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U.S. county prevalence of retail prescription opioid sales and opioid-related hospitalizations from 2011 to 2014

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ABSTRACT

Background: The role of prescription opioids in the opioid crisis has been well established. How the prevalence of prescription opioids relates to opioid hospitalizations has been understudied. Hospitalizations due to opioids are a distinct indicator of opioid misuse, have cost implications for health care systems, and may be an entry point into substance use treatment.

Methods: Administrative data were drawn for counties in 32 U.S. states from 2011 to 2014 to associate retail opioid sales rates with opioid-related hospitalization rates. Data on hospitalizations comes from the Healthcare Cost and Utilization Project. Data on opioid sales come from the Automation of Reports and Consolidated Orders System. Statistical models were run accounting for error in the opioid sales measure and controlled for county and year effects and other factors. Sub-analyses explored hospitalizations by metropolitan status and maternal/neonatal stays. As a point of comparison, the analysis estimated the relationship of opioid sales to alcohol hospitalizations.

Results: Retail opioid sales rates have a positive relationship with opioid-related hospitalization rates where a one morphine kilogram equivalent (MKE) increase in sales per 10,000 people predicts a 9.0% (CI 4.6%–13.7%) increase in opioid-related hospitalization rates. The relationship is higher in non-metropolitan counties. Maternal and neonatal opioid-related hospitalization rates increase by 14.1% (CI 4.9%–24.2%) with a one MKE increase in retail sales rates. There is no statistically significant relationship between opioid sales and alcohol hospitalizations.

Conclusions: Though not causal, results inform understanding of how opioid prescribing relate to adverse consequences of opioid use and misuse.

1. Introduction

The role of prescription opioids in the current opioid crisis in the United States has been well-established (Cicero et al., 2007; Compton et al., 2016; Han et al., 2017; Jones, 2017). For example, Seth at al. (2018) report that prescription opioid-related death rates rose by 33% from 2006 to 2016 or from 3.9 to 5.2 per 100,000 persons. How the prevalence of prescription opioids in a community relates to opioid-related hospitalizations has been understudied and has implications for policy and practice. Hospitalizations are a distinct indicator of substance use, have cost implications for health care systems, and may also be an entry point into substance use treatment as well as other support services (Houry et al., 2018; O'Toole et al., 2002). Using a measurement error approach on county-level data for 2011 through 2014 for most counties in the U.S., this study shows how changes in retail opioid sales rates predict opioid-related hospitalization rates in the United States.

Research has established that prescription opioids are a significant driver of opioid use disorder. Cicero et al. (2007) found a statistically significant relationship between therapeutic use of opioids and their misuse in communities. Individuals misusing prescription opioids are also more likely to use heroin and other synthetic opioids and vice versa (Compton et al., 2016). For example, Becker et al. (2008) found that heroin users were 3.9 times as likely to report nonmedical use of opioids in the previous year as persons who did not use heroin. Results from the 2015 National Survey on Drug Use and Health found that 10.4% of adults in the U.S. using an opioid prescription had opioid misuse without OUD, and 2.1% had an OUD (Han et al., 2017). From 2003 to 2013, the prevalence of OUD among adults age 18 to 64 increased from 0.6% of the population to 0.9% (Han et al., 2015). While this study focuses on the U.S., prescription opioids misuse has also been recognized as a problem internationally, particularly in the United Kingdom (Giraudon et al., 2013) and Canada (Fischer et al., 2015).

Urbanicity has been recognized as a key mediating factor in the prescription opioid crisis. The relationship between therapeutic use and

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misuse is particularly strong in small to medium sized urban and suburban areas and rural areas (Cicero et al., 2007), and increases in neonatal abstinence syndrome and maternal opioid use were higher in rural areas relative to urban areas over the 2004–2013 period (Villapiano et al., 2017). In a survey of individuals with OUD, those in rural areas were more likely to report experiencing an overdose than those in urban areas. Dunn et al. (2016) and Brown et al. (2018) found that rural and Appalachian counties in Kentucky had NAS rates between 2 and 2.5 times higher than urban and non-Appalachian counties. Rural areas are also recognized to have historically fewer substance use treatment options relative to urban areas (Sigmon, 2014). While much of the research points to greater risk in rural areas, Jones (2017) found that past year prescription opioid abuse or dependence increased by 47.3% in areas with more than 1 million habitants over the 2003–2014 period, while areas with smaller populations saw a much smaller increase or decrease.

