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Long-term use of hydrocodone vs. oxycodone in primary care

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ABSTRACT

Background: Hydrocodone and oxycodone are the Schedule II opioids most often prescribed in primary care. Notwithstanding the dangers of prescription opioid use, the likelihood of long-term use with either drug is presently unknown.

Methods: Using a retrospective cohort design and data from a commerical healthcare claims repository, we compared the likelihood of long-term use of hydrocodone and oxycodone in primary care patients presenting with acute back pain. Treatment was categorized as long-term if the prescription dates spanned ≥90 days from initial prescription to the run-out date of the last prescription, and included ≥120 days' supply or ≥10 fills. Instrumental variable methods and probit regression were used to model the effect of drug choice on long-term use, estimate the average treatment effect, and correct for confounding by indication.

Results: A total of 3,983 patients who were prescribed only hydrocodone or only oxycodone were followed for 270 days in 2016. Long-term opioid use was observed in 320 patients (8%). Controlling for potential confounders including morphine milligram equivalents and dosage, an estimated 12% (95 CI, 10%–14%) treated with hydrocodone transitioned to long-term use vs. 2% (95 CI, 1%–3%) on oxycodone. Among patients who received more than one prescription (n = 1,866), an estimated 23% (95 CI, 19%–26%) treated with hydrocodone transitioned to long-term use vs. 5% (95 CI, 3%–7%) on oxycodone. The difference between drugs was supported in sensitivity and subgroup analyses. Sample selection bias was not detected.

Conclusions: Long-term use was substantially greater for patients treated with hydrocodone than oxycodone, despite equianalgesia.

1. Introduction

Primary care physicians in the United States write tens of millions of opioid prescriptions annually, most commonly for musculoskeletal back pain, with hydrocodone and oxycodone the Schedule II opioids most often prescribed (Deyo et al., 2015; Han et al., 2017; Mundkur et al., 2018). Despite the known dangers of addiction and fatal overdose associated with long-term prescription opioid use (Von Korff, 2013; Chou et al., 2015), the duration of use of specific opioid drugs has not been examined in clinical trials. Nor has the issue been studied in observational research other than in a single post-surgery series (Basilico et al., 2019). In the current study, we used a national healthcare database of commercial insurance claims to compare the likelihood of long-term use of hydrocodone and oxycodone in primary care patients presenting with acute back pain (aBP). We tested the null hypothesis that patients taking different opioids of the same analgesic strength, measured in morphine milligram equivalents (MME, a standardized metric of analgesia in the first hours after ingestion), exhibit the same risk of long-term use.

MME, expressed as cumulative intake over a period of time (e.g., MME/d, MME/m), is the principal explanatory variable in the large and growing body of opioid research investigating the health consequences of long-term use. In converting the analgesic potency of different opioids like oxycodone and hydrocodone into a common metric (Zacny

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and Gutierrez, 2009), the tacit assumption of researchers is that opioids are fully interchangeable, at least for research purposes (National Center for Injury Prevention and Control, 2018). Exclusion of the opioid agent as a potential predictor of long-term outcomes is currently the *de facto* standard in the field.

There are practical reasons for the absence of research on the long-term effects of specific opioid agents. Beyond the ethical and regulatory considerations of protracted opioid exposure, any clinical trial comparing the duration of use for different opioids would face problems of insufficient power (Tayeb et al., 2016). In primary care, only a small fraction of patients treated for musculoskeletal pain continue in opioid therapy beyond a few months (Mundkur et al., 2018). Observational studies using administrative healthcare databases provide a larger sample size with longitudinal follow-up (Noble et al., 2008), but are encumbered by issues of potential confounding. Patients' unmeasured clinical indications (e.g., severity of condition, prognosis) are a major concern in observational research (Baiocchi et al., 2014). Confounding can occur when physicians channel individual patients toward one treatment or another on the basis of the indications and the indications are determinants of the study outcome. Instrumental variable (IV) methods – invented nearly a century ago to tackle endogeneity problems in economics (Stock and Trebbi, 2003) – have become the central technique for dealing with "confounding by indication" in drug prescription research (Chen and Briesacher, 2011). We used IV methods in the current paper to model the causal effects of opioid treatment (drug choice) on outcome (long-term use).

Another potential source of bias arises from the routine practice of opioid drug switching to find an acceptable balance between analgesia and side effects (Fine and Portenoy, 2009; Slatkin, 2009). In observational research, two approaches have been used to isolate the effect of a specific opioid drug when treatment has involved multiple opioids over time. One is to focus on the initial drug and disregard the effects of the successor opioids among the "switchers" (Basilico et al., 2019), presumably on the grounds that the successor drugs are irrelevant components of the treatment. We are not convinced of the logic of that approach, and believe that it could attenuate or suppress the true association between treatment and outcome (Harris, 2019). Here, we used an alternative approach – parallel sampling (Scherrer et al., 2016) – which selects cohorts of patients who remained on the same drug throughout treatment. While parallel sampling is nonrepresentative, selection bias can be investigated and, when appropriate, corrected through weighting or other procedures (Nohr and Liew, 2018).

Our combination of methods was novel but necessary to address the important question at hand. The United States is in the midst of a still-growing opioid crisis caused in part by long-term prescription opioid use (Chen et al., 2019). At the same time, physicians must respond to the suffering of patients who have high levels of acute pain (Rubin, 2019), and therefore the question of whether one opioid is inherently more dangerous than another remains urgently important.

2. Methods and materials

2.1. Ethics statement

This retrospective cohort study using de-identified data was exempted by the University of Pennsylvania Institutional Review Board.

2.2. Data source

Data were extracted from the Optum Clinformatics® DataMart (OptumInsight, Eden Prairie, MN), a clinically rich administrative claims database from a national insurance provider. The database includes inpatient and outpatient claims; International Classification of Diseases (ICD) diagnosis codes; prescription fill information including National Drug Code number, quantity dispensed, and days' supply; physician specialty codes; patient demographics; and health plan enrollment status. The enrollee population is geographically diverse and demographically similar to the United States population of privately insured people (Optum, 2018).

2.3. Inclusion/Exclusion criteria

We selected continuously enrolled (October 1, 2015 through December 31, 2016) primary care patients who were prescribed hydrocodone or oxycodone for aBP (ICD-10 M54.x) in the first quarter of 2016. Patients were followed for 270 days. All prescriptions were for immediate-release hydrocodone or oxycodone combined with acetaminophen in a single tablet (abbreviated as "hydro-acet" or "oxy-acet").

