs. 0.0, respectively), and emergency department encounters (1.7 vs. 0.3, respectively).

Mental health diagnoses also significantly differentiated the two groups, as shown in Table 3. OUDs were more likely to have diagnoses of anxiety, mood, pain, personality, somatoform, and psychotic disorders than non-OUDs. Whereas 57.7% of OUDs had another substance use disorder diagnosis, only 3.4% of non-OUDs did. In descending order of frequency, the most commonly given substance misuse diagnoses for OUDs were (with comparison percentages for non-OUDs in parentheses afterwards): 20.7% alcohol dependence (0.5%); 16.3% other, mixed, or unspecified drug abuse (0.1%); 13.6% unspecified drug dependence (0.1%); 12.5% combinations of drug dependence excluding opioid (0.1%); 12.1% tobacco dependence (2.4%); 9.4% alcohol abuse (0.5%); 7.1% cocaine dependence (0.0%); 4.1% cannabis dependence (0.1%); 3.9% cocaine abuse (0.0%); and 3.0% cannabis abuse (0.1%). All between-group differences were significant at the $p < 0.001$ level. Other drug abuse or dependence categories occurred in less than 3% of either group.

Medication utilization also significantly differentiated non-OUDs from OUDs. Commensurate with the findings regarding elevated rates of mood and anxiety disorders among OUDs, these individuals were more likely to use SSRI medications (44.7% vs. 14.6%) and benzodiazepines (52.6% vs. 19.5%) than non-OUDs. Tricyclic antidepressant use was also much greater for OUDs (39.3%) than non-OUDs (7.8%); much of this difference was accounted for by the rates of trazodone use (28.9% vs. 2.8%), which is often prescribed for insomnia. Rates of anticonvulsant use (33.5% vs. 6.7%) were also significantly greater among OUDs, with gabapentin accounting for much of this difference (22.7% vs. 4.5%). Medications related to pain also differentiated the two groups; OUDs were more likely to be prescribed skeletal muscle relaxants (40.4% vs. 16.5%), including cyclobenzaprine hydrochloride and carisoprodol, than non-OUDs. The receipt of non-steroidal anti-inflammatory medications, or NSAIDs, was also more common among OUDs than

Table 4
Concomitant medication usage within an opioid-using population with comparisons of non-OUDs (n = 2,838,880) and OUDs (n = 2,913).

Medication	Non-OUDs n (%)	OUDs n (%)	Comparison of non-OUDs and OUDs X^2
Alpha agonist	11,524 (0.4)	139 (4.8)	1346.50***
Anticonvulsant	190,228 (6.7)	977 (33.5)	3335.79***
Other antidepressants	338,870 (11.9)	1,321 (45.3)	3079.58***
SSRI	414,946 (14.6)	1,302 (44.7)	2103.63***
Tricyclics	220,385 (7.8)	1,146 (39.3)	4032.66***
Antipsychotic/neuroleptic	2,811 (0.1)	12 (0.4)	25.66***
Atypical antipsychotic	50,932 (1.8)	691 (23.7)	7832.31***
Antispasmodic	15,341 (0.5)	108 (3.7)	534.02***
Anxiolytic	31,280 (1.1)	235 (8.1)	1281.15***
Benzodiazepines	553,373 (19.5)	1,531 (52.6)	2022.54***
Beta blocker	41,238 (1.5)	132 (4.5)	190.14***
Calcium channel blockers	173,186 (6.1)	148 (5.1)	5.11*
Corticosteroids	432,342 (15.2)	576 (19.8)	46.18***
Cox 2 inhibitors	414,720 (14.6)	493 (16.9)	12.32**
Hemorrheological	8,965 (0.3)	3 (0.1)	3.54
Local anesthetic	39,520 (1.4)	159 (5.5)	346.52***
Neuroleptic	168 (0.0)	3 (0.1)	31.07***
NSAIDs	845,243 (29.8)	1,301 (44.7)	307.69***
Skeletal muscle relaxant	468,465 (16.5)	1,177 (40.4)	1203.54***
THC derivative for pain	1,812 (0.1)	10 (0.3)	31.27***
Sumatriptan	5,652 (0.2)	18 (0.6)	23.58***

* $p < 0.05$.
** $p < 0.001$.
*** $p < 0.0001$.

