Increased Healthcare Utilization and Expenditures Associated With Chronic Opioid Therapy

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ABSTRACT

OBJECTIVES: To assess the association of the transition from incident opioid use to incident chronic opioid therapy (COT) with the trajectories of healthcare utilization and expenditures.

STUDY DESIGN: We used a longitudinal, retrospective cohort design, including seven 120-day time periods covering preindex (t_1, t_2, and t_3), index (t_4), and postindex (t_5, t_6, and t_7) periods with data from adults aged 28 to 63 years at the index date, without cancer, and continuously enrolled in a primary commercial insurance plan (N = 20,201).

METHODS: Multivariable analyses were performed on utilization (population-averaged [PA] logistic regression), expenditures (PA generalized estimating equations), and expenditure estimates (counterfactual prediction). The data used were from a commercial claims database (10% random sample from the IQVIA Real-World Data Adjudicated Claims - US database) from 2006-2015.

RESULTS: Patients on COT were more likely to use inpatient services (adjusted odds ratio, 1.11; 95% CI, 1.01-1.21) compared with those who did not. Although expenditures peaked during the index period (t_4) for all users, differences in unadjusted average 120-day expenditures between COT and non-COT users were highest in t_4 for total ($4607) and inpatient ($2453) expenditures. COT users had significantly higher total ($\beta = 0.183$; $P < .01$) and inpatient ($\beta = 0.448$; $P < .001$) expenditures.

CONCLUSIONS: The period after incident opioid prescription but before transition to COT is an important time for payers to intervene.

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Half of Americans have experienced pain in the past year, and approximately 100 million experienced chronic pain.[1,2] The majority of these patients have chronic noncancer pain (CNCP) and are of working age.[1,3-6] CNCP can be managed using therapy regimens that include pharmacologic options and nonpharmacologic options (eg, electrical stimulation, physical therapy, psychological interventions, exercise), which have been shown effective.[7-9] Opioids have been recommended by the CDC to be used only after considering a nonopioid regimen. Nearly 1 in 5 patients who presented to their healthcare provider with a painful condition in 2010 were prescribed an opioid, although the effectiveness of opioids in relieving CNCP has not been proven.[10]

In addition to the lack of evidence that opioids effectively treat CNCP, opioid use leads to adverse health consequences.[7] Study results have documented increased healthcare utilization and expenditures to patients and payers due to adverse effects of opioids.[2,4,5,11] Patients prescribed opioids had higher emergency department (ED), inpatient, and outpatient visits, as well as increased analgesic use, out-of-pocket spending, and third-party spending, compared with patients not prescribed opioid medications.[11-14] For example, in 2017, approximately 16 of every 10,000 ED visits in the United States were for suspected opioid overdose.[15] The number of annual ED visits due to suspected opioid overdose increased by 27.7% from 2015 to 2016.[15] From 1993 to 2012, the rate of hospital inpatient stays related to opioid overuse increased by 153%.[16]

Patients who receive initial opioid therapy, even for only a few days, are at risk of transitioning to chronic opioid therapy (COT), defined as 90 days of use.[7,17] Our preliminary analysis has shown that initial opioid prescription characteristics (parent opioid [eg, hydrocodone, oxycodone, tramadol], duration of action, and standardized dose) are the leading predictors of transitioning to COT.[18] Both patients and payers can bear the economic consequences of COT, which result from exacerbation of current medical conditions, development of new physical and mental health conditions, and opioid-related adverse effects, including drug use disorder and opioid overdose.[7,13,15,16,19] An estimated $78 billion is spent annually on these adverse consequences of opioids.[20]