Patients were excluded if, in the 3 months prior to the initial visit for aBP, they had cauda equina syndrome, paraplegia, or quadriplegia; a spine or pelvis fracture; cancer; an emergency room visit; an inpatient or nursing home stay; or received services in hospice/palliative care or an ambulatory surgical facility. We reasoned that these patients may have been more likely to initiate or extend opioid therapy because of chronic painful conditions, rather than aBP. Similarly, we excluded patients who had filled an opioid prescription or received a diagnosis of aBP in the 3 months prior to the index visit, also on grounds that this group of patients were less likely to be experiencing acute pain. We also excluded patients aged 17 and under, as they were at lower risk of long-term prescription opioid use.

We focused on the subset of patients (N = 3,983) who received the same opioid-MME formulation from first prescription through last renewal, choosing the analgesic strengths most frequently prescribed in primary care: for hydro-acet, 5MME, 7.5MME, and 10MME; for oxy-acet, 7.5MME, 11.25MME, and 15MME. Fig. 1 diagrams cohort selection. Table S1 (Supplement) shows the drug-by-MME classification of the 6 parallel cohorts. The selected patients were analyzed as a single cohort.

2.4. Variables

Our outcome of interest was long-term prescription opioid use measured as a binary variable (presence or absence). Using the

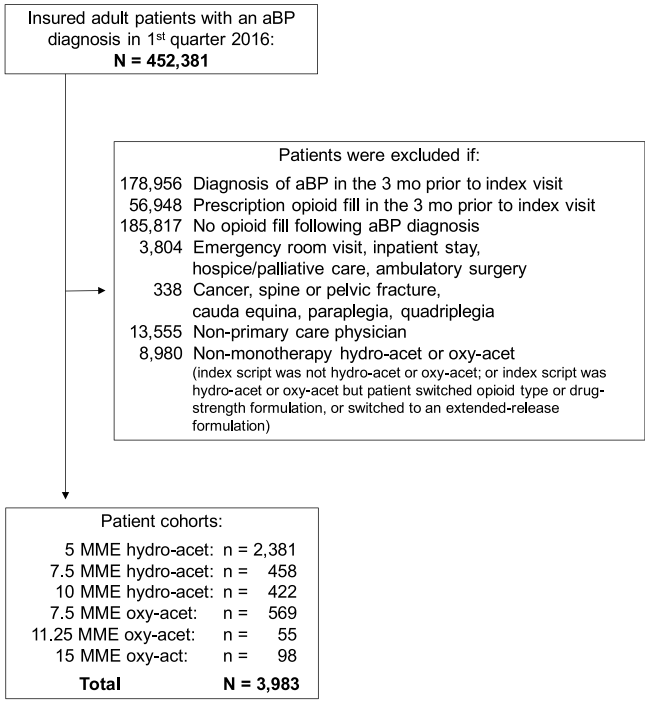

Fig. 1. Cohort selection flow chart.

Consortium to Study Opioid Risks and Trends (CONSORT) criteria, we categorized opioid use as long term if the prescription dates spanned at least 90 days from the initial prescription to the run-out date of the last prescription, and included at least 120 days' supply or 10 fills (Von Korff et al., 2008). Our treatment variable was the prescription drug choice between hydro-acet and oxy-acet.

We used an instrumental variable (IV) to address whether physicians preferred one opioid analgesic to another for patients whose aBP was anticipated to persist, a possible unmeasured confounder. Prescription drug choice was instrumented by geographic region of the United States, dichotomized into New England, Mid-Atlantic, and South Atlantic states vs. Central, Mountain, and Pacific states.

We also examined MME, average tablets per day, and patient age and gender as potential confounders of the association between drug choice and long-term use. In a sensitivity analysis, we investigated the influence of comoridities (Charlson comorbidity score), certain chronic diseases (liver disease, renal disease, COPD), psychiatric disorders (depression, anxiety, psychosis), recent use of other medications (antidepressant, benzodiazepine, muscle relaxant, anxiolytic/sedative/hypnotic, antipsychotic), and use of non-prescription drugs (alcohol, tobacco).

2.5. Statistical analysis

2.5.1. Instrumental variable (IV) analysis to control for confounding by indication

Because patients are not randomly assigned to treatment groups in an observational study, an important concern is whether there are unmeasured ways in which the treatment groups differ before treatment that may affect the outcome (Baiocchi et al., 2014). We used IV methods and probit regression ("IV-probit" for convenience) to effectively pseudo-randomize the treatment groups (Mack et al., 2015) and to estimate the association between treatment drug choice (oxy-acet vs. hydro-acet) and outcome (long-term opioid use).

There were three steps in the IV-probit analysis. First, we identified region of the United States as the instrumental variable. A valid IV is correlated with the treatment patients receive, but has no effect on the outcome except through its effect on treatment (also known as the "exclusion restriction"), and does not share any causes with the outcome (Ertefaie et al., 2017). Fig. 2 diagrams the key requirements for a valid instrument, as applied in this study.

Second, we regressed the treatment variable on the IV to generate a "new" treatment variable – the predicted value of treatment – and used this new variable to estimate the causal effect of treatment on outcome. We used a two-stage estimation procedure, as the treatment variable was endogenous (Clarke and Windmeijer, 2012) – i.e., in the middle of the causal chain between the IV (region of the United States) and our outcome variable of interest (long-term opioid use). Thus, treatment was both a dependent variable and an independent variable (see Fig. 2). In stage 1, treatment was the dependent variable and was regressed on the instrument and covariates. In stage 2, long-term use was the dependent variable and was regressed on the predicted treatment values obtained from the stage 1 and covariates. We defined our two-stage IV-probit model, as follows:

Stage 1: $x1_i = \gamma_0 + \gamma_1 z1_i + \gamma_2 x2_i + \gamma_3 x3_i + \gamma_4 x4_i + \gamma_5 x5_i + e_i.\times 1$

Stage 2: $y_i = \beta_0 + \beta_1 x1_i + \beta_2 x2_i + \beta_3 x3_i + \beta_4 x4_i + \beta_5 x5_i + e_i.y$

where

p = corr(e.×1, e.y) and is nonzero, and

y = long-term opioid use (0 = no, 1 = yes)

z1 = IV (region of the United States: East = 0, Central and West = 1)

x1 = drug choice (actual values in stage 1: oxy-acet = 0, hydro-acet = 1;

predicted values in stage 2

x2 = MME (values: 5MME, 7.5MME, 10MME, 11.25MME, 15MME)

x3 = mean tablets per day

x4 = age (years)

x5 = gender (0 = female, 1 = male)

γ = probit coefficients (stage 1)

β = probit coefficients (stage 2). The β estimates require the simultaneous

solution of the two equations

i = indexes individual observations

e = error term

In the third step of the IV-probit analysis, we estimated the average treatment effect from the model – i.e., the increased risk of long-term use posed by hydro-acet relative to oxy-acet. The IV-probit model was run in Stata Version 15.0 using the *eprobit* module (StataCorp LLC, College Station, Texas).

