First, Do No Harm: An Analysis of Prescribing Behavior

by Chase Barham

Abstract

In this paper econometric analysis is used to explore contributing factors to widespread opioid abuse in the United States. Using county-level data from the Centers for Disease Control and Prevention (CDC), multiple linear regressions are performed to estimate the correlation of opioid prescribing rates on accidental drug poisoning mortality. Based on the model presented in this paper, statistical significance is shown correlating drug overdose deaths and opioid prescribing rates. Given low importation of illegal prescription opioids and the high likelihood of transitioning to heroin from prescription opioids, it suggests physicians play a key role in the supply of opioids used by individuals with opioid use disorder.

Introduction

As the opioid crisis worsens, legislators and public health officials are scrambling to implement policies in order to combat rising overdose deaths. An estimated 72,306 people died from overdoses deaths in 2017, of which approximately 90% were opioid-related. This is a sharp increase from the 16,849 deaths in 1999 (National Institute on Drug Abuse 2018). There has been considerable progress made in policy efforts recently. In 2016 the Comprehensive Addiction and Recovery Act was signed into law by President Barack Obama and by 2018 all 50 states and Washington D.C. had passed legislation creating a Prescription Drug Monitoring Program. However, efforts to abate the role of prescription opioids in the epidemic have largely focused on decreasing demand. Promotional efforts by public health officials and government agencies have promoted misuse and diversion as the culprits behind prescription opioid abuse (Beauchamp, Winstanley, Ryan, & Lyons 2014). However, there still appears to be a more systemic issue with prescription opioids than previously thought.

In examining diversion and nonmedical use of prescription opioids alone, there would be a weak correlation between opioid prescriptions and drug overdose deaths using county-level data. The supply of illegal prescription opioids (i.e. not in possession of the person to whom it was prescribed) is relatively small compared to other illicit opioids. This is evidenced by two facts: low importation and high cost. Oxycodone accounts for only 2.8% of drug trafficking charges in the United States, compared to heroin's 14.4%¹ (United States Sentencing Commission 2017). Also, several studies suggest the transition from prescription opioids to heroin is partly due to the lower cost of heroin and wider availability (Cicero & Ellis, 2015; Monico & Mitchell 2018). This creates a lower likelihood of widespread diversion or misuse by patients with legitimate opioid prescriptions. This makes sense – the majority of people who receive prescription opioids are legitimate patients with medical necessity. In a study by Jones, Paulozzi, and Mack (2014) on nonmedical use of

¹ Prescription opioids other than oxycodone, along with other drugs not specified, are grouped into the "other" category, which accounts for 3.7% of arrests.

opioids, gifted by a friend or relative was the primary source of procurement in individuals with 1-29 days of nonmedical misuse in a year. In individuals who misused opioids for nonmedical purposes for 200-365 days in a year, prescriptions from one or more physicians were the primary source. Individuals who use opioids 200-365 days per year have a higher likelihood of having opioid use disorder, given the greater frequency of use.

This paper aims to test the hypothesis of a correlation between the number of opioid prescriptions and overdose mortality, a correlation between the two variables could suggest a more systemic problem beyond just misuse and diversion. Several studies have shown there is considerable evidence that marketing by pharmaceutical companies for their opioid products had a profound impact on clinicians prescribing opioids to noncancer patients (Cicero & Ellis, 2015; Griffin III & Spillane, 2012; Van Zee 2009). However, there are very few studies that analyze the impact of physician prescribing on addiction rates and subsequent overdose mortality. In addition, studies that focus on abusing prescription drugs do not differentiate between legally prescribed and illicitly obtained medications.

Data

For data collection, the Centers for Disease Control (CDC) and the United States Census Bureau (USCB) were the sources of data for each county, county-equivalent, and Washington, D.C. in the United States. There were seven county and county equivalents that were not included due to frequent omission across years by both the USCB and CDC². Opioid prescribing rates were obtained from the CDC for years 2010-2016. It includes all natural, semi-synthetic, and synthetic opioids ranging from Schedule II-V available by prescription in the United States. However, the prescribing data is only published in population-adjusted rates and is incomplete. Of 3141 counties utilized in the dataset, data were available for 702 - 907 counties depending on the year. Using the CDC's cited population source, per-capita rates were mathematically transformed into total prescriptions per county. The CDC WONDER database's detailed mortality data was utilized for drug poisoning deaths, using both unintentional (ICD-10: X40-X44) and undetermined (ICD-10: Y10-Y14) intent.