Several studies have examined trends in opioid-related hospitalizations in the U.S. In 2012 nearly one fourth of maternal stays related to substance use involved opioids, and the rate increased by 135 percent between 2006 and 2012 (Fingar et al., 2015). From 2000–2014 there was regional variation in prescription opioid-related hospitalization rates and trends with the highest rates in the U.S. South and lowest in the Northeast (Unick and Ciccarone, 2017). From 2007–2014, prescription opioid-related hospitalizations were higher in rural areas than in urban areas, while heroin-related visits showed the reverse pattern (Mosher et al., 2017).

For policy makers, the extent to which the distribution of prescription opioids is predictive of other measures has implications for policies and guidelines influencing prescribing. For example, efforts by the Centers for Medicaid and Medicare Services to reduce opioid prescribing among Medicare and Medicaid recipients and prescribing guidelines from the CDC all focus on the availability of prescription opioids (Dowell et al., 2016).

2. Materials and methods

2.1. Data sources

Data on opioid-related hospitalization rates include unduplicated hospital stays and emergency department visits related to opioids per 100,000 persons in the county. Data are derived from restricted use files from the State Inpatient Databases (SID) and State Emergency Department Databases (SEDD) within the Healthcare Cost and Utilization Project (HCUP). States voluntarily report patient-level hospital stay data to HCUP following standardized International Classification of Diseases (ICD) codes. Relevant ICD-9 codes, following established practice, were identified based on specific substances (ICD-10 codes were not yet in use for the period under study). Data were obtained through data use agreements with the U.S. Agency for Healthcare Research and Quality, the entity managing HCUP. Patient records were aggregated to the county-level based on county of patient residence. To provide a basis for comparing the effect size of opioid hospitalizations, hospitalizations related to alcohol are also modeled. More details on the specific ICD-9 codes used can be found in Appendix A in Supplementary material (Stock and Yogo, 2005).

Data for retail prescription opioid sales come from the U.S. Drug Enforcement Administration's (DEA) Automation of Reports and Consolidated Orders System (ARCOS) for all counties in the United States. Publicly-available ARCOS reports contain information on the inventories, acquisitions, and dispositions of certain controlled pharmaceuticals. Opioids that are schedules I, II, and III controlled substances based on the U.S. Controlled Substances Act (Public Law 91–513) are reported into ARCOS. Scheduled substances are published annually in Title 21 Code of Federal Regulations sections 1308.11 through 1308.15. Commonly prescribed and misused opioids which have been consistently reported to ARCOS over the time period of study were selected. These include buprenorphine, dextropropoxyphene, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, oxycodone, oxymorphone, and tapentadol. Though buprenorphine and methadone are commonly used to treat OUD, ARCOS does not identify specific formulations nor purpose of prescription. Excluding buprenorphine and methadone does not affect the results. ARCOS reports the weight of sales of each drug, and those weights were converted to kilogram morphine equivalents using conversion factors provided by Food and Drug Administration. The DEA publishes ARCOS data for three-digit zip codes (e.g., 209 would include zip codes 20902 and 20906). To convert to counties, the three-digit zip codes were first converted to five-digit zip codes by distributing the share of opioid sales across the appropriate zip codes based on population proportions. Retail opioid sales are measured in morphine kilogram equivalents (MKE) per 10,000 population.

There are important limitations to ARCOS that suggest it may contain substantial measurement error. Being self-reported administrative data, it is not collected for statistical purposes, and there are limited data verification procedures. The accuracy and reliability of reports submitted to ARCOS have not been the subject of the rigorous quality reviews that other commonly-used administrative collections are typically subjected to, and the mechanisms by which entities submit data may not be consistent (N. Jackson, DEA, oral communication, March 2018). A 2015 Government Accountability Office study (Government Accountability Office, 2015) found significant data reliability issues with ARCOS and quoted DEA officials pointing out "significant and inherent inaccuracies in the data." These quality limitations may be correlated with the prevalence of opioid misuse: areas that have higher prevalence of misuse may be more or less likely to accurately report.