2.5.2. Subgroup analyses of patients with > 1 prescription fill

If opioid agents differentially induce long-term use, we would expect that the risks would be more pronounced among patients whose opioid exposure exceeded a minimum threshold (Mundkur et al., 2019). Accordingly, we conducted subgroup analyses of the effects of treatment on outcome for patients who had at least one prescription refill.

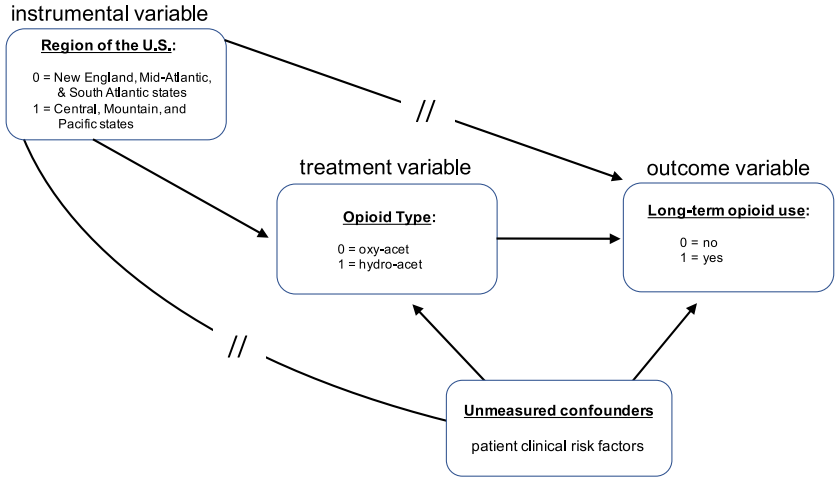

Fig. 2. Path diagram of requirements for inferring a causal relationship. between drug choice and outcome.

Table 1a
Descriptive statistics of study participants by long-term opioid use. Total sample N = 3,983. Long-term prescription use is the outcome variable (coded: 0, n = 3,663; or 1, n = 320).

	Long-term use[c]		P-value
	No	Yes	
Age in years: mean (sd)	55 (16)	60 (14)	< 0.0001
Female (%)	50	56	0.0464
Number of opioid prescriptions: mean (sd)	2 (1.1)	8 (3.0)	< 0.0001
Aggregate number of tablets: mean (sd)	71 (78)	611 (364)	< 0.0001
Aggregate number of days supplied: mean (sd)	20 (22)	203 (80)	< 0.0001
Patient's average number of tablets/day: mean (sd)[a]	4.5 (2.1)	3.1 (1.6)	< 0.0001
MME/d: mean (sd)[b]	28 (16)	24 (17)	< 0.0001
IV: Central and Western region (%)	66	67	0.8690
Prescribed hydro-acet rather than oxy-act (%)	82	84	0.2263

Abbreviations: IV, instrumental variable; MME/d, average morphine milligram equivalents per day.
[a]Calculated for each patient by dividing the aggregate number of tablets in prescription fills by the aggregate days supplied for the prescription fills.
[b]Calculated for each patient by multiplying drug MME by average number of tablets per day.
[c]Opioid treatment was categorized as long term if the prescription dates spanned at least 90 days from initial prescription to the run-out date of the last prescription, and included at least 120 days' supply or 10 fills.

2.6. Construction of the IV

As noted, our IV was region of the United States, dichotomized into New England (CT, ME, MA, NH, RI, VT), Mid-Atlantic (NY, NJ, PA), and South Atlantic states (DE, DC, FL, GA, MD, NC, SC, VA, WV) vs. the Central (IL, IN, MI, OH, WI, IA, KS, MN, MO, NE, ND, SD, AL, KY, MS, TN, AR, LA, OK, TX), Mountain (AZ, CO, ID, MT, NV, NM, UT, WY), and Pacific states (AK, CA, HI, OR, WA). An extensive body of research has documented that in the United States many prescribing practices, including opioid prescribing, vary by geographic region (e.g., Webster et al., 2009; McDonald et al., 2012; Brownstein et al., 2014; Paulozzi et al., 2014; Thumula et al., 2017; Melamed and Rzhetsky, 2018; Rolheiser et al., 2018; Schieber et al., 2019). Different factors may contribute to these differences, including different marketing strategies by pharmaceutical companies and the informal training of physician-trainees that occurs by observing the practices of their teaching faculty (Ertefaie et al., 2017). Region-level instruments have been shown in previous prescription drug research to be useful IVs (Chen and Briesacher, 2011).

The clinical indications for specific therapies – in Fig. 2, the unmeasured confounders – are not contained in insurance claims data and are seldom included in patient notes, i.e., indications for choosing a particular drug treatment rather than an alternative of comparable effectiveness. While not empirically testable, it is fair to assume that our IV, which divides the United States into two broad regions, satisfies the requirement of independence from the patient-specific indications that may lead a primary care physician to prescribe one opioid drug over another to treat aBP. In a *post-hoc* analysis, we examined this assumption more closely using a subgroup analysis of patients whose clinical indications would suggest longer-term opioid use.

2.7. Tests of sample selection bias

We used a parallel sampling design to help isolate the effects of drug treatment on outcome. However, parallel samples are non-random and could bias the results if an unmeasured variable influences both the likelihood of entering the sample and the outcome variable. We tested for this type of bias, called endogenous sample selection (Infante-Rivard and Cusson, 2018), by modeling the probability of a primary care patient with aBP meeting our cohort selection criteria, and then correlating the unobserved error that affected selection into the sample with the unobserved error of the outcome equation. When the correlation between error terms is non-zero, there is endogenous sample selection and a Heckman-type correction may be required (Heckman, 1979). In *a post-hoc* analysis, we used a drug-switching analysis to further explore the possibility that sample selection might have influenced the estimates of treatment effect.

2.8. Sensitivity analysis of average treatment effect (ATE)

We analyzed whether the ATE estimate was sensitive to case exclusion criteria (i.e., comorbidities, certain chronic diseases, psychiatric disorders, use of other medications, use of non-prescription drugs) or to regional influences.

2.9. Post-hoc analyses

In this study, we followed a pre-specified analysis plan but made allowances for additional comparisons and analyses (Rosenbaum, 2010). For convenience, the details of each of the additional analyses are described in the context of presented findings. They include a subgroup comparison (aBP patients with and without radiculopathy) to gauge compatibility with the exclusion assumption in IV analysis, propensity-score analysis to complement the IV analysis, and a drug-switching analysis to further explore the possibility of sample selection bias as a byproduct of parallel sampling. Each is labeled "*post-hoc*" to ensure clarity.