Researchers have estimated the economic burden of patients on opioid therapy who develop an opioid use disorder[14,20,21]; studies that systematically examine the effect of the transition to COT on healthcare utilization and expenditures are sparse.[19,22] Such studies are important because they assess a transition state earlier in the patient's continuum of care,[23] and this earlier period has been identified by the CDC as a time to take action to prevent the adverse consequences of opioid use.[7] To date, only 1 study has analyzed the association of long-term opioid therapy and other opioid therapy with healthcare utilization and expenditures.[19] Using data from commercial health plans, the study reported that healthcare expenditures were higher among long-term opioid users compared with other opioid users.[19] This study had some limitations, such as use of a nonstandard definition of long-term opioid therapy and unequal follow-up time periods between short- and long-term opioid users. The definition for chronic opioid use (>182 days) was different from the commonly used Agency for Healthcare Research and Quality (AHRQ) and CDC definition of at least 90 days.[7,24] Furthermore, the study was not restricted to working-aged adults, who may have different transition rates and factors affecting those rates. Our study addresses the limitations of the prior literature and analyzes the impact of transitions from initiation of opioids to COT on economic outcomes in a nationally representative sample of working-aged adults using definitions concordant with definitions used by the CDC, AHRQ, and current literature.[7,24-26]

Focusing on working-aged adults between 28 and 63 years is important because this group may have higher risk of transition to COT[27] and their healthcare utilization patterns may be unique compared with those of elderly patients.[28] Therefore, the objective of our study was to assess the association of transitioning from incident opioid use to incident COT with trajectories of healthcare utilization and expenditures using a nationally representative sample of commercially insured working-aged adults in the United States.

METHODS

Data Source

The data were derived from a 10% random sample of commercial enrollees released under licensing from the IQVIA Real-World Data Adjudicated Claims - US database.

Study Design

A retrospective cohort design, with longitudinal data for seven 120-day time periods covering preindex (t_1, t_2, and t_3), index (t_4), and postindex (t_5, t_6, and t_7) periods, was used. The patient cohort consisted of working-aged adults who did not have cancer and who were initiated on opioids between January 2007 and May 2014. The first observed prescription for an opioid represented the index date. The preindex periods were identified before the index date, the index period was identified as the 120 days after the index date, and the postindex periods were identified after the end of the index period.

Study Sample

The sample was restricted to adults who were continuously enrolled in a primary commercial insurance plan (with pharmacy and medical benefits) during their entire observation period. Cancer was identified using *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes. Patients with at least 1 claim with any cancer code, except for nonmelanoma skin cancer, in any of the 12 diagnosis code fields available in the claims data were considered to have cancer.[29] We excluded individuals who had more than 1 opioid prescription on the index date because we were unable to evaluate initial opioid regimen characteristics for these individuals. After applying the exclusion criteria, we observed 3776 adults in the COT group. A 5% random sample, approximately 5 controls per case, of patients without COT was selected to represent the non-COT group (n = 16,425) (**eAppendix** [available at **ajmc.com**]).

Measures

Dependent variables: healthcare utilization and expenditures. All healthcare utilization and expenditures were repeatedly measured for each time period. Utilization consisted of ED and inpatient services. ED use was identified using an algorithm based on place of service, procedure codes, and revenue center codes.[30] Inpatient use was identified based on the claim having a not-null value for confinement number (a unique number of room and board records within a series containing the same facility provider ID on overlapping or contiguous dates, indicating hospitalization). Inpatient claims with the same confinement number were aggregated to get the admission and discharge dates. We measured utilization by any use of ED or inpatient services, defined as having at least 1 claim for these services during the 120-day time period.

Expenditures were distinguished by type of service (ED, inpatient, physician, and other [eg, surgical services, diagnostics, and laboratory tests]). Total expenditures (without prescription drugs) were the sum of ED, inpatient, physician, and other. Expenditures were calculated using the actual amount paid by the insurance plan and were converted to 2015 US dollars using the US Bureau of Labor Statistics Consumer Price Index for Medical Care Services.[31]

Key independent variable: incident COT. Opioids were identified using National Drug Codes (NDCs). NDCs for opioids were extracted from the National Library of Medicine's RxNav and RxMix.[32] A patient was classified as having incident COT if they had at least a 90-day supply of opioids during the 120-day index period.