2.2. Study sample

The analysis focuses on counties in the U.S. from 2011 through 2014 in the 32 states reporting to the HCUP program over the study time period (see Appendix A in Supplementary material for a list). Data for West Virginia in 2014 were dropped due to data quality issues. Any county that never had an opioid-related hospitalization was also dropped; because the modeling approach used county fixed effects, these observations contributed no variance. After accounting for control variables, the final sample size for the primary model was 6047 county-year observations. The model for maternal and neonatal opioid hospitalizations had a sample size of 2107. The reduction in sample size was due to a large number of counties that never reported any maternal or neonatal opioid hospitalizations.

2.3. Statistical methods

This study uses negative binomial regression models with county and year fixed effects. Taking advantage of the panel nature of our data, county fixed effects allow us to look at the within-county change from year to year while also accounting for year-to-year shocks that influence all counties equally. Coefficients represent the relationship between a change in prescription opioid sale rates and opioid-related hospitalization rates from one year to the next in a given county. The strength of this approach rules out any confounding factor that remains stable across counties over time. Among other factors, these could include cultural and institutional norms, which are difficult to measure and likely do not change rapidly from year to year.

Hospitalization rates are positively skewed and non-negative, and because of this the study uses negative binomial regression models. Over-dispersion of the dependent variables indicates a negative binomial model is more appropriate than a Poisson model. Models include population (in 100,000 s) as an offset, permitting the interpretation of the coefficients as incidence rate ratios or the predicted proportional change in hospitalizations for a given change in the independent

variable.

To account for the measurement error in retail opioid sales, the study uses a control function approach, a version of an instrumental variables design appropriate for non-linear models (Guo and Small, 2016; Terza et al., 2008). In this method, the measurement error in ARCOS is cleaned up by a two-stage estimation procedure. An exogenous variable is identified that is correlated with ARCOS data but is only correlated with opioid hospitalization rates through its relationship with ARCOS after accounting for other covariates in the model. In the first estimation stage, ARCOS is regressed on the exogenous variable and controls (including county and year effects) using a linear ordinary least squares model, and the residuals are computed. The second stage regresses hospitalizations on ARCOS, the controls, and the residuals using the negative binomial regression model. Standard errors and confidence intervals are bootstrapped using 1000 replicates.

The instrument used is Medicare Part D opioid prescriptions rates measured as kilogram medical morphine equivalents per 100,000 population. Conceptually, Medicare Part D prescriptions can affect opioid hospitalizations either through the increased availability of opioids or as a measure of the number of elderly or disabled Medicare recipients, who may be more likely to use or misuse opioids (Morden et al., 2014). The latter relationship is accounted for by including the county's proportion of individuals receiving Medicare that are elderly and disabled in the model. As a result, the only way that Medicare Part D opioid prescriptions could relate to hospitalization rates is through the availability of opioid prescriptions, which are captured by ARCOS data.

While it cannot be formally tested, Medicare Part D prescriptions are not likely susceptible to the same type of measurement error as ARCOS data. Medicare data are used to process financial claims rather than for enforcement processes and are therefore more likely to be reliable, since providers cannot be reimbursed if the data are reported inaccurately. The Centers for Medicare and Medicaid Services also has better data quality procedures in place than DEA, including sophisticated fraud prevention procedures (Government Accountability Office (GAO, 2017). Finally, Medicare Part D claims are reported at the location of recipient, not retailer.

Medicare Part D covers a portion of Medicare beneficiaries: those who are either elderly or disabled. This is not the full range of the population misusing opioids. While these limitations would impede the use of Medicare prescriptions as the primary variable of interest, they do not affect their use as an instrument for all prescriptions.