3. Results

3.1. Descriptive statistics and crude associations

Of the 452,381 adults in the Optum research database during Q1 2016 who had a current aBP diagnosis, 3,983 were primary care patients (median age = 55 years, IQR = 43–68; 51% female) who (1) met the initial study selection criteria, and (2) were prescribed either immediate-release oxy-acet or immediate-release hydro-acet, and (3) did not switch drug type or drug strength during the 270 days of follow-up. Fig. 1 presents the cohort selection flow chart.

The mean number of opioid prescription fills per patient was 2.2 (sd = 2.1). Of the 3,983 patients, long-term use was observed in 320 patients (8%). Table 1 presents the descriptive statistics for the study sample of patients. Table 1a gives a breakdown by long-term opioid use, the study outcome variable. Tables 1b and 1c give the covariate breakdowns by treatment choice (hydro-acet vs. oxy-act) and instrumental variable (IV), respectively.

It should be noted that the crude association between drug choice and long-term use (Table 1a) was not significant (P = 0.226), due to case-mix differences between the treatment groups with regard to MME. Fig. 3 shows that when drugs at the same or similar level of MME were compared, the percentage of patients with long-term use was significantly greater with hydro-acet than oxy-acet. The difference was 7.4% (P < 0.001) for hydro-acet 7.5 MME compared with oxy-acet 7.5 MME, and 11.5% (P < 0.042) for hydro-acet 10 MME compared with oxy-acet 11.25 MME. The comparison between hydro-acet 10 MME and oxy-acet 11.25 MME was biased slightly because, at 11.25 MME, oxy-acet would be expected to have a larger proportion of patients in opioid therapy than hydro-acet at 10 MME. The null was rejected in both comparisons. Fig. 3 provides a clearer picture of the differences between drugs, although the comparisons remain crude. We used IV methods for the analysis of causal effects.

Table 1b
Descriptive statistics of study participants by treatment drug choice (oxy-acet coded 0, n = 722; hydro-acet coded 1, n = 3,261).

			P-value
	oxy-acet	hydro-acet	
Age in years: mean (sd)	55 (16)	55 (16)	0.5055
Female (%)	48	52	0.1322
Number of opioid prescriptions: mean (sd)	2.2 (2.1)	2.2 (2.1)	0.9641
Aggregate number of tablets: mean (sd)	113 (184)	115 (196)	0.8052
Aggregate number of days supplied: mean (sd)[a]	32 (54)	35 (60)	0.1584
Patient's average number of tablets/day: mean (sd)	4.6 (2.3)	4.3 (2.1)	0.0005
MME/d: mean (sd)[b]	40 (22)	25 (13)	< 0.0001
IV: Central and Western region (%)	50	70	< 0.0001
Long-term use (%)	6.9	8.3	0.2263

Abbreviations: IV, instrumental variable; MME/d, average morphine milligram equivalents per day.
[a]Calculated for each patient by dividing the aggregate number of tablets in prescription fills by the aggregate days supplied for the prescription fills.
[b]Calculated for each patient by multiplying drug MME by average number of tablets per day.

Table 1c
Descriptive statistics of study participants by instrumental variable (Eastern states coded 0, n = 1,336; Central and Western states coded 1, n = 2,647).

	IV = 0	IV = 1	P-value
Age in years: mean (sd)	58.0 (16)	54 (16)	< 0.0001
Female (%)	51.0	50	0.5858
Number of opioid prescriptions: mean (sd)	2.2 (2.1)	2.3 (2.1)	0.2154
Aggregate number of tablets: mean (sd)	111 (178)	117 (201)	0.3901
Aggregate number of days supplied: mean (sd)	35 (58)	34 (59)	0.6231
Patient's average number of tablets/day: mean (sd)[a]	4.1 (2.0)	4.5 (2.2)	< 0.0001
MME/d: mean (sd)[b]	27 (16)	29 (16)	0.0015
Prescribed hydro-acet rather than oxy-act (%)	73	86	< 0.0001
Long-term use (%)	7.9	8.1	0.8690

Abbreviations: IV, instrumental variable; MME/d, average morphine milligram equivalents per day.
[a]Calculated for each patient by dividing the aggregate number of tablets in prescription fills by the aggregate days supplied for the prescription fills.
[b]Calculated for each patient by multiplying drug MME by average number of tablets per day.

3.2. Exclusion restriction – the effect of IV on outcome

We examined the effect of the IV on long-term use. As shown in Table 1c, no difference was found in percentage terms between the eastern states, where 7.9% of patients transitioned to long-term use, and the middle and western states, where 8.1% transitioned to long-term use (P = 0.869). Table 2 shows the results of the multivariate logistic regression. Consistent with the exclusion restriction (Davies et al., 2013), the IV did not have a direct effect on outcome (OR = 1.22; P = 0.133), controlling for treatment (oxy-acet vs. hydro-acet) and covariates (MME, tablets per day, age and gender).

3.3. Strength of the IV

The ability of an IV to reduce unmeasured confounding and yield reasonably precise estimates depends on how strongly the treatment and the IV are associated, controlling for measured confounders, and on sample size (Small and Rosenbaum, 2008; Guo et al., 2014). Using logistic regression, Table 3 shows a highly significant association (P < 0.0001) between the IV and drug choice (odds ratio = 3.04,

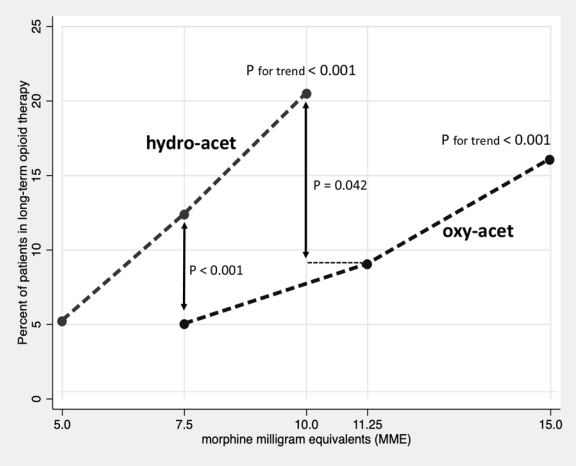

Fig. 3. Percentage of primary care patients with aBP on long-term hydro-acet or oxy-acet prescription therapy. The figure presents the crude comparisons without adjustment for unmeasured confounders and covariates. N = 3,983. Abbreviations: aBP, acute back pain; hydro-acet, hydrocodone-acetaminophen; oxy-acet, oxycodone-acetaminophen; MME, morphine milligram equivalent. At the same or similar levels of analgesia (hydro-acet 7.5 MME compared with oxy-acet 7.5 MME; hydro-acet 10 MME compared with oxy-acet 11.25 MME), the percentage of patients with long-term prescription opioid usage was greater with hydro-acet than oxy-acet, shown in the graph by the vertical distance between the dashed lines. The comparison between hydro-acet 10 MME and oxy-acet 11.25 MME is biased slightly in favor of the null hypothesis because, at 11.25 MME, oxyacet would be expected to have a larger proportion of patients in opioid therapy than hydro-acet at 10 MME. The null hypothesis was rejected.

