

ORIGINAL RESEARCH

Predictors of Transitioning to Incident Chronic Opioid Therapy Among Working-Age Adults in the United States

J. Douglas Thornton, PharmD, PhD; Nilanjana Dwibedi, PhD; Virginia Scott, PhD; Charles D. Ponte, PharmD; Douglas Ziedonis, MD; Nethra Sambamoorthi, PhD; Usha Sambamoorthi, PhD

BACKGROUND: Opioids have been prescribed and used for chronic noncancer pain at prolific rates in the United States during the past 2 decades. Patients who transition to incident chronic opioid therapy are at increased risk for significant negative health consequences, including cardiovascular risk, endocrine disorders, opioid use disorder, and death.

OBJECTIVE: To identify the leading predictors associated with transitioning to incident chronic opioid therapy among working-age adults without cancer.

METHODS: This retrospective observational cohort study is based on medical and pharmacy claims of a nationally representative sample of adults enrolled in commercial health insurance plans. Standard parametric (logistic regressions) and nonparametric methods based on a decision tree were used for prediction. To facilitate comparison with the available published literature, we also present adjusted odds ratios (AORs) and 95% confidence intervals (CIs). The 10% random sample of 491,442 patients included in the study who were working-age adults (age, 28-63 years) were insured in a commercial health plan, did not have cancer, and initiated opioid therapy between January 2007 and May 2015. Transition to incident chronic opioid therapy was defined as having claims for at least a 90-day supply of opioids within 120 days after the index date (ie, initiation of opioid therapy). Predictive models used for the analysis comprised a comprehensive list of factors available in the claims data, including opioid regimen characteristics, pain conditions, physical and mental health conditions, concomitant medications use (ie, benzodiazepine, stimulants, nonopioid analgesics, and polypharmacy), patient characteristics, and health insurance type.

RESULTS: In our sample, the transition to incident chronic opioid therapy was 1.3% and pain-specific diagnoses were documented for only one-third (31.7%) of patients. The 4 leading predictors of chronic opioid therapy were opioid duration of action (AOR, 12.28; 95% CI, 8.06-18.72), the parent opioid compound (eg, tramadol vs codeine; AOR, 7.26; 95% CI, 5.20-10.13), the presence of conditions that are very likely to cause chronic pain (AOR, 5.47; 95% CI, 3.89-7.68), and drug use disorders (AOR, 4.02; 95% CI, 2.53-6.40).

CONCLUSIONS: The initial opioid regimen's characteristics are powerful predictors of chronic opioid therapy. Predictive algorithms created from readily available claims data can be used to develop real-time predictions of the future risk for a patient's transition to chronic opioid use.

KEY WORDS: chronic opioid use, chronic pain, databases, decision tree, noncancer pain, opioid regimen, pharmacoepidemiology, predictive modeling

Stakeholder Perspective, page 20

Am Health Drug Benefits.
2018;11(1):12-21
www.AHDBonline.com

Manuscript received October 18, 2017
Accepted in final form December 5, 2017

Disclosures are at end of text
Supplemental materials online

Dr Thornton is Assistant Professor, College of Pharmacy, Department of Pharmaceutical Health Outcomes and Policy, University of Houston, TX; Dr Dwibedi is Assistant Professor, School of Pharmacy, Department of Pharmaceutical Systems and Policy, West Virginia University, Morgantown; Dr Scott is Professor, School of Pharmacy, Department of Pharmaceutical Systems and Policy, West Virginia University; Dr Ponte is Professor, Department of Clinical Pharmacy, School of Pharmacy, West Virginia University; Dr Ziedonis is Professor and Associate Vice Chancellor for Health Sciences, University of California San Diego; Dr N. Sambamoorthi is Adjunct Faculty, School of Professional Studies, Northwestern University, Chicago, IL; Dr U. Sambamoorthi is Professor, School of Pharmacy, Department of Pharmaceutical Systems and Policy, West Virginia University.

The views expressed in this article are those of the authors and do not reflect the official policy or position of West Virginia University or any other affiliated organizations.

Copyright © 2018 by Engage Healthcare Communications, LLC; protected by U.S. copyright law.
Photocopying, storage, or transmission by magnetic or electronic means is strictly prohibited by law.

KEY POINTS

- Opioids are widely prescribed for noncancer pain, but they are associated with serious consequences, including missed work or loss of employment, drug overdose, and death.
- This retrospective study is based on claims data for 491,442 US working-age adults enrolled in a commercial health insurance plan.
- This is the first study to investigate the risk of transitioning to incident chronic opioid use among patients with noncancer pain.
- The overall rate of transitioning to incident chronic opioid use was 1.3%.
- The likelihood of transitioning to chronic opioid use was higher with long-acting opioids (37.0%) than with immediate-release opioids (1.3%).
- The initial opioid regimen's characteristics are effective predictors of transitioning to chronic opioid use.
- The 4 key predictors were the opioid's duration of action, the parent opioid compound, presence of chronic pain, and drug use disorders.
- Prescribers can use these factors to determine the potential for a patient to transition to chronic opioid therapy when first prescribing opioid therapy.

Chronic noncancer pain is prevalent among US adults, costs approximately \$600 billion annually, and can be especially burdensome for working-age adults because of lost productivity and the negative impact of this condition on a patient's quality of life.¹⁻⁶ Many patients with chronic noncancer pain receive effective nonopioid treatments and opioid therapy, despite a lack of robust evidence about the efficacy and effectiveness of the latter.⁷⁻⁹ In 2012, a total of 259 million prescriptions for opioids were written in the United States.¹⁰

Patients who receive short-term opioid therapy may be at high risk for becoming users of chronic opioid therapy, which is defined as the use of an opioid for 90 days.^{7,11} Chronic use of opioid therapy places patients at risk for exacerbating their current condition, onset of new chronic physical and/or mental health conditions, and serious opioid-related adverse effects, such as a drug overdose, abuse, and death.^{7,12-15}

An estimated 1 in 550 patients treated with opioids for chronic noncancer pain die from an opioid-related cause in the United States, and the risk for death increased 24-fold for patients who were prescribed very high daily doses of an opioid.¹⁶ These findings suggest that opioid regimen characteristics play a crucial role in

escalating the risk for chronic opioid therapy use and its associated adverse consequences.