Other independent variables. Time-invariant characteristics (patient's sex, region of residence, and clinical factors) were measured during the 12 months before the index date. Age was calculated as of the index date for initial opioid prescription. Clinical factors were presence or absence of diagnoses for painful conditions,[33] mental illnesses,[34] drug use disorders, and number of other chronic conditions adapted from HHS priority conditions for research, program, and policy.[29] Painful conditions were categorized as conditions likely or highly likely to be associated with chronic pain.[33] Drug use disorders included *ICD-9-CM* codes for drug dependence (304), drug abuse (305.2-305.9), and drug-induced mental disorders (292). The *ICD-9-CM* codes did not overlap between lists.

The clinical complexity of a patient was also measured during each time period by the number of unique medication classes. We also assessed concomitant medication use, benzodiazepines, and prescription nonopioid analgesics (NOAs) at each time period. Generic Product Identifier (GPI) codes were used to identify number of unique medication classes, as well as benzodiazepines (GPI-4, 57.10) and NOAs (GPI-2, 66 or 64). Additional independent variables included continuous time (range of 0-6 corresponding to t_1-t_7) and an indicator variable for the index period (t_4) to capture the differential rates of healthcare utilization and expenditures.

Statistical Analyses

As we repeatedly measured healthcare utilization, expenditures, unique medication classes, and concomitant medication use every 120 days, each individual had 7 observations. These 7 observations were not independent, and applying standard regression techniques can lead to misleading results. Therefore, the unadjusted and adjusted relationships between COT and economic outcomes were analyzed with a repeated-measures design. Healthcare expenditures are unique (eg, nonnormal distribution, high number of enrollees with zero values, and nonnegative measurement of the outcomes of interest). Therefore, we used generalized linear mixed models (GLMMs), which can accommodate both linear and nonlinear outcome variables. Mixed-effects regressions can model both within and between subject variations. However, one needs to distinguish between population-averaged (PA) and subject-specific models for binary outcomes[35] as well as continuous outcomes within GLMMs. We used PA models with generalized estimating equations (GEEs) to analyze the relationship between COT and ED use, inpatient use, and expenditures. For this study, the PA approach was used because the objective was to estimate the average treatment effects between the COT and non-COT groups. In multivariable GEE models, we adjusted for time as a continuous variable (range, 0-6), number of other chronic conditions, sex, age, region, history of drug use disorder, painful conditions, benzodiazepine use, NOA use, and number of unique medication classes.

Three models were developed to analyze the relationship between the COT indicator and the dependent variables. The first model (model 1) is only adjusted for continuous time and the index period (t_4). Model 2 additionally adjusted for the number of chronic conditions, while model 3 is the fully adjusted model and includes sex, age, region, history of drug use disorder, painful conditions, benzodiazepine use, NOA use, and number of unique medication classes.

We calculated the differences in average expenditures between the COT and non-COT groups with a counterfactual prediction technique. This was done because exponentiating expenditures for the groups to derive absolute differences in dollar amount assumes a reference case scenario. Rather than comparing the expenditures between the groups, we used the counterfactual prediction technique by holding other variables constant. Under this technique, expenditures for counterfactual scenarios (eg, assuming all patients with and without COT while keeping their other characteristics as given) were calculated and differences in average expenditures were estimated.[36-39] Confidence intervals for these estimates were obtained using 1000 bootstrap replications using the percentile method. Data sets for these analyses were created using SAS version 9.4 (SAS Institute Inc; Cary, North Carolina) and analyses were performed using STATA version 14 (StataCorp; College Station, Texas).

Inverse Probability of Treatment Weighting

Patients receiving COT or non-COT regimens may systematically differ in observed characteristics (eg, painful conditions). Therefore, to control for observed selection bias between patients using COT and those not using COT, we used inverse probability of treatment weighting (IPTW).[40] Patient sex, age categories, region, and painful conditions were used in a logistic regression on COT use to derive IPTW and were used as patient weights in designated analyses.

RESULTS

Description of the Study Sample by COT

The sample characteristics (sex, age, region, and painful conditions) were significantly different between COT and non-COT groups (all P <.001). After adjustment for IPTW, there were no longer any significant differences. The sample comparison before and after IPTW is displayed in the **eAppendix Table**.