Table 2
Logistic regression analysis of the association between the instrumental variable (region of the United States) and the outcome variable (long-term prescription opioid use), adjusting for covariates. N = 3,983.

	OR	Z	95% CI		P-value
Dependent Variable: Outcome (long-term opioid use)					
IV (region)	1.22	1.50	0.94	1.59	0.1332
Treatment (oxy v. hydro)	2.62	4.81	1.77	3.88	< 0.0001
MME	1.31	10.19	1.24	1.37	< 0.0001
Tablets per day	0.64	−10.39	0.59	0.69	< 0.0001
Age	1.02	4.98	1.01	1.03	< 0.0001
Gender	0.79	1.84	0.62	1.02	0.0657

Abbreviations: 95% CI, 95% confidence interval; MME, morphine milligram equivalent.

Table 3
Logistic regression analysis* of the association between the instrumental variable (region of the United States) and the endogenous treatment variable (treatment choice of oxy-acet vs. hydro-acet), adjusting for covariates. N = 3,983.

	OR	Z	95% CI		P-value
Dependent Variable: Treatment (oxy-acet vs hydro-acet)					
IV (region)	3.04	10.92	2.49	3.71	< 0.0001
MME	0.56	−24.07	0.53	0.58	< 0.0001
Tablets per day	0.83	−8.23	0.79	0.87	< 0.0001
Age	1.00	1.38	1.00	1.01	0.1667
Gender	1.31	2.72	1.08	1.59	0.0065

Abbreviations: 95% CI, 95% confidence interval; MME, morphine milligram equivalent.
*Although we use logistic regression (LR) here to report the stage 1 association between the IV and treatment, LR is asymptotically biased for two-stage estimation due to the non-collapsibility of the odds ratio (OR). To avoid this complication, we used a probit model (Zhang et al., 2018).

Table 4
Two-stage probit regression with instrumental variable (IV) and estimation of average treatment effect (ATE). N = 3,983.

	Coef	95% CI		P-value
Stage 1: Endogenous Treatment Equation				
Dependent Variable: Treatment (oxy-acet vs. hydro-acet)				
IV (region)	0.60	0.49	0.71	< 0.0001
MME	−0.36	−0.37	−0.34	< 0.0001
Tablets per day	−0.10	−0.12	−0.08	< 0.0001
Age	0.01	−0.01	0.01	0.2449
Gender	0.14	0.03	0.25	0.0099
Stage 2: Main Equation				
Outcome: Long-term use				
Predicted values of treatment (from Stage 1)	0.99	0.67	1.32	< 0.0001
MME	0.19	0.15	0.22	< 0.0001
Tablets per day	−0.20	−0.25	−0.14	< 0.0001
Age	0.01	0.01	0.01	< 0.0001
Gender	−0.13	−0.26	−0.01	0.0336
Average Treatment Effect				
	ATE	**95% CI**		**P-value**
Treatment (oxy-acet vs. hydro-acet)	0.09	0.07	0.12	< 0.0001
Potential Outcome Means	**POM**	**95% CI**		**P-value**
oxy-act	0.02	0.01	0.03	< 0.0001
hydro-acet	0.12	0.10	0.14	< 0.0001

Abbreviations: IV, instrumental variable; MME, morphine milligram equivalent; ATE, average treatment effect; POM, potential outcome means; 95% CI, 95% confidence interval. The table shows the results of the IV-probit analysis with the treatment variable (oxy-acet vs. hydro-acet) as an endogenous variable in the causal chain between the IV (region of the United States) and the outcome variable (long-term opioid use). Region was included in the analysis to minimize the influence of unmeasured confounders that could bias the estimation of the drug choice / long-term use relationship.
The IV-probit model estimated the effect of treatment on long-term use in two stages. In Stage 1, the predicted value of the treatment variable was obtained by regressing treatment on IV (P < 0.0001) and the covariates of MME, tablets per day, age and gender. In Stage 2, the main equation, long-term use was regressed on the independent variables, i.e., the predicted value of the treatment variable from Stage 1 and the covariates. Substitution of predicted for actual treatment values effectively pseudo-randomizes the population to purge unmeasured confounders. The estimated correlation between the errors of the two equations was -0.30 (P = 0.0037).
The association was significant between drug choice and long-term opioid use (P < 0.0001). The ATE, defined as the difference between the POM of the two treatment groups, was 0.09 (95% CI, 0.07 to 0.12) indicating that an additional 9% of patients was estimated to remain on opioid treatment long-term when hydro-acet was the prescribed drug rather than oxy-acet. The POM for hydro-acet was 0.12 (95%CI, 0.10 to 0.14), the POM for oxy-acet was 0.02 (95% CI, 0.01 to 0.03).

adjusted for covariates; 95% CI, 2.49–3.71).

To evaluate the performance of the IV in reducing the influence of unmeasured variables, we also estimated the effect of treatment on outcome using the same regionally-based binary IV, but leaving out either the Mountain states or the South Atlantic states, or both. The correlation between IV and treatment was stronger with these exclusions (Ertefaie et al., 2018):

- **Excluding only the Mountain states:** OR = 4.31; 95% CI, 3.45–5.40; P < 0.0001; N = 3,488;
- **Excluding only the South Atlantic states**: OR = 7.77; 95% CI, 5.79–10.44; P < 0.0001; N = 2,957;
- **Excluding both the South Atlantic and Mountain states**: OR = 11.04; 95% CI, 8.03–15.19; P < 0.0001; N = 2,462.

3.4. Results of the IV-probit regression analysis

The IV-probit results (Table 4) show that hydro-acet was more likely to result in long-term prescription use than oxy-acet (P < 0.0001). The model controls for unmeasured confounders as well as measured covariates (MME, tablets per day, age, gender). An estimated 12% (95 CI, 10%–14%) of patients treated with hydro-acet transitioned to long-term use vs. 2% on oxy-acet (95 CI, 1%–3%). The overall increased risk, or average treatment effect (ATE), was 9% (95 CI, 7%–12%) (rounded to the nearest integer). Among patients who received more than one prescription (n = 1,866), an estimated 23% (95 CI, 19%–26%) treated with hydro-acet transitioned to long-term use vs. 5% on oxy-acet (95 CI, 3%–7%). The ATE was 17% (95 CI, 12%–23%) (rounded to nearest integer) (Table S2, Supplement).