However, the factors that influence the transition of working-age adults with chronic noncancer pain to chronic opioid therapy use are not well understood.^{7,17} It is important to examine the use of chronic opioid therapy among working-age adults, because they may suffer from unique and negative consequences, such as missed work days, loss of employment, and decreased productivity, in addition to opioid use–related complications such as high economic burden through increased emergency department, inpatient, and other healthcare utilization.^{12-15,18,19}

Given these potentially serious consequences, it is important to determine the predictors of transitioning from acute to chronic opioid therapy among working-age adults.²⁰ Identifying working-age adults who are at high risk for transitioning to chronic opioid therapy and determining the factors that place them at risk for the transition can augment clinicians' knowledge to aid with prescribing decisions, initial opioid regimen selection, or monitoring,^{21,22} as well as inform early risk mitigation efforts, which have shown some efficacy in preventing opioid-related overdose and death.^{7,23,24}

Previous researchers have assessed the transition from acute to chronic opioid therapy among several groups of patients, including veterans, patients using a single healthcare system, and low-income Medicaid beneficiaries.^{11,25,26} Other studies have used predictive models to identify patients who were diagnosed with incident substance use disorders or opioid abuse.^{27,28} To date, no study has analyzed the transition to incident chronic opioid therapy in working-age adults using nationwide data.

Therefore, the objective of this study was to identify the predictors of transition to incident chronic opioid therapy among working-age adults without cancer based on claims data of a nationally representative sample of commercially insured adults in the United States. This information can allow clinicians and insurers to personalize patients' treatment options, including nonopioid regimens for adults who are at high risk for transitioning to chronic opioid therapy. Changes to treatment guidelines based on these predictors can be assessed by researchers, policymakers, and government payers.

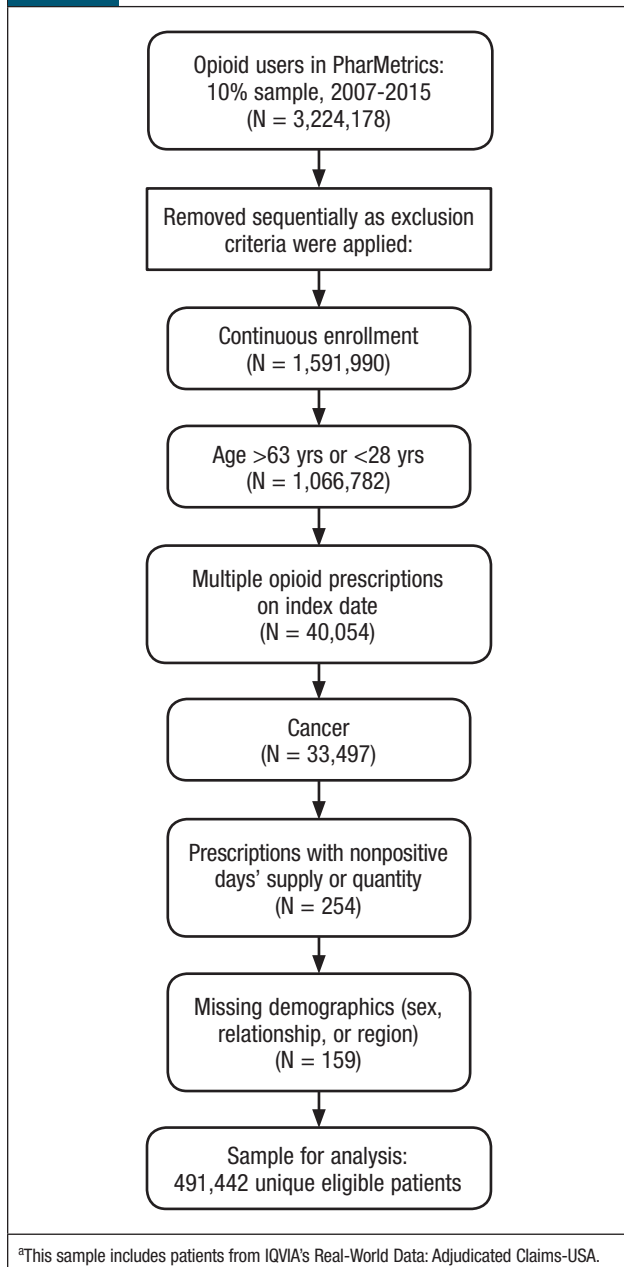
We used robust predictive modeling techniques to identify the leading predictors of incident chronic opioid therapy based on readily available information in medical and pharmacy claims databases; such modeling can be applied to real-time data customized to specific geographic regions, providers, or health insurers.^{27,28}

Methods

The study data were derived from an adjudicated

Figure 1

Study Sample: Inclusion and Exclusion Criteria Applied to Patients with Incident Opioid Prescriptions, 2007-2015^a



claims (ie, inpatient, outpatient, emergency department, and prescription) database that includes approximately 150 million enrollees in commercial health plans in the United States between 2006 and 2015. The database is owned by IQVIA (formerly IMS Health/Quintiles) information services (IQVIA's Real-World Data: Adjudicated Claims-USA), from which we used data on a 10% random sample. The full database from which the 10% was sampled covers 90% of hospitals, 80% of doctors, and

85% of large companies in the United States. These data only include health plans that submit data for all their members, and the data are considered nationally representative of the commercially insured US population.^{29,30}

We conducted a retrospective cohort study with baseline and follow-up periods. A patient's first prescription for an opioid between January 2007 and May 2015 was defined as the index date, which was used to create the baseline period (ie, 12 months before the index date) and the follow-up period (120 days after the index date).

