Prescription rate and its effect on the opioid overdose death rate: implications of pharmaceutical financial incentives

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Abstract:

Objectives. To examine the effect of pharmaceutical incentives to physicians to write opioid prescriptions and their effects on opioid-related deaths by county urbanicity, industry, and demographic characteristics.

Methods. We estimated a linear regression model on opioid-related death rates, obtaining unbiased estimates by treating prescription rates as endogenous and adjusting for suppressed or missing county level opioid-related death rates.

Results. Pharmaceutical payments are positively associated with prescription rates; a 1% increase in the prescription rate results in 3 deaths per 100,000 persons; mining dependence is independently associated with an additional 7.4 deaths per 100,000 persons. Rural counties have lower death rates than urban counties but have significant spatial heterogeneity.

Conclusions. Pharmaceutical companies incentivizing physicians to write opioid prescriptions for their patients has a strong positive relationship with increased opioid prescribing. Legal prescriptions are an important driver of opioid-related overdose deaths. Finally, the mining industry in rural mining counties (not rural farming counties) has the highest death rates in the opioid epidemic.

The opinions expressed in this paper are those of the authors and do not necessarily represent those of the U.S. Agency for International Development

Public Health Implications. Given the positive empirical relationship between incentives and prescribing and its role in overdose deaths, opioid-related mortality prevention should target pharmaceutical companies.

The opioid crisis has exacted a terrible toll of morbidity and mortality in the United States. It has claimed at least 400,000 lives since 1999, probably many more due to undercounting.[1,2] Death rates continue to rise despite Prescription Drug Monitoring Programs (PDMP), prescription guideline recommendations, and millions of dollars funneled toward opioid death prevention efforts.[3,4] Opioid-related overdoses have reduced US life expectancy, which fell for the first time in decades in 2015, propelled by an increase in deaths among younger white men and women.[5] This study is the first to quantify the direct effects of physician prescriptions on opioid related deaths by county and the indirect effects of pharmaceutical companies incentivizing physicians to prescribe opioid prescriptions. This study is also the first to compare rural mining counties to rural farming counties.

The opioid outbreak is not randomly distributed throughout the country; there are large regional and state-level differences in death rates.[6] Factors associated with spatial heterogeneity are the subject of this study and may inform where to target resources to most effectively combat opioid related overdose deaths. Providers and stakeholders have noted high opioid-related death rates in rural areas, prompting the United States Department of Agriculture (USDA) to issue a statement and provide millions in research funding.[7] Monnat found an exploratory regression of overall drug mortality on measures of social determinants of health that is associated with mining activity and economic distress.[8]

One factor that drives the opioid-related overdose mortality is the supply of physician prescriptions of opioids.[9] The dramatic increase in prescriptions overall has been well documented, and the millions of dollars in payments from pharmaceutical companies to physicians involving opioids have also come under scrutiny.[10-16] However, the role of prescription opioids in driving the epidemic has been debated, especially in recent years as prescriptions have fallen and deaths continue to rise.[17,18] There is evidence that physicians initiated opioid use disorder (OUD) by prescribing excessive numbers of pills for individuals. Afterwards, persons with OUD switched from prescription opioids to illicit opioids such as fentanyl or heroin.[19] This study focuses on physician prescribing practices between 2010-2016 to analyze the association between pharmaceutical payments to physicians and prescribing practices and to determine if variation in prescribing practices explains county-level variation in opioid overdose death rates. We also consider the role of industry, income and demographic characteristics.

Methods

Confidentiality policies and statistical unreliability result in suppressing death rates in counties with fewer deaths and smaller populations. Because the missing data are not *missing at random*, a traditional linear regression produces biased coefficients. To address this bias, we pool data from several years and use a generalized selection model to account for county-level data suppression. Second, determining the effect of opioid prescription rate on opioid-related death rates is complicated by the fact that prescription rates are likely endogenous; that is, many observable and unobservable factors that affect the rate of overdoses may also affect the rate at which doctors prescribe opioids.

Therefore, the second innovation of this study is estimating a model using 2 Stage Least Squares (2SLS). We leverage data on financial incentives pharmaceutical companies provide physicians for writing opioid prescriptions, which is associated with increased prescription rates of those drugs, which introduces exogenous variation in the prescription rates.

Our study relies on a specialized multivariate regression model to estimate the effect of opioid prescription rates on opioid-related death rates. We determine whether there is an association between the death rate by rurality, economic activities, and economic distress by including the prescription rate as an explanatory variable – that is, ‘are prescribing practices explaining part of the variation in other factors?’