Table 5
Odds ratio estimates and confidence intervals for variables in the final predictive model of opioid misuse.

Variable	Odds ratio	95% confidence interval	
		Lower	Upper
Demographics			
1. Age	0.97	0.96	0.97
2. Gender (male)	2.31	2.07	2.57
3. Employee (vs. dependent/spouse)	0.79	0.70	0.89
Diagnoses			
4. Any anxiety disorder	1.28	1.12	1.46
5. Unipolar mood disorder	2.01	1.77	2.28
6. Bipolar disorder	0.55	0.45	0.67
7. Other mood disorder	0.96	0.72	1.29
8. Adjustment disorder	1.21	1.03	1.43
9. Any pain disorder	1.28	0.82	2.00
10. Any somatoform disorder	1.19	0.62	2.31
11. Pain disorder due to a general med. condition	1.16	1.02	1.33
12. Chronic pain diagnosis	0.79	0.71	0.90
13. Any psychotic disorder	0.49	0.32	0.75
14. Antisocial personality disorder	0.03	0.002	0.42
15. Borderline personality disorder	0.26	0.12	0.58
16. Alcohol dependence	2.63	2.20	3.16
17. Barbiturate or sedative/hypnotic dependence	12.07	8.25	17.64
18. Cocaine dependence	2.12	1.57	2.88
19. Cannabis dependence	1.52	1.08	2.14
20. Amphetamine dependence	0.70	0.41	1.20
21. Hallucinogen dependence	5.34	1.36	20.94
22. Other unspecified drug dependence	1.36	0.31	19.94
23. Combinations of drug dependence excluding opioid	11.60	6.85	19.60
24. Unspecified drug dependence	64.46	38.60	107.66
25. Alcohol abuse	0.63	0.50	0.79
26. Tobacco dependence	1.48	1.24	1.77
27. Cannabis abuse	1.12	0.76	1.66
28. Barbiturate or sedative/hypnotic abuse	2.81	1.54	5.14
29. Cocaine abuse	1.55	1.05	2.28
30. Amphetamine abuse	1.10	0.55	2.21
31. Other unspecified drug abuse	7.42	4.64	11.86
32. Malingering	0.05	0.01	0.40
Opioid variables			
33. Long-acting opioids dispensed	1.42	1.34	1.50
34. Short-acting opioids dispensed	3.44	3.18	3.72
Health service utilization			
35. Emergency department encounters	1.04	1.02	1.05
36. Inpatient mental health admissions	1.32	1.16	1.50
37. Inpatient mental health days	1.02	1.01	1.03
38. Outpatient mental health visits	1.04	1.04	1.05
Interactions identified via CHAID (numbers correspond to vars. above)			
24 × 37	0.02	<0.001	2.13
34 × 37	2.24	2.11	2.37
24 × 36	21.68	0.18	>999
23 × 24	0.07	0.04	0.12
24 × 34	0.67	0.56	0.80
17 × 23	0.26	0.13	0.53
23 × 34	0.75	0.61	0.93
17 × 31	0.47	0.23	0.99
31 × 34	0.81	0.67	0.98
1 × 34	0.94	0.88	1.00

non-OUDs (44.7% vs. 29.8%). Medications are listed by category in Table 4.

3.2. Model selection for predicting OUD

The research team devised a series of models using the build set, which were then used to test for predicting OUD status within the validation set. These models were developed to include variables that could be reasonably expected to be present in other data sets. For example, one model was a "diagnostic data only" model including solely ICD-9 diagnoses, which are coded the same as DSM-IV-TR diagnoses for mental health conditions (American Psychiatric Association, 2000; World Health Organization, 1977). Another model was comprised of "medical utilization data only" measures and was designed to use variables that might be available in other insurance or health data sets. A "pharmacy data only" model included utilization variables related to medications and opioid use data, similar to what might be available to a pharmacy benefit manager researcher.