Healthcare Utilization

In the unadjusted analyses, ED utilization differed significantly across time periods (P <.001) between patients who transitioned to COT and those who did not (**Table 1**). For patients with COT, ED use increased from 6.0% (t_1) to 15.5% (t_4); similarly, for patients without COT, ED

Table 1. Rates of ED and Inpatient Use by Transition to COT After Initial Opioid Prescription[a]

	ED Use		Inpatient Use	
Time	COT (weighted %)	Non-COT (weighted %)	COT (weighted %)	Non-COT (weighted %)
t_1	6.0	4.3	1.5	1.1
t_2	5.5	4.1	1.7	0.9
t_3	11.2	12.4	5.9	9.2
t_4	15.5	15.3	10.9	5.4
t_5	11.4	5.3	5.9	1.9
t_6	10.1	5.7	4.5	2.2
t_7	9.3	5.2	4.0	1.6

COT indicates chronic opioid therapy; ED, emergency department.
[a]This sample includes patients from the IQVIA Real-World Data Adjudicated Claims - US database who were identified between 2007 and 2014 and had enrollment between 2006 and 2015. These patients were between 28 and 63 years old, were without cancer, had complete demographic information available, and had only 1 opioid prescription on the index date. Individual weights based on inverse probability of treatment weighting have been used for this analysis.

Table 2. AOR and 95% CI of Selected Variables From Population-Averaged Generalized Estimating Equations of Working-Aged Adults With Incident Opioid Prescription[a]

	ED Use	Inpatient Use
Variables	AOR (95% CI)	AOR (95% CI)
Model 1: Adjusted for COT, Time, and Index Period (t_4)		
COT	1.32 (1.25-1.42)***	1.78 (1.63-1.94)***
Time	1.04 (1.03-1.06)***	1.04 (1.03-1.06)***
Index period (t_4)	2.26 (2.12-2.40)***	1.62 (1.43-1.83)***
Model 2: Adjusted for COT, Time, Index Period (t_4), and Number of Other Chronic Conditions		
COT	1.25 (1.17-1.34)***	1.45 (1.33-1.58)***
Time	1.04 (1.03-1.06)***	1.05 (1.03-1.07)***
Index period (t_4)	2.27 (2.13-2.41)***	1.81 (1.62-2.02)***
Model 3: Adjusted for COT, Time, Index Period (t_4), Number of Other Chronic Conditions, Sex, Age, Region, History of Drug Use Disorder, Painful Conditions, Benzodiazepine Use, Nonopioid Analgesic Use, and Number of Unique Medication Classes		
COT	0.92 (0.86-0.99)*	1.11 (1.01-1.21)*
Time	0.99 (0.98-1.00)	0.98 (0.96-0.99)*
Index period (t_4)	1.64 (1.54-1.75)***	1.13 (1.00-1.29)

AOR indicates adjusted odds ratio; COT, chronic opioid therapy; ED, emergency department.
*P <.05; **P <.01; ***P <.001.
[a]This sample includes patients from the IQVIA Real-World Data Adjudicated Claims - US database who were identified between 2007 and 2014 and had enrollment between 2006 and 2015. These patients were between 28 and 63 years old, were without cancer, had complete demographic information available, and had only 1 opioid prescription on the index date. Individual weights based on inverse probability of treatment weighting have been used for this analysis.

use increased from 4.3% (t_1) to 15.3% (t_4). ED use remained higher in the COT group in the follow-up time periods (t_5-t_7). As displayed in **Table 2**, using adjusted models 1 and 2, patients who transitioned to COT were more likely to have ED utilization (adjusted odds ratio [AOR], 1.33; 95% CI, 1.25-1.42; and AOR, 1.26; 95% CI, 1.17-1.34, respectively). However, in model 3, the patients who transitioned to COT were less likely to have ED use (AOR, 0.92; 95% CI, 0.86-0.99).