To ensure that we captured individuals who were free of opioid use at baseline, we used the first prescription date between January 2007 and May 2015. The National Drug Codes for opioids were extracted from the National Library of Medicine's RxNav and RxMix.³¹ These conversions allowed for the categorization of opioids at a more granular level (eg, by parent opioid compound and duration of action).

The study sample consisted of 491,422 adults who were aged 28 to 63 years at the index date, did not have cancer, and were continuously enrolled in a primary commercial insurance plan during the entire observation period (ie, from baseline through the follow-up periods). Continuous enrollment in pharmacy benefits and in medical benefits was required. We excluded 10,594 individuals who had more than 1 opioid prescription on the index date, because we were unable to evaluate the initial opioid regimen characteristics for these individuals. We also excluded 23 individuals because they were missing data on the region in which they live (Figure 1).

Measures

Dependent Variable

An enrollee was classified as having incident chronic opioid therapy if he or she had at least a 90-day supply of opioids during the follow-up period (ie, 120 days after the index date).

Independent Variables

The opioid regimen characteristics included the opioid's duration of action (ie, long-acting and immediate-release), the standardized dose, and the parent opioid compound, which were assessed based on the first opioid prescription. The parent opioid compound was grouped into 5 categories—codeine, hydrocodone, oxycodone, tramadol, and other opioids. Because the data use agreement with the data's owner specified that opioids manufactured by a single manufacturer could not be isolated, we combined all the "single-manufacturer drugs" and "other opioids" into 1 category. Methadone can be used for the treatment of opioid use disorder or for pain; therefore it was not included as an eligible opioid in our sample. The standardized opioid dose was calculated in mil-

ligrams of morphine equivalents, using the opioid morphine equivalent conversion factors approved by the Centers for Medicare & Medicaid Services.³²

Patient enrollment characteristics included patient insurance plan type (ie, health maintenance organization [HMO], preferred provider organization [PPO], or other) and primary insured relationship (ie, self, spouse, other, and unknown). Patient demographics included age, sex, and US region (ie, East, Midwest, South, and West).

The clinical factors were the presence or absence of diagnoses for pain conditions, mental illnesses, and a set of chronic conditions adapted from the Department of Health & Human Services (HHS) priority conditions for research, program, and policy.^{33,34} Pain conditions were also categorized as (1) conditions that are highly likely for chronic pain, (2) likely for chronic pain, and (3) acute pain.^{35,36} Because arthritis is a pain condition as well as an HHS priority condition, arthritis was considered separately, so that it would not be counted twice.

International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes were used to assess each of the 3 pain conditions.³⁵ The ICD-9-CM codes did not overlap between the lists. The drug use disorders included drug dependence (ICD-9-CM code 304), drug abuse (ICD-9-CM code 305.2-305.9), and drug-induced mental disorders (ICD-9-CM code 292).

Generic Product Identifier (GPI) codes, a hierarchical classification system that identifies drugs from their primary therapeutic use to package size in 2-digit increments, were used to assess the medication-related characteristics. These characteristics included concomitant use of benzodiazepines (GPI-4 of 57.10), stimulants (GPI-4 of 61.10 or 61.40), or nonopioid analgesics (GPI-2 of 66 or 64). The pharmacotherapy burden was estimated, with polypharmacy defined as ≥ 5 medication classes.³⁷ Concomitant medications were measured during the last 4 months of the baseline period.

Statistical Analyses: Predictive Modeling

Standard parametric (logistic regressions) and nonparametric methods based on a decision tree were used for prediction. The nonparametric method—random forests—is a decision tree method that can be used for its predictive accuracy and protection of overfitting compared with other techniques. Random forests can be used to evaluate a vast set of predictor variables, even in the presence of complex interactions, by building a collection of decision trees and averaging them by bootstrapping (or resampling) both samples and variables.²¹

The parametric and nonparametric methods were compared using receiver operator characteristic curves. Predictive modeling differs from standard regression approaches in many ways. Although standard regression

analyses focus on the average relationship between the transition to chronic opioid therapy and the explanatory variables, predictive modeling can target patients who have the highest risk for transitioning to chronic opioid therapy, such as with efforts to develop interventions for patients with diabetes.³⁸

Standard regression analyses are typically conducted in a given sample, whereas predictive models use bootstrap samples of observations (ie, bagging) and a sample of variables (ie, attribute bagging) and test the estimated model in a holdout or test sample.^{21,39} To accomplish this, we randomly split the eligible sample into the 3 subsamples of training (60%), validation (20%), and testing (20%). After a final model was identified using the training and validation subsamples, the predictive model was tested on the holdout sample to assess performance and potential overfitting.

To increase the utility of a predictive model in a clinical setting, we used an abbreviated set of factors that could be easily assessed during a patient visit (ie, Model 1). We performed predictive modeling using the R software suite version 3.4.0 (R Development Core Team; Vienna, Austria). For comparison with the published literature, we present the adjusted odds ratios (AORs) and 95% confidence intervals (CIs) by conducting a logistic regression of the final models in the test subsample.

Results

In our sample of 491,442 working-age adults receiving opioid therapy, overall 6556 transitioned from their first opioid prescription to incident chronic opioid therapy, which translates to a rate of 1.3% (Table 1). Hydrocodone was the most frequently prescribed first opioid (61.0%), followed by oxycodone (19.3%), tramadol (9.9%), and codeine (9.1%).

The majority of eligible patients were female (52.5%), aged ≥ 45 years (56.7%), and covered by a PPO plan (73.9%). Less than one-third (31.7%) of these patients did not have a diagnosis code in their medical claims for acute pain, arthritis, or conditions that are likely or highly likely to be associated with chronic pain. Table 1 presents the selected key sample characteristics by transition to chronic opioid therapy. The opioid regimen characteristics (ie, parent opioid compound, duration of action, and standardized dose) were all associated with a transition from first opioid prescription to incident chronic opioid therapy.