The CDC does provide mortality data on opioid-related overdoses. However, the CDC does have data use restrictions. If the data pulled from the CDC WONDER database has a value lower than ten, but greater than zero, it is suppressed for privacy concerns. For example, if you wish to gather county-level data on drug overdose deaths of males under 18 years old, if a county has less than ten instances overdose deaths then a null value is given. If a county has zero deaths, then it is reported as being zero rather than suppressed. For this paper, all drug overdose deaths are used without specifying which drug(s) were the cause of death. The reporting accuracy of specific drugs, as opposed to an unspecified drug poisoning, as the cause of mortality ranges from 47.4 to 99% between states (Rudd, Seth, David, & Scholl 2016). Although, as stated previously, approximately 90% of all drug overdose deaths are opioid-related (National Institute on Drug Abuse 2018). For these reasons, it is more beneficial to include all drug overdose deaths than to attempt to use data that specifies which drugs are the cause of death.

² The county and county equivalents omitted are: Prince of Wales-Outer Ketchikan Census Area, Kusilvak Census Area, Skagway-Hoonah-Angoon Census Area, Wade-Hampton, and Wrangell-Petersburg Census Area of Alaska along with Bedford City County and Clifton Forge City County of Virginia.

The benefit of including all drug poisoning deaths is that individuals who may have transitioned from prescription opioids to other opioids, such as heroin or illegally-manufactured fentanyl are captured in the model. In a study done by Monico and Mitchell, 15 out of 20 individuals in a methadone treatment program for heroin addiction stated they had initiated opioid abuse through legally prescribed opioids for medical necessity (2018). As well, 66.4% of drug overdoses deaths in 2016 involved an opioid (Seth, Scholl, Rudd, & Bacon 2018). However, there is the issue of determining prescription opioids from illicitly obtained opioids. For instance, illicitly-manufactured fentanyl is impossible to discern from prescribed fentanyl in death certificates that list the type of opioid.

The USCB provided county-level data for income, health insurance coverage, population, and employment using the American FactFinder database. Five-year estimates, inflation-adjusted for the corresponding year were used for mean household income. The USCB's Small Area Health Insurance Estimates provided an aggregate number of individuals without health insurance. Employment is the average number of individuals employed who reside in the county for the given year.

Table 1			
Summary Statistics			
<u>Variable</u>	Observations	Mean	Standard Deviation
Overdose Deaths	5,409	46.49	69.12
Prescriptions	20,040	83,354.12	109,4803.90
Population	21,987	100,684.40	322,368.20
Uninsured	21,980	12,449.08	52,318.13
Income	21,987	59,701.44	14,565.87
Unemployment	21,980	3,563.69	13,326.80
1			

Note: The purpose of these statistics is to have a preview of the data and to have a reference for the results presented in Table 2. The number of observations gives insight into how many instances of the given variable are available to analyze. The mean is just the arithmetic mean. The standard deviation gives insight into the variation of the data compared to the mean. All figures in this table are not population adjusted.

Empirical Specification

To test the null hypothesis that there is no effect of prescribing rates on overdose deaths, several ordinary least squares regressions were performed. The dependent variable Y is the number of overdose deaths at year t and county c. Equation (OLS1) is the baseline linear regression of the main independent variable X^1 overdose deaths and the independent variable X^2 population on the dependent variable:

(OLS1)

 $Y_{ct} = \beta_0 + \beta_1 X_{ct}^1 + \beta_2 X_{ct}^2 + \varepsilon_{ct}$ Equation (OLS2) utilizes influencing factors of overdose including unemployment and mean income.

 $Y_{ct} = \beta_0 + \beta_1 X_{ct}^1 + \beta_2 X_{ct}^2 + \beta_3 X_{ct}^3 + \beta_4 X_{ct}^4 + \varepsilon_{ct}$ Equation (OLS3) expands on this adding other factors of overdose mortality including (OLS2)

income, unemployment, and lack of health insurance. (OLS3) $Y_{ct} = \beta_0 + \beta_1 X_{ct}^1 + \beta_2 X_{ct}^2 + \beta_3 X_{ct}^3 + \beta_4 X_{ct}^4 + \beta_5 X_{ct}^5 + \varepsilon_{ct}$ Equation (OLS4) adds fixed effects for both state S_{ct} and year T_{ct} to adjust for variations

among locations and over time.

 $Y_{ct} = \beta_0 + \beta_1 X_{ct}^1 + \beta_2 X_{ct}^2 + \beta_3 X_{ct}^3 + \beta_4 X_{ct}^4 + \beta_5 X_{ct}^5 + \beta_6 T_{ct} + \beta_7 S_{ct} + \varepsilon_{ct}$ (OLS4)

Econometric Issues

There are several potential issues with the model. While there are a host of factors that can lead to substance use disorders, there are three categories that are emphasized in available literature: psychosocial, environmental, and genetic. This model only sufficiently captures environmental effects, making it prone to omitted variable bias. Population-based genetic information for each county is not available. County mental health disorder rates would be beneficial if substance use disorders are excluded due to simultaneity issues. A large majority of individuals who died from overdose deaths could be classified as having a substance use disorder. However, given the established effect of mental health disorders leading to substance abuse, a great effort would have to be made to address endogeneity and simultaneity issues of integrating psychosocial effects into the model. By definition, a substance use disorder is a mental health disorder, which in itself could create simultaneity issues.