Standard validity tests show that Medicare opioid prescriptions rates are a valid instrument and are reported in Appendix A in Supplementary material Table A1. Additionally, a falsification test is used to assess the robustness of the instrument (Pizer, 2016). Incarceration rates were regressed against Medicare opioid prescriptions rates, including other controls from the main models. County incarceration rates were drawn from the National Corrections Reporting Program, sponsored by the Bureau of Justice Statistics. If Medicare prescriptions are predictive of incarceration rates– a variable found to be positively correlated with opioid-related hospitalizations– it would call into question the validity of the instrument. In the falsification model, Medicare opioid prescriptions do not have a statistically-significant relationship with incarceration rates ($p = 0.416$).

It is possible that any identifiable relationship between opioid sales and opioid hospitalizations is a result of broader relationships between sales and any substance-related hospitalizations, not solely opioids. This is particularly important to consider given high rates of poly-substance use among individuals with opioid use disorder. To test whether there is a unique relationship between opioid sales and opioid hospitalizations, the same regression models are used with alcohol-related hospitalizations as the outcome. If the estimated coefficients on opioid sales are comparable for the opioid hospitalization and alcohol hospitalization model, it would call into question the primary hypothesis.

2.4. Control variables

A number of potentially confounding variables are included in the model, including the total population, county race/ethnicity and age makeup, receipt of supplemental security income (SSI), inflation-adjusted median income, unemployment rate, the presence of prescription drug monitoring programs, and whether the state has instituted legislation restricting pill mills (Mallatt, 2017). These variables have been found to correlate with measures of substance use and prescription opioids in the literature. The models also included as a control the proportion of the county without health insurance. Over the time period, 16.4% of the population in the average county was estimated to be without health insurance. These individuals have differential access to opioid prescriptions and rely exclusively on out-of-pocket payments. The models also include an indicator for whether the county had at least one provider of medication-assisted treatment for opioid use disorder distributing either methadone or buprenorphine, which could mediate the impact of opioid use disorder on hospitalizations.

OUD is comorbid with other SUDs (Grella et al., 2009; Jarlenski et al., 2017; Manuby et al., 2015). For example, in the data for this study, alcohol and opioid-related hospitalization rates are highly correlated ($r = 0.51$, $p < 0.01$). To account for this comorbidity, models included alcohol-related hospitalizations and age-adjusted overdose death rates due to any substance (excluding alcohol) (Rossen et al., 2017).

3. Results

3.1. Summary statistics

Table 1 reports descriptive statistics for the measures included in this study, including control variables. The mean opioid-related hospitalization rate in our sample was 238.53 per 100,000 persons and was somewhat higher in metropolitan than non-metropolitan counties ($t = 28.43$, $p < 0.001$). Maternal and neonatal opioid hospitalizations were much less frequent than non-maternal and non-neonatal hospitalizations. The mean retail prescription opioid sales per 100,000 was 109.35 MKE.

3.2. Model results

Table 2 reports results from statistical models. The model shows that a one kilogram ME increase in retail opioid sales per 10,000 people predicts a 9.0% (CI 4.6% to 13.7%) increase in opioid-related hospitalization rates. The size of the coefficient on the first-stage residual (0.918) suggests substantial attenuation bias due to the measurement error in the ARCOS sales data.

When focusing exclusively on counties in metropolitan areas, the point estimate is smaller than all counties, where one MKE increase in sales rates predicted a 3.9% increase in opioid-related hospitalization rates (CI 1.0% to 6.9%). The point estimate for non-metropolitan counties is higher (1.4%), though it is not statistically significantly different from the estimate for metropolitan counties (Wald test, $p = 0.253$).

For maternal and neonatal opioid hospitalizations, the point estimate was a one MKE increase in opioid sales rates predicts a 14.1% (CI 4.9% to 24.2%) increase in hospitalization rates. The large confidence intervals suggest substantial uncertainty in the magnitude of the relationship, and the point estimate is not statistically different from the estimate for non-maternal and non-neonatal hospitalization rates ($p = 0.335$). The estimate for non-maternal and non-neonatal was on par with the estimate for all patients in all counties.