Overall, a greater percentage of patients with first opioid prescriptions for long-acting formulations than for immediate-release formulations (37.0% vs 1.3%), with prescriptions for tramadol than for codeine (4.2% vs 0.5%), with very high standardized doses than with lower standardized doses (5.1% vs 1.5%), patients who had

Table 1

Patients with Incident Opioid Use, by Transition to Chronic Opioid Use After Initial Opioid Prescription, 2007-2015^a

Patient sample	Total patients, N	Transition to chronic opioid therapy, N (%)	χ^2 value	P value	Patient sample	Total patients, N	Transition to chronic opioid therapy, N (%)	χ^2 value	P value
All patients	491,442	6556 (1.3)	—	—	Concomitant medications				
Opioid regimen characteristics					Benzodiazepine use within 4 months preceding opioid prescription			612.0	<.001
Duration of action of initial opioid prescription			7926.7	<.001	Yes	39,048	1059 (2.7)		
Long-acting	819	303 (37.0)			No	452,394	5497 (1.2)		
Immediate-release	490,623	6253 (1.3)			Stimulant use within 4 months preceding opioid prescription			105.2	<.001
Parent opioid compound of initial opioid prescription			4494.2	<.001	Yes	7642	204 (2.7)		
Codeine	44,588	201 (0.5)			No	483,800	6352 (1.3)		
Hydrocodone	300,008	3023 (1.0)			Nonopioid analgesic use within 4 months preceding opioid prescription			117.9	<.001
Oxycodone	94,822	1039 (1.1)			Yes	120,486	1983 (1.6)		
Tramadol	48,450	2039 (4.2)			No	370,956	4573 (1.2)		
All other opioids	3574	254 (7.1)			Polypharmacy (≥ 5 drug groups)			528.9	<.001
Standardized dose^b of initial opioid prescription			674.4	<.001	Yes	109,724	2234 (2.0)		
Lower (0-49 MME)	370,726	5520 (1.5)			No	381,718	4322 (1.1)		
Moderate (50-99 MME)	106,544	776 (0.7)			Patient characteristics				
High (100-149 MME)	11,399	118 (1.0)			Sex			94.0	<.001
Very high (≥ 150 MME)	2773	142 (5.1)			Male	233,393	3503 (1.5)		
Pain conditions					Female	258,049	3053 (1.2)		
Highly likely chronic pain condition			2883.8	<.001	Age			594.2	<.001
Yes	1508	259 (17.2)			28-34 yrs	81,462	602 (0.7)		
No	489,934	6297 (1.3)			35-44 yrs	130,917	1345 (1.0)		
Likely chronic pain condition			2029.9	<.001	45-54 yrs	156,191	2332 (1.5)		
Yes	144,644	3581 (2.5)			55-63 yrs	122,872	2277 (1.9)		
No	346,798	2975 (0.9)			Region			67.2	<.001
Acute pain condition			26.5	<.001	East	94,910	1075 (1.1)		
Yes	4247	95 (2.2)			Midwest	156,117	2090 (1.3)		
No	487,195	6461 (1.3)			South	194,746	2862 (1.5)		
Arthritis			1241.5	<.001	West	45,669	529 (1.2)		
Yes	30,811	1098 (3.6)			Insurance plan type			24.0	<.001
No	460,631	5458 (1.2)			HMO	63,181	798 (1.3)		
Physical and mental health conditions					PPO	363,414	5010 (1.4)		
Mental illness			462.5	<.001	Other ^b	64,847	748 (1.2)		
Yes	58,356	1338 (2.3)							
No	433,086	5218 (1.2)							
Any drug use disorder			1401.7	<.001					
Yes	1513	187 (12.4)							
No	489,929	6369 (1.3)							

NOTE: This sample includes patients from IQVIA's Real-World Data: Adjudicated Claims-USA. Because of data use requirements from the data provider, some categories were collapsed, including insurance plan type and other opioid use.

^aDoses of opioids were converted to a standardized dose (MME) using the Centers for Medicare & Medicaid Services conversion table.

^bIncludes fee-for-service, health savings account, and indemnity plans.

HMO indicates health maintenance organization; MME, morphine mg equivalents; PPO, preferred provider organization.

conditions most likely to cause chronic pain than those without these conditions (17.2% vs 1.3%), and patients with drug use disorders than those without these disorders (12.4% vs 1.3%), transitioned to chronic opioid therapy.

Predictive Modeling

In training and validation subsamples, some variables were the leading predictors after adjusting for sex, age, the presence of pain conditions, and readily available and modifiable opioid regimen factors (ie, opioid duration of action, parent opioid compound, and standardized dose). The variables of importance (ie, absolute value of the beta-coefficient) in descending order as they related to the transition to incident chronic opioid therapy included opioid duration of action, likely chronic pain condition, parent opioid compound, highly likely pain condition, and drug use disorder diagnoses.

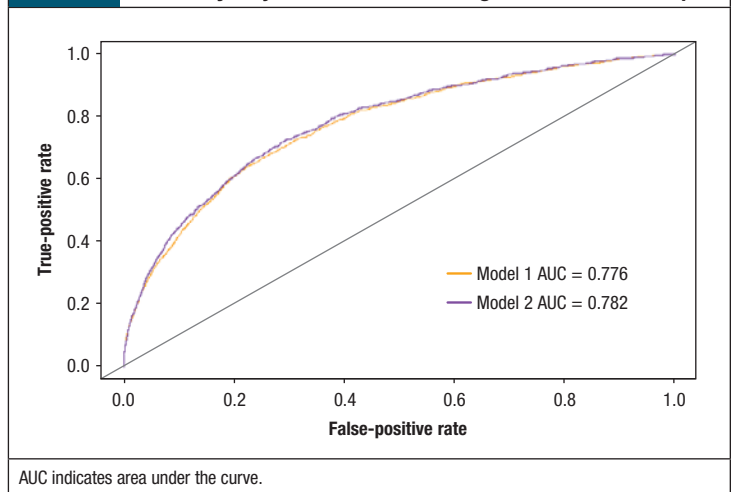
In the holdout (test) sample, the same predictors were found to be important, although the order changed slightly. For example, drug use disorders became the fourth leading predictor in the holdout sample as opposed to the second leading predictor in the training and validation samples. In the fully adjusted model (Model 2), the leading predictors remained the same in the training/validation and test samples. Again, the order of importance varied slightly with drug use disorders becoming the fifth leading predictor in the holdout sample versus the third leading predictor in the training/validation samples.