Data

Data on average age-adjusted opioid-related death rates between 2010-2016 were derived from death certificates.[20] The base population for age adjustment was the 2000 U.S. standard. An opioid-related death was defined according to the CDC when the Underlying Cause of Death *International Classification of Disease, 10th Revision* (ICD-10) code was related to poisoning (X40- 123 44, X60-64, X85, or Y10-14), and the Multiple Cause of Death codes included an opioid (T40.0-40.4 or T40.6).[21] Due to confidentiality standards, death rates were “Suppressed” when the total death count in a county was less than 10, and due to statistical unreliability, death rates were ”Unreliable” when the total death count in a county was between 10 and 20.[20] After censoring, 1,248 counties remained in the final data set.

The county demographic profile is derived from an average of the US Census decennial and intercensal estimates 2010-2016.[20] Race, gender, and age were divided by the total population to construct the average demographic composition of the county over the study period.

The 2013 Urban Influence Codes for each county are taken from the U.S. Department of Health and Human Services Area Health Resource File (AHRF).[22] Counties are classified on an integer scale from 1 to 12 from most urban to most rural. The classifications are as follows:[22]

Metropolitan counties: 1, In a large metro area of 1 million residents or more; 2, In a small metro area of less than 1 million residents. Non-Metropolitan Counties: 3, Micropolitan area adjacent to a large metro area; 4, Noncore adjacent to a large metro area; 5, Micropolitan area adjacent to a small metro area; 6, Noncore adjacent to a small metro area with a town of at least 2,500; 7, Noncore adjacent to a small metro area and does not contain a town of at least 2,500 reside; 8, Micropolitan area not adjacent to a metro area; 9, Noncore adjacent to a micro area and contains a town of at least 2,500 residents; 10, Noncore adjacent to micro area and does not contain a town of at least 2,500 residents; 11, Noncore not adjacent to a metro or micro area and contains a town of at least 2,500 or more; 12, Noncore not adjacent to a metro or micro area and does not contain a town of at least 2,500.

The AHRF provides the number of Medical Doctors per county and the economic dependence codes. A farming-dependent county is defined as “25% or more of the county’s average annual labor and proprietor’s earnings were derived from farming, or 16% or more of jobs were in farming,” and a mining-dependent county is defined as “13% or more of the county’s average annual labor and proprietors’ earnings were derived from mining, or 8% or more of jobs were in mining.”[22]

County-level Adjusted Gross Income (AGI) come from the 2015 Internal Revenue

Service (IRS) Statistics of Income (SOI) data sets.[23]

Prescription data and pharmaceutical payments to doctors come from Centers for Medicare and Medicaid Services (CMS). From Medicare Part D Prescription records, CMS provides the number of opioid prescriptions and total number of prescriptions by county in 2015.[24] The payments to physicians from pharmaceutical companies are derived from Dollars for Docs, a cleaned version of the CMS Open Payments Data from mid-2013 to 2015, distributed by ProPublica.[25] The dataset has 26 million observations of transactions that involved an opioid. Prescription opioids were classified from a list compiled by CMS for Medicare Part D prescription data. This yielded a dataset of 369,740 observations based on individual transactions involving a single physician. Because these data included addresses while the other data are aggregated to the county level, household prescription data were aggregated to the county level. First, transactions were searched using the US Department of Housing and Urban Development (HUD) 1st Quarter 2016 ZIP-FIPS crosswalk.[26] For those zip codes which are spread across several counties, the observation was placed in a county using GeoPy, a geocoder, using data from Google.[27]

Analysis

We start with a basic linear regression model:

$$y_j = \alpha_0 + \alpha_1 x_{1i} + \alpha_2 x_{2i} + \alpha_3 x_{3i} + \alpha_4 x_{4i} + \alpha_5 x_{5i} + \alpha_6 x_{6i} + \alpha_7 x_{7i} + \alpha_i x_{8i} + \sum_{j=2}^{12} \beta_j z_{ji} \qquad (1)$$

where y_i is the age-adjusted death rate for county i from opioids per 100,000 people, x_{1i} is the percentage of total Medicare Part D prescriptions for opioids, x_{2i} is the adjusted gross income in county i, x_{3i} is a dummy variable for agriculture-dependent counties, x_{4i} is a dummy variable for mining-dependent counties, x_{5i} is the number of males per 100 females in the county, x_{6i} is the percentage of the county which is white, x_{7i} is the percentage of the county that is between 45 and 54 years of age, x_{8i} is the percentage of the county between 55 and 64 years of age, and z_{ji} is a system of 11 dummy variables for county urban influence codes, using Urban Code 1 as the comparator.