Similarly, inpatient use increased from 1.5% (t_1) to 10.9% (t_4) in patients with COT; for patients without COT, inpatient use increased from 1.1% (t_1) to 5.4% (t_4) (Table 1). Inpatient use remained higher in the COT group compared with the non-COT group in the follow-up time periods (t_5-t_7). Patients who transitioned to COT were more likely to have inpatient use in all models (model 1, AOR, 1.78; 95% CI, 1.63-1.94; model 2, AOR, 1.45; 95% CI, 1.33-1.58; model 3, AOR, 1.11; 95% CI, 1.01-1.21) (Table 2). Finally, both ED and inpatient use were more likely to occur during the index period (t_4) compared with all other periods (P <.001) (Table 2).

Healthcare Expenditures

Average expenditures over time and by COT use are summarized in **Table 3**, and differences in unadjusted mean expenditures over time, by type of service, are graphed in the **eAppendix Figure**. Patients who transitioned to COT had higher total expenditures at every time point, and the difference in mean expenditures between these groups varied significantly with time. In t_1, the patients who transitioned to COT had only $511 higher total expenditures, but that difference increased to $4607 in t_4. The differences in average expenditures peaked during t_4 and remained higher than baseline through the entire follow-up period, driven mostly by inpatient expenditures.

Patients who transitioned to COT had significantly higher total (P = .002) and inpatient (P <.001) expenditures in the fully adjusted analyses (**Table 4**). Also, the index period (t_4) was associated with higher expenditures for every type compared with baseline. In the fully adjusted model, we observed a difference of $579 in t_4 between COT and non-COT users using the counterfactual prediction technique (**Figure**).

DISCUSSION

Generally, healthcare utilization and expenditures were higher during the index period (t_4) compared with all other time periods for all opioid users (regardless of transition to COT). The only exception to this was for non-COT users, whose inpatient expenditures were higher in t_3. For those with and without transition to COT, expenditures increased by 594% and 698%, respectively, in the period prior to the initial prescription of opioids (t_1-t_3), suggesting that the periods surrounding the initial opioid prescription are associated with high utilization and expenditures. However, COT users had a higher rate of increase in expenditures compared with non-COT users.

Most trajectories of healthcare utilization and expenditures (t_1-t_7) were different between COT and non-COT users. For example, among COT users, healthcare utilization and expenditures were

Table 3. Average Expenditures (2015 US$) Over Time by Type of Service and COT Use[a]

	COT		No COT	
	Mean	SD	Mean	SD
Time	Total Expenditures[b]***			
t_1	$1214.29	$5370.49	$702.98	$3381.23
t_2	$1533.36	$10,527.42	$718.73	$3020.19
t_3	$4750.20	$22,883.82	$3394.63	$13,281.89
t_4	$8086.02	$24,328.52	$3478.55	$9558.53
t_5	$4615.81	$16,668.22	$1480.62	$7397.14
t_6	$3951.71	$16,045.87	$1574.25	$8258.62
t_7	$3382.53	$12,654.83	$1289.55	$6838.75
Time	ED***			
t_1	$54.05	$329.90	$44.82	$586.10
t_2	$73.02	$730.37	$41.16	$417.54
t_3	$173.96	$1111.67	$147.68	$800.61
t_4	$222.88	$983.72	$176.51	$809.45
t_5	$153.36	$837.10	$69.24	$594.06
t_6	$146.19	$784.20	$70.24	$487.89
t_7	$138.94	$848.86	$66.82	$521.07
Time	Inpatient***			
t_1	$315.00	$3406.36	$130.71	$2358.01
t_2	$566.30	$9071.37	$93.45	$1654.38
t_3	$2997.45	$19,703.13	$1854.68	$11,325.91
t_4	$3173.69	$14,809.44	$720.86	$5742.17
t_5	$1697.03	$11,374.53	$400.90	$4628.53
t_6	$1425.95	$11,967.43	$479.34	$5169.43
t_7	$1185.19	$7703.07	$345.73	$4476.01
Time	Physician***			
t_1	$156.40	$320.98	$121.20	$250.30
t_2	$166.67	$334.31	$131.08	$267.03
t_3	$217.43	$391.12	$185.82	$309.58
t_4	$419.98	$687.52	$221.31	$434.49
t_5	$300.25	$536.57	$150.35	$312.71
t_6	$251.91	$438.32	$145.46	$332.52
t_7	$218.46	$401.72	$125.01	$302.37