The similarity between the 2 models was also confirmed by the prediction accuracy of Model 1 and the fully adjusted model (ie, Model 2; **Figure 2**). The areas under the curve (AUC) were similar for Model 1 (AUC = 0.776) and Model 2 (AUC = 0.782) using the holdout sample.

A comparison between Model 1 and Model 2 in the training and validation subsamples can be seen in the **Appendix** (at www.AHDBonline.com) in **Supplemental Figure 1**. Also, **Supplemental Figure 2** in the **Appendix** contains a comparison of Model 1 between the training and validation subsample and the holdout (test) subsample. The AUC of decision tree-based models using random forest on the variables from Model 1 and the fully adjusted model were 0.54 and 0.64, respectively, in the training and validation subsamples.

For ease of comparisons with the published literature, **Table 2** summarizes the findings in the form of AORs and 95% CIs from a logistic regression of the test sample. As seen in **Table 2**, fully adjusting the model did not make significant changes to the AORs. For example, the duration of action, namely, long-acting versus immediate-release agent (AOR = 12.43; 95% CI, 8.13-18.83) in Model 1 was similar to that in Model 2, the fully adjusted model (AOR = 12.28; 95% CI, 8.06-

Figure 2 Receiver Operator Characteristic Curves for Model 1 and Fully Adjusted Model 2 Using the Test Subsample



18.72). Additional information included in the 2 models is provided in the **Appendix** in the **Supplemental Table** (at www.AHDBonline.com).

Discussion

To our knowledge, this is the first study to identify incident chronic opioid therapy in a sample of working-age adults who initiated opioid therapy. This is an important group, because of the potential impact on their productivity and the increased likelihood to receive opioid therapy when they experience pain.²⁰ Nearly 500,000 working-age adults in this sample initiated opioid therapy over the study period. For example, in 2014, nearly 1.8 million prescriptions were written for opioid drugs in our 10% sample. We also found that 13 in 1000 patients with an initial prescription for opioids transitioned to chronic opioid therapy.

Another important finding is the differences between states in the United States. Although we are unable to provide the specific differences, the rates of patients who transitioned to incident chronic opioid therapy were higher in Ohio, West Virginia, Kentucky, Mississippi, and Nevada than in other states. We hope that more studies will examine state-specific issues, including monitoring of prescribers, educating the public and prescribers, and the availability of nonpharmacologic treatments for chronic noncancer pain.

Our findings demonstrate that a smaller set (compared with the fully adjusted model) of more easily assessed factors at opioid initiation, including duration of action, standardized dose, parent opioid compound, age, and sex, can be used to gauge the risk for transitioning to chronic opioid therapy. Our predictive models identified 4 leading predictors, including duration of action, type of

Table 2 Select Leading Predictors of Transitioning from Incident to Chronic Opioid Use After First Opioid Prescription, 2007-2015

Predictor ^a	Model 1 in test subsample		Fully adjusted Model 2 in test subsample	
	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Long-acting vs immediate-release	12.43 (8.13-18.83)	<.001	12.28 (8.06-8.72)	<.001
Tramadol vs codeine	7.59 (5.53-10.74)	<.001	7.26 (5.20-10.13)	<.001
Highly likely chronic pain vs none	5.91 (4.18-8.20)	<.001	5.47 (3.89-7.68)	<.001
All other opioids vs codeine	5.71 (3.38-9.59)	<.001	5.64 (3.34-9.53)	<.001
Drug use disorder diagnosis vs none	4.96 (3.13-7.58)	<.001	4.02 (2.53-6.40)	<.001
Oxycodone vs codeine	2.70 (1.92-3.90)	<.001	2.67 (1.87-3.81)	<.001
Likely chronic pain vs none	2.08 (1.84-2.34)	<.001	2.02 (1.79-2.28)	<.001
Hydrocodone vs codeine	2.04 (1.49-2.87)	<.001	1.97 (1.42-2.73)	<.001
Benzodiazepine prescription vs none	1.99 (1.69-2.33)	<.001	1.82 (1.54-2.16)	<.001
Arthritis vs none	1.92 (1.63-2.25)	<.001	1.86 (1.58-2.20)	<.001
Male vs female	1.43 (1.27-1.60)	<.001	1.46 (1.30-1.65)	<.001
Very high vs low dose^b	1.27 (0.73-2.08)		1.24 (0.74-2.08)	
Age (continuous)	1.02 (1.02-1.03)	<.001	1.02 (1.01-1.03)	<.001
High vs low dose^b	0.71 (0.47-1.05)		0.68 (0.45-1.02)	
Moderate vs low dose^b	0.45 (0.37-0.55)	<.001	0.45 (0.37-0.54)	<.001

NOTE: Data taken from IQVIA's Real-World Data: Adjudicated Claims-USA. Because of data use requirements from the data provider, some categories were collapsed, including insurance plan type and other opioids. Other variables included in Model 2 (fully adjusted model) can be seen in the Appendix Supplemental Table (available at www.AHDBonline.com).

^aPredictor indicated in bold type.

^bDoses of opioids were converted to a standardized dose (morphine mg equivalents) using the Centers for Medicare & Medicaid Services conversion table.