The CHAID procedure identified a number of significant interactions that met the criteria outlined in the Methods section. These interactions were added to the core variables for each model, but only if the variables involved in the interaction were also included in the model individually.

The model that was selected as the best fit for the data was comprised of mental health variables; specifically, this model included the diagnostic status for ICD-9 (World Health Organization, 1977)

mental disorders and the health service utilization variables that focused on mental health (e.g., number of mental health hospitalizations, number of outpatient mental health visits). This model provided the best fit for the data, as defined by AIC values (18,938.1 for this model, compared to a range of 18,582.9–25,763.8 for the models tested) and by overall parsimony. The log likelihood ratio test (LR) for the selected model was 12,695 ($df = 49$) ($p < 0.0001$). The remaining models had LR values ranging from 5785 ($df = 7$) to 13,095 ($df = 72$); all of these ratios were also statistically significant ($p < 0.0001$). Likewise, the results for the Wald and Score tests were significant across all models. In comparison to the selected model, the only other model with a lower AIC value contained all of the variables presented in the bivariate comparisons above, as well as all significant interactions involving these variables, while only providing a modest decrease in AIC. The resulting model is presented in Table 5. This predictive model was 79.5% concordant with actual OUDs in the validation data set, meaning that almost four-fifths of the OUDs were correctly identified when the model was applied to a different sample of participants.

As is noted in Table 5, the demographic variables significantly differentiate OUDs from non-OUDs, though the effect sizes for these variables are quite small. Diagnostic data, particularly variables of barbiturate abuse/dependence, unspecified drug abuse/dependence, and polysubstance (combination) drug dependence had strong effect sizes in differentiating OUDs from non-OUDs. The amount of short-acting opioid, measured in morphine equivalent units, dispensed was a better predictor than the amount of long-acting opioid. It should be noted that the magnitude and the directionality (in some instances) of the odds ratios in Table 5 differ from the bivariate comparisons in Table 3; in modeling multiple variables simultaneously, bivariate relationships are subject to change. Finally, ten interactions remained in this model, primarily involving the aforementioned variables of short-acting opioids dispensed, unspecified drug dependence, polysubstance dependence, and barbiturate dependence. Participant age, inpatient mental health admissions, and mental health inpatient days were also present in the significant interaction variables.

4. Discussion

The detection of opioid misuse is an important step in addressing the public health problems of prescription drug abuse, dependence, diversion, and overdose. Although previous studies have identified some of the factors that place individuals at greater risk for misuse of opioids, this investigation benefits from a comprehensive database that has illuminated more differences between those who develop opioid use disorders and those who receive an initial prescription but do not develop a diagnosis of opioid dependence or abuse. Additionally, this study may be useful in providing health plans with a method for monitoring claims data that may assist in detecting members who are at risk for substance misuse, potentially providing relevant feedback to medical providers.

The current study replicates the findings of previous studies that being male and younger are associated with increased risk of becoming an OUD; an additional significant difference captured in this dataset is that those who were OUDs are less likely to be the primary insured individual, and are more likely to be a dependent or spouse/partner of the primary insured.

OUDs significantly differed from non-OUDs in a number of other areas, as well. The prescription patterns for opioids were quite different between these groups, with OUDs receiving a larger supply of opioids, paying a significantly higher copayment for opioids, and receiving more short-acting opioids than non-OUDs. The directionality of this relationship is unclear from this study; it is possible that particular prescribing patterns place individuals at greater risk for developing a problem with opioids, but it is also possible that OUDs are more likely to request short-acting, and a greater number of, medications from a health care provider.

Health service utilization was also significantly greater among OUDs than among non-OUDs. This finding was present among inpatient and outpatient clinics, emergency department, general medical care, and mental health specialty care visits. As with the relationship between opioid prescribing and misuse, the directionality of this relationship is also unclear. OUDs are likely to be at risk for other health problems that may co-occur with their opioid misuse; depression, anxiety, infections, metabolic difficulties, and injuries are all possible correlates of opioid misuse. Conversely, individuals who have other health problems may start to use opioids, and to misuse them, as a means of coping with their difficulties, such as chronic pain or mental health difficulties.