There are potential issues with nonlinearity and a skewed distribution. Addressing these are important in the analysis to ensure that results are robust. Both the natural logarithmic and quadratic versions of the model were run; however, the results were indeterminate. The purpose of applying the natural logarithm and squaring the model is to account for nonlinearities or a skewed distribution. This can arise from variation among counties. For example, there may not be a constant increase in prescribing rates compared to the population. A county of 3,000 could have 3,000 prescriptions whereas a county of 5,000 may only 1,000 prescriptions for a given year. The results were either statistically insignificant and/or the coefficient switched from positive to negative correlation compared to the original equation. The spurious results also happened in using county fixed effects and the first difference. The purpose of using fixed effects and the first difference is to account for omitted variables. In statistical analysis, a great deal of effort is used to address omitted variable bias. There are variables which could impact the variable of interest, which is referred to as the dependent variable (it is overdose deaths in this paper), however, they are not included in the model. Fixed effects address potential variations among counties. For instance, some counties have expanded naloxone (an overdose reversal medication) access to be over-the-counter. That could lead some counties to have a lower number of overdose deaths. Using the first difference addresses variations over between years. Using the same example, a particular county could have implemented naloxone access in a particular year. The preceding years could have higher overdose deaths compared to the years that have expanded access.

Results

Table 2						
Regression Results of Overdose Deaths on Opioid Prescriptions 2010-2016						
Variable	OLS1	<u>OLS2</u>	OLS3	OLS4		
Prescriptions	.000101***	.0000972***	.0000976***	.0001374***		
_	(.0000158)	(.0000155)	(.0000154)	(.0000249)		
Population	.000038***	.0000148***	.0001219***	.0001300***		
	(.0000114)	(.0000524)	(.0000198)	(.0000295)		
Uninsured			0003453	0004490***		
			(.0002332)	(.0000976)		
Income		0001763***	0003668***	0004980***		
		(.0000524)	(.0000775)	(.0000922)		
Unemployment		0014409***	0004208***	0011308**		
		(.0002976)	(.0000775)	(.0000976)		
Observations	5,272	5,272	5,272	3,908		
R^2	.58	.62	.65	.67		

Notes: Numbers in parenthesis are robust standard errors.

OLS1 = Overdose deaths regressed on prescriptions and population

OLS2 = Overdose deaths regressed on prescriptions, population, income, and unemployment

OLS3 = Overdose deaths regressed on prescriptions, population, income, unemployment, and lack of health insurance

OLS4 = Overdose deaths regressed on prescriptions, population, income, unemployment, lack of health insurance, state fixed effects, year fixed effects.

* p < .10

** p < .05

*** p < .01

As evident in Table 2, the hypothesis held to be true as there is statistical evidence to reject the null hypothesis. All coefficients are significant at the 1% level, except for unemployment which is significant at the 5% level. Based on the model presented in this paper, there is a positive correlation between the number of opioid prescriptions and overdose deaths. It estimates an increase in 10,000 prescriptions yields an increase of 1.37 drug overdoses. Given there are over 200 million opioid prescriptions written every year in the United States, it is still a substantial ratio (Rudd, Seth, David, & Scholl 2016). As expected, there is a negative correlation between income, unemployment, and overdose deaths.

Based on this model, the lack of health insurance is a barrier to accessing health care. An increase in being uninsured leads to a higher likelihood of dying from overdose compared to counties with higher health insurance rates. This agrees with research that establishes that being uninsured does decrease the likelihood of utilizing medical care (Foutz, Damico, Squires, & Garfield 2017). It is not surprising, given the high cost of paying out-of-pocket for medical care.

In unemployment, the model provides further evidence of theorized declining labor force rates (Krueger 2017). To strengthen the correlation, it would be beneficial to include employment in the model to see if the negative correlation still holds. If there is a positive correlation, it could

suggest that there is a high cost of drug addiction where being gainfully employed enables engaging in addictive behaviors. However, the negative correlation between unemployment population suggests that substance use disorder is causing unemployment to decrease, likely from individuals exiting the labor force. Although it is impossible to discern, in this model, if individuals taking opioids are leaving the labor force due to opioid use disorder or from health-related reasons.