COT indicates chronic opioid therapy; ED, emergency department.
***P <.001.
[a]Based on working-aged adults without cancer who were initiated on opioid therapy between 2007 and 2014, were aged 28 to 63 years, had only 1 opioid prescription on the index date, and had continuous enrollment for 29 months in a commercial insurance plan. The data were from the IQVIA Real-World Data Adjudicated Claims - US database. Differences in average expenditures between COT users and non-COT users were tested using generalized estimating equation models.
[b]Total expenditures are sum of ED, inpatient, physician, and other costs and exclude prescription drug expenditures. "Other" category is not displayed; thus, the sum of average inpatient, ED, and physician expenditures will not add up to average total expenditures.

highest in the index period (t_4), but for non-COT users, the peak utilization and expenditures were observed in t_3, prior to initial opioid receipt. Furthermore, for patients who transitioned to COT, utilization and expenditures remained higher than baseline. For the non-COT group, utilization and expenditures returned to closer to initial preopioid levels measured at t_1, after adjusting for other characteristics.

In the fully adjusted models, transition to COT was associated with higher inpatient utilization and expenditures as well as total expenditures. This has implications for payers because inpatient use is the primary driver of total expenditures.[19] In our study, the proportion of inpatient expenditures to total expenditures varied from 50% (t_1) to 80% (t_3) in COT users.

Any intervention focused on curbing transition to COT has the potential to prevent inpatient use and can lead to cost savings for the payer(s). Interventions include extensive physician and patient education about pain management and opioids, the further interoperability of state-level prescription drug monitoring programs, and increased options for disposal of unused opioid medications.[41] Future research could use this study's findings as part of the way to assess the cost effectiveness of these interventions. In addition to expenditures, reduction in inpatient utilization has benefits for the patient, including improved quality of life and lower out-of-pocket costs.

Without adjustments for patient complexity, patients who transitioned to COT were more likely to use the ED compared with patients who did not. However, in the fully adjusted model, ED use was less likely among patients who transitioned to COT compared with those who did not. Although we do not know the reasons for this counterintuitive finding, we speculate that ED use may be due to patient complexity requiring pain management, which may have led to an initial opioid prescription in the index period (t_4). Initial prescriptions for opioids may have provided short-term relief, decreasing patients' need for emergency care.

Although not directly comparable, our study findings were similar to those of the study published by Kern et al assessing the transition from initial opioid prescription to long-term opioid use.[19] For example, Kern et al reported that for long-term users of opioids, healthcare utilization rates and costs decreased after the first 6 months of follow-up but remained above the baseline levels.[19] Kern et al also reported that the number of ED visits per patient-year of follow-up was lower for patients receiving long-term opioid therapy compared with short-term use (0.44 vs 0.93).

Strengths and Limitations

Strengths of this study include following individuals across multiple providers and settings. This longitudinal design, with repeated measures of utilization and expenditures for patients

Table 4. Weighted and Adjusted Expenditures Over Time for Patients With Incident Opioid Use by Transition to COT After First Opioid Prescription[a]