CI indicates confidence interval; OR, odds ratio.

parent opioid compounds, drug use disorders, and painful conditions, that increased the risk for a transition to chronic opioid therapy by at least 4 times.

Furthermore, in our sample of working-age adults, the highest likelihood of transition to chronic opioid therapy was among adults who were prescribed long-acting opioids as opposed to immediate-release opioids. These findings have implications for clinical practice. First, prescribers can use these factors to determine the potential for an individual patient to transition to incident chronic opioid therapy at the time of their first prescription for opioids. Also, knowledge of this potential risk can help to alter or increase the monitoring of the prescribed regimens. Pharmacists can also use these factors to provide counseling about the goals of pain management and the potential for chronic opioid use to a subset of patients who are at high risk for transitioning to chronic opioid therapy.

Future intervention efforts can effectively target these factors to change the prescribing practices for opioids.⁷ For example, low-dose immediate-release codeine can be a first-line treatment option. However, other opioids may be needed, because codeine is a weak opioid and certain pharmacogenomic differences (eg, poor metabolizers will have a reduced response) need to be considered when using codeine.⁴⁰

In addition, future studies using qualitative and quantitative analyses could assess prescriber logic in choosing to prescribe long-acting versus immediate-release opioids. What clinical characteristics or patient preference issues were considered in making these choices? The answer may help to uncover some underlying issues.

In our sample, only 32% of working-age adults with a first prescription of opioids had any diagnosis of pain conditions. Although it is plausible that ICD-9-CM codes may underreport pain conditions, without the full documentation of indications for opioid use, it is difficult to assess the appropriateness of the initial opioid prescription. This has implications for prescription monitoring programs, state-based insurers, healthcare systems, local hospitals, and outpatient practices, as well as emphasizes the need for documentation requirements and recommendations.

The strengths of this study include the availability of a nationally representative sample of the commercially insured US population, following individuals across multiple providers and settings, the use of statistical and machine-learning predictive methods, and the availability of dates so that we could identify the first index opioid prescription. Furthermore, this study assessed incident chronic opioid therapy, which other studies have not distinguished from the prevalent use of chronic or long-term opioid therapy.

By using the National Library of Medicine programs RxMix and RxNav to identify the clinical drug components, the drug's duration of action and the parent opioid compound for each prescription could be identified, which allowed for a more granular assessment of the opioid regimen using claims data. Finally, the data spanned many unique insurers and plan types, which allowed for tracking of patients over time and for the determination of an opioid-free period of 12 months.

Limitations

The study has some potential limitations. First, prescription claims do not have information on variables such as pain, socioeconomic status, social capital, medication beliefs, and response to pain treatment, which may affect the transition to chronic opioid therapy. Also, claims data allow for the identification of pre-

scription medications, but not for the actual use of these medications.

In addition, predictive modeling results have some limitations as well. The models were assessed in a unique subsample (ie, testing data) of the overall sample. However, the validity of the model and its predicted probabilities will be more generalizable if applied to a different sample of patients, potentially from other commercial healthcare plans. The importance of factors could change, and even improve, if other types of information were added to the data set (eg, social determinants of health, medication use behaviors, prescribers' characteristics).

Finally, recent (from 2015 to the present) changes to prescribing practices of opioids could affect the overall incidence of the transition to chronic opioid therapy or the types of opioids prescribed.

Conclusion

Our findings suggest that an individual's transition to chronic opioid therapy can be predicted by information that is readily available in a clinical setting, such as the initial opioid regimen characteristics, a history of drug use disorder, and medical conditions associated with pain. Our study further demonstrates that predictive models can be used to aid clinicians' decision-making; develop real-time predictions about the future risk for transitioning to chronic opioid therapy; influence policy, prescriber education, and prescription monitoring programs; and be applied to other patient populations. Future research may include other factors, such as medication-taking behaviors, which are not measured in our study, to improve prediction accuracy. ■

Acknowledgments

The statements, findings, conclusions, views, and opinions contained and expressed in this article are based in part on data obtained under license from the following IQVIA information services: IQVIA's Real-World Data: Adjudicated Claims—USA (also known as PharMetrics Plus), 10% sample January 2006–December 2015. All Rights Reserved. The statements, findings, conclusions, views, and opinions contained and expressed herein are not necessarily those of IQVIA or any of its affiliated or subsidiary entities.

Author Disclosure Statement

Dr Thornton received a grant (5T32GM081741-08) from the National Institutes of Health, National Institute of General Medical Sciences; Dr Dwibedi, Dr Scott, Dr Ponte, Dr Ziedonis, and Dr N. Sambamoorthi reported no conflicts of interest; Dr U. Sambamoorthi was partially supported by the National Institutes of Health, National Institute of General Medical Sciences (grant U54GM104942).