Equation 1 requires correcting for the endogenous effects of the opioid prescription rate; that is, we cannot isolate the effect of the prescription rate on deaths with simple regression due to probable confounding of unobserved factors. Second, our dataset on opioid death rates is not exhaustive across counties due to suppression which results in smaller counties being systematically excluded unless their death rate is exceptionally high. The result is selectivity bias by including only counties with large populations or remarkably higher death rates. This biases the effect by overestimating exogeneous factors, especially when the variable of interest is correlated with suppressing causes.

We use the two-stage least squares approach to adjust for endogeneity. We first estimate the opioid prescription rate for each county using the variables from Equation 1 along with payments made by pharmaceutical companies to physicians, the % physicians in each county who receive these payments, and the total number of physicians in each county. The goal is to estimate the variation in prescription rates that do not affect the death rates at the county level. To adjust for selectivity bias of suppressed county death rates, we estimate whether or not the opioid death rate for a county is observed as a probit function

$$d_i = \Phi\left(\beta_0 + \beta_1\hat{x}_{1i} + \beta_2 x_{2i} + \beta_3 x_{9i}\right) \quad (2)$$

where $\hat{x}_{1i}$ is the expected opioid prescription rate, x_{9i} is the natural logarithm of population. Using these results, we then re-estimate the death rate from opioids as

$$y_j = \tilde{\alpha}_0 + \tilde{\alpha}_1 x_{1i} + \tilde{\alpha}_2 x_{2i} + \tilde{\alpha}_3 x_{3i} + \tilde{\alpha}_4 x_{4i} + \tilde{\alpha}_5 x_{5i} + \tilde{\alpha}_6 x_{6i} + \tilde{\alpha}_7 x_{7i} + \tilde{\alpha}_8 x_{8i} + \sum_{j=2}^{12}\tilde{\beta}_j z_{ji} + \tilde{\alpha}_9 IM\left(\hat{d}_i\right) \quad (3)$$

where $IM\left(\hat{d}_i\right)$ is the inverse Mills ratio based on the probit model in Equation 2.

Results

Table 1 shows the naïve simple ordinary least squares regression results. The death rate from opioids appears to be positively related to the opioid prescription rate, the county's dependence on mining, % White, and the county's population age structure. Further, the opioid death rate is a decreasing function of the share of the population that is male and county income. From the Urban Influence codes, compared to County Group 1 (the most urban group), death rate from opioid use appears significantly lower for County Group 2 and significantly higher for County Groups 4, 7, 9, 10, 11, and 12 – non-core counties or counties removed from a metropolitan area.

Table 2 predicts the opioid prescription rate based on income, log population, urban influence code, and measures of pharmaceutical payments to physicians: total number of MDs in the county, number of MDs receiving payments related to opioids, and the average payment per receiving MD. The number of MDs receiving opioid-related payments is positively associated with opioid prescription rate. Table 3 estimates a probit model for the probability of a death rate being observed (not suppressed) with predicted prescription rate, average gross income, and log population as the factors. The coefficient for population is statistically significant at p<.01.

Table 4 reports the main regression results, modified from the model reported in Table 1 by incorporating predicted prescription rates estimated using 2SLS and the Inverse Mills Ratio of the probit model for whether a county death rate is reported. The death rate from opioids is positively associated with the prescription rate, income, mining dependence, % population white, and age structure. The opioid death rate is negatively associated with the sex ratio (#males per 100 females). In terms of Urban Influence groups, compared to Urban Group 1 (the most urban), the opioid death rate is positively associated with Urban Group 10 and negatively associated with Urban Groups 2, 3, 5, 6, and 8. The coefficient of the Inverse Mills Ratio is significantly positive, indicating that the switch from a non-reported county to a reported county is associated with a higher opioid death rate.

Notable differences between the naïve simple regression and the final regression include an increase in the effect of the prescription rate (0.33 vs 2.98), a switch of the sign of the income effect (-0.00003 vs 0.00003), and a switch of the signs of the effects associated with non-core counties other than Urban Group 10 (positive to negative).