Cost Type	COT			Index Period (t_4)			Intercept		
	β	SE	*P*	β	SE	*P*	β	SE	*P*
Total (no prescription)									
Model 1	0.11	0.04	<.001	0.81	0.04	<.001	6.97	0.03	<.001
Model 2	0.41	0.05	<.001	0.92	0.04	<.001	6.52	0.04	<.001
Model 3	0.18	0.06	.002	0.68	0.04	<.001	6.44	0.10	<.001
ED									
Model 1	0.38	0.06	<.001	0.72	0.05	<.001	4.05	0.05	<.001
Model 2	0.31	0.06	<.001	0.79	0.05	<.001	3.74	0.05	<.001
Model 3	0.01	0.08	.884	0.42	0.05	<.001	4.12	0.10	<.001
Inpatient									
Model 1	0.78	0.07	<.001	0.49	0.07	<.001	6.09	0.06	<.001
Model 2	0.69	0.09	<.001	0.67	0.08	<.001	5.26	0.06	<.001
Model 3	0.45	0.11	<.001	0.31	0.10	.002	5.70	0.17	<.001
Physician									
Model 1	0.27	0.02	<.001	0.49	0.02	<.001	4.82	0.02	<.001
Model 2	0.18	0.03	<.001	0.51	0.02	<.001	4.54	0.02	<.001
Model 3	−0.01	0.02	.582	0.29	0.02	<.001	4.32	0.04	<.001

COT indicates chronic opioid therapy; ED, emergency department; SE, semirobust standard error.
[a]This sample includes patients from the IQVIA Real-World Data Adjudicated Claims - US database who were identified between 2007 and 2014 and had enrollment between 2006 and 2015. These patients were between 28 and 63 years old, were without cancer, had complete demographic information available, and had only 1 opioid prescription on the index date. Individual weights based on inverse probability of treatment weighting were used for this analysis. Model 1 is only adjusted for time and COT. Model 2 is also adjusted for number of other chronic conditions. Model 3 is also adjusted for number of other chronic conditions, sex, age, region, history of drug abuse, painful conditions, benzodiazepine use, nonopioid analgesic use, and number of unique medication classes.

with and without transition to COT, allowed for an assessment of baseline utilization and expenditures and to control for profiles of utilization, expenditures, and patient complexity. The data spanned many insurers and plan types, which allowed for the tracking of patients to determine an opioid-free period of 12 months (t_1-t_3). Furthermore, we applied robust statistical methods to control for observed selection bias.

This study also has some potential limitations. We observed only prescription claims and not actual use of medications. The database did not have information on variables such as pain, socioeconomic status, social capital, medication beliefs, and response to pain treatment, which may have affected the transition and associated healthcare utilization and expenditures.

CONCLUSIONS

Transitioning to COT can place a significant economic burden on payers and patients in terms of healthcare utilization and expenditures. Despite having similar baseline values to patients with acute opioid use, patients making the

Figure. Difference in Average Total Expenditures (no prescription drug costs) Between COT and No COT Transition Using a Counterfactual Prediction Technique

COT indicates chronic opioid therapy.

transition to COT had persistently high levels of utilization and expenditures even 12 months after the transition to COT. The period of time after incident opioid prescription but before COT is an important time for intervention for payers and clinicians.

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eAppendix Table. Patient Characteristics Before and After Applying IPTW for Patients With Incident Opioid Use by Transition to COT After First Opioid Prescription, QuintilesIMS Real-World Data Adjudicated Claims Database – US, 2006-2015