3.4.1. Unmeasured confounding

A statistically significant correlation between the error terms of the stage 1 and stage 2 equations indicates the presence of unmeasured confounding. In our model, ρ = -0.30 (P = 0.0037). As the estimate was significant, we rejected the hypothesis that there was no unmeasured confounding. (The finding substantiated the need for an IV.) As the correlation was negative, we concluded that the unobserved factors that increased the likelihood of physicians' prescribing oxy-acet also increased the likelihood of long-term opioid use. Importantly, the negative correlation runs counter to the argument that unmeasured confounding could explain patients' higher rate of long-term use with hydro-acet. Additional support for this conclusion comes from comparing the probit coefficients in a two-stage vs. a one-stage multiple regression analysis of the effects of drug choice and covariates on long-term use. Our two-stage regression takes nonobservable factors into account, a one-stage regression ignores them. Table S4 (Supplement) displays the results of the two regressions. Both probit coefficients relating treatment to oucome were positive and significant. However, the one-stage or simple probit (γ = 0.42, P < 0.0006) was half as large as the two-stage probit (β = 0.98, P < 0.0001) indicating that the bias from unobserved factors was in a negative direction. The negative bias identified is consistent with an unmeasured tendency of prescribers to favor oxy-acet for persistent pain. The positive coefficients identified point to a stronger impact of hydro-acet on long-term use.

3.4.1.1. Subgroup analysis to assess consistency of findings. In a *post-hoc* analysis (Yang et al., 2014), we checked the compatibility of the finding of negative bias – the unmeasured tendency of prescribers to favor oxy-acet for persistent pain – to the results of a subgroup analysis of patients in which the groups are thought to differ in their likelihood of a longer period of recovery. Patients presenting with acute back pain with radiculopathy (aBPR), for whom slower improvement times were anticipated (Delgado et al., 2018), were compared to patients presenting with acute back pain without radiculopathy. A binary variable identified aBPR patients (ICD-10 codes M5410 to M5418; absence of radiculopathy coded 0, presence coded 1). Of the 3,983 patients in our sample who received a prescription for hydro-acet or oxy-acet, 645 (16%) presented with aBPR.

In keeping with the assumption of independence between the IV and patient clinical indications (the lower-left path in Fig. 2), we predicted that the IV and aBPR variable would be unrelated; the simple probit showed no association (P = 0.953). We also predicted that aBPR would be negatively correlated with drug choice, as our analysis of unmeasured confounding had shown a preference for oxy-acet for persistent pain; the probit was negative and significant (γ = - 0.14, P < 0.020). Finally, we predicted aBPR would be positively correlated with long-term opioid use due to the slower resolution of pain in patients with aBPR; the probit was positive and significant (γ = 0.27, P < 0.001). The pattern of associations squares with our finding of negative bias and lends additional support for the validity of the regional IV.

3.4.2. Results of the IV-probit regression analysis using the stronger IVs

Our model returned very similar results using the stronger IVs – that is, when the Mountain and/or South Atlantic states were excluded. Table S3 (Supplement) reports the relevant parameter estimates. The

size of the drug choice coefficients was unaffected (β ranged from 0.95 to 1.04), and the sign, magnitude, and significance of the correlations between error terms, p, were unchanged.

3.5. Using propensity-score analysis to estimate ATE

The ATE is the average effect of giving each patient treatment T_1 instead of treatment T_2 (Angrist et al., 1996; Rubin, 2005). In a *post-hoc* examination, we estimated the ATE using propensity-score analysis. The aim was to compare the propensity-score estimate, which is based solely on measured variables, with the IV-probit analysis, which considers both measured and unmeasured variables. Using propensity-score methods, we would expect the ATE estimates of the long-term use of hydro-acet to be smaller (partially suppressed) relative to those for oxy-acet, if, as reported above, unobserved factors that increased the likelihood of physicians' prescribing oxy-acet also increased the likelihood of long-term opioid use. The propensity-score analysis used inverse probability weighting and was run in STATA using the *teffects ipwra* module. The model outcome was long-term use (coded 0 = no, 1 = yes), treatment was drug choice (oxy-acet = 0, hydro-acet = 1), and the covariates were MME, tablets per day, aBPR, recent history of antidepressant use, age and gender. The propensity-score estimate of ATE was 5% (95 CI, 3%–7%; P < 0.0001) indicating a 5% increased risk of long-term use posed by hydro-acet relative to oxy-acet. Among patients who received more than one prescription, the ATE was 8% (95 CI, 3%–12%; P = 0.0008). Both estimates were consistent with the IV-probit analysis in that they showed a significantly increased risk of long-term use with hydro-acet. Also consistent with expectation, the propensity-score estimates of ATE were roughly half as large as the estimates of the IV-probit model.

3.6. Sensitivity analyses of average treatment effect (ATE)

We conducted a sensitivity analysis to determine whether additional case exclusion criteria (i.e., comorbidities, certain chronic diseases, psychiatric disorders, use of other medications, use of non-prescription drugs) would affect the estimate of the ATE. None of the exclusion criteria increased or decreased the ATE by more than 1 percent (Table 5).

We repeated the sensitivity analysis for the subset of patients with at least 1 refill (Table S5, Supplement). Among the exclusion categories examined, only the use of antidepressants lowered the ATE more than 1 percentage point (the estimate of 14% was still within the 95% CI for the broader sample), suggesting that antidepressants were associated with extended opioid use. When we incorporated antidepressant use into the main equation, the coefficient for antidepressants was positive (β = 0.30) and significant (P < 0.0001), our drug choice treatment variable was unaffected (β = 1.02, P < 0.0001), and the ATE estimate with antidepressants as a covariate in the main equation was 18% (95% CI, 13%–23%). Finally, we examined the sensitivity of the ATE estimate to regional influences. Fig. S1 (Supplement) reports the ATE after excluding, one by one, each of the nine regions. No outliers were found.

Table 5
Sensitivity analysis of average treatment effect (ATE) to alternative case exclusion criteria. N = 3,983.