As a point of comparison, after accounting for the covariates in the models, retail opioid sales have no statistically significant, identifiable relationship with alcohol-related hospitalization rates.

Table 1
Descriptive Statistics.

	Mean	SD	25th Pctl	Median	75th Pctl
Opioid hospitalization rate	238.53	214.62	104.36	188.03	306.36
Opioid hospitalization rate (metropolitan)	258.13	212.52	121.28	215.22	329.42
Opioid hospitalization rate (non-metro)	222.07	215.02	92.35	166.85	288.05
Opioid hospitalization rate, non-maternal and non-neonatal	231.84	206.02	103.15	184.46	296.37
Opioid hospitalization rate, maternal or neonatal	6.69	16.99	0	0	4.9
Retail opioid sales (MKE per 10,000)	109.35	103.46	62.16	89.35	127.19
Medicare opioid prescriptions (kg ME per 100,000)	40,660.9	22,152.63	25,295.88	35,523.18	51,563.11
Alcohol hospitalization rate	901.82	555.03	509.79	798.6	1,163.05
All hospitalizations	39,195.17	23,009.88	15,228.03	40,483.28	56,683.65
Age-adjusted overdose death rate	14.85	7.04	9.98	13.44	18.3
Population (1000s)	144,859.75	420,859.47	20,509.5	40,968	10,8152.5
Median income	34,130.95	8,590.38	28,457.67	32,538.09	38,184.26
Poverty	17.21	5.98	13	16.8	20.7
Unemployment rate	8.11	2.63	6.3	7.8	9.6
White (percent of pop)	78.74	18.88	68.91	85.47	93.59
Black (percent of pop)	8.17	11.76	1.07	2.98	9.68
Hispanic (percent of pop)	9.33	13.41	2.1	4.27	9.94
Prescription drug monitoring program[a]	0.87	–	–	–	–
PDMP (mandatory check)[a]	0.13	–	–	–	–
Pill mill legislation[a]	0.27	–	–	–	–
Metropolitan[a]	0.46	–	–	–	–
Non-metropolitan[a]	0.54	–	–	–	–
Medicare (total enrolled)	19.5	4.73	16.27	19.51	22.35
Medicare (disabled)	3.59	1.49	2.53	3.36	4.38
Uninsured (percent of pop)	16.43	5.39	12.3	16.5	20
Primary care physicians per capita	56.28	32.19	35.56	50.94	71.82
Age, over 65 (percent of pop)	16.48	4.21	13.78	16.14	18.58
Age, 0 to 18 (percent of pop)	22.81	3.05	20.99	22.76	24.41
SSI (percent of pop)	2.9	1.88	1.68	2.48	3.59

[a] categorical variable. All continuous variables are presented in levels, but are transformed in natural logarithms in models.

4. Limitations

This study has several limitations. First, it does not cover all states in the U.S., and to the extent that states included differ systematically from those excluded, results may not be nationally representative. Also, individuals with OUD may be admitted to a hospital or visit the emergency room upon using dangerous levels of opioids or after a non-fatal overdose. Not every individual suffering a non-fatal overdose or other dangerous symptom of OUD gets admitted to a hospital. Hospitals may also incorrectly report admissions due to opioid poisoning; for example, hospital staff may enter diagnosis codes that relate to the medical symptoms without indicating that opioids were related. This could underestimate the prevalence.

An additional limitation is that the results are correlational in nature and should not be interpreted as causal. While the models account for measurement error in the opioid sales measure and control for a number of factors, they do not account for all unobservable variables that may confound the relationship between sales and opioid hospitalizations. Another limitation is that, as this is an ecological study, one cannot be certain that the individuals using opioid prescriptions are the same as those being hospitalized due to opioids. Finally, instrumental variables models are designed to reduce measurement error when present, but they are less efficient than standard regression models, resulting in greater uncertainty in estimates as manifested in larger standard errors and confidence intervals.