References

- Institute of Medicine. *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*. Washington, DC: National Academies Press; 2011.
- Birnbaum HG, White AG, Schiller M, et al. Societal costs of prescription opioid abuse, dependence, and misuse in the United States. *Pain Med*. 2011; 12:657-667.
- Substance Abuse and Mental Health Services Administration, US Department of Health & Human Services; RTI International. Results from the 2006 National Survey on Drug Use and Health: National Findings. NSDUH Series H-32, DHHS Publication No SMA 07-4293. 2007. www.asipp.org/documents/2006NSDUH.pdf. Accessed April 15, 2017.
- Fudin J. The economics of opioids: abuse, REMS, and treatment benefits. *Am J Manag Care*. 2015;21(9a suppl):S188a-S194a.
- Benyamin R, Trescot AM, Datta S, et al. Opioid complications and side effects. *Pain Physician*. 2008;11(2S suppl):S105-S120.
- Tsang A, Von Korff M, Lee S, et al. Common chronic pain conditions in developed and developing countries: gender and age differences and comorbidity with depression-anxiety disorders. *J Pain*. 2008;9:883-891. Erratum in: *J Pain*. 2009;10:553.
- Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain—United States, 2016. *JAMA*. 2016;315:1624-1645.
- Chou R, Deyo R, Devine B, et al. *The Effectiveness and Risks of Long-Term Opioid Treatment of Chronic Pain*. Evidence report/technology assessment No 218. AHRQ Publication No 14-E005-EF. September 2014. <http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=1988&pageaction=displayproduct>. Accessed April 13, 2017.
- Nadler SF. Nonpharmacologic management of pain. *J Am Osteopath Assoc*. 2004;104(suppl 8):S6-S12.
- Centers for Disease Control and Prevention. Opioid painkiller prescribing. CDC Vital Signs. July 2014. www.cdc.gov/vitalsigns/opioid-prescribing/. Accessed April 15, 2017.
- Thielke SM, Shortreed SM, Saunders K, et al. A prospective study of predictors of long-term opioid use among patients with chronic noncancer pain. *Clin J Pain*. 2017;33:198-204.
- Substance Abuse and Mental Health Services Administration, US Department of Health & Human Services; RTI International. *Drug Abuse Warning Network, 2011: National Estimates of Drug-Related Emergency Department Visits*. HHS Publication No (SMA) 13-4760, DAWN Series D-39. May 2013. www.samhsa.gov/data/sites/default/files/DAWN2k11ED/DAWN2k11ED/DAWN2k11ED.pdf. Accessed April 14, 2017.
- Kern DM, Zhou S, Chavoshi S, et al. Treatment patterns, healthcare utilization, and costs of chronic opioid treatment for non-cancer pain in the United States. *Am J Manag Care*. 2015;21:e222-e234.
- Owens PL, Barrett ML, Weiss AJ, et al. Hospital inpatient utilization related to opioid overuse among adults, 1993–2012: Statistical Brief #177. Healthcare Cost and Utilization Project Statistical Briefs. Rockville, MD; August 2014.
- Centers for Disease Control and Prevention. Prescription drug overdose in the United States: fact sheet. www.mayorsinnovation.org/images/uploads/pdf/1_-_Prescription_Drug_Overdose_in_the_United_States.pdf. Accessed April 30, 2017.
- Kaplovitch E, Gomes T, Camacho X, et al. Sex differences in dose escalation and overdose death during chronic opioid therapy: a population-based cohort study. *PLoS One*. 2015;10:e0134550.
- Chou R, Turner JA, Devine EB, et al. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Ann Intern Med*. 2015;162:276-286.
- Zhou C, Florence CS, Dowell D. Payments for opioids shifted substantially to public and private insurers while consumer spending declined, 1999–2012. *Health Aff (Millwood)*. 2016;35:824-831.
- Florence CS, Zhou C, Luo F, Xu L. The economic burden of prescription opioid overdose, abuse, and dependence in the United States, 2013. *Med Care*. 2016;54:901-906.
- Thumula V, Wang D, Liu T. Concomitant use of opioids and benzodiazepines, other central nervous systems depressants. *Interstate Variations in Use of Narcotics, 4th Ed*. WC-17-28. Cambridge, MA: Workers Compensation Research Institute; June 2017.
- Phytel. Predictive modeling and population health management. Whitepaper. 2013. <https://app.compendium.com/uploads/user/863cc3c6-3316-459a-a747-3323bd3b6428/4c5909e8-1708-4751-873e-4129cb2ed878/File/86f9d9a5e2f21fb11a5ad8ef2239a76e/1393861691669.pdf>. Accessed February 10, 2017.
- Regierer B, Zazu V, Sudbrak R, et al. Future of medicine: models in predictive diagnostics and personalized medicine. *Adv Biochem Eng Biotechnol*. 2013; 133:15-33.

23. Center for the Application of Prevention Technologies, Substance Abuse and Mental Health Services Administration. Finding interventions to prevent or reduce opioid abuse and overdose: selected resources. www.samhsa.gov/capt/sites/default/files/resources/interventions-opioid-overdose.pdf. Accessed April 20, 2017.
24. Walley AY, Xuan Z, Hackman HH, et al. Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. *BMJ*. 2013;346:f174.
25. Hudson TJ, Painter JT, Martin BC, et al. Pharmacoepidemiologic analyses of opioid use among OEF/OIF/OND veterans. *Pain*. 2017;158:1039-1045.
26. Garg R. *Risk of Opioid-Related Adverse Events Among Medicaid and Workers' Compensation Patients Receiving Long-Term Opioid Therapy*. Thesis. Seattle, WA: University of Washington; 2015. <https://digital.lib.washington.edu/researchworks/handle/1773/33877>. Accessed April 30, 2017.
27. Cochran BN, Flentje A, Heck NC, et al. Factors predicting development of opioid use disorders among individuals who receive an initial opioid prescription: mathematical modeling using a database of commercially-insured individuals. *Drug Alcohol Depend*. 2014;138:202-208.
28. Dufour R, Mardekian J, Pasquale MK, et al. Understanding predictors of opioid abuse: predictive model development and validation. *Am J Pharm Benefits*. 2014;6:208-216.
29. DGI. Database detail: QuintilesIMS Real-World Data Adjudicated Claims: USA [QuintilesIMS PharMetrics Plus]. B.R.I.D.G.E. TO DATA. www.bridgetodata.org/node/824. Accessed February 12, 2017.
30. IMS Health. IMS' PharMetrics Plus Adjudicated Claims Data User Guide and Data Dictionary. 2016. Data on file at IQVIA.
31. Peters L, Mortensen J, Nguyen T, Bodenreider O. Enabling complex queries to drug information sources through functional composition. *Stud Health Technol Inform*. 2013;192:692-696.
32. Centers for Disease Control and Prevention. Opioid morphine equivalent conversion factors. May 2014. www.cms.gov/medicare/prescription-drug-coverage/prescriptiondrugcovcontra/downloads/opioid-morphine-eq-conversion-factors-march-2015.pdf. Accessed February 2, 2017.
33. Substance Abuse and Mental Health Services Administration, US Department of Health & Human Services; RTI International. Behavioral Health Trends in the United States: Results from the 2014 National Survey on Drug Use and Health. HHS Publication No SMA 15-4927, NSDUH Series H-50. September 2015. www.samhsa.gov/data/sites/default/files/NSDUH-FRR1-2014/NSDUH-FRR1-2014.pdf. Accessed February 10, 2017.
34. Goodman RA, Posner SF, Huang ES, et al. Defining and measuring chronic conditions: imperatives for research, policy, program, and practice. *Prev Chronic Dis*. 2013;10:E66.
35. Tian TY, Zlateva I, Anderson DR. Using electronic health records data to identify patients with chronic pain in a primary care setting. *J Am Med Inform Assoc*. 2013;20:e275-e280.
36. Zeisset A. Coding guidelines for pain. *J AHIMA*. 2007;78:78-79, quiz 81-82.
37. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. *Expert Opin Drug Saf*. 2014;13:57-65.
38. Weber C, Neeser K. Using individualized predictive disease modeling to identify patients with the potential to benefit from a disease management program for diabetes mellitus. *Dis Manag*. 2006;9:242-256.
39. Bryll R, Gutierrez-Osuna R, Quek F. Attribute bagging: improving accuracy of classifier ensembles by using random feature subsets. *Pattern Recognit*. 2003;36:1291-1302.
40. Yiannakopoulou E. Pharmacogenomics and opioid analgesics: clinical implications. *Int J Genomics*. 2015;2015:368979.