Patients excluded with recent history of:	N_{in} / N_{out}	ATE	95% CI	P-value
Comorbidities (Charlson score > 0)	3,664 / 319	.09	.06 - .11	< 0.0001
Chronic diseases:				
liver disease	3,972 / 11	.09	.07 - .12	< 0.0001
renal disease	3,954 / 29	.09	.07 - .12	< 0.0001
COPD	3,940 / 43	.09	.07 - .12	< 0.0001
Psychiatric disorders:				
depression	3,935 / 48	.10	.07 - .12	< 0.0001
anxiety	3,884 / 99	.09	.06 - .12	< 0.0001
psychosis	3,972 / 11	.09	.07 - .12	< 0.0001
Use of other prescription drugs:				
antidepressant	3,179 / 804	.08	.05 - .11	< 0.0001
benzodiazepine	3,637 / 346	.08	.05 - .11	< 0.0001
muscle relaxant	3,824 / 159	.09	.06 - .11	< 0.0001
anxiolytic, sedative, hypnotic	3,799 / 184	.10	.07 - .12	< 0.0001
anti-psychotic	3,932 / 51	.09	.06 - .11	< 0.0001
Use of non-prescription drugs:				
tobacco	3,944 / 39	.10	.07 - .12	< 0.0001
alcohol abuse/dependence	3,981 / 2	.09	.07 - .12	< 0.0001

Abbreviations: ATE, average treatment effect; COPD, chronic obstructive pulmonary disease; 95% CI, 95% confidence interval.
Recent history was defined as preceding the index visit by ≤3 months.

3.7. Sample selection bias

A nonrandom sample potentially biases the results when an unmeasured variable influences both the likelihood of entering the sample and the outcome variable (Swanson et al., 2015; Ertefaie et al., 2016; Swanson, 2017). We fit a probit model to estimate the selection parameter – the probability of a primary care patient with aBP meeting the cohort selection criteria. As we were again modeling endogeneity, this time, "sample selection-induced endogeneity," we employed a two-stage procedure similar to that used to estimate the effect of treatment on outcome (Heckman, 1976; Imbens and Rubin, 2015). The outcome variable in the stage 1 equation was the probability of selection. The independent variables were age, gender, antidepressant use to capture "adverse selection" (Braden et al., 2009; Weisner et al., 2009; Edlund et al., 2010; Deyo et al., 2015; Vowles et al., 2015), comorbidities (Carlson Index), and IV. The outcome variable in the stage 2 main equation was long-term use, and the independent variables were the selection parameter, the predicted values of the treatment variable, MME, tablets per day, age, gender, and antidepressant use (based on the results of the sensitivity analysis, above). To avoid functional-form identification (the same variables specified in both equations), we omitted comorbidities and IV in the stage 2 equation, as they were unrelated to outcome (STATA Extended Regression Model Reference Manual, 2017). The correlation between the error terms of the selection and main equations was not significant (r = 0.39, P = 0.730) indicating the absence of endogeneity.

3.7.1. Potential selection bias from excluding patients who switched drugs

Many patients who receive more than one opioid prescription switch drugs to obtain a satisfactory balance between analgesia and adverse effects (Fine and Portenoy, 2009; Slatkin, 2009). In a *post-hoc* analysis, we examined whether the rates of drug-switching from the index drug to an alternative (or supplementary) opioid differed for hydro-acet and oxy-acet. We also examined the rates of drug-strength switching from the index drug formulation to a weaker (lower MME) or stronger (higher MME) formulation of the same immediate-release drug. Along the same line, we calculated the rate of switching from the immediate-release index drug to an extended-release version of the same drug. A minimum of 2 opioid fills were required for inclusion in the switching analysis. A switch was defined as at least 1 fill that differed from the index prescription.

The percentage of patients who switched the type of opioid drug was 37% when oxy-acet was the index drug and 33% when hydro-acet was the index drug (P = 0.037). Among the patients who did not switch opioid type (i.e., all their prescription fills were immediate-release hydro-acet or immediate-release oxy-acet), the rate of drug-strength switching was 13% for oxy-acet and 15% for hydro-acet (P = 0.159). With respect to extended-release formulations, when oxy-acet was the index drug, 1% switched to the extended-release oxycodone formulation (OxyContin); when hydro-acet was the index drug, none of the patients switched to an extended-release hydrocodone product (e.g., Hysingla ER) (P < 0.001).

Taken together, the data do not suggest a pattern of opioid

switching that could account for a higher rate of long-term prescription use with hydro-acet. The extent of switching was similar for both drugs.[2] To put it another way, some inter-individual variability in the therapeutic response to opioids is natural – given, e.g., genetic variants in drug disposition (absorption, metabolism, distribution, excretion) and drug targets (μ-opioid receptor and signal transduction modulators) – but the modest extent and arbitrary direction of variability between treatment groups in these data does not support the counterfactual hypothesis, i.e., that had the switches not occurred the differences in long-term use between oxy-acet and hydro-acet would have been less or zero.

4. Discussion

Using a nationwide insurance database for a real-world view of opioid prescribing (Franklin and Schneeweiss, 2017), we found that aBP patients treated with hydro-acet were more likely to transition to long-term opioid therapy than patients treated with oxy-acet, contradicting the assumption that drugs of the same MME have the same risk of prolonged use. Although claims data cannot capture a patient's pain experience or the perceptions or reasoning of a physician, no evidence was found that patient medical factors or physician prescribing practices accounted for the differences between oxy-acet and hydro-acet.

To our knowledge, this is the first study to identify the effect of a specific opioid drug on long-term use in the primary care setting, and the first to quantify the separate effects of drug, analgesic strength (MME), and dosage (tablets per day). We found that choice of drug, with MME and dosage held constant, had a large effect on long-term use. Specifically, the risk of long-term use was substantially greater with hydro-acet than oxy-acet. We also found that higher MME formulations increased the risk of long-term use, as anticipated, and that average tablets per day was lower among patients who had transitioned to long-term use, in contrast to expectation.

Studies of long-term opioid use generally rely on the composite measure of morphine milligram equivalents per day (MME/d) or cumulative MMEs over a defined time period (Turner et al., 2016; Deyo et al., 2017; Shah et al., 2017). The CDC recommendations for opioid prescribing are also framed in terms of MME/d (Dowell et al., 2016). Because MME/d is a composite measure, the separate and relative effects of its 3 components (drug, MME, tablets per day) are obscured. Reliance on MME/d may be due to the fact that many patients switch drugs or change dosage, or have concurrent or overlapping prescriptions for different opioids, which makes analysis of the separate elements in the composite a challenge.[3] We addressed this problem by selecting 6 parallel cohorts on the basis of drug and analgesic strength (Table S1). The selection strategy made it possible to disentangle the long-term effect of opioid drug from the simultaneous effects of MME and tablets per day.