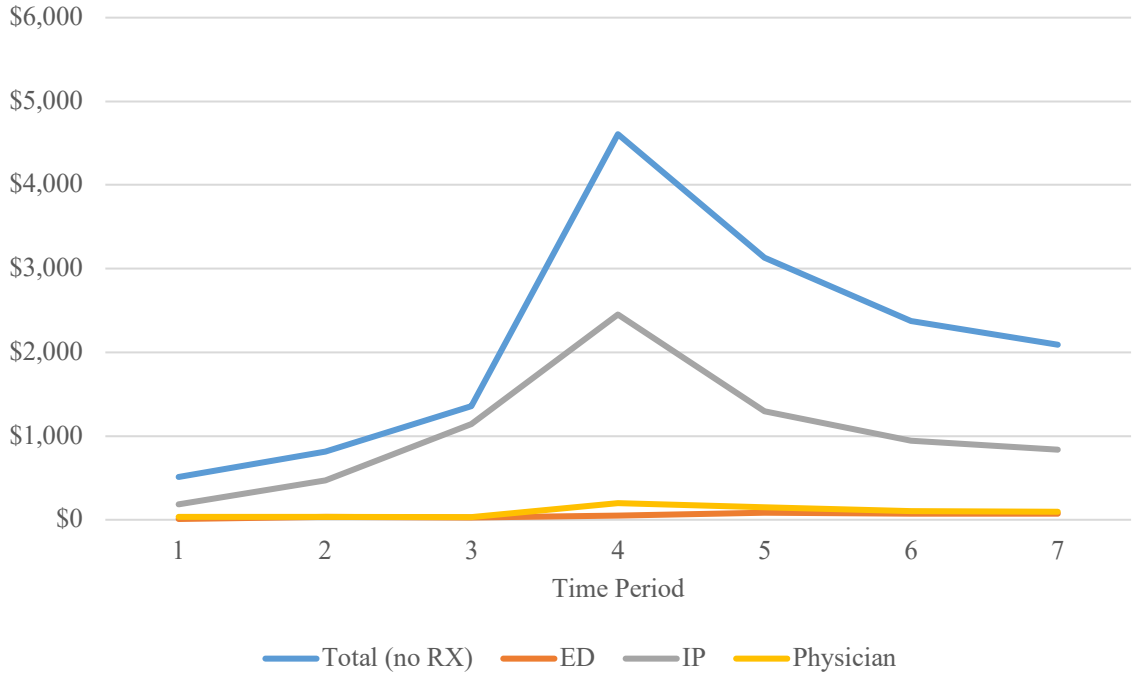
		Before IPTW							After IPTW				
All		**COT**		**No COT**					**COT**	**No COT**			
		n = 3,776	**%**	**n = 16,425**	**%**	**χ^2**	***P***	**Sig.**	**Wt. %**	**Wt. %**	**χ^2**	***P***	**Sig.**
Sex						29.49	<0.001	***			1.18	0.277	
	Male	2,000	53.0	7,895	48.1				49.8	49.0			
	Female	1,776	47.0	8,530	51.9				50.2	51.0			
Age						307.36	<0.001	***			7.61	0.055	
	28-34 years	305	8.1	2,522	15.4				12.8	13.9			
	35-44 years	757	20.0	4,402	26.8				25.1	25.5			
	45-54 years	1,377	36.5	5,402	32.9				34.0	33.6			
	55-63 years	1,337	35.4	4,099	25.0				28.2	27.0			
Region						30.18	<0.001	***			1.80	0.614	
	East	580	15.4	2,991	18.2				17.9	17.7			
	Midwest	1,290	34.2	5,478	33.4				34.3	33.6			
	South	1,642	43.5	6,587	40.1				40.0	40.7			
	West	264	7.0	1,369	8.3				7.8	8.1			
Highly likely chronic pain condition						301.41	<0.001	***			0.02	0.890	
	Yes	112	3.0	41	0.2				0.8	0.8			
	No	3,664	97.0	16,384	99.8				99.2	99.2			
Likely chronic pain condition						938.71	<0.001	***			0.88	0.347	
	Yes	2,064	54.7	4,693	28.6				34.1	33.5			
	No	1,712	45.3	11,732	71.4				65.9	66.5			

COT indicates chronic opioid therapy; IPTW, inverse probability of treatment weighting; wt., weighted.

Sig: $0 < p < 0.001$ = ***, $0.001 \leq p$ 0.01 = **, $0.01 \leq p < 0.05$ = *

Note: This sample includes patients from QuintilesIMS RWD Adjudicated Claims – US, which were identified between 2007 and 2014 and had enrollment between 2006 and 2015. These patients were between 28-63 years old, without cancer, had complete demographic information available, and had only 1 opioid prescription on the index date. Individual weights based on IPTW have been used for this analysis.

eAppendix Figure. Difference in Unweighted Average Expenditures Between COT and No COT Transition for Total (no prescription drug), ED, IP, and Physician Costs



COT indicates chronic opioid therapy; ED, emergency department; IP, inpatient.