STAKEHOLDER PERSPECTIVE



Addiction Prediction: Preventing Iatrogenic Opioid Dependence

By Albert Tzeel, MD, MHA, CPE, FAAPL

Regional Medical Director, Senior Products, North Florida, Humana, Tampa

An ancient Danish proverb (sometimes attributed to the quantum physicist Niels Bohr) states that “prediction is difficult, especially about the future.”¹ Moreover, even if one feels that she or he is well skilled at making predictions, especially with significant clinical savvy, one usually expresses overconfidence in such endeavors. The late psychologist, Paul E. Meehl, in his seminal book, *Clinical Versus Statistical Prediction: A Theoretical Analysis and a Review of the Evidence*, argued that “mechanical” and other objective methods of looking at data to make predictions outperformed clinical and other subjective methods of looking at that same data for predictive value: mechanical methods incorporate less subjective bias into their views and lead to more consistent results.² Meehl’s thesis has been studied and validated.^{3,4}

In this context, the very timely article by Thornton and colleagues can play a role in addressing our current epidemic of opioid abuse.⁵ According to the Centers for Disease Control and Prevention, in 2016, nearly 5 people died every hour because of opioid-related drug overdoses.⁶ It is well known that prescribing opioid medications, especially those with protracted durations of action or over a longer time frame, increases the risk for an individual using these medications to become addicted to and/or physiologically dependent on them. It is in this realm that the article by Thornton and colleagues becomes extremely valuable.

PHYSICIANS/PRESCRIBERS: The article by Thornton and colleagues spells out how prescribers can potentially identify the risk that a given patient will de-

STAKEHOLDER PERSPECTIVE *Continued*

velop the need for chronic opioid therapy, by using readily available information from the clinical setting. Awareness of such a risk in a consistent manner allows a prescriber to take appropriate actions to mitigate that risk; these actions can include, but are certainly not limited to, the use of other classes of pain medications (eg, nonsteroidal anti-inflammatory drugs), use of less potent opioids with a shorter duration of action, or prescribing the medication dosages for a limited number of days that should, one hopes, prevent addiction. It should be feasible to add such decision support factors to an electronic medical record for review at the point of contact.

PAYERS: This article also develops some predictive models for prescribers' behavior. Given payers' involvement in population health strategies, such insights can be used to foster collaborations with prescribers, with the ultimate goal of preventing progression to chronic opioid therapy and promoting improved health. Furthermore, given the vast number of claims that are typically available to a payer, the ability to use these data to augment further mechanical data review should not be underestimated.

PATIENTS: Ultimately, the prevention of transitioning to chronic opioid therapy is a win-win for all parties involved. It is especially beneficial to the patient,

because although opioids are intended to alleviate suffering by decreasing pain, having an addiction to these medications can promote the exact opposite effect.

In summary, predictive models, such as the one developed by Thornton and colleagues, may not be perfect, but they are certainly a good start in the prevention of iatrogenic opioid addiction. In the words of the late statistician George E.P. Box, "all models are wrong, but some are useful."⁷ ■

1. Quote Investigator. It's difficult to make predictions, especially about the future. Updated July 13, 2016. <https://quoteinvestigator.com/2013/10/20/no-predict/>. Accessed February 5, 2018.

2. Meehl PE. *Clinical Versus Statistical Prediction: A Theoretical Analysis and a Review of the Evidence*. Minneapolis, MN: University of Minnesota; 1954 [Brattleboro, VT: Echo Point Books & Media; 2013].

3. Grove WM, Zald DH, Lebow BS, et al. Clinical versus mechanical prediction: a meta-analysis. *Psychol Assess*. 2000;12:19-30.

4. Ægisdóttir S, White MJ, Spengler PM, et al. The meta-analysis of clinical judgment project: fifty-six years of accumulated research on clinical versus statistical prediction. *Couns Psychol*. 2006;34:341-382.

5. Thornton JD, Dwibedi N, Scott V, et al. Predictors of transitioning to incident chronic opioid therapy among working-aged adults in the United States. *Am Health Drug Benefits*. 2018;11(1):12-21.

6. US Department of Health & Human Services. About the epidemic: the U.S. opioid epidemic. December 21, 2017. www.hhs.gov/opioids/about-the-epidemic/. Accessed February 5, 2018.

7. Box GE, Draper NR. *Empirical Model-Building and Response Surfaces*. New York, NY: John Wiley & Sons; 1987:424.