5. Discussion

This study finds that retail opioid sales rates were positively associated with opioid-related hospitalization rates over the 2011–2014 period in 32 states in the U.S. When sales rates rose in a county, opioid-related hospitalization rates also rose. What's more, the results suggest a relationship unique to opioid hospitalizations relative to other substances. Indicators of substance use more generally– alcohol-related hospitalizations and drug overdose death rates– were included among the various factors accounted for in models. In addition, in a separate model no relationship was found between opioid sales and alcohol-related hospitalization rates. The models also accounted for economic and demographic factors, providing further support to the arguments that the availability of prescription opioids is a driving force behind the

Table 2
Model Results.

			95% Confidence Interval		
Sample	Estimate	Standard Error	Low	High	N
Opioid Hospitalization Rate					
All counties, all patients	1.090*	0.023	1.046	1.137	6,071
Metropolitan counties, all patients	1.039*	0.015	1.010	1.069	2,744
Non-metropolitan counties, all patients	1.092*	0.045	1.008	1.183	3,327
All counties, maternal and neonatal	1.141*	0.049	1.049	1.242	2107
All counties, non-maternal and non-neonatal	1.090*	0.024	1.044	1.137	6,071
Alcohol Hospitalization Rate					
All counties, all patients	0.995	0.009	0.978	1.012	6,071

Note: Coefficients are incident rate ratios. Confidence intervals are based on 1000 bootstrap replicates. * $p < 0.01$.

epidemic independent of economic and demographic conditions (see Ruhm, 2018).

Research has found that the opioid crisis manifests itself differently in rural and urban areas. Generally, misuse of prescription opioids and prescription OUD has been found to be more prevalent in rural areas (Brown et al., 2018; Dunn et al., 2016; Jones, 2017; Sigmon, 2014; Villapiano et al., 2017). In the current study, the point estimate for the relationship between opioid sales rates and opioid hospitalization rates was stronger in counties in non-metropolitan areas than those in metropolitan areas, though the differences were not statistically significant. This is one of the limitations of using instrumental variables approaches, which can lead to higher imprecision of estimates. These results suggest that the relationship between prescription opioid sales and opioid-related hospitalizations is on average different in metropolitan and non-metropolitan areas, though the specific nature of that difference cannot be observed in the data on hand.

Substantial attention by researchers and policymakers has been paid to the rising prevalence of neonatal abstinence syndrome (NAS) as a result of the opioid crisis (Brown et al., 2018; Saunders et al., 2017). Researchers have identified substantial increases in the number of pregnant women with opioid use (including medical, non-medical, and medication assisted treatment), increases in the incidence of NAS (Patrick et al., 2015; Tolia et al., 2015), and have documented an increase in children with NAS reported to child welfare systems in a number of states (Lynch et al., 2018). Federal legislation has been passed to target NAS (Protecting Our Infants Act of 2015), and the Substance Abuse and Mental Health Services Administration has issued guidance for treating pregnant and parenting mothers with OUD and their infants (Substance Abuse and Mental Health Services Administration (SAMHSA, 2018). This study's results on the relationship between opioid sales and maternal and neonatal opioid hospitalizations lends support to those research findings and efforts. The findings suggest that, relative to all demographic groups, maternal and neonatal hospitalization rates have a much stronger relationship with retail opioid sales. However, the degree of uncertainty in the estimation leads to large confidence intervals, and the relationship between opioid sales and maternal/neonatal rates is statistically indistinguishable from the relationship with rates for all patients.

While not causal, these results can inform efforts by policymakers and public health professionals to understand how opioid prescribing relates to the opioid crisis in the United States. In particular, the results lend statistical support to the potential impact of prescribing changes at the population level. The impact of the opioid crisis on hospital costs resulting from hospital stays and emergency department visits is also a matter of concern, where total in-patient costs for prescription opioid overdose hospitalizations increased by $46 million per year from 2001 to 2012 (Hsu et al., 2017). Finally, hospitals may provide a unique entry point into treatment for OUD and other associated medical complications, and understanding how prescription opioid prevalence predicts opioid hospitalizations can help in planning and identifying risk (Binswanger et al., 2017).

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Contributors

Robin Ghertner is the sole author for this study. He conducted the research plan, analysis, and write-up of the results and has approved the final article.

Conflict of interest

No conflict declared.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2018.10.031.

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