Discussion

The need to understand factors driving the morbidity and mortality of the opioid epidemic is crucially important to inform efforts to end the death toll. Certain county-level economic factors and social determinants of health have previously correlated with mortality from all drugs as a *whole*, but there is a dearth of research exploring economic factors specific to *opioids* and the direct and indirect effects of prescribing practices.

There is an increase in white middle-aged people and a decrease in younger males in counties associated with high opioid-related deaths. Poisoning from prescription and illicit opioids constitute a major source of years per life lost (YPLL). The positive association between opioid overdose death and the sex ratio are due to the age crossover of females outnumbering males at a younger age; at birth, 105 males are born per 100 females.[28] Males have higher birth rates than females, and a decrease in the male/female ratio is indicative of higher male mortality that results in females outnumbering males earlier than expected in healthy populations.[29] Similarly, the association with age 55-64 could be a proxy for deleterious public health conditions that reduce the population of younger people.

The associations between non-core (more rural) county categorizations and the death rate are largely *negative* in the final model. This may seem surprising because of the high death rates recorded and special attention paid to the opioid crisis in rural areas. In order for ruralness *overall* to be negatively associated with opioid mortality, it must be that most rural counties are relatively *less* affected by the epidemic in terms of opioid mortality than average. This is consistent with previous findings that the opioid epidemic is not truly an overall rural crisis – in fact, urban death rates are higher overall – but rather one in which rural counties are heterogeneously affected and include both some of the hardest hit and least affected counties.[6] Our results provide additional evidence that rural counties should not be treated as a monolith; rather, resources should be targeted specifically to distressed areas where opioid-related deaths cluster.

The effect of prescription rates on the death rate in the final model is large and positive; as the proportion of Medicare Part D opioid scripts in a county increases by one percentage point, the death rate increases by 3 deaths per 100,000. There was also a statistically significant association between the number of MDs in a county receiving opioid-related payments, the average payment from pharmaceutical companies and the county opioid prescription rate ($p<0.01$). These findings have significant policy implications and legal ramifications. The Drug Enforcement Agency and the Department of Justice have enforcement power to prosecute pill mills and physicians for illegal prescribing.[30] Furthermore, the Food and Drug Administration has jurisdiction to stop pharmaceutical companies from producing certain medications.[30] Surely, pharmaceutical companies that incentivize physicians to write opioid prescriptions is counterintuitive to legal and prevention activities. Civil and criminal charges have been filed against pharmaceutical companies for failing to warn physicians and patients about the dangers of opioid use.[31] Thus, these findings are consistent with pharmaceutical companies' role in encouraging more prescriptions that drive the opioid epidemic that contribute to opioid-related deaths.

Income has a positive association with opioid mortality, but the magnitude is small; a $10,000 increase in AGI is associated with 0.3 per 100,000 persons increase in the opioid death rate. These findings suggest that income *per se* may have a heterogeneous effect wherein particular low income and high income populations both have high rates of opioid abuse. Mining dependence is strongly associated with opioid death rates, accounting for an additional 7.4 deaths per 100,000. The strong association between mining and opioid-related deaths is likely related to the high rates of injury, pain, and loss of productivity from the dangers of mining work and increased susceptibility to OUD owing to anxiety, depression, and other mental health insults stemming from the collapse of the mining industry.[33,34]

This study has some limitations. Death certificate coding is subject to differences in reporting practices and capabilities to determine causes of death, and the number of deaths coded with opioids as a cause is under-counted. Deaths were pooled over seven years in order to obtain sufficient data with which to run the models, which precludes analysis of temporal trends. Medicare Part D prescription records are a subset of all scripts written in the United States, but insofar as they reflect underlying physician prescribing practices, they are a valid proxy for overall prescriptions even with incomplete case ascertainment. The pharmaceutical incentives data for writing opioid prescriptions were only available for mid 2013 to 2015. Furthermore, pharmaceutical companies that keep incentives beneath a certain threshold are not required to report payments. Thus, the effect we found underestimates the total impact of pharmaceutical company incentives for physicians.

Public Health Implications

There is a significant association between opioid-related payments to physicians and physician prescription rates of opioids. Prescription rates, in turn are an important driver of overdose deaths. However, they do not account for continued associations with certain factors such as economic dependence on mining. This suggests that purely increasing vigilance on the supply of prescription opioids with programs such as Prescription Drug Monitoring Programs (PDMPs) is unlikely to control death rates by itself. Spatial heterogeneity in the distribution of deaths, particularly within the category of rural geography, calls for targeting of resources to the areas of most need. Additional research is needed to determine which treatment and harm reduction strategies are most efficacious within particular contexts such as mining communities.