The patterns of medication usage help to clarify, to some extent, the differences between OUDs and non-OUDs. OUDs are more likely to be receiving treatment for anxiety, depression, chronic pain, and many other conditions than non-OUDs.

The mathematical modeling of opioid misuse, and the resultant predictors of misuse that were identified in the final model, underscore the relationship between mental health, other substance misuse, and opioid abuse/dependence. It is noteworthy that of the different models that were tested to identify OUDs, diagnostic and mental health care variables rose to be among the most robust predictors. This finding has implications for future research and practice. In settings that serve individuals at high risk for opioid misuse, collecting data on co-occurring mental health conditions, mental health treatment history, and psychotropic medication usage is imperative in identifying those who may be at risk for developing an opioid use disorder. Those identified as at-risk may benefit from indicated prevention programs that educate individuals about signs of prescription drug misuse and the relationship between opioid use and mental health conditions. Treating co-occurring mental health difficulties is an important part of addressing the health of individuals who are prescribed opioids.

Variables that significantly predicted OUDs must, in some cases, be interpreted within the context of significant interactions that were identified through CHAID analysis. Due to the atheoretical nature of CHAID analysis, the significant interactions were not anticipated prior to the analytic process; however, several variables (units of short-acting opioids dispensed and a diagnosis of unspecified drug dependence, for example) frequently appeared in the significant interaction terms. Implications of these interactions include, for example, the finding that the impact of receiving short-acting opioids depends on co-occurring substance use diagnoses when predicting OUDs. These interactions may be of clinical utility in identifying individuals, through data readily available to health plans, who are at risk for OUDs and may benefit from prevention efforts.

The model developed in this study was designed for use in the entire population of patients in the database, regardless of where they live. Given the significant regional differences in the distribution of diagnosed OUDs, future studies should test the model at the regional level to determine whether location impacts model performance.

This investigation has a number of limitations that prevent broader conclusions from being drawn about opioid abuse and dependence. The key limitations are the use of an existing data set and the reliance on a physician's diagnosis of abuse and dependence. Many individuals may develop an opioid use disorder that does not come to the attention of their physician(s). Those who have a diagnosis of abuse or dependence may represent an unusual opioid using population, in that they may have either talked with their physician directly about a potential problem or have such florid difficulties with misuse that it is evident

to their health care provider or providers. The operationalization of co-occurring mental health and other substance use disorders as any lifetime diagnosis is also a limitation of this study, as important temporal relationships between opioid misuse and other mental health problems cannot be established. Given the possible bidirectional development of such difficulties, the research team did not specify a priori any time frame for co-occurring disorders, though such analysis could be an important line of future research in this area.

The primary strengths of this study are the large sample size, the comprehensive number of variables regarding study participants, and the use of claims data, the likes of which may be generally available to health plans for use in their own risk stratification and intervention. Those interested in the prediction of opioid misuse may not have all of the significant variables present in their data sets, and thus may not be able to directly apply the particular mathematical model created here.

To summarize, the detection of opioid misuse has important implications for public health; better identification of individuals at risk may help to reduce morbidity and mortality that is often associated with opioid use disorders. The current study made use of a large, comprehensive data set that may aid researchers and clinicians in their attempts to address this important issue.

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Contributors

Author Bryan Cochran was involved in study design, writing of the report, and data interpretation. Annesa Flentje and Nicholas Heck were involved in data interpretation, background literature review, and manuscript writing. Author Jill Van Den Bos led a data analysis team at Milliman that included Dan Perlman and Jorge Torres; these authors all conducted the relevant analyses and provided feedback on the manuscript. As a consultant on the project, author Robert Valuck assisted in the translation of variables into opioid equivalence units and provided direction on the pharmaceutical variable selection process; he also reviewed the manuscript prior to submission. Author Jean Carter was involved in study design and manuscript review. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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