Conclusion

In light of statistical significance between drug overdose deaths and the number of prescription opioids, there should be a greater concern among clinicians and health officials in the risks of opioid therapy. This should include long-term risks not associated with acute treatment. In the United States, physicians take a largely liberal approach to treating pain compared to other countries. It has been suggested this is due to the pain as the fifth vital sign campaign by the American Pain Society in the 1990s and increased marketing by pharmaceutical companies for opioid use in noncancer pain (Cicero & Ellis, 2015; Griffin III & Spillane, 2012; Van Zee 2009). With the low importation of illicit pharmaceutical opioids, clinicians are responsible for the majority of the supply of opioids used in drug overdose deaths in the United States. While a conservative approach to prescribing opioids could lead to a decrease in overdose deaths, it is equally important to ensure adequate funding for developing non-opioid pain medications and increase the availability of harm reduction methods like naloxone access to further prevent overdose deaths. However, a multifaceted approach with law enforcement, clinicians, along with state and federal legislators is needed to make a meaningful impact in the ongoing opioid crisis.

References

- Beauchamp G.A., Winstanley E.L., Ryan, S.A., & Lyons, M.S. (2014). Moving Beyond Misuse and Diversion: The Urgent Need to Consider the Role of Iatrogenic Addiction in the Current Opioid Epidemic. *American Journal of Public Health*, 104(11), 2023-2029. doi:10.2105/AJPH.2014.302147
- Centers for Disease Control and Prevention. (2017). U.S. Prescribing Rate Maps. Retrieved from https://www.cdc.gov/drugoverdose/maps/rxrate-maps.html
- Centers for Disease Control and Prevention. (2017). CDC WONDER: Underlying Cause of Death 1999-2016. Available from http://wonder.cdc.gov/ucd-icd10.html
- Cicero T.J. & Ellis, M.S. (2015). Abuse-Deterrent Formulations and the Prescription Opioid Abuse Epidemic in the United States. *JAMA Psychiatry*, 72(5), 424-429. doi:10.1001/jamapsychiatry.2014.3043
- Foutz, J., Damico, A., Squires, E., Garfield, R. (2017). The Uninsured: A Primer Key Facts about Health Insurance and the Uninsured Under the Affordable Care Act. *Kaiser Family Foundation*. Retrieved from https://www.kff.org/report-section/the-uninsured-a-primerkey-facts-about-health-insurance-and-the-uninsured-under-the-affordable-care-act-howdoes-lack-of-insurance-affect-access-to-health-care/
- Griffin III, O.H. & Spillane, J.F. (2012). Pharmaceutical Regulation Failures and Changes: Lessons Learned From OxyContin Abuse and Diversion. *Journal of Drug Issues*, 43(2), 164-175. doi: 10.1177/0022042612467990
- Jones, C.M., Paulozzi, L.J., & Mack, K.A. (2014). Sources of Prescription Opioid Pain Relievers by Frequency of Past-Year Nonmedical Use: United States, 2008-2011. JAMA Internal Medicine, 174(5), 802-803. doi:10.1001/jamainternmed.2013.12809
- Krueger, A.B. (2017). Where Have All the Workers Gone? An Inquiry into the Decline of the U.S. Labor Force Participation Rate. *Brookings Papers on Economic Activity*, Fall 2017, 1-87. Retrieved from https://www.brookings.edu/bpea-articles/where-have-all-theworkers-gone-an-inquiry-into-the-decline-of-the-u-s-labor-force-participation-rate/
- Monico, L.B. & Mitchell, S.G. (2018). Patient perspectives of transitioning from prescription opioids to heroin and the role of route of administration. *Substance Abuse Treatment, Prevention, and Policy*, *13*(4), 1-8. doi: 10.1186/s13011-017-0137-y
- National Institute on Drug Abuse. (2018). Overdose Death Rates. Retrieved from https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates
- Rudd, R.A., Seth, P., David, F., Scholl, L. (2016). Increases in Drug and Opioid-Involved Overdose Deaths: United States, 2010–2015. *Morbidity and Mortality Weekly Report*, 65(50-51), 1445-1452. doi: http://dx.doi.org/10.15585/mmwr.mm655051e1
- Seth, P., Scholl, L., Rudd, R.A., Bacon, S. (2018). Overdose Deaths Involving Opioids, Cocaine, and Psychostimulants — United States, 2015–2016. *Morbidity and Mortality Weekly Report*, 67(12), 349-358. doi: http://dx.doi.org/10.15585/mmwr.mm6712a1
- Triumph, Public Health Tragedy. American Journal of Public Health, 99(2), 221-227. doi: 10.2105/AJPH.2007.131714
- United States Census Bureau. American FactFinder: American Community Survey. Available from https://factfinder.census.gov/

 United States Sentencing Commission. (2017). Quick Facts: Drug Trafficking Offenses. Retrieved from https://www.ussc.gov/sites/default/files/pdf/research-and-publications/quick-facts/Quick_Facts_Drug_Trafficking_2016.pdf
Van Zee, A. (2009). The Promotion and Marketing of OxyContin: Commercial.