Tables

Table 1. Naïve Model of Factors Affecting Opioid Death Rates

Factor	Estimate (SE)		Factor	Estimate (SE)
Constant	-0.31549		Urban Group 3	-0.99623
	(4.82367)			(1.00926)
Prescription Rate	0.32895**		Urban Group 4	2.89793**
	(0.14313)			(1.41759)
Income	-0.00003**		Urban Group 5	-1.03142
	(0.00001)			(0.95560)
Farm Dependent	1.46176		Urban Group 6	1.18689
	(3.17345)			(1.20230)
Mining Dependent	8.33919***		Urban Group 7	10.26051***
	(1.09486)			(2.27027)
Male	-0.10296**		Urban Group 8	-0.68077
	(0.04175)			(1.07420)
White	0.09468***		Urban Group 9	4.51029**
	(0.01871)			(1.95408)
45-54	-0.02404		Urban Group 10	20.70779***
	(0.22363)			(2.71060)
55-64	1.01876***		Urban Group 11	4.85740**
	(0.17364)			(2.25839)
Urban Group 2	-1.60739**		Urban Group 12	13.97716***
	(0.65105)			(3.25104)

***Denotes statistical significance at the 0.01 level of confidence, **denotes statistical significance at the 0.05 level of confidence, and *denotes statistical significance at the 0.10 level of confidence.

Table 2. Predicting the Prescription Rate

Factor	Estimate (SE)		Factor	Estimate (SE)
Constant	3.19015***		Urban Group 5	0.00106
	(0.57797)			(0.19400)
Income	-0.00003**		Urban Group 6	0.03326
	(0.00001)			(0.18811)
Log(Population)	0.22030***		Urban Group 7	0.49336
	(0.05045)			(0.24796)
Total MDs	-0.00016		Urban Group 8	0.40849**
	(0.00012)			(0.19399)
MDs Receiving Payments	0.00074***		Urban Group 9	0.00873**
	(0.00022)			(0.22585)
Average Payment	0.01663		Urban Group 10	0.03939
	(0.01732)			(0.24685)
Urban Group 2	0.13638		Urban Group 11	0.65635**
	(0.14557)			(0.25519)
Urban Group 3	-0.02737		Urban Group 12	0.44483*
	(0.23598)			(0.26217)
Urban Group 4	-0.31061			
	(0.23493)			

***Denotes statistical significance at the 0.01 level of confidence, **denotes statistical significance at the 0.05 level of confidence, and *denotes statistical significance at the 0.10 level of confidence.

Table 3. Probit Estimation for Reported Death Rate	
Factor	Estimate (SE)
Constant	-15.86223***
	(0.78758)
Prescription Rate	-0.07619
	(0.15236)
Income	-0.00002
	(0.00002)
Log(Population)	1.54085***
	(0.06517)
***Denotes statistical significance at the 0.01 level of confidence, **denotes statistical significance at the 0.05 level of confidence, and *denotes statistical significance at the 0.10 level of confidence.	

Table 4. Final Model for Factors Affecting Opioid Death Rates

Factor	Estimate (SE)		Factor	Estimate (SE)
Constant	-13.04107*		Urban Group 4	-2.03776
	(6.70199)			(1.43329)
Prescription Rate	2.98382***		Urban Group 5	-2.66006***
	(0.77218)			(0.91393)
Income	0.00003**		Urban Group 6	-4.16497***
	(0.00002)			(1.20692)
Farm Dependent	-2.43536		Urban Group 7	-0.70020
	(2.98711)			(2.28683)
Mining Dependent	7.43323***		Urban Group 8	-4.66842***
	(1.02855)			(1.05810)
Males/ 100 Females	-0.09734**		Urban Group 9	-2.59833
	(0.03903)			(1.91585)
White	0.06696***		Urban Group 10	10.84701***
	(0.01765)			(2.64401)
45-54	-0.26404		Urban Group 11	-1.75877
	(0.20431)			(2.19765)
55-64	1.01933***		Urban Group 12	-1.19612
	(0.16116)			(3.25176)
Urban Group 2	-1.70355***		Inverse Mills Ratio	8.92607***
	(0.61355)			(0.67752)
Urban Group 3	-2.24767**			
	(0.96022)			

***Denotes statistical significance at the 0.01 level of confidence, **denotes statistical significance at the 0.05 level of confidence, and *denotes statistical significance at the 0.10 level of confidence.

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