An additional strength of this study is that we followed a predefined analysis plan. However, with insurance claims as our data source, the plan could not include an examination of the neurobiological mechanisms that may underpin the different effects of oxycodone and hydrocodone over time. Moreover, those mechanisms are still incompletely defined. While both drugs are selective for the μ-opioid receptor (μOR) and have similar binding affinities (Volpe et al., 2011), oxycodone more easily crosses the blood-brain barrier, yielding a higher drug concentration at the receptors which could account for oxycodone's greater analgesic effect (Boström et al., 2008). We conjecture that opioid dependence hinges on drug efficacy, defined in the pharmacodynamic sense of action of a drug once binding has occurred, more than on availability to the receptors. That is, the neural pathways underlying reward and dependence – and by extension, long-term use – may be primed by repeated exposure to higher-efficacy agonists, such as hydrocodone, even at lower concentrations at the binding sites. Present knowledge of μOR structure and signaling does not provide a foundation for a precise theory, although the solution of the μOR crystal structures (Manglik et al., 2012) and, more recently, the cryo-electron microscopy of the ligand binding pocket (Koehl et al., 2018), are large steps forward. More research is needed to elucidate how different ligands selectively activate the signaling pathways (Emery et al., 2016; Stoeber et al., 2018; Valentino and Volkow, 2018).

An alternative explanation – that primary care physicians, perhaps from beliefs about safety or effectiveness, prefer hydrocodone for clinical indications that suggest extended treatment – was contradicted by the data. The IV analysis of unmeasured confounders pointed to physician preference for oxy-acet, not hydro-acet, when persistent pain was anticipated. That finding was supported by a subgroup analysis that compared patients with and without radiculopathy. In short, the tendency of physicians to prescribe oxy-acet for more enduring pain was clearly present, but eclipsed by a generally high rate of transition to long-term use with hydro-acet. Thus, we assert two separate forces driving long-term use: a prognosis of slow recovery leading to physicians ordering (and renewing) oxy-acet prescriptions, and the inherent power of hydro-acet to induce long-term use regardless of prognosis.

We had not anticipated rejecting the null hypothesis given that the literature does not report systematic differences between drugs related to the duration of use such as pain relief and side effects (VA/DoD, 2017). If our findings are validated in future research, clinicians should be advised that the risk of long-term use is substantially greater in patients prescribed only immediate-release hydro-acet than those prescribed only immediate-release oxy-acet, despite equianalgesia. Patients with aBP using either of these opioids, and especially those prescribed hydro-acet, should be monitored closely. It is important to recognize that the heavy caseloads and time pressures in primary care clinics can erode the best efforts at monitoring, with long-term use an unintended consequence. To ensure that all opioid prescriptions are based on a considered decision (Deyo et al., 2011; Foster et al., 2018), clinical pathways should be restructured to discourage refills without an in-person appointment. A single prescriber for each patient will also strengthen the monitoring of treatment and patient progress. Incentives will be needed to keep these measures in place.

4.1. Limitations of the study

The findings of the present study should be considered in light of several limitations. First, we did not measure opioid misuse, abuse, or dependence, though each of these clinically important outcomes is a function, in part, of long-term use (Boscarino et al., 2010; Edlund et al., 2014; Chou et al., 2015; Fleming et al., 2007).

Second, the prescription claims data in Optum refer to medications dispensed (pharmacy fills); we did not have data on tablets actually consumed.

Third, we were unable to measure pain intensity or persistence using claims data, and therefore used IV methods to account for the unobservables. Even with the supporting evidence of the stronger versions of the regional IV and the ATE sensitivity analyses, the possibility of residual confounding affecting the association between treatment and outcome cannot be ruled out. Residual association would suggest that the instrumental variable assumptions are not completely satisfied (Brookhart et al., 2010; Garabedian et al., 2014).

Fourth, the Optum database included participants in commercial insurance plans and Medicare Advantage plans, about 19% of the

[2] Comparability in the rates of drug type switching makes sense as patients taking oxycodone and hydrocodone report a common array of side effects (e.g., fatigue, cognitive dysfunction, constipation, nausea, sedation, itching, vomiting, dry mouth, peripheral edema, impotence, ataxia). Studies disagree as to which drug more often produces side effects (e.g., Marco et al., 2005; Manchikanti et al., 2009; Solomon et al., 2010).

[3] Drug switching may also be a reason for the absence of long-term randomized control studies in which specific opioids are compared head-to-head (Solomon et al., 2010).

privately insured US population (Optum, 2018). Research is needed to check our results in other populations, such as fee-for-service Medicare beneficiaries, Medicaid beneficiaries, and the unemployed (Jeffery et al., 2018). By focusing on primary care, our study may not generalize to other major prescribers of opioids such as surgeons, dentists, and pain management specialists.

And fifth, causal questions should be addressed with a body of research that uses different samples, methods, and assumptions to assess the robustness of the findings (Rosenbaum, 2017).[4] Until our findings are validated in other studies, and buttressed by a better understanding of the neurobiological mechanisms, the results should be interpreted with caution.

5. Conclusions

The probability of long-term prescription use was substantially greater for patients treated with hydro-acet than oxy-acet, negating the widespread assumption that drugs of the same MME pose the same risk. However, we cannot conclude that oxycodone is safer to prescribe than hydrocodone. Opioid safety is multi-dimensional and context-specific (Throckmorton et al., 2018), and our study considered only a single outcome, condition, and population. Given the current state of research, our results make the strong, but more limited case that the assessment of individual opioid drugs for risk of extended use should become a high-priority line of inquiry. In 2017, opioids were associated with 47,600 drug overdose deaths in the United States, 36% of which involved a prescription opioid (Scholl et al., 2018). A better understanding of the differences among opioid drugs will help inform policy and clinical decision-making.

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[4] Microeconomics provides an example of a different set of assumptions that can be applied to the research question. Viewing patients as economic actors and opioids as consumer goods, the price elasticity of demand could be used to measure the capacity of an opioid to induce long-term use and dependence. Consumer theory would posit that individuals taking a more habit-forming opioid would be less responsive, at the margin, to higher out-of-pocket costs (copays, deductibles, coinsurance) and, therefore, less prone to discontinue use than individuals taking a less habit-forming opioid at the identical MME.

Contributors

Concept and design (R.A.H., C.A.D., R.G.); obtain funding (C.A.D.); acquisition of data (C.A.D., R.A.H.); statistical analysis (R.A.H., R.G.); interpretation of findings (R.A.H., R.G., H.R.K., K.M.C., C.A.D.); drafting the manuscript (R.A.H.); critical revision of manuscript for important intellectual content (R.A.H., R.G., H.R.K., K.M.C., C.A.D.). All authors have read and approved the final manuscript.

Declaration of Competing Interest

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Appendix A. Supplementary data

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